­Stress-Induced Mutagenesis Breaks the Trade-Off Between Adaptability and Adaptedness

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# Abstract

Evolutionary theory suggests that the mutation rate must balance between *adaptability* – the ability to adapt – and *adaptedness* – the ability to remain adapted.

We model a population crossing a fitness valley and analyze the rate of complex adaptation with and without stress-induced mutagenesis - the increase of mutation rates in response to stress or maladaptation. We show that stress-induced mutagenesis breaks this evolutionary trade-off, increasing the *adaptability* of asexual populations without reducing their *adaptedness*. Our theoretical results support the hypothesis that stress-induced mutagenesis is an adaptive trait.

# Introduction

There is experimental, clinical and theoretical evidence that high mutation rates increase the rate of adaptation and that during adaptive evolution, constitutive mutators - alleles that constitutively increase the mutation rate - can rise in frequency because of the beneficial mutations they generate (Sniegowski et al. 2000). However, during evolution in a constant environment, constitutive mutators become associated with poor genetic backgrounds due to increased accumulation of deleterious mutations. Therefore, these mutator alleles are selected against, leading to "the rise and fall of the mutator allele" (Sniegowski et al. 1997; Taddei et al. 1997; Kessler and Levine 1998; Denamur and Matic 2006; Wielgoss et al. 2012). Leigh (1970) suggested that the mutation rate must balance between two evolutionary traits: *adaptability* – the capacity to adapt to new environmental conditions - and *adaptedness* – the capacity to remain adapted to existing conditions.

Stress-induced mutagenesis (SIM), the increase of mutation rates in stressed or maladapted individuals, was demonstrated in many species, including both prokaryote and eukaryote (Galhardo et al. 2007; Sharp and Agrawal 2012; MacLean et al. 2013). Several stress responses regulate the mutation rate by shifting replication to error-prone DNA polymerases (Ponder et al. 2005) and by inhibiting the mismatch repair system (Debora et al. 2010). In *Escherichia coli* these stress responses include the SOS DNA-damage response, the RpoS-controlled general or starvation stress response, and the RpoE membrane protein stress response (Al Mamun et al. 2012).

Some authors propose that SIM has a significant impact on *adaptability* or *evolvability* (Tenaillon et al. 2004; Rosenberg et al. 2012), but there is no theoretical treatment of this impact. On the other hand, the effect of SIM on *adaptedness* was modeled by Agrawal and later by Shaw and Baer (Agrawal 2002; Shaw and Baer 2011), who showed that without beneficial mutations SIM doesn't affect the mean fitness of asexual populations in constant environments. More recently, we showed that with rare beneficial mutations, increasing the mutation rate of maladapted individuals increases the mean fitness of asexual populations (Ram and Hadany 2012).

Here, we analyze population genetic models of adaptive evolution. We develop general analytical expressions and stochastic simulations and compare normal, stress-induced, and constitutive mutagenesis. We show that stress-induced mutagenesis breaks the trade-off between *adaptability* and *adaptedness* by increasing the adaptation rate without decreasing the population mean fitness.

# Model

## Overview

We consider a population of *N* haploid asexual individuals. The number of deleterious mutations occurring at replication is Poisson distributed with an average of *U* mutations per genome per replication. The effects of deleterious mutations on fitness are multiplicative (*i.e.*, independent), such that the fitness of an individual with *x* deleterious mutations is *ω*=(1-*s*)*x*, where *s* is the selection coefficient.

We consider three mutational strategies: normal mutagenesis (NM), where there is no increase in mutation rates; constitutive mutagenesis (CM), where all individuals increase their mutation rate by *τ*,the mutation rate fold increase; and stress-induced mutagenesis (SIM), where only stressed or maladapted individuals increase their mutation rate by *τ*.

