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:

.

So *M* is a triangle matrix and its largest eigenvalue is the largest main diagonal element: .

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:

.

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

# 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