Effects of Interference Between Selected Loci on the Mutation Load, Inbreeding Depression, and Heterosis

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ABSTRACT A classical prediction from single-locus models is that inbreeding increases the efficiency of selection against partially recessive deleterious alleles (purging), thereby decreasing the mutation load and level of inbreeding depression. However, previous multilocus simulation studies found that increasing the rate of self-fertilization of individuals may not lead to purging and argued that selective interference among loci causes this effect. In this article, I derive simple analytical approximations for the mutation load and inbreeding depression, taking into account the effects of interference between pairs of loci. I consider two classical scenarios of nonrandomly mating populations: a single population undergoing partial selfing and a subdivided population with limited dispersal. In the first case, correlations in homozygosity between loci tend to reduce mean fitness and increase inbreeding depression. These effects are stronger when deleterious alleles are more recessive, but only weakly depend on the strength of selection against deleterious alleles and on recombination rates. In subdivided populations, interference increases inbreeding depression within demes, but decreases heterosis between demes. Comparisons with multilocus, individual-based simulations show that these analytical approximations are accurate as long as the effects of interference stay moderate, but fail for high deleterious mutation rates and low dominance coefficients of deleterious alleles.

KEYWORDS deleterious mutation; multilocus population genetics; population structure; selective interference; self-fertilization

ACCORDING to current estimates of spontaneous deleterious mutation rates in multicellular organisms (*e.g.*, Baer *et al.* 2007; Haag-Liautard *et al.* 2007; Keightley 2012) and estimated distributions of fitness effects of these mutations (*e.g.*, Eyre-Walker and Keightley 2007; Keightley and Eyre-Walker 2007; Boyko *et al.* 2008; Haddrill *et al.* 2010), individuals may typically carry large numbers (possibly up to thousands) of deleterious alleles. Possible consequences of this load of deleterious mutations have been discussed since the early ages of theoretical population genetics (*e.g.*, Haldane 1937). In particular, it may reduce population mean rates of fecundity and viability, thereby increasing vulnerability to extinction (Lynch *et al.* 1995a, b). It may also affect a number of evolutionary processes, such as the evolution of sex or mating systems: for example, the fact that deleterious alleles are often partially recessive generates inbreeding depression, favoring outcrossing over self-fertilization (*e.g.*, Lande and Schemske 1985; Charlesworth and Charlesworth 1987; Charlesworth 2006).

In very large, panmictic populations and in the absence of epistasis between mutations, genetic associations between deleterious alleles at different loci should remain weak and may be neglected. In diploids, and assuming that the dominance coefficient of deleterious alleles is significantly greater than zero, the mutation load (reduction in mean fitness of the population due to deleterious alleles at mutation–selection balance) is $\sim 1-e^{-2U}$, where U is the deleterious mutation rate per haploid genome (Crow 1970; Agrawal and Whitlock 2012). Furthermore, assuming for simplicity that all deleterious alleles have the same dominance coefficient h, inbreeding depression (defined here as the reduction in fitness of offspring produced by self-fertilization, relative to offspring produced by outcrossing) is $\sim 1-e^{-U(1-2h)/(2h)}$ (Charlesworth and Charlesworth 2010). Analytical results on the effects of genetic

doi: 10.1534/genetics.115.178533
Manuscript received May 22, 2015; accepted for publication August 7, 2015; published Early Online August 12, 2015.
Supporting information is available online at www.genetics.org/lookup/suppl/doi:10.1534/genetics.115.178533/-/DC1.
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drift and nonrandom mating mainly stem from single-locus models. Inbreeding increases the efficiency of selection against deleterious alleles, lowering the mutation load and inbreeding depression (Lande and Schemske 1985). Genetic drift may also lead to better purging of partially recessive deleterious alleles (Kimura *et al.* 1963), but this effect causes only a moderate reduction of the mutation load compared to the effect of nonrandom mating and occurs only when the effects of drift and selection are of the same order of magnitude (Glémin 2003). Drift has more noticeable effects when it becomes stronger than selection and allows deleterious alleles to reach fixation, which may increase the load by several orders of magnitude and lowers inbreeding depression (Bataillon and Kirkpatrick 2000). Population subdivision has similar consequences, due to the effects of drift within each local population (Whitlock 2002; Glémin *et al.* 2003; Roze and Rousset 2004).

These previous studies are based on single-locus models and therefore do not consider the effects of genetic associations between loci on the mutation load and inbreeding depression. Between-locus associations are generated, however, as soon as population size is finite or mating is nonrandom (even in the absence of epistasis): in particular, correlations in homozygosity, described as "identity disequilibria" (Weir and Cockerham 1973; Vitalis and Couvet 2001), and linkage disequilibria between selected loci (Hill and Robertson 1966; Roze and Lenormand 2005; Kamran-Disfani and Agrawal 2014). Effects of deleterious mutations occurring at many loci have been explored using simulation models of finite or infinite populations (*e.g.*, Charlesworth *et al.* 1990, 1991, 1992, 1993; Lande *et al.* 1994; Wang *et al.* 1999), sometimes showing important deviations from single-locus predictions. In particular, using Kondrashov's (1985) model to simulate recessive lethal mutations occurring at a very large (effectively infinite) number of unlinked loci in a partially selfing population, Lande *et al.* (1994) observed that contrary to the predictions of single-locus models, recessive lethals cannot be purged by selfing unless the selfing rate exceeds a threshold value (see also Kelly 2007). Lande *et al.* (1994) argued that this effect (called "selective interference") is caused by identity disequilibria. Intuitively, selfing increases homozygosity at each locus and should thus purge recessive lethal mutations; however, if many such mutations segregate in the population, any selfed offspring will almost certainly carry at least one mutation in the homozygous state and will thus not survive. When this is the case, the population is effectively outcrossing, and purging does not occur.

To date, the effects of selective interference in partially inbred populations have been explored only numerically. How these effects scale with the strength of selection against deleterious alleles, dominance coefficients, and recombination rates between loci thus remains unclear. In this article, I derive analytical approximations describing the effect of interference between pairs of loci on the mean frequency of deleterious alleles, the mean and variance in fitness, and the strength of inbreeding depression, assuming weak selection against deleterious alleles. I consider two classical scenarios of nonrandomly mating populations: a single, large population in which individuals self-fertilize at a given rate and a subdivided population with local mating followed by dispersal (island model of population structure). In the first case, interference between loci tends to reduce mean fitness and increase inbreeding depression. These effects are stronger when deleterious alleles are more recessive, but depend only weakly on the strength of selection against deleterious alleles and on recombination rates. In the case of a subdivided population, I first show that combining two different approximations used in previous works (Glémin *et al.* 2003; Roze and Rousset 2004) yields more accurate expressions for the mutation load, inbreeding depression, and heterosis generated by a single deleterious allele. In a second step, I derive approximations for the effects of interference between loci and show that interference increases inbreeding depression within demes, but decreases heterosis between demes. Comparisons with individual-based, multilocus simulation results show that analytical approximations incorporating the effects of associations between pairs of loci often provide accurate predictions for the mutation load and inbreeding depression as long as the dominance coefficient h of deleterious alleles is not too low. These approximations fail when h becomes close to zero and when the deleterious mutation rate is high, however, probably due to the fact that higher-order interactions (involving three or more loci) become important.

Methods

I consider a diploid population with discrete generations, in which deleterious mutations occur at rate U per haploid genome per generation. For simplicity, I generally assume that all deleterious alleles have the same selection and dominance coefficients (s, h), although distributions of s and h will be considered in the case of a partially selfing population. Deleterious alleles at different loci have multiplicative effects (no epistasis), so that the fitness of an organism carrying j heterozygous and k homozygous mutations is proportional to $(1-hs)^j(1-s)^k$. In the first model (partial selfing), a parameter α measures the proportion of offspring produced by selfing, while a proportion $1-\alpha$ is produced by random union of gametes. The second model corresponds to the island model of population structure: the population is subdivided into a large number of demes, each containing N adult individuals. These individuals produce large numbers of gametes (in proportion to their fitness), which fuse randomly within each deme to form juveniles. A proportion m of these juveniles disperses, reaching any other deme with the same probability. Finally, N individuals are sampled randomly within each deme to form the next adult generation. I assume soft selection; that is, all demes contribute equally to the migrant pool. In Supporting Information, File S1 and File S2, I derive approximations for the mutation load and inbreeding depression that incorporate effects of pairwise associations between loci, assuming $s \ll U$ (so that individuals tend to carry many deleterious alleles) and that drift at the whole-population level is negligible relative to selection. In the next sections,

these analytical predictions are compared with individual-based, multilocus simulation results. The simulation programs (available from Dryad) are similar to those used in previous work (*e.g.*, Roze and Rousset 2009). Briefly, they represent a finite population of diploids, whose genome consists of a linear chromosome. Each generation, the number of new mutations per chromosome is drawn from a Poisson distribution with parameter U, the position of each mutation along the chromosome being drawn from a uniform distribution (in practice, a chromosome is represented by the positions of the deleterious alleles it carries). To form the next generation, a maternal parent is sampled for each offspring, either among all parents (in the case of a single population undergoing partial selfing) or among all parents from the offspring's deme of origin (in the case of a subdivided population). In the first case, the parent self-fertilizes with probability α, while with probability $1-\alpha$ a second parent is sampled. In the second case (subdivided population), a second parent is sampled from the same deme as the first. In all cases, the probability that a given parent is sampled is proportional to its fitness. Parents produce gametes by meiosis, a parameter R measuring the genome map length: for each meiosis, the number of crossovers is sampled from a Poisson distribution with parameter R, the position of each crossover being drawn from a uniform distribution. Map length is fixed to 10 M in most simulations, to mimick a whole genome with multiple chromosomes. The program runs for a large number of generations (generally 2×10^5) and measures the mean number of deleterious alleles per genome, mean fitness, variance in fitness, inbreeding depression, and heterosis (in the case of a subdivided population) every 50 generations.

Data availability

Dryad DOI: doi:10.5061/dryad.sp01m.

Partial Self-Fertilization

In File S1, I derive approximate expressions for the mean and variance in log fitness under weak selection (incorporating effects of associations between pairs of loci) and show that, neglecting higher moments of log fitness, the average fitness is approximately

$$\bar{W}\approx e^{\overline{\ln W}}\left(1+\frac{\mathrm{Var}[\ln W]}{2}\right), \tag{1}$$

where $\overline{\ln W}$ and $\mathrm{Var}[\ln W]$ are the average and variance in log fitness, respectively. Alternatively, an approximation for $\bar{W}$ can be obtained by assuming that the number of heterozygous mutations per outcrossed offspring follows a Poisson distribution, while the number of homozygous and heterozygous mutations per selfed offspring follows a bivariate Gaussian distribution—a similar method was used by Charlesworth *et al.* (1991) to compute inbreeding depression, using numerical recursions. However, both methods yield very similar results and only the first one is presented here.

In the following, I first assume that all deleterious alleles have the same selection and dominance coefficients and then turn to the more realistic situation where s and h vary among loci. Throughout, I assume that deleterious alleles stay at a low frequency in the population. In that case, and assuming fixed s and h, the average log fitness is approximately

$$\overline{\ln W}\approx -\sum_i s\Big[2h+(1-2h)F_i\Big]p_i, \tag{2}$$

where the sum is over all loci, p_i is the equilibrium frequency of the deleterious allele at locus i, and F_i is the probability of identity-by-descent at locus i due to partial selfing (generating an excess of homozygosity at locus i). Note that under random mating, Equation 2 holds only when the dominance coefficient of deleterious alleles (h) is significantly greater than zero (otherwise, terms in p_i^2 must be included in Equation 2); however, Equation 2 holds for all values of h under partial selfing ($F_i>0$), as long as deleterious alleles stay at a low frequency.

As shown in File S1, the variance in log fitness is approximately

$$\begin{aligned}\mathrm{Var}[\ln W]\approx{}&2(sh)^2\sum_i p_i+s^2\big(1-2h^2\big)\sum_i F_i\,p_i\\&+s^2(1-2h)^2\sum_{i\neq j}G_{ij}\,p_i\,p_j,\end{aligned} \tag{3}$$

where G_{ij} is the identity disequilibrium between loci i and j (covariance in identity-by-descent, generating a correlation in homozygosity across loci). As explained in File S1, the terms in the first line of Equation 3 are proportional to sU, while the term in the second line is proportional to U^2. Therefore, assuming $s\ll U$ and $h\neq0.5$, the terms in the first line of Equation 3 are relatively weak when the population is partially selfing. Neglecting those terms, we have

$$\mathrm{Var}[\ln W]\approx s^2(1-2h)^2\sum_{i\neq j}G_{ij}\,p_i\,p_j. \tag{4}$$

Identity disequilibria thus affect mean fitness through the term in $\mathrm{Var}[\ln W]$ in Equation 1. However, they also affect allele frequencies p_i and excesses of homozygotes F_i that appear in Equation 2. Indeed, we have (see File S1)

$$F_i\approx\frac{\alpha}{2-\alpha}\left[1-s(1-2h)\sum_{j\neq i}G_{ij}\,p_j\right], \tag{5}$$

while changes in allele frequencies due to selection are approximately

$$\begin{aligned}\Delta_s p_i\approx-s\Bigg[&h+(1-h)F_i\\&-s(1-h)(1-2h)\left(1+\frac{\alpha}{2-\alpha}\right)\sum_{j\neq i}G_{ij}\,p_j\Bigg]p_i.\end{aligned} \tag{6}$$

Intuitively, homozygosity at locus i (measured by F_i) is decreased by the fact that homozygotes at locus i (either for the wild-type or for the deleterious allele) tend to be also homozygous at other loci and that homozygotes at these loci have a lower fitness than heterozygotes when deleterious alleles are partially recessive (Equation 5). Note that homozygosity at locus i is also affected by selection acting at this locus, but this effect is negligible relative to the effects of all other loci when the number of segregating loci is large (*i.e.*, when $s \ll U$). This decrease in homozygosity reduces the efficiency of selection against deleterious alleles, through the term in F_i in Equation 6. However, identity disequilibria further decrease the strength of selection against partially recessive deleterious alleles through two additional effects (explained below): (1) they reduce the "effective" dominance coefficient of deleterious alleles and (2) they generate a relative excess of heterozygosity at locus j among individuals carrying a deleterious allele at locus i (measured by the association $D_{ij,j}$ in File S1). These two effects generate the last term within the brackets of Equation 6 (see File S1 for derivation).

