

2 **Outcrossing population.** A general expression for inbreeding depression, including
 3 the effects of interactions between pairs of loci can be obtained from equation A1 in
 4 Supplementary File S1. We will first consider the case of a fully outcrossing population
 5 ($\sigma = 0$). Using the fact that associations $\tilde{D}_{j,j}$, $\tilde{D}_{j,k}$ and $\tilde{D}_{jk,j}$ equal zero among offspring
 6 produced by random mating, the mean fitness of offspring produced by mating between
 7 randomly sampled parents divided by the mean fitness of the parental population is
 8 given by:

$$\frac{\overline{W}^{\text{out}}}{\overline{W}} = 1 + 2 \sum_{j < k} a_{jk} \left(\tilde{D}_{jk}^{\text{out}} - \tilde{D}_{jk} \right) + \sum_{j < k} a_{jk,jk} \left(D_{jk,jk}^{\text{out}} - D_{jk,jk} \right) \quad (\text{B1})$$

9 where $\tilde{D}_{jk}^{\text{out}}$ and $D_{jk,jk}^{\text{out}}$ are measured among offspring, and \tilde{D}_{jk} , $D_{jk,jk}$ among parents.
 10 The association $D_{jk,jk}$ equals \tilde{D}_{jk}^2 under random mating, while \tilde{D}_{jk} is reduced by a
 11 factor $1 - \rho_{jk}$ by recombination (assuming no selection among parents), giving:

$$\frac{\overline{W}^{\text{out}}}{\overline{W}} = 1 - 2 \sum_{j < k} \rho_{jk} a_{jk} \tilde{D}_{jk} - \sum_{j < k} \rho_{jk} (2 - \rho_{jk}) a_{jk,jk} \tilde{D}_{jk}^2. \quad (\text{B2})$$

12 The mean fitness of offspring produced by selfing from randomly sampled parents,
 13 divided by the mean fitness of the parental population is given by (from equation A1):

$$\begin{aligned} \frac{\overline{W}^{\text{self}}}{\overline{W}} &= 1 + \sum_j a_{j,j} D_{j,j}^{\text{self}} + 2 \sum_{j < k} a_{jk} \left(\tilde{D}_{jk}^{\text{self}} - \tilde{D}_{jk} \right) \\ &+ 2 \sum_{j < k} a_{j,k} \tilde{D}_{j,k}^{\text{self}} + 2 \sum_{j,k} a_{jk,j} \tilde{D}_{jk,j}^{\text{self}} + 2 \sum_{j < k} a_{jk,k} \tilde{D}_{jk,k}^{\text{self}} \\ &+ \sum_{j < k} a_{jk,jk} \left(D_{jk,jk}^{\text{self}} - \tilde{D}_{jk}^2 \right). \end{aligned} \quad (\text{B3})$$

14 Associations $D_{U,V}^{\text{self}}$ in the expression above are measured among selfed offspring. Taking
 15 into account the possible configurations of genes within parental individuals, and using

16 equation A21 in Supplementary File S1 to eliminate repeated indices, one obtains:

$$D_{j,j}^{\text{self}} = \frac{1}{2} p_j q_j, \quad \tilde{D}_{jk}^{\text{self}} = (1 - \rho_{jk}) \tilde{D}_{jk}, \quad \tilde{D}_{j,k}^{\text{self}} = \frac{1}{2} \tilde{D}_{jk}, \quad (\text{B4})$$

17

$$D_{jk,j}^{\text{self}} = \frac{1}{2} (1 - 2p_j) (1 - \rho_{jk}) \tilde{D}_{jk}, \quad \tilde{D}_{jk,k}^{\text{self}} = \frac{1}{2} (1 - 2p_k) (1 - \rho_{jk}) \tilde{D}_{jk}, \quad (\text{B5})$$

18

$$D_{jk,jk}^{\text{self}} = \frac{1}{2} [1 - 2\rho_{jk} (1 - \rho_{jk})] (p_j q_j p_k q_k + \tilde{D}_{jk}^2). \quad (\text{B6})$$

19 Inbreeding depression is defined as

$$\delta = 1 - \frac{\overline{W}^{\text{self}}}{\overline{W}^{\text{out}}} = 1 - \frac{\overline{W}^{\text{self}} / \overline{W}}{\overline{W}^{\text{out}} / \overline{W}}. \quad (\text{B7})$$

