

SUPPLEMENTARY FIGURES

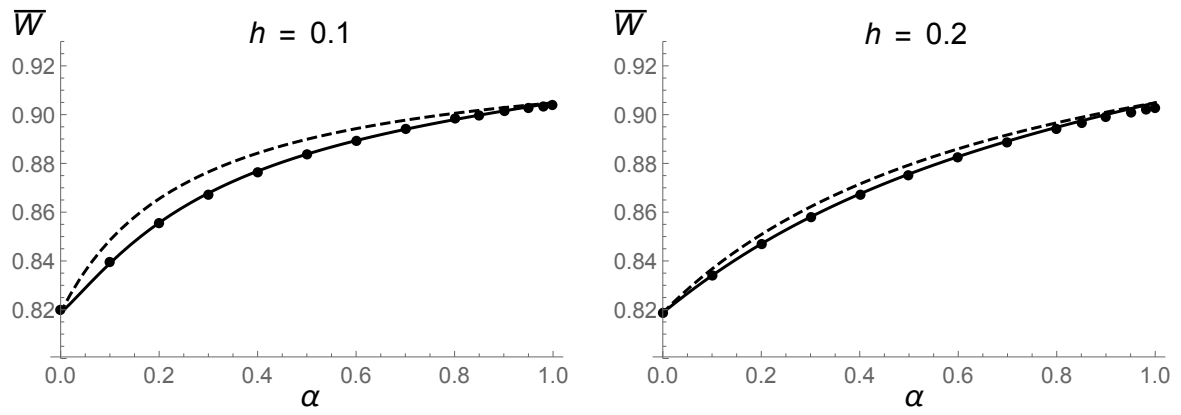


Figure S1. Equivalent to Figure 1 in the main text, with $U = 0.1$ (and other parameters as in Figure 1).

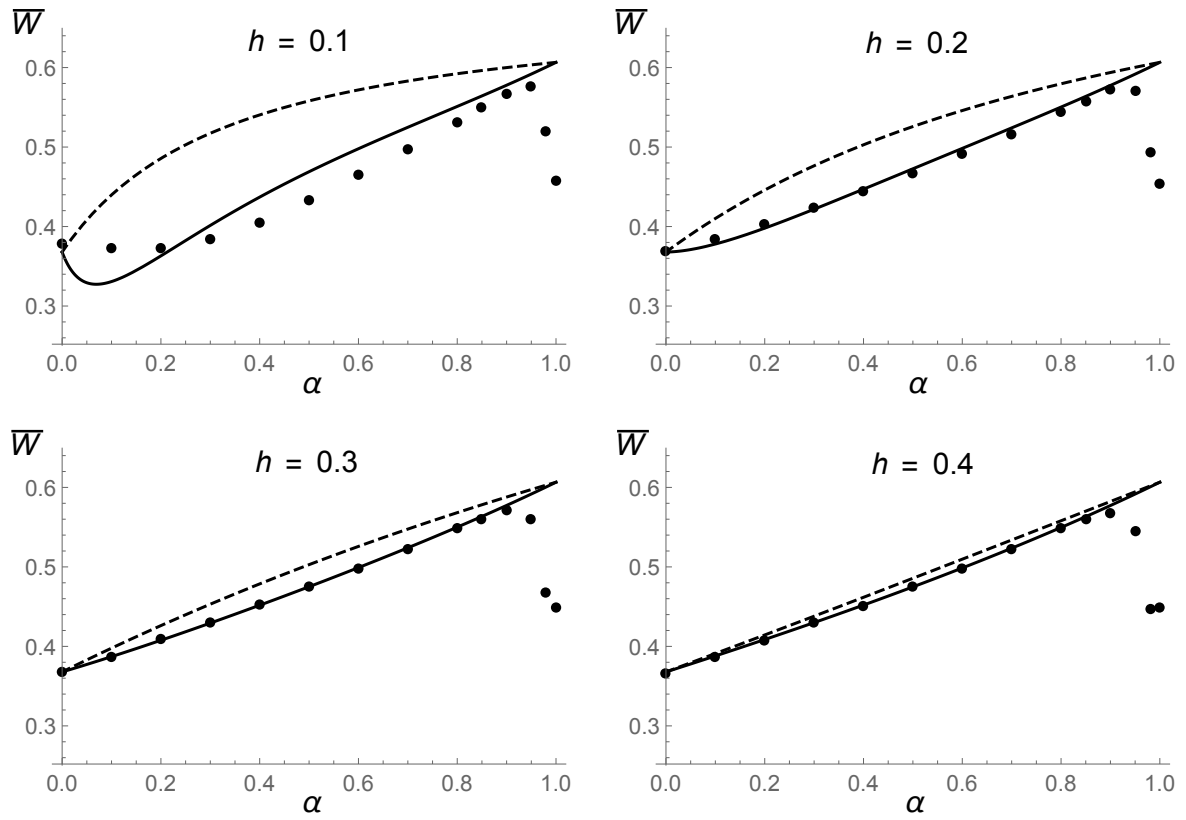


Figure S2. Equivalent to Figure 1 in the main text, with $s = 0.01$ (and other parameters as in Figure 1).

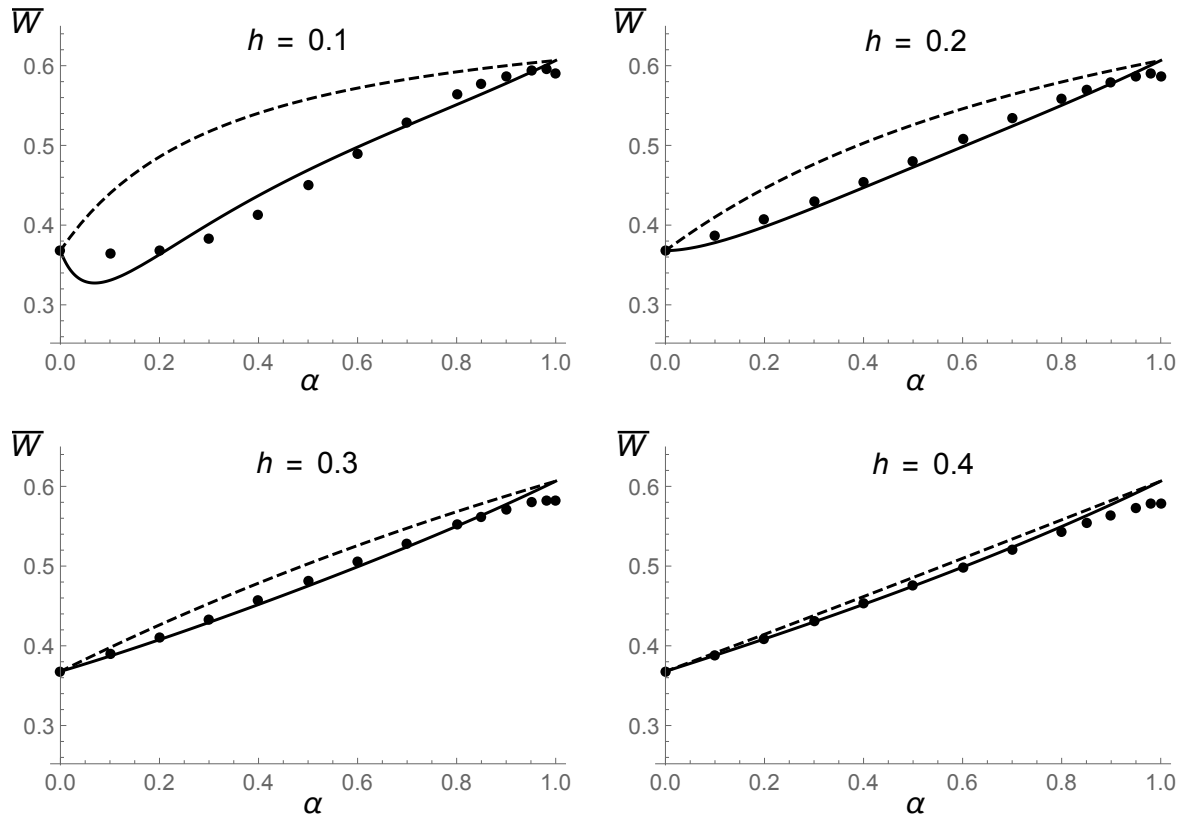


Figure S3. Equivalent to Figure 1 in the main text, with $s = 0.1$ (and other parameters as in Figure 1).

