SUPPLEMENTARY MATERIALS FOR

Evidence for Adaptive Elevation of Gene Expression Noise in Yeast

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Supplementary materials include:
Supplementary Notes 1-2
Supplementary Tables S1-S6
Supplementary Figure Legends
Supplementary Figures S1-S6

Supplementary Note 1

Genotypes with different levels of expression noise can have different fitness values

Let us consider two genotypes A and B. The only difference between them is that A has a higher level of expression noise than B for gene X. The mean expression level (m) of X is identical between A and B cells. The distributions of the expression noise (e) of X in A and B cells are described by probability density functions $g_A(e)$ and $g_B(e)$, respectively. Genome-wide expression noise data showed that e generally follows a normal distribution, although the only requirement for our proof below is that the distribution is symmetric relative to e=0. That is, we require $g_A(e) = g_A(-e)$ and $g_B(e) = g_B(-e)$. Let us assume that a population consisting of A and B cells experiences an environmental change such that the mean expression level of X becomes suboptimal. Let $f(x)=f(m+e)$ be the fitness of the cell that has an expression level of X equal to x.

So, the fitness of genotype A, or the mean fitness of A cells, equals $F_A = \int_{-\infty}^{\infty} f(m+e)g_A(e)\mathrm{d}e$.

Similarly, the fitness of genotype B equals $F_B = \int_{-\infty}^{\infty} f(m+e)g_B(e)\mathrm{d}e$.

Fig. S1 shows the distribution of gene expression level x for A and B genotypes in blue and red curves, respectively. The shaded area shows the overlap between the areas under the two curves. In other words, many A and B cells have the same expression levels. Obviously, the mean fitness of A cells equals that of B cells for those cells under the shaded area.

Let us first assume that $f(x)$ is a concave function, or the second derivative of $f(x)$ is positive (i.e., $f''(x)>0$). Let $a>b$. We have

$$\begin{aligned} f(m+a) - f(m+b) &> (a-b) f'(m+b) \\ &> [(-b)-(-a)] f'(m-b) \\ &> f(m-b) - f(m-a) \end{aligned} \quad , \qquad (1)$$

where $f'()$ is the first derivative of f. From (1), we have

$$f(m-a) + f(m+a) > f(m-b) + f(m+b). \qquad (2)$$

Thus, a pair of cells with symmetric expression levels relative to the mean expression will have a greater mean fitness when their expression levels are more distant from the mean. In Fig. S1, we can see that in unshaded areas, every A cell is more distant from the mean of the distribution than every B cell. Because the blue and red curves are both symmetric and because the number of cells in the unshaded areas under the blue curve is identical to the corresponding number under the red curve, it becomes obvious that the mean fitness of A cells exceeds that of B cells for those cells in unshaded areas. Because the mean fitness values of A cells and B cells are identical for cells in the shaded area, the overall mean fitness of all A cells exceeds that of all B cells.

It can be similarly shown that when $f(x)$ is a convex function, or the second derivative of $f(x)$ is negative (i.e., $f''(x)<0$), the mean fitness of A cells is smaller than that of B cells. When $f(x)$ is a linear function, or the second derivative of $f(x)$ is 0 (i.e., $f''(x)=0$), the mean fitness of A cells equals that of B cells.

The same mutation can have different fitness consequences in different genotypes

Let us continue to study the genotypes A and B. Now, assume that a mutation alters the mean expression level of X to a new level n (n > m) that has an increased fitness. We further assume that the effect of the mutation on the mean expression level is the same in A and B cells and that the mutation has no impact on expression noise. An interesting question is whether the mean fitness gain caused by the mutation is the same for A cells and B cells. The mean fitness of A cells with the mutation is now $F_A' = \int_{-\infty}^{\infty} f(n+e) g_A(e) de$. Similarly, the mean fitness of B cells with the mutation equals $F_B' = \int_{-\infty}^{\infty} f(n+e) g_B(e) de$. So, the expected fitness gain of A cells offered by the mutation is $F_A' - F_A = \int_{-\infty}^{\infty} [f(n+e) - f(m+e)] g_A(e) de$. Similarly, the expected fitness gain of B cells offered by the mutation is $F_B' - F_B = \int_{-\infty}^{\infty} [f(n+e) - f(m+e)] g_B(e) de$.

Fig. S3 shows the distribution of gene expression level x for genotypes A, B, A with the mutation, and B with the mutation, in solid blue, solid red, dotted blue, and dotted red curves, respectively. The shaded areas show the overlap between the areas under the blue and red curves (either solid or dotted). Obviously, the mean fitness gain caused by the mutation is equal for A cells and B cells in the shaded area.

Now let us consider cells in the unshaded areas. Consider two A cells with expression levels being $m+a$ and $m-a$, respectively, and two B cells with expression levels being $m+b$ and $m-b$, respectively. Obviously, $a>b$. After the mutation, these A and B cells have the expression levels of $n+a$, $n-a$, $n+b$, $n-b$, respectively. Let us assume that the third derivative of $f(x)$ is positive (i.e., $f'''(x)>0$). We have

$$f(n+a)-f(n+b)=\int_0^{a-b} f'(n+b+y)\mathrm{d}y\,, \tag{3}$$

$$f(n-b)-f(n-a)=\int_0^{a-b} f'(n-a+y)\mathrm{d}y\,, \tag{4}$$

$$f(m+a)-f(m+b)=\int_0^{a-b} f'(m+b+y)\mathrm{d}y\,, \tag{5}$$

$$f(m-b)-f(m-a)=\int_0^{a-b} f'(m-a+y)\mathrm{d}y \tag{6}$$

Let Δ be the total fitness gain of the two A cells caused by the mutation, minus the total fitness gain of the two B cells. Thus,

$$\begin{aligned}\Delta &= \{[f(n+a)+f(n-a)]-[f(m+a)+f(m-a)]\}\\ &\quad -\{[f(n+b)+f(n-b)]-[f(m+b)+f(m-b)]\}\\ &= \int_0^{a-b} f'(n+b+y)\mathrm{d}y-\int_0^{a-b} f'(n-a+y)\mathrm{d}y-\int_0^{a-b} f'(m+b+y)\mathrm{d}y+\int_0^{a-b} f'(m-a+y)\mathrm{d}y\\ &= \int_0^{a-b}\{[f'(n+b+y)-f'(n-a+y)]-[f'(m+b+y)-f'(m-a+y)]\}\mathrm{d}y.\end{aligned} \tag{7}$$

For any given y,

$$f'(n+b+y)-f'(n-a+y)=\int_{z=0}^{a+b} f''(n-a+y+z)\mathrm{d}z \tag{8}$$

and $$f'(m+b+y)-f'(m-a+y)=\int_{z=0}^{a+b} f''(m-a+y+z)\mathrm{d}z\,. \tag{9}$$

Thus, we have

$$\Delta = \int_{y=0}^{a-b} \{ \int_{z=0}^{a+b} [f''(n-a+y+z) - f''(m-a+y+z)]dz\}dy . \quad (10)$$

Because $f'''(x)>0$ and because $(n-a+y+z) > (m-a+y+z)$, we have

$$f''(n-a+y+z) > f''(m-a+y+z) \quad (11)$$

Thus, $\Delta > 0$. In other words, in unshaded areas, any pair of A cells with symmetric expression levels relative to the mean expression will have a greater total fitness gain (caused by the mutation) than any pair of B cells. Because the blue and red curves are both symmetric and because the number of cells in the unshaded areas under the blue curve is identical to the corresponding number under the red curve, the mean fitness gain of A cells exceeds that of B cells for those cells in unshaded areas. Because the mean fitness gains of A cells and B cells are identical for cells in the shaded area, the overall mean fitness gain of all A cells exceeds that of all B cells. It can be similarly shown that when $f'''(x)<0$, the mean fitness gain of A cells is smaller than that of B cells. When $f'''(x)=0$, the mean fitness gain of A cells equals that of B cells.

