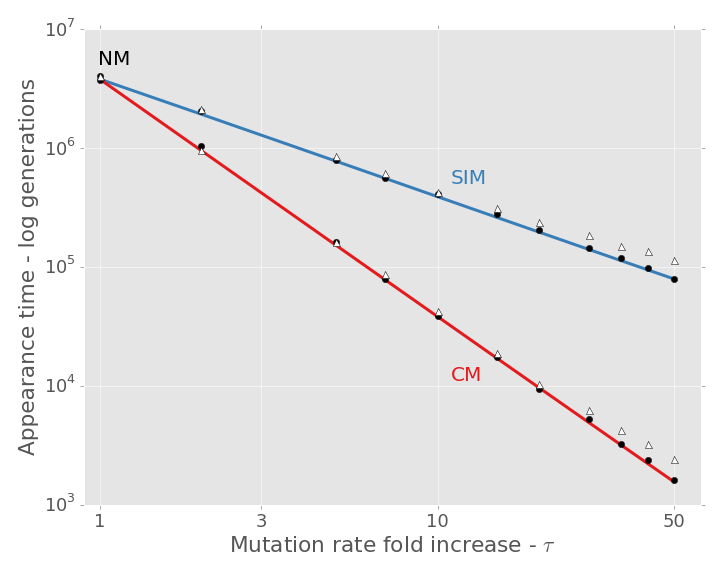
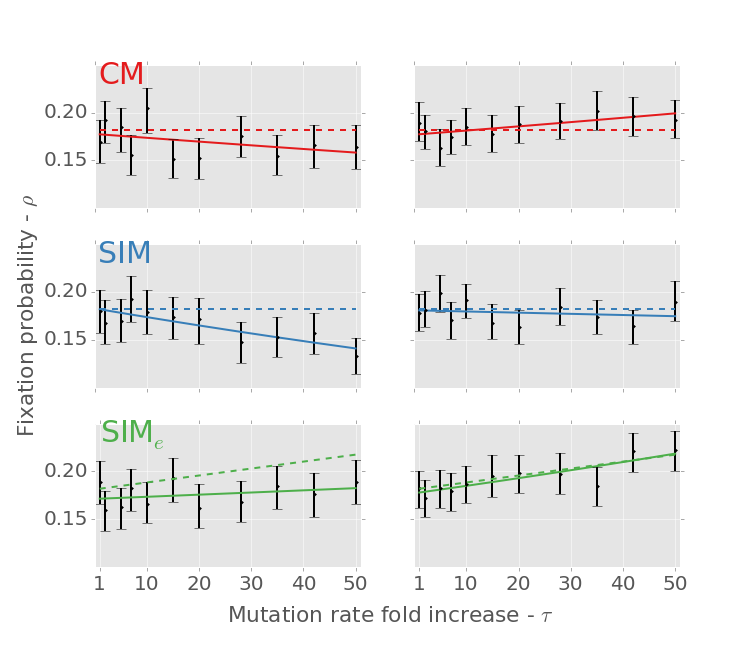
­Supporting information for "Stress-Induced Mutagenesis Breaks the Trade-Off Between Adaptability and Adaptedness"

Yoav Ram and Lilach Hadany

# Supporting figures



­**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.

# 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:

,

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 raw data which is deposited at XXX and is necessary for Figures 2, S1 and S2.

# References

Agrawal, A. F. 2002. Genetic loads under fitness-dependent mutation rates. J. Evol. Biol. 15:1004–1010. Wiley Online Library.

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

Otto, S. P., and T. Day. 2007. A biologist’s guide to mathematical modeling in ecology and evolution. Princeton University Press.

Ram, Y., and L. Hadany. 2012. The evolution of stress-induced hypermutation in asexual populations. Evolution (N. Y). 66:2315–28.