­Stress-induced mutagenesis breaks the trade-off between adaptability and adaptedness

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# 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 generation of beneficial mutations (Sniegowski et al. 2000). However, during evolution in a constant environment, constitutive mutators become associated with bad genetic backgrounds due to increased accumulation of deleterious mutations and are purged from the population, leading to "the rise and fall of the mutator allele" (Taddei et al. 1997; Denamur and Matic 2006; Wielgoss et al. 2012). Hence, Leigh (1970) suggested that the mutation rate must balance between two 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 the mutation rate in stressed or maladapted individuals, has been demonstrated in numerous species, including both prokaryote and eukaryote (Galhardo et al. 2007; Sharp and Agrawal 2012; MacLean et al. 2013). Various stress responses regulate the mutation rate by shifting cells to error-prone DNA polymerases (Ponder et al. 2005) and by inhibiting the mismatch repair system (Debora et al. 2010). 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 proposed that SIM has a significant impact on *adaptability* or *evolvability* (Tenaillon et al. 2004; Rosenberg et al. 2012). However, there is currently no theoretical treatment of this impact. The effect of SIM on *adaptedness* received theoretical treatment by Agrawal (2002), who showed numerically that in asexual populations in constant environments SIM doesn't affect the population mean fitness. In a more recent work, we have showed that if rare beneficial mutations occur than SIM slightly increases the population mean fitness in comparison with normal mutagenesis (Ram and Hadany 2012).

Here, we analyze population genetic models of asexual populations. We develop general expressions that demonstrate that SIM increases both the adaptation rate and the mean fitness of such populations. By comparing SIM to constitutive mutagenesis and normal mutagenesis we show that SIM is more successful because it allows populations to increase their *adaptability* without compromising their *adaptedness*.

# Model

We consider a population of *N* haploid asexual individuals. The number of new deleterious mutations 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 analyze two models: one of evolution towards a mutation-selection balance (MSB) in a constant environment, the other of adaptive evolution of a complex trait in a rugged fitness landscape. We develop analytic approximations for the mean fitness and adaptation rate of populations and use stochastic simulations to verify our approximations.

## 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:

,

where *mx,y* is the transition probability from *y* mutations to *x* 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:

.

We use this system to calculate the population mean fitness of the population at the mutation-selection balance (MSB) – in which the frequency of individuals with *x* deleterious mutations does not change from one generation to the next (*f'x*=*fx*). See Appendix 1 for more details.

## Complex adaptation

Consider a population 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). As before, new deleterious mutations occur with rate *U*.

After the population has reached a MSB it goes through adaptive evolution to an environmental change which changed the fitness of the *AB* genotype from (1-*s*)2to 1+*sH* (*H* is the double mutant relative advantage), making it the optimal genotype. See Figure 1 for an illustration of the adaptive evolution model.



**Figure 1 – Adaptation on a rugged fitness landscape.** Nodes represent genotypes: the alleles *a* or *A* and *b* or *B*, and in panel b the number of deleterious alleles across the genome as well. Mutagenesis is induced in stressed genotypes (fitness <1), indicated by ellipses, while adapted genotypes (fitness >1) do not hypermutate. Solid arrows represent site-specific mutations at the *a/A* and *b/B* loci, which occur with probability *µ*. Dashed arrows represent deleterious mutations across the genome which are Poisson distributed with an average *U*. Node color represents fitness (see colorbar), from pale brown 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 accumulated 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" (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 concurrently but are not shown for simplicity of the illustration.

We analyze this model with two distinct 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, also see Appendix 1). These assumptions require that mutation is weaker than selection:

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

The second model is a stochastic Wright-Fisher simulation with selection, mutation and drift (Figure 1b, Supplementary File SX), in which we: (i) let individuals with accumulated deleterious mutations contribute to adaptation, and (ii) let the MSB evolve from a mutation-free population (*fab/0*=1).