In the above, we assumed $n > m$. If $n < m$, the results will be opposite. That is, the mean fitness gain of A is greater than that of B when $f'''(x)<0$ and is lower than that of B when $f'''(x)>0$.

We can similarly consider deleterious mutations that shift the mean expression level away from the optimum. When the mean expression level of a genotype is lower than the optimal level and the third derivative of $f(x)$ is positive, or when the mean expression level of a genotype is higher than the optimal level and the third derivative of $f(x)$ is negative, a deleterious

mutation that renders the mean expression level further away from the optimal level will result in a bigger fitness loss for the genotype with a higher level of noise (Fig. S3). In other words, under such conditions, negative selection against deleterious mutations that affect the mean expression level will be stronger for noisier genotypes.

Supplementary Note 2

Cellular fitness as a function of the expression level of a plasma-membrane transporter

It is generally accepted that in a certain environment, numerous ions and other compounds should be maintained at certain concentrations in the cell to keep the right osmotic pressure and to accomplish cellular functions. Higher or lower concentrations may lead to reduced cellular fitness. In a simple model, let us assume that the cellular concentration (S) of an ion or compound A determines the fitness (f) of the cell. Let S_o be the optimal concentration of A in the cell that leads to the highest fitness. Let us assume that f is linearly determined by S in the following way (Fig. S6A).

$$f = \begin{cases} \dfrac{S}{S_o} & \text{, when } S < S_o \\ 2 - \dfrac{S}{S_o} & \text{, when } S_o < S < 2S_o \\ 0 & \text{, when } S > 2S_o \end{cases} \qquad (1)$$

In our model, A can be transported out of the cell by a plasma-membrane transporter B, which has a concentration of T. If A_{in} and A_{out} represent A molecules inside and outside the cell, respectively, the chemical reaction of the transportation can be described as follows.

$$A_{in} + B \xrightarrow{k_1} AB \xrightarrow{k_2} A_{out} + B$$

Let us assume that the first step to generate the AB complex is the rate-limiting step. Thus, the speed of transportation of A from inside to outside the cell is k_1ST. Let us assume that A_{in} is also produced inside the cell by a metabolic pathway at a certain rate k_3 that is independent of S. When the concentration of A_{in} is at equilibrium, we have $k_3 = k_1ST$, which gives

$$f = \begin{cases} \dfrac{k_3}{k_1 S_o T} & \text{, when } T > \dfrac{k_3}{k_1 S_o} \\ 2 - \dfrac{k_3}{k_1 S_o T} & \text{, when } \dfrac{k_3}{k_1 S_o} > T > \dfrac{k_3}{2k_1 S_o} \\ 0 & \text{, when } T < \dfrac{k_3}{2k_1 S_o} \end{cases} \quad (2)$$

It can be shown easily that the fitness function has a convex region when T exceeds $k_3/(k_1S_o)$ (Fig. S6B), because the second derivative of f is positive in this region.

To keep the right osmotic pressure and to accomplish cellular functions, S_o may be different under different environments. Consequently, the optimal T may change when the environment changes, rendering the mean expression level of the transporter suboptimal. In our model, if the actual T is higher than the optimal T, higher noise would be beneficial, because the fitness function has a convex region when T is higher than the optimal level. Although our model has a number of simplifying assumptions, it at least shows the feasibility of a convex region in the fitness function. We note that because the energy cost of gene expression is likely a linear function of expression level unless the expression is extremely high, the second derivative of the energy cost is 0. Thus, our results will not change when the energy cost is considered.

Table S1. GO categories with significantly greater-than-expected expression noise in YPD after the control for gene importance by dividing genes into 11 bins.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0006732	coenzyme metabolic process	57	$<5.00\times10^{-5}$	$<7.48\times10^{-3}$
		GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<7.48\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<7.48\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<7.48\times10^{-3}$
		GO0006519	amino acid and derivative metabolic process	104	5.00×10^{-4}	7.48×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	7.00×10^{-4}	7.48×10^{-3}
		GO0006811	ion transport	45	4.50×10^{-4}	7.48×10^{-3}
		GO0006812	cation transport	37	5.00×10^{-4}	7.48×10^{-3}
		GO0009056	catabolic process	173	6.00×10^{-4}	7.48×10^{-3}
		GO0009060	aerobic respiration	32	6.00×10^{-4}	7.48×10^{-3}
		GO0009117	nucleotide metabolic process	56	7.00×10^{-4}	7.48×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	6.50×10^{-4}	7.48×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	7.00×10^{-4}	7.48×10^{-3}
		GO0044248	cellular catabolic process	168	7.00×10^{-4}	7.48×10^{-3}
		GO0006520	amino acid metabolic process	99	1.10×10^{-3}	1.12×10^{-2}
		GO0016310	phosphorylation	59	3.55×10^{-3}	3.43×10^{-2}
		GO0008152	metabolic process	1227	3.80×10^{-3}	3.51×10^{-2}
		GO0044271	nitrogen compound biosynthetic process	66	5.65×10^{-3}	4.99×10^{-2}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	5.00×10^{-5}	4.21×10^{-4}
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<2.63\times10^{-3}$
		GO0005215	transporter activity	159	$<5.00\times10^{-5}$	$<2.63\times10^{-3}$
		GO0015077	monovalent inorganic cation transporter activity	33	2.00×10^{-4}	2.63×10^{-3}
		GO0015078	hydrogen ion transporter activity	32	2.50×10^{-4}	2.63×10^{-3}
		GO0015075	ion transporter activity	68	1.25×10^{-3}	1.05×10^{-2}
		GO0008324	cation transporter activity	61	2.10×10^{-3}	1.47×10^{-2}
		GO0016829	lyase activity	35	6.05×10^{-3}	3.63×10^{-2}
After excluding mitochondrial proteins and enzymes	CC	GO0005886	plasma membrane	56	1.00×10^{-4}	3.80×10^{-3}
	MF	GO0005215	transporter activity	73	7.50×10^{-4}	6.00×10^{-3}

P-values were calculated by the randomization test described in the main text. When none of the 20,000 random samples show greater mean noise than the observed mean noise of a GO category, we consider <1 random sample to have a greater noise than the observed.
BP, biological process; CC, cellular component; MF, molecular function.

