Effects of partial selfing on the equilibrium genetic variance, mutation load and inbreeding depression under stabilizing selection

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ABSTRACT

The mating system of a species is expected to have important effects on its genetic diversity. In this paper, we explore the effects of partial selfing on the equilibrium genetic variance V_{g}, mutation load L and inbreeding depression δ under stabilizing selection acting on a arbitrary number n of quantitative traits coded by biallelic loci with additive effects. Three different regimes are observed. When the U/n ratio is low (where U is the total mutation rate on selected traits) and effective recombination rates are sufficiently high, genetic associations between loci are negligible and the mutation load and inbreeding depression are well predicted by approximations based on single-locus models. For higher values of U/n and/or lower effective recombination, moderate genetic associations generated by epistasis tend to increase V_{g}, L and δ, this regime being well predicted by approximations including the effects of pairwise associations between loci. For yet higher values of U/n and/or lower effective recombination, a different regime is reached under which the maintenance of coadapted gene complexes reduces V_{g}, L and δ. Simulations indicate that the values of V_{g}, L and δ are little affected by assumptions regarding the number of possible alleles per locus.

INTRODUCTION

Genetic diversity maintained within populations plays an important role in defining their adaptive potential (for a species to evolve, there must be heritable phenotypic variation on which selection can act). The ultimate source of this diversity is mutation, with a substantial proportion of new mutations being of a slightly deleterious nature (Eyre-Walker and Keightley, 2007): hence, a corollary to the maintenance of genetic diversity is the existence of a mutation load, defined as the reduction in mean fitness of a population relative to the fitness of an optimal genotype (Haldane, 1937). Furthermore, the fact that most deleterious alleles are partially recessive causes inbred offspring to have a lower fitness (on average) than outbred ones, as they tend to carry higher numbers of homozygous mutations (inbreeding depression, Charlesworth and Charlesworth, 1987). By affecting the average degree of homozygosity of individuals and the efficiency of recombination between loci, the reproductive system of a species is expected to have an important influence on the effect of selection against deleterious alleles, and thus on the mutation load, inbreeding depression and level of diversity maintained within populations. One mating system that has received considerable attention is self-fertilization, a reproductive strategy occurring at various rates in an important proportion of plant and animal species (Jarne and Auld, 2006; Goodwillie et al., 2005; Igic and Kohn, 2006).

Self-fertilization, and inbreeding in general, may have different effects on genetic polymorphisms depending on the strength of selection acting on them (Glémin, 2007). When directional selection against deleterious alleles is sufficiently strong relative to drift ($N_{\mathrm{e}}s \gg 1$), the increased homozygosity caused by inbreeding is expected

to improve the efficiency of selection against those alleles (purging), reducing the mutation load and inbreeding depression (Lande and Schemske, 1985; Charlesworth et al., 1990). At the other extreme, polymorphism at neutrally-behaving loci ($N_{\mathrm{e}}s \ll 1$) should also be lowered by inbreeding, as the effective population size is reduced by identity-by-descent within loci (Pollak, 1987) and by stronger interference effects between loci — background selection, hitchhiking (Nordborg, 1997; Glémin and Ronfort, 2013; Roze, 2016). In intermediate regimes ($N_{\mathrm{e}}s \sim 1$), however, the reduction in N_{e} caused by inbreeding may cause an increased frequency of deleterious alleles, which may explain the higher π_N/π_S ratio observed in various selfing species compared with their outcrossing relatives (Brandvain et al., 2013; Burgarella et al., 2015, and other references listed in Table 1 of Hartfield, 2015).

Most classical results on the effects of selfing on genetic diversity, mutation load and inbreeding depression are based on single-locus models, and thus neglect the effects of linkage disequilibria and other forms of genetic associations among loci. Previous analytical and simulation models showed that intermediate selfing rates generate correlations in homozygosity between loci, termed "identity disequilibria" (Weir and Cockerham, 1973; Vitalis and Couvet, 2001), which tend to reduce the efficiency of purging when deleterious alleles are partially or fully recessive (an effect called "selective interference" by Lande et al., 1994). When the number of highly recessive mutations segregating within genomes is sufficiently high, these correlations in homozygosity may entirely suppress purging unless the selfing rate exceeds a given threshold (Lande et al., 1994; Scofield and Schultz, 2006; Kelly, 2007; Roze, 2015). Linkage disequilibrium corresponds to another form of association between loci that may also affect the efficiency of selection: in particular, selection may be strongly lim-

ited by Hill-Robertson effects in highly selfing populations, due to the fact that selfing reduces the efficiency of recombination between loci — recombination having no effect when it occurs in homozygous individuals (Kamran-Disfani and Agrawal, 2014; Hartfield and Glémin, 2016). Epistatic interactions represent another possible source of linkage disequilibrium between selected loci. Charlesworth et al. (1991) considered a model in which epistasis between deleterious alleles is fixed and synergistic (the effects of mutations alone being smaller than when combined with others), and showed that the effect of the selfing rate on the load and inbreeding depression may be non-monotonic under this form of epistasis. However, although models with fixed epistasis have lead to important insights, epistatic interactions are known to vary across pairs of loci, and this variation may have important evolutionary consequences (Phillips et al., 2000; Martin et al., 2007). Interestingly, several aspects of the complexity of epistatic interactions (such as possible compensatory effects between deleterious alleles, *i.e.*, reciprocal sign epistasis) are captured by models of stabilizing selection acting on quantitative traits, such as Fisher's geometric model (Fisher, 1930). Furthermore, the distributions of epistasis generated by this type of model seem compatible with our empirical knowledge on epistasis (Martin et al., 2007).

Only a few models have explored the effect of self-fertilization on genetic variance for quantitative traits at equilibrium between mutation and stabilizing selection. Modeling a quantitative trait coded by additive loci, Wright (1951) showed that, in the absence of selection, the genetic variance for the trait is increased by a factor $1 + F$ (where F is the inbreeding coefficient), due to the increased homozygosity of the underlying loci. Selection will oppose this increase in variance, however, by eliminating genotypes that are too far from the optimum (purging). Stabilizing selection

is also known to generate positive linkage disequilibrium between alleles at different loci having opposite effects on the trait (Bulmer, 1971), the immediate consequence of which is to reduce the genetic variance. These linkage disequilibria should also affect the efficiency of selection at each locus, and thus indirectly affect the genetic variance. Lande (1977) proposed a model of stabilizing selection acting on a single trait coded by additive loci in a partially selfing population, in which a Gaussian distribution of allelic effects is assumed to be maintained at each locus. He found that, as the increase in variance due to homozygosity is exactly compensated by the effect of purging, and the decrease in variance caused by linkage disequilibria is exactly compensated by the decreased efficiency of selection acting at each locus due to these linkage disequilibria, overall the equilibrium genetic variance is not affected by the selfing rate of the population. More recently, Lande and Porcher (2015) extended this model to multiple selected traits, using a method developed by Kelly (2007) to take into account the effects of correlations in homozygosity across loci by splitting the population into selfing age classes (corresponding to classes of individuals having the same history of inbreeding) and assumed a Gaussian distribution of allelic effects at each locus within each class. Numerical iterations of the model showed that above a threshold selfing rate, a different regime is reached, in which strong compensatory associations between alleles at different loci reduce the genetic variance and may generate outbreeding depression (*i.e.*, lower fitness of outcrossed offspring relative to selfed offspring).

The hypothesis made by Lande (1977) and Lande and Porcher (2015) of a Gaussian distribution of allelic effects maintained at each locus (either in the whole population or in each selfing age class) has been criticized on the grounds that it implicitly assumes an unrealistically high mutation rate per locus and/or very weak

fitness effects of mutations (Turelli, 1984). Lande and Porcher (2015) also considered an infinitesimal model (in which traits are coded by an infinite number of loci, selection having a negligible effect on allele frequencies at each locus), and showed that a similar threshold pattern emerges, although the effect of selfing on the genetic variance and inbreeding depression above the threshold differs between the two models (in particular, outbreeding depression is not observed in the infinitesimal model). However, the effect of selfing on the genetic variance of quantitative traits under more general assumptions regarding the strength of selection at the underlying loci remains unclear.

In this paper, we introduce partial self-fertilization into previous models of stabilizing selection acting on quantitative traits coded by biallelic loci (Latter, 1960; Bulmer, 1972; Barton, 1986, 1989; Turelli and Barton, 1990; Roze and Blanckaert, 2014). Charlesworth and Charlesworth (1995) had extended such models to take complete selfing into account, and found that the genetic variance under stabilizing selection should be lower under complete selfing than under random mating. The present paper generalizes these results to arbitrary selfing rates and multiple selected traits. We develop approximations incorporating the effects of pairwise associations between selected loci, and compare these approximations with results from individual-based simulations. Our results indicate that different regimes are possible depending on the relative effect of genetic associations on the genetic variance, the effect of genetic associations increasing as the overall mutation rate U and selfing rate σ increase, and decreasing as the genome map length R, mean fitness effect of mutations $\overline{s}$ and number of selected traits n increase. When U and σ are sufficiently low and R, $\overline{s}$ and n sufficiently high, the effect of associations is negligible and the mutation load and inbreeding depression are well predicted by classical expressions ignoring associ-

ations. As the strength of associations increases, a second regime is entered in which the overall effect of associations is to reduce purging, thereby increasing the genetic variance, mutation load and inbreeding depression; this "weak association" regime is generally well predicted by our approximations. For yet higher U, σ and/or lower R, $\overline{s}$ or n, a third regime is reached in which strong associations between loci caused by compensatory effects among mutations reduce the genetic variance, load and inbreeding depression. Although our approximations break down in this "strong association" regime, the approximation proposed by Charlesworth and Charlesworth (1995) provides accurate results under complete selfing when the mutation rate is sufficiently high and the mean fitness effect of mutations sufficiently low.