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

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

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) |

### 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 on the population size *N* we get:

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

From conservative estimations in Table 1, the population size *N* must be between105and107, but the constraint can also be met for other combinations of the parameter values. These values are 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 *q* that a random individual in the next generation is a double mutant, given there are no double mutants in this generation is therefore:

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

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

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

The right-hand side of Eqs. (3) and (4) are 1st order approximations, see Appendix 2 for more details.

### Fixation probability with stress-induced mutagenesis

Assuming that the advantage of the double mutant is considerable (for example, *H>1)* and that the population size is large (constraint 2 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 3 for full derivation):

|  |  |
| --- | --- |
| . | (5) |

That is, the fixation probability of the double mutant is roughly twice its adaptive advantage, which is a classic result of population genetics theory (Eshel 1981).

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*.

### 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: . Constraint 2 guarantees that *Nq* is very small and therefore this probability can be approximated by *Nq*. Once a double mutant appears it has a probability *ρ* to go to fixation.

The time for adaptation *T* can be approximated by the waiting time for a double mutant that will go to fixation, *Tw*. This is true as long as fixation is much faster than mutation (guaranteed by *µ*2<2 which is a weaker constraint than that given by Eq. (1)). *Tw* follows a geometric distribution with probability *Nqρ* and therefore the expected time for adaptation can be approximated by 1/*Nqρ*. The adaptation rate is the inverse of the expected adaptation time:

|  |  |
| --- | --- |
| . | (12) |

# Results

## Mutation-selection balance

Without beneficial mutations (*β*=0) and with constitutive mutagenesis (CM), the mean fitness equals *e-τU*(Kimura and Maruyama 1966; see also Appendix 1). Therefore, with CM the population mean fitness exponential decays as a function of the mutation rate fold increase *τ*. In contrast, stress-induced mutagenesis (SIM), as was numerically shown by Agrawal (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), *e-U* is still a good approximation (because *β*<<1), but as we have shown before (Ram and Hadany 2012), 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. Constraint (1) ensures that that *s*>*U* and therefore *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. We explore the magnitude of this increase in Figure 2.



**Figure 2 – Mean fitness at the MSB with stress-induced mutagenesis.** The figure shows the relative fitness advantage of SIM in comparison to NM at the MSB. The x-axis is *β,* the fraction of mutations that are beneficial; the y-axis is *τ*, the mutation rate fold increase under stress. "X" marks the point with(*β*=1/5000, *τ*=10) in which the fitness advantage of SIM is ~5⋅10-9.

## Complex adaptation

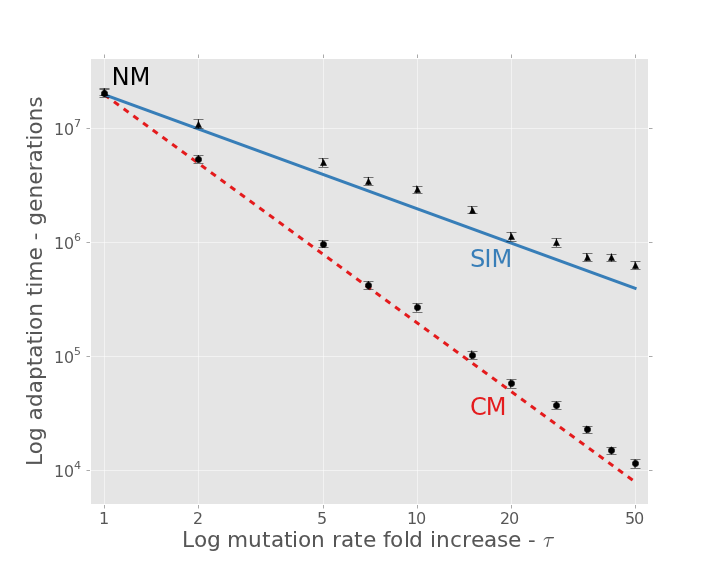
In 1931, Wright introduced the problem of complex adaptation (Wright 1931): if two or more mutations are required for adaptation, but each mutation is deleterious on its own, then adaptation will be very slow. For adaptations that require a combination of two mutations, the rate of adaptation *ν* is:

|  |  |
| --- | --- |
|  | (13) |
|  | (14) |
|  | (15) |

In these equations, the right-hand sides are approximations for small values of *U* and *τU*, respectively. The dynamics of the adaptation rate as a function of *τ*, the mutation rate fold increase, are shown in Figure 3.

