File S1

Stability and response of polygenic traits to stabilizing selection and mutation. Supplementary Information 1

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1 Stability analyses

Our goal is to derive criteria for the equilibria. First, we will calculate the eigenvalues for a polygenic system without mutation. Then by perturbation analyses we will consider small mutation rates,

Stability in the absence of mutation.

In the absence of mutation (μ=0) there are three equilibrium points given by a simpler version of Eq. 6 of the main text, namely:

$$0 = -S\gamma_i p_i(1-p_i)[2\Delta z + \gamma_i(1-2p_i)] \ . \tag{1}$$

The solutions are the two fixed states, and the point where the gradient of mean fitness vanishes, which occurs at

$$p_i = \frac{1}{2} + \frac{\Delta z}{\gamma_i} \ . \tag{2}$$

Since Δz couples all the alleles, the stability of any given point is determined by the whole genetic background which determines the value of Δz. The stability of each equilibrium is determined by the Jacobian matrix, $\mathbb{J} = \{\partial \dot{p}_i/\partial p_j\}_{i,j=1}^{n}$, where the elements are shown in Table 1. It follows that if alleles are fixed at all loci, $\mathbb{J}$ is diagonal with eigenvalues

$$\lambda_i = -S\gamma_i\left(\gamma_i \pm 2\Delta z\right) \ , \tag{3}$$

where the signs depend on whether the locus i has the allele '-' or '+', respectively. Hence, if the trait matches the optimum ($\Delta z = 0$) all fixed states

Table 1: Elements of the Jacobian matrix for a polygenic trait under stabilizing selection and no mutation.

p_i	0	$\frac{1}{2} + \frac{\Delta z}{\gamma_i}$	1
$\frac{\partial \dot{p}_i}{\partial p_i}$	$-S\gamma_i\left(\gamma_i + 2\Delta z\right)$	$-2S\gamma_i^2\left[\frac{1}{4} - \left(\frac{\Delta z}{\gamma_i}\right)^2\right]$	$-S\gamma_i\left(\gamma_i - 2\Delta z\right)$
$\frac{\partial \dot{p}_i}{\partial p_j}$	0	$-4S\gamma_i\gamma_j\left[\frac{1}{4} - \left(\frac{\Delta z}{\gamma_i}\right)^2\right]$	0

are stable. If the trait deviates from the optimum, any locus i for which $|\Delta z| > \gamma_i/2$ will become unstable and sweep to an alternative state.

Under equal effects, if the deviation from the trait optimum surpasses $\gamma/2$, all alleles in one fixation corner become unstable simultaneously, whereas in the case of unequal effects this happens only for a fraction of loci, if they fulfill the above condition.

Clearly, large deviations from the optimum will favour fixation of some alleles, which do not contribute to the genetic variance. However, small deviations in principle allow some alleles to be at intermediate frequencies, and thus generate genetic variance. In that case, each polymorphic allele will contribute to the genetic variance by $\frac{1}{2}\left(\gamma_s + 2\Delta z\right)^2$, where s indicates loci that are polymorphic.

Now we will prove that at most one locus can be polymorphic. First we prove exactly for $n_s = 1, 2$, and then for a general case. Without loss of generality we will assume that the vector of allelic effects is ordered, is bounded and positive, i.e. $0 < \gamma_1 \leq \gamma_2 \ldots \leq \gamma_n < \infty$.

Notice that the Jacobian is a block diagonal matrix:

$$\mathbb{J} = \begin{pmatrix} \mathbb{A}_s & \mathbb{A}_o \\ \mathbb{O} & \mathbb{A}_f \end{pmatrix} \tag{4}$$

the sub-matrices for the polymorphic states, $\mathbb{A}_s$ and $\mathbb{A}_0$ contain the Jacobian terms given by the central column of Table A1, and are of dimensions $n_s \times n_s$ and $n_s \times n_f$, respectively. The sub matrix $\mathbb{A}_f$ is a diagonal matrix corresponding to fixed loci, and its elements are given by the left and right columns of Table A1; it has dimension $n_f \times n_f$. $\mathbb{O}$ is a zero matrix of dimensions $n_f \times n_s$.

