Supporting material

Derivation of the fluctuation-response relationship (based on Sato et al. PNAS 2003 100:14086-14090).

We refer to a measurable phenotype quantity (e.g. the concentration of a protein) as a "variable" x of the system, while we assume the existence of a "parameter" a which controls the change of the variable. In the case of environmental responsiveness, this parameter is a quantity to specify the environmental condition, while in the case of evolution the parameter is an index of genotype that governs the corresponding phenotype variable.

Even among individuals sharing the identical condition or genotype (the parameter a), the variable x is distributed. The distribution $P(x;a)$ of the variable x over cells is defined for a given parameter a (e.g., genotype). Here the "average" and "variance" of x are defined with regards to the distribution $P(x;a)$ where $<x>_a$ and $<(\delta x)^2>=<(x-<x>)^2>$ are the average and variance of the variable x for a given parameter value a, respectively, with regards to this distribution, such that $<x>_a=\int xP(x;a)dx$.

Consider the change in the parameter value $a \rightarrow a+\Delta a$. Then, the proposed fluctuation-response relationship is derived by assuming that the distribution $P(x;a)$ is approximately Gaussian (i.e. normal or bell-shaped) and that the change in a is not so large. Considering the distribution around its peak value X_0 at $a = a_0$, it is written as

$$P(x;a) = N_0 exp(-\frac{(x - X_0)^2}{2\alpha(a)} + v(x,a)). \quad (2)$$

with N_0 a normalization constant so that $\int P(x:a)dx = 1$.

Here the term $v(x,a)$ gives a deviation from the distribution at $a = a_0$, so that $v(x,a)$ can be expanded as $v(x,a) = C(a - a_0)(x - X_0) + ...$, with C as a constant, where ... is a higher order term in $(a - a_0)$ and $(x - X_0)$. By neglecting these higher order terms, and neglecting the deviation between $\alpha(a_0 + \Delta a)$ and $\alpha(a_0) =< (\delta x)^2 >$, we obtain [12,32]:

$$\frac{< x >_{a=a_0+\Delta a} - < x >_{a=a_0}}{\Delta a} = C < (\delta x)^2 > . \quad (3)$$

This relationship is a general result that holds for Gaussian-like distributions and if changes in parameters are represented by a “linear coupling term", which brings about a shift of the average of the corresponding variable.

Although this formula is formally akin to that used in statistical physics [10], ours is approximate. It holds for (nearly) Gaussian distributions, and provided a change in parameter is not so large such that higher order terms other than $C(a - a_0)(x - x_0) + ...$ can be neglected. In reality many distributions in biology are close to a Gaussian distribution, or a log-normal distribution in which case *log(x)* is taken as the variable.