

# Stress-Induced Mutagenesis and the Evolution of Complex Traits

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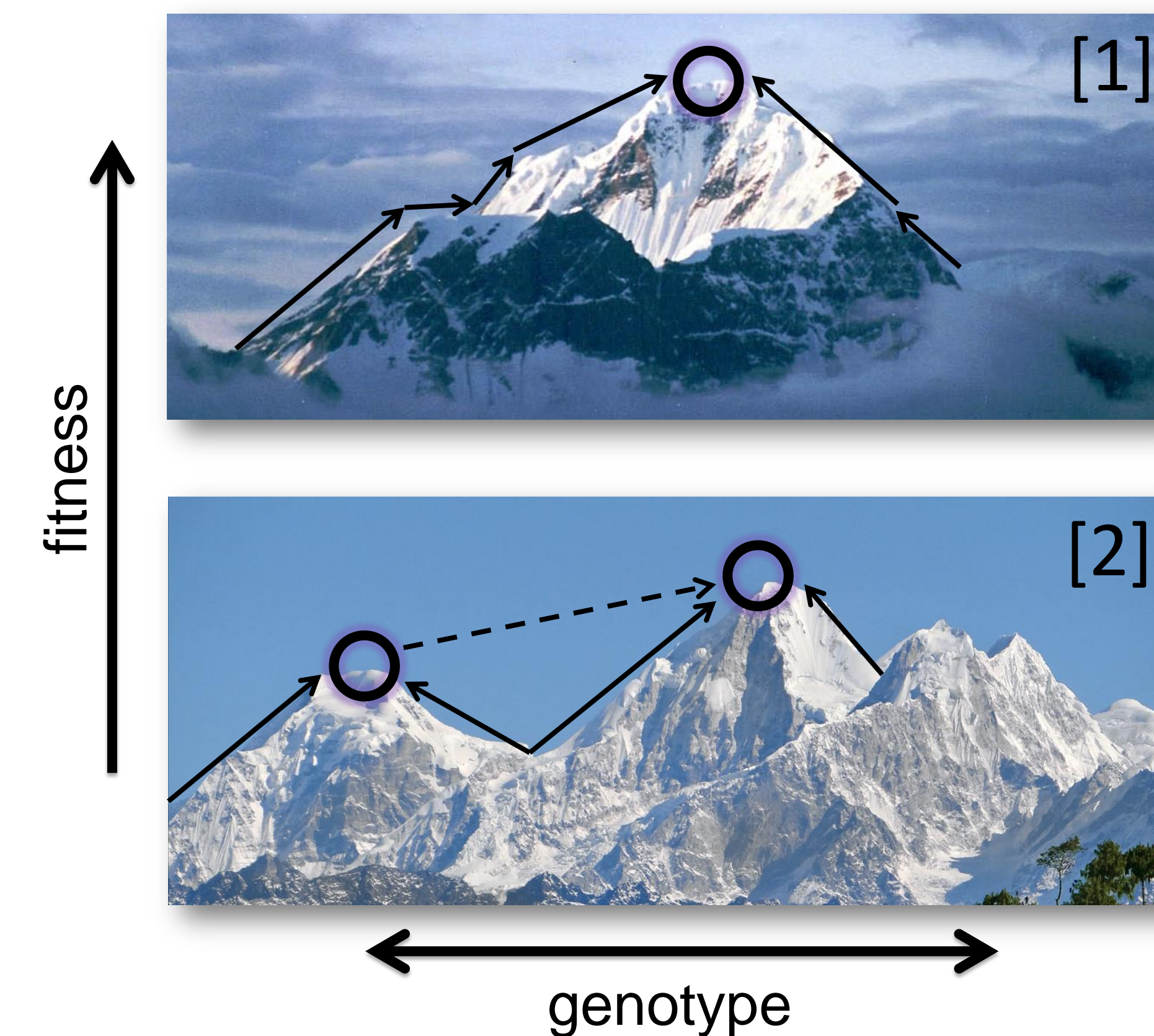
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## Background