The first effect stems from the fact that the fitnesses of mutant and wild-type homozygotes at locus i are decreased by the same factor from associations with homozygotes at other selected loci; however, the fitness of heterozygotes at locus i is decreased by a smaller factor, since these tend to be associated with heterozygotes at other loci, which have a higher fitness than homozygotes (provided $h < 0.5$). Therefore, identity disequilibria have a stronger impact on the fitness of homozygotes than on that of heterozygotes, decreasing the effective dominance coefficient of deleterious alleles and thereby reducing the efficiency of selection against those alleles.

The second effect (deleterious alleles tend to be associated with more heterozygous backgrounds) stems from the fact that because heterozygotes at locus i tend to be heterozygous at locus j (while homozygotes at locus i tend to be homozygous at locus j) and because selection is more efficient among homozygotes than among heterozygotes, selection against the deleterious allele at locus i is less efficient among heterozygotes at locus j than among homozygotes. This effect causes the deleterious allele at locus i to be more frequent among heterozygotes than among homozygotes at locus j, in turn decreasing the efficiency of selection at locus i, since heterozygous backgrounds are fitter than homozygous ones when $h < 0.5$.

In the following, expressions for mean fitness $\bar{W}$ and inbreeding depression δ are obtained by replacing identity disequilibria G_{ij} by their equilibrium values under neutrality. Because allele frequencies p_i are of order u/s (where u is the deleterious mutation rate per locus), this will generate terms of order U^2 in the expressions for $\bar{W}$ and δ below. Taking into account the effect of selection acting at loci i and j on G_{ij} would generate terms of order sU^2, which should be negligible relative to terms in U and U^2 as long as selection is weak (s small). However, G_{ij} is also affected by selection acting at other loci, due to three-locus identity disequilibria. Taking into account the effects of these three-locus associations would introduce terms of order U^3 in the expressions for $\bar{W}$ and δ, which may become important when U is sufficiently large. As we will see, some discrepancies are observed between the analytical predictions and the simulation results for high U and low h, probably due to the fact that these higher-order genetic associations (between three or more loci) are not taken into account in the analysis.

Because the identity disequilibrium G_{ij} depends on the recombination rate r_{ij} between loci i and j (see File S1), F_i and p_i may depend on the position of locus i within the genome. However, the expression for G_{ij} under neutrality only weakly depends on r_{ij} and is often close to the expression obtained for freely recombining loci:

$$G_{ij} = \frac{4\alpha(1-\alpha)}{(4-\alpha)(2-\alpha)^2}. \tag{7}$$

Injecting this expression into Equations 5 and 6 yields the following approximation for the average number of deleterious alleles per haplotype ($n = \sum_i p_i$) at mutation–selection balance (to the second order in U),

$$n \approx \frac{U(2-\alpha)}{s[2h+\alpha(1-2h)]}(1+I_1), \tag{8}$$

where

$$I_1 = 2U(1-h)(1-2h)\frac{2+\alpha}{2-\alpha}\,T, \tag{9}$$

$$T = \frac{2\alpha(1-\alpha)}{(4-\alpha)[2h+\alpha(1-2h)]^2} \geq 0. \tag{10}$$

The term I_1 in Equation 8 represents the effect of identity disequilibria, increasing the mean number of deleterious alleles when $h < 0.5$ (due to the three effects described above). From this, and neglecting terms in $o(U^2)$, we obtain the following approximation for mean fitness,

$$\bar{W} \approx (1+I_2)\exp\left[-U\,\frac{4h+\alpha(1-4h)}{2h+\alpha(1-2h)}(1+I_1) + \frac{2\alpha}{2-\alpha}\,I_2\right], \tag{11}$$

with

$$I_2 = U^2(1-2h)^2 T. \tag{12}$$

As shown by Equation 11 and the previous equations, identity disequilibria have three different effects on mean fitness (represented by the term in I_1 and the two terms in I_2 in Equation 11), which can be interpreted as follows:

1. Correlations in homozygosity directly increase mean fitness when $h \neq 0.5$, because double homozygotes and double heterozygotes have a higher fitness (on average) than genotypes that are homozygous at one locus and heterozygous at the other (*e.g.*, Roze 2009): this effect is represented by the term in Var[ln W] in Equation 1 (approximated by Equation 4), corresponding to the factor $1 + I_2$ in Equation 11.

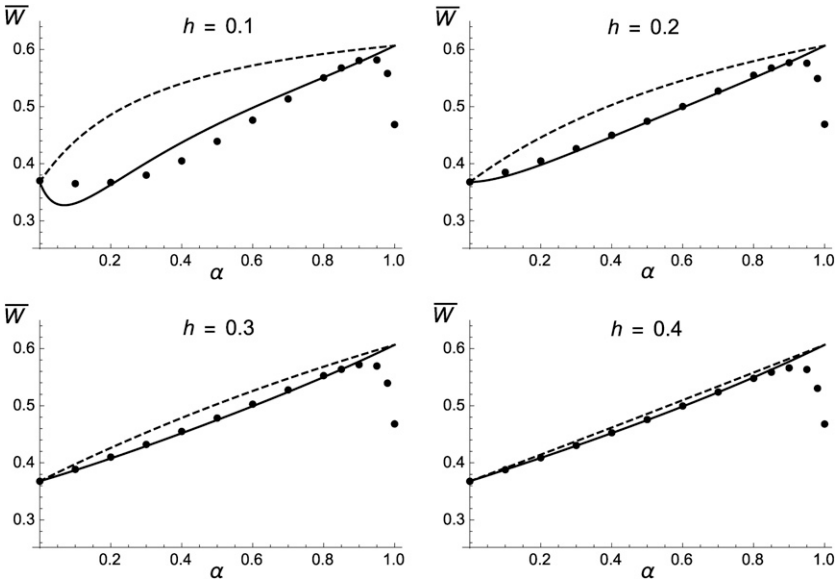

Figure 1 Average fitness at equilibrium as a function of the rate of self-fertilization α, for different values of the dominance coefficient of deleterious alleles (h), and deleterious mutation rate per haploid genome $U = 0.5$. Solid curves, analytical approximation including effects of identity disequilibria (Equation 11); dashed curves, neglecting effects of identity disequilibria (obtained by setting $I_1 = I_2 = 0$ in Equation 11); solid circles, simulation results (in this and the following figures, error bars are smaller than the size of circles). In the simulations, $s = 0.05$, $N = 20,000$, and $R = 10$ M.

2. Identity disequilibria tend to decrease the excess of homozygosity F_i at each locus when $h < 0.5$ (Equation 5), increasing mean fitness since homozygotes have a lower fitness than heterozygotes when $h < 0.5$ (term in $e^{\overline{\ln W}}$ in Equation 1, which increases as F_i decreases if $h < 0.5$, as shown by Equation 2). If $h > 0.5$, F_i is now increased by identity disequilibria, but this again increases mean fitness since homozygotes have a higher fitness than heterozygotes. This second effect corresponds to the term $2\alpha I_2/(2-\alpha)$ in Equation 11.
3. Finally, identity disequilibria increase the frequency of deleterious alleles at mutation–selection balance when $h < 0.5$ (as explained above), which decreases mean fitness: this corresponds to the factor $1 + I_1$ in Equation 11.

One can show that effect 3 is stronger than effects 1 and 2 when $h < 0.5$, causing identity disequilibria to decrease mean fitness (while when $h > 0.5$, all three effects increase mean fitness). An approximation for the variance in fitness at equilibrium is provided in File S1 (Equation A46); from this expression, it is possible to show that identity disequilibria generally increase the variance in fitness (unless $h = 0.5$, in which case their effect vanishes).

Finally, the effect of identity disequilibria on inbreeding depression is obtained as follows. Inbreeding depression is classically defined as

$$\delta = 1 - \frac{\bar{W}_{\text{self}}}{\bar{W}_{\text{out}}}, \tag{13}$$

where $\bar{W}_{\text{self}}$ and $\bar{W}_{\text{out}}$ are the average fitnesses of individuals produced by selfing and by outcrossing, respectively (Charlesworth and Charlesworth 1987). These quantities can be calculated as above, using expressions for F_i and G_{ij} in selfed individuals (for $\bar{W}_{\text{self}}$) and in outcrossed individuals (for $\bar{W}_{\text{out}}$). Because the last quantities equal zero, we have $\bar{W}_{\text{out}} \approx e^{-2sh\sum_i p_i}$. Furthermore, denoting $F_{i,\text{self}}$ and $G_{ij,\text{self}}$ the excess of homozygosity and the identity disequilibrium among offspring produced by selfing, we have $F_{i,\text{self}} = (1 + F_i)/2$, while at the neutral equilibrium and under free recombination $G_{ij,\text{self}} = G_{ij}/4$. From this, we obtain

$$\delta \approx 1 - \left(1 + \frac{I_2}{4}\right)\exp\left[-U\,\frac{1-2h}{2h + \alpha(1-2h)}(1 + I_1) + \frac{\alpha}{2-\alpha}\,I_2\right], \tag{14}$$

where I_1 and I_2 are given by Equations 9 and 12. The three terms generated by identity disequilibria in Equation 14 correspond to the three effects affecting mean fitness described above: (1) correlations in homozygosity tend to increase the fitness of inbred offspring whenever $h \neq 0.5$, thereby reducing inbreeding depression ($1 + I_2/4$ factor); (2) identity disequilibria reduce the excess homozygosity of inbred offspring, which also reduces inbreeding depression [term $\alpha I_2/(2-\alpha)$]; and (3) identity disequilibria increase the equilibrium frequency of partially recessive deleterious alleles, which increases inbreeding depression ($1 + I_1$ factor). Here again, the third effect is stronger than the first two, and the overall effect of identity disequilibria is thus to increase δ.

Figure 1 shows that Equation 11 provides accurate predictions for mean fitness when $U = 0.5$ and $h \geq 0.2$, while discrepancies are observed for $h = 0.1$. By contrast, ignoring effects of identity disequilibria overestimates mean fitness, in particular when h is low. Figure 1 also shows that $\bar{W}$ is systematically lower than predicted when the selfing rate approaches 1; this effect is likely due to the fact that in the simulations, the effective population size is greatly reduced by background selection effects when outcrossing is very rare, in which case deleterious alleles may increase in frequency due to drift. As shown by Figure S1, reducing the mutation rate from $U = 0.5$ to $U = 0.1$ reduces the effects of identity disequilibria and leads to a better match between

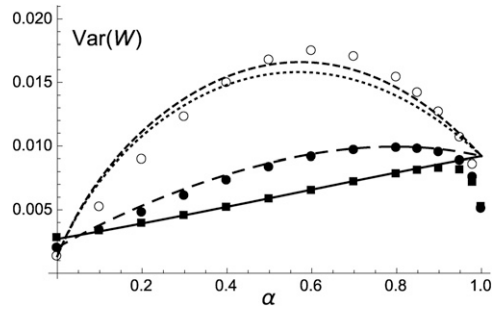

Figure 2 Variance in fitness in the population at equilibrium, as a function of the rate of self-fertilization α and for different values of the dominance coefficient of deleterious alleles. Curves correspond to predictions from Equation A46 in File S1 (dotted, $h = 0.2$; long dashed, $h = 0.3$; solid, $h = 0.4$). Short-dashed curve, adding the term given in Equation A47 in File S1 for $h = 0.2$; symbols, simulation results for $h = 0.2$ (open circles), $h = 0.3$ (solid circles), and $h = 0.4$ (solid squares). Parameter values are the same as in Figure 1.

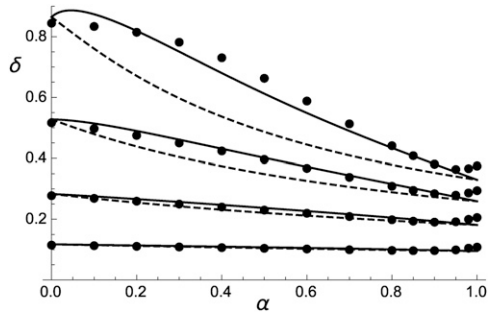

Figure 3 Inbreeding depression as a function of the rate of self-fertilization α, for different values of the dominance coefficient of deleterious alleles ($h = 0.1$, 0.2, 0.3, and 0.4 from top to bottom), and deleterious mutation rate per haploid genome $U = 0.5$. Solid curves, analytical approximation including effects of identity disequilibria (Equation 14); dashed curve, neglecting effects of identity disequilibria (setting $I_1 = I_2 = 0$ in Equation 14); solid circles, simulation results (same parameter values as in Figure 1).

predictions from Equation 11 and simulation results for $h = 0.1$. Figure S2 and Figure S3 show that changing the selection coefficient of deleterious alleles to $s = 0.01$ or $s = 0.1$ leads to very similar results (indeed, Equation 11 does not depend on s), except that the effects of drift at high α are stronger for lower values of s. Genomic map length (R) was set to 10 M in these simulations; additional simulations were run for the case of freely recombining loci, but yielded undistinguishable results unless α is close to 1 (in which case free recombination lowers the effects of drift—results not shown). The variance in fitness in the population at equilibrium is shown in Figure 2: when h is low, the variance in fitness is maximized for intermediate values of the selfing rate α, mainly due to the effects of identity disequilibria (which are maximized for intermediate values of α).

