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

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# Figure reproduction

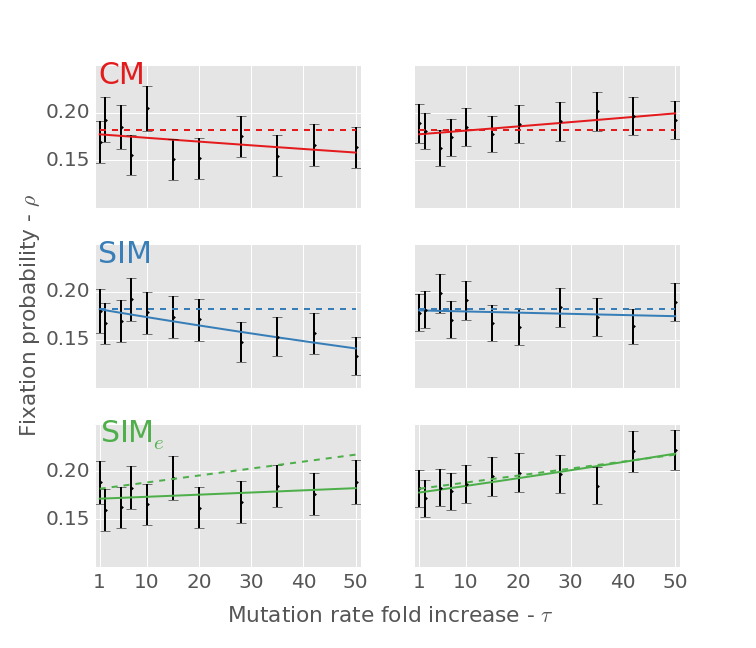
All figures were produced with Python on an [IPython](http://ipython.org/) Notebook (Perez and Granger 2007). The notebook includes the analytic approximations as Python functions and uses the simulation raw data which is necessary for Figures 2, 3, 5, S1, and S2. The notebook and the raw data will be deposited on Dryad.

# Supporting figures



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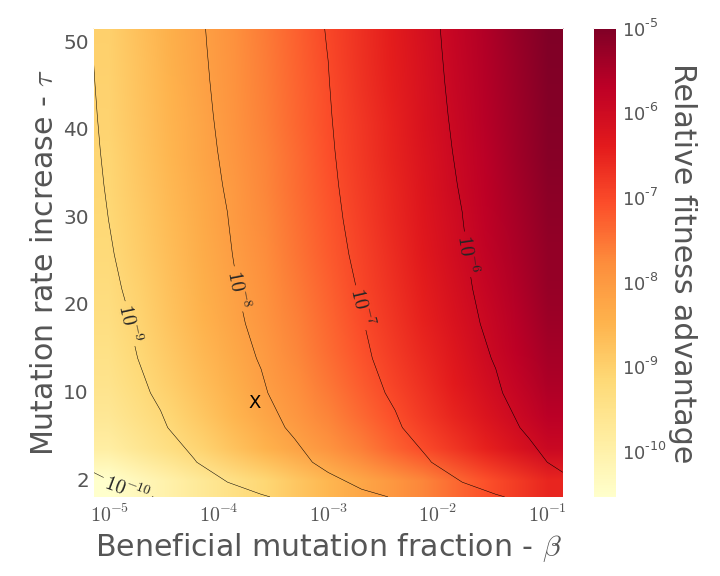
**Figure S1 – Waiting time for the appearance of a double mutant** as a function of the mutation rate fold increase *τ*. Normal mutagenesis (NM) is *τ*=1; constitutive mutagenesis (CM) in red; stress-induced mutagenesis (SIM) in blue. Lines are analytic approximations (eqs. 2, 3 in main text). Markers are means of simulation results - black circles for the standard 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 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 slightly longer if *AB* only appears on 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 3.5 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 simulations 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. 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 (Johnson and Barton 2002). 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 relationships between stress and mutation.** The figure shows continuous relationships between fitness (x-axis) and mutation rate (y-axis) in solid lines and threshold relationships in dashed lines. The threshold relationship is defined in section 2 of the main text. The continuous relationships are defined in section 3.6 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 (*ab/0*) and single mutants (*Ab/0*, *aB/0*, *ab/1*). Figure 2B in the main text shows that the adaptation rate with such threshold relationship approximates the adaptation rate with a continuous relationship.

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**Figure S4 – Mean fitness at the mutation-selection balance with stress-induced mutagenesis.** The brightness represents the fitness advantage of stress-induced mutagenesis over normal mutagenesis at the mutation-selection balance. The x-axis is the fraction of mutations that are beneficial *β*. The y-axis is the mutation rate fold increase under stress *τ*. "X" marks the parameter set *β*=1/5000 and *τ*=10, in which the fitness advantage of SIM is ~5⋅10-9.

# Mean fitness at the mutation-selection balance

Denote the frequency of individuals with *x* deleterious alleles by *fx*. The frequency of such individuals in the next generation *f'x* is given by

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where *mx,y* is the transition probability from *y* deleterious alleles to *x* deleterious alleles and is the population mean fitness. The term *mx,y* includes the fitness of individuals with *y* deleterious alleles, *ωy*, and the probability that the precise number of mutations occurred. Specifically, if *y≥x* then exactly *y-x* beneficial mutation must occur; if *y≤x* then exactly *x-y* deleterious mutations must occur:

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Using the probability mass function of a Poisson distribution, we can expand the above equation to

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where *ωy* is the fitness with *y* deleterious alleles, 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 *Uy*is the average number of new mutations per generation in an individual with *y* deleterious mutations.

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

At the mutation-selection balance (MSB), *f\** solves the equation (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 population mean fitness at the MSB is *e-τU*: it decays exponentially as a function of *τ* the mutation rate fold increase. In contrast, stress-induced mutagenesis (SIM), as shown by Agrawal (2002), does not change the population mean fitness with respect to normal mutagenesis (NM). This is 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 the population mean fitness increases with the mutation rate of individuals with a below–average fitness:

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Nevertheless, this framework allows the numerical calculation of the population mean fitness for finite *n*-by-*n* mutation-selection matrices by defining *n* such that . The mean fitness of populations with different mutational strategies is then calculated by manipulating *Ux*.

Figure S4 shows that *e-U* is still a good approximation to the population mean fitness (because *β*<<1), but SIM slightly 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, for SIM to increase the population mean fitness it must increase the mutation rate in individuals with at least one deleterious mutation.

# References

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