MODEL

Genotype-phenotype map. Our model represents a diploid population of size N with discrete generations. Offspring are produced by self-fertilization with probability σ, and by random union of gametes with probability $1-\sigma$. The fitness of an organism represents its overall relative fecundity (assumed very large for all individuals), and depends on the values of n quantitative phenotypic traits under stabilizing selection. In the following we use subscripts α, β, γ... to denote phenotypic traits, while subscripts i, j, k... denote loci. The value of trait α in a given individual is denoted z_α, and can be decomposed into a genetic and an environmental component:

$$z_\alpha = g_\alpha + e_\alpha \tag{1}$$

where the environmental component e_α is sampled from a Gaussian distribution with mean zero and variance V_e (the same for all traits). The genetic component g_α ("breed-

ing value") is controlled by a large number of biallelic loci with additive effects. The two alleles at each locus are denoted 0 and 1, while X_i^{M} and X_i^{P} are defined as indicator variables that equal zero if the individual carries allele 0 at locus i on its maternally (X_i^{M}) or paternally (X_i^{P}) inherited chromosome, while they equal 1 if allele 1 is present. We also assume that $g_\alpha = 0$ in an individual homozygous for allele 0 at all loci, so that:

$$g_\alpha = \sum_{i=1}^{\ell} r_{\alpha i} \left(X_i^{\mathrm{M}} + X_i^{\mathrm{P}} \right) \tag{2}$$

where ℓ is the number of loci affecting phenotypic traits, and $r_{\alpha i}$ the effect on phenotype α of changing the allelic state of one gene copy at locus i from 0 to 1 (note that $r_{\alpha i}$ may be negative).

Following Chevin et al. (2010), Lourenço et al. (2011) and Roze and Blanckaert (2014), a parameter m measures the degree of pleiotropy of mutations: each locus affects a subset of m phenotypic traits, sampled randomly (and independently for each locus) among the n traits. Therefore, $m = 1$ means that each locus affects a single trait, while $m = n$ corresponds to full pleiotropy (each locus affecting all traits), as in Fisher's geometric model (Fisher, 1930). We assume that the distribution of mutational effects $r_{\alpha i}$ over all loci affecting trait α has average zero and variance a^2 (the same for all traits); if locus i does not affect trait α, then $r_{\alpha i} = 0$. Finally, u denotes the mutation rate from allele 0 to allele 1 and from allele 1 to allele 0 at each locus, while $U = u\ell$ is the mutation rate over all loci (per generation).

From the previous definitions, and assuming that population size is sufficiently large, mean trait values are given by:

$$\overline{z_\alpha} \approx \overline{g_\alpha} = 2 \sum_{i=1}^{\ell} r_{\alpha i}\, p_i \tag{3}$$

where p_i is the frequency of allele 1 at locus i. As we assume no $G \times E$ interaction, the variance in trait α is given by:

$$V_{\mathrm{p},\alpha} = V_{\mathrm{g},\alpha} + V_{\mathrm{e}} \tag{4}$$

where $V_{\mathrm{g},\alpha}$ is the variance in g_α (genetic variance). In the next subsection, we show how $V_{\mathrm{g},\alpha}$ can be expressed in terms of genetic associations within and between loci.

Genetic associations and decomposition of the genetic variance. Genetic associations are defined as in Kirkpatrick et al. (2002). In particular, the centered variables $\zeta_{i,\emptyset}$ and $\zeta_{\emptyset,i}$ are defined as:

$$\zeta_{i,\emptyset} = X_i^{\mathrm{M}} - p_i, \qquad \zeta_{\emptyset,i} = X_i^{\mathrm{P}} - p_i. \tag{5}$$

Furthermore, products of $\zeta_{i,\emptyset}$, $\zeta_{\emptyset,i}$ variables are denoted:

$$\zeta_{\mathbb{U},\mathbb{V}} = \left(\prod_{i\in\mathbb{U}} \zeta_{i,\emptyset}\right)\left(\prod_{j\in\mathbb{V}} \zeta_{\emptyset,j}\right) \tag{6}$$

where $\mathbb{U}$ and $\mathbb{V}$ represent sets of loci. For example, for $\mathbb{U} = \mathbb{V} = \{i\}$, we have:

$$\zeta_{i,i} = \left(X_i^{\mathrm{M}} - p_i\right)\left(X_i^{\mathrm{P}} - p_i\right) \tag{7}$$

while for $\mathbb{U} = \{i, j\}$ and $\mathbb{V} = \{i\}$:

$$\zeta_{ij,i} = \left(X_i^{\mathrm{M}} - p_i\right)\left(X_j^{\mathrm{M}} - p_j\right)\left(X_i^{\mathrm{P}} - p_i\right). \tag{8}$$

Finally, genetic associations $D_{\mathbb{U},\mathbb{V}}$ are defined as averages of $\zeta_{\mathbb{U},\mathbb{V}}$ variables over all individuals:

$$D_{\mathbb{U},\mathbb{V}} = \mathrm{E}\left[\zeta_{\mathbb{U},\mathbb{V}}\right] \tag{9}$$

where E stands for the average over all individuals in the population. We also define $\tilde{D}_{\mathbb{U},\mathbb{V}}$ as $\left(D_{\mathbb{U},\mathbb{V}} + D_{\mathbb{V},\mathbb{U}}\right)/2$, and write $\tilde{D}_{\mathbb{U},\emptyset}$ as $\tilde{D}_{\mathbb{U}}$ (for simplicity). In particular, $D_{i,i}$ is

a measure of excess homozygosity (due, for example, to non-random mating) at locus i ($D_{i,i} = 0$ at Hardy-Weinberg equilibrium), while $\tilde{D}_{ij}$ is the linkage disequilibrium between loci i and j. We will see that associations involving repeated indices (such as $\tilde{D}_{iij} = \frac{1}{2}\,\mathrm{E}\Big[\left(X_i^{\mathrm{M}} - p_i\right)^2 \left(X_j^{\mathrm{M}} - p_j\right) + \left(X_i^{\mathrm{P}} - p_i\right)^2 \left(X_j^{\mathrm{P}} - p_j\right)\Big]$) often appear in intermediate steps of computations. Using the fact that $\left(X_i^{\mathrm{M}}\right)^2 = X_i^{\mathrm{M}}$ and $\left(X_i^{\mathrm{P}}\right)^2 = X_i^{\mathrm{P}}$ (since these variables equal 0 or 1), repeated indices can be eliminated using the relation:

$$\tilde{D}_{\mathbb{U}ii,\mathbb{V}} = p_i q_i\, \tilde{D}_{\mathbb{U},\mathbb{V}} + (1 - 2p_i)\, \tilde{D}_{\mathbb{U}i,\mathbb{V}} \tag{10}$$

with $q_i = 1 - p_i$ (e.g., equation 5 in Kirkpatrick et al., 2002). In particular (and because $\tilde{D}_j = 0$), we have $\tilde{D}_{iij} = (1 - 2p_i)\, \tilde{D}_{ij}$. Similarly, $\tilde{D}_{iijj} = p_i q_i p_j q_j + (1 - 2p_i)\,(1 - 2p_j)\, \tilde{D}_{ij}$, while $\tilde{D}_{ii,jj} = p_i q_i p_j q_j + (1 - 2p_i)\,(1 - 2p_j)\, \tilde{D}_{i,j}$.

From these definitions, and using equations 2 and 3, the genetic variance for trait α can be written as:

$$\begin{aligned} V_{\mathrm{g},\alpha} &= \mathrm{E}\left[\left(g_\alpha - \overline{g_\alpha}\right)^2\right] \\ &= \mathrm{E}\left[\sum_{i,j} r_{\alpha i} r_{\alpha j} \left(\zeta_{i,\emptyset} + \zeta_{\emptyset,i}\right)\left(\zeta_{j,\emptyset} + \zeta_{\emptyset,j}\right)\right] \end{aligned} \tag{11}$$

where the last sum is over all i and j (including $i = j$). Using the fact that $\tilde{D}_{ii} = p_i q_i$, one obtains from equation 9:

$$V_{\mathrm{g},\alpha} = 2\sum_{i=1}^{\ell} {r_{\alpha i}}^2 \left(p_i q_i + D_{i,i}\right) + 2\sum_{i,\, j \neq i} r_{\alpha i} r_{\alpha j} \left(\tilde{D}_{ij} + \tilde{D}_{i,j}\right). \tag{12}$$

Following previous usage (e.g., Bulmer, 1985), we will call *genic variance* (denoted $V^0_{g,\alpha}$) the quantity $2\sum_{i=1}^{\ell} {r_{\alpha i}}^2\, p_i q_i$, corresponding to the genetic variance in a population with the same allele frequencies, but in the absence of genetic association (within and between loci). As shown by equation 12, excess homozygosity tends to increase the genetic variance through the term in $D_{i,i}$. The second term of equation 12 (the

effect of between-locus associations) tends to be negative under stabilizing selection, since the allele increasing the value of trait α at locus i tends to be associated with the allele decreasing its value at locus j (e.g., Bulmer, 1971, 1974; Lande, 1976; Turelli and Barton, 1990). However, below we show that that excess homozygosity and associations between loci also affect equilibrium allele frequencies, and thus the genic variance.

Fitness function. Most of the results derived in this paper assume an isotropic, Gaussian fitness function, the fitness of an individual being given by:

$$W = \exp\left[-\frac{d^2}{2\omega^2}\right] \tag{13}$$

where ω^2 measures the strength of selection, and $d = \sqrt{\sum_{\alpha=1}^{n} z_\alpha^2}$ is the Euclidean distance (in phenotypic space) between the individual's phenotype and the optimum, which we assume is located at $\mathbf{z} = (0, 0, \ldots, 0)$. From equation 13, the fitness associated with a given genotype (obtained by averaging over environmental effects) is also Gaussian, and given by:

$$W_{\mathrm{g}} = W_{\mathrm{g,max}} \exp\left[-\frac{{d_{\mathrm{g}}}^2}{2V_{\mathrm{s}}}\right] \tag{14}$$

with $V_{\mathrm{s}} = \omega^2 + V_{\mathrm{e}}$, $W_{\mathrm{g,max}} = (\omega^2/V_{\mathrm{s}})^{n/2}$ (the mean fitness of an optimal genotype), and $d_{\mathrm{g}} = \sqrt{\sum_{\alpha=1}^{n} g_\alpha^2}$ (the Euclidean distance between the breeding value of the individual and the optimum). Under our mutational model, the mean reduction in $\log W_{\mathrm{g}}$ caused by a heterozygous mutation present in an optimal genotype is:

$$\overline{s} = \frac{m a^2}{2V_{\mathrm{s}}} \tag{15}$$

(e.g., Martin and Lenormand, 2006b). Under our assumption of additivity of phenotypic effects it is easy to show that the reduction in $\log W_{\mathrm{g}}$ caused by a homozygous deleterious allele (in an optimal genotype) is four times the reduction caused by the

same allele in the heterozygous state. Provided that most mutations have weak fitness effects (so that $\log(1-s) \approx -s$), the dominance coefficient of deleterious alleles is thus close to 0.25 at the fitness optimum (see Manna et al., 2011 for more general results on dominance in Fisher's geometric model).

