

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

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Acknowledgments



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Presentation & code available online at:
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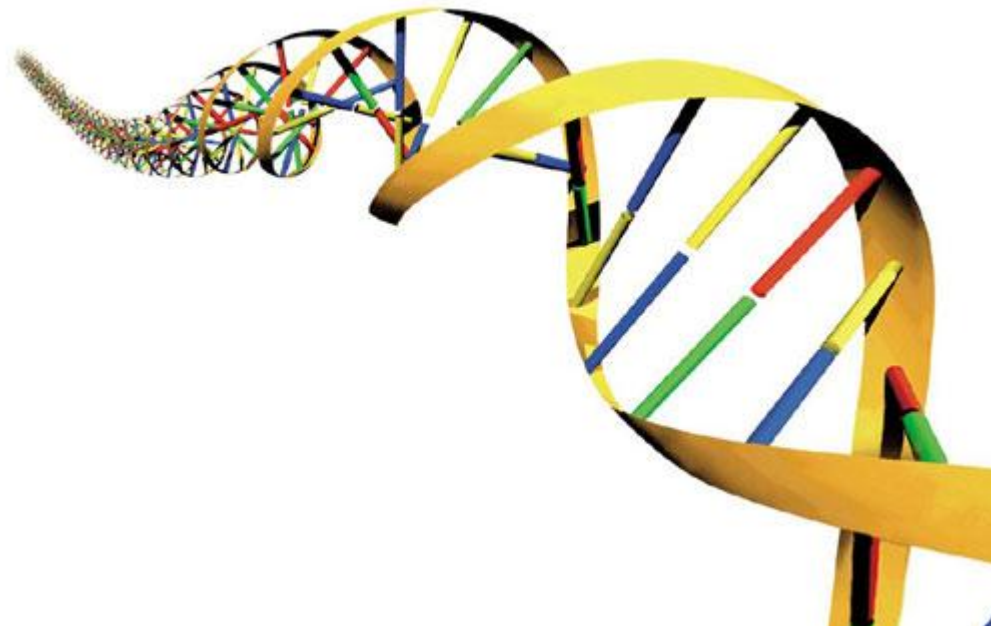
Mutation

“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

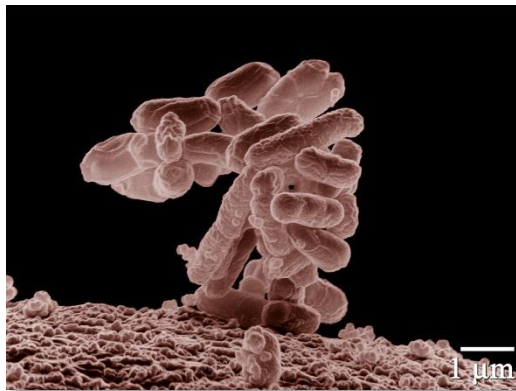


Variation in mutation rates

Between species

“Noticeable” mutations per genome per generation

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



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



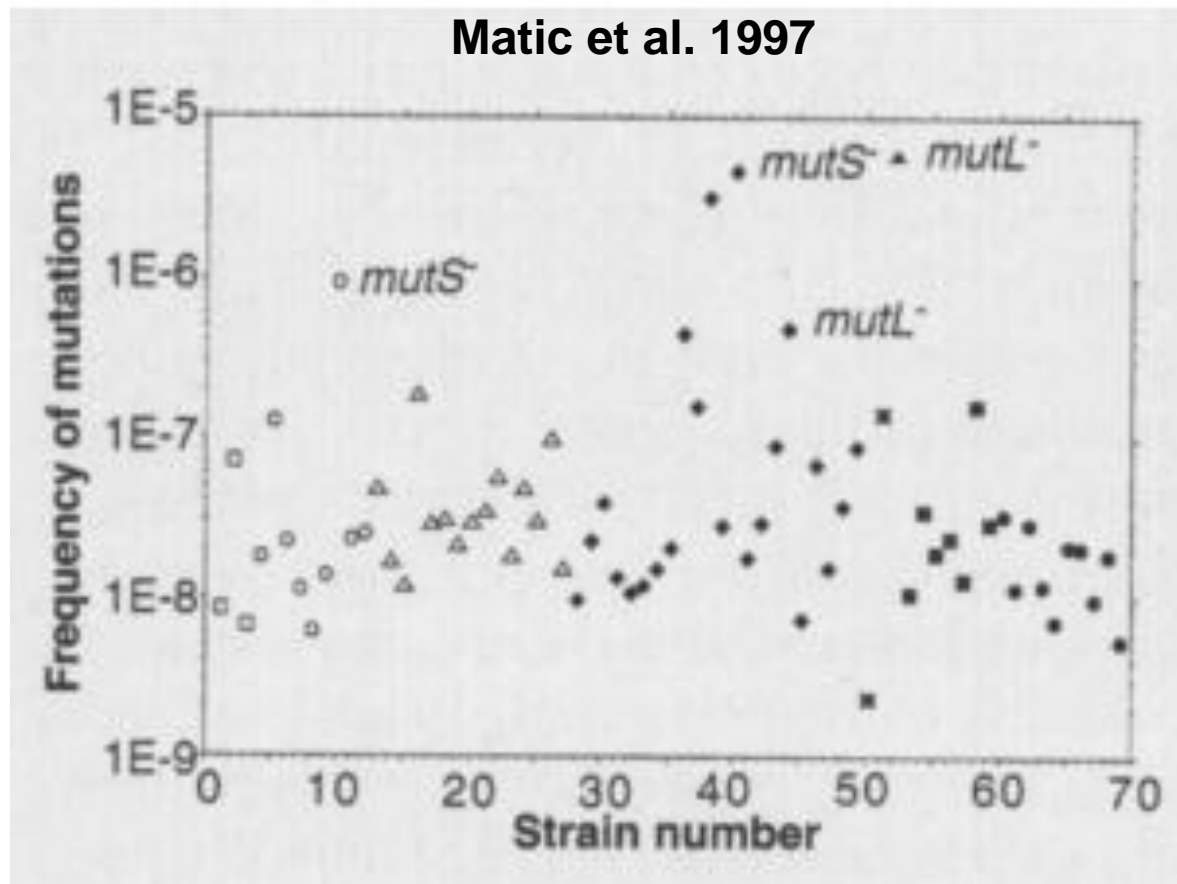
Mammals (*H. sapiens*):
41 (Lynch PNAS 2010)