We focus on two bi-allelic loci in which the wildtype genotype is *ab* and its fitness is 1. Mutations at these loci change *a* to *A* and *b* to *B* at reproduction with probability *µ* (without back-mutations). After the population has reached a mutation-selection balance (MSB) it goes through adaptive evolution to an environmental change which changes the fitness of the *AB* genotype from (1-*s*)2to 1+*sH* (*H*>0 is the double mutant relative advantage), making it the optimal genotype (Figure 1).

The adaptation process can be separated to two ­­­­distinct stages. In the first stage, a double mutant *AB* appears in the population in a single copy. In the second stage, the single copy of the double mutant avoids extinction, increases in frequency, and goes to fixation.

We analyzed this model with two methods. The first is analytic (Figure 1a), in which we assume that: (i) genotypes with deleterious alleles (except *Ab* and *aB*) do not contribute to the adaptation process, and (ii) the number of deleterious mutations per individual at the MSB is Poisson distributed (Haigh 1978). These assumptions require that mutation is weaker than selection ().

The second method is a stochastic Wright-Fisher simulation with selection, mutation and drift (Figure 1b), in which we: (i) let individuals with deleterious mutations contribute to adaptation, and (ii) let the MSB evolve from a mutation-free population.

Table 1 summarizes the model parameters with estimated values for *Escherichia coli*.

## Appearance of a double mutant

We are interested in the waiting time for the appearance of a double mutant either by a double mutation in a wildtype individual *ab*, or via a single mutation in a single mutant *Ab* or *aB* (see Figure 1a). Denoting the population size by *N,* we note that (i) if *N(µ*/*s*)2>1 then there are already double mutants in the population at the MSB and adaptation will not require new mutations, and (ii) if *Nµ*/*s*<1 then there are no single mutants at the MSB and double mutants must be generated by a double mutation in a wildtype individual. In this case, increasing the mutation rate of individuals with fitness below 1 will not have an effect on the appearance of the double mutant and there is no point in analyzing the effect of SIM.

Combining these two constraints we get the following constraint on the population size *N*: . This constraint is reasonable for bacterial populations (see Table 1).

The frequencies of wildtype *ab* and single mutants *aB* and *Ab* that are mutation-free at the MSB are and . The probability that an individual does not generate new deleterious mutations in the next generation is . Therefore, the probability *q* that a random individual in the next generation is a double mutant, given there are no double mutants in this generation is:

|  |  |
| --- | --- |
| . | (1) |

With SIM the mutation rate of single mutants is increased *τ*-fold and the appearance probability is:

|  |  |
| --- | --- |
| . | (2) |

The right-hand side of Eqs. (1) and (2) are 1st order approximations (see Appendix 1).

## Fixation probability with stress-induced mutagenesis

Assuming a considerable advantage to the double mutant (*H*>1)and a large population size (the constraint on *N* ensures that), a double mutant has two possible fates after its appearance: fixation or extinction. Following Eshel (1981), the fixation probability *ρ* of the double mutant is (see Appendix 2):

|  |  |
| --- | --- |
| . | (3) |

That is, the fixation probability of the double mutant is roughly twice its adaptive advantage. This is a classic result of population genetics theory (Fisher 1930 p. 76).

The fixation probability with SIM equals that of NM and CM because the mutation rate of the wildtype *ab* equals that of the double mutant *AB* (but see an exception below).

## Adaptation rate

From the probability *q* that a random newborn is a double mutant, we can derive the probability that some double mutants appear in the next generation: . The constraint on *N* guarantees that *Nq* is very small and therefore this probability can be approximated by *Nq*. Once a double mutant appears it has a oes to fixation with probability *ρ*.

The time for adaptation *T* can be approximated by the waiting time for a double mutant that goes to fixation. This is true as long as fixation is much faster than mutation (guaranteed by (*τµ*)2<2). This waiting time follows a geometric distribution with rate *Nqρ* and therefore the adaptation rate is approximately:

|  |  |
| --- | --- |
| . | (4) |

## Wright-Fisher simulations

We used Wright-Fisher simulations with selection, mutation and drift (Figure 1b). The simulations start with a mutation-free population (*fab/0*=1) which evolves to a MSB over the first 500 generations of the simulation (with *s*=0.01-0.1, 500 generations are enough to get the average number of deleterious mutations per individual to 99.3% of its MSB value (Gordo and Dionisio 2005)).