Table S2. GO categories with significantly greater-than-expected expression noise in YPD after the control for gene importance by dividing genes into 26 bins.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0006732	coenzyme metabolic process	57	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0006811	ion transport	45	1.00×10^{-4}	2.54×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	2.00×10^{-4}	4.06×10^{-3}
		GO0006812	cation transport	37	3.00×10^{-4}	5.08×10^{-3}
		GO0009056	catabolic process	173	5.50×10^{-4}	6.98×10^{-3}
		GO0009060	aerobic respiration	32	5.00×10^{-4}	6.98×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	5.00×10^{-4}	6.98×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	5.50×10^{-4}	6.98×10^{-3}
		GO0006520	amino acid metabolic process	99	6.00×10^{-4}	7.16×10^{-3}
		GO0006519	amino acid and derivative metabolic process	104	9.00×10^{-4}	9.14×10^{-3}
		GO0009117	nucleotide metabolic process	56	9.00×10^{-4}	9.14×10^{-3}
		GO0044248	cellular catabolic process	168	8.50×10^{-4}	9.14×10^{-3}
		GO0016310	phosphorylation	59	2.15×10^{-3}	2.08×10^{-2}
		GO0008152	metabolic process	1227	2.60×10^{-3}	2.40×10^{-2}
		GO0044237	cellular metabolic process	1197	4.45×10^{-3}	3.93×10^{-2}
		GO0006796	phosphate metabolic process	78	5.75×10^{-3}	4.49×10^{-2}
		GO0044249	cellular biosynthetic process	402	5.35×10^{-3}	4.49×10^{-2}
		GO0044271	nitrogen compound biosynthetic process	66	5.70×10^{-3}	4.49×10^{-2}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	5.00×10^{-5}	4.21×10^{-4}
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<5.25\times10^{-4}$
		GO0005215	transporter activity	159	$<5.00\times10^{-5}$	$<5.25\times10^{-4}$
		GO0015078	hydrogen ion transporter activity	32	$<5.00\times10^{-5}$	$<5.25\times10^{-4}$
		GO0015077	monovalent inorganic cation transporter activity	33	5.00×10^{-5}	5.25×10^{-4}
		GO0015075	ion transporter activity	68	4.00×10^{-4}	3.36×10^{-3}
		GO0008324	cation transporter activity	61	8.00×10^{-4}	5.60×10^{-3}
		GO0016829	lyase activity	35	6.00×10^{-3}	3.60×10^{-2}
After excluding mitochondrial proteins and enzymes	CC	GO0005886	plasma membrane	56	1.00×10^{-4}	3.80×10^{-3}
	MF	GO0005215	transporter activity	73	9.00×10^{-4}	7.20×10^{-3}

P-values were calculated by the randomization test described in the main text. When none of the 20,000 random samples show greater mean noise than the observed mean noise of a GO category, we consider <1 random sample to have a greater noise than the observed.
BP, biological process; CC, cellular component; MF, molecular function.

Table S3. GO categories with significantly greater-than-expected expression noise in minimal media after the control for gene importance by dividing genes into 21 bins.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<1.27\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<1.27\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<1.27\times10^{-3}$
		GO0006732	coenzyme metabolic process	57	5.00×10^{-5}	1.27×10^{-3}
		GO0006812	cation transport	37	1.00×10^{-4}	2.26×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	2.50×10^{-4}	4.61×10^{-3}
		GO0006811	ion transport	45	2.50×10^{-4}	4.61×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	3.50×10^{-4}	5.92×10^{-3}
		GO0009117	nucleotide metabolic process	56	4.50×10^{-4}	6.53×10^{-3}
		GO0009056	catabolic process	173	5.50×10^{-4}	7.16×10^{-3}
		GO0009060	aerobic respiration	32	6.00×10^{-4}	7.16×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	6.00×10^{-4}	7.16×10^{-3}
		GO0006519	amino acid and derivative metabolic process	104	6.50×10^{-4}	7.33×10^{-3}
		GO0006520	amino acid metabolic process	99	7.50×10^{-4}	8.01×10^{-3}
		GO0044248	cellular catabolic process	168	9.50×10^{-4}	9.64×10^{-3}
		GO0008152	metabolic process	1227	2.40×10^{-3}	2.31×10^{-2}
		GO0016310	phosphorylation	59	2.50×10^{-3}	2.31×10^{-2}
		GO0044237	cellular metabolic process	1197	4.50×10^{-3}	3.97×10^{-2}
		GO0044271	nitrogen compound biosynthetic process	66	4.75×10^{-3}	4.02×10^{-2}
		GO0044249	cellular biosynthetic process	402	5.85×10^{-3}	4.75×10^{-2}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	5.00×10^{-5}	4.21×10^{-4}
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0005215	transporter activity	159	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0015077	monovalent inorganic cation transporter activity	33	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0015078	hydrogen ion transporter activity	32	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0015075	ion transporter activity	68	2.50×10^{-4}	2.10×10^{-3}
		GO0008324	cation transporter activity	61	9.50×10^{-4}	6.65×10^{-3}
		GO0016829	lyase activity	35	6.15×10^{-3}	3.69×10^{-2}
After excluding mitochondrial proteins and enzymes	CC	GO0005886	plasma membrane	56	1.00×10^{-4}	3.80×10^{-3}
	MF	GO0005215	transporter activity	73	5.00×10^{-4}	4.00×10^{-3}

P-values were calculated by the randomization test described in the main text. When none of the 20,000 random samples show greater mean noise than the observed mean noise of a GO category, we consider <1 random sample to have a greater noise than the observed.
BP, biological process; CC, cellular component; MF, molecular function.

Table S4. GO categories with significantly greater-than-expected expression noise in minimal media after the control for gene importance by dividing genes into 11 bins.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0006732	coenzyme metabolic process	57	5.00×10^{-5}	1.45×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	3.50×10^{-4}	7.11×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	3.50×10^{-4}	7.11×10^{-3}
		GO0006519	amino acid and derivative metabolic process	104	7.00×10^{-4}	8.36×10^{-3}
		GO0006811	ion transport	45	6.00×10^{-4}	8.36×10^{-3}
		GO0006812	cation transport	37	7.00×10^{-4}	8.36×10^{-3}
		GO0009056	catabolic process	173	7.00×10^{-4}	8.36×10^{-3}
		GO0009060	aerobic respiration	32	6.00×10^{-4}	8.36×10^{-3}
		GO0009117	nucleotide metabolic process	56	6.00×10^{-4}	8.36×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	8.00×10^{-4}	8.55×10^{-3}
		GO0044248	cellular catabolic process	168	8.00×10^{-4}	8.55×10^{-3}
		GO0006520	amino acid metabolic process	99	9.50×10^{-4}	9.64×10^{-3}
		GO0008152	metabolic process	1227	2.75×10^{-3}	2.66×10^{-2}
		GO0016310	phosphorylation	59	3.10×10^{-3}	2.86×10^{-2}
		GO0044237	cellular metabolic process	1197	5.40×10^{-3}	4.77×10^{-2}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0005215	transporter activity	159	$<5.00\times10^{-5}$	$<2.10\times10^{-3}$
		GO0015077	monovalent inorganic cation transporter activity	33	1.50×10^{-4}	2.10×10^{-3}
		GO0015078	hydrogen ion transporter activity	32	3.00×10^{-4}	3.15×10^{-3}
		GO0015075	ion transporter activity	68	1.00×10^{-3}	8.40×10^{-3}
		GO0008324	cation transporter activity	61	1.80×10^{-3}	1.26×10^{-2}
		GO0016829	lyase activity	35	6.10×10^{-3}	3.66×10^{-2}
After excluding mitochondrial proteins and enzymes	CC	GO0005886	plasma membrane	56	1.50×10^{-4}	5.70×10^{-3}
	MF	GO0005215	transporter activity	73	7.00×10^{-4}	5.60×10^{-3}

P-values were calculated by the randomization test described in the main text. When none of the 20,000 random samples show greater mean noise than the observed mean noise of a GO category, we consider <1 random sample to have a greater noise than the observed.
BP, biological process; CC, cellular component; MF, molecular function.