Variation in mutation rates

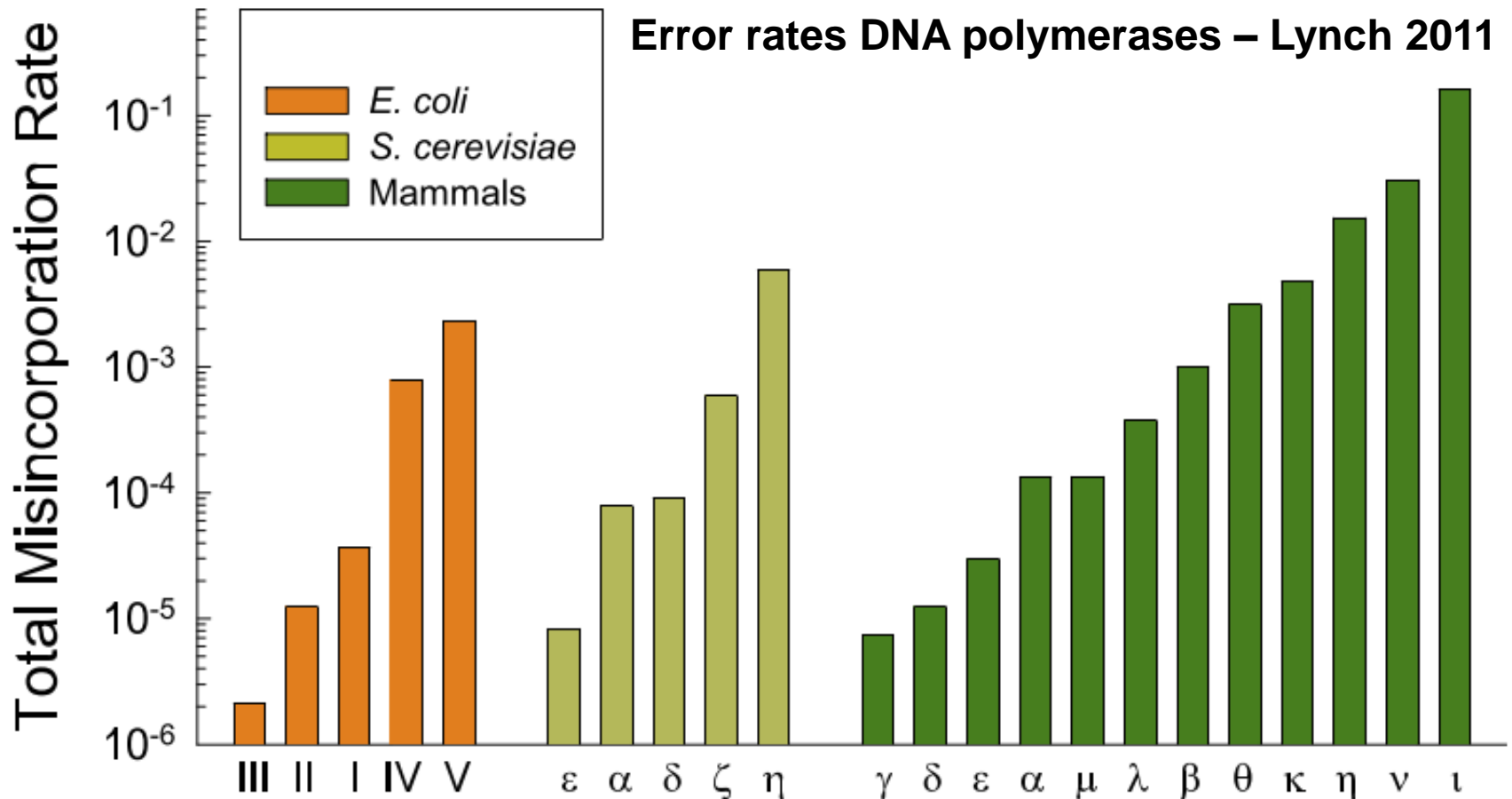
Between populations

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



Variation in mutation rates

Within individuals

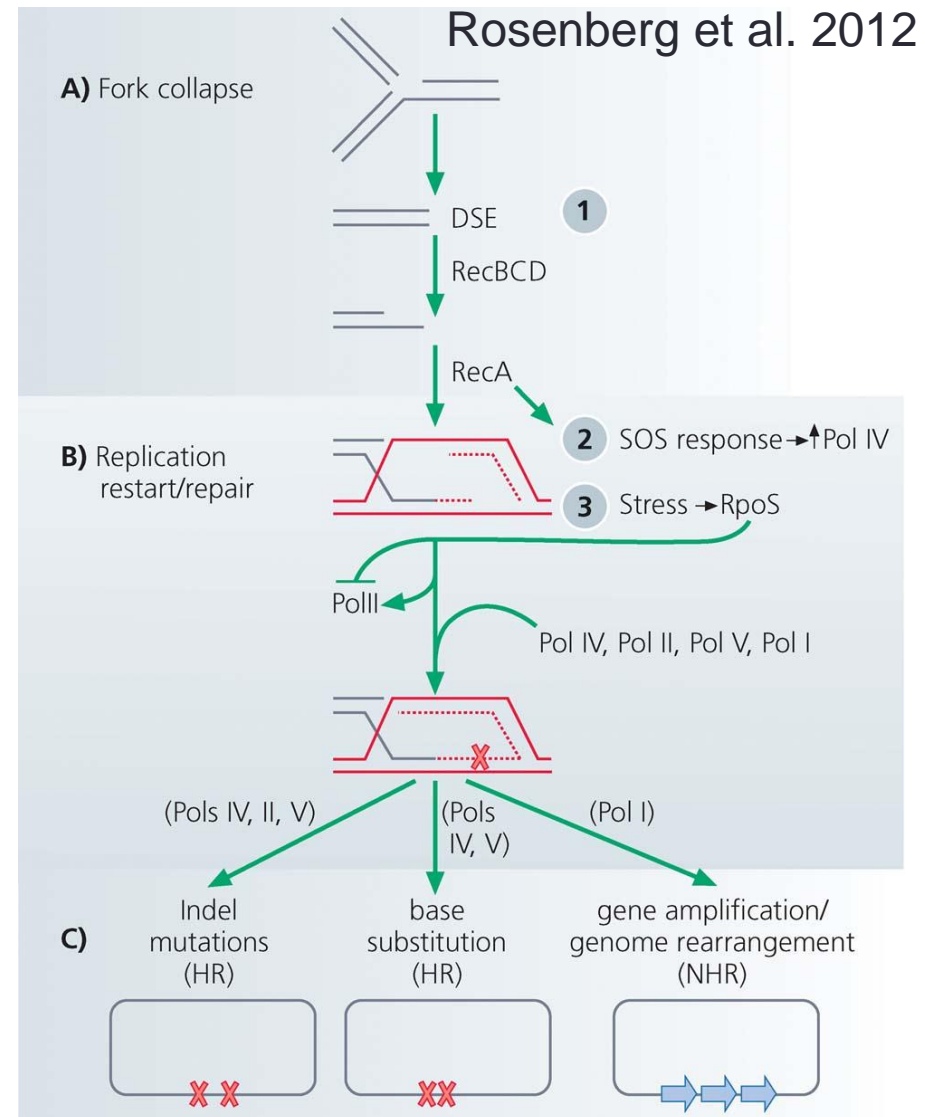


Stress-induced mutation

E. coli:

Error prone DNA polymerases are induced by stress responses:

- SOS response
- Carbon starvation
- DNA damage



Evidence

Bacteria

- *Escherichia coli*
- *Bacillus subtilis*
- *Pseudomonas putida*
- *Pseudomonas aeruginosa*
- *Listeria monocytogenes*
- *Staphylococcus aureus*
- *Mycobacterium tuberculosis*

Bjedov et al. 2003

Sung & Yasbin 2002

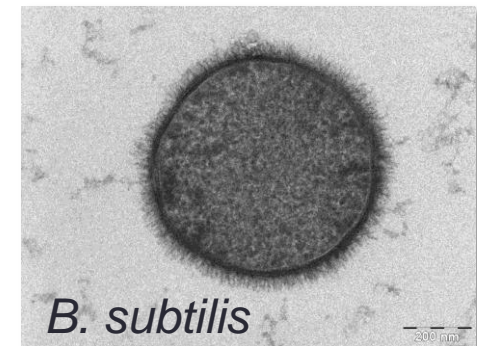
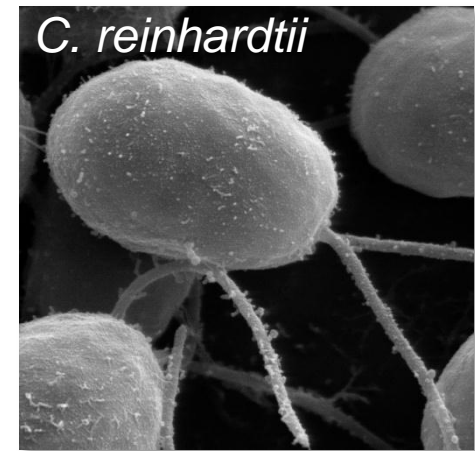
Kivisaar 2010

Weigand & Sundin 2012

van der Veen et al. 2010

Cirz et al. 2007

Boshoff et al. 2003



Eukaryotes

- *Chlamydomonas reinhardtii*
- *Saccharomyces cerevisiae*
- *Caenorhabditis elegans* & *briggsae*
- *Drosophila melanogaster*
- *Human cancer cells*

Goho & Bell 2000

Hall 1992; Heidenreich 2007

Matsuba et al. 2012

Sharp & Agrawal 2012

Hara et al. 2005; Bristow & Hill 2008

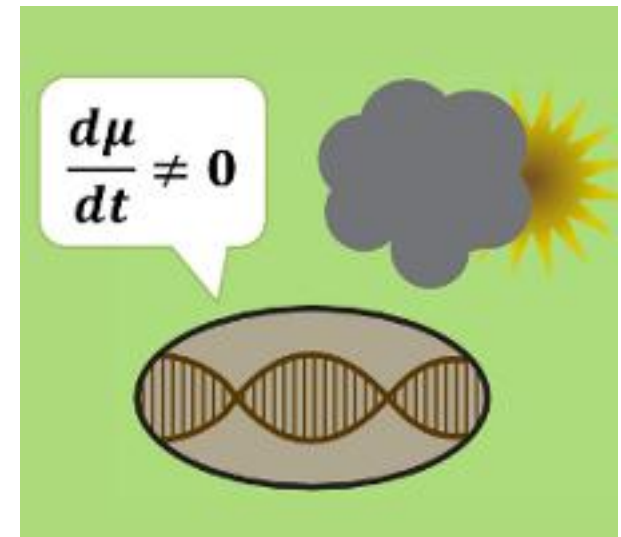
Evolution of stress-induced mutation

- **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...”