After establishing a MSB, an environmental change occurs, altering the fitness of the *AB* genotype from (1-*s*(2 to 1+*sH* and making it the optimal genotype. The simulation then proceeds until an *AB* individual appears and either goes extinct or fixates in the population (reaching *f(AB)*=0 or *f(AB)*=1, respectively). Therefore, each simulation provides one sample of the waiting time for the appearance of a double mutant (*Nq)* and one sample of the probability of fixation of a double mutant (*ρ)*.

# Results

## Complex adaptation

In our model, adaptation is achieved by the appearance and fixation of a double mutant *AB* in the population. The rate of adaptation *ν* for the different mutational strategies is (NM – normal mutagenesis; CM – constitutive mutagenesis; SIM – stress-induced mutagenesis; see Table 1 for description of model parameters):

|  |  |
| --- | --- |
|  | (5) |
|  | (6) |
| . | (7) |

The right-hand sides of these equations are approximations for small values of *U* and *τU*. The dynamics of the adaptation rate *ν* as a function of the mutation rate fold increase *τ* are shown in Figure 2.

We draw several conclusions from these expressions: First, adaptation with CM is faster than with NM because of faster appearance of double mutants, and the adaptation rate increases with the square of *τ*. Second, adaptation with SIM is also faster than with NM, but not as fast as with CM because only single mutants (*aB* and *Ab*) hypermutate, so the adaptation rate increases linearly with *τ*. Third, because the fixation probability is the same for NM, CM and SIM, the difference in adaptation rate is caused by differences in the appearance probability *q* (Figure S1). See below for a different scenario in which SIM increases the fixation probability.

These conclusions depend on the constraint that hypermutation is weaker than selection (*τU<s*). Deleterious mutation rates in microbes are generally around 10-4-10-2 mutations per genome per generation, and selection coefficients are estimated to be between 10-1 and 10-2 (see Table 1), so the limit on *τ* is between 1 and 1,000. Figure 2 compares these analytical approximations and the results of simulations in which we do not assume that *τU<s* or that individuals with deleterious mutations don’t contribute to adaptation. When the mutation rate fold increase *τ* is high, adaptation is slightly slower in the simulations in comparison with the analytic approximations. This is because as *τ* increases the double mutant is more likely to appear on a deleterious background (*AB/1* instead of *AB/0*). This deleterious background results in lower fitness and a lower fixation probability for the double mutant (Hartfield and Otto 2011) (Figure S2).

## The trade-off between adaptability and adaptedness

We extended a previous model (Ram and Hadany 2012) to calculate the population mean fitness at the mutation-selection balance of populations with NM, CM and SIM (see Figure 3 and supporting information for more details) and used the model presented above to calculate adaptation rates.

Figure 4 shows the *adaptedness* (rate of adaptation to environmental change) and *adaptability* (mean fitness in a constant environment) of different mutational strategies. Every rate of adaptation *ν* can be realized using both CM and SIM. The highest mean fitness will always be attained with SIM (which even has a slight advantage over NM that cannot be seen in this figure, but see Figure 3). If the mutation rate fold increase *τ* required by SIM is too high (*i.e.*, *τU*>*s*) the same adaptation rate can be realized by a mixed strategy (dashed green line). For example, a ~100-fold increase in adaptation rate can be achieved with CM with *τ*=10, with SIM with *τ*=100 or with a mixed strategy with *τCM*=7and *τSIM*=2 in which all individuals increase their mutation rate 7-fold and stressed individuals further increase their mutation rate 2-fold. However, these increases in adaptation rates have a price: the mutational load will decrease the population mean fitness from 0.9996 with NM to 0.996 with CM and 0.9972 with the mixed strategy. This price in not paid by populations with SIM because the mean fitness mainly depends on the mutation rate of fit individuals. In fact, with beneficial mutations the mean fitness with SIM with *τ*=100 is higher than that of NM by ~3⋅10-8.