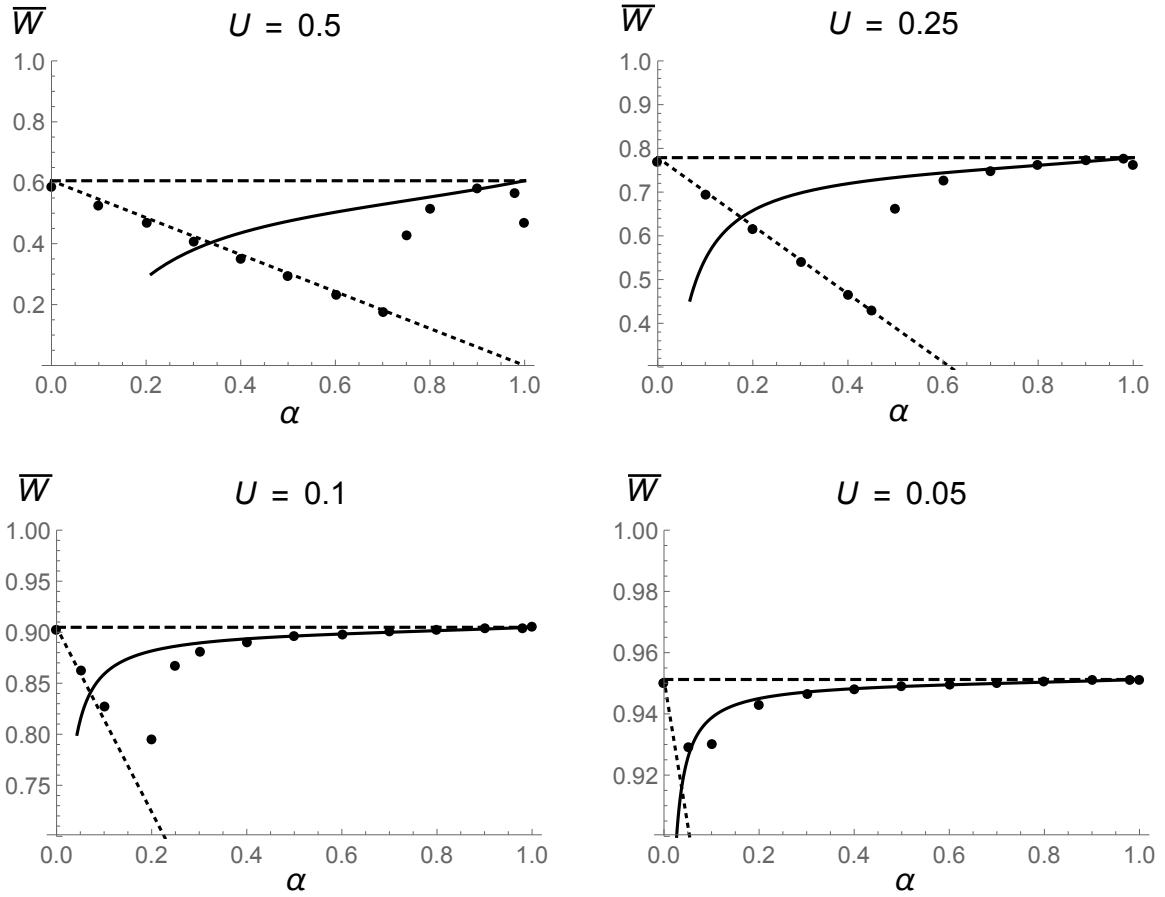


Figure S4. Mean fitness when deleterious alleles are fully recessive (same parameter values as in Figure 4 in the main text). As in Figures 1 and S1–S3, dashed and solid curves represent analytical predictions ignoring (dashed, $\bar{W} \approx e^{-U}$) and including (solid, equation 10 in the main text) the effects of identity disequilibria, while dotted lines show $(1 - \alpha)e^{-U}$.

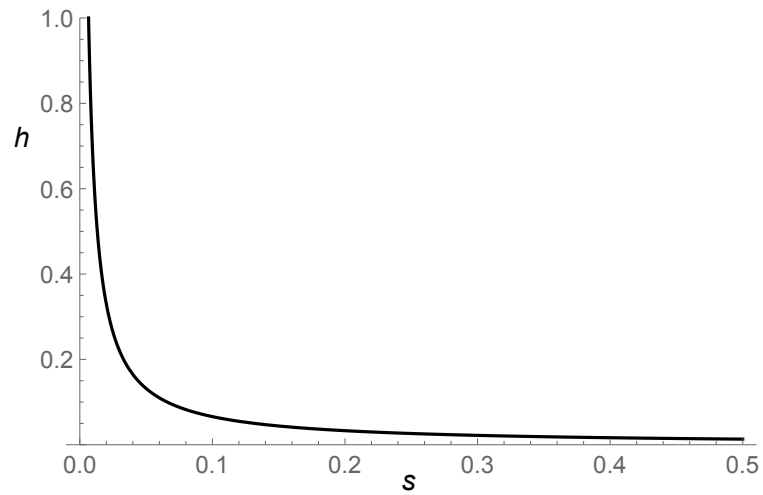


Figure S5. Dominance coefficient h of deleterious alleles as a function of their selection coefficient s , assuming a log-normal distribution of selection coefficients (s) and fixed heterozygous effect (sh) of deleterious alleles. Parameter values are as in Figure 5 in the main text.

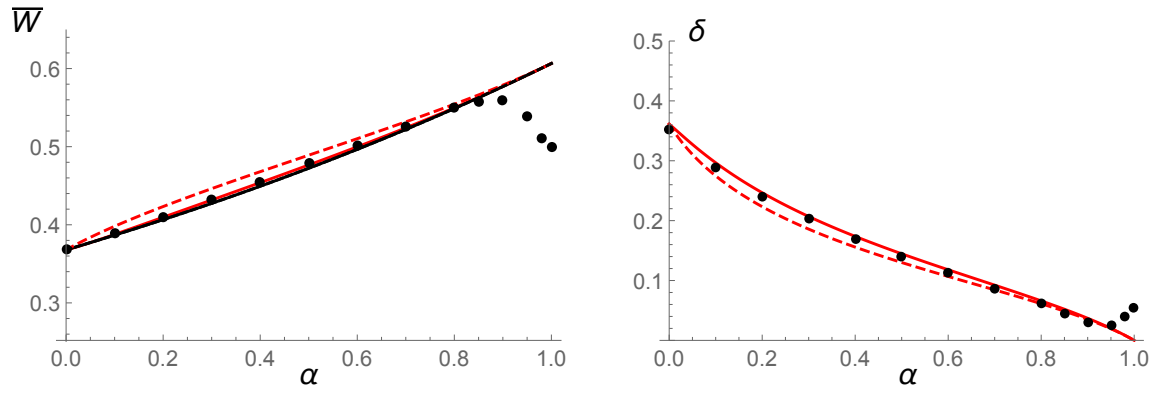


Figure S6. Same as Figure 5 in the main text, setting $\theta = 0.5 \exp[\mu - \sigma^2/2] \approx 0.01318$ so that $\bar{h} = 0.5$.