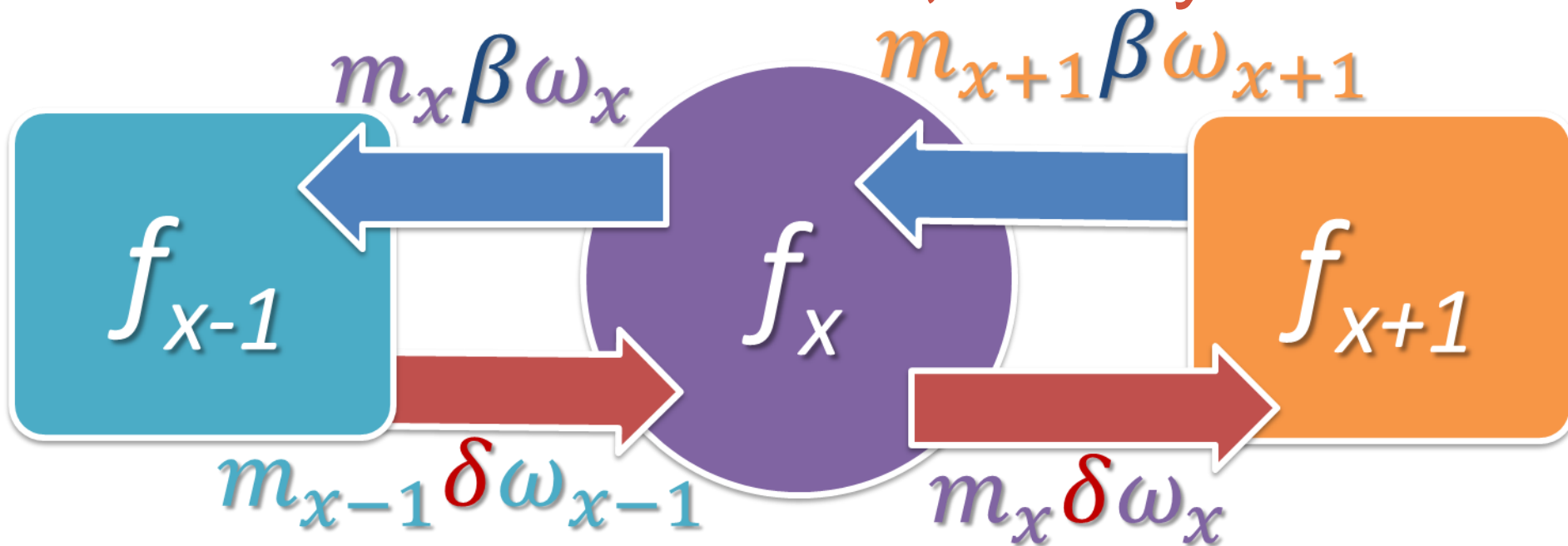
MacLean et al. 2013



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

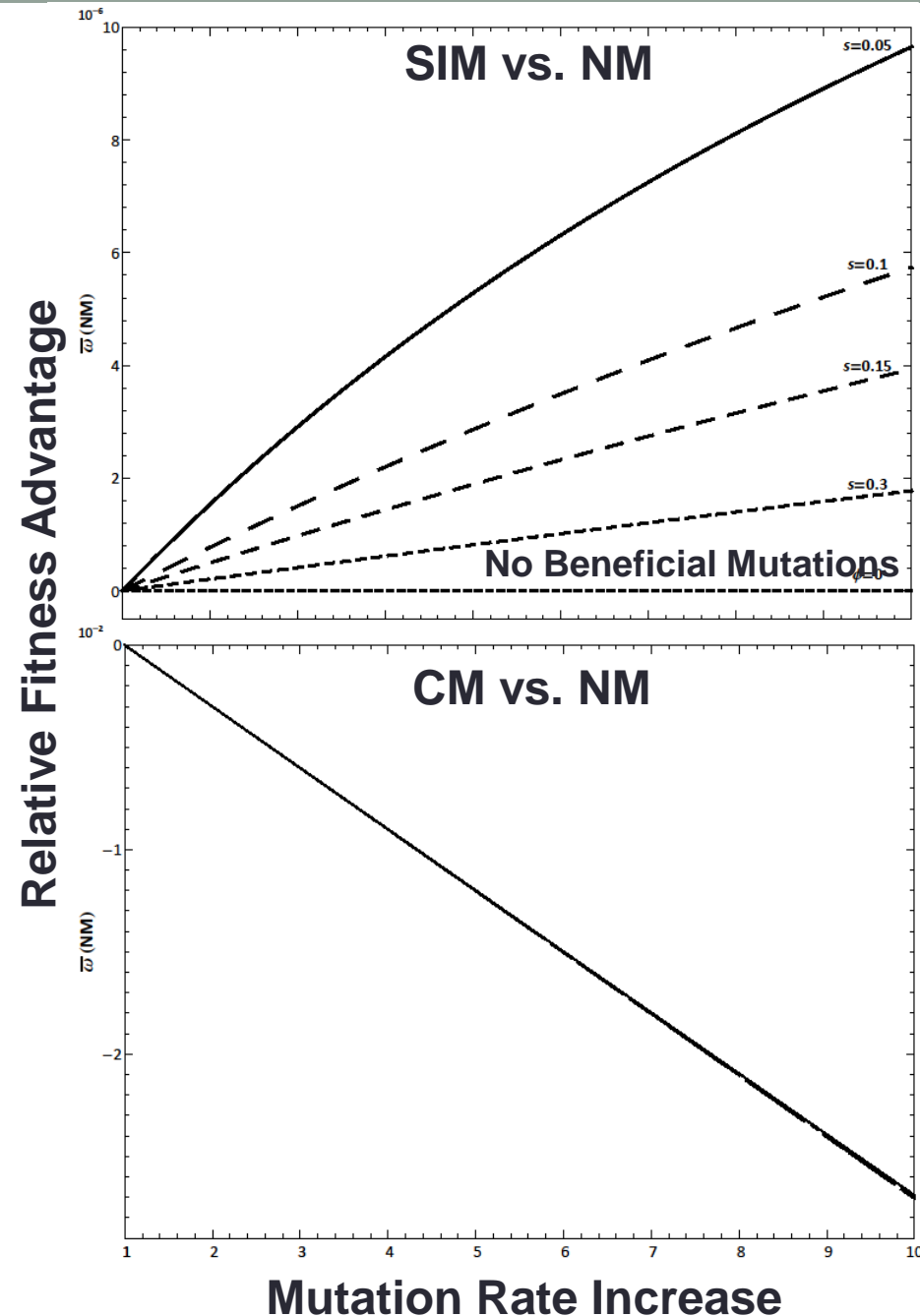
Model predictions: The unfit should hypermutate

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

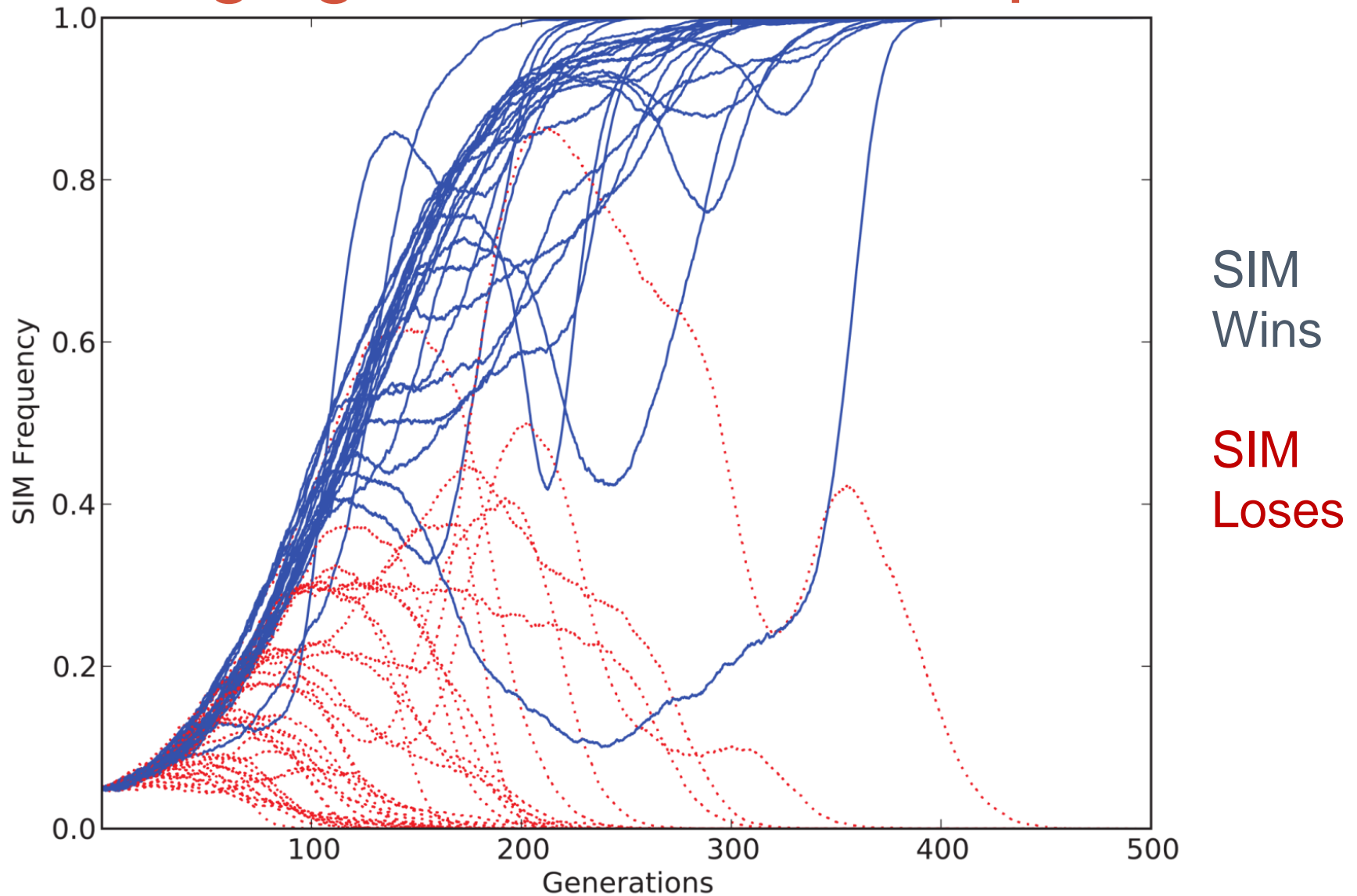
Increasing the mutation rate of individuals with below average fitness increases the population mean fitness