Figure 3 compares the value of inbreeding depression measured in simulations with predictions from Equation 14, also showing that taking into account the effects of identity disequilibria leads to more accurate predictions (although discrepancies appear for $h = 0.1$). Results for the case of fully recessive mutations ($h = 0$) are shown in Figure 4: in agreement with Lande *et al.* (1994), for high mutation rates ($U = 0.25$ or 0.5) purging occurs only when the selfing rate exceeds a threshold value. Below this threshold, the population is effectively outcrossing, which is confirmed by the fact that mean fitness stays very close to the average fitness of a panmictic population ($\bar{W} \approx e^{-U}$ when $h = 0$) multiplied by the outcrossing rate (see Figure S4). Figure 4 also shows that while Equation 14 provides better predictions than the equivalent expression ignoring identity disequilibria, it does not fully capture the effect of selective interference for intermediate selfing rates and high values of U, indicating that higher-order genetic associations (in particular, joint homozygosity at multiple loci) must have important effects for these parameter values.

The previous results assume that all deleterious alleles have the same selection and dominance coefficients. However, File S1 shows that they are easily extended to the more realistic situation where s and h vary among loci, as long as we can assume that selection is much stronger than drift at most loci. In that case, mean fitness and inbreeding depression at equilibrium do not depend on the strength of selection against deleterious alleles and can be obtained by integrating terms appearing in the equations above over the distribution of dominance coefficients of these alleles (see Equations A56 and A57 in File S1). To test these results, I modified the simulation program so that the distribution of selection coefficients of deleterious alleles is log-normal, with density function $\phi(s) = \exp[-(\ln s - \mu)^2/(2\sigma^2)]/(s\sigma\sqrt{2\pi})$ (where μ and σ^2 are the mean and variance of $\ln s$), truncated at $s = 1$ (this has a negligible effect for the parameter values considered here). Available data on fitness effects of deleterious alleles point to an absence of correlation between homozygous and heterozygous effects of deleterious mutations (at least for mutations having sufficiently large homozygous effect, *e.g.*, Manna *et al.* 2012), the distribution of heterozygous effects (sh) being much less variable than the distribution of homozygous effects (s). Here, I assume for simplicity that all deleterious alleles have the same heterozygous effect θ: as a consequence, s and h are negatively correlated, and the distribution of dominance coefficients ($h = \theta/s$) is given by $\psi(h) = (\theta/h^2)\phi(\theta/h)$. Figure 5 shows the distributions of s and h for $\sigma = 0.8$, setting μ and θ so that $\bar{s} = \exp[\mu + \sigma^2/2] = 0.05$ and $\bar{h} = \theta/\exp[\mu - \sigma^2/2] = 0.25$ (that is, $\mu \approx -3.316$ and $\theta \approx 0.00659$); Figure S5 shows h as a function of s for these parameter values. As shown by Figure 5, Equations A56 and A57 in File S1 provide accurate predictions for mean fitness and inbreeding depression when s and h vary across loci (as before, discrepancies appear when α approaches one, due to finite population size effects). It also shows that introducing a variance in h has little effect on mean fitness (its value being well predicted by the expression assuming fixed h), while it strongly increases inbreeding depression, in particular when the selfing rate is small. This

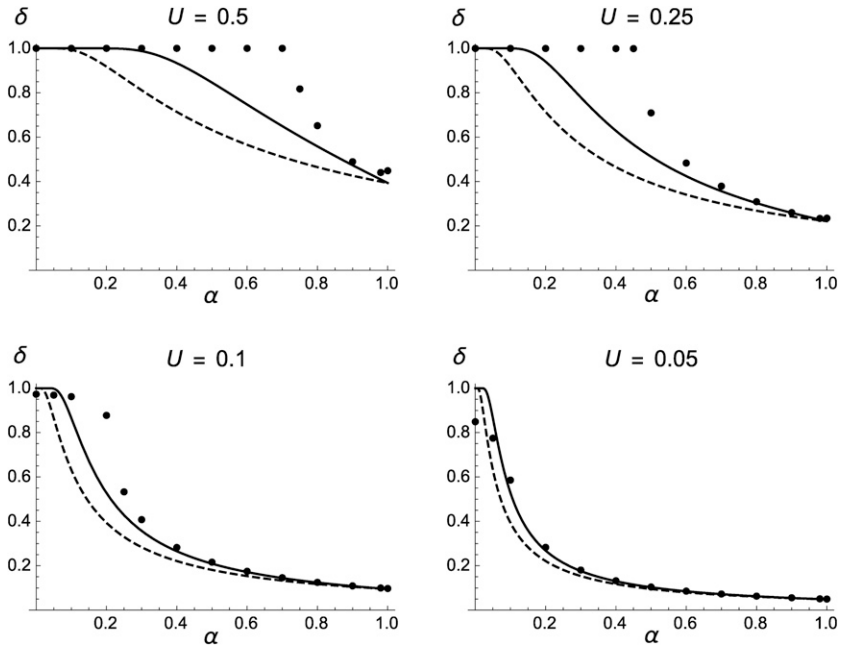

Figure 4 Inbreeding depression as a function of the selfing rate α: same as Figure 3 with fully recessive deleterious alleles ($h = 0$) and different values of the deleterious mutation rate U.

may be understood from single-locus results: inbreeding depression increases faster than linearly as h decreases (the effect of h on δ being more marked when α is small), causing inbreeding depression to increase as the variance of h increases. By contrast, the effect of h on mean fitness is weaker and vanishes when $\alpha = 0$. Finally, Figure S6 shows that when $\bar{h} = 0.5$, the variance of h generates positive inbreeding depression, which is slightly increased by identity disequilibria.

Population Structure

The mutation load L, inbreeding depression δ, and heterosis H in a subdivided population may be defined as (*e.g.*, Theodorou and Couvet 2002; Whitlock 2002; Glémin *et al.* 2003; Roze and Rousset 2004)

$$L = 1 - \frac{\bar{W}}{W_{\max}}, \quad \delta = 1 - E_x\left[\frac{W_{\text{self},\,x}}{W_{\text{out},\,x}}\right], \quad H = 1 - \frac{E_x[W_{\text{out},\,x}]}{W_{\text{between}}}, \tag{15}$$

where $\bar{W}$ is the average fitness over the whole metapopulation, $W_{\max}$ is the maximal possible fitness, $W_{\text{self},\,x}$ and $W_{\text{out},\,x}$ are the average fitnesses of individuals produced by selfing and by outcrossing in deme x (respectively), W_{between} is the average fitness of offspring produced by crosses between parents from two different demes, and E_x stands for the average over all demes x. In the present model $W_{\max} = 1$, while the assumption of random mating within demes yields $E_x[W_{\text{out},\,x}] = \bar{W}$. The definition of inbreeding depression given by Equation 15 is equivalent to the "within-deme inbreeding depression" δ_{IS} in Roze and Rousset (2004) (or δ_1 in Whitlock 2002). Note that Theodorou and Couvet (2002) use a slightly different definition of within-deme inbreeding depression: $\delta = 1 - E_x[W_{\text{self},\,x}]/E_x[W_{\text{out},\,x}]$; however, we will see that both expressions often yield very similar results.

File S2 shows how approximations for L, δ, and H can be derived, assuming that deme size N is large, while the migration rate m and strength of selection s are small. As in the previous section, the total population size is supposed very large (large number of demes), so that the effects of drift at the whole population level can be neglected. In a first step, I show that improved approximations for L, δ, and H generated by mutation at a single locus can be obtained by combining previous results (Glémin *et al.* 2003; Roze and Rousset 2004). Then, I extend these results to the case of deleterious alleles occurring at a large number of loci, incorporating effects of pairwise associations among loci.

Single-locus results

As shown in File S2 (see also Whitlock 2002; Glémin *et al.* 2003; Roze and Rousset 2004) the mutation load, inbreeding depression, and heterosis generated by a single deleterious allele in a subdivided population (with random mating within demes) are approximately

$$L \approx 2sh\,p + s(1-2h)F_{\text{ST}}\,p \tag{16}$$

$$\delta \approx \frac{1}{2}\,s(1-2h)(1-F_{\text{ST}})p \tag{17}$$

$$H \approx s(1-2h)F_{\text{ST}}\,p, \tag{18}$$

where p is the frequency of the deleterious allele in the whole population, and F_{ST} measures the average genetic diversity within demes, relative to the genetic diversity in the whole metapopulation (Wright 1969). As the number of demes tends to infinity, F_{ST} becomes equivalent to the probability that two genes sampled from the same deme are identical by

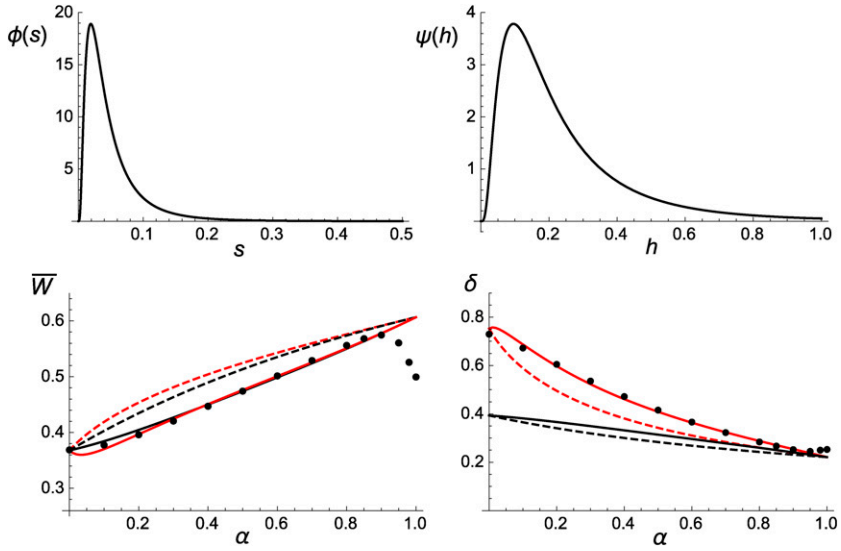

Figure 5 (Top) Distributions of s and h assuming a log-normal distribution of s with $\mu \approx -3.316$ and $\sigma = 0.8$ (so that $\bar{s} = 0.05$) and fixed heterozygous effects of deleterious alleles $\theta \approx 0.00659$ (so that $\bar{h} = 0.25$). See text for more explanations. (Bottom) Mean fitness and inbreeding depression as a function of the selfing rate α. Black circles, simulations results, using the distributions of s and h shown at the top; black curves, analytical predictions for fixed h, set to $\bar{h}$ (from Equations 11 and 14); red curves, analytical predictions for varying h (from Equations A56 and A57 in File S1); dashed/solid curves, neglecting/including the effects of identity disequilibria. The mutation rate is set to $U = 0.5$; in the simulations, $N = 20,000$ and $R = 10$ M.

descent (*e.g.*, Rousset 2002), that is, that their ancestral lineages coalesce in a finite number of generations—which is possible only if these lineages stay in the same deme until coalescence occurs, since it takes an infinite time for lineages present in different demes to coalesce.

Assuming N is large while s and m are small, the change in frequency of the deleterious allele due to selection is approximately (see File S2)

$$\Delta_s p \approx -shp - s(1-3h)F_{ST}\, p + s(1-2h)\gamma\, p, \tag{19}$$

where γ is the probability that three genes sampled from the same deme are identical by descent (*i.e.*, that their ancestral lineages coalesce before migrating to different demes). To compute $\Delta_s p$ in terms of the model parameters (s, h, N, m), we may then assume that under weak selection F_{ST} and γ remain close to their equilibrium values under neutrality and replace F_{ST} and γ by these values in Equation 19 (Whitlock 2002, 2003; Wakeley 2003; Roze and Rousset 2003, 2004). While this approximation yields accurate results as long as $s \ll m$, it generally fails when $s \geq m$, as the effect of selection on F_{ST} and γ cannot be neglected (Roze and Rousset 2003, 2004). However, File S2 shows that when N is sufficiently large, F_{ST} and γ can be approximated by

$$F_{ST} \approx \frac{1}{1+4N(m+sh)}, \qquad \gamma \approx \frac{1}{[1+2N(m+sh)][1+4N(m+sh)]}. \tag{20}$$

Replacing F_{ST} and γ by these expressions in Equation 19 yields, at mutation–selection equilibrium,

$$p \approx \frac{(1+2\Gamma)(1+4\Gamma)}{2\Gamma(1+4\Gamma h)}\,\frac{u}{s} \tag{21}$$

with $\Gamma = N(m+sh)$ and where u is the mutation rate toward the deleterious allele. From Equations 16–18, we then obtain

$$L \approx \frac{(1+2\Gamma)(1+8\Gamma h)}{2\Gamma(1+4\Gamma h)}\, u \tag{22}$$

$$\delta \approx \frac{(1-2h)(1+2\Gamma)}{1+4\Gamma h}\, u \tag{23}$$

$$H \approx \frac{(1-2h)(1+2\Gamma)}{2\Gamma(1+4\Gamma h)}\, u. \tag{24}$$

When $s \ll m$ (so that $\Gamma \approx Nm$), Equations 21–24 become equivalent to the results obtained using expressions for F_{ST} and γ under neutrality (*e.g.*, equations 35–39 in Roze and Rousset 2004). As shown in Figure 6, however, taking into account the effect of selection on F_{ST} and γ (by using Equation 20) greatly improves analytical predictions when $m \leq s$. Interestingly, the expression for F_{ST} given by Equation 20 was already 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). However, Glémin *et al.* (2003) neglected the effect of population structure on the mean allele frequency p (assuming that selection is strong relative to local drift) and thus replaced p by $u/(s\,h)$ in Equations 16–18. In effect, Equations 21–24 thus combine the results of Glémin *et al.* (2003), which take into account the effect of selection on F_{ST} but neglect the effect of population structure on mean allele frequency, and the results of Roze and Rousset (2004), which take into account the effect of population structure on mean allele frequency but neglect the effect of selection on F_{ST}. Figure S7 compares these different approximations and shows that Equations 21–24 lead to significant improvement over these previous results.