Because $\mathbb{J}$ is a triangular matrix, its eigenvalues are given by $\|\mathbb{A}_f - \lambda\mathbb{I}\|\|\mathbb{A}_s - \lambda\mathbb{I}\| = 0$. This implies that we can find the eigenvalues for each matrix separately. Therefore, there will be n_f eigenvalues of the form $\lambda_i = -S\gamma_i\left(\gamma_i \pm 2\Delta\mathrm{z}\right)$ for the fixed alleles, just as in Eq. 3.

Assume now that there is only one polymorphic allele, i.e. that $\mathbb{A}_s = -2S\gamma_i^2\left[\frac{1}{4} - \left(\frac{\Delta z}{\gamma_i}\right)^2\right]$ for a given i. Then, as long as the deviation from the optimum is less than half the effect, the polymorphic allele is stable.

Suppose now that $\mathbb{A}_s$ is a 2×2 matrix. Call $\boldsymbol{f} = (f_1, f_2)$, with

$$f_i = S\gamma_i\left[\frac{1}{4} - \left(\frac{\Delta z}{\gamma_i}\right)^2\right], \tag{5}$$

and the vector of effect of polymorphic loci $\boldsymbol{g} = (\gamma_1, \gamma_2)$. Then irrespective of the magnitude of the deviation from the optimum we get:

$$\lambda_s = -\boldsymbol{f} \cdot \boldsymbol{g} \pm \sqrt{(\boldsymbol{f} \cdot \boldsymbol{g})^2 + 12 f_1 f_2 \gamma_1 \gamma_2} \tag{6}$$

where $\boldsymbol{f} \cdot \boldsymbol{g}$ denotes the dot product between the two vectors. Thus, one eigenvalue is negative and one is positive, making the configuration with two polymorphic alleles unstable.

A more general case is hard to compute exactly, but we can approach the problem by partitioning the matrix $\mathbb{A}_s$ into two simpler matrices whose eigenvalues can be computed exactly, and then by applying Weyl's inequality (see also Horn's conjecture; Horn, 1962; Knutson and Tao, 2001), we can bound the eigenvalues of $\mathbb{A}_s$ in terms of the eigenvalues of the other two matrices.

Assume that the vectors $\boldsymbol{f}$ and $\boldsymbol{g}$ are of dimension $n_s > 0$. Consider the following two matrices: $\mathbb{B} = -2\boldsymbol{f} \otimes \boldsymbol{g}$ and $\mathbb{C} = \text{Diag}\{f_i \gamma_i\}_{i=1}^{n_s}$, where $\otimes$ denotes the outer product of the vectors. Then $\mathbb{A}_s = 2S(\mathbb{B} + \mathbb{C})$. The matrix $\mathbb{B}$ has rank one, and therefore has eigenvalues $\beta = (0, \ldots, 0, -2\boldsymbol{f} \cdot \boldsymbol{g})$ where there are $n_s - 1$ zeroes. The matrix $\mathbb{C}$, being diagonal, has eigenvalues $\zeta = (\gamma_{n_s} f_{n_s}, \ldots, \gamma_1 f_1)$, where the eigenvalues are written in decreasing order, and therefore ζ has the reverse order of $\boldsymbol{g}$. Then if α are the eigenvalues of $\mathbb{A}_s$, Weyl's inequality states that $\zeta_i + \beta_1 \leq \alpha_i \leq \zeta_i + \beta_{n_s}$, which implies the following two inequalities:

$$0 < g_1 f_1 \leq \alpha_i \leq g_{n_s} f_{n_s} \ , 1 < i < n \tag{7}$$

$$g_1 f_1 - 2\boldsymbol{g} \cdot \boldsymbol{f} \leq \alpha_n \leq g_{n_s} f_{n_s} - 2\boldsymbol{g} \cdot \boldsymbol{f} < 0 \tag{8}$$

The first inequality implies that there are $n_s - 1$ positive eigenvalues, and the second inequality that there is one negative eigenvalue. (We confirmed this result using numerical calculations; data not shown). This, as stated above, requires that $|\Delta z| < \gamma_1/2$; there are no fixed points that allow larger deviations.

In conclusion, only one allele can be maintained polymorphic; any configuration with more than one polymorphic allele is unstable.

Stability under small mutation rates.