### Adaptive peak shifts

The evolution of complex traits coded by multiple genes presents an open evolutionary question, first described by Sewall Wright in 1931 (1): **if different alleles are separately deleterious but jointly advantageous, how can a population evolve from one co-adapted gene complex to a better one?**

The problem is illustrated using the *fitness landscape* metaphor:



In a **single-peak fitness landscape** selection drives the population uphill towards the global maximum (Figure 1). In a **multi-peak rugged fitness landscape** selection drives the population uphill towards the closest peak, **preventing it from shifting to the higher peak** (Figure 2).

### Stress-Induced Mutagenesis

**Mutagenesis is induced by stress responses in various species of bacteria** (2-4).

In a previous work (5) we studied the evolution of stress-induced mutagenesis in constant and changing environments. We showed that **stress-induced mutagenesis is favored by selection** over constant rate mutagenesis because it generates beneficial mutations when they are most needed.

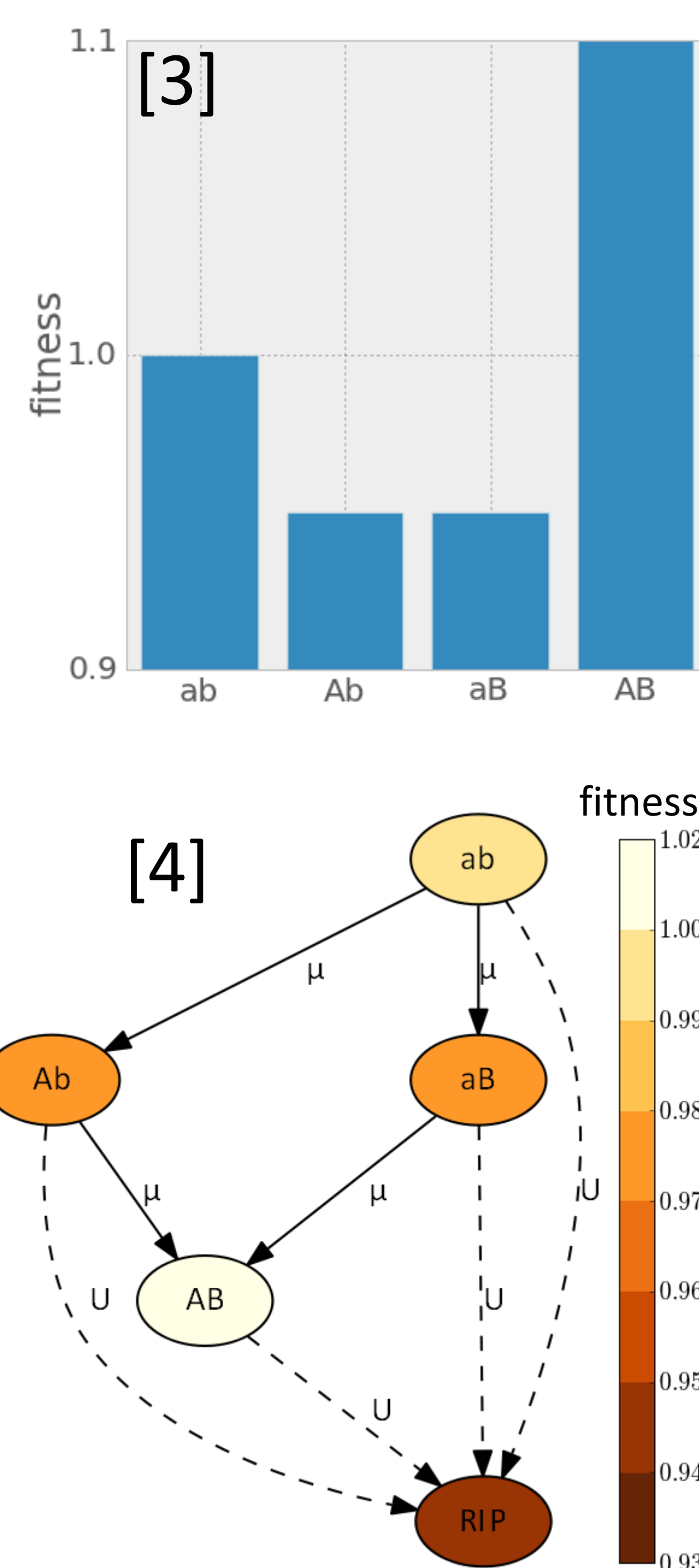
## Analytic Model

We model two loci,  $A/a$  and  $B/b$ . Genotype  $ab$  is the low peak and  $AB$  is the higher peak.

Figure 4 described the model. **Each node represents a genotype**. The **“RIP”** node represents genotypes with deleterious mutations that will not contribute to adaptation.