Finally, we can note that when the migration rate m is set to zero, the model represents an infinite number of replicates of a single population of size N. The above results thus predict that the variance in frequency of a deleterious allele due to drift in a single finite population should be $\sim \bar{p}\bar{q}/(1+4Nsh)$ as long as the average frequency $\bar{p}$ of the deleterious allele

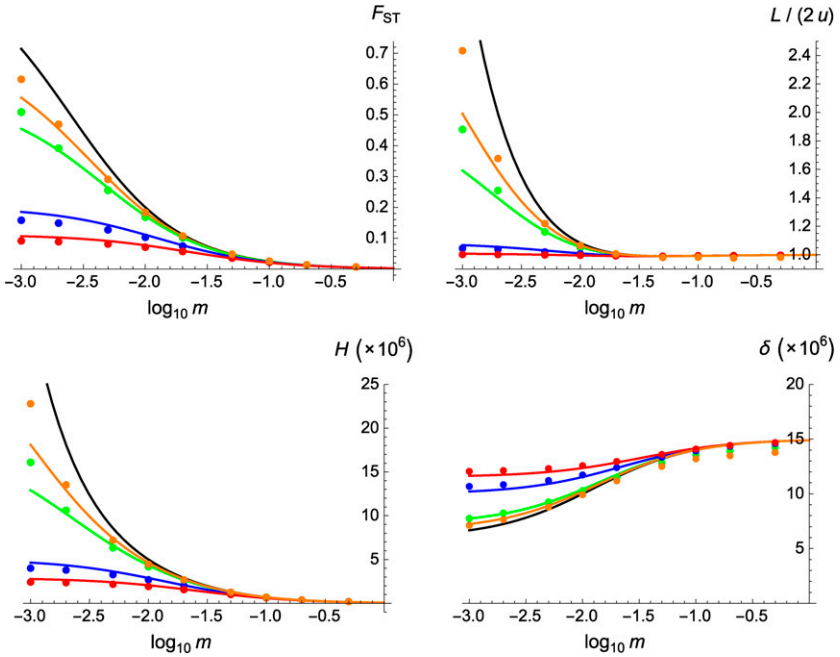

Figure 6 Equilibrium values of F_{ST}, mutation load L (divided by its value in a panmictic population, $2u$), heterosis, and inbreeding depression in a subdivided population, when selection acts at a single locus. The x-axes show the migration rate between demes (on a log scale), and the different colors correspond to different values of s: 0.005 (orange), 0.01 (green), 0.05 (blue), and 0.1 (red). Colored curves, predictions from Equations 20 and 22–24; circles, one-locus simulation results (30 replicates of 10^7 generations; error bars are smaller than the size of circles); black curves, predictions from Roze and Rousset (2004) (obtained by replacing Γ by Nm in Equations 20 and 22–24). Other parameter values: $h = 0.2$, $N = 100$, $u = 10^{-5}$; in the simulations the number of demes is set to 200, and back mutations occur at rate 10^{-7}.

remains small (from Equation 20, with $\bar{q} = 1 - \bar{p}$). Furthermore, expressions for the average allele frequency, mutation load, and inbreeding depression are obtained by setting $m = 0$ in Equations 21–23. Figure 7 shows that these approximations are indeed accurate as long as N is not too small (so that the deleterious allele stays rare in the population).

Effects of interference between selected loci

In the multilocus case, population structure generates different types of associations between alleles at different loci, either from the same individual or from different individuals from the same deme. As shown in File S2, selection against deleterious alleles is affected by these associations, through extra terms that appear in Equation 19 (see Equation B33 in File S2) and also through the fact that F_{ST} and γ at each locus are affected by interactions between loci. Assuming large deme size and weak selection and migration (so that $1/N$, m, and s are of order ε, where ε is a small term), fixed s and h, and freely recombining loci, we obtain

$$F_{ST} \approx \frac{1}{1+4N(m+sh)}\left[1 - s(1-2h)\frac{8Nm}{[1+4N(m+sh)]^2}\sum_j p_j\right], \tag{25}$$

which is equivalent to equation 79 in Roze and Rousset (2008) when $sh \ll m$, while

$$\gamma \approx \frac{1}{[1+2N(m+sh)][1+4N(m+sh)]} \times \left[1 - s(1-2h)\frac{4Nm[3+8N(m+sh)]}{[1+2N(m+sh)][1+4N(m+sh)]^2}\sum_j p_j\right] \tag{26}$$

(where p_j is the frequency of the deleterious allele at locus j in the metapopulation).

Equations 25 and 26 show that F_{ST} and γ at a given locus are decreased by partially recessive deleterious alleles segregating at other loci: this effect stems from the fact that offspring from migrant individuals tend to be more heterozygous and thus have higher fitness than offspring from philopatric individuals when deleterious alleles are partially recessive (heterosis). This increases the effective migration rate and thus reduces genetic correlations between individuals within demes (*e.g.*, Ingvarsson and Whitlock 2000). As shown by Equation 19, a lower F_{ST} decreases selection against deleterious alleles when $h < 1/3$ (and increases selection otherwise), while a lower γ increases selection against deleterious alleles when $h < 1/2$ and increases it otherwise. As a result, the effects of between-locus interactions on F_{ST} and γ may either increase or decrease the efficiency of selection against deleterious alleles, depending on parameter values. Furthermore, File S2 shows that all other effects of between-locus interactions should be negligible when $1/N$, s, and m are small, $h \neq 0.5$, and assuming each deleterious allele remains rare in the metapopulation (p_j small). From Equations 19, 25, and 26, we obtain for the mean number of deleterious alleles per haplotype at equilibrium (to the second order in U)

$$n \approx (1 - I_3)\frac{(1+2\Gamma)(1+4\Gamma)}{2\Gamma(1+4\Gamma h)}\frac{U}{s}, \tag{27}$$

where I_3 represents the effect of interactions between loci:

$$I_3 = (1-2h)\left(\frac{Nm}{\Gamma}\right)\frac{1+8\Gamma[h-(1-3h)\Gamma]}{\Gamma(1+4\Gamma)(1+4\Gamma h)^2}\,U. \tag{28}$$

Note that the sign of I_3 depends on parameter values: while I_3 is always positive when $1/3 < h < 1/2$, it may become negative when $h < 1/3$, in particular if Γ is large. Therefore,

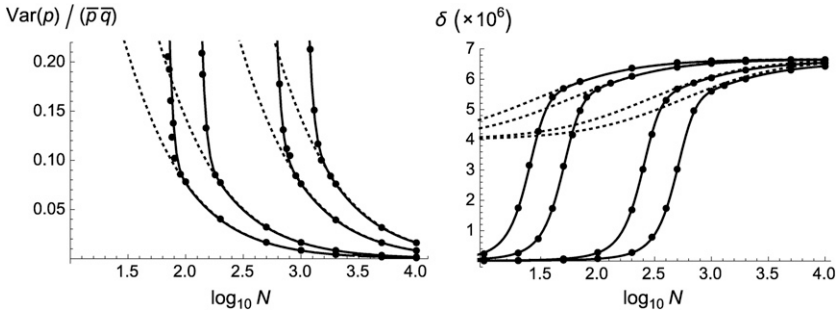

Figure 7 Variance of deleterious allele frequency (scaled by $\bar{p}\bar{q}$) and inbreeding depression in a single finite population, as a function of population size N (on a log scale). Solid curves correspond to predictions obtained from numerical integration over the standard diffusion result for the distribution of allele frequency (*e.g.*, equation 9.3.4 in Crow and Kimura 1970; see also Bataillon and Kirkpatrick 2000), while dashed curves correspond to $1/(1+4Nsh)$ (left) and to the expression obtained by replacing Γ by Nsh in Equation 23 (right). Circles, one-locus simulation results (averages over 30 replicates of 10^8–10^9 generations). Parameter values: $s = 0.005, 0.01, 0.05, 0.1$ (from right to left); $h = 0.3$; $u = 10^{-5}$; back mutation rate, $v = 10^{-7}$.

interference between loci may either increase or decrease the frequency of deleterious alleles. Furthermore, we obtain for the mutation load

$$L \approx 1 - \exp\left[-(1-I_4)\frac{(1+2\Gamma)(1+8\Gamma h)}{2\Gamma(1+4\Gamma h)}\ U\right] \qquad (29)$$

with

$$I_4 = (1-2h)\left(\frac{Nm}{\Gamma}\right)\frac{1+8\Gamma h[1-(1-4h)\Gamma]}{\Gamma(1+4\Gamma h)^2(1+8\Gamma h)}\ U. \qquad (30)$$

Again, the sign of I_4 (representing the effect of interactions between loci) depends on parameter values: I_4 is always positive if $1/4 < h < 1/2$ (in which case interactions reduce the load), but becomes negative if $h < 1/4$ and Γ is sufficiently large.

By contrast, the sign of the expressions obtained for the effects of interactions between loci on heterosis and inbreeding depression stays constant when $h < 1/2$. Indeed, we obtain for heterosis (see File S2 for derivation)

$$H \approx 1 - \exp\left[-\left(1-I_5\right)\frac{(1-2h)(1+2\Gamma)}{2\Gamma[1+4\Gamma h]}\ U\right] \qquad (31)$$

with

$$I_5 = (1-2h)\left(\frac{Nm}{\Gamma}\right)\frac{1+8\Gamma h(1+\Gamma)}{\Gamma(1+4\Gamma h)^2}\ U, \qquad (32)$$

showing that interactions between loci always decrease heterosis when $h < 1/2$. Finally, inbreeding depression is given by

$$\delta \approx 1 - \exp\left[-(1+I_6)\frac{(1-2h)(1+2\Gamma)}{1+4\Gamma h}\ U\right] \qquad (33)$$

with

$$I_6 = 2(1-2h)^2\left(\frac{Nm}{\Gamma}\right)\frac{1}{\Gamma(1+4\Gamma h)^2}\ U, \qquad (34)$$

showing that interactions between loci always increase inbreeding depression within demes. Indeed, heterosis and inbreeding depression scale with $F_{ST}\ n$ and $(1-F_{ST})n$, respectively (from Equations 17 and 18), and we obtain from Equations 25 and 27 that the effect of between-locus interactions on these products stays constant as long as $h < 1/2$ (to the second order in U). As shown by Figure 8, simulation results confirm that interactions between loci tend to increase inbreeding depression and decrease heterosis, fitting reasonably well with predictions from Equations 31 and 33 (although discrepancies appear when m is very small). The effects of interactions between loci on inbreeding depression stay rather small for the parameter values used in Figure 8A, but become more important for lower values of s and h or higher values of U, as shown by Figure 8, C and D. As an aside, File S2 also shows that defining inbreeding depression as $1 - E_x[W_{\text{self},x}]/E_x[W_{\text{out},x}]$ or as $1 - E_x[W_{\text{self},x}/W_{\text{out},x}]$ (where again E_x stands for the average over all demes x, while $W_{\text{self},x}$ and $W_{\text{out},x}$ are the mean fitnesses of offspring produced by selfing and by outcrossing in deme x) should yield very similar results under our assumptions (N large, s and m small, and p_j small), since the variance of $W_{\text{out},x}$ and the covariance between $W_{\text{self},x}$ and $W_{\text{out},x}$ across demes remain small under these conditions. Indeed, both measures were used in the simulations and gave nearly undistinguishable results (not shown).

Discussion

Theoretical predictions regarding the effect of the mating system of organisms on the mutation load and inbreeding depression are often based on single-locus models. However, as previously shown by Lande *et al.* (1994), some of these predictions may not hold when considering more realistic situations involving multiple selected loci. In particular, when the genomic mutation rate toward recessive deleterious alleles is sufficiently high, inbreeding depression is maintained at high levels irrespective of the selfing rate of individuals (contrary to the predictions of single-locus models), unless selfing exceeds a threshold value. This selective interference effect has been invoked by Scofield and Schultz (2006) and by Winn *et al.* (2011) to explain the lack of evidence of purging in meta-analyses comparing species with intermediate selfing rates to species with a low selfing rate (while species with high selfing rates show reduced inbreeding depression): for example, Winn *et al.* (2011) observed

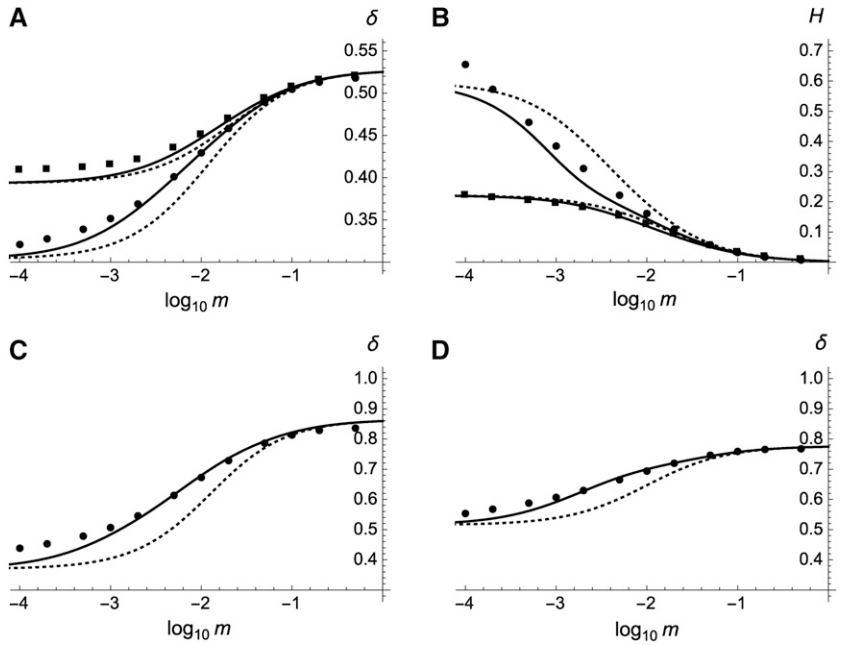

Figure 8 Inbreeding depression (A, C, and D) and heterosis (B) when deleterious mutations occur at a large number of loci, as a function of the migration rate between demes (on a log scale). Circles, multilocus simulation results; solid curves, predictions from Equations 31 and 33; dotted curves, predictions ignoring effects of interactions between loci (setting I_5 and I_6 to zero in Equations 31 and 33). Parameter values: (A and B) $U = 0.5$, $h = 0.2$, $s = 0.05$ (squares, top curves in A, bottom curves in B), $s = 0.01$ (circles, bottom curves in A, top curves in B); (C) $U = 0.5$, $h = 0.1$, $s = 0.01$; and (D) $U = 1$, $h = 0.2$, $s = 0.01$. Deme size: $N = 100$. In the simulations the number of demes is set to 200 and genome map length to $R = 20$ M.

that species with intermediate selfing rates (between 0.2 and 0.8) present similar levels of inbreeding depression to those of species with lower selfing rates (<0.2). Furthermore, it has been proposed that this effect may allow the stable maintenance of mixed mating systems (involving both selfing and outcrossing), since the classical prediction that only complete selfing or complete outcrossing should be evolutionarily stable (Lande and Schemske 1985) is based on the assumption that inbreeding depression is a decreasing function of the selfing rate.

