

Appendix 1: Exact distribution of mutation fitness effects and displaced gamma approximation

The distribution of the log-relative fitness among random mutants in the general version of the FM can be expressed as (MARTIN and LENORMAND 2006)

$$s = \log \left(\frac{W(\mathbf{z}_0 + \mathbf{dz})}{W(\mathbf{z}_0)} \right) = -\mathbf{z}_0^T \cdot \mathbf{S} \cdot \mathbf{dz} - \frac{1}{2} \mathbf{dz}^T \cdot \mathbf{S} \cdot \mathbf{dz}, \quad (\text{A.1.1})$$

where \mathbf{dz} (the mutational effects on phenotypic traits) is distributed as a multivariate normal $\mathbf{dz} \sim N(\mathbf{0}, \mathbf{M})$. This is a quadratic form in Gaussian vectors; it can always, without loss of generality, be expressed in diagonal form (JASCHKE *et al.* 2004), i.e. in a new basis where the new phenotypic vectors (\mathbf{x}) are linear combinations of the original phenotypic vectors (\mathbf{z}).

$$s = \log \left(\frac{W(\mathbf{x}_0 + \mathbf{dx})}{W(\mathbf{x}_0)} \right) = \boldsymbol{\delta}^T \cdot \mathbf{dx} + \frac{1}{2} \mathbf{dx}^T \cdot \boldsymbol{\Lambda} \cdot \mathbf{dx}, \quad (\text{A.1.2})$$

where $\boldsymbol{\Lambda} = \text{diag}(\lambda_1, \dots, \lambda_n)$ is an $n \times n$ diagonal matrix where the $\lambda_i \leq 0$ are the n eigenvalues of $-\mathbf{S} \cdot \mathbf{M}$, \mathbf{dx} is distributed as a standard multivariate Gaussian: $\mathbf{dx} \sim N(\mathbf{0}, \mathbf{I}_n)$, and $\boldsymbol{\delta}^T = \mathbf{x}_0^T \cdot \boldsymbol{\Lambda} = \{\delta_1, \dots, \delta_n\}$. $\mathbf{x}_0 = \{x_1, \dots, x_n\}$ is simply \mathbf{z}_0 expressed in the new basis. It is important to note that the expression in (A.1.2) is a particular type of quadratic form as $\boldsymbol{\delta} = \boldsymbol{\Lambda} \cdot \mathbf{x}_0$, it has a zero element wherever there is a zero eigenvalue in matrix $\boldsymbol{\Lambda}$. This implies that the dimension of the whole system is not n , but the number $m \leq n$ of non-zero eigenvalues λ_i (i.e. the rank of $\boldsymbol{\Lambda}$). As a consequence, we can always express (A.1.2) in a positive-definite form by focusing only on these m dimensions by setting $\boldsymbol{\Lambda} = \text{diag}(\lambda_1, \dots, \lambda_m)$ where all $\lambda_i < 0$ and $\boldsymbol{\delta}^T = \mathbf{x}_0^T \cdot \boldsymbol{\Lambda} = \{\delta_1, \dots, \delta_m\}$ where, by identification, $\delta_i = \lambda_i x_i$. This argument guarantees that we can apply JASCHKE *et al.*'s (2004) proposition 3.3, which is valid for positive definite $\boldsymbol{\Lambda}$, even when \mathbf{S} and \mathbf{M} are not positive-definite but only semi-definite. The distribution of s defined in (A.1.2) is bounded on its rightmost end by $s_0 = -\log(W(\mathbf{0})/W(\mathbf{x}_0)) = -\frac{1}{2} \mathbf{x}_0 \cdot \boldsymbol{\Lambda} \cdot \mathbf{x}_0 \geq 0$, which is the selection coefficient of the optimum phenotype ($\mathbf{x} = \mathbf{0}$) relative to the wild type ($\mathbf{x} = \mathbf{x}_0$). For consistency with JASCHKE *et al.*'s (2004) notation, note that s_0 can also be expressed as $s_0 = -\frac{1}{2} \mathbf{x}_0 \cdot \boldsymbol{\Lambda} \cdot \mathbf{x}_0 = -\sum_{i=1}^m \lambda_i x_i^2 / 2$, or equivalently as $s_0 = -\sum_{i=1}^m \delta_i^2 / (2\lambda_i)$.

Displaced gamma approximation: The distribution of s on its whole range $[-\infty, s_0]$ can be approximated by a displaced gamma distribution which has been introduced by SHAW *et al.* (SHAW *et al.* 2002) for the analysis of mutation fitness effects distributions with beneficial mutations. The resulting approximate pdf of s is given by

$$f_{\Gamma}(s) = \frac{e^{-\frac{s-s_0}{\alpha}} (s-s_0)^{\beta-1} \alpha^{-\beta}}{\Gamma(\beta)}, \quad (\text{A.1.3})$$

where $\Gamma(\cdot)$ is the gamma function, the shape β , and scale α are chosen to fit the mean and variance of $f(s)$ and the displacement parameter is s_0 , the maximum s (MARTIN and LENORMAND 2006). When the wild – type is at any fitness distance s_0 from the optimum, these parameters are approximately (from eq. (6) of MARTIN and LENORMAND 2006)

$$\beta \approx \beta_0 \frac{(1+\varepsilon)^2}{(1+2\varepsilon)} \quad \text{and} \quad \alpha \approx \alpha_0 \frac{(1+2\varepsilon)}{(1+\varepsilon)}, \quad (\text{A.1.4})$$

Where β_0 and α_0 are the shape and scale (respectively) of the gamma distribution that fits $f(s)$ at the optimum (i.e. when there are only deleterious mutations), and where $\varepsilon = s_0/\bar{s}$ is the distance to the optimum of the wild – type (s_0), measured in terms of fitness and scaled by the average fitness effect of mutation $\bar{s} \equiv -E(s)$. The variable ε describes the degree of adaptation of the wild-type (s_0) relative to the average fitness effect of single mutations (\bar{s}). Note that the expressions for α and β in (A.1.4) are only approximate, based on an approximation for the moments of $f(s)$ as a function of s_0 , eq. A4 of (MARTIN and LENORMAND 2006), but the displaced gamma remains a good approximation of $f(s)$, even when the best fitting parameters are not exactly those given in (A.1.4) (see **Supplementary Figure 1**).

References:

- JASCHKE, S., C. KLUPPELBERG and A. LINDNER, 2004 Asymptotic behavior of tails and quantiles of quadratic forms of Gaussian vectors. *Journal of Multivariate Analysis* 88: 252-273.
- MARTIN, G., and T. LENORMAND, 2006 A general multivariate extension of Fisher's geometrical model and the distribution of mutation fitness effects across species. *Evolution* 60: 893-907.
- SHAW, F. H., C. J. GEYER and R. G. SHAW, 2002 A comprehensive model of mutations affecting fitness and inferences for *Arabidopsis thaliana*. *Evolution* 56: 453-463.