20 From the expressions above, we have to the second order in $a_{\text{U,V}}$ coefficients (and thus

21 neglecting the terms in \tilde{D}_{jk}^2):

$$\begin{aligned} \delta \approx & -\frac{1}{2} \sum_j a_{j,j} p_j q_j - \frac{1}{2} \sum_{j < k} a_{jk,jk} [1 - 2\rho_{jk} (1 - \rho_{jk})] p_j q_j p_k q_k - \sum_{j < k} a_{j,k} \tilde{D}_{jk} \\ & - \sum_{j < k} a_{jk,j} (1 - 2p_j) (1 - \rho_{jk}) \tilde{D}_{jk} - \sum_{j < k} a_{jk,k} (1 - 2p_k) (1 - \rho_{jk}) \tilde{D}_{jk} \end{aligned} \quad (\text{B8})$$

22 which corresponds to equation 17 in the main text.

23 When the deleterious mutation rate is high, equation B8 may be higher than 1

24 (while from equation B7, inbreeding depression cannot be higher than 1). In general,

25 more accurate expressions for parameter values leading to high inbreeding depression

26 can be obtained by assuming that the effects of individual loci (and their interac-

27 tions) on δ do multiply (rather than sum). Using the present framework, and to

28 the first order in $a_{\text{U,V}}$ coefficients, this can be achieved by assuming that the vari-

29 ance in log-fitness among individuals stays small, so that $\overline{W} \approx e^{\overline{\ln W}}$, leading to

30 $\delta \approx 1 - e^{\overline{\ln W}^{\text{self}} - \overline{\ln W}^{\text{out}}}$. To the first order in $a_{\text{U,V}}$ coefficients, equation 8 in the main

31 text yields $\ln W - \ln \overline{W} \approx \sum_{\text{U,V}} a_{\text{U,V}} (\zeta_{\text{U,V}} - D_{\text{U,V}})$. Using the same reasoning as above,

32 one obtains (still to the first order in $a_{\text{U,V}}$ coefficients) $\overline{\ln W}^{\text{out}} - \ln \overline{W} \approx 0$, while

33 $\overline{\ln W}_{\text{self}} - \ln \overline{W} \approx \frac{1}{2} \sum_j a_{j,j} p_j q_j + \frac{1}{2} \sum_{j < k} a_{jk,jk} [1 - 2\rho_{jk} (1 - \rho_{jk})] p_j q_j p_k q_k$, leading to
 34 $\delta \approx 1 - \exp \left[\frac{1}{2} \sum_j a_{j,j} p_j q_j + \frac{1}{2} \sum_{j < k} a_{jk,jk} [1 - 2\rho_{jk} (1 - \rho_{jk})] p_j q_j p_k q_k \right]$ (which cannot
 35 be greater than 1). In a population undergoing partial selfing, the same reasoning
 36 leads to equation 24 in the main text.

37 Equation B8 is modified when inbreeding depression is measured after selection,
 38 that is, when the contribution of parents to the pools of selfed and outcrossed offspring
 39 is proportional to their fitness. In that case, we have $\tilde{D}_{jk}^{\text{out}} = \tilde{D}_{jk}^{\text{self}} = (1 - \rho_{jk}) \tilde{D}'_{jk} +$
 40 $\rho_{jk} \tilde{D}'_{j,k}$ where \tilde{D}'_{jk} and $\tilde{D}'_{j,k}$ are measured after selection, while $\tilde{D}_{jk}^{\text{self}} = \frac{1}{2} (\tilde{D}'_{jk} + \tilde{D}'_{j,k})$
 41 and $\tilde{D}_{jk,j}^{\text{self}} = \frac{1}{2} (1 - 2p_j) [(1 - \rho_{jk}) \tilde{D}'_{jk} + \rho_{jk} \tilde{D}'_{j,k}]$. This yields:

$$\begin{aligned} \delta' \approx & -\frac{1}{2} \sum_j a_{j,j} p_j q_j - \frac{1}{2} \sum_{j < k} a_{jk,jk} [1 - 2\rho_{jk} (1 - \rho_{jk})] p_j q_j p_k q_k \\ & - \sum_{j < k} a_{j,k} (\tilde{D}'_{jk} + \tilde{D}'_{j,k}) - \sum_{j,k} a_{jk,j} (1 - 2p_j) [(1 - \rho_{jk}) \tilde{D}'_{jk} + \rho_{jk} \tilde{D}'_{j,k}] \end{aligned} \quad (\text{B9})$$

42 where δ' stands for inbreeding depression measured after selection.