Table S5. GO categories with significantly greater-than-expected expression noise in minimal media after the control for gene importance by dividing genes into 26 bins.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<1.45\times10^{-3}$
		GO0006732	coenzyme metabolic process	57	5.00×10^{-5}	1.45×10^{-3}
		GO0006811	ion transport	45	1.00×10^{-4}	2.54×10^{-3}
		GO0009060	aerobic respiration	32	2.00×10^{-4}	3.69×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	3.00×10^{-4}	5.08×10^{-3}
		GO0006812	cation transport	37	4.00×10^{-4}	6.09×10^{-3}
		GO0009117	nucleotide metabolic process	56	4.50×10^{-4}	6.09×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	4.50×10^{-4}	6.09×10^{-3}
		GO0006519	amino acid and derivative metabolic process	104	6.50×10^{-4}	7.48×10^{-3}
		GO0006520	amino acid metabolic process	99	7.00×10^{-4}	7.48×10^{-3}
		GO0009056	catabolic process	173	6.00×10^{-4}	7.48×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	7.00×10^{-4}	7.48×10^{-3}
		GO0044248	cellular catabolic process	168	1.05×10^{-3}	1.07×10^{-2}
		GO0016310	phosphorylation	59	2.10×10^{-3}	2.03×10^{-2}
		GO0008152	metabolic process	1227	2.25×10^{-3}	2.08×10^{-2}
		GO0044237	cellular metabolic process	1197	3.85×10^{-3}	3.40×10^{-2}
		GO0044271	nitrogen compound biosynthetic process	66	4.35×10^{-3}	3.68×10^{-2}
		GO0044249	cellular biosynthetic process	402	6.05×10^{-3}	4.91×10^{-2}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<1.40\times10^{-3}$
		GO0005215	transporter activity	159	$<5.00\times10^{-5}$	$<1.40\times10^{-3}$
		GO0015077	monovalent inorganic cation transporter activity	33	1.00×10^{-4}	1.40×10^{-3}
		GO0015078	hydrogen ion transporter activity	32	1.50×10^{-4}	1.58×10^{-3}
		GO0008324	cation transporter activity	61	6.50×10^{-4}	4.55×10^{-3}
		GO0015075	ion transporter activity	68	5.50×10^{-4}	4.55×10^{-3}
		GO0016829	lyase activity	35	4.75×10^{-3}	2.85×10^{-2}
After excluding mitochondrial proteins and enzymes	CC	GO0005886	plasma membrane	56	1.00×10^{-4}	3.80×10^{-3}
	MF	GO0005215	transporter activity	73	6.00×10^{-4}	4.80×10^{-3}

P-values were calculated by the randomization test described in the main text. When none of the 20,000 random samples show greater mean noise than the observed mean noise of a GO category, we consider <1 random sample to have a greater noise than the observed.
BP, biological process; CC, cellular component; MF, molecular function.

Table S6. GO categories with significantly greater-than-expected expression noise in YPD after the control for gene importance by dividing genes into 21 bins. All GO categories with significant *P*-values (before controlling for multiple testing) are listed.

		GO ID	GO term	# of genes	*P*-value	*Q*-value
All genes	BP	GO0006732	coenzyme metabolic process	57	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0015980	energy derivation by oxidation of organic compounds	112	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0044262	cellular carbohydrate metabolic process	81	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0051186	cofactor metabolic process	71	$<5.00\times10^{-5}$	$<2.54\times10^{-3}$
		GO0006811	ion transport	45	1.00×10^{-4}	2.54×10^{-3}
		GO0006807	nitrogen compound metabolic process	116	3.00×10^{-4}	5.08×10^{-3}
		GO0006812	cation transport	37	3.00×10^{-4}	5.08×10^{-3}
		GO0032787	monocarboxylic acid metabolic process	48	3.50×10^{-4}	5.47×10^{-3}
		GO0006519	amino acid and derivative metabolic process	104	4.00×10^{-4}	5.80×10^{-3}
		GO0009060	aerobic respiration	32	5.00×10^{-4}	6.77×10^{-3}
		GO0009117	nucleotide metabolic process	56	5.50×10^{-4}	6.98×10^{-3}
		GO0006520	amino acid metabolic process	99	6.50×10^{-4}	7.76×10^{-3}
		GO0009056	catabolic process	173	7.50×10^{-4}	8.46×10^{-3}
		GO0016051	carbohydrate biosynthetic process	32	8.00×10^{-4}	8.55×10^{-3}
		GO0044248	cellular catabolic process	168	8.50×10^{-4}	8.63×10^{-3}
		GO0016310	phosphorylation	59	2.15×10^{-3}	2.08×10^{-2}
		GO0008152	metabolic process	1227	2.55×10^{-3}	2.35×10^{-2}
		GO0044249	cellular biosynthetic process	402	4.30×10^{-3}	3.80×10^{-2}
		GO0044237	cellular metabolic process	1197	4.60×10^{-3}	3.82×10^{-2}
		GO0044271	nitrogen compound biosynthetic process	66	4.70×10^{-3}	3.82×10^{-2}
		GO0008652	amino acid biosynthetic process	63	7.45×10^{-3}	5.82×10^{-2}
		GO0006793	phosphorus metabolic process	78	8.20×10^{-3}	6.16×10^{-2}
		GO0006796	phosphate metabolic process	78	8.50×10^{-3}	6.16×10^{-2}
		GO0006950	response to stress	171	1.17×10^{-2}	8.16×10^{-2}
		GO0017038	protein import	50	1.40×10^{-2}	9.47×10^{-2}
		GO0009058	biosynthetic process	445	1.85×10^{-2}	1.21×10^{-1}
		GO0050896	response to stimulus	259	3.35×10^{-2}	2.12×10^{-1}
	CC	GO0005739	mitochondrion	388	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005740	mitochondrial envelope	100	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005743	mitochondrial inner membrane	49	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005759	mitochondrial matrix	92	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0009277	chitin- and beta-glucan-containing cell wall	36	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0019866	organelle inner membrane	52	$<5.00\times10^{-5}$	$<4.21\times10^{-4}$
		GO0005618	cell wall	36	5.00×10^{-5}	4.21×10^{-4}
	MF	GO0003824	catalytic activity	794	$<5.00\times10^{-5}$	$<1.05\times10^{-3}$
		GO0015077	monovalent inorganic cation transporter activity	33	$<5.00\times10^{-5}$	$<1.05\times10^{-3}$
		GO0015078	hydrogen ion transporter activity	32	$<5.00\times10^{-5}$	$<1.05\times10^{-3}$
		GO0005215	transporter activity	159	1.00×10^{-4}	1.05×10^{-3}
		GO0015075	ion transporter activity	68	5.50×10^{-4}	4.62×10^{-3}
		GO0008324	cation transporter activity	61	7.50×10^{-4}	5.25×10^{-3}
		GO0016829	lyase activity	35	6.00×10^{-3}	3.60×10^{-2}

Supplementary figure legends

Fig. S1. A diagram to help understand the mathematical proof that a high-noise genotype has higher fitness than a low-noise genotype when the fitness function $f(x)$ (shown in green) is convex. The frequency distributions of the cells of the high-noise genotype and the cells of the low-noise genotype are shown by the blue and red curves, respectively. The shaded area is the overlap between the two distributions. The mean expression levels of the two genotypes are both equal to m. Two cells with the high-noise genotype (blue dots) and two cells with the low-noise genotype (red dots) are highlighted for comparison.