There are several conclusions to draw 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 *τ2*. 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 S5). See below for a different scenario in which SIM increases the fixation probability.

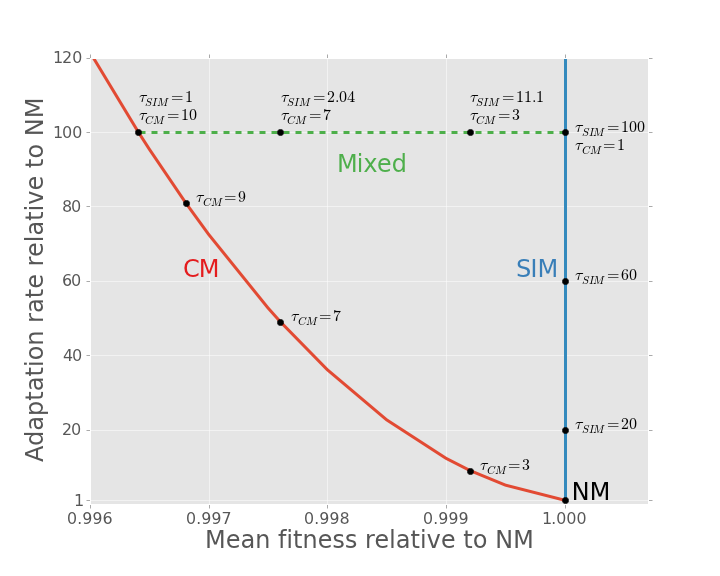
These approximations, and therefore these results, depend on the constraint that *τU<s*. When this constraint is met, the approximations agree with the results of our stochastic simulations (Figure 3). Deleterious mutation rates in microbes are generally on the order of 10-4-10-2 and selection coefficients are between 10-1 and 10-2 (see Table 1), so the limit on *τ* is between 1 and 1,000. More generally, we can expect that if selection is strong and mutation rates are low, then CM and SIM will have an adaptive advantage over NM.



**Figure 3 – Complex adaptation with three mutational strategies.** The figure shows the waiting time for adaptation (the inverse of the adaptation time *ν*) as a function of *τ* the mutation rate increase in a rugged fitness landscape with two bi-allelic loci (Figure1). NM (represented by *τ*=1) is normal mutagenesis; CM (dashed red with circles) is constitutive mutagenesis; SIM (solid blue with triangles) is stress-induced mutagenesis. Lines are analytic approximations, markers are means of stochastic simulations results and error bars are standard error of the mean (at least 130 simulations per point). Both axes are in log scale. The figure shows that the adaptation time decreases as a function of *τ*2 and *τ* with CM and SIM, respectively (Eqs. 15-16). Parameters (see Table 1): *U*=0.0004, *s*=0.05, *β*=0.002, *H*=2, *N*=106.

## The trade-off between adaptability and adaptedness

Figure 4 shows the mean fitness and adaptation rate 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 2). If the mutation rate fold increase *τ* required by SIM is too high (*i.e.*, *τU*>*s*) the same adaptation rate can be realized via a mixed strategy (dashed green line) which combines SIM and CM. For example, a ~100-fold increase in adaptation rate can be achieved with CM with *τ*=10, SIM with *τ*=100 or 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, this increase in adaptation rate has 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 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 *τ*=100 is higher by ~3⋅10-8.