Advantage to SIM

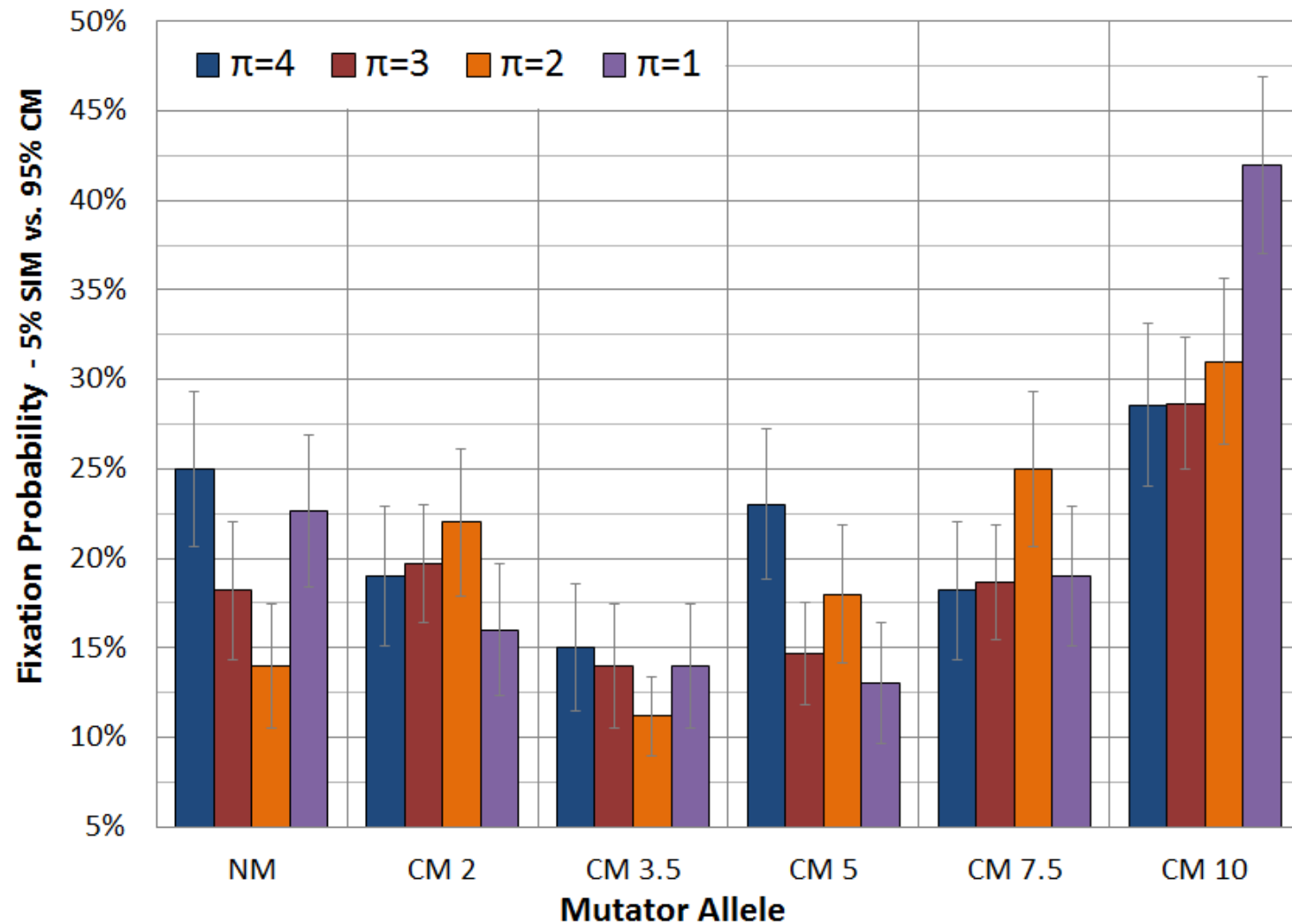
- **NM - Non-mutators**
 - constant low rate of mutation
- **CM - Constitutive mutators**
 - Constant high rate of mutation
- **SIM - Stress-induced mutators**
 - Low mutation rate when well-adapted
 - High mutation rate when stressed