Fig. S2. Heat map showing the absolute fitness difference between the high-noise genotype and the low-noise genotype. As in the numerical example given in the main text, we assumed the fitness function to be $f(x) = e^{-(x-\mu)^2/(2\sigma^2)}$ and used $\mu = 6.2$. We further assumed that the expression noise in genotypes A and B follows $N(0, \sigma_1)$, and $N(0, 0.7)$, respectively, and that the mean expression levels of the two genotypes are both $m = 3$. The fitness map shows the fitness difference between the two genotypes when σ and σ_1 vary. It is clear that in a large space the fitness difference is higher than 10^{-7}, the inverse of the effective population size of yeast. It is also clear that even for genes with a tiny fitness effect upon deletion (e.g., <1%), a large parameter space allows the fitness difference between the two genotypes to be greater than 10^{-7}. The black star represents the numerical example in the main text.

Fig. S3. A diagram to help understand the mathematical proof that a high-noise genotype acquires a greater fitness gain than a low-noise genotype when the same advantageous mutation occurs, under certain conditions. The green curve shows $f(x)$, the fitness of the cell with the

expression level of gene X equal to *x*. The solid blue and red curves show the frequency distributions of the expression levels (*x*) of the high-noise and low-noise genotypes, respectively, and the grey shaded area shows the overlap between the two distributions. The dotted blue and red curves show the frequency distributions of the expression levels (*x*) of the high-noise and low-noise genotypes with the advantageous mutation that right-shifts the mean expression level, and the brown shaded area shows the overlap between the two distributions. The mean expression levels of the two genotypes are both equal to *m* before the occurrence of the mutation and are both equal to *n* after the mutation. Four cells (blue dots) with the high-noise genotype (before and after mutation) and four cells (red dots) with the low-noise genotype (before and after the mutation) are highlighted for comparison.

Fig. S4. Heat map showing the difference in fitness gain between the high-noise genotype and low-noise genotype when the same amount of mean expression change occurs toward the optimal expression level. As in the numerical example given in the main text, we used the fitness function of $f(x) = e^{-(x-\mu)^2/(2\sigma^2)}$, where $\mu = 11$. The expression noise in genotypes A and B follows $N(0, \sigma_1)$ and $N(0, 0.7)$, respectively, and the mean expression levels of the two genotypes are both $m = 3.0$. The advantageous mutation shifts the mean expression of both genotypes to $n = 7.1$. The heat map shows the variation in the difference in fitness gain when σ and σ_1 vary. It is clear that in a large space the difference is substantially greater than 0. The black star represents the numerical example in the main text.

Fig. S5. Heat map showing the parameter space in which the high-noise genotype adapts significantly faster than the low-noise genotype to the optimal expression level. The X-axis

shows the expression noise ratio between the high- and low-noise genotypes (σ_1/σ_2). The Y-axis shows $\log_{10}$(mutation rate). Colors show $\log_{10}P$, where P is the P-value in the t-test of the null hypothesis that the mean time required for adaptation is the same for the two genotypes, against the alternative hypothesis that the time is shorter for the high-noise genotype. It can be seen that for a broad parameter space the adaptation is significantly faster for the high-noise genotype. The black star represents the parameters used in generating Fig. 4.

Fig. S6. Cellular fitness varies when the expression level of a plasma-membrane transporter changes. (A) Fitness as a function of the concentration (S) of molecule A inside the cell. S_o is the optimal concentration of A. (B) Fitness as a function of the expression level (T) of the plasma-membrane transporter B. The parameter $k_3/(k_1S_o)$ is set at 1 in this figure. When T is larger than 1, the fitness function is convex.

