Adaptive peak shifts with stress-induced mutation

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# Introduction

In 1931, Sewall Wright presented a problem which is still an open problem in evolutionary biology (Wright 1931). Given that the selective value of many alleles depends on other alleles, Wright suggested that "Two superior combinations that differ by two or more gene replacements may both be superior to the intermediate ones" (Wright 1988). The solution Wright suggested was called the "shifting-balance theory" [REF] and is still taught today in many "Introduction to Evolution" courses. This solutions appears to be valid (Crow et al., 1990; Wade and Goodnight, 1991; Coyne et al., 1997) but it seems that the range of parameters for which it works is limited (Moore and Tonsor, 1994; Gavrilets, 1996; Phillips, 1996).

Mutation is a major factor in this process: It creates the new alleles which later fix. If creating new favorable alleles was the only effect of mutation on evolution, a high mutation rate would have been very favored, but of course most mutations are deleterious and the mutation rate is reduced by natural selection to very low levels (Kimura 1967; Lynch 2011).

However, stress-induced mutation, in which stressed individuals increase their mutation rates, is an exception to this rule. In a previous work we have shown that stress-induced mutation is likely to evolve due to natural selection in asexual populations and that it increases the mean fitness of populations due to the increased generation of beneficial mutations in unfit individuals. Additionally, stress-induced mutation has been demonstrated in various species, both prokaryote and eukaryote (Galhardo, Hastings, and Rosenberg 2007; Sharp and Agrawal 2012; MacLean, Torres-Barceló, and Moxon 2013).

Here, we analyze a simple population genetic model of an asexual population with two bi-allelic loci. We derive analytical expressions that suggest that stress-induced mutation greatly increases the population adaptation rate. We use stochastic simulations to validate our analytic approximations.

# Model

Consider the two bi-allelic loci *A/a* and *B/b* and a population that reached a mutation-selection balance (MSB) in an environment in which *ab* is the optimal genotype with a fitness value of 1, single mutants (*Ab* and *aB*) suffer from a selective disadvantage *s* and have a fitness value of *1-s*, and double mutants (*AB)* have a fitness value of *(1-s)2*. This corresponds to a fitness function in which the effect of deleterious mutations are independent of each other and therefore the fitness of an individual is *(1-s)m* where *m* is the number of deleterious mutations the individual has accumulated.

Mutation from *a* to *A* and from *b* to *B* occurs with a probability *µ* at reproduction and we disregard back-mutation. In addition, new deleterious mutations occur across the genome at reproduction, and the number of such mutations follows a Poisson distribution with a mean *U*. Although there is a direct relation between *U* and *µ* (for example, *µ=U/5000*), having two separate parameters helps to distinguish between the two effects of mutation on adaptive evolution – the generation of beneficial mutations (*µ*) and the generation of deleterious mutations (*U*).

We define stress-induced mutation as the case in which an individual with a fitness below 1 hypermutates, increasing both his mutation rates *τ*-fold.

At the MSB, the frequency of wildtype (*ab*) individuals is *1-µ/s+O(µ2)*, the frequency of single mutants (*Ab* and *aB* combined) is *2µ/s+O(µ2)* and the frequency of double mutants (*AB*) is (*µ/s)2+O(µ3)* [REF].

To incorporate random sampling into the model, we denote the population size by *N*.

We are interested in the ability of the population to adapt to a new environment in which the genotype *AB* inhabits a new adaptive peak with a fitness value of *1+sH*, where *H* is scales the hight of the new peak in comparison with the existing peak at *ab*.

There are several considerations on the relations between the main parameters:

1. The above MSB approximations are only valid when *µ/s<1* or *µ<s*.
2. If *N*(*µ/s)2>1* there are already double mutants and therefore adaptation to the environmental change will be rapid and will not require new mutations.
3. If *Nµ/s<1* then there are no single mutants and double mutatns must be generated by a double mutation in a wild-type individual. Therefore, increasing the mutation rate of individuals with fitness below 1 will not affect the process.
4. If we assume that individuals loaded with deleterious mutations are "evolutionary dead-ends" and cannot be the origin of adaptation, then we want the fraction of loaded individuals to be small - *U/s<1* or *U<s*.