## Effect of environmental stress

So far, we considered stress as a mismatch between the individual and the environment. Another source of stress can be an environmental condition that reduces the fitness of all maladapted individuals, such as a new antibiotic drug. This scenario has an important biological relevance, as SIM has been implicated in the evolution of drug resistance in bacteria and yeast (Cirz and Romesberg 2007; Obolski and Hadany 2012; Shor et al. 2013).

In this scenario, the new drug makes all genotypes less fit, and the double mutant *AB* confers resistance to the drug. This makes *AB* the optimal genotype again, but in this scenario SIM induces hypermutation in all other genotypes, including *ab*. We denote quantities related with this scenario by a subscript *e*.

The adaptation rate with SIM in this scenario is (see Appendix 3):

|  |  |
| --- | --- |
| , | (8) |

That is, adaptation with SIMe is faster than with CM. This is because (i) the appearance of double mutants is the same as with CM, and (ii) the fixation probability of double mutants is higher with SIMe because the mutation rate of double mutants is lower than that of the rest of the population, which confers an additional selective advantage to the double mutants:

|  |  |
| --- | --- |
| . | (9) |

This additive advantage increases linearly with *τ* with a slope of 2*U*/(1+*sH*), which can be quite small (*≈*7⋅10-4 for typical values, see Table 1). This increase in the fixation probability was verified by simulations (Figure S2).

# Discussion

We studied the effect of stress-induced mutagenesis (SIM) on both *adaptability* – the capacity of populations to adapt to new conditions – and on *adaptedness* – the ability of populations to stay adapted to existing conditions (Leigh 1970). We showed that stress-induced mutagenesis breaks the trade-off between *adaptability* and *adaptedness*, allowing rapid adaptation to complex environmental changes without compromising the population mean fitness in a constant environment.

In addition to the pure strategies of constitutive mutagenesis (CM) and SIM, our model also considers a mixed mutational strategy. There are two examples of such a mixed strategy. First, if individuals have incomplete information regarding their condition (the case in most realistic biological scenarios) then we expect errors in the stress-induction of mutagenesis - induction of mutagenesis without stress and failure to induce mutagenesis under stress. In this case the population would, on average, use a mixed strategy. Second, a mutator allele can increase the mutation rate constitutively and further increase it under stress – for example, a recent study with *Pseudomonas aeruginosa* found that although the *mutS*, *mutY* and *mutM* mutator alleles always increase the mutation rate in comparison with the wildtype, the level of this increase depends on the level of stress the cell experiences (Torres-Barceló et al. 2013).

Mean fitness and adaptation rate are both population-level traits. Even though SIM has the most efficient balance between these traits, it will not necessarily evolve, because individual-level selection can act in a different direction than population-level selection. Moreover, even if SIM does evolve, it may be the result of selection on *adaptability* and *adaptedness* (2nd order selection (Tenaillon et al. 2001)), or a result of other factors, such as pleiotropic effects of mutator alleles (Torres-Barceló et al. 2013; Turrientes et al. 2013), the cost of DNA replication fidelity (Dawson 1998), and the effect of drift on the fidelity of rarely expressed proteins - the "drift barrier hypothesis" (Sung et al. 2012). Nevertheless, in a previous work we demonstrated that 2nd order selection can lead to the evolution of SIM (Ram and Hadany 2012).

Complex traits, coded by multiple genes, present an open evolutionary question, first described by Sewall Wright in 1931 (Wright 1931): if different alleles are separately deleterious but jointly advantageous, how can a population evolve from one co-adapted gene complex to a fitter one? Wright suggested the "shifting-balance theory of evolution" (Wright 1988). His solution is valid (Crow et al. 1990; Wade and Goodnight 1991; Peck et al. 2000) but is possibly limited to specific parameter ranges (Moore and Tonsor 1994; Gavrilets 1996; Coyne et al. 2000; Whitlock and Phillips 2000). As a result, other mechanisms were proposed (Whitlock 1995, 1997; Hadany 2003; Hadany and Beker 2003; Weissman et al. 2009). In this work we analyzed the effect of SIM on complex adaptation (Figure 2). Our results suggest that SIM is an alternative mechanism that can help resolve this problem.