The effect of the shape of the fitness peak will be explored using a generalized version of equation 14 (e.g., Martin and Lenormand, 2006a; Tenaillon et al., 2007):

$$W_{\mathrm{g}} = W_{\mathrm{g,max}} \exp\left[-\left(\frac{d_{\mathrm{g}}}{\sqrt{2V_{\mathrm{s}}}}\right)^{Q}\right]. \tag{16}$$

Gaussian fitness (equation 14) thus corresponds to $Q = 2$, while the fitness peak is sharper around the optimum when $Q < 2$, and flatter when $Q > 2$. Importantly, Q affects the average dominance coefficient of deleterious alleles, making them more dominant for $Q < 2$ and more recessive for $Q > 2$ (Manna et al., 2011), as well as the average epistasis (on fitness) between alleles, positive for $Q < 2$, and negative for $Q > 2$ (Gros et al., 2009). Approximations for the mutation load and inbreeding depression can be derived for $Q \neq 2$ as long as the distribution of breeding values in the population is approximately Gaussian.

Individual-based simulations. Our simulation program (written in C++ and available on Dryad) is similar to the program used in Roze and Blanckaert (2014). The genome of each individual consists of two copies of a linear chromosome carrying ℓ equidistant loci, represented by sequences of ℓ bits (0 or 1). A table holds the phenotypic effects $r_{\alpha i}$ of changing the allelic state from 0 to 1 at each locus, and is filled at the start of the simulation: for each locus the m traits it affects are sampled at random, and the effects of allele 1 on each of these traits are sampled independently from a

centered Gaussian distribution with variance a^2. Every generation, the breeding values g_α of each individual are computed according to its genotype and environmental effects e_α are sampled from a Gaussian distribution with variance V_e. Individual fitnesses are then computed using equation 13. The strength of selection ω^2 is fixed at 10 in all simulation runs, while the environmental variance V_e is set to $1/n$ in order to prevent very low fitnesses due to environmental effects when the number of traits is large. The variance of mutational effects a^2 is then adjusted to achieve a given mean deleterious effect of mutations $\overline{s}$ (see equation 15). Note that from equation 14, the parameters a^2, ω^2 and V_e should only affect selection through the compound parameter a^2/V_s; *i.e.* as long as a^2/V_s (hence $\overline{s}$) stays constant, different combinations of these parameters should yield the same results.

Each individual of the next generation is produced by selfing with probability σ, and by random mating with probability $1-\sigma$. Parental individuals are sampled with probabilities proportional to their fitness. During meiosis, the number of cross-overs is sampled from a Poisson distribution with parameter R (genome map length, generally 20 Morgans), and the position of each cross-over along the chromosome is sampled from a uniform distribution (no interference). According to Haldane's mapping function (Haldane, 1919), the recombination rate between two adjacent loci is thus $r = \frac{1}{2}\left[1-\exp\left[-2R/\left(\ell-1\right)\right]\right]$. Finally, the number of new mutations par chromosome per generation is sampled from a Poisson distribution with parameter U, and for each new mutation the allelic state of a random locus is swapped.

At the start of the simulation, all individuals are homozygous for allele 0 at all loci and are thus at the fitness optimum. Simulations generally run for 10^5 generations; mean fitness, inbreeding depression and the first 6 moments of the distributions

of breeding values are recorded every 100 generations (inbreeding depression is estimated by computing the mean fitness of 200 selfed and 200 outcrossed offspring). Results shown in the figures correspond to averages over the last 70,000 generations. A parallelized version of the program (using the MPI library) was used for runs with large population size and large number of loci (N = 50,000, ℓ = 10,000). The same program was used to explore the effect of the shape of the fitness function (parameter Q, equation 16), except that environmental effects e_α were set to zero in this case.

Another version of the program was used to consider a different genetic architecture, under which an infinite number of alleles are possible at each locus. In this case, whenever a mutation occurs at a given locus, values sampled from a centered Gaussian distribution with variance a^2 are added to the effects of the mutant allele on the m traits affected by the locus. In addition to the variables mentioned above, the program also keeps track of the average number of alleles per locus maintained in the population at equilibrium.

RESULTS

Neglecting associations between loci. In the following section we show that genetic associations between loci may be neglected when the genomic mutation rate U is sufficiently low. In this case, equation 12 simplifies to:

$$V_{\mathrm{g},\alpha} \approx 2 \sum_{i=1}^{\ell} {r_{\alpha i}}^2 \left(p_i q_i + D_{i,i}\right). \tag{17}$$

Expressions for $p_i q_i$ and $D_{i,i}$ at equilibrium, assuming weak selection ($V_{\mathrm{g},\alpha} \ll V_{\mathrm{s}}$) and neglecting associations among loci are derived in Supplementary File 1. To leading order, $D_{i,i} \approx F\, p_i q_i$ where $F = \alpha/\left(2-\alpha\right)$ is the inbreeding coefficient. Neglecting

associations between loci and assuming that mean phenotypes are at the optimum ($\overline{g_\alpha} = 0$), the effect of selection on $p_i q_i$ is given by:

$$\Delta_{\mathrm{sel}} p_i q_i \approx -s_i \left(1 - 2p_i\right)^2 \left(1 + 3F\right) p_i q_i \tag{18}$$

where $s_i = \sum_{\alpha=1}^{n} r_{\alpha i}^2 / \left(2V_{\mathrm{s}}\right)$ is the heterozygous effect of a mutation at locus i on log fitness in an optimal genotype. Furthermore, because mutation changes p_i to $p_i \left(1 - u\right) + u \left(1 - p_i\right)$, the change in $p_i q_i$ due to mutation is (to the first order in u):

$$\Delta_{\mathrm{mut}} p_i q_i \approx u \left(1 - 2p_i\right)^2 . \tag{19}$$

In regimes where genetic drift can be neglected, $\Delta_{\mathrm{sel}} p_i q_i = -\Delta_{\mathrm{mut}} p_i q_i$ at mutation-selection balance, leading to either $p_i = 1/2$ or:

$$s_i \, p_i q_i \approx \frac{u}{1 + 3F}, \tag{20}$$

in agreement with results of previous biallelic models under random mating (e.g., Bulmer, 1972; Barton, 1986). A stability analysis indicates that the equilibrium given by equation 20 is stable when $p_i q_i < 1/4$ (that is, when $s_i \left(1 + 3F\right) > 4u$), otherwise $p_i = 1/2$ is stable. When all loci are at the equilibrium where $p_i q_i < 1/4$, summing both sides of equation 20 over i yields:

$$\sum_{\alpha=1}^{n} V_{\mathrm{g},\alpha}^0 \approx \frac{4V_{\mathrm{s}} U}{1 + 3F} \tag{21}$$

where again $V_{\mathrm{g},\alpha}^0 = 2 \sum_{\alpha=1}^{n} r_{\alpha i}^2 \, p_i q_i$ is the genic variance. By symmetry the equilibrium genic variance should be the same for all traits, and thus:

$$V_{\mathrm{g},\alpha}^0 \approx \frac{4V_{\mathrm{s}} U}{n \left(1 + 3F\right)} = \frac{2V_{\mathrm{s}} U}{n} \, \frac{2 - \sigma}{1 + \sigma} . \tag{22}$$

From equations 17 and 22, the equilibrium genetic variance is:

$$V_{\mathrm{g},\alpha} \approx V_{\mathrm{g},\alpha}^0 \left(1 + F\right) \approx \frac{4V_{\mathrm{s}} U}{n \left(1 + \sigma\right)} , \tag{23}$$

equivalent to previous results when $\sigma = 0$ and $n = 1$ (e.g., Latter, 1960; Bulmer, 1972; Turelli, 1984).

Assuming that the variance in log-fitness is small, mean fitness is approximately $\overline{W} \approx e^{\overline{\log W_{\mathrm{g}}}}$. Defining the mutation load L as the reduction in $\overline{W}$ relative to the average fitness of an optimal genotype, one obtains from equation 14:

$$\begin{aligned} L &= 1 - \frac{\overline{W}}{W_{\mathrm{g,max}}} \\ &\approx 1 - \exp\left[-\frac{\sum_{\alpha=1}^{n} V_{\mathrm{g},\alpha}}{2V_{\mathrm{s}}}\right]. \end{aligned} \tag{24}$$

Equations 23 and 24 yield:

$$L \approx 1 - \exp\left[-\frac{2U}{1+\sigma}\right]. \tag{25}$$

Inbreeding depression δ measures the mean fitness of selfed offspring, relative to the mean fitness of outcrossed offspring. Under the same assumptions, it is given by:

$$\begin{aligned} \delta &= 1 - \frac{\overline{W}_{\mathrm{self}}}{\overline{W}_{\mathrm{out}}} \\ &\approx 1 - \exp\left[-\frac{\sum_{\alpha=1}^{n}\left(V_{\mathrm{g},\alpha}^{\mathrm{self}} - V_{\mathrm{g},\alpha}^{\mathrm{out}}\right)}{2V_{\mathrm{s}}}\right] \end{aligned} \tag{26}$$

where $V_{\mathrm{g},\alpha}^{\mathrm{self}}$ and $V_{\mathrm{g},\alpha}^{\mathrm{out}}$ are the genetic variances for trait α among selfed and outcrossed offspring, respectively (e.g., Lande and Schemske, 1985). The intralocus association $D_{i,i}$ among selfed offspring is $D_{i,i}^{\mathrm{self}} = \frac{1}{2}\left(1 + D_{i,i}\right)$ and therefore $V_{\mathrm{g},\alpha}^{\mathrm{self}} = V_{\mathrm{g},\alpha}^{0}\left[1 + \frac{1}{2}\left(1+F\right)\right]$, while $V_{\mathrm{g},\alpha}^{\mathrm{out}} = V_{\mathrm{g},\alpha}^{0}$, yielding (using equation 22):

$$\delta \approx 1 - \exp\left[-\frac{\sum_{\alpha=1}^{n} V_{\mathrm{g},\alpha}}{4V_{\mathrm{s}}}\right] \approx 1 - \exp\left[-\frac{U}{1+\sigma}\right]. \tag{27}$$

Equations 25 and 27 are equivalent to the classical expressions obtained for the load and inbreeding depression at mutation-selection balance when the dominance coefficient h of deleterious alleles is set to 0.25 (e.g., Charlesworth and Charlesworth, 2010), in

agreement with the fact that $h \approx 0.25$ under Gaussian stabilizing selection when mutations have additive effects on phenotypes (see previous section).

