

FILE S1: PARTIAL SELF-FERTILIZATION

I consider a very large (effectively infinite) population with discrete generations. Individuals are hermaphroditic, and a parameter α measures the proportion of offspring produced by selfing (while the other $1 - \alpha$ are produced by random union of gametes). Deleterious mutations occur at a rate U per haploid genome per generation. I assume for simplicity that all deleterious alleles have the same selection (s) and dominance (h) coefficients, although this assumption will be relaxed at the end. Throughout, the effects of deleterious alleles at different loci are assumed to be multiplicative (no epistasis).

Genetic associations. Following previous work (Barton and Turelli, 1991; Kirkpatrick et al., 2002), genetic associations within and between loci may be defined as follows. The frequencies of the deleterious allele at locus i on the first and second haplotype of an individual are denoted $X_{i(1)}$ and $X_{i(2)}$, respectively (these variables equal 0 or 1, depending on whether the deleterious allele is present or not on this haplotype). Centered variables $\zeta_{i(1)}$ and $\zeta_{i(2)}$ are defined as:

$$\zeta_{i(1)} = X_{i(1)} - p_i, \quad \zeta_{i(2)} = X_{i(2)} - p_i \tag{A1}$$

where p_i is the frequency of the deleterious allele at locus i in the whole population. The association between the sets \mathbb{S} and \mathbb{T} of loci present in the two haplotypes of the same individual is defined as:

$$D_{\mathbb{S},\mathbb{T}} = E[\zeta_{\mathbb{S},\mathbb{T}}] \tag{A2}$$

where E stands for the average over the whole population, and where

$$\zeta_{\mathbb{S},\mathbb{T}} = \frac{\zeta_{\mathbb{S}(1)} \zeta_{\mathbb{T}(2)} + \zeta_{\mathbb{S}(2)} \zeta_{\mathbb{T}(1)}}{2}, \quad (\text{A3})$$

$$\zeta_{\mathbb{S}(1)} = \prod_{i \in \mathbb{S}} \zeta_{i(1)}, \quad \zeta_{\mathbb{T}(2)} = \prod_{i \in \mathbb{T}} \zeta_{i(2)}$$

(note that $D_{\mathbb{S},\mathbb{T}} = D_{\mathbb{T},\mathbb{S}}$). Associations between genes present on the same haplotype of an individual ($D_{\mathbb{S},\emptyset}$) will be simply denoted $D_{\mathbb{S}}$. For example, $D_{i,i} = E[\zeta_{i(1)} \zeta_{i(2)}]$ measures the departure from Hardy-Weinberg equilibrium at locus i , while $D_{ij} = E[\zeta_{i(1)} \zeta_{j(1)} + \zeta_{i(2)} \zeta_{j(2)}] / 2$ is the linkage disequilibrium between deleterious alleles at loci i and j . Finally, associations with repeated indices (such as $D_{ii,j}$) usually appear when deriving recursions; however, these repeated indices can be eliminated using the relation:

$$D_{\mathbb{S}ii,\mathbb{T}} = p_i q_i D_{\mathbb{S},\mathbb{T}} + (1 - 2p_i) D_{\mathbb{S}i,\mathbb{T}} \quad (\text{A4})$$

(e.g., equation 5 in Kirkpatrick et al., 2002). In particular, $D_{ii,j} = (1 - 2p_i) D_{i,j}$.

Recursions on genetic associations. General expressions for the effects of selection, reproduction (recombination and gamete fusion, with selfing rate α) and mutation on genetic associations can be obtained using the methods developed by Barton and Turelli (1991) and Kirkpatrick et al. (2002). In particular, $D_{\mathbb{S},\mathbb{T}}$ after selection (denoted $D_{\mathbb{S},\mathbb{T}}^{\mathbb{S}}$) is given by:

$$D_{\mathbb{S},\mathbb{T}}^{\mathbb{S}} = D_{\mathbb{S},\mathbb{T}}^{\bullet} + \sum_{\mathbb{X} \subset \mathbb{S}} \sum_{\mathbb{Y} \subset \mathbb{T}} D_{\mathbb{S} \setminus \mathbb{X}, \mathbb{T} \setminus \mathbb{Y}}^{\bullet} \prod_{i \in \mathbb{X}} (-\Delta_s p_i) \prod_{j \in \mathbb{Y}} (-\Delta_s p_j) \quad (\text{A5})$$

where

$$D_{\mathbb{S},\mathbb{T}}^{\bullet} = E \left[\frac{W}{\bar{W}} \zeta_{\mathbb{S},\mathbb{T}} \right]. \quad (\text{A6})$$