Now we will derive an approximation for the eigenvalues of the Jacobian matrix when the trait matches the optimum and mutation rates are small compared to selection, ($\mu << S$). However, we will assume that all alleles are of large effect, i.e. $\gamma > 2\sqrt{\mu/S}$, and hence contribute to the Jacobian by $-S\gamma_i^2$ in the diagonal, and $-4\mu\frac{\gamma_j}{\gamma_i}$ in the non-diagonal. If mutation is absent, then the Jacobian is simply $\mathbb{J}_0 = -S\text{Diag}\left\{\gamma_1^2, \ldots, \gamma_n^2\right\}$, with eigenvalues $\lambda_i = -S\gamma_i^2$, as above (Eqn. 3) when $\Delta z = 0$. For simplicity, we will scale the eigenvalues as $\lambda \to \lambda/S$. We write the Jacobian as $\mathbb{J} = \mathbb{J}_0 + \mu\mathbb{J}_\mu$, where

$$\mathbb{J}_\mu = \begin{cases} -4\frac{\gamma_i}{\gamma_j} & i \neq j \\ 0 & i = j \end{cases}$$

We are therefore looking for the solution to the equation

$$\|\mathbb{J}_0 + \epsilon\mathbb{J}_\mu - \lambda\mathbb{I}\| = 0 \tag{9}$$

where ϵ=μ/S. This equation is a polynomial of degree n on λ. The central idea is to treat the determinant as a function $F(\epsilon, \lambda)$, and to perform a perturbation analysis on ϵ, and solve for λ. The eigenvalues are expanded as $\lambda = \lambda_0 + \epsilon\lambda_1 + \epsilon^2\lambda_2 + \ldots$, making $F(\epsilon, \lambda) = F\left(\epsilon, \lambda_0 + \epsilon\lambda_1 + \epsilon^2\lambda_2 + \ldots\right)$, which in turn is written as $F\left(\epsilon, \lambda_0, \lambda_1, \lambda_2, \ldots\right)$. Following we expand the determinant in series of ϵ up to second order:

$$F\left(\epsilon, \lambda_0, \lambda_1, \lambda_2, \ldots\right) \simeq F\left(0, \lambda_0\right) + \epsilon F'\left(0, \lambda_0, \lambda_1\right) + \frac{\epsilon^2}{2}F''\left(0, \lambda_0, \lambda_1, \lambda_2\right) + \mathcal{O}(\epsilon^3). \tag{10}$$

In general, the derivatives $F^{(n)}$ are polynomials on ϵ. Grouping terms of equal order of ϵ, leads to system of equations that give the λ_i. Since a general formula for the coefficients of the polynomial on λ is complicated, we use matrix algebra as a general framework to perform the approximations, since the compact notation of matrix algebra makes it more convenient to derive general results. For convenience, define the following $n \times n$ matrix:

$$\mathbb{F} = \mathbb{J}_0 - \lambda_0\mathbb{I} + \epsilon\left(\mathbb{J}_\mu - \lambda_1\mathbb{I}\right) - \left(\epsilon^2\lambda_2 + \ldots\right)\mathbb{I} \tag{11}$$

therefore, the characteristic equation is

$$F\left(\epsilon, \lambda_0, \lambda_1, \lambda_2, \ldots\right) = \|\mathbb{F}\| = 0 \tag{12}$$

The first term in the perturbation method is the unperturbed solution (order ϵ^0) which emerges from the first term of the Taylor expansion: $F(0) \Rightarrow \|\mathbb{J}_0 - \lambda_0\mathbb{I}\| = 0$; its roots are as above (Eq. 3).

The second term (order ϵ) follows from the derivative F', where we use Jacobi's formula, i.e. $F' = \frac{d}{d\epsilon}\|\mathbb{F}\| = \mathrm{Tr}\left(\mathbb{F}^{\dagger}\frac{d\mathbb{F}}{d\epsilon}\right)$, where $\mathbb{F}^{\dagger}$ is the adjugate (a.k.a. classic adjoint) matrix of $\mathbb{F}$. The only relevant term of $\mathbb{F}'$ is $(\mathbb{J}_{\mu} - \lambda_1 \mathbb{I})$ (higher order terms vanish when $\epsilon = 0$). Then at ϵ=0 we get that $\left(\mathbb{F}^{\dagger}\mathbb{F}'\right)_{i\,j} = -\alpha_{i\,j}\prod_{k\neq j}^{n}(\gamma_k^2 + \lambda_0)$ where $\alpha_{i\,i} = \lambda_1$ and $\alpha_{i\,j} = 4\gamma_i/\gamma_j$. This leads to $\mathrm{Tr}\left(\mathbb{F}^{\dagger}\frac{d\mathbb{F}}{d\epsilon}\right) = -\lambda_1^{(i)}\prod_{k\neq j}^{n}\left(\gamma_k^2 + \lambda_0^{(i)}\right)$. Since we require that $F'\left(0, \lambda_0^{(i)}, \lambda_1^{(i)}\right) = 0$, this implies that $\lambda_1^{(i)} = 0$, concluding that there are no terms of order ϵ.