Arrows define the direction of mutation and denote the relevant mutation rate:  $U$  (dashed lines) for deleterious mutation and  $\mu$  (solid lines) for beneficial mutations.

Node color indicates the **fitness** of a genotype, from pale brown for high fitness to dark brown for low fitness.



## Analytic Approximations

The **appearance probability**  $q$  of the double mutant  $AB$  is approximated with or without stress-induced mutagenesis (SIM):

$$q \approx (1-U)(2-U)\frac{\mu^2}{s}$$
$$q_{sim} \approx (1-\tau U)2\tau\frac{\mu^2}{s}$$

where  $U$  is the genomic deleterious mutation rate,  $\mu$  is the beneficial mutation rate in the  $a/A$  and  $b/B$  loci,  $\tau$  is the mutation rate fold increase and  $s$  is the selection coefficient.

It can be shown that  $q_{sim} > q$  if  $0.5 > \tau U > U$  – **SIM increases the appearance probability  $q$  if the increased mutation rate is below 0.5.**

The **fixation probability**  $\rho$  of the double mutant  $AB$  is approximated by:

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

where  $H$  is the relative selective advantage of the double mutant. This means that  $\rho_{sim} > \rho$  if  $\tau > 1$  – **SIM always increases the fixation probability  $\rho$ .**

The **adaptation time**  $T$  is approximated by a geometric distribution with  $1/Nq\mu$  as the probability and  $N$  as the population size:

$$T \approx 1/2NH\mu^2(1-U)(2-U)$$
$$T_{sim} \approx 1/4N\tau\mu^2(1-\tau U)\left(H + \frac{U^2}{s^2}(1-s)(\tau-1)\right)$$