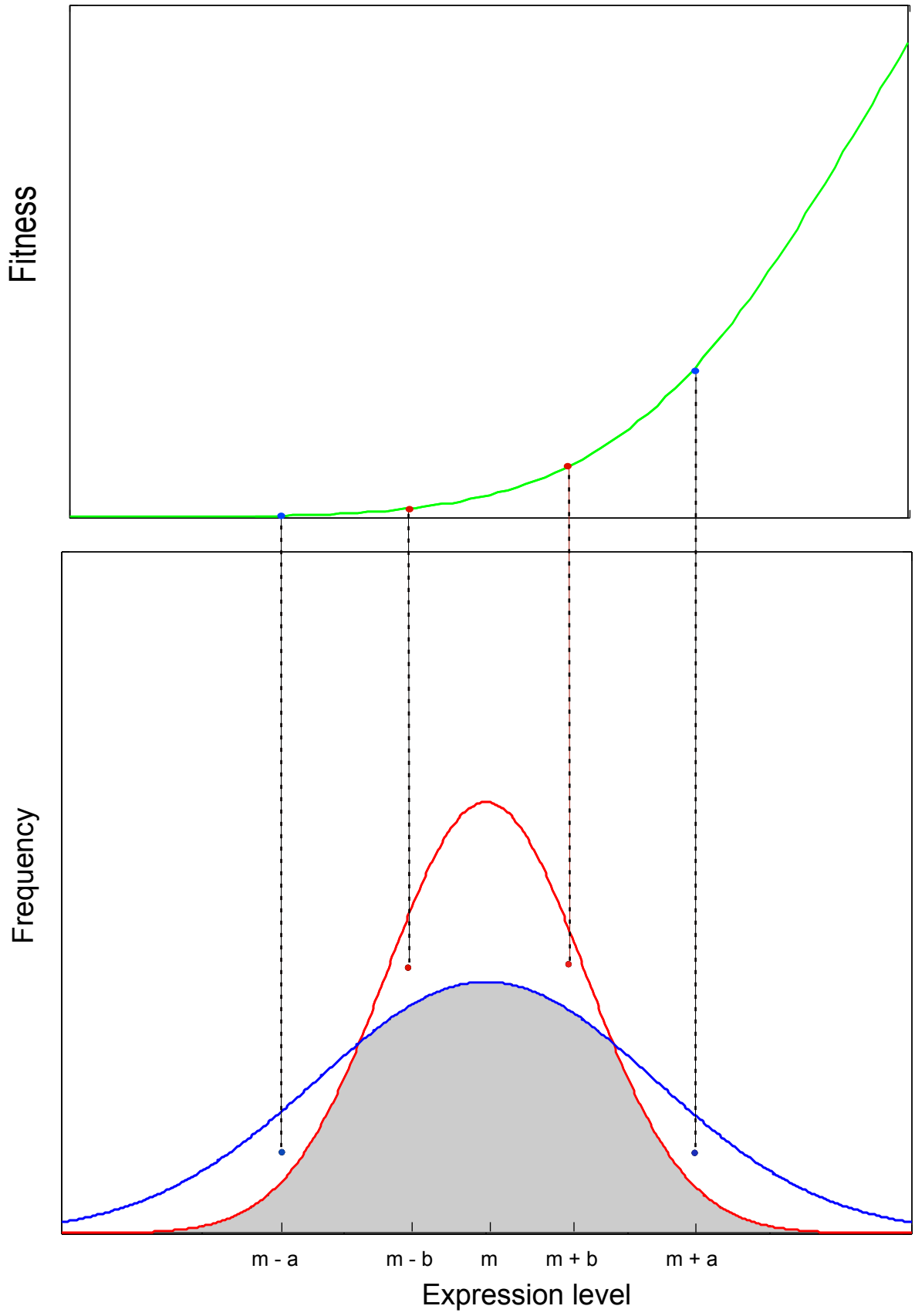


Figure S1

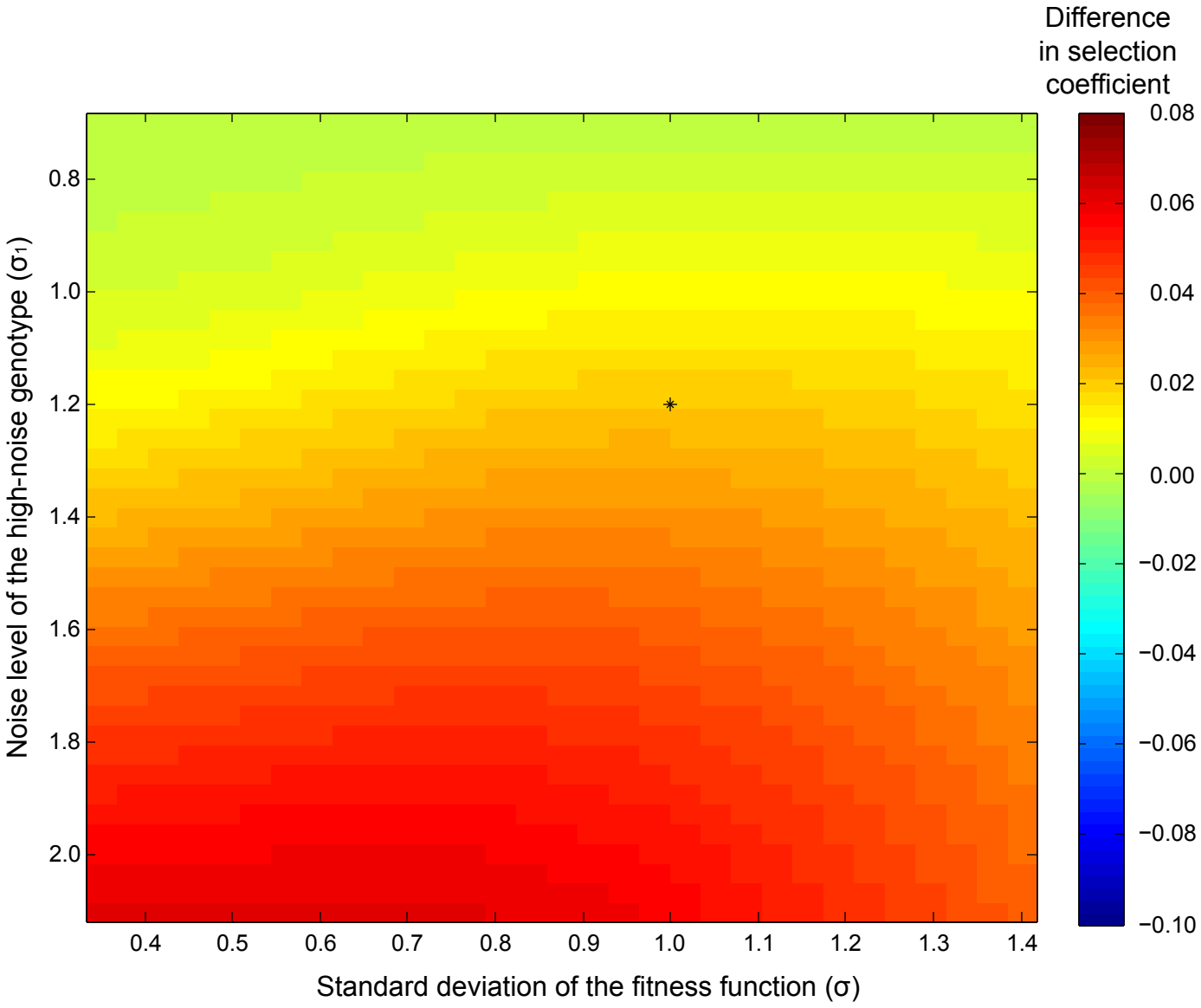

Difference
in selection
coefficient
0.08
0.06
0.04
0.02
0.00
−0.02
−0.04
−0.06
−0.08
−0.10
Noise level of the high-noise genotype (σ1)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0.4
0.5
0.6
0.7
0.8
0.9
1.0
1.1
1.2
1.3
1.4
Standard deviation of the fitness function (σ)