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

## Effect of environmental stress

So far, we considered stress that results from a mismatch between the individual and the environment. Another possible interpretation of stress is an environmental condition which reduces the fitness of all individuals which are not adapted to it, such as a new antibiotic drug.

In this scenario, the drug renders all genotypes less fit, and the double mutant *AB* confers resistance to the drug. This makes *AB* the optimal genotype, 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 in this scenario is (see Appendix 4):

|  |  |
| --- | --- |
| , | (16) |

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 of double mutants is more likely with SIME:

|  |  |
| --- | --- |
| , | (11) |

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. This advantage increases linearly with *τ* but with a modest slope of 2*U*/(1+*sH*), which can be quite small (*≈*0.00073 for typical values, see Table 1). This increase in the fixation probability was verified by simulations (Figure S6).

# Discussion

We developed a theoretical basis to study the effect of stress-induced mutagenesis 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 SIM breaks the trade-off between *adaptability* and *adaptedness*, allowing rapid adaptation without compromising the population mean fitness.

One of the features included in our model was that of a mixed strategy – a mutational strategy that combines CM and SIM. There are two examples of such a strategy. First, if individuals' information is not complete (which is the case in most realistic scenarios) then we expect that there would be errors in the 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 – 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 population-level traits. Even though SIM has the most efficient balance between these traits, it will not necessarily evolve, because individual-level selection can work 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), the cost of DNA replication fidelity (Dawson 1998), and the effect of drift on fidelity of rarely expressed proteins, aka the "drift barrier hypothesis" (Sung et al. 2012). Nevertheless, in a previous work we demonstrated that indirect selection on the generation of beneficial mutations can lead to the evolution of stress-induced mutagenesis, at least in asexual population (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 better 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 3). Our results suggest that SIM is an alternative mechanism that can help resolve this problem.

Our work provides a formal theoretical basis to the conjecture that SIM facilitates adaptation and increases the evolvability of populations. The next step would be to experimentally verify our results. This can be done, for example, with *E. coli*, in which one can interfere with the regulation of hypermutation by stress (Cirz and Romesberg 2007). If an experimental population evolves under conditions similar to those in our model, it will be interesting to measure the adaptation time and mean fitness with and without SIM and compare it to our analytical 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 indeed 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 such a fundamental factor in every biological process, these results have an important implication on many fields in the medical and life sciences, including epidemiology, ecology and evolutionary biology

# Appendices

## Appendix 1

The master equation for the change in *fx*, the frequency of individuals with *x* deleterious mutations is:

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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*)*, *U* is the mutation rate and mutations are Poisson distributed.

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

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

Because *M* is a positive matrix and 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 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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However, this framework allows to calculate the population mean fitness numerically for finite *n*-by-*n* matrices by defining *n* such that – see the *mean\_fitness* function in the Python code in Supplementary File X.

## Appendix 2

The above expressions can be simplified by using first-order approximations. Starting with Eq. (3) for populations without SIM-I:

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Now, we assume that 2 is much larger than *s* which is much larger than 2*µ*. This gives us:

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For a population with SIM the first-order approximation is based on the full expression in Eq. (4):

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

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

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

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

## Appendix 3

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

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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:

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Here, we only take the fraction of progeny that do not have deleterious mutations - *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, the mean fitness evaluates to (see ‎Appendix 1). Therefore:

Assuming *sH* is small we can simplify this to the well known:

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## Appendix 4

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 3, we derive the relative fitness of SIME by:

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Plugging that in the fixation probability:

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

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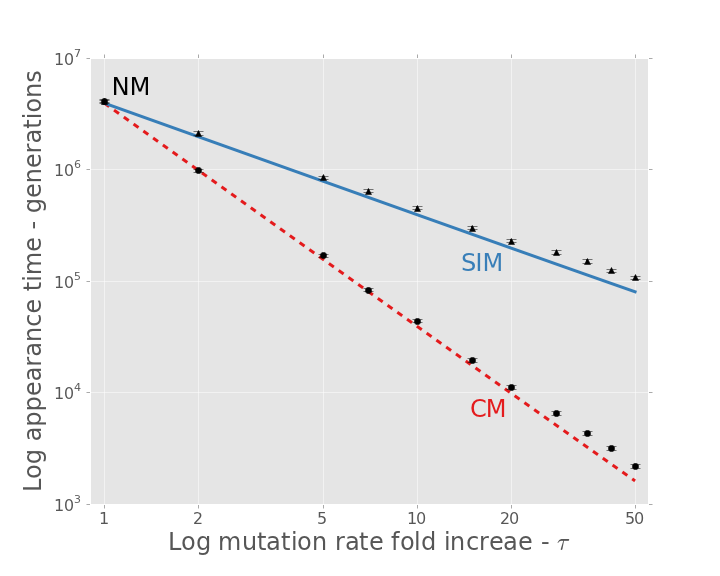
Because , the right hand side is greater than 1 and therefore:

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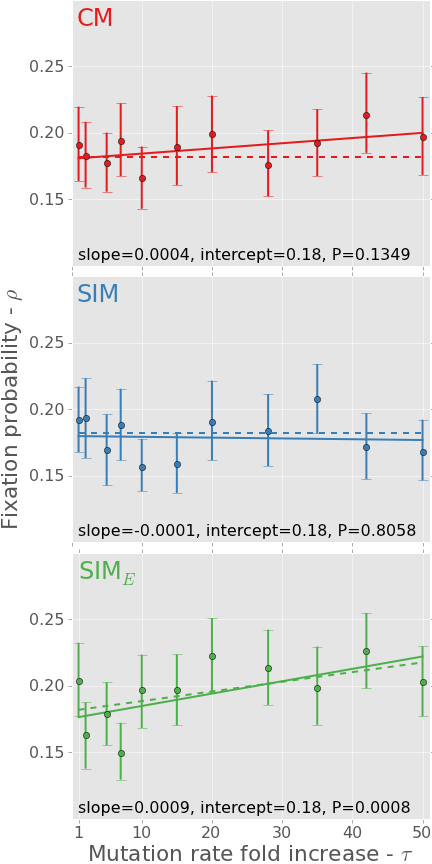
Because the appearance with SIME is the same as with CM, the adaptation rate with SIME can now be written as:

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# Supporting figures

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**Figure S5 – Waiting time for the appearance of a double mutant** as a function of *τ* the mutation rate increase in a rugged fitness landscape with two bi-allelic loci (Figure1). NM (represented by *τ*=1) is normal mutagenesis; CM (dashed red with circles) is constitutive mutagenesis; SIM (solid blue with triangles) is stress-induced mutagenesis. Lines are analytic approximations, markers are means of stochastic simulations results and error bars are standard error of the mean (at least 130 simulations per point). Both axes are in log scale. The figure shows that the appearance time decreases as a function of *τ*2 and *τ* with CM and SIM, respectively (Eqs. 3-4). The parameters are the same as in Figure 3.



**Figure S6 – Fixation probability.** The fixation probability of the double mutant *AB* with three mutational strategies: constitutive mutagenesis (CM; top panel in red), stress-induced mutagenesis (SIM; middle panel in blue) and stress-induced mutagenesis with environmental stress (SIME; bottom panel in green). Dashed lines are the analytic approximations, circles are the fixation probability estimations from simulation results, error bars are 95% confidence intervals (computed using bootstrap), solid lines are the GLM regression predictions computed from the simulation results with the inverse link function. Only SIME­ has a significant effect on fixation (P≈0.0008). The corresponding slope 0.0009 is close to the approximated slope for this parameter set: 2*U*/1+*sH*≈0.00073. The parameters are the same as in Figure 3.