Most previous studies of selective interference were based on Kondrashov's (1985) simulation model, representing deleterious alleles occurring at an infinite number of unlinked loci, in an infinite population. Lande *et al.* (1994) considered the case of fully (or almost fully, *i.e.*, $h = 0.02$) recessive lethal mutations ($s = 1$) and found that selective interference becomes important when the genomic deleterious mutation rate is sufficiently high (0.2–1). Kelly (2007) showed that strong homozygous effects of deleterious alleles are not necessarily needed for interference to occur (the effect being actually stronger with $s = 0.1$ than with $s = 1$), while h has to be sufficiently low to observe interference. Winn *et al.* (2011) modeled transitions from outcrossing to partial selfing and showed that increased selfing leads to lower levels of inbreeding depression (purging) when $s = 0.05$ and $h = 0.2$ and when $s = 0.001$ and $h = 0.4$, but not when $s = 1$ and $h = 0.02$ (for a genomic mutation rate of 1), inbreeding depression staying close to 1 in the last situation.

To date, no analytical model has explored the mechanisms of selective interference. In this article, I showed that analytical approximations can be obtained in regimes where interference stays moderate, by considering the effects of pairwise interactions between selected loci and assuming weak selection. As we have seen, the mechanisms underlying interference in partially inbred populations depend on the form of inbreeding considered. In a single, large population undergoing partial selfing, interference between loci is mainly driven by identity disequilibria between those loci (as long as the fitness of heterozygotes departs from the average of both homozygotes a each locus, *i.e.*, $h \neq 0.5$). However, identity disequilibria affect inbreeding depression through several mechanisms: correlations in homozygosity directly reduce δ, but also indirectly decrease homozygosity at each locus (which also reduces δ) and decrease the efficiency of selection against deleterious alleles, allowing them to be maintained at higher frequencies (thereby increasing δ). This last effect (which predominates over the first two) corresponds to the verbal explanation proposed previously to explain selective interference (purging is prevented by identity disequilibria, *e.g.*, Lande *et al.* 1994; Winn *et al.* 2011). However, we have seen that this effect itself involves three different mechanisms: reduction of the effective dominance coefficient of deleterious alleles, decrease in homozygosity at each locus, and positive correlations between the presence of a deleterious allele at a given locus and heterozygosity at other loci. The results presented here also show that interference is affected little by the strength of selection against deleterious alleles (at least as long as selection is weak to moderate) or by linkage, as long as genome map length is sufficiently high—in agreement with the simulation results obtained by Charlesworth *et al.* (1992), showing that the effect of linkage on mean fitness and inbreeding depression in partially selfing populations often remains slight.

When inbreeding results from limited dispersal (population structure), interference effects are more complicated as they involve associations between loci as well as between different individuals from the same spatial location. However, we have seen that when selection and migration are weak

while deme size is large, the main effect of interference between loci (assuming partially recessive deleterious alleles) is to increase the effective migration rate at each locus (Ingvarsson and Whitlock 2000), thereby reducing probabilities of identity between alleles present in different individuals from the same deme. This may either increase or decrease the strength of selection against deleterious alleles, depending on parameter values, but it always increases inbreeding depression within demes, while reducing heterosis between demes. In contrast to the case of partial selfing in a single population, this effect does not involve identity disequilibria (correlations in homozygosity across loci), but does involve other types of associations between alleles present in different individuals from the same deme (moments of linkage disequilibrium and allele frequencies, see Equations B44 and B45 in File S2). Furthermore, an important difference between partial selfing and population structure is that the mutation load and inbreeding depression in a structured population may be affected by the strength of selection against deleterious alleles (in particular when migration is weak, see Figure 6). The effects of interference between loci also depend on the strength of selection, being more marked for lower values of s.

Is selective interference likely to have important consequences in natural populations? Confirming previous results, we have seen that interference leads to substantial deviations from single-locus results for parameter values leading to strong inbreeding depression (high U, low h), independently of the strength of selection against deleterious alleles. In particular, the total absence of purging as the selfing rate increases (up to a threshold value) is observed only when inbreeding depression is close to 1 (while for lower values of δ, interference only dampens the decline of inbreeding depression with selfing). As observed by Winn *et al.* (2011), this condition may be fulfilled in gymnosperms, which show very high levels of inbreeding depression. In contrast, angiosperms show lower values of inbreeding depression (on average), for which selective interference may not be sufficiently strong to prevent purging. According to the results shown here, interference between deleterious alleles may thus not represent a sufficient explanation for the lack of evidence for purging in angiosperms in Winn *et al.*'s (2011) meta-analysis (for selfing rates between 0 and 0.8). Other possible explanations may be a lack a sufficient power to detect purging or synergistic epistasis between deleterious alleles, which tends to flatten the relationship between inbreeding depression and the selfing rate (Charlesworth *et al.* 1991). Note also that, as discussed by Winn *et al.* (2011), most estimates of inbreeding depression compiled in their data set were obtained under greenhouse conditions and may thus be biased downward if inbreeding depression tends to be stronger in harsher environments (Armbruster and Reed 2005). More empirical studies of inbreeding depression in different sets of conditions are thus needed to assess the potential importance of interactions between loci on selection against deleterious alleles.

Finally, because the suppression of purging due to interference occurs only when inbreeding depression is maximal, this mechanism does not seem a likely explanation for the evolutionary maintenance of mixed mating systems (as proposed in previous articles), since selfing should be strongly disfavored when δ is close to 1. Nevertheless, the effects of associations between loci on the evolution of mating systems remain little explored (but see Kamran-Disfani and Agrawal 2014). Besides affecting inbreeding depression, between-locus associations may modulate the advantage of selfers due to more efficient purging (*e.g.*, Uyenoyama and Waller 1991; Epinat and Lenormand 2009) and possibly generate additional selective forces acting on a modifier locus affecting the selfing rate. These effects are still waiting for analytical exploration.

Acknowledgments

I thank the bioinformatics and computing service of the Roscoff Biological Station for computing time and Joachim Hermisson and two anonymous reviewers for helpful suggestions and comments. This work was supported by the French Agence Nationale de la Recherche (ANR-11-BSV7-013).

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Communicating editor: J. Hermisson

GENETICS

Supporting Information
www.genetics.org/lookup/suppl/doi:10.1534/genetics.115.178533/-/DC1

Effects of Interference Between Selected Loci on the Mutation Load, Inbreeding Depression, and Heterosis

Denis Roze

DOI: 10.1534/genetics.115.178533

SUPPLEMENTARY FIGURES

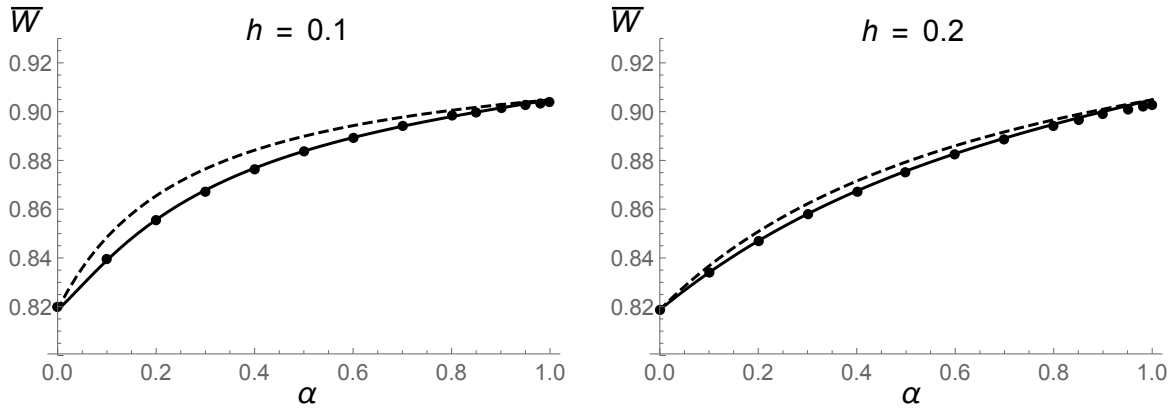

Figure S1. Equivalent to Figure 1 in the main text, with $U = 0.1$ (and other parameters as in Figure 1).

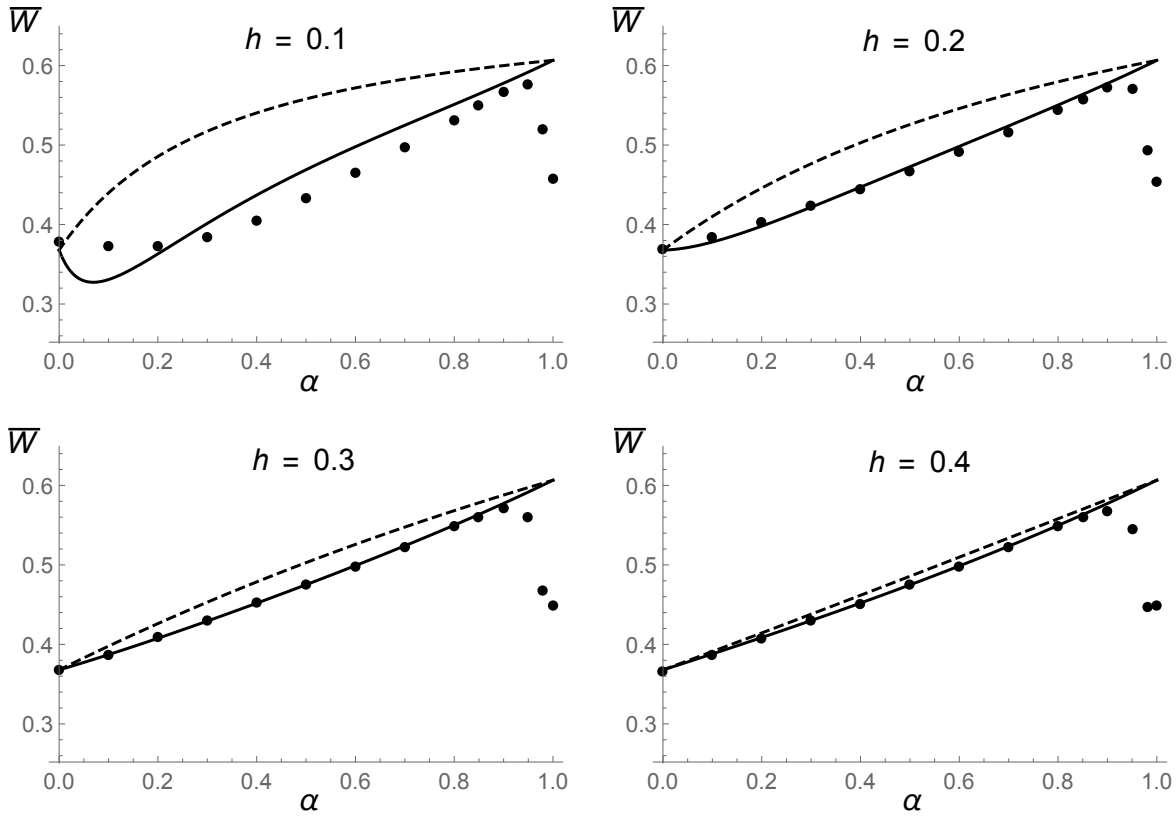

Figure S2. Equivalent to Figure 1 in the main text, with $s = 0.01$ (and other parameters as in Figure 1).