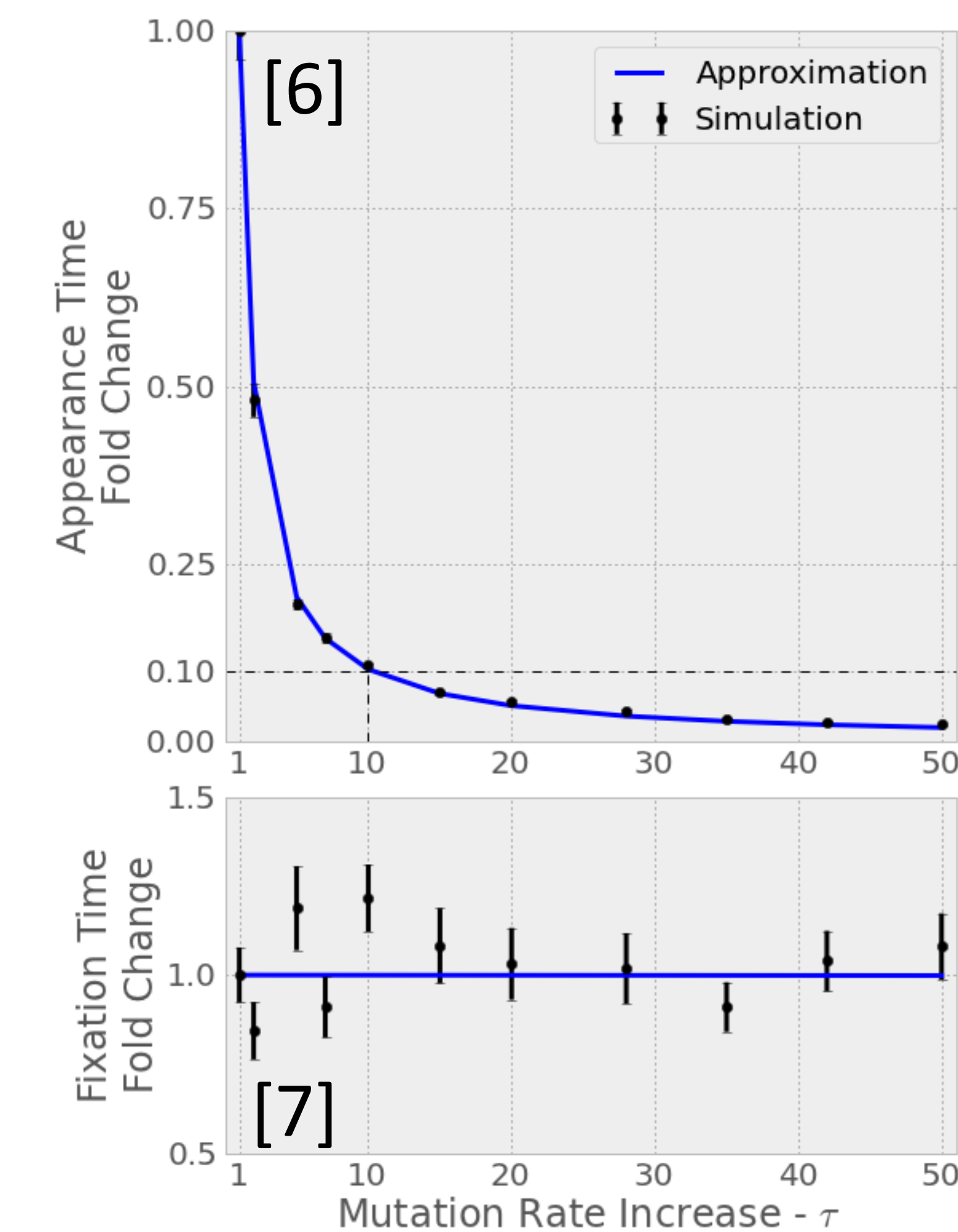
Here  $T_{sim} < T$  if  $1 > \tau U > U$  – **SIM decreases the waiting time for adaptation  $T$  if the increased mutation rate is below 1.**

Sign	Name	Estimate	Citation
$s$	Selection coefficient	0.001-0.01	6,7
$H$	Double mutant advantage	1-10	8
$U$	Genomic mutation rate	0.003-0.0004	8,9
$\mu$	Beneficial site mutation rate	$U/5000$	7
$\tau$	Mutation rate increase	1-100	10
$N$	Population size	$10^4$ - $10^{10}$	-