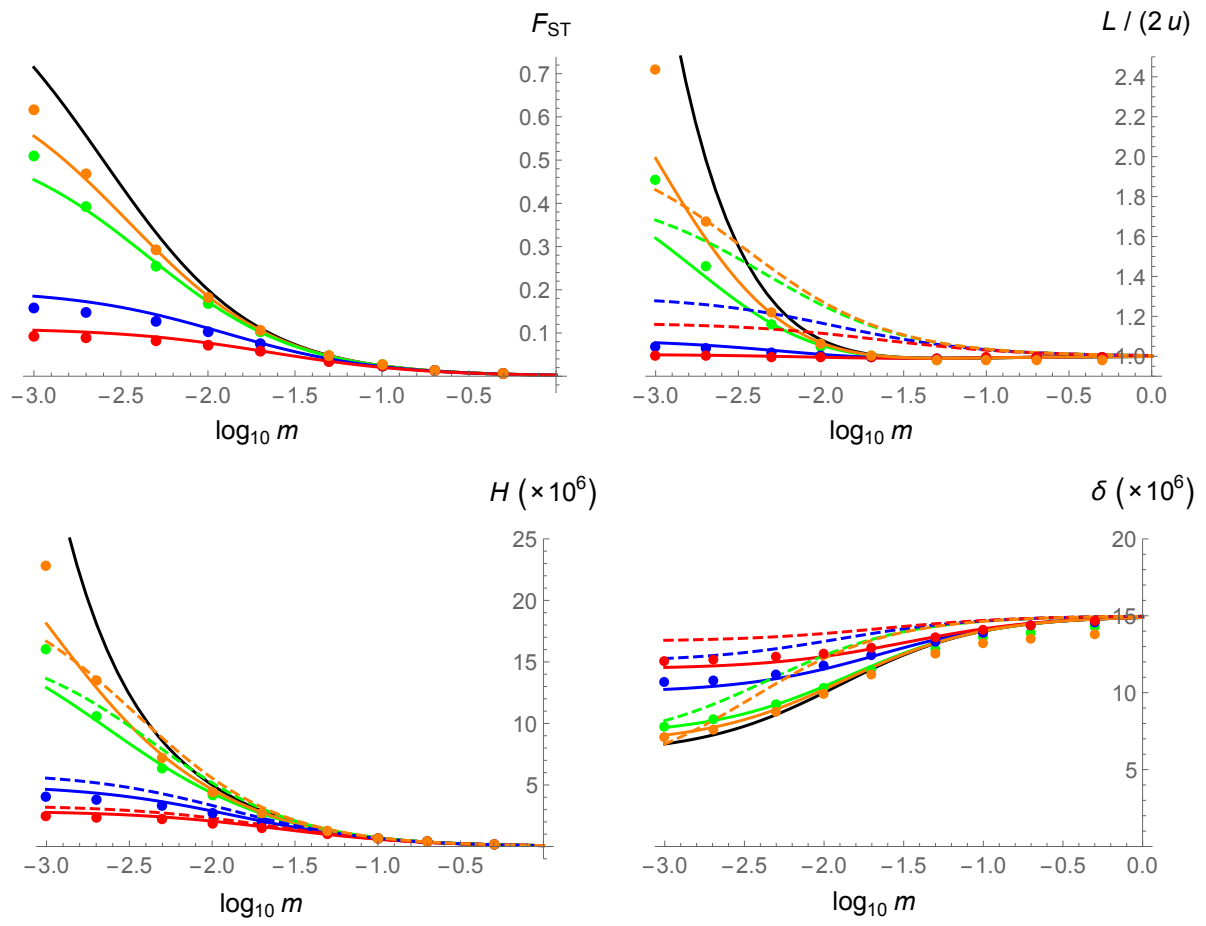


Figure S7. Same as Figure 6 in the main text, showing approximations from Glémin et al (2003) for the mutation load, inbreeding depression and heterosis (dashed curves).

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 $D_{ij,ij}^{\text{self}} = \frac{1}{4}(pq_{ij} + D_{ij,ij} + p_i q_i D_{j,j} + p_j q_j D_{i,i})$, 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*.

LITERATURE CITED

- Barton, N. H. and M. Turelli. 1991. Natural and sexual selection on many loci. *Genetics* 127:229–255.
- Kirkpatrick, M., T. Johnson, and N. H. Barton. 2002. General models of multilocus evolution. *Genetics* 161:1727–1750.
- Lynch, M. and J. B. Walsh. 1998. *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Sunderland, MA.

FILE S2: POPULATION STRUCTURE

In order to explore the effects of population subdivision, I use the infinite island model of population structure: the population consists in an infinite number of demes, each containing N hermaphroditic, diploid adults. These individuals produce a very large (effectively infinite) number of gametes, which fuse at random to form diploid juveniles. Each juvenile then migrates (to any other deme) with probability m . Finally, N individuals are sampled randomly from each deme to form the next adult generation.

Recursions on genetic associations. The methods developed in Roze and Rousset (2008) and Roze (2009) can be used to define genetic associations, and derive recursions representing the effects of selection, recombination, migration and coalescence within demes on allele frequencies and genetic associations. For this, $X_{i(xy1)}$ and $X_{i(xy2)}$ are defined as indicator variables that equal 1 if individual y in deme x carries a deleterious allele at locus i on its first or second haplotype (respectively). Calling p_i the frequency of the deleterious allele at locus i in the whole metapopulation, centered variables $\zeta_{i(xy1)}$ and $\zeta_{i(xy2)}$ are defined as:

$$\zeta_{i(xy1)} = X_{i(xy1)} - p_i, \quad \zeta_{i(xy2)} = X_{i(xy2)} - p_i. \quad (\text{B1})$$

As before, genetic associations between genes present on the same or on different haplotypes of an individual are defined as:

$$D_{\mathbb{S}, \mathbb{T}} = \text{E} [\zeta_{\mathbb{S}, \mathbb{T}(xy)}] \quad (\text{B2})$$

where E stands for the average over all demes x and all individuals y , and where

$$\zeta_{\mathbb{S},\mathbb{T}(xy)} = \frac{\zeta_{\mathbb{S}(xy1)} \zeta_{\mathbb{T}(xy2)} + \zeta_{\mathbb{S}(xy2)} \zeta_{\mathbb{T}(xy1)}}{2}, \quad (\text{B3})$$

$$\zeta_{\mathbb{S}(xy1)} = \prod_{i \in \mathbb{S}} \zeta_{i(xy1)}, \quad \zeta_{\mathbb{T}(xy2)} = \prod_{i \in \mathbb{T}} \zeta_{i(xy2)}$$