In the expressions above, W and \bar{W} stand for the fitness of an individual and the average fitness of the population. The sums in the second term are over all subsets \mathbb{X}

and \mathbb{Y} of the sets \mathbb{S} and \mathbb{T} (including the empty set), while $\mathbb{S} \setminus \mathbb{X}$ stands for the set \mathbb{S} , from which the elements of the set \mathbb{X} have been removed. Finally, $\Delta_s p_i$ is the change in frequency of the deleterious allele at locus i due to selection.

Associations after recombination and fertilization (denoted $D_{\mathbb{S},\mathbb{T}}^r$) are given by:

$$D_{\mathbb{S},\mathbb{T}}^r = \sum_{\mathbb{X}\mathbb{Y}=\mathbb{S}} \sum_{\mathbb{U}\mathbb{V}=\mathbb{T}} t_{\mathbb{X},\mathbb{Y}} t_{\mathbb{U},\mathbb{V}} \left[(1 - \alpha) D_{\mathbb{X},\mathbb{Y}}^s D_{\mathbb{U},\mathbb{V}}^s + \frac{\alpha}{2} (D_{\mathbb{X}\mathbb{U},\mathbb{Y}\mathbb{V}}^s + D_{\mathbb{X}\mathbb{V},\mathbb{Y}\mathbb{U}}^s) \right] \quad (\text{A7})$$

where (\mathbb{X}, \mathbb{Y}) is a partition of the set \mathbb{S} , and $t_{\mathbb{X},\mathbb{Y}}$ is the probability that loci in the set \mathbb{X} come from one of the haplotypes of the parent, and loci in the set \mathbb{T} come from the other haplotype (when \mathbb{S} contains only one locus i we have $t_{i,\emptyset} = 1$, while when $\mathbb{S} = ij$, we have $t_{ij,\emptyset} = 1 - r_{ij}$ and $t_{i,j} = r_{ij}$, where r_{ij} is the recombination rate between the two loci).

Finally, the effect of mutation on associations writes:

$$D'_{\mathbb{S},\mathbb{T}} = (1 - u)^{|\mathbb{S}|+|\mathbb{T}|} D_{\mathbb{S},\mathbb{T}} \quad (\text{A8})$$

where u is the deleterious mutation rate per locus, and $|\mathbb{S}|$ is the number of elements in the set \mathbb{S} . However, in the following we will neglect the effect of mutation when deriving recursions on genetic associations, as it only has a negligible effect on expressions at equilibrium (as long as $u \ll s$).

Effects of genetic associations on mean fitness. Using the notations defined above, the fitness of an individual can be written as:

$$W = \prod_i [1 - sh (X_{i(1)} + X_{i(2)}) - s(1 - 2h) X_{i(1)} X_{i(2)}] \quad (\text{A9})$$

Expressing in terms of $\zeta_{i(1)}$, $\zeta_{i(2)}$ variables and rearranging, one obtains:

$$W = \prod_i [1 + T_i + a_i (\zeta_{i(1)} + \zeta_{i(2)}) + a_{i,i} (\zeta_{i(1)} \zeta_{i(2)} - D_{i,i})] \quad (\text{A10})$$

where

$$T_i = -2sh p_i - s(1 - 2h)(p_i^2 + D_{i,i}) \quad (\text{A11})$$

$$a_i = -s[h + (1 - 2h)p_i], \quad a_{i,i} = -s(1 - 2h).$$

Through the following, I assume that deleterious alleles stay at low frequency in the population (p_i small), so that $T_i \approx -2sh p_i - s(1 - 2h)D_{i,i}$ and $a_i \approx -sh$. From equation A10, and assuming that s is small, log-fitness is given by:

$$\ln W \approx \sum_i [T_i + a_i (\zeta_{i(1)} + \zeta_{i(2)}) + a_{i,i} (\zeta_{i(1)}\zeta_{i(2)} - D_{i,i})]. \quad (\text{A12})$$

Therefore, the mean log-fitness is approximately:

$$\overline{\ln W} \equiv \text{E}[\ln W] \approx \sum_i T_i \approx - \sum_i (2sh p_i + s(1 - 2h)D_{i,i}). \quad (\text{A13})$$

Note that terms in p_i^2 should be included in the equations above to deal with the effects of fully recessive deleterious alleles (h close to zero) under panmixia, since $D_{i,i} = 0$ when mating is random; however, in the following we will assume that either h or α is significantly greater than zero.