Figure S2

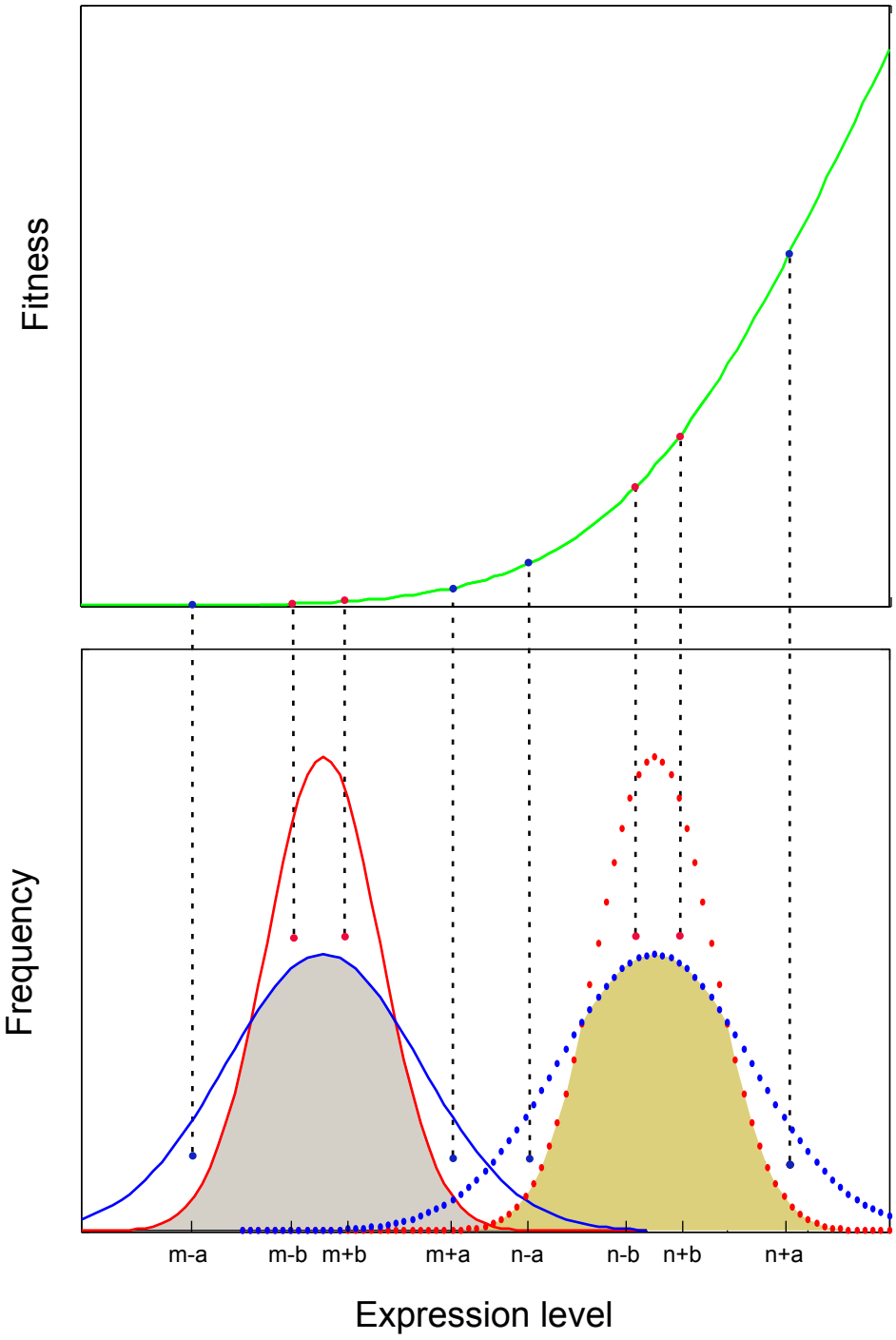
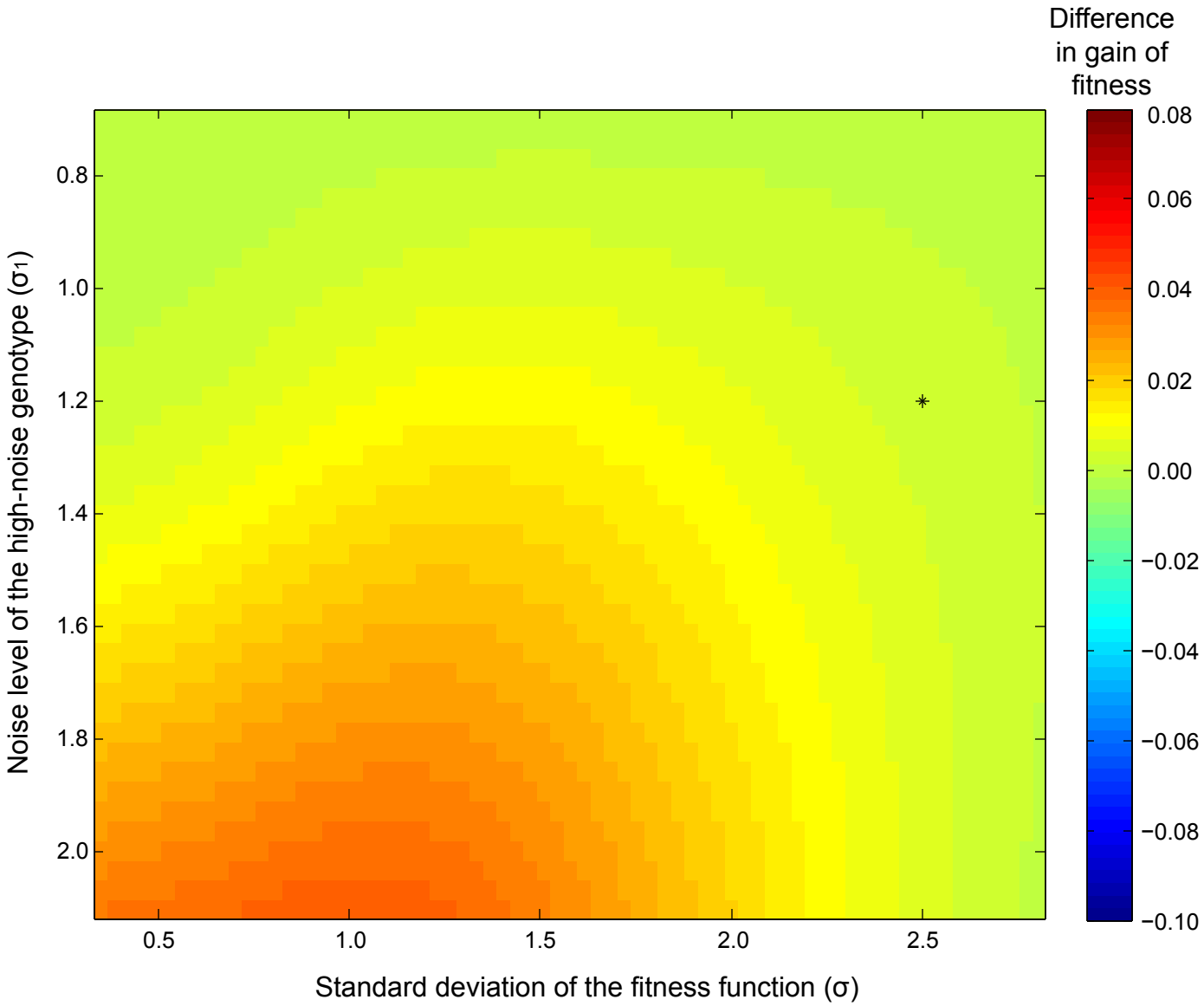


Figure S3


Difference in gain of fitness
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0.06
0.04
0.02
0.00
−0.02
−0.04
−0.06
−0.08
−0.10
Noise level of the high-noise genotype (σ1)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
0.5
1.0
1.5
2.0
2.5
Standard deviation of the fitness function (σ)