(as before, $D_{\mathbb{S},\emptyset}$ will be simply denoted $D_{\mathbb{S}}$). Additionally, we need to define associations between genes present in different individuals from the same deme. The association between the sets \mathbb{S} and \mathbb{T} of genes present on the first and second haplotype of an individual, and the sets \mathbb{U} and \mathbb{V} of genes present on the first and second haplotype of a different individual from the same deme is denoted $D_{\mathbb{S},\mathbb{T}/\mathbb{U},\mathbb{V}}$, and defined as:

$$D_{\mathbb{S},\mathbb{T}/\mathbb{U},\mathbb{V}} = E \left[\zeta_{\mathbb{S},\mathbb{T}(xy)} \zeta_{\mathbb{U},\mathbb{V}(xz)} \right] \quad (\text{B4})$$

where E stands for the average over all demes x and all pairs of individuals y, z , with $y \neq z$. Associations between genes present in three or more individuals from the same deme (such as $D_{\mathbb{S},\mathbb{T}/\mathbb{U},\mathbb{V}/\mathbb{X},\mathbb{Y}}$) can be defined similarly. In the following we will also consider associations between genes from individuals sampled *with replacement* from the same deme, denoted $D_{\mathbb{S},\mathbb{T}/\hat{\mathbb{U}},\mathbb{V}}$ and defined as in equation B4, excepts that the average is over all individuals y and z including $y = z$. Note that we have:

$$D_{\mathbb{S},\mathbb{T}/\hat{\mathbb{U}},\mathbb{V}} = \frac{D_{\mathbb{S}\mathbb{U},\mathbb{T}\mathbb{V}} + D_{\mathbb{S}\mathbb{V},\mathbb{T}\mathbb{U}}}{2N} + \left(1 - \frac{1}{N}\right) D_{\mathbb{S},\mathbb{T}/\mathbb{U},\mathbb{V}}. \quad (\text{B5})$$

Finally, because we assume random fusion of gametes within demes, it will be convenient to define associations at the gamete stage, since these will only involve haploid “individuals” (where an individual now corresponds to a gamete). These are denoted $D_{\mathbb{S}}^g, D_{\mathbb{S}/\mathbb{T}}^g \dots$ and are defined as above, except that averages are taken over all demes and all gametes (note that because we assume an infinite number of gametes per deme, we have $D_{\mathbb{S}/\hat{\mathbb{T}}}^g = D_{\mathbb{S}/\mathbb{T}}^g$).

Recursions describing the effects of migration, recombination and coalescence within demes can be obtained by considering the possible origins of genes in a given set at the previous generation (see Roze and Rousset, 2008; Roze, 2009 for general expressions). For example, $D_{i/i}^g$ measures the association between two genes at locus i , sampled from two different gametes from the same deme. In the absence of selection, these gametes have been produced by the same parent with probability $1/N$, and by two different parents with probability $1 - 1/N$; therefore:

$$D_{i/i}^g = D_{i/i}^{\widehat{}} = \frac{p_i q_i + D_{i,i}}{2N} + \left(1 - \frac{1}{N}\right) D_{i/i} \quad (\text{B6})$$

where associations $D_{i/i}^{\widehat{}}$, $D_{i,i}$ and $D_{i/i}$ are measured in the diploid parents. Two genes present on different haplotypes of a parent were carried by two gametes produced in the same deme at the previous generation; the same is true for two genes present in different parents, if these parents come from the same deme (while the association between two genes sampled from two different demes is zero, due to our assumption of an infinite number of demes). Therefore, a recursion for $D_{i/i}^g$ under neutrality is given by:

$$D_{i/i}^{g'} = \frac{p_i q_i + D_{i/i}^g}{2N} + \left(1 - \frac{1}{N}\right) (1 - m)^2 D_{i/i}^g \quad (\text{B7})$$

When N is large and m small, this is approximately:

$$D_{i/i}^{g'} \approx \frac{p_i q_i}{2N} + \left(1 - \frac{1}{2N} - 2m\right) D_{i/i}^g, \quad (\text{B8})$$

which gives at equilibrium:

$$D_{i/i}^g \approx \frac{p_i q_i}{1 + 4Nm} \quad (\text{B9})$$

that is, $F_{ST} p_i q_i$ (Roze and Rousset, 2008). Finally, selection can be incorporated by weighting each parent by its fitness. For example assuming soft selection, so that

the fitness of parent y in deme x only depends on the number of gametes it produces (denoted W_{xy}), relative to the average number of gametes produced in deme x (denoted W_x), the change in allele frequency p_i due to selection is given by:

$$\Delta_s p_i = \text{E} \left[\frac{W_{xy}}{W_x} \frac{X_{i(xy1)} + X_{i(xy2)}}{2} \right] - p_i = \text{E} \left[\frac{W_{xy}}{W_x} \frac{\zeta_{i(xy1)} + \zeta_{i(xy2)}}{2} \right] \quad (\text{B10})$$

where again the average is over all demes x and individuals y . Furthermore, the association between genes at locus i present in two different gametes ($D_{i/i}^g$) can be expressed in terms of genetic associations among parents from the relation:

$$D_{i/i}^g = \text{E} \left[\left(\frac{W_{xy}}{W_x} \frac{\zeta_{i(xy1)} + \zeta_{i(xy2)}}{2} \right) \left(\frac{W_{xz}}{W_x} \frac{\zeta_{i(xz1)} + \zeta_{i(xz2)}}{2} \right) \right] - (\Delta_s p_i)^2 \quad (\text{B11})$$

where the average is over all demes x and all pairs of parents y and z (including $y = z$).

Assuming weak selection, equations B10 and B11 can then be expressed in terms of associations among parents, as shown in the next section.

A single selected locus. We will first consider the case of a single locus (denoted i) and assume that the fecundity (number of gametes produced) of heterozygous individuals is reduced by a factor $1 - hs$ relative to wild type individuals, while the fecundity of homozygous individuals for the deleterious allele is reduced by a factor $1 - s$. As shown in the single population case (equation A10 in Supplementary File A), the fecundity W_{xy} of individual y in deme x can be written as:

$$W_{xy} \approx 1 + T_i - sh (\zeta_{i(xy1)} + \zeta_{i(xy2)}) - s(1 - 2h) (\zeta_{i,i(xy)} - D_{i,i}) \quad (\text{B12})$$

with $T_i = -2sh p_i - s(1 - 2h) D_{i,i}$ (assuming that the frequency of the deleterious allele in the metapopulation p_i is small). The average fecundity in deme x is thus given by:

$$W_x \approx 1 + T_i - 2sh \zeta_{i(x)} - s(1 - 2h) (\zeta_{i,i(x)} - D_{i,i}) \quad (\text{B13})$$

where $\zeta_{S,\mathbb{T}(x)}$ stands for the average over all individuals y of $\zeta_{S,\mathbb{T}(xy)}$. From this, we have to the first order in s :

$$\frac{W_{xy}}{W_x} \approx 1 - sh (\zeta_{i(xy1)} + \zeta_{i(xy2)} - 2\zeta_{i(x)}) - s(1 - 2h) (\zeta_{i,i(xy)} - \zeta_{i,i(x)}). \quad (\text{B14})$$