When the average strength of selection $\overline{s}$ is sufficiently small so that most loci are at the equilibrium where $p_i = 1/2$, one obtains from equations 15 and 17:

$$V_{\mathrm{g},\alpha} \approx \frac{\overline{s}\,\ell}{n}\,(1+F)\,V_{\mathrm{s}} \tag{28}$$

yielding:

$$L \approx 1 - \exp\left[-\frac{\overline{s}\,\ell}{2-\sigma}\right], \quad \delta \approx 1 - \exp\left[-\frac{\overline{s}\,\ell}{2\,(2-\sigma)}\right]. \tag{29}$$

However, genetic drift may have important effects on allele frequencies when $\overline{s}$ is small. More precise approximations for the regime where drift is stronger than selection at most loci can be obtained by replacing $p_i q_i$ by its expectation at mutation-drift equilibrium, which is approximately $2N_{\mathrm{e}}u/\,(1+8N_{\mathrm{e}}u)$ where $N_{\mathrm{e}} = N/\,(1+F)$ (Pollak, 1987). This yields the following expressions for the genetic variance, mutation load and inbreeding depression when $\overline{s} \ll 1/N$:

$$V_{\mathrm{g},\alpha} \approx \frac{8V_{\mathrm{s}}NU\overline{s}}{n\,(1+8N_{\mathrm{e}}u)} = \frac{8V_{\mathrm{s}}NU\overline{s}}{n\,[1+4Nu\,(2-\sigma)]}, \tag{30}$$

$$L \approx 1 - \exp\left[-\frac{4NU\overline{s}}{1+4Nu\,(2-\sigma)}\right], \quad \delta \approx 1 - \exp\left[-\frac{2NU\overline{s}}{1+4Nu\,(2-\sigma)}\right]. \tag{31}$$

As population size tends to infinity, equation 30 tends to equation 28 and selfing increases the genetic variance (by increasing homozygosity). When the per-locus mutation rate is low ($N_{\mathrm{e}}u \ll 1$, so that the denominator of equation 30 is approximately n), the genetic variance, load and inbreeding depression become independent of σ: the increase in variance caused by excess homozygosity is exactly compensated by the reduction in variance caused by the lower effective population size.

Following Bulmer (1972), a diffusion model can be used to compute the expected value of $p_i q_i$ under selection, mutation and drift. As shown in Supplementary File 2,

the result can then be integrated over the distribution of s_i across loci to obtain the equilibrium genetic variance, inbreeding depression and mutation load. Figure 1 shows the mutation load as a function of σ for $U = 0.1$ and different values of $\overline{s}$, N and ℓ (the genetic variance and inbreeding depression are plotted in Supplementary Figures S1 and S2, but show similar patterns). As can be seen in Figure 1, the diffusion result generally provides accurate predictions, except when selfing is very high (see also Supplementary Figure S3, showing the load as a function of $\overline{s}$ for different values of σ). The discrepancies observed at high selfing rates are partly due to the reduction in effective population size N_e due to background selection (which is not accounted for in the diffusion model). An estimation of N_e using the equilibrium diversity at a neutral locus (with an infinite number of possible alleles) at the mid-point of the chromosome (as in Roze, 2016) yielded an N_e of approximately 740, 300 and 200 for $\overline{s} = 10^{-4}$, 10^{-3} and 10^{-2} (respectively) for $N = 5{,}000$, $\ell = 10{,}000$ and $\sigma = 1$ (right-most points in Figure 1B). Replacing N by $N_\mathrm{e}\,(1 + F)$ in the diffusion model provides predictions that closely match the simulation results for $\overline{s} = 10^{-4}$ and 10^{-3}, suggesting that the initial discrepancy was indeed caused by background selection reducing N_e (results not shown). However, for $\overline{s} = 10^{-2}$, the diffusion model still performs poorly despite the corrected N_e. This implies that the discrepancy between analytical and simulation results is more likely due to interactions among loci, and possibly also to deviations of mean phenotypes from the optimum caused by genetic drift (that are not taken into account in the analysis).

Simulation results for very high selfing rates aside, the deterministic mutation-selection balance approximation (equation 25, black curves in Figure 1) generally provides good approximations for regimes where drift has little effect and selection at

each locus is strong compared to the per locus mutation rate (for example, for all values of $\overline{s}$ in Figure 1A with $N = 50{,}000$ and $\ell = 10{,}000$). Keeping the genomic mutation rate constant and increasing the per locus mutation rate by decreasing ℓ, we observe a switch to a regime where allele frequencies are close to 1/2 at most loci (when population size is large). This regime is well predicted by the mutation-drift and diffusion approximations (compare Figure 1A to 1C for $\overline{s} = 10^{-4}$ and 1E for $\overline{s} = 10^{-4}$ and 10^{-3}). By reducing population size ($N = 5000$ in Figures 1B, 1D and 1F), we observe that increasing genetic drift increases the genetic variance in regimes where $p_i q_i$ tends to stay small, and decreases it in regimes where $p_i q_i$ is high at most loci at the deterministic equilibrium. The former can be observed when comparing Figure 1A to 1B (or C to D) for $\overline{s} = 10^{-3}$ (blue) where there is an increase in the mutation load, and the latter when comparing Figure 1A to 1B (or C to D) for $\overline{s} = 10^{-4}$ (red) where there is a decrease in the mutation load.

In Supplementary File 3, we derive expressions for the genetic variance, mutation load and inbreeding depression (for both the mutation-selection and the mutation-drift regimes) under the generalized fitness function given by equation 16. In the mutation-selection regime ($s_i \gg 1/N$, u at most loci), one obtains:

$$\frac{V_{\mathrm{g}}}{V_{\mathrm{s}}} \approx \left[\frac{4U}{Q\left(1+\sigma\right)} \frac{\Gamma\left(\frac{n}{2}\right)}{\Gamma\left(\frac{Q+n}{2}\right)}\right]^{\frac{2}{Q}} \tag{32}$$

(where Γ is Euler's Gamma function), while

$$L \approx 1 - \exp\left[-\frac{4U}{Q\left(1+\sigma\right)}\right] \tag{33}$$

$$\delta \approx 1 - \exp\left[-\frac{4U}{Q\left(1+\sigma\right)}\left[\left(\frac{3-\sigma}{2}\right)^{\frac{Q}{2}} - \left(\frac{2-\sigma}{2}\right)^{\frac{Q}{2}}\right]\right], \tag{34}$$

these equations being equivalent to equations 23, 25 and 27 when $Q = 2$. As shown by Figure 2, equations 32 – 34 provide good predictions of the simulation results when

the population size and number of loci are sufficiently large (and selfing is not too high). As Q increases, the fitness peak becomes flatter around the optimum, and the equilibrium genetic variance increases (Figure 2A). However, despite increasing the genetic variance, higher values of Q lead to lower mutation loads due to the fact that deleterious alleles are more often eliminated when present in combination within the same genome: this corresponds to the classical result that negative epistasis reduces the mutation load in sexually reproducing populations (e.g., Kimura and Maruyama, 1966; Kondrashov and Crow, 1988). Indeed, the average epistasis between deleterious alleles equals zero for $Q = 2$, but becomes negative when $Q > 2$, and positive when $Q < 2$ (Gros et al., 2009). By contrast, inbreeding depression is less affected by Q, δ slightly increasing or decreasing as Q increases, depending on the selfing rate.

Figure 3 shows the effects of the parameters m and n (for $Q = 2$). The degree of pleiotropy m of mutations affects their distribution of fitness effects (e.g., Lourenço et al., 2011). In Figure 3A, $\overline{s}$ is kept constant by decreasing the variance of mutational effects a^2 as m increases (see equation 15). Increasing m (while keeping $\overline{s}$ constant) decreases the variance in fitness effects of mutations: indeed, one can show that the variance of mutational effects on log fitness (at the optimum) is given by $2\overline{s}^2/m$. Figure 3A shows that $m = 5$ and $m = 50$ yield very close results when $\overline{s} = 10^{-4}$, as selection has a negligible effect at most loci for both values of m (for the parameter values used here), and the genetic variance does not depend on m at mutation-drift equilibrium (see equation 30). When $\overline{s} = 10^{-2}$, most loci are at mutation-selection balance ($s_i \gg 1/N$, u) for both $m = 5$ and $m = 50$, and the genetic variance is again not affected by m (see equation 23). Slightly different results are obtained for $m = 1$, due to the higher variance in fitness effects of mutations, causing a larger fraction of

loci to be substantially affected by both selection and drift (this effect being captured by the diffusion model). Similarly, the effect of m is more pronounced when $\overline{s} = 10^{-2}$ and $\sigma = 1$, as N_{e} is greatly reduced by background selection when selfing is high, causing higher proportions of loci to be substantially affected by drift.

As shown by Figure 3B, the number of selected traits n has only little effect on the load in the mutation-drift regime ($\overline{s} = 10^{-4}$), in agreement with equation 31. However, while the diffusion model also predicts very little effect of n in the mutation-selection regime ($\overline{s} = 10^{-2}$), larger effects are observed in the simulations, with larger deviations from the analytical predictions (and higher load) for lower values of n. These deviations are caused by associations between loci (which are neglected in equation 25 and in the diffusion model). In the next subsection, we show that the relative effect of these associations is stronger when n is lower, and derive an approximation including the effect of pairwise genetic associations that better matches the simulation results.