Assuming that the variance in fitness in the population remains small, mean fitness $\overline{W} \equiv \text{E}[W]$ can be expressed in terms of the mean and variance in log-fitness through the following argument. Denoting $z = \ln W$, $\bar{z} = \overline{\ln W}$ and $dz = z - \bar{z}$, we have:

$$\overline{W} = \text{E}[e^z] = \text{E}[e^{\bar{z}+dz}], \quad (\text{A14})$$

and a Taylor series to the second order in dz yields:

$$\overline{W} \approx e^{\overline{\ln W}} \left(1 + \frac{\text{Var}[\ln W]}{2} \right). \quad (\text{A15})$$

Using a similar reasoning, one obtains for the variance in fitness (neglecting terms in $\text{Var}[\ln W]^2$):

$$\text{Var}[W] \approx e^{2\overline{\ln W}} \text{Var}[\ln W]. \quad (\text{A16})$$

From equations A12 and A13, the variance in log-fitness is given by:

$$\begin{aligned} \text{Var} [\ln W] &= \text{E} \left[\left(\sum_i (a_i (\zeta_{i(1)} + \zeta_{i(2)}) + a_{i,i} (\zeta_{i(1)}\zeta_{i(2)} - D_{i,i})) \right)^2 \right] \\ &= \text{E} \left[\sum_{i,j} (a_i (\zeta_{i(1)} + \zeta_{i(2)}) + a_{i,i} (\zeta_{i(1)}\zeta_{i(2)} - D_{i,i})) \right. \\ &\quad \left. \times (a_j (\zeta_{j(1)} + \zeta_{j(2)}) + a_{j,j} (\zeta_{j(1)}\zeta_{j(2)} - D_{j,j})) \right] \end{aligned} \quad (\text{A17})$$

where the last sum is over all i and j , including $i = j$. Equation A17 finally yields:

$$\begin{aligned} \text{Var} [\ln W] &\approx 2 (sh)^2 \sum_{i,j} (D_{ij} + D_{i,j}) + 2s^2h(1-2h) \sum_{i,j} (D_{ij,i} + D_{ij,j}) \\ &\quad + s^2(1-2h)^2 \sum_{i,j} (D_{ij,ij} - D_{i,i}D_{j,j}) . \end{aligned} \quad (\text{A18})$$

In an infinite, randomly mating population, all associations within and between loci should be zero at equilibrium, and using the fact that $D_{ii} = p_i q_i$ and $D_{ii,ii} = (p_i q_i)^2$ (from equation A4), equation A18 simplifies to the classical expression for the variance of a quantitative trait in the absence of epistasis, under random mating: $2 (sh)^2 \sum_i p_i q_i + s^2 (1-2h)^2 \sum_i (p_i q_i)^2$ (e.g., Lynch and Walsh, 1998, p. 69). At mutation-selection balance, and assuming again that h is significantly greater than zero, $p_i \approx u / (hs)$ (where u is the deleterious mutation rate per locus), and the variance in log-fitness is thus approximately $2shU$ (neglecting terms in p_i^2).

With inbreeding, all the associations that appear in equation A18 differ from zero at equilibrium. However, we will see that under weak selection, different types of associations are of different orders of magnitude: $D_{i,i}$ and $D_{ij,ij}$ are generated by inbreeding (even in the absence of selection), $D_{ij,i}$ is generated by inbreeding and by selection acting on locus j and is of order s , while D_{ij} , $D_{i,j}$ are generated by inbreeding and by selection acting on both loci, and are of order s^2 . Neglecting associations generated by selection, and noting from equation A4 that $D_{ii,ii} = (1-2p_i) D_{i,i}$ while