From equations B10 and B14, the change in frequency of the deleterious allele due to selection is given by:

$$\Delta_s p_i \approx -sh (p_i q_i + D_{i,i} - 2D_{i,\hat{i}}) - s(1 - 2h) (D_{i,i} - D_{i,\hat{i}}) \quad (\text{B15})$$

where $D_{i,i} = (1 - 2p_i) D_{i,i} \approx D_{i,i}$ when p_i is small. Expressing $D_{i,i}$, $D_{i,\hat{i}}$ and $D_{i,\hat{i}/i}$ in terms of associations between gametes produced by parents of the previous generation, one obtains:

$$\begin{aligned} \Delta_s p_i \approx & -sh \left(1 - \frac{1}{N}\right) \left[p_i q_i + [1 - 2(1 - m)^2] D_{i/i}^g\right] \\ & - s(1 - 2h) \left(1 - \frac{1}{N}\right) \left(D_{i/i}^g - (1 - m)^2 D_{i/i/i}^g\right). \end{aligned} \quad (\text{B16})$$

A similar expression is derived in Roze and Rousset (2003) and Roze and Rousset (2004). In these previous works, an approximation of $\Delta_s p_i$ to the first order in s is then obtained by replacing associations $D_{i/i}^g$ and $D_{i/i/i}^g$ in equation B16 by their equilibrium values under neutrality — a similar method has been used by Whitlock (2002, 2003) and Wakeley (2003). While the expression obtained is generally accurate as long as $m \gg s$, it may greatly overestimate the effect of population structure when m is of the same order of magnitude as s or lower (Roze and Rousset, 2003, 2004), as selection may generate important deviations of genetic associations from their neutral values. The methods of Roze and Rousset (2008) can be used to compute the effect of selection on genetic associations (assuming weak selection), but this leads to an infinite system of recursions (as the recursion for $D_{i/i}^g$ depends on $D_{i/i/i}^g$ and $D_{i/i/i/i}^g$, which in

turn depend on associations between genes present in 5 or 6 different gametes from the same deme, and so on). When $1/N \ll m$ and s , however, associations between genes present in two different gametes from the same deme should be of order $1/N$, while associations between genes present in 3, 4, ... gametes should be of order $1/N^2$, $1/N^3$, ... (as these associations are ultimately generated by identity-by-descent, and probabilities of identity by descent between genes present in 2, 3... gametes are of order $1/N$, $1/N^2$...). To leading order in $1/N$, one may thus neglect associations involving 3 or more gametes in the recursion for $D_{i/i}^g$ (and similarly, neglect associations involving 4 or more gametes in the recursion for $D_{i/i/i}^g$). As we will see, the results obtained by doing so improve considerably the approximations obtained by replacing associations by their neutral equilibrium values, even when $1/N$, m and s have the same order of magnitude. Through the following, we assume that $1/N$, m and s are of order ϵ , and derive recursions to leading order in ϵ . From equations B11 and B14, one obtains to the first order in ϵ (neglecting associations between genes from 3 or more gametes, and neglecting terms in p_i^2):

$$D_{i/i}^g \approx (1 - 2sh) D_{i/i}^g \quad (\text{B17})$$

wich, together with equation B7, yields:

$$D_{i/i}^g \approx \frac{p_i}{2N} + \left(1 - 2sh - \frac{1}{2N} - 2m\right) D_{i/i}^g. \quad (\text{B18})$$

Thus, at equilibrium:

$$D_{i/i}^g \approx \frac{p_i}{1 + 4N(m + sh)}. \quad (\text{B19})$$

Interestingly, the same result has been obtained by Glémin et al. (2003) using a method developed by Ohta and Kimura (1969, 1971) to compute moments of allele frequencies

in finite populations (equation 11a in Glémin et al., 2003). Similarly, one obtains:

$$D_{i/i}^g \approx \frac{3}{2N} D_{i/i}^g + \left(1 - 3sh - \frac{3}{2N} - 3m\right) D_{i/i}^g \quad (\text{B20})$$

giving at equilibrium:

$$D_{i/i}^g \approx \frac{p_i}{[1 + 2N(m + sh)][1 + 4N(m + sh)]}. \quad (\text{B21})$$

Expressing equation B16 to the first order in ϵ , we have:

$$\Delta_s p_i \approx -sh p_i - s(1 - 3h) D_{i/i}^g + s(1 - 2h) D_{i/i}^g \quad (\text{B22})$$

which, together with equations B19 and B21 gives at mutation-selection equilibrium:

$$p_i \approx \frac{[1 + 2N(m + sh)][1 + 4N(m + sh)] u}{2Ns(m + sh)[1 + 4Nh(m + sh)]}. \quad (\text{B23})$$

Furthermore, from equation B12 the mutation load L is given by:

$$L = 1 - \overline{W} \approx 2sh p_i + s(1 - 2h) D_{i/i}^g \quad (\text{B24})$$

which, from equations B19 and B23, becomes:

$$L \approx \frac{[1 + 2N(m + sh)][1 + 8Nh(m + sh)] u}{2N(m + sh)[1 + 4Nh(m + sh)]}. \quad (\text{B25})$$

Heterosis H can be defined as the increase in fitness of offspring generated by crossing parents from two different demes (denoted W_{between}), relative to the mean fitness of offspring produced by random mating within demes, which is simply \overline{W} (e.g., Whitlock et al., 2000; Theodorou and Couvet, 2002; Roze and Rousset, 2004). From equation B12, and using the fact that the average of $\zeta_{i,i(xy)}$ over offspring whose parents come from different demes is zero, we have $W_{\text{between}} \approx 1 - 2sh p_i$, yielding (to the first order in s):

$$H = 1 - \frac{\overline{W}}{W_{\text{between}}} \approx s(1 - 2h) D_{i/i}^g. \quad (\text{B26})$$

From equations B19 and B23, one obtains:

$$H \approx \frac{(1 - 2h) [1 + 2N(m + sh)] u}{2N(m + sh) [1 + 4Nh(m + sh)]}. \quad (\text{B27})$$

Finally, inbreeding depression δ may be defined as the decrease in fitness of selfed offspring relative to offspring produced by random mating within demes (see equation 14 in the main text). From equation B12, and using the fact that the average of $\zeta_{i,i(xy)}$ over selfed offspring is $(p_i + D_{i/i}^g)/2$, one obtains:

$$\delta \approx \frac{1}{2} s (1 - 2h) (p_i - D_{i/i}^g), \quad (\text{B28})$$

yielding:

$$\delta \approx \frac{(1 - 2h) [1 + 2N(m + sh)] u}{1 + 4Nh(m + sh)}. \quad (\text{B29})$$

When $m \gg sh$, equations B23, B25, B27 and B29 become equivalent to equations 35-39 in Roze and Rousset, 2004. Furthermore, the reasoning described above can be generalized to the case where individuals self-fertilize at a rate α , which leads to the same expressions as equations 35-39 in Roze and Rousset (2004), except that m is changed to $m + sh$.

Many selected loci. As in the single population case, I assume that all deleterious alleles have the same selection and dominance coefficients. The methods of Roze and Rousset (2008) can be used to derive expressions for equilibrium allele frequencies, mutation load, inbreeding depression and heterosis, taking into account the effects of pairwise interactions between selected loci. For this, general expressions have been implemented in a *Mathematica* notebook (available as a supplementary file) in order to automatically generate recursions for allele frequencies and genetic associations in a two-locus model. The results can then be extrapolated to many loci, neglecting

higher-order interactions (involving three or more loci). The main steps of the derivations are shown in the following. As before, I assume that the equilibrium frequency of deleterious alleles is small, so that terms in p_i^2 can be neglected. I also assume that $1/N$, m and s are small (of order ϵ). More general results can be derived for arbitrary values of N and m , but the expressions obtained are cumbersome and thus not shown here.