Effects of associations between loci. In Supplementary File 1, we derive approximations for the effects of associations between pairs of loci on the genetic variance at mutation-selection balance, under a Gaussian fitness function ($Q = 2$). For this, we assume that these associations remain weak, and neglect the effects of all associations involving more than two loci. As shown by equation 12, associations $\tilde{D}_{ij}$, $\tilde{D}_{i,j}$ (between alleles at loci i and j, either on the same or on different haplotypes) directly affect the genetic variance. At equilibrium, these associations are approximately given by:

$$\tilde{D}_{ij} \approx \frac{1}{1-F}\left(\frac{1}{\rho_{ij}} + 2F\right)\Delta_{\mathrm{sel}}\tilde{D}_{ij} \tag{35}$$

$$\tilde{D}_{i,j} \approx \frac{F}{1-F}\left(\frac{1}{\rho_{ij}} + 2\right)\Delta_{\mathrm{sel}}\tilde{D}_{ij}, \tag{36}$$

where again $F = \sigma/(2-\sigma)$, ρ_{ij} is the recombination rate between loci i and j, and $\Delta_{\text{sel}}\tilde{D}_{ij}$ is the change in $\tilde{D}_{ij}$ and $\tilde{D}_{i,j}$ due to selection:

$$\Delta_{\text{sel}}\tilde{D}_{ij} \approx -\frac{\sum_{\alpha=1}^{n} r_{\alpha i}\, r_{\alpha j}}{V_{\text{s}}} \left[(1+F)^2 + G_{ij}\right] p_i q_i p_j q_j \,. \tag{37}$$

The term G_{ij} in equation 37 represents the identity disequilibrium between loci i and j: the correlation in identity by descent between loci, generating a correlation in homozygosity (Weir and Cockerham, 1973, Supplementary File 1). Equation 37 shows that stabilizing selection generates a positive association between alleles at loci i and j that tends to displace phenotypes in opposite directions (allele 1 with allele 1, and allele 0 with allele 0 if $\sum_{\alpha=1}^{n} r_{\alpha i}\, r_{\alpha j} < 0$): the effect of the deleterious allele at locus i is then partially compensated by its associated allele at locus j (e.g., Bulmer, 1974; Lande, 1976; Turelli and Barton, 1990). This effect of selection is strengthened by homozygosity (and correlations in homozygosity between loci) caused by selfing. As may be seen from equations 35 and 36, $\tilde{D}_{ij} \approx F\,\tilde{D}_{i,j}$ when loci are tightly linked ($\rho_{ij} \ll 1$), as expected from separation of timescales arguments (e.g., Nordborg, 1997; Roze, 2016). However, our approximations diverge as recombination tends to zero (or as the selfing rate tends to 1), due to the assumption that genetic associations remain weak.

We show in Supplementary File 1 how $\tilde{D}_{ij}$ and $\tilde{D}_{i,j}$ can be summed over all pairs of loci in order to compute their overall direct effect on the genetic variance (second term of equation 12). Because the identity disequilibrium G_{ij} only weakly depends on the recombination rate, and because $\rho_{ij} \approx 1/2$ between most pairs of loci if the genome map length is sufficiently large, we approximate G_{ij} by its expression

for freely recombining loci (denoted G):

$$G = \frac{4\sigma\,(1-\sigma)}{(4-\sigma)\,(2-\sigma)^2}\,. \tag{38}$$

Assuming that the number of loci is large, one then obtains for the direct effect of linkage disequilibria on the genetic variance (see Supplementary File 1):

$$2\sum_{i,\,j\neq i} r_{\alpha i}\, r_{\alpha j}\left(\tilde{D}_{ij}+\tilde{D}_{i,j}\right) \approx -\frac{2}{V_{\mathrm{s}}}\frac{2+\sigma}{(1-\sigma)\,(2-\sigma)\,(4-\sigma)}\left[\frac{1}{\rho_{\mathrm{H}}}+2\sigma\right]\left(V^0_{g,\alpha}\right)^2 \tag{39}$$

where ρ_{H} is the harmonic mean recombination rate between all pairs of loci, and where the genic variance $V^0_{g,\alpha}$ may be replaced by its expression to leading order, given by equation 22. Equation 39 shows that the immediate effect of associations between alleles with compensatory phenotypic effects is to reduce the genetic variance. Although selfing increases the strength of associations (the fraction in equation 39 is an increasing function of σ), the direct effect of linkage disequilibria on $V_{\mathrm{g},\alpha}$ may remain approximately constant (or even slightly decrease) as σ increases from zero, due to the fact that the genic variance decreases (equation 22).

Associations between loci also affect the first term of equation 12, by affecting the efficiency of purging (and thus the genic variance) and the homozygosity at each locus. The latter is mainly driven by identity disequilibria: indeed, neglecting associations between 3 or more loci, one obtains (see Supplementary File 1):

$$D_{i,i} \approx F\left[1-2\sum_{j\neq i} s_j\, G_{ij}\, p_j q_j\right] p_i q_i\,. \tag{40}$$

Equation 40 is equivalent to equation 5 in Roze (2015), showing that identity disequilibria tend to reduce homozygosity at each locus: this is due to the fact that homozygotes at locus i are more likely to be also homozygous at locus j, while homozygotes at locus j have a lower fitness than heterozygotes when deleterious alleles

are partially recessive. This decrease in homozygosity caused by identity disequilibria reduces the genetic variance, by an amount that can be obtained by summing the term in G_{ij} in equation 40 over all pairs of loci. Approximating G_{ij} by its expression for freely recombining loci (equation 38), one obtains that $V_{\mathrm{g},\alpha}$ is reduced (through the term in $D_{i,i}$ in equation 12) by approximately $-n\,F\,G\left(V^0_{g,\alpha}\right)^2/\left(2V_{\mathrm{s}}\right)$, where again $V^0_{g,\alpha}$ may be replaced by the expression given by equation 22, to leading order (see Supplementary File 1).

Although pairwise associations between loci tend to reduce the genetic variance through the terms in $D_{i,i}$ and $\tilde{D}_{ij}+\tilde{D}_{i,j}$ in equation 12, an indirect effect of these associations is to increase the genic variance (term in p_iq_i in equation 12). Indeed, we show in Supplementary File 1 that an expression for the effect of selection on p_iq_i that includes the effects of pairwise associations is, to leading order:

$$\begin{aligned}\Delta_{\mathrm{sel}}p_iq_i \approx -s_i\left(1-2p_i\right)^2&\left[p_iq_i+3D_{i,i}-6\left(1+F\right)\sum_{j\neq i}s_j\,G_{ij}\,p_iq_i\,p_jq_j\right]\\&+2\left(1-2p_i\right)^2\sum_{j\neq i}a_{ij}\left[\left(1+2F\right)\tilde{D}_{ij}+\tilde{D}_{i,j}\right.\\&\left.\qquad+a_{ij}\frac{16\left(1+\sigma\right)\left(2+\sigma\right)}{\left(2-\sigma\right)^2\left(4-\sigma\right)}p_iq_i\,p_jq_j\right]\end{aligned}\tag{41}$$

with $a_{ij}=-\sum_\alpha r_{\alpha i}r_{\alpha j}/\left(2V_{\mathrm{s}}\right)$, and where $\tilde{D}_{ij}$, $\tilde{D}_{i,j}$ and $D_{i,i}$ are given by equations 35, 36 and 40. The first line of equation 41 is equivalent to equation 6 in Roze (2015), showing that identity disequilibria reduce the efficiency of purging by decreasing homozygosity ($D_{i,i}$), and by two additional effects represented by the term in $6\left(1+F\right)$ (see Roze (2015) for interpretation of these effects). The term on the second and third lines (in a^2_{ij}) represents the effect of epistasis between loci: this term also reduces purging, since selection against deleterious alleles is less efficient when these alleles are partially compensated by alleles at other loci.

An expression for the genic variance at mutation-selection balance is given by equation A65 in Supplementary File 1. From this, one obtains for the genetic variance:

$$V_{\mathrm{g},\alpha} = \frac{4V_{\mathrm{s}}U}{n\left(1+\sigma\right)}\left[1 + 2U\,\frac{\sigma\left(1-\sigma\right)\left[6+\sigma\left(2-\sigma\right)\right]}{\left(2-\sigma\right)\left(4-\sigma\right)\left(1+\sigma\right)^2} + \frac{4U}{n}\,\frac{\left(2-\sigma\right)\left(2+\sigma\right)}{\left(1-\sigma\right)\left(4-\sigma\right)\left(1+\sigma\right)}\left(\frac{1}{2\rho_{\mathrm{H}}} + \frac{2+\sigma\left(1-\sigma\right)\left(2-\sigma\right)}{2+\sigma\left(1-\sigma\right)}\right)\right] \tag{42}$$

where the term between the brackets corresponds to the effect of between-locus associations. It decomposes into a term in U (on the first line of equation 42) representing the effect of identity disequilibria, and a term in U/n (on the second line) representing the effect of epistasis (compensatory effects between alleles at different loci). Both terms are positive, indicating that the overall effect of interactions between loci is to increase the genetic variance, due to the fact that correlations in homozygosity and compensatory effects between mutations both reduce the efficiency of purging (equation 41). Furthermore, while the effect of identity disequilibria scales with U, the effect of epistasis scales with U/n: indeed, it becomes less and less likely that alleles at different loci have compensatory effects on all of the traits as the dimensionality of the fitness landscape increases. Finally, the effect of epistasis is more strongly affected by linkage between loci (through the term in $1/\rho_{\mathrm{H}}$); the effect of linkage on the term in U representing the effect of linkage disequilibria is weaker, and has been neglected in equation 42. Under random mating ($\sigma = 0$), equation 42 simplifies to:

$$V_{\mathrm{g},\alpha} = \frac{4V_{\mathrm{s}}U}{n}\left[1 + \frac{2U}{n}\left(\frac{1}{\rho_{\mathrm{H}}} + 2\right)\right] \tag{43}$$

which takes a similar form as equation 4.16 in Turelli and Barton (1990) in the case of a single selected trait ($n = 1$).