43

44 **Partially selfing population.** Under partial selfing, equation B1 becomes:

$$\begin{aligned} \frac{\overline{W}^{\text{out}}}{\overline{W}} = & 1 - \sum_j a_{j,j} D_{j,j} + 2 \sum_{j < k} a_{jk} (\tilde{D}_{jk}^{\text{out}} - \tilde{D}_{jk}) - 2 \sum_{j < k} a_{j,k} D_{j,k} \\ & - 2 \sum_{j < k} a_{jk,j} D_{jk,j} - 2 \sum_{j < k} a_{jk,k} D_{jk,k} + \sum_{j < k} a_{jk,jk} (D_{jk,jk}^{\text{out}} - D_{jk,jk}) \end{aligned} \quad (\text{B10})$$

45 while equation B3 becomes:

$$\begin{aligned} \frac{\overline{W}^{\text{self}}}{\overline{W}} = & 1 + \sum_j a_{j,j} (D_{j,j}^{\text{self}} - D_{j,j}) + 2 \sum_{j < k} a_{jk} (\tilde{D}_{jk}^{\text{self}} - \tilde{D}_{jk}) \\ & + 2 \sum_{j < k} a_{j,k} (\tilde{D}_{j,k}^{\text{self}} - \tilde{D}_{j,k}) + 2 \sum_{j < k} a_{jk,j} (\tilde{D}_{jk,j}^{\text{self}} - \tilde{D}_{jk,j}) \\ & + 2 \sum_{j < k} a_{jk,k} (\tilde{D}_{jk,k}^{\text{self}} - \tilde{D}_{jk,k}) + \sum_{j < k} a_{jk,jk} (D_{jk,jk}^{\text{self}} - D_{jk,jk}). \end{aligned} \quad (\text{B11})$$

46 Associations among selfed and outcrossed offspring are given by:

$$D_{j,j}^{\text{self}} = \frac{1}{2} (p_j q_j + D_{j,j}), \quad (\text{B12})$$

47

$$\tilde{D}_{jk}^{\text{self}} = \tilde{D}_{jk}^{\text{out}} = (1 - \rho_{jk}) \tilde{D}_{jk} + \rho_{jk} \tilde{D}_{j,k}, \quad D_{jk,jk}^{\text{out}} = \left(\tilde{D}_{jk}^{\text{out}} \right)^2, \quad (\text{B13})$$

48

$$\tilde{D}_{j,k}^{\text{self}} = \frac{1}{2} \left(\tilde{D}_{jk} + \tilde{D}_{j,k} \right), \quad (\text{B14})$$

49

$$\tilde{D}_{jk,j}^{\text{self}} = \frac{1}{2} \left[\tilde{D}_{jk,j} + (1 - 2p_j) \left[(1 - \rho_{jk}) \tilde{D}_{jk} + \rho_{jk} \tilde{D}_{j,k} \right] \right], \quad (\text{B15})$$

50

$$\begin{aligned} \tilde{D}_{jk,jk}^{\text{self}} = & \frac{1}{2} \left[(1 - \rho_{jk})^2 \left[p_j q_j p_k q_k + D_{jk,jk} + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{jk} \right] \right. \\ & + 2\rho_{jk} (1 - \rho_{jk}) \left[p_j q_j D_{k,k} + p_k q_k D_{j,j} + (1 - 2p_j) \tilde{D}_{j,k} + (1 - 2p_k) \tilde{D}_{j,k,j} \right] \\ & \left. + \rho_{jk}^2 \left[p_j q_j p_k q_k + D_{jk,jk} + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{j,k} \right] \right]. \end{aligned} \quad (\text{B16})$$

51 Throughout the following, ϵ stands for the order of magnitude of the largest of $a_{\text{U,V}}$
52 coefficients in absolute value. Associations \tilde{D}_{jk} , $\tilde{D}_{j,k}$, $\tilde{D}_{jk,j}$, $\tilde{D}_{jk,k}$ are generated by
53 selection and are thus of order ϵ . By contrast, associations $D_{j,j}$ and $D_{jk,jk}$ are generated
54 by partial selfing even in the absence of selection, in which case they equal $F p_j q_j$ and
55 $(G_{jk} + F^2) p_j q_j p_k q_k$ at equilibrium (respectively), where F is the inbreeding coefficient
56 and G_{jk} the identity disequilibrium between loci j and k (e.g., Roze, 2015). From this,