From equation A38 in Supplementary File A, the fecundity of individual y in deme x (W_{xy}) relative to the average fecundity in the whole metapopulation (\bar{W}) can be written as (to the second order in s):

$$\begin{aligned}
\frac{W_{xy}}{\bar{W}} \approx & 1 - 2sh \sum_j \zeta_{j(xy)} - s(1-2h) \sum_j (\zeta_{j,j(xy)} - D_{j,j}) \\
& + (sh)^2 \sum_{i \neq j} (\zeta_{ij(xy)} + \zeta_{i,j(xy)}) + 2s^2h(1-2h) \sum_{i \neq j} (\zeta_{ij,j(xy)} - \zeta_{i(xy)}D_{j,j}) \\
& + \frac{1}{2}s^2(1-2h)^2 \sum_{i \neq j} (\zeta_{ij,ij(xy)} - \zeta_{i,i(xy)}D_{j,j} - \zeta_{j,j(xy)}D_{i,i} - D_{ij,ij} + 2D_{i,i}D_{j,j})
\end{aligned} \tag{B30}$$

where $\zeta_{U,V(xy)}$ is given by equation B3. The mean fecundity in deme x (W_x) relative to the average fecundity in the whole population is given by the same expression, replacing each $\zeta_{U,V(xy)}$ by its average over all individuals in the deme x , $\zeta_{U,V(x)}$. From this, one obtains the following expression for the ratio W_{xy}/W_x , to the second order

in s :

$$\begin{aligned}
\frac{W_{xy}}{W_x} &\approx 1 - 2sh \sum_i (\zeta_{i(xy)} - \zeta_{i(x)}) - s(1-2h) \sum_i (\zeta_{i,i(xy)} - \zeta_{i,i(x)}) \\
&+ s^2 h^2 \sum_{i \neq j} [\zeta_{ij(xy)} - \zeta_{ij(x)} + \zeta_{i,j(xy)} - \zeta_{i,j(x)} - 4(\zeta_{i(xy)} - \zeta_{i(x)}) \zeta_{j(x)}] \\
&+ 2s^2 h(1-2h) \sum_{i \neq j} [\zeta_{ij,j(xy)} - \zeta_{ij,j(x)} - \zeta_{i(xy)} \zeta_{j,j(x)} - \zeta_{j,j(xy)} \zeta_{i(x)} + 2\zeta_{i(x)} \zeta_{j,j(x)}] \\
&+ \frac{1}{2} s^2 (1-2h)^2 \sum_{i \neq j} [\zeta_{ij,ij(xy)} - \zeta_{ij,ij(x)} - 2\zeta_{i,i(xy)} \zeta_{j,j(x)} + 2\zeta_{i,i(x)} \zeta_{j,j(x)}].
\end{aligned} \tag{B31}$$

The change in frequency of the deleterious allele at locus i due to selection is given by:

$$\Delta_s p_i = E \left[\frac{W_{xy}}{W_x} \zeta_{i(xy)} \right] \tag{B32}$$

where the average is over all demes and all individuals. Using equation B31, one obtains:

$$\begin{aligned}
\Delta_s p_i &\approx -sh p_i - s(1-3h) D_{i/i}^g + s(1-2h) D_{i/i/i}^g \\
&- s(1-2h) \sum_{j \neq i} \left(D_{ij/j}^g - D_{i/j/j}^g \right) \\
&+ s^2(1-2h) \sum_{j \neq i} \left[(1-h) \left(D_{ij/ij}^g - D_{i/i/j/j}^g \right) - 4h \left(D_{ij/i/j}^g - D_{i/i/j/j}^g \right) \right] \\
&- s^2(1-2h)^2 \sum_{j \neq i} \left(D_{ij/ij/i}^g + D_{ij/j/i/i}^g - 2D_{i/i/i/j/j}^g \right).
\end{aligned} \tag{B33}$$

Note that equation B33 involves a term in sp_i (first line, which is equivalent to the term derived in the single-locus model) and a sum over all loci j of terms in $s^2 p_i p_j$, that vanish when $h = 1/2$ (when $h = 1/2$, interactions between loci affect changes in allele frequencies through terms in $s^4 p_i p_j$, that are not considered here). In equation B33, these terms are expressed to leading order in ϵ . Associations with at least two i and two j indices ($D_{ij/ij}^g$, $D_{ij/i/j}^g$, $D_{i/i/j/j}^g$, $D_{ij/ij/i}^g$, $D_{ij/j/i/i}^g$ and $D_{i/i/i/j/j}^g$) are generated

by population structure (even in the absence of selection), while associations $D_{ij/j}^g$ and $D_{i/j/j}^g$ are generated by population structure and by selection acting at locus i .

Recursions for the first series of associations to the first order in ϵ are given by:

$$D_{i/i/j/j}^g ' \approx \left(1 - \frac{6}{2N} - 4m - 4hs\right) D_{i/i/j/j}^g + \frac{1}{2N} \left(p_i D_{j/j}^g + p_j D_{i/i}^g + 4D_{ij/i/j}^g\right) \quad (\text{B34})$$

$$D_{ij/i/j}^g ' \approx \left(1 - \frac{3}{N} - 3m - 4hs\right) \left[(1 - r_{ij}) D_{ij/i/j}^g + r_{ij} D_{i/i/j/j}^g\right] \\ + \frac{1}{2N} \left[p_i D_{j/j}^g + p_j D_{i/i}^g + 3D_{ij/i/j}^g + (1 - r_{ij}) D_{ij/i/j}^g + r_{ij} D_{i/i/j/j}^g\right] \quad (\text{B35})$$

$$D_{ij/ij}^g ' \approx \left(1 - \frac{1}{N} - 2m - 4hs\right) \left[(1 - r_{ij})^2 D_{ij/ij}^g + 2r_{ij} (1 - r_{ij}) D_{ij/i/j}^g + r_{ij}^2 D_{i/i/j/j}^g\right] \\ + \frac{1}{2N} \left[[1 - 2r_{ij} (1 - r_{ij})] (p_i + D_{ij/ij}^g) + 2r_{ij} (1 - r_{ij}) (p_i D_{j/j}^g + p_j D_{i/i}^g)\right] \quad (\text{B36})$$

$$D_{i/i/i/j/j}^g ' \approx \left(1 - \frac{5}{N} - 5m - 5hs\right) D_{i/i/i/j/j}^g + \frac{1}{2N} \left(p_j D_{i/i/i}^g + 6D_{ij/j/i/i}^g + 3D_{i/i/j/j}^g\right) \quad (\text{B37})$$

$$D_{ij/j/i/i}^g ' \approx \left(1 - \frac{6}{N} - 4m - 5hs\right) \left[(1 - r_{ij}) D_{ij/j/i/i}^g + r_{ij} D_{i/i/i/j/j}^g\right] \\ + \frac{1}{2N} \left[p_j D_{i/i/i}^g + (1 - r_{ij}) \left(6D_{ij/j/i/i}^g + 2D_{ij/ij/i}^g + 3D_{ij/i/j}^g\right) \right. \\ \left. + r_{ij} \left(5D_{ij/j/i/i}^g + 3D_{i/i/i/j/j}^g + 3D_{i/i/j/j}^g\right)\right] \quad (\text{B38})$$

$$D_{ij/ij/i}^g ' \approx \left(1 - \frac{3}{N} - 3m - 5hs\right) \\ \times \left[(1 - r_{ij})^2 D_{ij/ij/i}^g + 2r_{ij} (1 - r_{ij}) D_{ij/j/i/i}^g + r_{ij}^2 D_{i/i/i/j/j}^g\right] \\ + \frac{(1 - r_{ij})^2}{2N} \left(p_j D_{i/i}^g + 3D_{ij/ij/i}^g + 2D_{ij/ij}^g\right) \\ + \frac{r_{ij} (1 - r_{ij})}{N} \left(p_j D_{i/i/i}^g + D_{ij/j/i/i}^g + D_{ij/ij/i}^g + 3D_{ij/i/j}^g\right) \\ + \frac{r_{ij}^2}{2N} \left(p_j D_{i/i}^g + 2D_{ij/j/i/i}^g + D_{ij/ij/i}^g + 2D_{i/i/j/j}^g\right). \quad (\text{B39})$$