Assuming that $\overline{W} \approx e^{\overline{\log W_{\mathrm{g}}}}$, an approximation for the load at mutation-selection

balance is $1 - \exp\left[-n\,V_{\mathrm{g}}/\left(2V_{\mathrm{s}}\right)\right]$, where V_{g} is the genetic variance given by equation 42 (the same for all traits). A slightly better approximation can be obtained by using $\overline{W} \approx e^{\overline{\log W_{\mathrm{g}}}}\left(1 + \frac{1}{2}\mathrm{Var}\left[\log W_{\mathrm{g}}\right]\right)$, where $\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ is the variance in log fitness in the population (Roze, 2015). To leading order, it is given by (see Supplementary File 1):

$$\mathrm{Var}\left[\log W_{\mathrm{g}}\right] \approx 2\overline{s}\,U\,\frac{1+3\sigma}{1+\sigma} + 4U^2\frac{\sigma\left(1-\sigma\right)}{\left(4-\sigma\right)\left(1+\sigma\right)^2} + \frac{8U^2}{n}\frac{\left(2-\sigma\right)\left(2+\sigma\right)}{\left(4-\sigma\right)\left(1+\sigma\right)^2}, \tag{44}$$

simplifying to $2U\left(\overline{s} + 4U/n\right)$ in the absence of selfing. The first term of equation 44 represents the sum of single-locus contributions to the variance in log fitness, while the second and third term correspond to the effects of identity disequilibria and epistasis (respectively), both increasing the variance in fitness. The mutation load is then given by:

$$L \approx 1 - \left(1 + \frac{1}{2}\mathrm{Var}\left[\log W_{\mathrm{g}}\right]\right)\exp\left[-\frac{n\,V_{\mathrm{g}}}{2V_{\mathrm{s}}}\right]. \tag{45}$$

Similarly, we show in Supplementary File 1 that an expression for inbreeding depression including the effects of pairwise associations between loci is:

$$\delta \approx 1 - \left(1 + \frac{1}{2}\Delta\mathrm{Var}\left[\log W_{\mathrm{g}}\right]\right)\exp\left[-\frac{n\,V_{\mathrm{g}}}{4V_{\mathrm{s}}}\right] \tag{46}$$

where $\Delta\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ is the difference in variance in log fitness between selfed and outcrossed offspring, given by:

$$\Delta\mathrm{Var}\left[\log W_{\mathrm{g}}\right] \approx \frac{7\overline{s}U}{1+\sigma} + U^2\frac{\sigma\left(1-\sigma\right)}{\left(4-\sigma\right)\left(1+\sigma\right)^2} + \frac{2U^2}{n}\frac{\left(10-\sigma\right)\left(2-\sigma\right)}{\left(4-\sigma\right)\left(1+\sigma\right)^2} \tag{47}$$

(the terms in $\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ and $\Delta\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ in equations 45 and 46 are often small, however, and may thus be neglected). After replacing V_{g}, $\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ and $\Delta\mathrm{Var}\left[\log W_{\mathrm{g}}\right]$ by the expressions given by equations 42, 44 and 47, the approximations obtained for the load and inbreeding depression include terms in U^2 representing the effect of identity disequilibria, and terms in U^2/n representing the effect of epistasis between loci.

The terms in U^2 are identical to the terms representing the effect of identity disequilibria in a model with purely multiplicative selection against deleterious alleles (no epistasis) when setting the dominance coefficient h of deleterious alleles to 1/4 (equations 11 and 14 in Roze, 2015). The novelty here thus corresponds to the effect of epistasis (compensatory effects between deleterious alleles), that tends to increase L and δ by reducing the efficiency of purging.

Figure 3B shows that equations 42, 44 and 45 capture the increase in load observed in the simulations as the number of traits n decreases (see Supplementary Figure S4 for the genetic variance and inbreeding depression). Note that the harmonic mean recombination rate ρ_{H} between pairs of loci under our simulated genetic architecture (linear chromosome with equally spaced loci) can be obtained from:

$$\frac{1}{\rho_{\mathrm{H}}} = \frac{2}{\ell\left(\ell-1\right)} \sum_{i=1}^{\ell-1} \frac{2\left(\ell-i\right)}{1-\exp\left[-2i\frac{R}{\ell-1}\right]} \tag{48}$$

(see Appendix 2 in Roze and Blanckaert, 2014), yielding $\rho_{\mathrm{H}} \approx 0.42$ for $\ell = 1{,}000$ and $R = 20$. Figure 4 shows that for low or moderate selfing rates, decreasing the genome map length from $R = 20$ to $R = 1$ increases the mutation load, by increasing the strength of linkage disequilibria caused by epistasis, that in turn reduce the efficiency of purging. In this regime, equations 42, 44 and 45 provide an accurate prediction for the load (see Supplementary Figure S5 for genetic variance and inbreeding depression). At high selfing rates, however, a different regime is entered, in which the assumption of weak genetic associations breaks down. As can be seen in Figure 4, in this regime (which spans a broader parameter range under tighter linkage) the load decreases more rapidly as σ increases. Increasing linkage tends to reduce the mutation load when the selfing rate is high, although the effect of R vanishes when $\sigma = 1$. When linkage is

extremely tight, the approximations given above break down for all values of σ: as shown by Figures 4 and S5, decreasing R has a non-monotonic effect on the genetic variance, load and inbreeding depression when selfing is small to moderate, the lowest values of V_{g}, L and δ being reached when $R = 0$ (in which case selfing has no effect). An approximation for the genetic variance under complete linkage can be obtained by treating the whole genome as a single locus with a very large number of possible alleles, and assuming a Gaussian distribution of allelic effects in the population (Lande, 1977; Supplementary File 4). This yields:

$$\frac{V_{\mathrm{g}}}{2V_{\mathrm{s}}} \approx 2\sqrt{\frac{\overline{s}U}{2n}\,\frac{2}{2+\sigma\,(1-\sigma)}}, \tag{49}$$

$$L \approx 1 - \exp\left[-\frac{nV_{\mathrm{g}}}{2V_{\mathrm{s}}}\right], \quad \delta \approx 1 - \exp\left[-\frac{nV_{\mathrm{g}}}{4V_{\mathrm{s}}}\right]. \tag{50}$$

Note that equation 49 is equivalent to equation 3A in Charlesworth and Charlesworth (1995) when $\sigma = 1$ and $n = 1$. As shown by Figures 4 and S5, equations 49 and 50 only slightly overestimate V_{g}, L and δ when $\sigma = 1$ and/or $R = 0$. As shown below, better predictions are observed for higher values of U/n and lower values of $\overline{s}$.

The effects of identity disequilibria between loci remain negligible for the parameter values used in Figures 3 and 4. As shown by Figure 5, identity disequilibria become more important for higher values of the mutation rate U. The difference between the black and red curves in Figure 5 represents the predicted effect of identity disequilibria on the load, while the difference between the red and green curves corresponds the the effect of epistasis. Simulations indicate that the change in regime observed above a threshold selfing rate (around $\sigma = 0.5$ for $U = 1$ in Figure 5) is due to epistasis, since this threshold is not observed in simulations without epistasis (red dots). Supplementary Figure S6 shows that this threshold pattern is little affected by

population size N, as long as the effects of drift remain small. Similarly, the results only weakly depend on the number of loci ℓ, as long as the mutation rate per locus $u = U/\ell$ is small enough so that $p_i q_i < 1/4$ at most loci (see Supplementary Figure S7 for distributions of allele frequencies in simulations with $\ell = 1{,}000$ and $\ell = 10{,}000$). Figure S6 also shows that the results are little affected by the degree of pleiotropy of mutations m, as long as $\overline{s}$ remains constant. However, $\overline{s}$ does affect V_{g}, L and δ in the regime where our approximations break down. As shown by Figure 6, decreasing $\overline{s}$ lowers the threshold selfing rate above which our approximations are not valid and results in lower equilibrium mutation loads (see Supplementary Figure S8 for results on V_{g} and δ). Figures 6 and S8 also show that, when $\overline{s}$ is sufficiently small, the single-locus, Gaussian model (equations 49 and 50, dotted curves on the figures) provides accurate predictions for V_{g}, L and δ under complete selfing ($\sigma = 1$).

In Figure 7 we show that decreasing the number of traits under selection n decreases the threshold selfing rate above which our approximations break down (see Supplementary Figure S9 for inbreeding depression and scaled genetic variance). Below the threshold, the mutation load decreases as n increases, as predicted by our analytical results (although our approximations become less precise for low n and high U), while n has the opposite effect above the threshold. Overall, we observe that in this second regime (in which interactions between loci have important effects), the mutation load generally increases with the number of selected traits, the fitness effects of mutations $\overline{s}$, the mutation rate U and recombination rate (through the parameter R). However, Figure 8 shows that the effects of these parameters on inbreeding depression are more complicated. In particular, outbreeding depression (negative δ) may occur in regimes where the effects of epistasis are particularly strong (high U, low n) and when

the selfing rate is high (but below 1), outbreeding depression becoming stronger when $\overline{s}$, U and R increase (approximation 46 fails for all values of σ for the parameter values used in Figure 8, and is not shown here). Supplementary Figures S10 and S11 show that for the same parameter values, V_{g} and L always increase when $\overline{s}$, U and R increase.

Effect of the number of alleles per locus. The previous analytical and simulation results were obtained under the assumption of biallelic loci. In order to explore the effect of the number of alleles per locus, we used a different simulation program in which an infinite number of alleles are possible at each locus (whenever a mutation occurs at a given locus, allelic effects are changed by values sampled in a multivariate Gaussian distribution). Figure 9 shows that the effect of the number of alleles per locus is negligible in the deterministic regime, both when genetic associations have negligible effects ($U = 0.1$ in Figure 9) and when they have stronger effects ($U = 1$). Similar results are obtained when $\ell = 1{,}000$ (Supplementary Figure S12), in which case higher numbers of alleles per locus are maintained in the infinite allele model (about 70 alleles per locus on average when $U = 1$ and $\sigma = 0$). Small discrepancies between the biallelic and the infinite allele model appear when $\ell = 1{,}000$ and $U = 1$, due to the fact that a fraction of loci have reached the maximum level of polymorphism ($p_i q_i = 1/4$) in the biallelic case (see also Figure S7). Differences between the biallelic and infinite allele model also appear in regimes where drift has a stronger effect on allele frequencies (results not shown).

DISCUSSION

The response of a population to environmental change depends critically on its genetic diversity. Our results predict that the level of genetic variation maintained at equilibrium under stabilizing selection acting on quantitative traits is generally lower in more highly selfing population, due to more efficient purging (although increasing selfing may sometimes increase genetic variation, for example when mutations have weak fitness effects, as shown by Figures 1 and S2). This finding agrees with Charlesworth and Charlesworth's (1995) theoretical prediction that fully selfing populations should maintain lower genetic variance for quantitative traits under stabilizing selection than fully outcrossing ones, and with several empirical studies comparing levels of genetic variation for morphological traits in closely related pairs of plant species with contrasted mating systems (Charlesworth and Charlesworth, 1995; Geber and Griffen, 2003; Bartkowska and Johnston, 2009 and references therein). We also show that the lower level of variation present in more highly selfing populations is associated with lower values of the mutation load and inbreeding depression. The meta-analysis carried out by Winn et al. (2011) showed that inbreeding depression is indeed lower in highly selfing plant species compared to species with lower selfing rates, while no significant difference is observed between species with low vs. intermediate selfing rates. It has been put forth that correlations in homozygosity between selected loci may suppress purging at moderate selfing rates ("selective interference", Lande et al., 1994; Winn et al., 2011); this, however, would imply that a large number of segregating deleterious alleles have very low dominance coefficients, generating very high inbreeding depression (Kelly, 2007; Roze, 2015), which seems unlikely. Another possible explanation for the lack of purging at intermediate selfing rates involves epistasis (compensatory effects between mutations coding for the same quantitative trait, Lande and Porcher, 2015).