$D_{ii,ii} = (p_i q_i)^2 + (1 - 2p_i)^2 D_{i,i}$, which are both approximately equal to $D_{i,i}$ when p_i is small, one obtains (to the first order in p_i):

$$\begin{aligned} \text{Var} [\ln W] \approx & 2 (sh)^2 \sum_i p_i + s^2 (1 - 2h^2) \sum_i D_{i,i} \\ & + s^2 (1 - 2h)^2 \sum_{i \neq j} (D_{ij,ij} - D_{i,i} D_{j,j}) . \end{aligned} \quad (\text{A19})$$

Because $D_{i,i}$ and $D_{ij,ij}$ are proportional to p_i and to $p_i p_j$, respectively (for p_i, p_j small), while p_i and p_j are proportional to u/s at equilibrium, the terms on the first line of equation A19 are proportional to sU , while the term on the second line is proportional to U^2 . Because we will focus on situations where $s \ll U$ (so that many deleterious alleles may be present in a single genome, and interactions between these alleles may thus have noticeable effects), in the following we will neglect the terms on the first line of equation A19. Although the expression obtained for $\text{Var} [\ln W]$ may not be accurate when the average number of mutations per genome is low or when h is close to 0.5, the term in $\text{Var} [\ln W]$ in equation A15 should be negligible in these situations. Using this approximation, one obtains (from equations A13, A15 and A19):

$$\bar{W} \approx e^{-2sh \sum_i p_i - s(1-2h) \sum_i D_{i,i}} \left[1 + \frac{1}{2} s^2 (1 - 2h)^2 \sum_{i \neq j} (D_{ij,ij} - D_{i,i} D_{j,j}) \right]. \quad (\text{A20})$$

Interference between loci appears in the terms between brackets in equation A20, but also affects the equilibrium values of $D_{i,i}$ and p_i . We now derive expressions for these different terms to the order U^2 , that is, neglecting the effects of higher-order interactions (between three or more loci), which would generate terms of higher order in U .

Expressions for genetic associations under neutrality. As mentioned before, the term $D_{ij,ij} - D_{i,i} D_{j,j}$ is generated by partial selfing even in the absence of selection. Recursions for $D_{i,i}$ and $D_{ij,ij}$ under neutrality are obtained from equation

A7:

$$D'_{i,i} = \frac{\alpha}{2} (D_{i,i} + p_i q_i) \quad (\text{A21})$$

$$D'_{ij,ij} = \frac{\alpha}{2} \left[[1 - 2r_{ij} (1 - r_{ij})] (D_{ij,ij} + p q_{ij}) + 2r_{ij} (1 - r_{ij}) (p_i q_i D_{j,j} + p_j q_j D_{i,i}) \right] \quad (\text{A22})$$

with $p q_{ij} = p_i q_i p_j q_j$. At equilibrium, one obtains:

$$D_{i,i} = F p_i q_i, \quad D_{ij,ij} = \phi_{ij} p q_{ij} \quad (\text{A23})$$

with

$$F = \frac{\alpha}{2 - \alpha}, \quad \phi_{ij} = \frac{\alpha}{2 - \alpha} \frac{2 - \alpha - 2(2 - 3\alpha) r_{ij} (1 - r_{ij})}{2 - \alpha [1 - 2r_{ij} (1 - r_{ij})]}. \quad (\text{A24})$$

Therefore,

$$D_{ij,ij} - D_{i,i} D_{j,j} = G_{ij} p q_{ij} \approx G_{ij} p_i p_j \quad (\text{A25})$$

(assuming p_i, p_j small), where $G_{ij} = \phi_{ij} - F^2$ is the identity disequilibrium between loci i and j . Under free recombination ($r_{ij} = 1/2$), G_{ij} simplifies to:

$$G = \frac{4\alpha (1 - \alpha)}{(4 - \alpha) (2 - \alpha)^2}. \quad (\text{A26})$$

Because G_{ij} is only weakly dependent on r_{ij} , it is often close to G even when $r_{ij} < 1/2$.