From this, one obtains at equilibrium, to leading order,

$$D_{ij/ij}^g \approx D_{ij/i/j}^g \approx D_{i/i/j/j}^g \approx \frac{p_i p_j}{[1 + 4N(m + sh)]^2} \quad (\text{B40})$$

$$D_{ij/ij/i}^g \approx D_{ij/j/i/i}^g \approx D_{i/i/i/j/j}^g \approx \frac{p_i p_j}{[1 + 2N(m + sh)][1 + 4N(m + sh)]^2}. \quad (\text{B41})$$

indicating that the last two lines of equation B33 are of order $s^2 \epsilon p_i \sum_j p_j$ (since these lines cancel when equations B40 and B41 are used).

Recursions for $D_{ij/j}^g$ and $D_{i/j/j}^g$ to leading order are given by:

$$\begin{aligned} D_{ij/j}'^g &\approx \frac{1}{2N} D_{ij/j}^g + \left(1 - \frac{1}{N} - 2m - 3hs\right) \left[(1 - r_{ij}) D_{ij/j}^g + r_{ij} D_{i/j/j}^g \right] \\ &\quad - sh \left[(1 - r_{ij}) \left(D_{ij/ij}^g - 2D_{ij/i/j}^g + D_{i/i}^g D_{j/j}^g \right) \right. \\ &\quad \quad \left. + r_{ij} \left(2D_{ij/i/j}^g - 3D_{i/i/j/j}^g + D_{i/i}^g D_{j/j}^g \right) \right] \\ &\quad - s(1 - 2h) \left[(1 - r_{ij}) \left(D_{ij/ij/j}^g - 2D_{ij/i/j/j}^g + D_{i/i/i}^g D_{j/j}^g \right) \right. \\ &\quad \quad \left. + r_{ij} \left(D_{ij/i/j/j}^g - 2D_{i/i/i/j/j}^g + D_{i/i/i}^g D_{j/j}^g \right) \right] \\ &\quad - s(1 - 2h) \left(D_{ij/i/j}^g - D_{i/i}^g D_{j/j}^g \right) \end{aligned} \quad (\text{B42})$$

$$\begin{aligned} D_{i/j/j}'^g &\approx \frac{1}{N} D_{ij/j}^g + \left(1 - \frac{3}{2N} - 3m - 3hs\right) D_{i/j/j}^g \\ &\quad - sh \left(2D_{ij/i/j}^g - 3D_{i/i/j/j}^g + D_{i/i}^g D_{j/j}^g \right) \\ &\quad - s(1 - 2h) \left(2D_{ij/i/j/j}^g - 3D_{i/i/i/j/j}^g + D_{i/i/i}^g D_{j/j}^g \right) \\ &\quad - s(1 - 2h) \left(D_{i/i/j/j}^g - D_{i/i}^g D_{j/j}^g \right). \end{aligned} \quad (\text{B43})$$

From equations B34–B39 and B42–B43, one obtains that $D_{ij/j}^g$ and $D_{i/j/j}^g$ are both of order $s p_i p_j$ at equilibrium. However, leading-order expressions for these associations are identical, causing the term on the second line of equation B33 to cancel. Therefore, the second line of equation B33 is also of order $s^2 \epsilon p_i \sum_j p_j$.

Finally, recursions for $D_{i/i}^g$ and $D_{i/i/i}^g$, taking into account effects of pairwise interactions between loci are given by (to leading order):

$$D_{i/i}^{g'} \approx \frac{p_i}{2N} + \left(1 - \frac{1}{2N} - 2m - 2hs\right) D_{i/i}^g - 2s(1-2h) \sum_{j \neq i} \left(D_{ij/i/j}^g - D_{i/i/j/j}^g\right) \quad (\text{B44})$$

$$D_{i/i/i}^{g'} \approx \frac{3}{2N} D_{i/i}^g + \left(1 - \frac{3}{2N} - 3m - 3hs\right) D_{i/i/i}^g - 3s(1-2h) \sum_{j \neq i} \left(D_{ij/j/i/i}^g - D_{i/i/i/j/j}^g\right). \quad (\text{B45})$$

At equilibrium, and assuming freely recombining loci, one obtains:

$$D_{i/i}^g \approx \frac{p_i}{1 + 4N(m + sh)} \left[1 - s(1-2h) \frac{8Nm}{[1 + 4N(m + sh)]^2} \sum_j p_j\right] \quad (\text{B46})$$

$$D_{i/i/i}^g \approx \frac{p_i}{[1 + 2N(m + sh)][1 + 4N(m + sh)]} \times \left[1 - s(1-2h) \frac{4Nm[3 + 8N(m + sh)]}{[1 + 2N(m + sh)][1 + 4N(m + sh)]^2} \sum_j p_j\right]. \quad (\text{B47})$$

In order to obtain equations B46 and B47, the terms $D_{ij/i/j}^g - D_{i/i/j/j}^g$ and $D_{ij/j/i/i}^g - D_{i/i/i/j/j}^g$ that appear in equations B44 and B45 must be expressed to the first order in ϵ . From equations B34–B39, one obtains:

$$D_{ij/i/j}^g - D_{i/i/j/j}^g \approx \frac{m p_i p_j}{r_{ij} [1 + 4N(m + sh)]^2} \quad (\text{B48})$$

$$D_{ij/j/i/i}^g - D_{i/i/i/j/j}^g \approx \frac{m p_i p_j}{r_{ij} [1 + 2N(m + sh)][1 + 4N(m + sh)]^2} \quad (\text{B49})$$

(note that although these expressions diverge when r_{ij} tends to zero, expressions that do not diverge can be obtained by assuming that r_{ij} is of order ϵ).

From equations B46 and B47, one can see that interactions between loci affect the first line of equation B33 through a term of order $s^2 p_i \sum_j p_j$, which is thus higher in magnitude than the terms on the last three lines (which are of order $s^2 \epsilon p_i \sum_j p_j$).