57 one obtains to the second order in ϵ :

$$\begin{aligned}
\delta = & -\frac{1}{2} \sum_j a_{j,j} (p_j q_j + D_{j,j}) \left(1 + \sum_k a_{k,k} D_{k,k} \right) - \sum_{j < k} a_{j,k} \left(\tilde{D}_{jk} + \tilde{D}_{j,k} \right) \\
& - \sum_{j,k} a_{jk,j} \left[\tilde{D}_{jk,j} + (1 - 2p_j) \left[(1 - \rho_{jk}) \tilde{D}_{jk} + \rho_{jk} \tilde{D}_{j,k} \right] \right] \\
& - \frac{1}{2} \sum_{j < k} a_{jk,jk} \left[(1 - \rho_{jk})^2 \left[p_j q_j p_k q_k + D_{jk,jk} + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{jk} \right] \right. \\
& \quad + 2\rho_{jk} (1 - \rho_{jk}) \left[p_j q_j D_{k,k} + p_k q_k D_{j,j} \right. \\
& \quad \quad \left. \left. + (1 - 2p_j) \tilde{D}_{j,k,k} + (1 - 2p_k) \tilde{D}_{j,k,j} \right] \right. \\
& \quad \left. + \rho_{jk}^2 \left[p_j q_j p_k q_k + D_{jk,jk} + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{j,k} \right] \right]. \tag{B17}
\end{aligned}$$

58 To the first order in ϵ and when $\rho_{jk} = 1/2$, equation B17 is equivalent to equation 19
59 in the main text. Expressions for genetic associations to the first order in ϵ can be
60 obtained using standard multilocus techniques (e.g., Kirkpatrick et al., 2002). Using
61 a rare allele approximation — that is, neglecting terms in $(p_j q_j)^2$ — and assuming
62 $a_{jk} = a_{j,k}$, one obtains:

$$D_{j,j} = F (p_j q_j + \Delta_{\text{sel}} D_{j,j}), \tag{B18}$$

$$\tilde{D}_{jk} = \frac{2 - \sigma (1 - 2\rho_{jk})}{2\rho_{jk} (1 - \sigma)} \Delta_{\text{sel}} \tilde{D}_{jk}, \quad \tilde{D}_{j,k} = \frac{\sigma (1 + 2\rho_{jk})}{2\rho_{jk} (1 - \sigma)} \Delta_{\text{sel}} \tilde{D}_{jk}, \tag{B19}$$

$$\tilde{D}_{jk,j} = F \left[\Delta_{\text{sel}} \tilde{D}_{jk,j} + (1 - 2p_j) \tilde{D}_{jk} \right], \tag{B20}$$

65 with

$$\Delta_{\text{sel}} D_{j,j} = \sum_k \left(a_{k,k} G_{jk} + [a_{jk,k} (1 - 2p_j) + a_{jk,jk}] (G_{jk} + F^2) \right) p_j q_j p_k q_k, \tag{B21}$$

$$\begin{aligned}
\Delta_{\text{sel}} \tilde{D}_{jk} = & \left[a_{jk} \left[(1 + F)^2 + G_{jk} \right] + a_{jk,jk} (1 - 2p_j) (1 - 2p_k) (G_{jk} + F^2) \right. \\
& \left. + [a_{jk,j} (1 - 2p_j) + a_{jk,k} (1 - 2p_k)] [F (1 + F) + G_{jk}] \right] p_j q_j p_k q_k, \tag{B22}
\end{aligned}$$

$$\begin{aligned} \Delta_{\text{sel}} \tilde{D}_{jk,j} = & \left[[a_k + a_{k,k} (1 - 2p_k)] G_{jk} + [2a_{jk} (1 - 2p_j) + a_{jk,j}] [F (1 + F) + G_{jk}] \right. \\ & \left. + [2a_{jk,k} (1 - 2p_j) + a_{jk,jk}] (1 - 2p_k) (G_{jk} + F^2) \right] p_j q_j p_k q_k . \end{aligned} \quad (\text{B23})$$