Our results provide theoretical basis to the conjecture that SIM facilitates adaptation. This conjecture can be tested experimentally with, for example, *E. coli*, in which it is possible to interfere with the regulation of mutagenesis (Cirz and Romesberg 2007). The adaptation time with and without SIM can be measured in an experimental population adapting to a two-peak fitness landscape. These measurements can then be compared to our analytic approximations to determine the relative advantage and disadvantage of the different mutational strategies.

## Conclusions

Stress-induced mutagenesis has been implicated as a driver of adaptive evolution for several decades (Cairns et al. 1988; Tenaillon et al. 2004). Here we provided theoretical treatment of this concept. We showed that stress-induced mutagenesis increases the rate of complex adaptation, and that in contrast to constitutive mutagenesis it does not jeopardize the fitness of populations under stable conditions. Because mutation is a fundamental element in every biological system, these results have important implications on many fields in the medical and life sciences, including epidemiology, ecology and evolutionary biology.

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# Appendices

## Appendix 1

The probability *q* that a random individual in the next generation is *AB* given there are no *AB* in the current generation can be approximated by:

.

Now, we assume that *2µ/s<<s*<<2. This gives us:

.

For a population with SIM:

.

The last approximation assumes that *Us*<*U* and that *µ*/*s*<*τU.* Now,

.

The last approximation assumed that *s*<2*τ* and 1/2<*τ*2 (because *τ*>1). Rearranging the last expression gives us the first order approximation for populations with SIM:

|  |  |
| --- | --- |
| . |  |

Note that by setting *τ*=1 and because *U*<<2, *qSIM* is consistent with *q*.

## Appendix 2

Following Eshel (1981), the fixation probability *ρ* of the double mutant is:

,

where *α* is the fitness of the double mutant relative to the population mean fitness and assuming that fitness is measured by the number of progeny which is Poisson distributed:

.

Here, we only consider progeny without deleterious mutations – their fraction is *e-U*. This factor cannot be ignored because there is variation in mutation rates in the population. At this stage, double mutants are still very rare, so we can use the population mean fitness at the MSB.

Without SIM and neglecting beneficial mutations (β=0), the mean fitness evaluates to (see Supporting information). Therefore:

Assuming *sH* is small we can simplify this to:

.

## Appendix 3

With SIMe the mutation rate of *ab* is *τU* while that of *AB* is only *U*. We assume the population reached a MSB after the environmental change because convergence to MSB is much faster than adaptation (Gordo and Dionisio 2005). Following the derivation in Appendix 2, we derive the relative fitness of SIMe by:

.

Plugging that in the fixation probability:

.

This can be simplified by a 1st order approximation for :

.

Because , the right hand side is greater than 1 and therefore:

.

Because the appearance with SIMe is the same as with CM, the adaptation rate with SIMe can now be written as:

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# Figures



**Figure 1 – Adaptation of a complex trait.** Nodes represent genotypes: the alleles *a* or *A* and *b* or *B*. Panel b also includes the number of deleterious alleles across the genome after the forward-slash. Mutagenesis is induced in stressed genotypes (fitness <1, ellipses), and fit genotypes (fitness ≥1, squares) do not hypermutate. Solid arrows represent mutations at the *a/A* and *b/B* loci. Dashed arrows represent deleterious mutations across the genome. Arrow labels denote the rates. Node brightness represents fitness (see color bar): from white for the fittest genotype (1+*sH*, where *s*=0.05 is the selection coefficient and *H*=2 is the double mutant advantage) to dark brown for genotypes with deleterious mutations ((1-*s*)*x*, where *x* is the number of deleterious mutations). (a) In the analytic model genotypes with deleterious mutations are considered "evolutionary dead-ends" (marked with RIP) and do not contribute to adaptation. (b) In the stochastic model individuals can accumulate up to 25 deleterious mutations (the figure only shows as much as three). Multiple mutations can occur simultaneously but are not shown for simplicity of the illustration.