Associations $D_{i,i}$ and $D_{ij,j}$ to the first order in s . The effect of identity disequilibria on the term in $\sum_i D_{i,i}$ (which appears in the exponential in equation A20) can be obtained as follows. From equations A12 and A20, we have to the first order in s :

$$\frac{W}{\overline{W}} \approx -sh \sum_j (\zeta_{j(1)} + \zeta_{j(2)}) - s(1 - 2h) \sum_j (\zeta_{j(1)} \zeta_{j(2)} - D_{j,j}). \quad (\text{A27})$$

From equation A5, the association $D_{i,i}$ after selection is given by:

$$D_{i,i}^s = \text{E} \left[\frac{W}{\overline{W}} \zeta_{i(1)} \zeta_{i(2)} \right] - (\Delta_s p_i)^2. \quad (\text{A28})$$

However, $(\Delta_s p_i)^2$ is of order s^2 and can be neglected. Using equation A27, one obtains:

$$D_{i,i}^s \approx -2sh \sum_j D_{ij,i} - s(1-2h) \sum_j (D_{ij,ij} - D_{i,i}D_{j,j}). \quad (\text{A29})$$

The sums in equation A29 are over all loci j , including $j = i$; however we may neglect terms with $j = i$ when the number of segregating loci is large ($s \ll U$). Furthermore, the first term of equation A29 is of order s^2 , since $D_{ij,i}$ is of order s . Neglecting these terms, one obtains the following recursion for $D_{i,i}$:

$$D'_{i,i} \approx \frac{\alpha}{2} \left[p_i q_i + D_{i,i} - s(1-2h) \sum_{j \neq i} (D_{ij,ij} - D_{i,i}D_{j,j}) \right]. \quad (\text{A30})$$

Therefore, at equilibrium:

$$D_{i,i} \approx F \left[1 - s(1-2h) \sum_{j \neq i} G_{ij} p_j \right] p_i. \quad (\text{A31})$$

In order to calculate allele frequencies at mutation-selection balance, we will also need an expression for associations $D_{ij,j}$ at equilibrium, to the first order in s .

From equation A5, we have (to the first order in s):

$$D_{ij,j}^s = \text{E} \left[\frac{W}{\bar{W}} \frac{\zeta_{ij,j} + \zeta_{j,ij}}{2} \right] - (\Delta_s p_i) D_{j,j}. \quad (\text{A32})$$

Furthermore,

$$\Delta_s p_i = \text{E} \left[\frac{W}{\bar{W}} \frac{X_{i(1)} + X_{i(2)}}{2} \right] - p_i = \text{E} \left[\frac{W}{\bar{W}} \frac{\zeta_{i(1)} + \zeta_{i(2)}}{2} \right] \quad (\text{A33})$$

and thus, to the first order in s (using equation A27):

$$\Delta_s p_i = -sh p_i - s(1-h) D_{i,i}. \quad (\text{A34})$$

From equations A27, A32 and A34, one obtains:

$$D_{ij,j}^s \approx D_{ij,j} - s(1-h) (D_{ij,ij} - D_{i,i}D_{j,j}). \quad (\text{A35})$$

A recursion for $D_{ij,j}$ over the whole life cycle (to the first order in s) is given by:

$$D'_{ij,j} \approx \frac{\alpha}{2} D_{ij,j}^s \approx \frac{\alpha}{2} [D_{ij,j} - s(1-h)(D_{ij,ij} - D_{i,i}D_{j,j})] \quad (\text{A36})$$

giving at equilibrium:

$$D_{ij,j} \approx -s(1-h) F G_{ij} p_i p_j \quad (\text{A37})$$

(assuming p_i, p_j small).

Allele frequencies. To take into account the effects of between-locus interactions on equilibrium allele frequencies, we need to express W/\bar{W} to the second order in s .

From equations A12 and A20, this is:

$$\begin{aligned} \frac{W}{\bar{W}} &\approx 1 - sh \sum_j (\zeta_{j(1)} + \zeta_{j(2)}) - s(1-2h) \sum_j (\zeta_{j(1)}\zeta_{j(2)} - D_{j,j}) \\ &+ (sh)^2 \sum_{i<j} (\zeta_{i(1)} + \zeta_{i(2)}) (\zeta_{j(1)} + \zeta_{j(2)}) \\ &+ s^2 h(1-2h) \sum_{i \neq j} (\zeta_{i(1)} + \zeta_{i(2)}) (\zeta_{j(1)}\zeta_{j(2)} - D_{j,j}) \\ &+ s^2(1-2h)^2 \sum_{i<j} [(\zeta_{i(1)}\zeta_{i(2)} - D_{i,i}) (\zeta_{j(1)}\zeta_{j(2)} - D_{j,j}) - (D_{ij,ij} - D_{i,i}D_{j,j})] \end{aligned} \quad (\text{A38})$$