68 Finally, $D_{jk,jk}$ is obtained by solving:

$$\begin{aligned} \tilde{D}_{jk,jk} = & \frac{\sigma}{2} \left[(1 - \rho_{jk})^2 [p_j q_j p_k q_k + D_{jk,jk}' + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{jk}'] \right. \\ & + 2\rho_{jk} (1 - \rho_{jk}) [p_j q_j D_{k,k}' + p_k q_k D_{j,j}' + (1 - 2p_j) \tilde{D}_{jk,k}' + (1 - 2p_k) \tilde{D}_{jk,j}'] \\ & \left. + \rho_{jk}^2 [p_j q_j p_k q_k + D_{jk,jk}' + (1 - 2p_j) (1 - 2p_k) \tilde{D}_{j,k}'] \right], \end{aligned} \quad (\text{B24})$$

69 where associations $D_{\mathbb{U},\mathbb{V}'}$ are measured after selection and are given by $D_{\mathbb{U},\mathbb{V}'} = D_{\mathbb{U},\mathbb{V}} +$

70 $\Delta_{\text{sel}} D_{\mathbb{U},\mathbb{V}}$, with:

$$\begin{aligned} \Delta_{\text{sel}} \tilde{D}_{jk,jk} = & \left[2a_j (1 - 2p_j) + 2a_k (1 - 2p_k) + a_{j,j} + a_{k,k} + 4a_{jk} (1 - 2p_j) (1 - 2p_k) \right. \\ & \left. + 2a_{jk,j} (1 - 2p_k) + 2a_{jk,k} (1 - 2p_j) + a_{jk,jk} \right] (G_{jk} + F^2) p_j q_j p_k q_k . \end{aligned} \quad (\text{B25})$$

71 Computing δ also requires an expression for $p_j q_j$ at equilibrium. Assuming the same

72 mutation rate u between both alleles at the same locus, this can be obtained from

73 $-\Delta_{\text{sel}} p_j q_j = u$, with:

$$\begin{aligned} \Delta_{\text{sel}} p_j q_j = & a_j (1 - 2p_j) (p_j q_j + D_{j,j}) + \sum_{k \neq j} a_k (1 - 2p_j) (\tilde{D}_{jk} + \tilde{D}_{j,k}) \\ & + a_{j,j} D_{j,j} + \sum_{k \neq j} a_{k,k} (1 - 2p_j) \tilde{D}_{jk,k} + \sum_{k \neq j} a_{jk,jk} D_{jk,jk} \\ & + \sum_{k \neq j} a_{jk} [\tilde{D}_{jk} + \tilde{D}_{j,k} + 2(1 - 2p_j) \tilde{D}_{jk,j}] + 2 \sum_{k \neq j} a_{jk,j} \tilde{D}_{jk,j} \\ & + \sum_{k \neq j} a_{jk,k} [\tilde{D}_{jk,k} + (1 - 2p_j) (p_j q_j D_{k,k} + D_{jk,jk})] . \end{aligned} \quad (\text{B26})$$

74 **Relation to previous results.** Previous expressions for inbreeding depression in-
75 cluding the effect of identity disequilibria between pairs of loci (Roze, 2015) and of
76 epistasis generated by Gaussian stabilizing selection (Abu Awad and Roze, 2018) can
77 be recovered as special cases of the general equations given above. In the case of
78 uniformly deleterious alleles without epistasis (Roze, 2015), selection coefficients are
79 given by equations A10 – A14 in Supplementary File S1, with $e_{\text{axa}} = e_{\text{axd}} = e_{\text{dxd}} = 0$.
80 To the second order in s and assuming free recombination among loci, the equations
81 above simplify to:

$$\begin{aligned} \delta \approx & -\frac{1}{2} \sum_j a_{j,j} (p_j q_j + D_{j,j}) \left(1 + \sum_k a_{k,k} D_{k,k} \right) \\ & - \frac{1}{4} \sum_{j < k} a_{jk,jk} [(1 + F)^2 + G] p_j q_j p_k q_k \end{aligned} \quad (\text{B27})$$

82 where G is the identity disequilibrium,

$$\begin{aligned} \Delta_{\text{sel}} p_j q_j = & a_j (p_j q_j + D_{j,j}) + a_{j,j} D_{j,j} + \sum_{k \neq j} a_{k,k} \tilde{D}_{jk,k} \\ & + \sum_{k \neq j} a_{jk,k} (p_j q_j D_{k,k} + D_{jk,jk}) + \sum_{k \neq j} a_{jk,jk} D_{jk,jk} \end{aligned} \quad (\text{B28})$$