**Figure 2 – Complex adaptation with three mutational strategies.** The figure shows the adaptation rate *ν* as a function of the mutation rate increase *τ*. NM (represented by *τ*=1) is normal mutagenesis; CM (red with circles) is constitutive mutagenesis; SIM (solid blue with squares) is stress-induced mutagenesis; SIMe (dashed green with triangles) is stress-induced mutagenesis with environmental stress. Lines are analytic approximations; markers are the means of stochastic simulations results; error bars represent 95% confidence intervals of the mean (at least 1,000 replicates per point). Both axes are in log scale. Parameters (see Table 1): *U*=0.0004, *s*=0.05, *β*=0.0002, *H*=2, *N*=106.



**Figure 3 – Mean fitness at the mutation-selection balance with stress-induced mutagenesis.** The figure shows the relative fitness advantage of SIM in comparison to NM at the mutation-selection balance. The x-axis is *β,* the fraction of mutations that are beneficial and the y-axis is *τ*, the mutation rate fold increase under stress. "X" marks the point (*β*=1/5000, *τ*=10) in which the fitness advantage of SIM is ~5⋅10-9.



**Figure 4 – The trade-off between *adaptedness* and *adaptability*.** The figure shows the *adaptedness* (population mean fitness at the MSB; x-axis) and the *adaptability* (adaptation rate; y-axis) of different mutational strategies relative to normal mutagenesis (NM). Constitutive mutagenesis (CM; in red) increases the mutation rate of all individuals *τCM*-fold; Stress-induced mutagenesis (SIM; in blue) increases the mutation rate of stressed or maladapted individuals *τSIM*-fold; Mixed strategies (in dashed green) increase the mutation rate of all individuals *τCM*-fold and of stressed individuals *τSIM*-fold. SIM breaks off the *adaptability-adaptedness* trade-off of CM, increasing the *adaptability* without compromising the *adaptedness* of the population. Parameters (see Table 1): *N*=106, *U*=­0.0004, *β*=0.002, *s*=0.05, *H*=2.

# Tables

Table 1 – Model parameters and estimated values for *Escherichia coli*

|  |  |  |  |
| --- | --- | --- | --- |
| Symbol | Name | Estimate | References |
| *s* | Selection coefficient | 0.001-0.03 | (Kibota and Lynch 1996; Gordo et al. 2011) |
| *H* | Double mutant advantage | 1-10 | (Gordo et al. 2011) |
| *U* | Genomic deleterious mutation rate | 0.0004-0.003 | (Drake et al. 1998; Wielgoss et al. 2011) |
| *µ* | Site-specific beneficial mutation rate | U/5000 | (Gordo et al. 2011) |
| *τ* | Fold-increase in mutation rate | 1-100 | (Bjedov et al. 2003; Hall and Henderson-Begg 2006) |
| *N* | Population size | 105-1010 | (Pupo and Richardson 1995; Berg 1996) |

# Supporting figures

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**Figure S1 – Waiting time for the appearance of a double mutant** as a function of the mutation rate fold increase *τ*. NM (represented by *τ*=1) is normal mutagenesis; CM (dashed red) is constitutive mutagenesis; SIM (solid blue) is stress-induced mutagenesis. Lines are analytic approximations; markers are means of stochastic simulations results - black circles for the regular simulation, white triangles for simulations in which *AB* cannot appear on deleterious background. Error bars were too small to show, at least 1,000 simulations per point. Both axes are in log scale. The appearance time decreases as a function of *τ*2 and *τ* with CM and SIM, respectively. Appearance time is longer if *AB* is limited to unloaded background (white triangles) which explains the difference between the analytical approximations and the simulation results in Figure 2. The parameters are the same as in Figure 2.