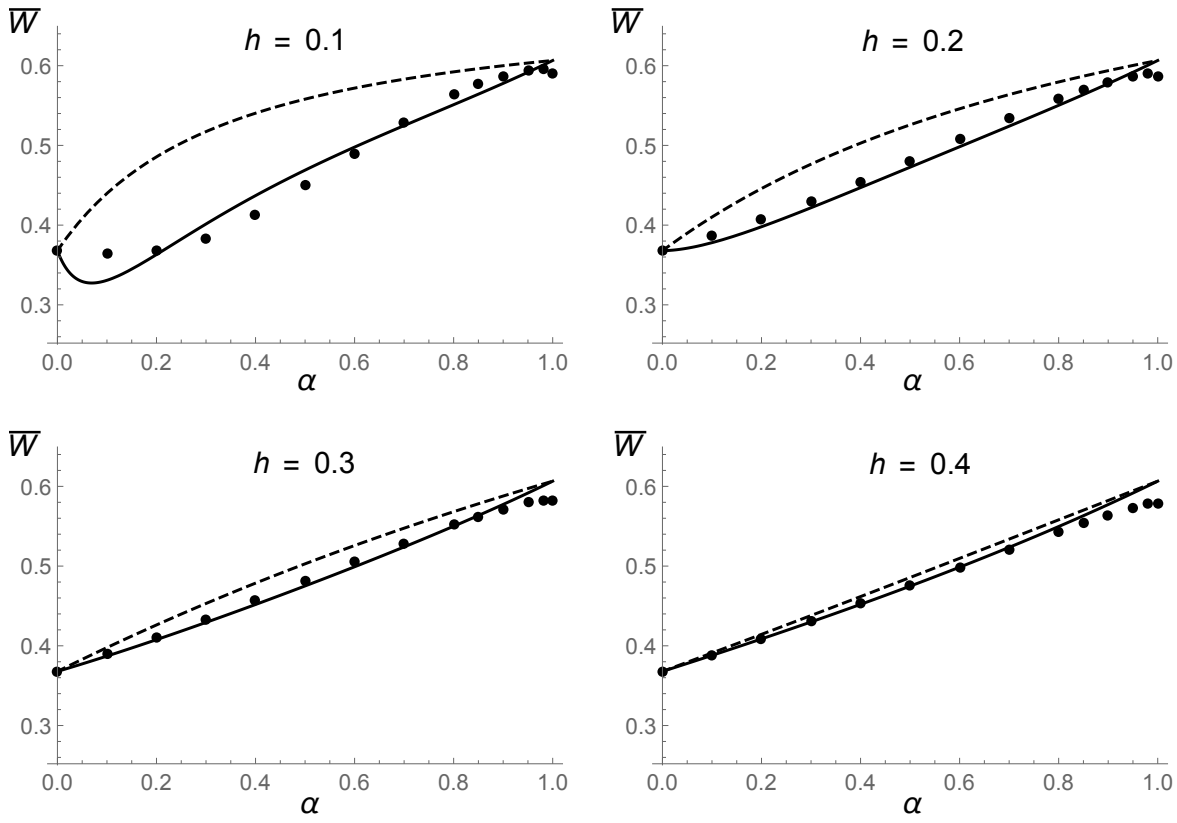

Figure S3. Equivalent to Figure 1 in the main text, with $s = 0.1$ (and other parameters as in Figure 1).

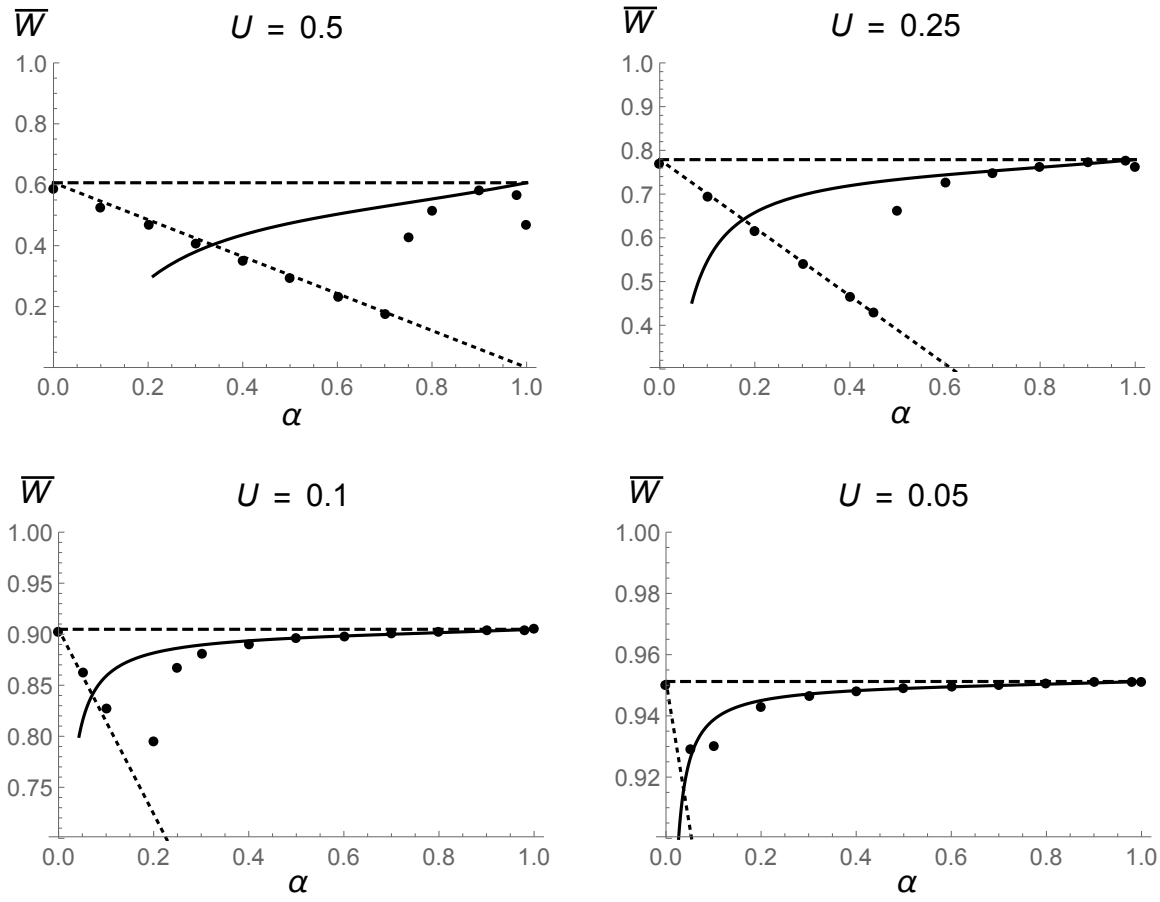

Figure S4. Mean fitness when deleterious alleles are fully recessive (same parameter values as in Figure 4 in the main text). As in Figures 1 and S1–S3, dashed and solid curves represent analytical predictions ignoring (dashed, $\overline{W} \approx e^{-U}$) and including (solid, equation 10 in the main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

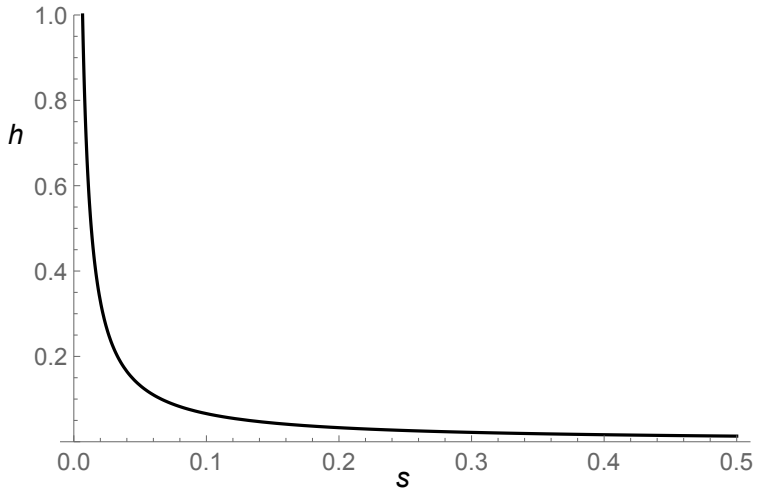

Figure S5. Dominance coefficient h of deleterious alleles as a function of their selection coefficient s, assuming a log-normal distribution of selection coefficients (s) and fixed heterozygous effect (sh) of deleterious alleles. Parameter values are as in Figure 5 in the main text.

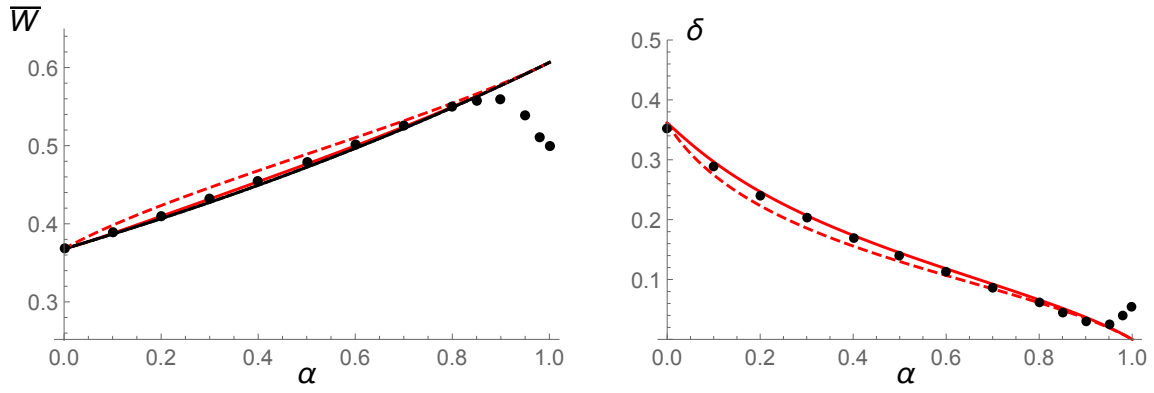

Figure S6. Same as Figure 5 in the main text, setting $\theta = 0.5 \exp[\mu - \sigma^2/2] \approx 0.01318$ so that $\overline{h} = 0.5$.

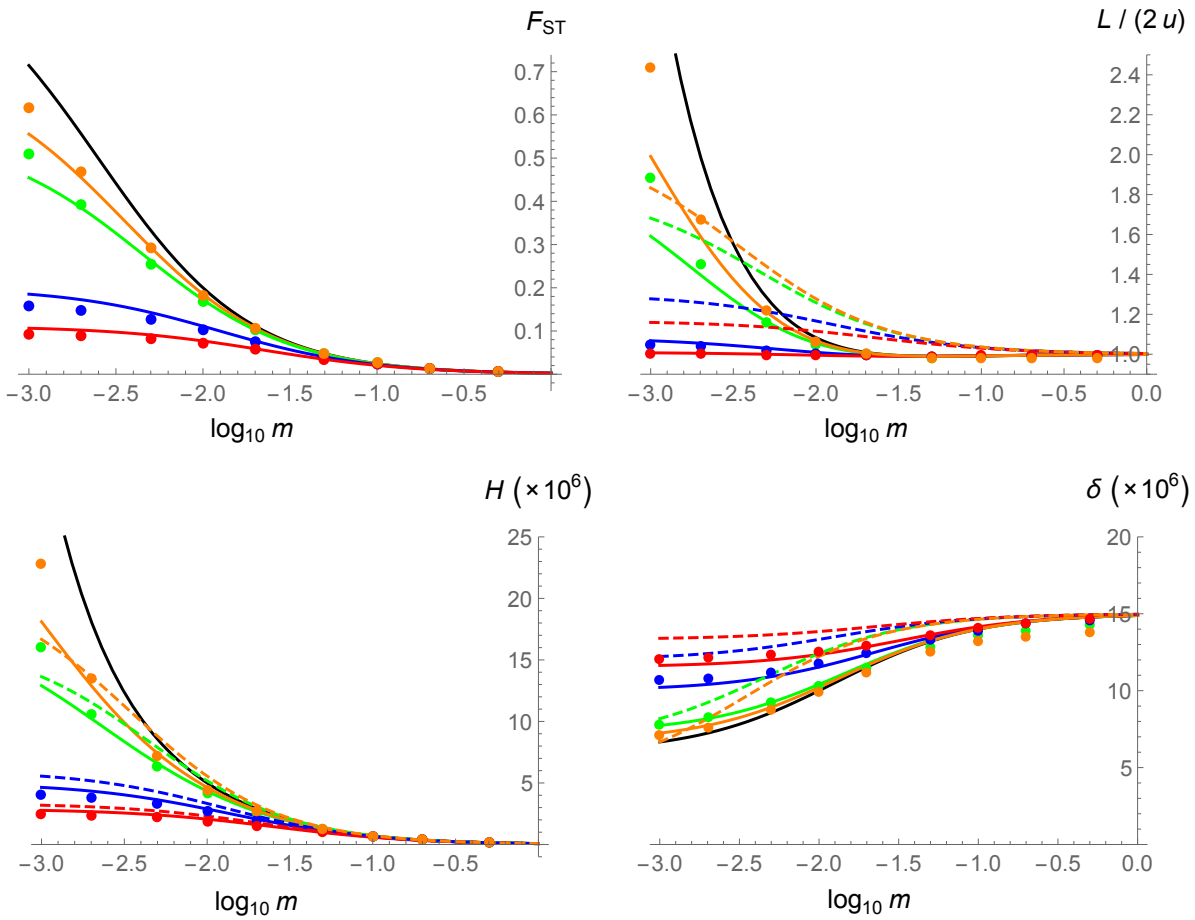

Figure S7. Same as Figure 6 in the main text, showing approximations from Glémin et al (2003) for the mutation load, inbreeding depression and heterosis (dashed curves).