83 with:

$$D_{j,j} = F \left[1 + \sum_{k \neq j} a_{k,k} G p_k q_k \right] p_j q_j, \quad (\text{B29})$$

$$\tilde{D}_{jk,k} = F (a_j + a_{j,j}) G p_j q_j p_k q_k, \quad D_{jk,jk} = (G + F^2) p_j q_j p_k q_k. \quad (\text{B30})$$

85 Equations B27 – B30 yield equation 14 in Roze (2015), expressed to the second order
86 in U .

87 Selection coefficients under Gaussian stabilizing selection are given by equations
88 A22 – A26 in Supplementary File S1. Approximating the identity disequilibrium G_{jk}

89 by its expression under free recombination (G), we have:

$$\begin{aligned} \delta = & -\frac{1}{2} \sum_j a_{j,j} (p_j q_j + D_{j,j}) \left(1 + \sum_k a_{k,k} D_{k,k} \right) - \sum_{j < k} a_{jk} \left(\tilde{D}_{jk} + \tilde{D}_{j,k} \right) \\ & - \frac{1}{4} \sum_{j < k} a_{jk,jk} \left[(1 + F)^2 + G \right] p_j q_j p_k q_k \end{aligned} \quad (\text{B31})$$

90

$$\begin{aligned} \Delta_{\text{sel}} p_j q_j = & a_j (1 - 2p_j) (p_j q_j + D_{j,j}) + a_{j,j} D_{j,j} + \sum_{k \neq j} a_{k,k} (1 - 2p_j) \tilde{D}_{jk,k} \\ & + \sum_{k \neq j} a_{jk} \left[\tilde{D}_{jk} + \tilde{D}_{j,k} + 2(1 - 2p_j) \tilde{D}_{jk,j} \right] \\ & + \sum_{k \neq j} a_{jk,k} (1 - 2p_j) (p_j q_j D_{k,k} + D_{jk,jk}) + \sum_{k \neq j} a_{jk,jk} D_{jk,jk} \end{aligned} \quad (\text{B32})$$

91 with:

$$D_{j,j} = F \left[1 + \sum_{k \neq j} a_{k,k} G p_k q_k \right] p_j q_j, \quad (\text{B33})$$

92

$$\tilde{D}_{jk} + \tilde{D}_{j,k} = a_{jk} \left[(1 + F)^2 + G \right] \frac{1 + 2\rho_{jk}\sigma}{\rho_{jk}(1 - \sigma)} p_j q_j p_k q_k, \quad (\text{B34})$$

93

$$\tilde{D}_{jk,j} = F [a_k + a_{k,k} (1 - 2p_k)] G p_j q_j p_k q_k \quad (\text{B35})$$

$$+ F (1 - 2p_j) \left[\tilde{D}_{jk} + 2a_{jk} [F(1 + F) + G] p_j q_j p_k q_k \right],$$

94

$$D_{jk,jk} = (G + F^2) p_j q_j p_k q_k. \quad (\text{B36})$$

95 Equations B31 – B36 yield equations 37 and 41 – 42 in Abu Awad and Roze (2018),

96 expressed to the second order in U (and neglecting the term in $\bar{\sigma}U$ in equation 42).

97

98 **Non-Gaussian stabilizing selection.** Expressions for inbreeding depression under

99 the fitness function given by equation 15 in the main text can be obtained from the

100 equations given above, and using the expressions for $a_{\text{U,V}}$ coefficients derived in Sup-

101 plementary File S1. These expressions show that while the coefficient $a_{jk,jk}$ (represent-

102 ing dominance-by-dominance epistasis on an additive scale) is an order of magnitude

103 smaller than $a_{j,j}$ and a_{jk} under Gaussian stabilizing selection ($Q = 2$), it becomes of the

104 same order of magnitude as $a_{j,j}$, a_{jk} when $Q > 2$: therefore, dominance-by-dominance
 105 epistasis is expected to have stronger effects on inbreeding depression when $Q > 2$. To
 106 the first order in the strength of selection, and approximating the identity disequilib-
 107 rium G_{jk} by its expression under free recombination G (see Figure S5 in Abu Awad
 108 and Roze, 2018 for justification), we have:

$$\delta \approx -\frac{1}{2} \sum_j a_{j,j} (1+F) p_j q_j - \frac{1}{4} \sum_{j < k} a_{jk,jk} [(1+F)^2 + G] p_j q_j p_k q_k. \quad (\text{B37})$$