**Figure S2 – Fixation probability** **of the double mutant *AB*** as a function of the mutation rate fold increase *τ* with three mutational strategies: constitutive mutagenesis (CM; top panels in red), stress-induced mutagenesis (SIM; middle panels in blue) and stress-induced mutagenesis with environmental stress (SIMe; bottom panels in green). Dashed lines are the analytic approximations; black error bars represent simulation results with 95% CI (computed using bootstrap); solid lines are the logistic regression lines computed from the simulation results. The three left panels are results of the standard simulations (described in the Model section). The three right panels are results of simulations in which *AB* could not appear on a deleterious background. If *AB* cannot appear on a deleterious background (right panels) than the differences between the simulation results and our analytic approximations are not statistically significant (compare solid and dashed lines; P<0.001). However, if *AB* can appear on a deleterious background (left panels) then its fixation probability is lower, . In addition, the figure shows that SIMe­ has a higher fixation probability than CM and SIM. The parameters are the same as in Figure 2.

# Supporting Information

## Mean fitness at the mutation-selection balance

Denote the frequency of individuals with *x* deleterious mutations by *fx*. The frequency of individuals with *x* deleterious mutations in the next generation *f'x* can be described by:

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| --- | --- | --- |
|  | , |  |

where *mx,y* is the transition probability from *y* deleterious mutations to *x* deleterious mutations and is the population mean fitness. The term *mx,y* includes the fitness *ωy* of individuals with *y* deleterious mutations and the probability of deleterious or beneficial mutations occurring, assuming that a small fraction of the mutations are beneficial (here *P(A)* denotes the probability of *A*):

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Replacing *P* with the probability mass function of a Poisson distribution, we can expand the former master equation to:

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where *ωx* is the fitness with *x* deleterious mutations, is the population mean fitness (), *δ* and *β* are the fraction of mutations that are deleterious and beneficial, respectively (*δ+β*=1 and 0≤*β*<*δ*≤1*)* and *Ux*is the average number of new mutations at replication in an individual with *x* deleterious mutations.

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

At the mutation-selection balance (MSB), *f\** fulfills (a star \* denotes equilibrium quantities):

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Because *M* is a positive matrix, by the *Perron-Frobenius Theorem* (Otto and Day 2007, p. 709) is the largest eigenvalue of *M* and *f\** is its unique non-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 (constant uniform mutation rate) then the frequencies vector is , that is, the number of deleterious mutations per individual is Poisson distributed with average *U/s* (Haigh 1978). With constitutive mutagenesis (CM), the mean fitness equals *e-τU* – it decays exponentially as a function of *τ*, the mutation rate fold increase. In contrast, stress-induced mutagenesis (SIM), as was demonstrated by Agrawal (2002), does not change the population mean fitness with respect to normal mutagenesis (NM), because the least loaded individuals (*x*=0), with fitness *ω*0=1, also have the lowest mutation rate, *U*, and therefore the population mean fitness is *e-U*.

With beneficial mutations (β>0) this eigenvalue problem is harder to solve analytically. By neglecting elements outside the main three diagonals of *M* we have shown before (Ram and Hadany 2012) that:

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Nevertheless, this framework allows the calculation of the population mean fitness numerically for finite *n*-by-*n* matrices by defining *n* such that and we can calculate the mean fitness of populations with different mutational strategies by manipulating *Ux*. Evaluating the numerical results (Figure 3), we can see that *e-U* is still a good approximation to the population mean fitness (because *β*<<1), 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. Since we assume that *U*<*s*,then *e-U* ≈ 1-*U* > 1-s. Therefore, if SIM increases the mutation rate in individuals with at least one deleterious mutation, then it increases the population mean fitness.

## Figure reproduction

The figures were produced using an IPython Notebook (<http://ipython.org/>) which is available at XXX. The notebook code can be used to reproduce all the figures using the analytical approximations, given as Python functions, and the simulation data. The simulation data is deposited at XXX and is necessary for Figures 2, S1 and S2.