From equations A33 and A38, neglecting terms in p_i^2 and neglecting terms in sU relative to terms in U^2 , one obtains:

$$\begin{aligned} \Delta_s p_i &= -sh p_i - s(1-h) D_{i,i} - s(1-2h) \sum_{j \neq i} D_{ij,j} \\ &+ s^2(1-h)(1-2h) \sum_{j \neq i} (D_{ij,ij} - D_{i,i}D_{j,j}). \end{aligned} \quad (\text{A39})$$

Using equations A25, A31 and A37, this is:

$$\Delta_s p_i = -s \left[h + (1-h)F - s(1-h)(1-2h)(1+2F) \sum_{j \neq i} G_{ij} p_j \right] p_i. \quad (\text{A40})$$

while the change in p_i due to mutation is approximately u . Assuming unlinked loci ($G_{ij} = G$), one obtains for the average number of deleterious alleles per haploid genome, $n = \sum_i p_i$, to the order U^2 :

$$n \approx \frac{U}{s[h + (1-h)F]} \left[1 + \frac{U(1-h)(1-2h)(1+2F)G}{[h + (1-h)F]^2} \right] \quad (\text{A41})$$

or in terms of the selfing rate α :

$$n \approx \frac{U(2-\alpha)}{s[2h + \alpha(1-2h)]} \left[1 + \frac{4U(1-h)(1-2h)\alpha(1-\alpha)(2+\alpha)}{(2-\alpha)(4-\alpha)[2h + \alpha(1-2h)]^2} \right]. \quad (\text{A42})$$

Finally, equations A20, A25, A26, A31 and A42 yield the following expressions for mean fitness:

$$\bar{W} \approx (1 + I_2) \exp \left[-U \frac{4h + \alpha(1-4h)}{2h + \alpha(1-2h)} (1 + I_1) + \frac{2\alpha}{2-\alpha} I_2 \right] \quad (\text{A43})$$

with:

$$I_1 = 2U(1-h)(1-2h) \frac{2+\alpha}{2-\alpha} T, \quad I_2 = U^2(1-2h)^2 T \quad (\text{A44})$$

and

$$T = \frac{2\alpha(1-\alpha)}{(4-\alpha)[2h + \alpha(1-2h)]^2}. \quad (\text{A45})$$

Furthermore, from equations A13, A16, A19, A25, A31 and A42, one obtains for the variance in fitness:

$$\text{Var}[W] \approx \left(sU \frac{4h^2(1-\alpha) + \alpha}{2h + \alpha(1-2h)} + 2I_2 \right) \exp \left[-2U \frac{4h + \alpha(1-4h)}{2h + \alpha(1-2h)} (1 + I_1) + \frac{4\alpha}{2-\alpha} I_2 \right] \quad (\text{A46})$$

simplifying to $2shUe^{-4U}$ when $\alpha = 0$, and $sUe^{-2(2-\alpha)U}$ when $h = 1/2$. Note that a term in sU^2 has been neglected in the first parenthesis of equation A46, this term being given by:

$$sU^2(1-2h) \frac{4\alpha(1-\alpha)[8h^2(1-h) + \alpha(1-2h)(2-4h^2 + \alpha h)]}{(2-\alpha)(4-\alpha)[2h + \alpha(1-2h)]^3}. \quad (\text{A47})$$

Inbreeding depression. Using the same reasoning as for the derivation of equation A20 above, one obtains that the mean fitness of selfed offspring is given by:

$$\overline{W}_{\text{self}} \approx e^{-2shn - s(1-2h)\sum_i D_{i,i}^{\text{self}}} \left[1 + \frac{1}{2}s^2(1-2h)^2 \sum_{i \neq j} (D_{ij,ij}^{\text{self}} - D_{i,i}^{\text{self}} D_{j,j}^{\text{self}}) \right] \quad (\text{A48})$$

where $D_{i,i}^{\text{self}}$ and $D_{ij,ij}^{\text{self}}$ correspond to the averages of $\zeta_{i,i}$ and $\zeta_{ij,ij}$ over selfed offspring.