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:

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

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

$$\begin{aligned}\zeta_{\mathbb{S},\mathbb{T}} &= \frac{\zeta_{\mathbb{S}(1)}\,\zeta_{\mathbb{T}(2)} + \zeta_{\mathbb{S}(2)}\,\zeta_{\mathbb{T}(1)}}{2},\\ \zeta_{\mathbb{S}(1)} &= \prod_{i\in\mathbb{S}} \zeta_{i(1)}, \quad \zeta_{\mathbb{T}(2)} = \prod_{i\in\mathbb{T}} \zeta_{i(2)}\end{aligned} \tag{A3}$$

(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, $D_{i,i} = \mathrm{E}\left[\zeta_{i(1)}\,\zeta_{i(2)}\right]$ measures the departure from Hardy-Weinberg equilibrium at locus i, while $D_{ij} = \mathrm{E}\left[\zeta_{i(1)}\,\zeta_{j(1)} + \zeta_{i(2)}\,\zeta_{j(2)}\right]/2$ 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:

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

(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 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 $D^{\mathrm{s}}_{\mathbb{S},\mathbb{T}}$) is given by:

$$D^{\mathrm{s}}_{\mathbb{S},\mathbb{T}} = D^{\bullet}_{\mathbb{S},\mathbb{T}} + \sum_{\mathbb{X}\subset\mathbb{S}}\sum_{\mathbb{Y}\subset\mathbb{T}} D^{\bullet}_{\mathbb{S}\setminus\mathbb{X},\mathbb{T}\setminus\mathbb{Y}} \prod_{i\in\mathbb{X}} (-\Delta_{\mathrm{s}} p_i) \prod_{j\in\mathbb{Y}} (-\Delta_{\mathrm{s}} p_j) \tag{A5}$$

where

$$D^{\bullet}_{\mathbb{S},\mathbb{T}} = \mathrm{E}\left[\frac{W}{\overline{W}}\,\zeta_{\mathbb{S},\mathbb{T}}\right]. \tag{A6}$$

In the expressions above, W and $\overline{W}$ 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 $\mathbb{S}\backslash\mathbb{X}$ 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 $D^{\mathrm{r}}_{\mathbb{S},\mathbb{T}}$) are given by:

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

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:

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

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:

$$W = \prod_i \left[1 - s\,h \left(X_{i(1)} + X_{i(2)} \right) - s\,(1-2h)\, X_{i(1)} X_{i(2)} \right] \tag{A9}$$

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

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

where

$$T_i = -2sh\,p_i - s\,(1-2h)\left({p_i}^2 + D_{i,i}\right)$$
$$a_i = -s\left[h + (1-2h)\,p_i\right], \quad a_{i,i} = -s\,(1-2h)\ . \tag{A11}$$

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:

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

Therefore, the mean log-fitness is approximately:

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

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 $\overline{W} \equiv \mathrm{E}\left[W\right]$ can be expressed in terms of the mean and variance in log-fitness through the following argument. Denoting $z = \ln W$, $\overline{z} = \overline{\ln W}$ and $dz = z - \overline{z}$, we have:

$$\overline{W} = \mathrm{E}\left[e^{z}\right] = \mathrm{E}\left[e^{\overline{z}+dz}\right], \tag{A14}$$

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

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

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

$$\mathrm{Var}\left[W\right] \approx e^{2\overline{\ln W}}\,\mathrm{Var}\left[\ln W\right]. \tag{A16}$$

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

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

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

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

In an infinite, randomly mating population, all associations within and between loci should be zero at equilibrium, and using the fact that $D_{ii} = p_iq_i$ and $D_{ii,ii} = \left(p_iq_i\right)^2$ (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: $2\left(sh\right)^2\sum_i p_iq_i + s^2\left(1-2h\right)^2\sum_i\left(p_iq_i\right)^2$ (e.g., Lynch and Walsh, 1998, p. 69). At mutation-selection balance, and assuming again that h is significantly greater than zero, $p_i \approx u/\left(hs\right)$ (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 $D_{ii,i} = \left(1-2p_i\right)D_{i,i}$ 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):

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

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 $\mathrm{Var}\left[\ln W\right]$ 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 $\mathrm{Var}\left[\ln W\right]$ in equation A15 should be negligible in these situations. Using this approximation, one obtains (from equations A13, A15 and A19):

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

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:

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

$$\begin{aligned} D'_{ij,ij} = \frac{\alpha}{2}\Big[&\left[1 - 2r_{ij}\left(1 - r_{ij}\right)\right]\left(D_{ij,ij} + pq_{ij}\right) \\ &+ 2r_{ij}\left(1 - r_{ij}\right)\left(p_i q_i D_{j,j} + p_j q_j D_{i,i}\right)\Big] \end{aligned} \tag{A22}$$

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

$$D_{i,i} = F\, p_i q_i, \quad D_{ij,ij} = \phi_{ij}\, pq_{ij} \tag{A23}$$

with

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

Therefore,

$$D_{ij,ij} - D_{i,i}D_{j,j} = G_{ij}\, pq_{ij} \approx G_{ij}\, p_i p_j \tag{A25}$$

(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:

$$G = \frac{4\alpha\left(1 - \alpha\right)}{\left(4 - \alpha\right)\left(2 - \alpha\right)^2}\,. \tag{A26}$$

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:

$$\frac{W}{\overline{W}} \approx -s\,h \sum_j \left(\zeta_{j(1)} + \zeta_{j(2)}\right) - s\left(1 - 2h\right) \sum_j \left(\zeta_{j(1)}\zeta_{j(2)} - D_{j,j}\right). \tag{A27}$$

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

$$D^{\mathrm{s}}_{i,i} = \mathrm{E}\left[\frac{W}{\overline{W}}\,\zeta_{i(1)}\zeta_{i(2)}\right] - \left(\Delta_{\mathrm{s}} p_i\right)^2. \tag{A28}$$

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

$$D^{\rm s}_{i,i} \approx -2sh \sum_j D_{ij,i} - s\,(1-2h) \sum_j \left(D_{ij,ij} - D_{i,i} D_{j,j}\right) . \tag{A29}$$

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 $D_{i,i}$:

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

Therefore, at equilibrium:

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

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):

$$D^{\rm s}_{ij,j} = {\rm E} \left[\frac{W}{\overline{W}} \, \frac{\zeta_{ij,j} + \zeta_{j,ij}}{2} \right] - (\Delta_{\rm s} p_i)\, D_{j,j} \,. \tag{A32}$$

Furthermore,

$$\Delta_{\rm s} p_i = {\rm E} \left[\frac{W}{\overline{W}} \, \frac{X_{i(1)} + X_{i(2)}}{2} \right] - p_i = {\rm E} \left[\frac{W}{\overline{W}} \, \frac{\zeta_{i(1)} + \zeta_{i(2)}}{2} \right] \tag{A33}$$

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

$$\Delta_{\rm s} p_i = -sh\, p_i - s\,(1-h)\, D_{i,i} \,. \tag{A34}$$

From equations A27, A32 and A34, one obtains:

$$D^{\rm s}_{ij,j} \approx D_{ij,j} - s\,(1-h)\left(D_{ij,ij} - D_{i,i} D_{j,j}\right) . \tag{A35}$$

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

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

giving at equilibrium:

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

(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 $W/\overline{W}$ to the second order in s. From equations A12 and A20, this is:

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

From equations A33 and A38, neglecting terms in ${p_i}^2$ and neglecting terms in $s\,U$ relative to terms in U^2, one obtains:

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

Using equations A25, A31 and A37, this is:

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

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:

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

or in terms of the selfing rate α:

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

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

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

with:

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

and

$$T = \frac{2\alpha\,(1-\alpha)}{(4-\alpha)\left[2h + \alpha\,(1-2h)\right]^2}. \tag{A45}$$

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

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

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:

$$sU^2\,(1-2h)\,\frac{4\alpha\,(1-\alpha)\left[8h^2\,(1-h) + \alpha\,(1-2h)\,(2-4h^2+\alpha\,h)\right]}{(2-\alpha)\,(4-\alpha)\left[2h + \alpha\,(1-2h)\right]^3}. \tag{A47}$$

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:

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

where $D^{\text{self}}_{i,i}$ and $D^{\text{self}}_{ij,ij}$ 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 $\overline{W}_{\text{out}} \approx e^{-2sh n}$, and therefore:

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

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

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

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:

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

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

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

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:

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

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

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:

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

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:

$$\overline{W} \approx \exp\Big[-U\big[\Lambda_1 + GU\left(\left(1 + 2F\right)\Lambda_2 - F\,\Lambda_3\right)\Lambda_3\big]\Big]\left(1 + \frac{1}{2}\,GU^2\Lambda_3^2\right) \tag{A56}$$

$$\begin{aligned}\delta \approx 1 - \exp\Big[-U\big[1 + F + GU\left(\left(1 + F\right)\left(1 + 2F\right)\Lambda_2 - F\,\Lambda_3\right)\big]\frac{\Lambda_3}{2}\Big] \\ \times\left(1 + \frac{1}{8}\,GU^2\Lambda_3^2\right)\end{aligned} \tag{A57}$$

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

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

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

$$\Lambda_3 = \int \psi\left(h\right) \frac{1 - 2h}{h + \left(1 - h\right) F}\, dh\,. \tag{A60}$$

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

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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:

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

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

$$D_{\mathbb{S},\mathbb{T}} = \mathrm{E}\left[\zeta_{\mathbb{S},\mathbb{T}(xy)}\right] \tag{B2}$$

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

$$\begin{aligned}\zeta_{\mathbb{S},\mathbb{T}(xy)} &= \frac{\zeta_{\mathbb{S}(xy1)}\,\zeta_{\mathbb{T}(xy2)} + \zeta_{\mathbb{S}(xy2)}\,\zeta_{\mathbb{T}(xy1)}}{2}, \\ \zeta_{\mathbb{S}(xy1)} &= \prod_{i\in\mathbb{S}} \zeta_{i(xy1)}, \quad \zeta_{\mathbb{T}(xy2)} = \prod_{i\in\mathbb{T}} \zeta_{i(xy2)}\end{aligned} \tag{B3}$$

(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:

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

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 $D_{\mathbb{S},\mathbb{T}\widehat{/}\mathbb{U},\mathbb{V}}$ and defined as in equation B4, excepts that the average is over all individuals y and z including $y = z$. Note that we have:

$$D_{\mathbb{S},\mathbb{T}\widehat{/}\mathbb{U},\mathbb{V}} = \frac{D_{\mathbb{SU},\mathbb{TV}} + D_{\mathbb{SV},\mathbb{TU}}}{2N} + \left(1 - \frac{1}{N}\right) D_{\mathbb{S},\mathbb{T}/\mathbb{U},\mathbb{V}}\,. \tag{B5}$$

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 $D^{\mathrm{g}}_{\mathbb{S}}$, $D^{\mathrm{g}}_{\mathbb{S}/\mathbb{T}}$... 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 $D^{\mathrm{g}}_{\mathbb{S}\widehat{/}\mathbb{T}} = D^{\mathrm{g}}_{\mathbb{S}/\mathbb{T}}$).

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, $D^{\mathrm{g}}_{i/i}$ 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:

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

where associations $D_{\widehat{i/i}}$, $D_{i,i}$ 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 $D^{\mathrm{g}}_{i/i}$ under neutrality is given by:

$$D^{\mathrm{g}}_{i/i}{}' = \frac{p_i q_i + D^{\mathrm{g}}_{i/i}}{2N} + \left(1 - \frac{1}{N}\right) (1-m)^2 D^{\mathrm{g}}_{i/i} \tag{B7}$$

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

$$D^{\mathrm{g}}_{i/i}{}' \approx \frac{p_i q_i}{2N} + \left(1 - \frac{1}{2N} - 2m\right) D^{\mathrm{g}}_{i/i}, \tag{B8}$$

which gives at equilibrium:

$$D^{\mathrm{g}}_{i/i} \approx \frac{p_i q_i}{1 + 4Nm} \tag{B9}$$

that is, $F_{\mathrm{ST}}\, p_i q_i$ (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:

$$\Delta_{\rm s} p_i = {\rm E}\left[\frac{W_{xy}}{W_x}\,\frac{X_{i(xy1)}+X_{i(xy2)}}{2}\right] - p_i = {\rm E}\left[\frac{W_{xy}}{W_x}\,\frac{\zeta_{i(xy1)}+\zeta_{i(xy2)}}{2}\right] \tag{B10}$$

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 ($D^{\rm g}_{i/i}$) can be expressed in terms of genetic associations among parents from the relation:

$$D^{\rm g}_{i/i} = {\rm E}\left[\left(\frac{W_{xy}}{W_x}\,\frac{\zeta_{i(xy1)}+\zeta_{i(xy2)}}{2}\right)\left(\frac{W_{xz}}{W_x}\,\frac{\zeta_{i(xz1)}+\zeta_{i(xz2)}}{2}\right)\right] - (\Delta_{\rm s} p_i)^2 \tag{B11}$$

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:

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

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:

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

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

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

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

$$\Delta_{\mathrm{s}} p_i \approx -s\,h\left(p_i q_i + D_{i,i} - 2D_{i\widehat{/i}}\right) - s\,(1-2h)\left(D_{ii,i} - D_{i,i\widehat{/i}}\right) \tag{B15}$$

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

$$\begin{aligned}\Delta_{\mathrm{s}} p_i \approx -s\,h\left(1-\frac{1}{N}\right)\left[p_i q_i + \left[1-2\,(1-m)^2\right] D^{\mathrm{g}}_{i/i}\right] \\ - s\,(1-2h)\left(1-\frac{1}{N}\right)\left(D^{\mathrm{g}}_{i/i} - (1-m)^2\, D^{\mathrm{g}}_{i/i/i}\right).\end{aligned} \tag{B16}$$