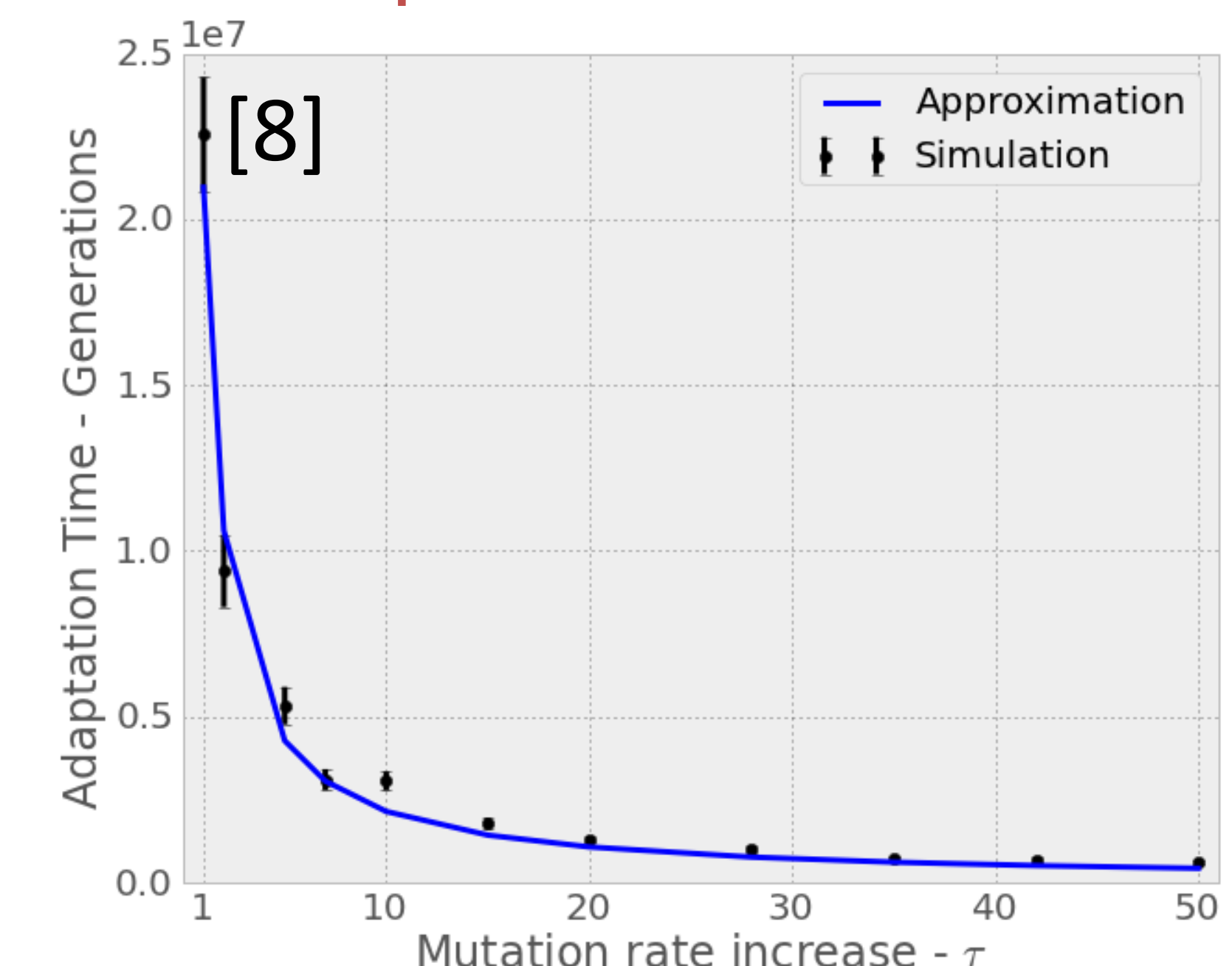
Table 1. Model parameters and estimated values for bacteria.

## Results

**SIM decreases the waiting time for the appearance** of a double mutant and slightly decreases the number of appearances until fixation.