Our analysis of the effects of epistasis (under assumptions that differ from those made in Lande and Porcher's model) shows that different regimes are possible, and outlines how the parameters affect transitions between these regimes.

In our model, the effect of epistasis on the equilibrium genetic variance V_g scales with U/n (where n is the number of selected traits and U the total mutation rate on those traits), and is inversely proportional to effective recombination rates between selected loci. When U/n is small (*i.e.* small U and large n) and map length R is sufficiently large, associations between loci have little effect. Under Gaussian stabilizing selection ($Q = 2$), the average coefficient of epistasis between mutations (on fitness) is zero (Martin and Lenormand, 2006b) while the dominance coefficient of deleterious alleles (in an optimal genotype) is close to 0.25 under the assumption of additive effects on phenotypes. In this case, we found that classical deterministic expressions based on single-locus models (hence neglecting the variance in epistatic interactions) provide accurate predictions for the mutation load L and inbreeding depression δ. Simple approximations are also obtained under the more general fitness function given by equation 16, confirming that the mutation load is an increasing function of the average coefficient of epistasis between mutations (Kimura and Maruyama, 1966; Kondrashov and Crow, 1988; Phillips et al., 2000; Roze and Blanckaert, 2014). Neglecting the effect of associations between loci also allowed us to explore the effects of drift using diffusion methods. As in previous studies (e.g., Charlesworth, 2013; Roze and Blanckaert, 2014), we found that drift may lower the mutation load by reducing V_g. However, this result probably strongly depends on the assumption that mutations may increase or decrease phenotypic traits with the same probability (no mutational bias): indeed, previous works showed that drift may increase the load in the presence of a muta-

tional bias by displacing mean phenotypes away from the optimum (Zhang and Hill, 2008; Charlesworth, 2013). Given that partial selfing reduces effective population size, it would be of interest to study the combined effects of drift and mutational bias in models with selfing.

The variance in epistasis has stronger effects as the U/n ratio increases and/or as the effective recombination rate decreases (*i.e.* due to selfing). Our results showed that two different regimes are possible. (1) When genetic associations (linkage disequilibria) generated by epistasis stay moderate, the overall effect of epistasis is to increase V_{g}, L and δ by decreasing the efficiency of selection against deleterious alleles. This regime is generally well described by our model taking into account the effects of associations between pairs of loci. This result bears some similarity with the result obtained by Phillips et al. (2000), showing that the variance in epistasis between deleterious alleles increases the mutation load. Equation 2.1 in Phillips et al. (2000) is not fully equivalent to our expression for the load under random mating, however, which may be due to different assumptions on the relative orders of magnitude of s_i, s_j and e_{ij} (where s_i and s_j are the strength of selection at loci i and j and e_{ij} is epistasis between those loci) and how they covary. Nevertheless, it is interesting to note that both results become equivalent if $\mathrm{Var}\left[e_{ij}/\left(s_i s_j\right)\right]$ in Phillips et al. (2000) is replaced by $\mathrm{Var}\left[e_{ij}/\overline{s}^2\right]$ (where Var stands for the variance across all pairs of loci), using the fact that $\mathrm{Var}\left[e_{ij}\right] = 4\overline{s}^2/n$ in our model (with a Gaussian fitness function). (2) Increasing the value of U/n and/or reducing effective recombination rates or $\overline{s}$ generates a transition to a different regime in which the effect of the variance in epistasis switches, reducing V_{g}, L and δ. Because our analytical approach fails in this regime (presumably due to higher-order associations between loci), it is more difficult to obtain an intuitive understanding of

the selective mechanisms involved. However, it is likely that selection operates on multilocus genotypes (comprising combinations of alleles with compensatory effects) that can be maintained over many generations due to high selfing rates and/or low recombination. A similar transition from genic to genotypic selection as recombination decreases was described by Neher and Shraiman (2009), using a haploid model in which epistasis is randomly assigned to genotypes.

Although our results show some qualitative similarities with those obtained by Lande and Porcher (2015) — e.g., the same transition between regimes occurs in both models as selfing increases — several differences can be observed. In particular, Lande and Porcher's model predict little or no effect of selfing on V_{g} below the threshold selfing rate corresponding to the change in regime, and an abrupt change in V_{g} at the threshold (except in their infinitesimal model). A step change such as this is never observed in our model, even for parameter values at which the effect of drift should be negligible at most loci. These differences between the models are not due to the different genetic architectures considered (biallelic vs. multiallelic), since our biallelic and multiallelic simulations yielded very similar results (Figure 9). Rather, they must be due to Lande and Porcher's assumption of a Gaussian distribution of allelic effects maintained at each locus in each selfing age class, implicitly assuming a sufficiently high mutation rate per locus u and low fitness effect of mutations $\overline{s}$ (Turelli, 1984). In our multiallelic simulations (with $u = 10^{-5}$ to 10^{-3} and $\overline{s} = 0.01$), the number of alleles maintained at each locus is not sufficiently large to generate a Gaussian distribution of segregating allelic effects (see Figures 9 and S12). One may also note that the effect of the number of selected traits n seems different in both models (compare Lande and Porcher's Figure 5 and 6 to our Figure 7), but this is due to the fact that the overall

mutation rate U is proportional to n in Lande and Porcher's model (while U is fixed in Figure 7). Increasing both n and U in order to maintain a constant U/n ratio, we indeed observed that the transition between regimes occurs at lower selfing rates when n is larger, as in Lande and Porcher's Figure 5 and 6 (results not shown). In general, whether U should scale with n depends on the degree of pleiotropy of mutations (Lande and Porcher assume no pleiotropy). Our model allowed us to explore the effects of pleiotropy through the parameter m, showing that pleiotropy mostly affects the results through its effect on $\overline{s}$. However, pleiotropy may have stronger effects under different assumptions regarding the genetic architecture of traits, for example when different sets of traits are affected by different sets of loci (modular pleiotropy, Welch and Waxman, 2003).

In the regime where genetic associations generated by epistasis reduce V_{g} (regime (2) mentioned above), outbreeding depression may occur due to the lower fitness of recombinants between selfing lineages maintaining coadapted gene complexes (Figure 8), a result shared with Lande and Porcher's (2015) Gaussian Allele Model. In our additive model of phenotypic effects, outbreeding depression should only be expressed in F2 individuals (that is, among the offspring of an individual produced by a cross between different selfing lineages), once recombination has disrupted compensatory associations between alleles at different loci. This explains why outbreeding depression is not observed under complete (or nearly complete) selfing in Figure 8, as all outcrossed individuals are F1 hybrids between selfing lineages. Outbreeding depression between lineages collected from the same geographical location has been observed in highly selfing plants (Parker, 1992; Volis et al., 2011) and *Caenorhabditis* nematodes (Dolgin et al., 2007; Gimond et al., 2013). In all cases, estimated selfing rates are higher than

those leading to $\delta < 0$ in our simulations, however, and outbreeding depression was observed in F1 offspring of crosses between inbred lines of nematodes. The occurrence of outbreeding depression at higher selfing rates may be partly explained by the fact that experimental crosses were often performed between genetically different lines; by contrast, in our simulations the parents of an outcrossed individual may share the same genotype (in particular when the number of genetically different selfing lineages is reduced due to the low effective size of highly selfing populations), reducing the magnitude of outbreeding depression. However, the occurrence of outbreeding depression in F1 individuals must involve dominance effects which are absent from our model. Exploring the effects of dominance/recessivity of mutations on phenotypic traits would be an interesting extension of this work.

Due to the lower genetic diversity of self-fertilizing populations, it has been suggested that they should be less able to adapt to a changing environment (e.g., Stebbins, 1957; Williams, 1992; Takebayashi and Morrell, 2001). In the absence of epistasis, existing models indeed predict that selfing populations should have lower rates of adaptation than outcrossing ones (Glémin and Ronfort, 2013; Hartfield and Glémin, 2016). When compensatory effects between mutations are possible, however, a substantial amount of genetic variance may be hidden by genetic associations between loci in highly selfing populations (Lande and Porcher, 2015, the present study). After a change in environment, this variance may be liberated by rare outcrossing events, increasing the short-term evolutionary response of highly (but not fully) selfing populations. Exploring how selfing affects adaptation under directional selection, and more generally how the variability of epistatic interactions between loci may influence the evolution of mating systems represents a natural next step of this work.

