­Supporting information for "Stress-Induced Mutagenesis Breaks the Trade-Off Between Adaptability and Adaptedness"

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# Figure reproduction

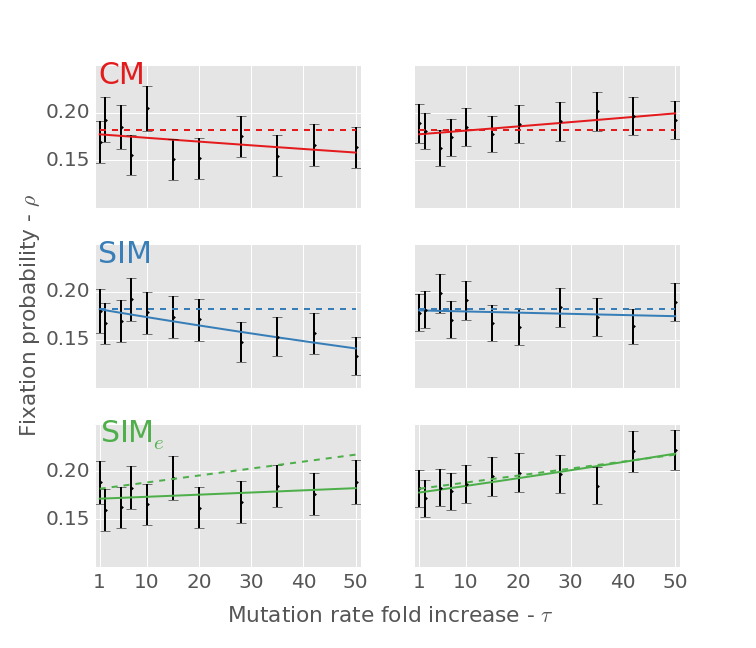
All figures were produced with Python on an [IPython](http://ipython.org/) Notebook (Perez and Granger 2007). The notebook includes the analytic approximations as Python functions and uses the simulation raw data which is necessary for Figures 2, 5, S1, and S2. The notebook and the raw data will be deposited on Dryad.

# 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 (red) is constitutive mutagenesis; SIM (solid blue) is stress-induced mutagenesis. Lines are analytic approximations (eqs. 2, 3 in main text); markers are means of stochastic simulation results - black circles for the regular simulations, white triangles for alternative simulations in which *AB* cannot appear on deleterious backgrounds. The standard error of the mean was too small to show. At least 1,000 simulation replicates 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 slightly longer if *AB* is limited to unloaded background (white triangles) which explains the difference between the analytic approximations and the simulation results for SIM in Figure 2. 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; see section 3.3 in main text). Dashed lines are analytic approximations; black error bars represent simulation results with 95% confidence interval of the mean (at least 1,000 replicates per point; computed with bootstrap with 10,000 samples per point); 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 of the main text). The three right panels are results of simulations in which *AB* cannot appear on deleterious backgrounds - in these cases there is no significant difference between the simulation results and our analytic approximations (compare solid and dashed lines; regression slope tests with α=0.05). However, if *AB* can appear on a deleterious background (left panels) then its fixation probability is lower, for example, the fixation probability of *AB* with a single deleterious mutation is . In addition, the figure shows that SIMe­ has a higher fixation probability than CM and SIM. Parameters are the same as in Figure 2.



**Figure S3 – Different stress-induced mutagenesis relationships.** The figure shows a comparison of a continuous relationship between fitness (x-axis) and mutation rate (y-axis) in solid lines and a threshold relationship in dashed lines. The threshold relationship is defined in section 2.1 of the main text. The continuous relationships are defined in section 3.4 of the main text. Each panel shows a pair of relationships, with *k* increasing from 1/10 (convex relationship), to 1 (linear relationship) to 10 and 100 (concave relationships). Each continuous relationship is compared with a threshold relationship that has the same mutation rate for wildtypes and single mutants. Figure 2B in the main text shows that the adaptation rate with such threshold relationship approximates the adaptation rate with a continuous relationship.

# 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 (Ram and Hadany 2012). 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.

# References

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Haigh, J. 1978. The accumulation of deleterious genes in a population - Muller’s Ratchet. Theor. Popul. Biol. 14:251–267.

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