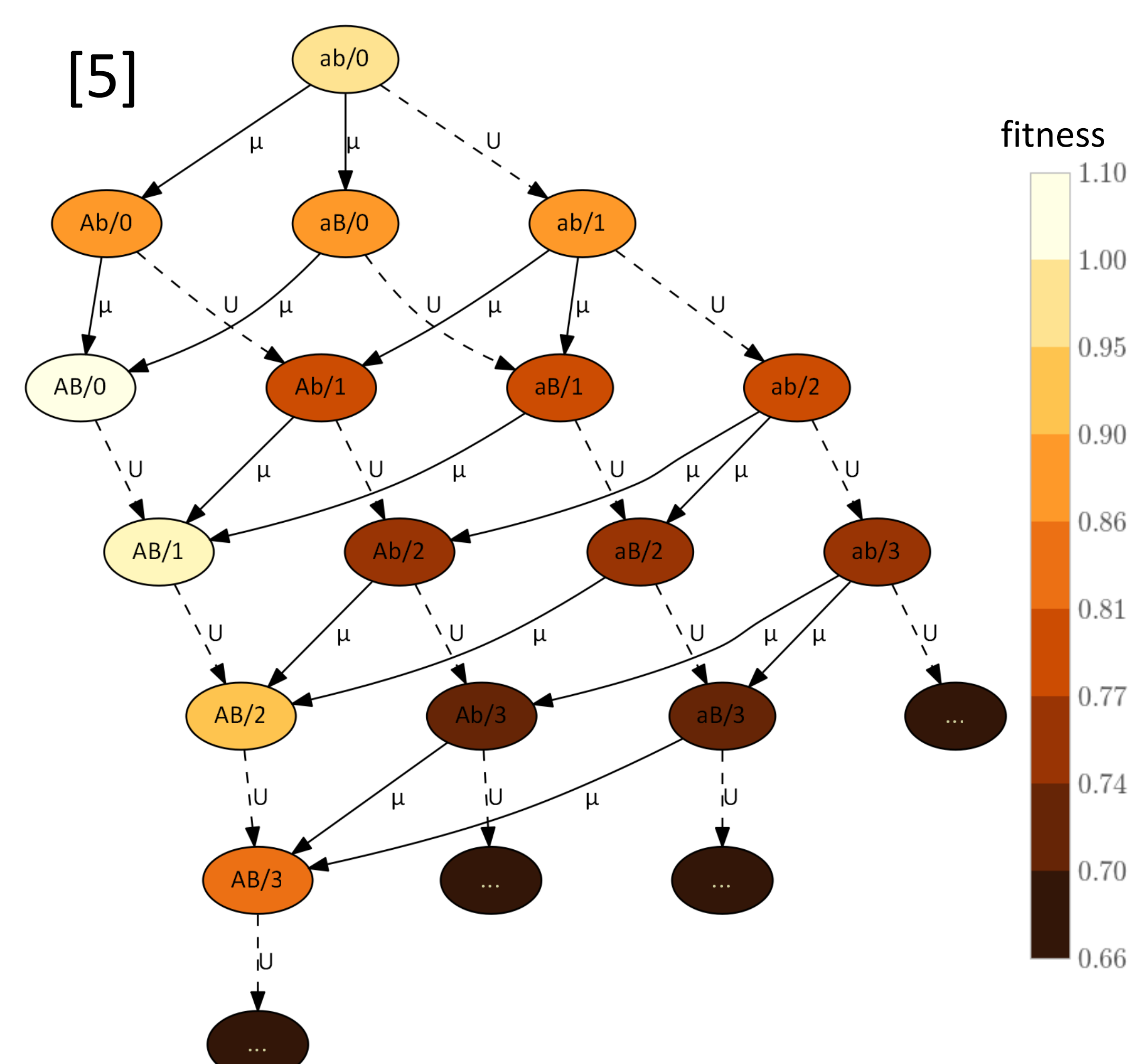


### SIM decreases adaptation time



## Simulations

Figure 5 describes our **multi-locus Wright-Fisher simulations**. The major difference from Figure 4 is that nodes also specify the **number of deleterious mutations after the forward slash**. The figure shows as much as three mutations for simplicity; the simulations had as much as 25.



## Summary

We analyzed the adaption time on a rugged fitness landscape with and without stress-induced mutagenesis.

Our results suggest that **stress-induced mutagenesis can help to resolve the problem of adaptive peak shifts by facilitating complex adaptation**. This is achieved without the burden of deleterious mutations that is created by constitutive mutagenesis in asexual populations.

## Literature cited

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