Stress-induced mutagenesis, adaptability and adaptedness

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# Model

We consider a population of *N* haploid asexual individuals. The number of new mutations at replication is Poisson distributed with an average of *U* mutations per genome. A mutation is deleterious or beneficial with probabilities *δ* and *β* such that *δ*+*β=1*. The effect of deleterious mutations on fitness are multiplicative (i.e., independent), such that the fitness of an individual with *x* deleterious mutations is *(1-s)x*, where *s* is the selection coefficient which we assume is higher than the mutation rate: *s>U*. Unless otherwise mentioned, beneficial mutations have an opposite effect, essentially reducing the number of deleterious mutations in the individual. Mutational strategies are defined by two parameters: the fold increase in mutation rate, *τ*, and the minimum number of deleterious mutations sufficient to induce hypermutation, *π*. The three prototypical strategies are: normal mutagenesis (NM), with *π=0* and *τ=1*, where there is no increase in mutation rates; constitutive mutagenesis (CM) with *π=0* and *τ>1*, where all individuals increase their mutation rate by *τ*; and stress-induced mutagenesis (SIM), with *π>0* and *τ>1*, where only individuals with at least π deleterious mutations increase their mutation rate by *τ*.

We develop four distinct models: (i) mutation-selection balance in a constant environment, (ii) adaptive evolution of a one-locus trait in a smooth fitness landscape, (iii) adaptive evolution of a double-locus trait in a rugged fitness landscape, and (iv) the loss of the fittest genotype by drift, aka *Muller's ratchet*. We use a mixture of analytic approximations and stochastic simulation to compare the effect of different mutational strategies (NM, CM and SIM) in these models.

## Mutation-selection balance

Denote the frequency, fitness and mutation rate of individuals with *x* deleterious mutations by , and , and the population mean fitness by . The frequency of individuals with *x* deleterious mutations in the next generation can therefore be described by:

.

This can also be written as a matrix equation by multiplying the frequencies vector f by the mutation-selection matrix *M*:

The MSB distribution of *x* *f\** fulfills:

*M* is a positive matrix, and therefore by the *Perron-Frobenius Theorem* (Otto and Day 2007, p. 709) is the largest eigenvalue of *M* and *f\** is its unique

n-negative eigenvector with .

Without beneficial mutations, δ=1 and *β=0*, the above equation simplifies to:

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So *M* is a triangle matrix and its largest eigenvalue is the largest main diagonal element: . If and then the frequencies vector has been shown to be , that is, the number of deleterious mutations per individual is Poisson distributed with an average *U/s* (Haigh 1978).

With beneficial mutations this eigenvalue problem is harder to solve analytically. By neglecting elements outside the main three diagonals we have shown before (Ram and Hadany 2012) that:

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However, this framework allows to easily calculate the population mean fitness numerically for finite *n*-by-*n* matrices (by defining *n* such that ).

## Adaptation in a simple fitness landscape

Consider a population at a MSB in which a new adaptation is now available. Assume this new adaptation requires a single beneficial mutation provides the same fitness advantage as other beneficial mutations. This scenario is equivalent to increasing the number of deleterious mutation in all the population by one after reaching an MSB.

### Appearance of the beneficial mutation

The probability that a random individual in the next generation will have the adaptation but will not have any additional deleterious mutations:

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Assuming we neglect the effect of beneficial mutations on the MSB and assume a Poisson distribution of deleterious mutations in the population (Haigh 1978), as well as (this will be justified later):

,

where is the modified Bessel function of the first kind.

By neglecting the less significant terms in the above sum () we can approximate this by:

.

### Fixation of the beneficial mutation

After the beneficial mutation appears it can either go to fixation by selection or to extinction by drift. Following Eshel (1981) The probability of fixation is:

where *α* is the growth rate of individuals with the beneficial mutation (and without any deleterious mutations). This can be calculated as:

,

where is the population mean fitness before adaptation. Therefore:

.

Or, assuming :

# Results

## Mutation-selection balance

Without beneficial mutations and with a mutation rate constant in time and uniform across the population, the mean fitness equals (Kimura and Maruyama 1966). Constitutive mutagenesis causes the population mean fitness to exponential decay as a function of the mutation rate fold-increase *τ*. Stress-induced mutagenesis, as was numerically shown by Agrawal (Agrawal 2002), does not change the population mean fitness with respect to NM, because the fittest individuals, with fitness *1*, also have the lowest mutation rate, *U*, and therefore the largest eigenvalue of the mutation-selection matrix is .

With beneficial mutations, this is still a good approximation, but the actual value of the population mean fitness is slightly higher than . As we have shown before (Ram and Hadany 2012), CM decreases the population mean fitness with respect to NM, but SIM can increase the population mean fitness with respect to NM. A sufficient condition is that the mutation rate of individuals with below average fitness is increased. Because we assume that *,* then , so setting *π=1* ensures that the condition is met and therefore SIM increases the population mean fitness. We explore the magnitude of this increase for specific parameter ranges in Fig. X.

## Adaptation in a simple fitness landscape

### Appearance of the beneficial mutation

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### Fixation of the beneficial mutation

In NM and CM all individuals have the same mutation rate, so:

which is a classical result in population genetics (Eshel 1981).

In SIM, if we assume that all individuals without the beneficial mutation increase their mutation rates by *τ*:

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Because as long as , this means that and that fixation of a beneficial mutator has a higher probability with SIM. Also, as *τ* increases, the fixation probability increases - the derivative w.r.t *τ* is positive and for *s=0.05*, *U=0.0004*, SIM with *τ=10* and *τ=10* increase the fixation probability from 0.1 to 0.174 and 0.107.