A similar expression is derived in Roze and Rousset (2003) and Roze and Rousset (2004). In these previous works, an approximation of $\Delta_{\mathrm{s}} p_i$ to the first order in s is then obtained by replacing associations $D^{\mathrm{g}}_{i/i}$ and $D^{\mathrm{g}}_{i/i/i}$ 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 $D^{\mathrm{g}}_{i/i}$ depends on $D^{\mathrm{g}}_{i/i/i}$ and $D^{\mathrm{g}}_{i/i/i/i}$, 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 $D^{\mathrm{g}}_{i/i}$ (and similarly, neglect associations involving 4 or more gametes in the recursion for $D^{\mathrm{g}}_{i/i/i}$). 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 ${p_i}^2$):

$$D^{\mathrm{g}}_{i/i} \approx (1 - 2sh)\, D_{\widehat{i/i}} \tag{B17}$$

wich, together with equation B7, yields:

$$D^{\mathrm{g}}_{i/i}{}' \approx \frac{p_i}{2N} + \left(1 - 2sh - \frac{1}{2N} - 2m\right) D^{\mathrm{g}}_{i/i}\,. \tag{B18}$$

Thus, at equilibrium:

$$D^{\mathrm{g}}_{i/i} \approx \frac{p_i}{1 + 4N\,(m + sh)}\,. \tag{B19}$$

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:

$$D^{\mathrm{g}}_{i/i/i}{}' \approx \frac{3}{2N} D^{\mathrm{g}}_{i/i} + \left(1 - 3sh - \frac{3}{2N} - 3m\right) D^{\mathrm{g}}_{i/i/i} \tag{B20}$$

giving at equilibrium:

$$D^{\mathrm{g}}_{i/i/i} \approx \frac{p_i}{[1 + 2N(m + sh)][1 + 4N(m + sh)]}\,. \tag{B21}$$

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

$$\Delta_{\mathrm{s}} p_i \approx -sh\,p_i - s(1 - 3h)\,D^{\mathrm{g}}_{i/i} + s(1 - 2h)\,D^{\mathrm{g}}_{i/i/i} \tag{B22}$$

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

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

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

$$L = 1 - \overline{W} \approx 2sh\,p_i + s(1 - 2h)\,D^{\mathrm{g}}_{i/i} \tag{B24}$$

which, from equations B19 and B23, becomes:

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

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 $W_{\mathrm{between}} \approx 1 - 2sh\,p_i$, yielding (to the first order in s):

$$H = 1 - \frac{\overline{W}}{W_{\mathrm{between}}} \approx s(1 - 2h)\,D^{\mathrm{g}}_{i/i}\,. \tag{B26}$$

From equations B19 and B23, one obtains:

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

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 $\left(p_i + D^{\mathrm{g}}_{i/i}\right)/2$, one obtains:

$$\delta \approx \frac{1}{2}s\left(1-2h\right)\left(p_i - D^{\mathrm{g}}_{i/i}\right), \tag{B28}$$

yielding:

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

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 ($\overline{W}$) can be written as (to the second order in s):

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

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

in s:

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

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

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

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

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

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 $s^2p_ip_j$, that vanish when $h = 1/2$ (when $h = 1/2$, interactions between loci affect changes in allele frequencies through terms in $s^4p_ip_j$, 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 ($D^{\mathrm{g}}_{ij/ij}$, $D^{\mathrm{g}}_{ij/i/j}$, $D^{\mathrm{g}}_{i/i/j/j}$, $D^{\mathrm{g}}_{ij/ij/i}$, $D^{\mathrm{g}}_{ij/j/i/i}$ and $D^{\mathrm{g}}_{i/i/i/j/j}$) are generated

by population structure (even in the absence of selection), while associations $D^{\mathrm{g}}_{ij/j}$ and $D^{\mathrm{g}}_{i/j/j}$ 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:

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

$$\begin{aligned} D^{\mathrm{g}}_{ij/i/j}{}' \approx{}& \left(1-\frac{3}{N}-3m-4hs\right)\left[(1-r_{ij})\, D^{\mathrm{g}}_{ij/i/j} + r_{ij} D^{\mathrm{g}}_{i/i/j/j}\right] \\ &+ \frac{1}{2N}\left[p_i D^{\mathrm{g}}_{j/j} + p_j D^{\mathrm{g}}_{i/i} + 3D^{\mathrm{g}}_{ij/i/j} + (1-r_{ij})\, D^{\mathrm{g}}_{ij/ij} + r_{ij} D^{\mathrm{g}}_{i/i/j/j}\right] \end{aligned} \tag{B35}$$

$$\begin{aligned} D^{\mathrm{g}}_{ij/ij}{}' \approx{}& \left(1-\frac{1}{N}-2m-4hs\right)\left[(1-r_{ij})^2 D^{\mathrm{g}}_{ij/ij} + 2r_{ij}(1-r_{ij}) D^{\mathrm{g}}_{ij/i/j} + {r_{ij}}^2 D^{\mathrm{g}}_{i/i/j/j}\right] \\ &+ \frac{1}{2N}\left[\left[1-2r_{ij}(1-r_{ij})\right]\left(p_i + D^{\mathrm{g}}_{ij/ij}\right) + 2r_{ij}(1-r_{ij})\left(p_i D^{\mathrm{g}}_{j/j} + p_j D^{\mathrm{g}}_{i/i}\right)\right] \end{aligned} \tag{B36}$$

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

$$\begin{aligned} D^{\mathrm{g}}_{ij/j/i/i}{}' \approx{}& \left(1-\frac{6}{N}-4m-5hs\right)\left[(1-r_{ij})\, D^{\mathrm{g}}_{ij/j/i/i} + r_{ij} D^{\mathrm{g}}_{i/i/i/j/j}\right] \\ &+ \frac{1}{2N}\Big[p_j D^{\mathrm{g}}_{i/i/i} + (1-r_{ij})\left(6D^{\mathrm{g}}_{ij/j/i/i} + 2D^{\mathrm{g}}_{ij/ij/i} + 3D^{\mathrm{g}}_{ij/i/j}\right) \\ &\quad + r_{ij}\left(5D^{\mathrm{g}}_{ij/j/i/i} + 3D^{\mathrm{g}}_{i/i/i/j/j} + 3D^{\mathrm{g}}_{i/i/j/j}\right)\Big] \end{aligned} \tag{B38}$$

$$\begin{aligned} D^{\mathrm{g}}_{ij/ij/i}{}' \approx{}& \left(1-\frac{3}{N}-3m-5hs\right) \\ &\times \left[(1-r_{ij})^2 D^{\mathrm{g}}_{ij/ij/i} + 2r_{ij}(1-r_{ij}) D^{\mathrm{g}}_{ij/j/i/i} + {r_{ij}}^2 D^{\mathrm{g}}_{i/i/i/j/j}\right] \\ &+ \frac{(1-r_{ij})^2}{2N}\left(p_j D^{\mathrm{g}}_{i/i} + 3D^{\mathrm{g}}_{ij/ij/i} + 2D^{\mathrm{g}}_{ij/ij}\right) \\ &+ \frac{r_{ij}(1-r_{ij})}{N}\left(p_j D^{\mathrm{g}}_{i/i/i} + D^{\mathrm{g}}_{ij/j/i/i} + D^{\mathrm{g}}_{ij/ij/i} + 3D^{\mathrm{g}}_{ij/i/j}\right) \\ &+ \frac{{r_{ij}}^2}{2N}\left(p_j D^{\mathrm{g}}_{i/i} + 2D^{\mathrm{g}}_{ij/j/i/i} + D^{\mathrm{g}}_{ij/ij/i} + 2D^{\mathrm{g}}_{i/i/j/j}\right). \end{aligned} \tag{B39}$$

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

$$D^{\mathrm{g}}_{ij/ij} \approx D^{\mathrm{g}}_{ij/i/j} \approx D^{\mathrm{g}}_{i/i/j/j} \approx \frac{p_i p_j}{\left[1+4N\left(m+s\,h\right)\right]^2} \tag{B40}$$

$$D^{\mathrm{g}}_{ij/ij/i} \approx D^{\mathrm{g}}_{ij/j/i/i} \approx D^{\mathrm{g}}_{i/i/i/j/j} \approx \frac{p_i p_j}{\left[1+2N\left(m+s\,h\right)\right]\left[1+4N\left(m+s\,h\right)\right]^2}. \tag{B41}$$

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 $D^{\mathrm{g}}_{ij/j}$ and $D^{\mathrm{g}}_{i/j/j}$ to leading order are given by:

$$\begin{aligned}
{D^{\mathrm{g}}_{ij/j}}' \approx & \frac{1}{2N} D^{\mathrm{g}}_{ij/j} + \left(1 - \frac{1}{N} - 2m - 3h\,s\right)\left[\left(1-r_{ij}\right) D^{\mathrm{g}}_{ij/j} + r_{ij} D^{\mathrm{g}}_{i/j/j}\right] \\
& - s\,h\Bigg[\left(1-r_{ij}\right)\left(D^{\mathrm{g}}_{ij/ij} - 2D^{\mathrm{g}}_{ij/i/j} + D^{\mathrm{g}}_{i/i} D^{\mathrm{g}}_{j/j}\right) \\
& \qquad + r_{ij}\left(2D^{\mathrm{g}}_{ij/i/j} - 3D^{\mathrm{g}}_{i/i/j/j} + D^{\mathrm{g}}_{i/i} D^{\mathrm{g}}_{j/j}\right)\Bigg] \\
& - s\left(1-2h\right)\Bigg[\left(1-r_{ij}\right)\left(D^{\mathrm{g}}_{ij/ij/j} - 2D^{\mathrm{g}}_{ij/i/j/j} + D^{\mathrm{g}}_{i/i/i} D^{\mathrm{g}}_{j/j}\right) \\
& \qquad + r_{ij}\left(D^{\mathrm{g}}_{ij/i/j/j} - 2D^{\mathrm{g}}_{i/i/i/j/j} + D^{\mathrm{g}}_{i/i/i} D^{\mathrm{g}}_{j/j}\right)\Bigg] \\
& - s\left(1-2h\right)\left(D^{\mathrm{g}}_{ij/i/j} - D^{\mathrm{g}}_{i/i} D^{\mathrm{g}}_{j/j}\right)
\end{aligned} \tag{B42}$$

$$\begin{aligned}
{D^{\mathrm{g}}_{i/j/j}}' \approx & \frac{1}{N} D^{\mathrm{g}}_{ij/j} + \left(1 - \frac{3}{2N} - 3m - 3h\,s\right) D^{\mathrm{g}}_{i/j/j} \\
& - s\,h\left(2D^{\mathrm{g}}_{ij/i/j} - 3D^{\mathrm{g}}_{i/i/j/j} + D^{\mathrm{g}}_{i/i} D^{\mathrm{g}}_{j/j}\right) \\
& - s\left(1-2h\right)\left(2D^{\mathrm{g}}_{ij/i/j/j} - 3D^{\mathrm{g}}_{i/i/i/j/j} + D^{\mathrm{g}}_{i/i/i} D^{\mathrm{g}}_{j/j}\right) \\
& - s\left(1-2h\right)\left(D^{\mathrm{g}}_{i/i/j/j} - D^{\mathrm{g}}_{i/i} D^{\mathrm{g}}_{j/j}\right).
\end{aligned} \tag{B43}$$

From equations B34–B39 and B42–B43, one obtains that $D^{\mathrm{g}}_{ij/j}$ and $D^{\mathrm{g}}_{i/j/j}$ 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 $D^{\mathrm{g}}_{i/i}$ and $D^{\mathrm{g}}_{i/i/i}$ taking into account effects of pairwise interactions between loci are given by (to leading order):

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

$$\begin{aligned} D^{\mathrm{g}}_{i/i/i}{}' \approx & \frac{3}{2N} D^{\mathrm{g}}_{i/i} + \left(1 - \frac{3}{2N} - 3m - 3hs\right) D^{\mathrm{g}}_{i/i/i} \\ & - 3s\,(1-2h) \sum_{j \neq i} \left(D^{\mathrm{g}}_{ij/j/i/i} - D^{\mathrm{g}}_{i/i/i/j/j}\right). \end{aligned} \quad \text{(B45)}$$

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

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

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

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

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

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

(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:

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

with:

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

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:

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

From equations B46 and B50, one obtains:

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

with:

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

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

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

with:

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

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

$$\delta = 1 - \mathrm{E}_x\left[\frac{W_{\text{self},x}}{W_{\text{out},x}}\right] \tag{B57}$$

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):

$$\delta \approx 1 - \frac{\mathrm{E}_x\left[W_{\text{self},\,x}\right]}{\mathrm{E}_x\left[W_{\text{out},\,x}\right]}\left[1 + \frac{\mathrm{Var}_x\left[W_{\text{out},\,x}\right]}{\mathrm{E}_x\left[W_{\text{out},\,x}\right]^2} - \frac{\mathrm{Cov}_x\left[W_{\text{out},\,x}, W_{\text{self},\,x}\right]}{\mathrm{E}_x\left[W_{\text{out},\,x}\right]\mathrm{E}_x\left[W_{\text{self},\,x}\right]}\right] \tag{B58}$$

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

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

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

$$\delta \approx 1 - \frac{\mathrm{E}_x\left[W_{\text{self},\,x}\right]}{\mathrm{E}_x\left[W_{\text{out},\,x}\right]} \tag{B60}$$

where $\mathrm{E}_x\left[W_{\text{out},\,x}\right]$ is equivalent to $\overline{W} \approx e^{-2shn - s(1-2h)\sum_i D_{i,i}}$, while $\mathrm{E}_x\left[W_{\text{self},\,x}\right]$ is given by $e^{-2shn - s(1-2h)\sum_i D^{\text{self}}_{i,i}}$ (where $D^{\text{self}}_{i,i}$ is the average of $\zeta_{i,i(xy)}$ over selfed offspring). Using the fact that $D^{\text{self}}_{i,i} \approx \left(p_i + D_{i,i}\right)/2$, one obtains $\delta \approx 1 - e^{-\frac{s}{2}(1-2h)\left(n - \sum_i D_{i,i}\right)}$. From equations B46 and B50, this is:

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

with:

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

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FILE S3

Mathematica notebook

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