Figure S4

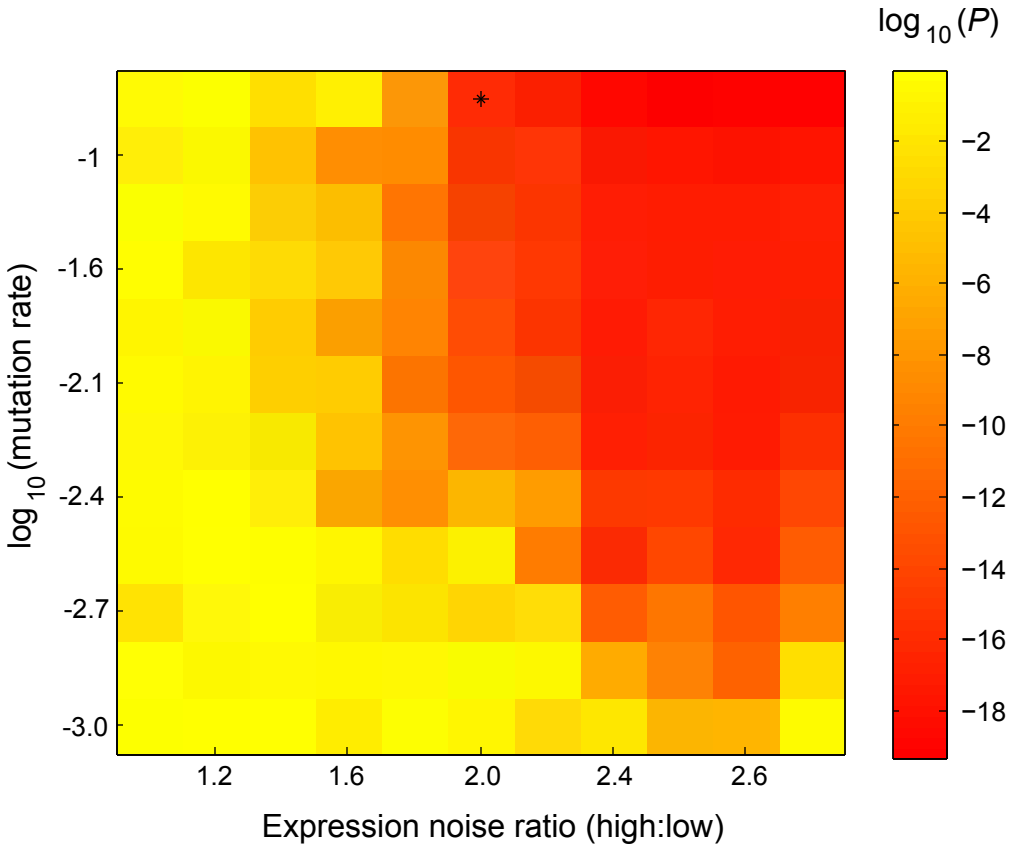
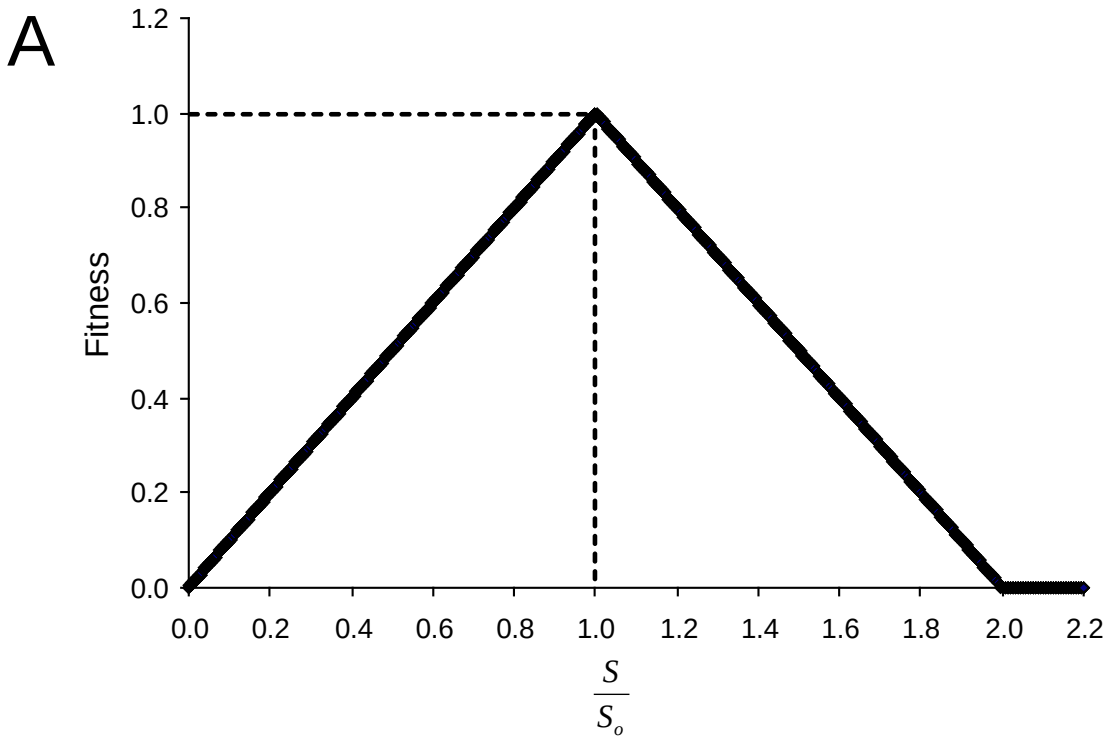

log 10 (P)
-1
-1.6
-2.1
-2.4
-2.7
-3.0
log 10 (mutation rate)
1.2
1.6
2.0
2.4
2.6
Expression noise ratio (high:low)
−2
−4
−6
−8
−10
−12
−14
−16
−18

Figure S5


A
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Fitness
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
$\frac{S}{S_o}$

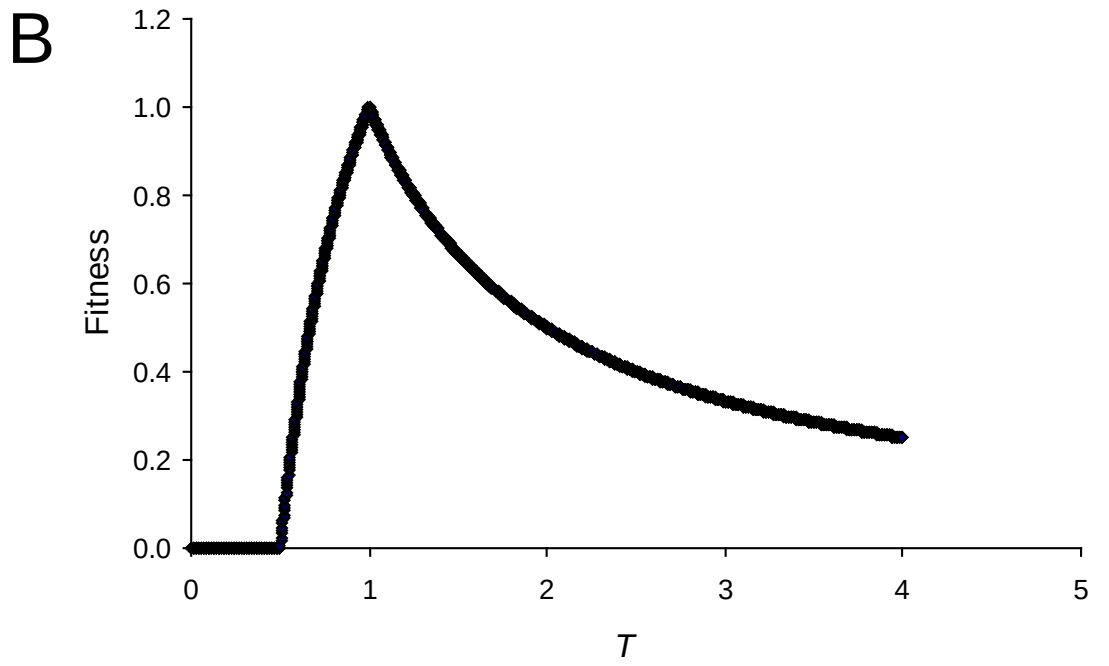

B
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Fitness
0
1
2
3
4
5
T

Figure S6