109 From equation B26, one obtains to the first order in selection coefficients:

$$\begin{aligned} \Delta_{\text{sel}} p_j q_j &= a_j (1 - 2p_j) (1+F) p_j q_j + a_{j,j} (1 - 2p_j)^2 F p_j q_j \\ &+ \sum_{k \neq j} a_{jk,k} (1 - 2p_j) [F(1+F) + G] p_j q_j p_k q_k \\ &+ \sum_{k \neq j} a_{jk,jk} (1 - 2p_j)^2 (F^2 + G) p_j q_j p_k q_k \end{aligned} \quad (\text{B38})$$

110 which must equal $-u(1 - 2p_j)^2$ at mutation-selection balance. Summing equation
 111 B38 over j , using expressions for selection coefficients derived in Supplementary File
 112 S1 (equations A35, A36, A52 and A53), and the fact that $\sum_j r_{\alpha_j}^2 p_j q_j = nV_g^0/2$,
 113 while $\sum_{j,k} (\sum_{\alpha} r_{\alpha_j} r_{\alpha_k})^2 p_j q_j p_k q_k = n(V_g^0/2)^2$, one obtains after simplification (and
 114 assuming that the equilibrium at which $p_j = 1/2$ is not stable):

$$\left(\frac{V_g^0}{V_s}\right)^{\frac{Q}{2}} \frac{\Gamma\left(\frac{Q+n}{2}\right)}{\Gamma\left(\frac{n}{2}\right)} = \frac{4U}{Q} \frac{1}{1 + 3F + \frac{Q-2}{2} [F(1+3F) + 3G]}. \quad (\text{B39})$$

115 Using equation B37 and A36, A53 in Supplementary File S1, this yields:

$$\delta = U \frac{1 + F + \frac{Q-2}{8} [(1+F)^2 + G]}{1 + 3F + \frac{Q-2}{2} [F(1+3F) + 3G]}. \quad (\text{B40})$$

116 Equation B40 differs from equation 29 in Abu Awad and Roze (2018), that was derived
 117 assuming a Gaussian distribution of phenotypic traits at equilibrium; however one
 118 can show that both expressions often give very similar quantitative results. Under

119 random mating ($F = G = 0$), equation B40 yields equation 28 in the main text,
 120 while when $Q = 2$ (Gaussian fitness function), one recovers the classical expression for
 121 inbreeding depression when the dominance coefficient of deleterious alleles is $h = 1/4$,
 122 *i.e.* $\delta \approx U/(1 + \sigma)$ (Abu Awad and Roze, 2018).

123 Although the general expressions given above may be used to compute an ex-
 124 pression for inbreeding depression to the second order in U (including the effects of
 125 genetic associations between pairs of loci), we only performed this calculation for the
 126 case of a randomly mating population. When $\sigma = 0$, equation B26 simplifies to:

$$\Delta_{\text{sel}} p_j q_j \approx a_j (1 - 2p_j) p_j q_j + \sum_{k \neq j} [a_k (1 - 2p_j) + a_{jk}] \tilde{D}_{jk}. \quad (\text{B41})$$

127 When summed over a sufficiently large number of loci, the term in $a_k (1 - 2p_j)$ should
 128 vanish, due to the fact that about half the loci will be at the equilibrium where
 129 $p_j < 1/2$, while the other half will be at the symmetric equilibrium with $p_j > 1/2$, so
 130 that:

$$\Delta_{\text{sel}} p_j q_j \approx a_j (1 - 2p_j) p_j q_j + \sum_{k \neq j} a_{jk} \tilde{D}_{jk}. \quad (\text{B42})$$

131 From equation A57 in Supplementary File S1, we have:

$$\sum_j a_j (1 - 2p_j) p_j q_j \approx -\frac{Q}{4} [Z(Q, n) [1 + Z(Q, n)] - Z(2Q, n)] \quad (\text{B43})$$

132 with:

$$Z(Q, n) = \left(\frac{V^0_g}{V_s} \right)^{\frac{Q}{2}} \frac{\Gamma(\frac{Q+n}{2})}{\Gamma(\frac{n}{2})}, \quad (\text{B44})$$

133 while from equations A47 and A49 in Supplementary File S1:

$$\sum_{j,k} a_{jk} \tilde{D}_{jk} \approx \frac{4U^2}{n \rho_H} \quad (\text{B45})$$