Changing environment, competitions



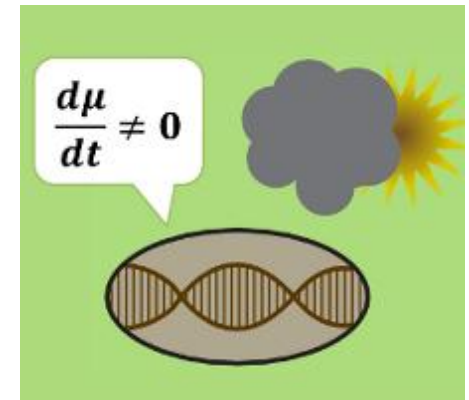
SIM wins all competitions



Evolution of stress-Induced mutation

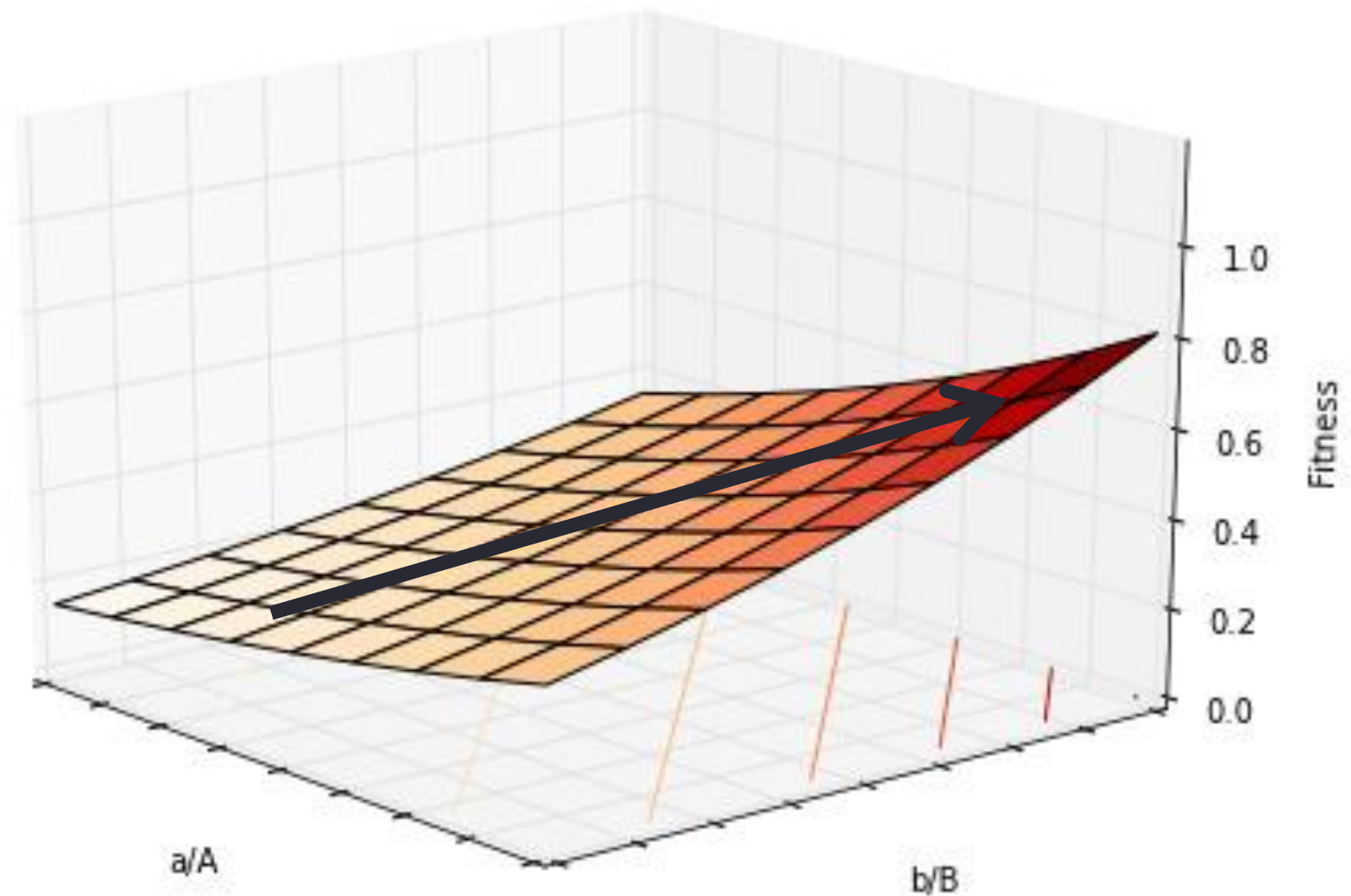
Part I Summary

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



Smooth fitness landscape

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



Rugged fitness landscape

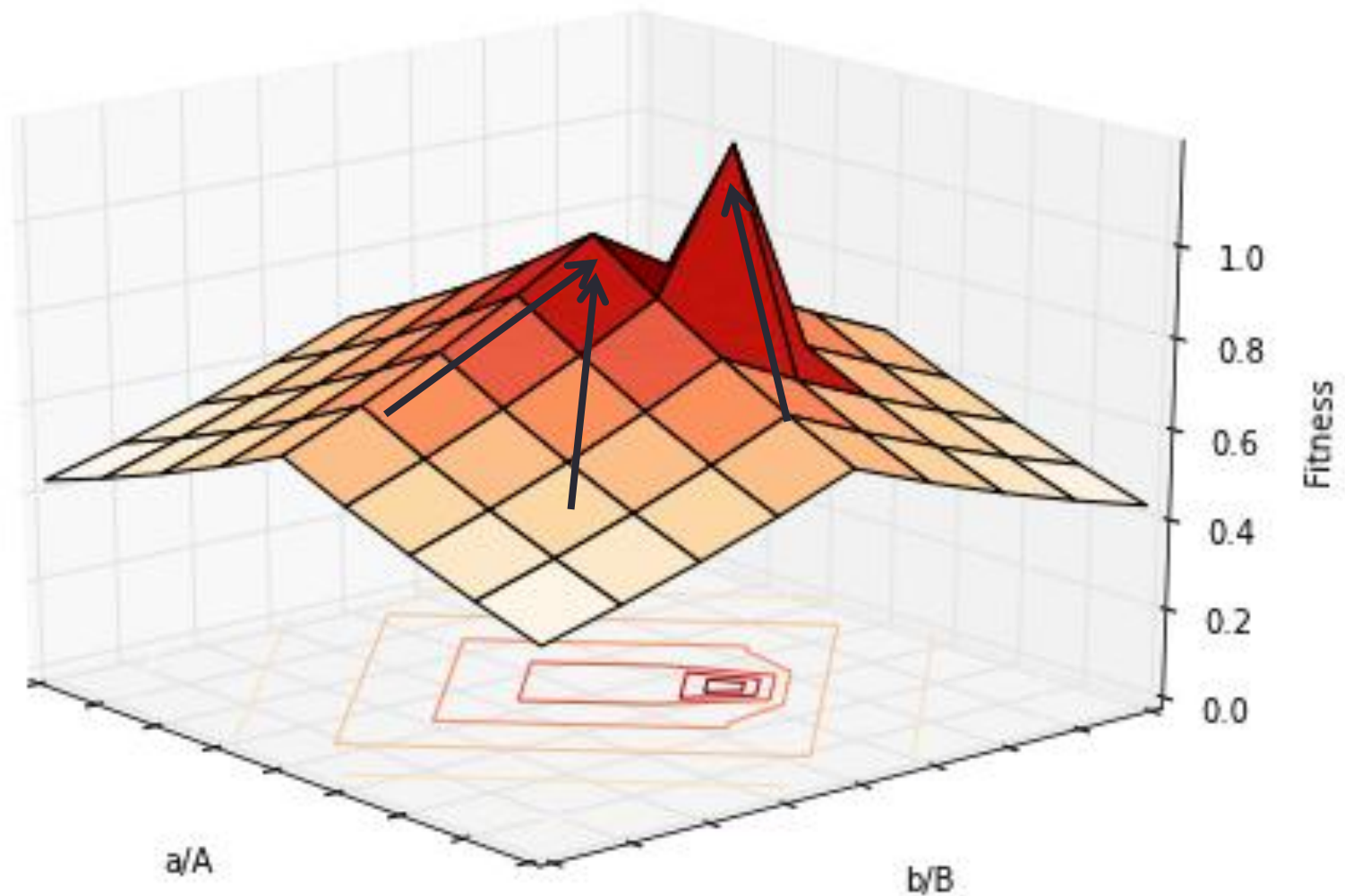
Fitness:

ab 1

Ab 1-s

aB 1-s

AB 1+s



Rugged landscape examples

Criteria

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

Wings and bones

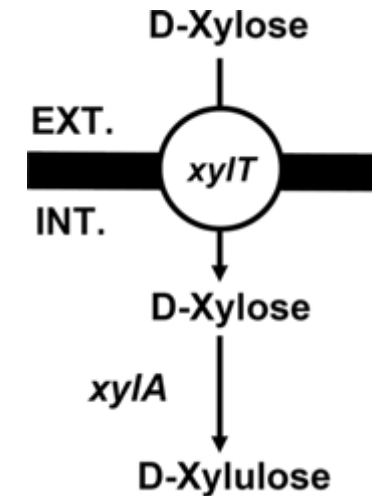
- Flying with heavy bones is wasteful
- Walking and climbing with light bones is risky

New carbon source

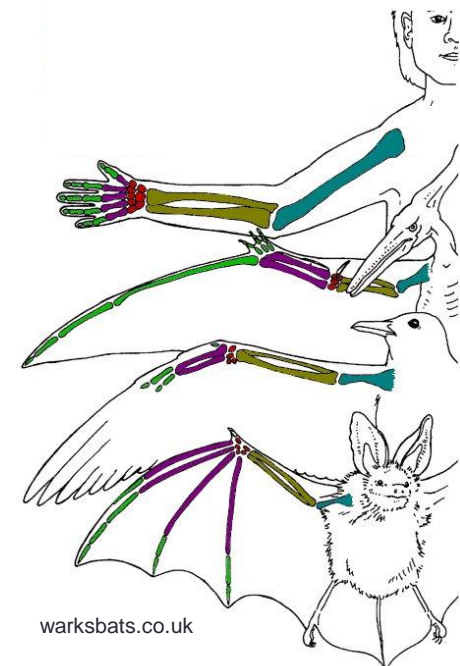
- Two new proteins required, but each is costly on its own:
 - Pump to transport new sugar into cell
 - Enzyme to metabolize sugar

Signaling and language

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



Xiao et al. 2011



Shifting to a higher fitness peak

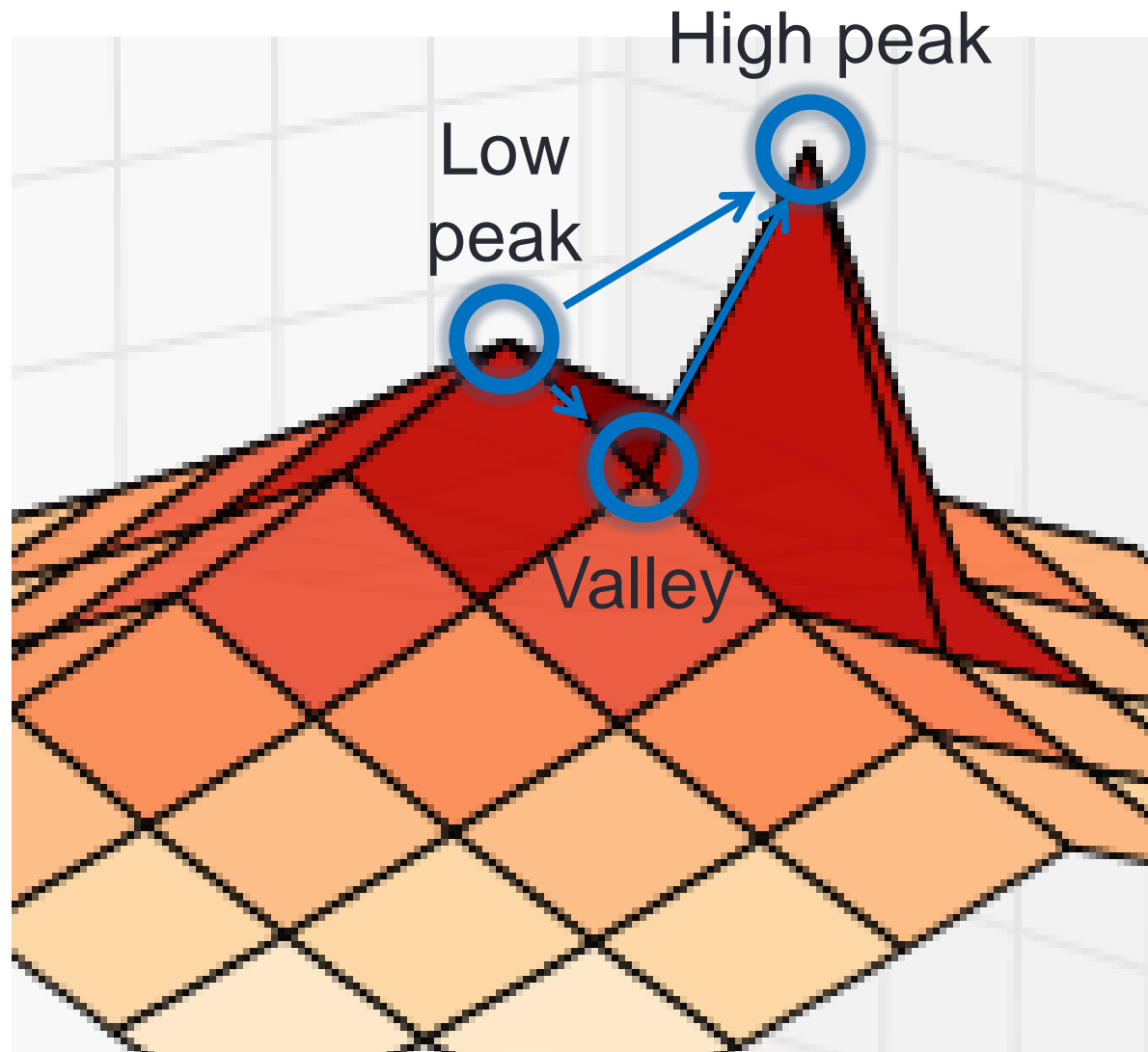
Fitness:

ab 1

Ab 1-s

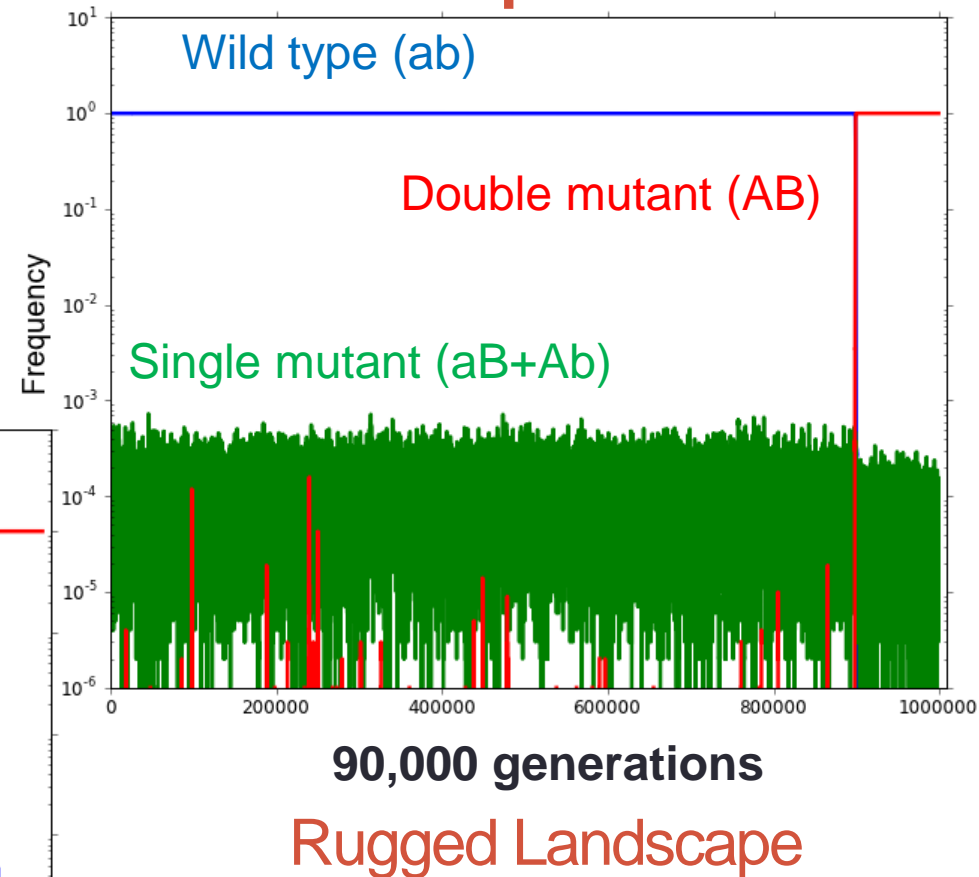
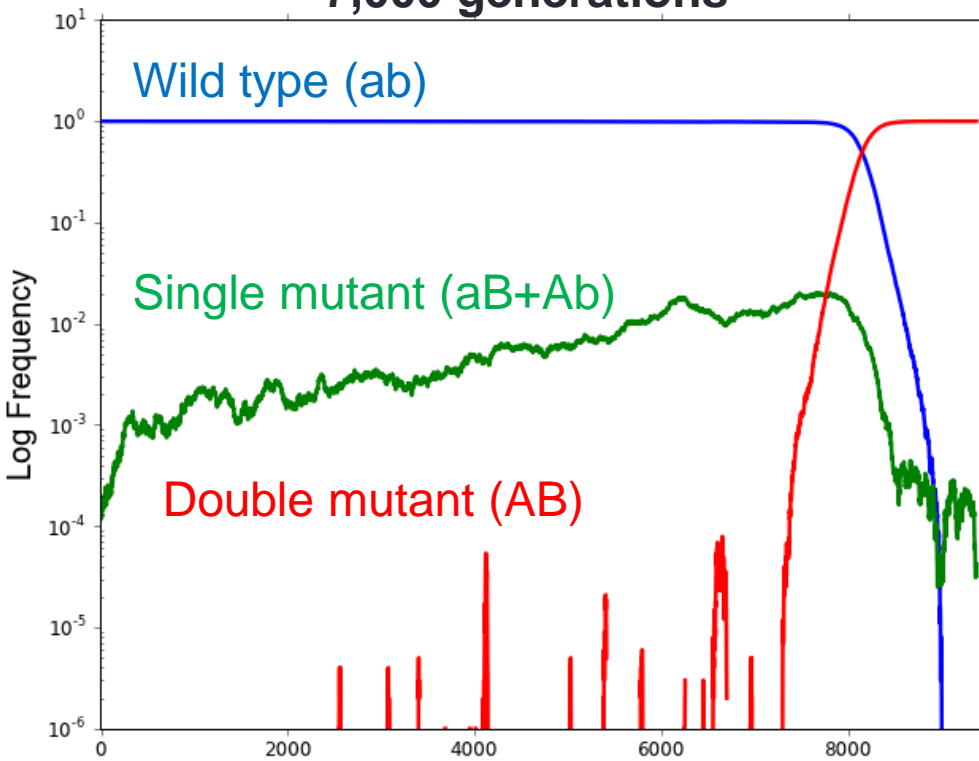
aB 1-s