Because the same quantities averaged over outcrossed offspring equal zero, the mean fitness of outcrossed offspring is simply $\overline{W}_{\text{out}} \approx e^{-2shn}$, and therefore:

$$\begin{aligned} \delta &= 1 - \frac{\overline{W}_{\text{self}}}{\overline{W}_{\text{out}}} \\ &\approx 1 - e^{-s(1-2h)\sum_i D_{i,i}^{\text{self}}} \left[1 + \frac{1}{2}s^2(1-2h)^2 \sum_{i \neq j} (D_{ij,ij}^{\text{self}} - D_{i,i}^{\text{self}} D_{j,j}^{\text{self}}) \right]. \end{aligned} \quad (\text{A49})$$

Finally, noting that $D_{i,i}^{\text{self}} = \frac{1}{2}(p_i q_i + D_{i,i})$, while under free recombination $D_{ij,ij}^{\text{self}} = \frac{1}{4}(p q_{ij} + D_{ij,ij} + p_i q_i D_{j,j} + p_j q_j D_{i,i})$, one obtains after simplification:

$$\delta \approx 1 - \left(1 + \frac{I_2}{4} \right) \exp \left[-U \frac{1-2h}{2h + \alpha(1-2h)} (1 + I_1) + \frac{\alpha}{2-\alpha} I_2 \right] \quad (\text{A50})$$

where I_1 and I_2 are given by equation A44.

Variable selection and dominance coefficients across loci. The above analysis can easily be extended to the case where s and h vary across loci, if we can assume that drift remains negligible at most loci. Denoting s_i and h_i the selection and dominance coefficient of the deleterious allele at locus i , equation A13 becomes:

$$\overline{\ln W} \approx - \sum_i s_i (2h_i p_i + (1-2h_i) D_{i,i}) \quad (\text{A51})$$

while from equation A19, the variance in log-fitness is approximately

$$\text{Var} [\ln W] \approx \sum_{i \neq j} s_i (1-2h_i) s_j (1-2h_j) (D_{ij,ij} - D_{i,i} D_{j,j}) \quad (\text{A52})$$

when $\alpha > 0$ and $h \neq 1/2$. Furthermore, first order expressions for $D_{i,i}$ and $D_{ij,j}$ at equilibrium (equations A31 and A37 above) become:

$$D_{i,i} \approx F \left[1 - \sum_{j \neq i} s_j (1 - 2h_j) G_{ij} p_j \right] p_i \quad (\text{A53})$$

$$D_{ij,j} \approx -s_i (1 - h_i) F G_{ij} p_i p_j. \quad (\text{A54})$$

From this, one obtains the following expression for the frequency of the deleterious allele at locus i at mutation-selection balance, taking into account effects of identity disequilibria:

$$p_i \approx \frac{u}{s_i [h_i + (1 - h_i) F]} \left[1 + \frac{(1 - h_i) (1 + 2F) G}{h_i + (1 - h_i) F} \sum_{j \neq i} \frac{u (1 - 2h_j)}{h_j + (1 - h_j) F} \right]. \quad (\text{A55})$$

From equations A15 and A51 – A55, and assuming that the total number of loci is large, one obtains that mean fitness and inbreeding depression are approximately given by:

$$\bar{W} \approx \exp \left[-U [\Lambda_1 + GU ((1 + 2F) \Lambda_2 - F \Lambda_3) \Lambda_3] \right] \left(1 + \frac{1}{2} GU^2 \Lambda_3^2 \right) \quad (\text{A56})$$

$$\delta \approx 1 - \exp \left[-U \left[1 + F + GU ((1 + F) (1 + 2F) \Lambda_2 - F \Lambda_3) \right] \frac{\Lambda_3}{2} \right] \times \left(1 + \frac{1}{8} GU^2 \Lambda_3^2 \right) \quad (\text{A57})$$

where Λ_1 , Λ_2 and Λ_3 are integrals over the distribution of h across loci, $\psi(h)$:

$$\Lambda_1 = \int \psi(h) \frac{2h + (1 - 2h) F}{h + (1 - h) F} dh, \quad (\text{A58})$$

$$\Lambda_2 = \int \psi(h) \frac{(1 - h) [2h + (1 - 2h) F]}{[h + (1 - h) F]^2} dh, \quad (\text{A59})$$

$$\Lambda_3 = \int \psi(h) \frac{1 - 2h}{h + (1 - h) F} dh. \quad (\text{A60})$$

Figure 5 in the main text has been obtained by calculating numerically these integrals using the NIntegrate function of *Mathematica*.

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