Because the first order perturbation vanishes, it suggests that the configuration will be stable. The leading value of the eigenvalue is given by the unperturbed solution, and it will change by order of $(\mu/S)^2$. Thus even if λ_2 is positive, as long as it is bounded the eigenvalue will remain negative.

Now we will calculate the second order term to verify that it remains finite. For the term of order ϵ^2 we need to evaluate F'', that is

$$F'' = \frac{d^2}{d\epsilon^2}\|\mathbb{F}\| = \frac{d}{d\epsilon}\mathrm{Tr}\left(\mathbb{F}^{\dagger}\frac{d\,\mathbb{F}}{d\epsilon}\right) \tag{13}$$

the the differential operator can be exchanged with the trace, and using the additive property we get

$$F'' = \mathrm{Tr}\left(\frac{d\mathbb{F}^{\dagger}}{d\epsilon}\frac{d\,\mathbb{F}}{d\epsilon}\right) + \mathrm{Tr}\left(\mathbb{F}^{\dagger}\frac{d^2\,\mathbb{F}}{d\,\epsilon^2}\right) \tag{14}$$

Since $d^2\mathbb{F}/d\epsilon^2 \simeq 2\lambda_2\mathbb{I}$, substitution of this identity gives

$$\lambda_2 = -\mathrm{Tr}\left(\frac{d\,\mathbb{F}^{\dagger}}{d\,\epsilon}\frac{d\,\mathbb{F}}{d\,\epsilon}\right)\Big/\,2\mathrm{Tr}\left(\mathbb{F}^{\dagger}\right) \tag{15}$$

At $\epsilon = 0$ and readily using that $\lambda_1 = 0$ we have that $d\mathbb{F}/d\epsilon = \mathbb{J}_{\mu}$ and that

$$\left\{\frac{d\mathbb{F}^{\dagger}}{d\epsilon}\right\}_{ij} = \begin{cases} -4\frac{\gamma_j}{\gamma_i}\prod_{k\neq i,j}^{n}(\gamma_k^2 + \lambda_0) & i \neq j \\ 0 & i = j \end{cases}$$

By multiplying the last two matrices we get the numerator of Eq. 15; the denominator is $\mathrm{Tr}\left(\mathbb{F}^{\dagger}\right) = \sum_{j=1}^{n}\prod_{k\neq j}^{n} - \left(\gamma_k^2 + \lambda_0^{(i)}\right)$. Substituting the corresponding λ_0 gives the second order terms of the eigenvalues, which are:

$$\lambda_2^{(i)} = -\frac{8\sum_{j\neq i}^{n}\sum_{m\neq i}^{n}\prod_{k\neq j,m}^{n}(\gamma_k^2 - \gamma_i^2)}{\sum_{j\neq i}^{n}\prod_{k\neq j}^{n}(\gamma_i^2 - \gamma_k^2)}. \tag{16}$$

Assuming that there $\gamma_i \neq \gamma_j \forall i, j$, the last expression simplifies to

$$\lambda_2^{(i)} = -16 \sum_{j \neq i}^{n} \frac{1}{\gamma_j^2 - \gamma_i^2}. \tag{17}$$

Thus the second order term is finite. If two or more effects are the same, the previous expression does not apply. Nevertheless, multiplicities can be incorporated in the more general expression of Eq. 16, but we leave that case aside as it is unlikely that two effects are exactly the same.

Summarizing, the perturbation parameter is $\epsilon = \mu / S$, thus the eigenvalues are as

$$\lambda^{(i)} = -\gamma_i^2 + \left(\frac{\mu}{S} \right)^2 \lambda_2^{(i)} + \mathcal{O}\left(\left[\frac{\mu}{S} \right]^3 \right) \tag{18}$$

which completes the approximation up to second order.