AB 1+s



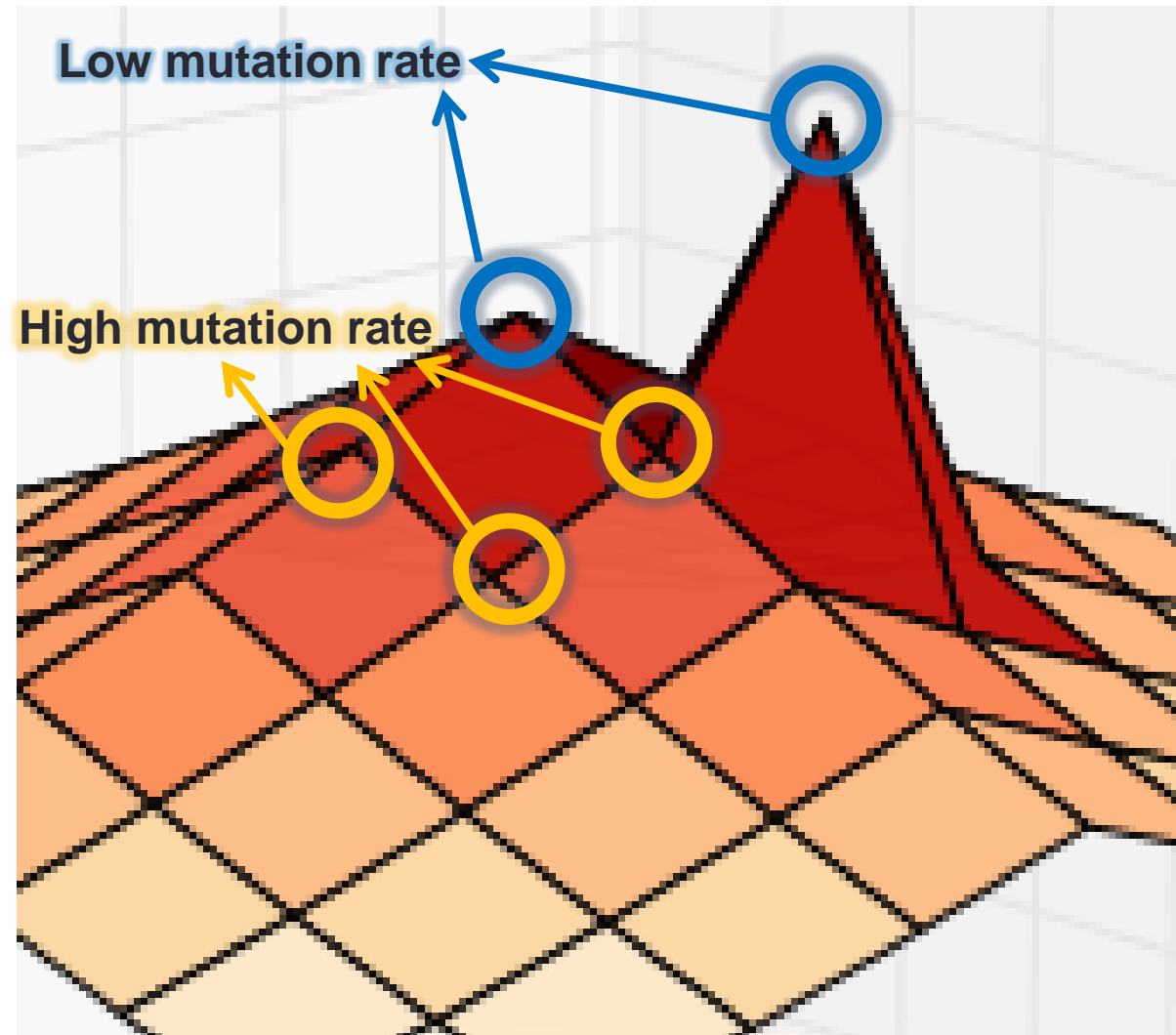
Adaptation on fitness landscapes

Smooth Landscape
7,000 generations



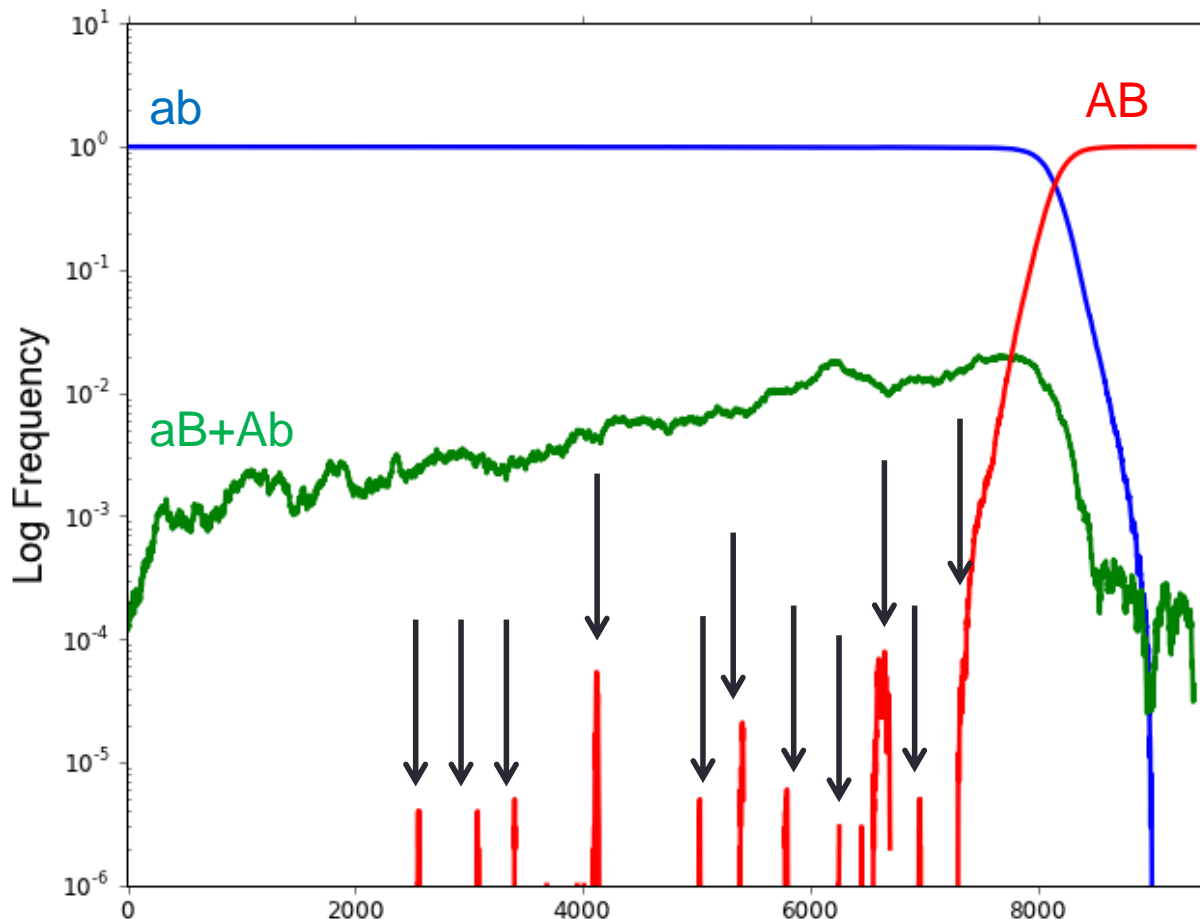
Stress-induced mutation on rugged landscapes

Mutation rate increased in individuals *below the peaks*



Appearance of a double mutant

- The probability of the appearance of a double mutant



Non-mutator:

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

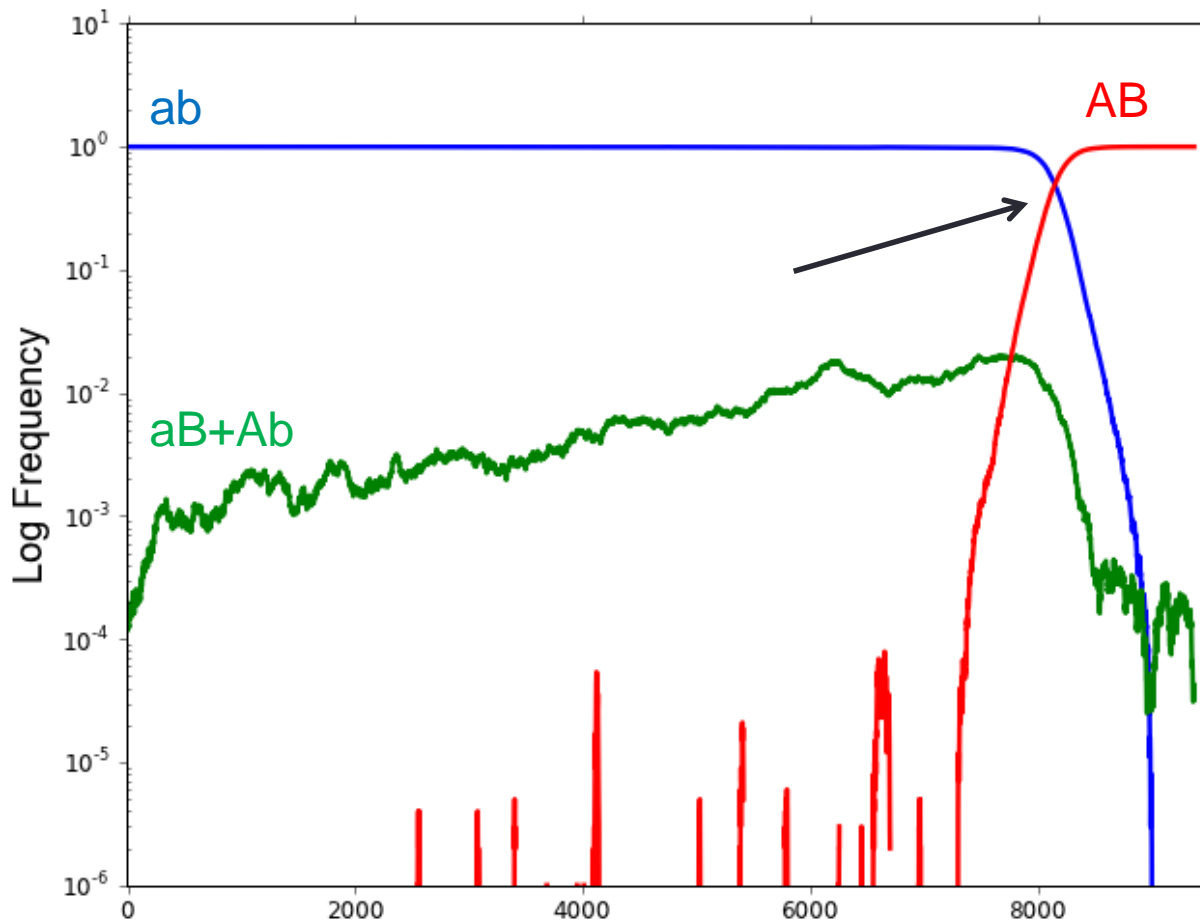
Stress-induced mutator:

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

SIM > NM

Fixation of a double mutant

- The probability of the fixation of a double mutant



Non-mutator:

$$\approx 2s$$

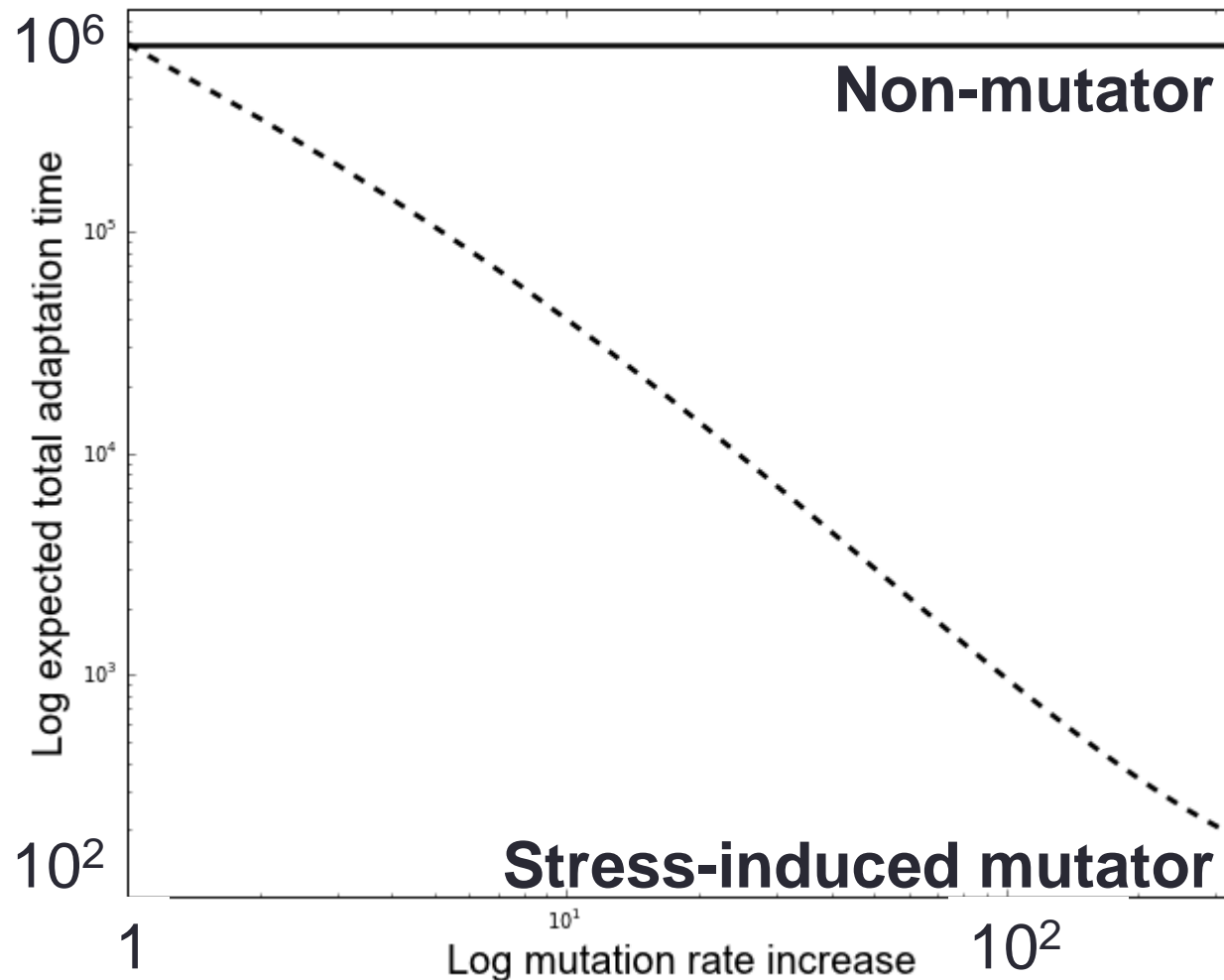
Stress-induced mutator:

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

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

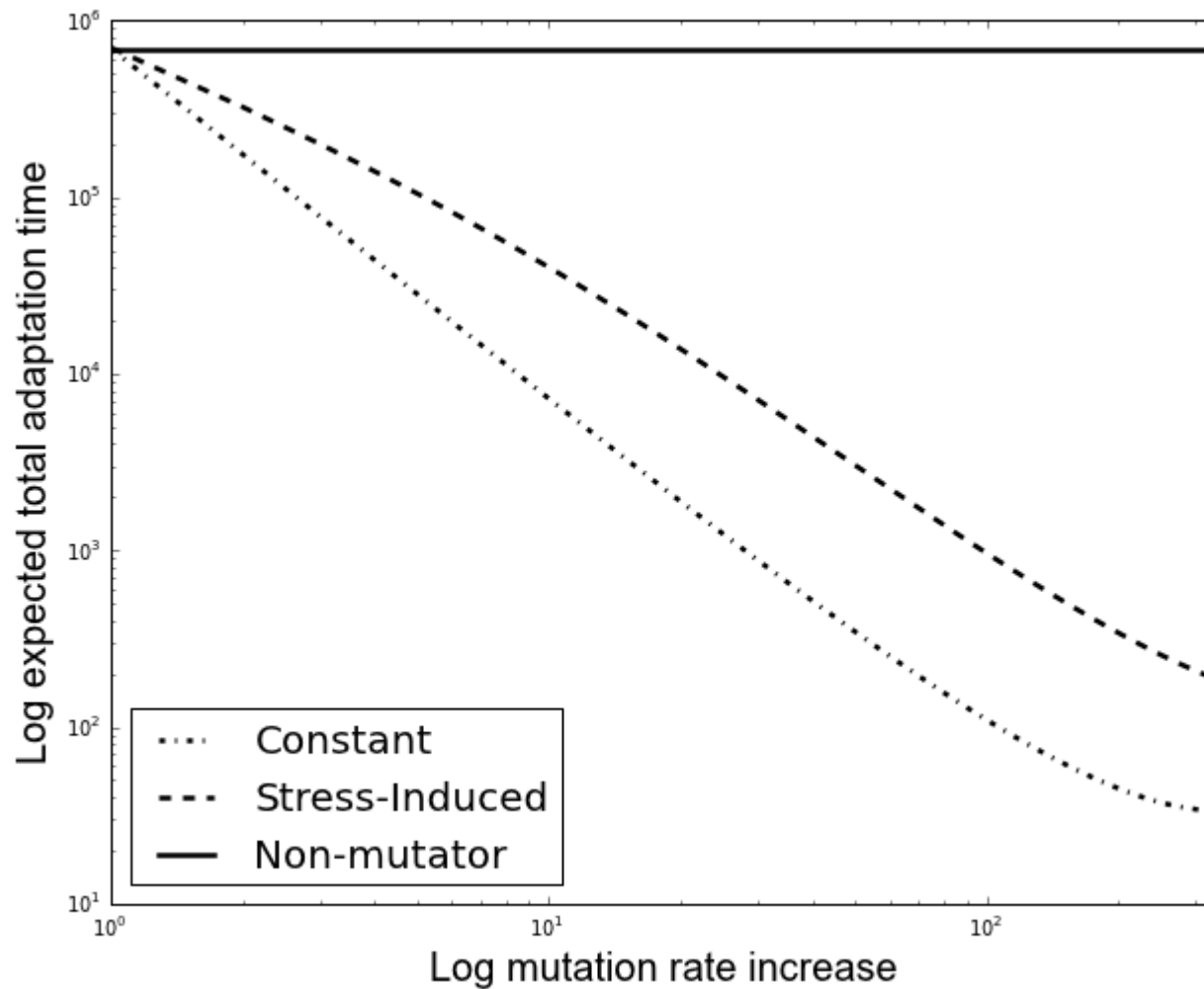
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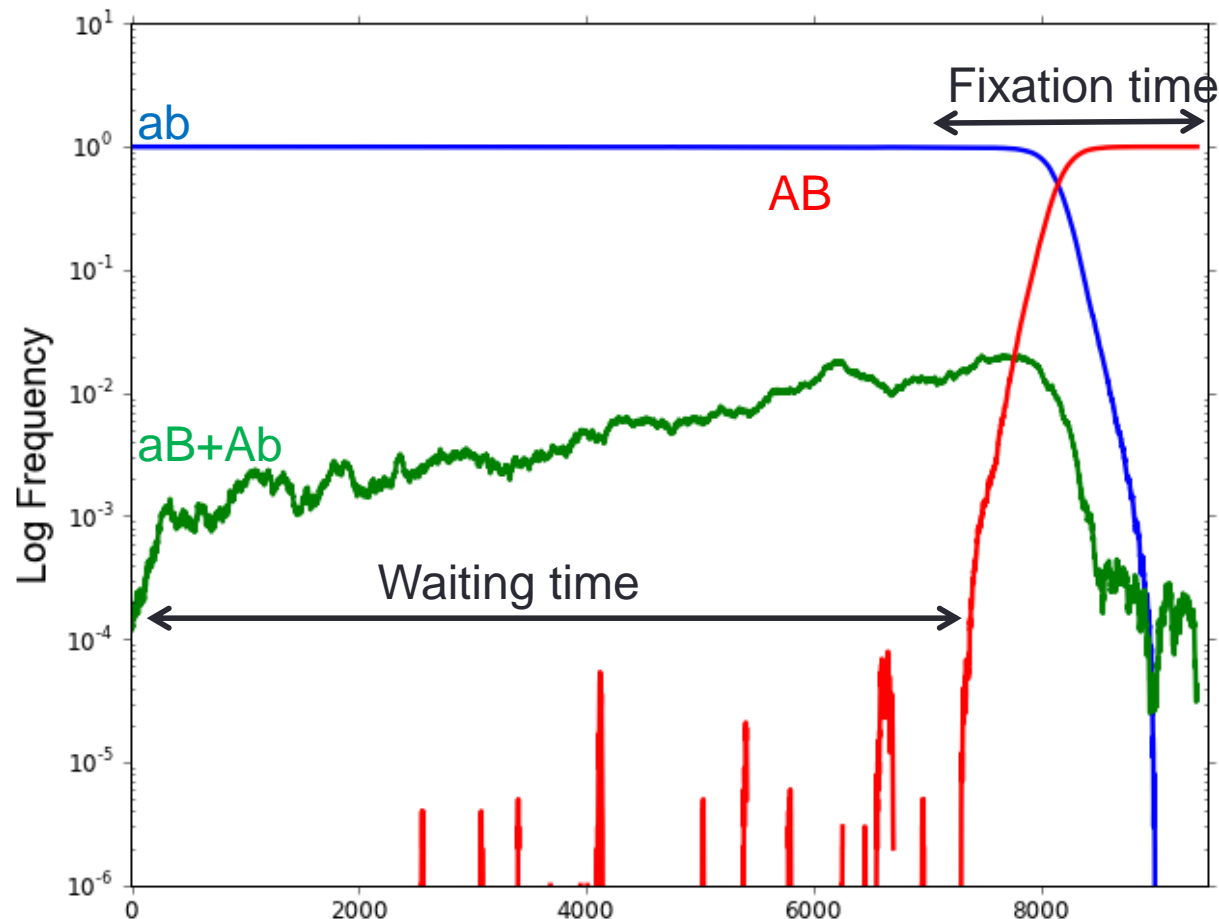
Additional slides

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