Neglecting these terms, one finally obtains the following approximation for the mean number of deleterious alleles per haplotype, $n = \sum_i p_i$ at equilibrium:

$$n \approx (1 - I_3) \frac{[1 + 2N(m + sh)][1 + 4N(m + sh)]U}{2Ns(m + sh)[1 + 4Nh(m + sh)]} \quad (\text{B50})$$

with:

$$I_3 = (1 - 2h)U \frac{m}{m + sh} \frac{1 + 8N(m + sh)[h - (1 - 3h)N(m + sh)]}{N(m + sh)[1 + 4N(m + sh)][1 + 4Nh(m + sh)]^2}. \quad (\text{B51})$$

From equation A20 in Supplementary File A, and neglecting the term in $D_{ij,ij} - D_{i,i}D_{j,j}$ which is of order ϵ , we have:

$$\bar{W} \approx e^{-2shn - s(1-2h)\sum_i D_{i,i}} \quad (\text{B52})$$

From equations B46 and B50, one obtains:

$$\bar{W} \approx \exp \left[- (1 - I_4) \frac{[1 + 2N(m + sh)][1 + 8Nh(m + sh)]U}{2N(m + sh)[1 + 4Nh(m + sh)]} \right] \quad (\text{B53})$$

with:

$$I_4 = (1 - 2h)U \frac{m}{m + sh} \frac{1 + 8Nh(m + sh)[1 - (1 - 4h)N(m + sh)]}{N(m + sh)[1 + 4Nh(m + sh)]^2[1 + 8Nh(m + sh)]}. \quad (\text{B54})$$

As we have seen in the previous section, heterosis is defined as $H = 1 - \bar{W}/\bar{W}_{\text{between}}$, where \bar{W}_{between} is the fitness of offspring obtained by crossing parents from two different demes. Since $\bar{W}_{\text{between}} \approx e^{-2shn}$, we have $H \approx 1 - e^{-s(1-2h)\sum_i D_{i,i}}$, which yields:

$$H \approx 1 - \exp \left[- (1 - I_5) \frac{(1 - 2h)[1 + 2N(m + sh)]U}{2N(m + sh)[1 + 4Nh(m + sh)]} \right] \quad (\text{B55})$$

with:

$$I_5 = (1 - 2h)U \frac{m}{m + sh} \frac{1 + 8Nh(m + sh)[1 + N(m + sh)]}{N(m + sh)[1 + 4Nh(m + sh)]^2}. \quad (\text{B56})$$

Finally, the average inbreeding depression within demes is given by:

$$\delta = 1 - \mathbb{E}_x \left[\frac{W_{\text{self},x}}{W_{\text{out},x}} \right] \quad (\text{B57})$$

where $W_{\text{self},x}$ and $W_{\text{out},x}$ are the average fitnesses of individuals produced by selfing and by outcrossing in deme x (respectively), while E_x stands for the average over all demes x (e.g., Whitlock, 2002; Glémin et al., 2003; Roze and Rousset, 2004). Assuming that the variances of $W_{\text{self},x}$ and $W_{\text{out},x}$ across demes remain small, we have (e.g., Appendix 1 in Lynch and Walsh, 1998):

$$\delta \approx 1 - \frac{E_x [W_{\text{self},x}]}{E_x [W_{\text{out},x}]} \left[1 + \frac{\text{Var}_x [W_{\text{out},x}]}{E_x [W_{\text{out},x}]^2} - \frac{\text{Cov}_x [W_{\text{out},x}, W_{\text{self},x}]}{E_x [W_{\text{out},x}] E_x [W_{\text{self},x}]} \right] \quad (\text{B58})$$

where Var_x and Cov_x stand for the variance and covariance across demes. Expressions for $\text{Var}_x [W_{\text{out},x}]$ and $\text{Cov}_x [W_{\text{out},x}, W_{\text{self},x}]$ can be computed using the same methods as above. One obtains in particular:

$$\text{Var}_x [W_{\text{out},x}] \approx s^2 (1 - 2h)^2 \sum_{i \neq j} \left(D_{i/i/j/j}^g - D_{i/i}^g D_{j/j}^g \right) \quad (\text{B59})$$

which is of order ϵU^2 when $1/N$, m and s are of order ϵ , since from equation B40 $D_{i/i/j/j}^g - D_{i/i}^g D_{j/j}^g$ is of order $\epsilon p_i p_j$. Similarly, one obtains that $\text{Cov}_x [W_{\text{out},x}, W_{\text{self},x}]$ is also of order ϵU^2 . Neglecting these terms, we thus have:

$$\delta \approx 1 - \frac{E_x [W_{\text{self},x}]}{E_x [W_{\text{out},x}]} \quad (\text{B60})$$

where $E_x [W_{\text{out},x}]$ is equivalent to $\bar{W} \approx e^{-2shn - s(1-2h)\sum_i D_{i,i}}$, while $E_x [W_{\text{self},x}]$ is given by $e^{-2shn - s(1-2h)\sum_i D_{i,i}^{\text{self}}}$ (where $D_{i,i}^{\text{self}}$ is the average of $\zeta_{i,i(xy)}$ over selfed offspring). Using the fact that $D_{i,i}^{\text{self}} \approx (p_i + D_{i,i})/2$, one obtains $\delta \approx 1 - e^{-\frac{s}{2}(1-2h)(n - \sum_i D_{i,i})}$.

From equations B46 and B50, this is:

$$\delta \approx 1 - \exp \left[- (1 + I_6) \frac{(1 - 2h) [1 + 2N(m + sh)] U}{1 + 4Nh(m + sh)} \right] \quad (\text{B61})$$

with:

$$I_6 = 2(1 - 2h)^2 U \frac{m}{m + sh} \frac{1}{N(m + sh) [1 + 4Nh(m + sh)]^2}. \quad (\text{B62})$$

LITERATURE CITED

- Glémin, S., J. Ronfort, and T. Bataillon. 2003. Patterns of inbreeding depression and architecture of the load in subdivided populations. *Genetics* 165:2193–2212.
- Lynch, M. and J. B. Walsh. 1998. *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Sunderland, MA.
- Ohta, T. and M. Kimura. 1969. Linkage disequilibrium at steady state determined by random genetic drift and recurrent mutation. *Genetics* 63:229–238.
- . 1971. Linkage disequilibrium between two segregating nucleotide sites under the steady flux of mutations in a finite population. *Genetics* 68:570–580.
- Roze, D. 2009. Diploidy, population structure and the evolution of recombination. *Am. Nat.* 174:S79–S94.
- Roze, D. and F. Rousset. 2003. Selection and drift in subdivided populations: a straightforward method for deriving diffusion approximations, and examples involving dominance, selfing and local extinctions. *Genetics* 165:2153–2166.
- . 2004. Joint effects of self-fertilization and population structure on mutation load, inbreeding depression and heterosis. *Genetics* 167:1001–1015.
- . 2008. Multilocus models in the infinite island model of population structure. *Theor. Popul. Biol.* 73:529–542.
- Theodorou, K. and D. Couvet. 2002. Inbreeding depression and heterosis in a subdivided population: influence of the mating system. *Genet. Res.* 80:107–116.

Wakeley, J. 2003. Polymorphism and divergence for island-model species. *Genetics* 163:411–420.

Whitlock, M. C. 2002. Selection, load and inbreeding depression in a large metapopulation. *Genetics* 160:1191–1202.

———. 2003. Fixation probability and time in subdivided populations. *Genetics* 164:767–779.

Whitlock, M. C., P. K. Ingvarsson, and T. Hatfield. 2000. Local drift load and the heterosis of interconnected populations. *Heredity* 84:452–457.

FILE S3

Mathematica notebook

Available for download at www.genetics.org/lookup/suppl/doi:10.1534/genetics.115.178533/-/DC1