134 at equilibrium, where ρ_H is the harmonic mean recombination rate between pairs of
 135 loci controlling the selected traits. Furthermore, $Z(Q, n) \approx 4U/Q$ to leading order

136 (equation A41 in Supplementary File S1), so that $(V_g^0)^{Q/2}$ is of order U , and the terms
 137 $[Z(Q, n)]^2$ and $Z(2Q, n)$ (proportional to $(V_g^0)^Q$) are of order U^2 :

$$[Z(Q, n)]^2 \approx \left(\frac{4U}{Q}\right)^2, \quad Z(2Q, n) \approx \left(\frac{4U}{Q}\right)^2 \left(\frac{\Gamma(\frac{n}{2})}{\Gamma(\frac{Q+n}{2})}\right)^2 \frac{\Gamma(Q + \frac{n}{2})}{\Gamma(\frac{n}{2})}. \quad (\text{B46})$$

138 Using equations B42 – B46, and $\sum_j (\Delta_{\text{sel}} p_j q_j) = -U$ at equilibrium yields the following
 139 expression:

$$\frac{Q}{4} \left[Z(Q, n) + \left(\frac{4U}{Q}\right)^2 \left[1 - \frac{\Gamma(\frac{n}{2}) \Gamma(Q + \frac{n}{2})}{[\Gamma(\frac{Q+n}{2})]^2} \right] \right] = U \left(1 + \frac{4U}{n\rho_H} \right) \quad (\text{B47})$$

140 that can be solved to express $Z(Q, n)$ to the second order in U :

$$Z(Q, n) = \frac{4U}{Q} \left[1 + \frac{4U}{n\rho_H} + \frac{4U}{Q} \left[\frac{\Gamma(\frac{n}{2}) \Gamma(Q + \frac{n}{2})}{[\Gamma(\frac{Q+n}{2})]^2} - 1 \right] \right]. \quad (\text{B48})$$

141 Equation B48 is equivalent to equation A66 in Abu Awad and Roze (2018) when
 142 $Q = 2$. Neglecting linkage in the expression for inbreeding depression under random
 143 mating (equation B8), we have:

$$\delta \approx -\frac{1}{2} \sum_j a_{j,j} p_j q_j - \frac{1}{4} \sum_{j < k} a_{j,k,j,k} p_j q_j p_k q_k - \sum_{j < k} a_{j,k} \tilde{D}_{j,k}. \quad (\text{B49})$$

144 Using equation A58 in Supplementary File S1 yields:

$$-\frac{1}{2} \sum_j a_{j,j} p_j q_j = \frac{Q}{4} [Z(Q, n) [1 + Z(Q, n)] - Z(2Q, n)]. \quad (\text{B50})$$

145 Using B46 and B48, this simplifies to:

$$-\frac{1}{2} \sum_j a_{j,j} p_j q_j = U \left(1 + \frac{4U}{n\rho_H} \right) \quad (\text{B51})$$

146 independent of Q . From equation A59 in Supplementary File S1, we have:

$$-\frac{1}{4} \sum_{j < k} a_{j,k,j,k} p_j q_j p_k q_k = \frac{Q}{32} [(Q - 2) Z(Q, n) [1 + Z(Q, n)] - (2Q - 2) Z(2Q, n)] \quad (\text{B52})$$

147 which gives, using B46 and B48:

$$-\frac{1}{4} \sum_{j < k} a_{jk,jk} p_j q_j p_k q_k = \frac{(Q-2)U}{8} \left(1 + \frac{4U}{n\rho_H}\right) - \frac{U^2}{2} \frac{\Gamma(\frac{n}{2}) \Gamma(Q + \frac{n}{2})}{[\Gamma(\frac{Q+n}{2})]^2}. \quad (\text{B53})$$

148 Altogether, equations B45, B49, B51 and B53 yield the following expression for δ to

149 the second order in U :

$$\delta \approx U \left(1 + \frac{2U}{n\rho_H}\right) + \frac{(Q-2)U}{8} \left(1 + \frac{4U}{n\rho_H}\right) - \frac{U^2}{2} \frac{\Gamma(\frac{n}{2}) \Gamma(Q + \frac{n}{2})}{[\Gamma(\frac{Q+n}{2})]^2}. \quad (\text{B54})$$

150 It is possible to show that for $Q = 2$, equation B54 is equivalent to equations 41 – 42

151 in Abu Awad and Roze (2018), expressed to the second order in U .

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