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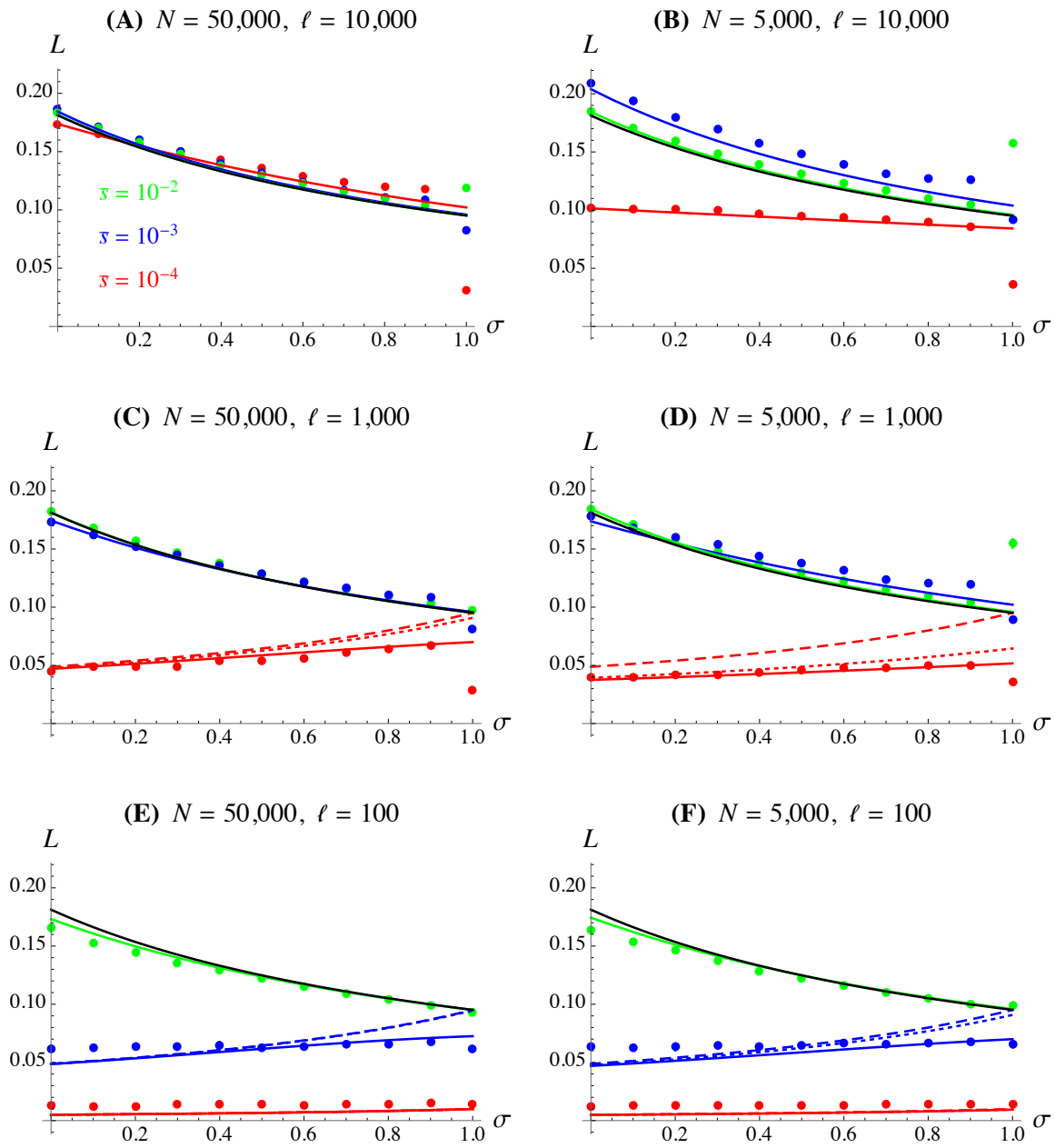

Figure 1. Mutation load L as a function of the selfing rate σ, for different values of population size N and number of selected loci ℓ. Black curve: approximation for mutation-selection regime neglecting genetic associations (equation 25). The different colors correspond to different values of $\overline{s}$ as shown in A. Colored solid curves: results from the diffusion model (Supplementary File 2). Dotted curves: approximation for

mutation-drift regime (equation 31); dashed curves: approximation assuming $p_i = 1/2$ at all loci (equation 29). The red solid, dashed and dotted curves cannot be distinguished in E and F, while the blue dashed and dotted curves cannot be distinguished in C. Dots correspond to simulation results; in this and the following figures, error bars (computed by splitting the last 70,000 generations into 7 batches of 10,000 generations and calculating the standard error over batches) are smaller than the size of symbols in most cases. For $\ell = 100$, the results correspond to averages over 10 replicate simulations (but all 10 simulations gave similar results). Other parameter values are $U = 0.1$, $R = 20$, $n = 50$, $m = 5$.

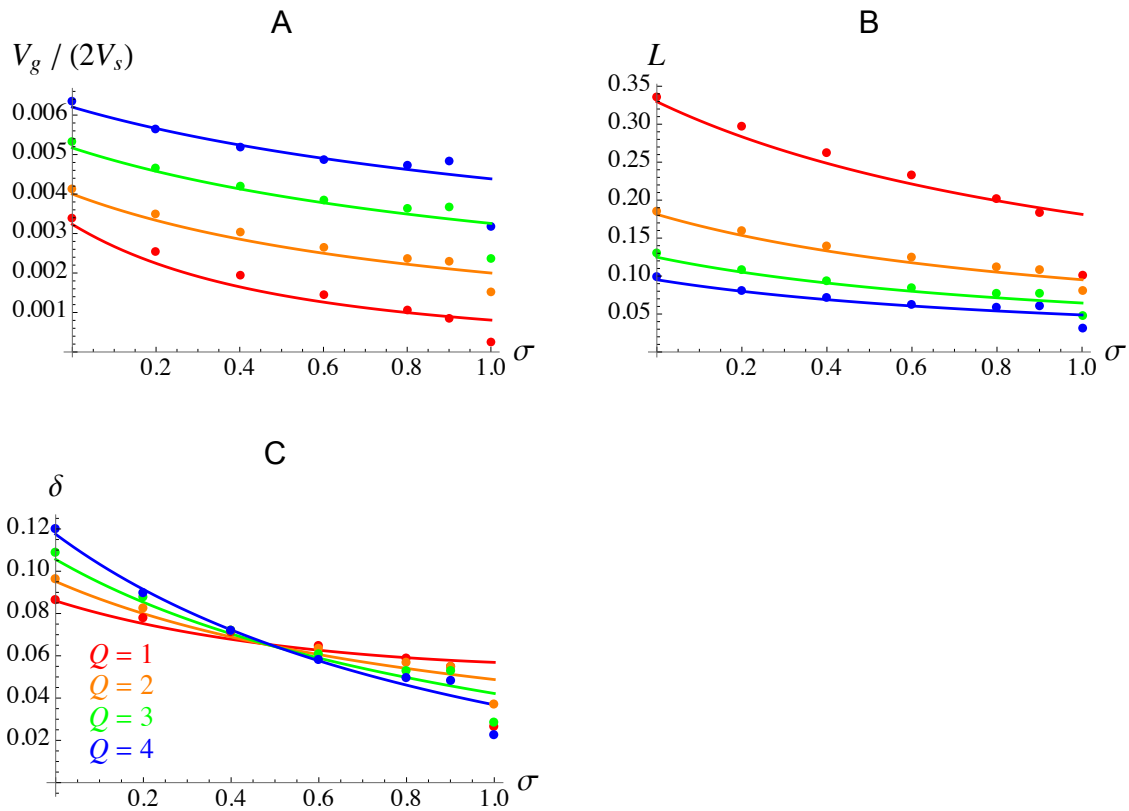

Figure 2. Scaled genetic variance (A), mutation load (B) and inbreeding depression (C) as a function of the selfing rate σ, for different values of the parameter Q describing the shape of the fitness peak (see legend in C). The curves represent the analytical results (neglecting associations between loci) at mutation-selection balance (equations 33 and 34), while the dots correspond to simulation results. Parameter values: $N = 50{,}000$, $\ell = 10{,}000$, $U = 0.1$, $R = 20$, $n = 50$, $m = 5$, $a^2/(2V_s) = 0.0002$ (yielding $\overline{s} = 0.001$ for $Q = 2$).

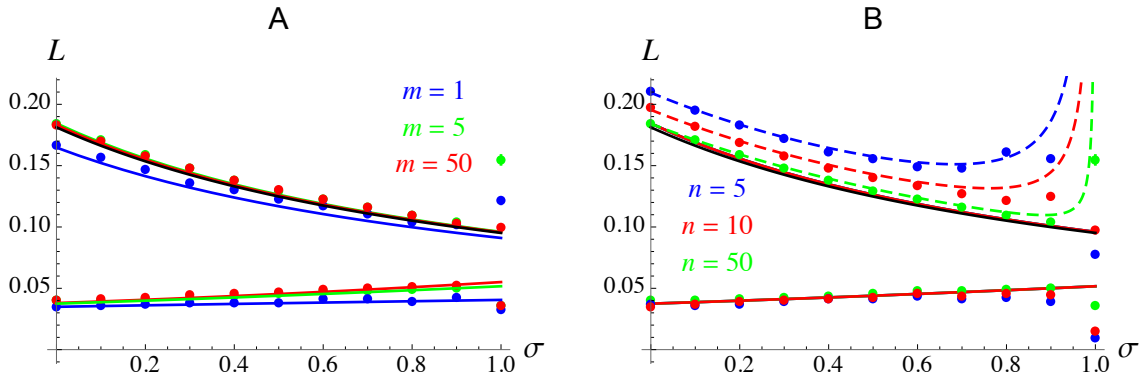

Figure 3. Mutation load L as a function of the selfing rate σ for $\overline{s} = 10^{-2}$ (top) and $\overline{s} = 10^{-4}$ (bottom). A: the different colors correspond to different values of m (degree of pleiotropy of mutations); B: the different colors correspond to different values of n (number of selected traits). Black curve: approximation for mutation-selection regime, neglecting genetic associations (equation 25). Colored solid curves: results from the diffusion model (Supplementary File 2). Colored dashed curves (in B): approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45). Other parameter values are $U = 0.1$, $R = 20$, $N = 5{,}000$, $\ell = 1{,}000$, $n = 50$ (in A), $m = 5$ (in B).

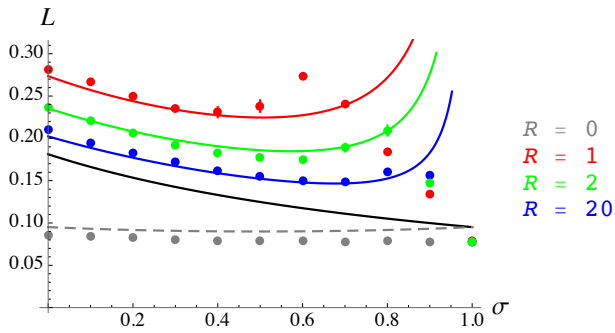

Figure 4. Mutation load L as a function of the selfing rate σ, for $\overline{s} = 0.01$, $n = m = 5$ and different values of the genome map length R, yielding (using equation 43) $\rho_{\mathrm{H}} \approx 0.07$, 0.13 and 0.42 for $R = 1$, 2, 20 (respectively). Dots: simulation results; black curve: approximation for mutation-selection regime neglecting genetic associations (equation 25); colored curves: approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45); dashed grey curve: single-locus model with many alleles, assuming a Gaussian distribution of allelic values (equations 49 and 50). Other parameter values are as in Figure 3.

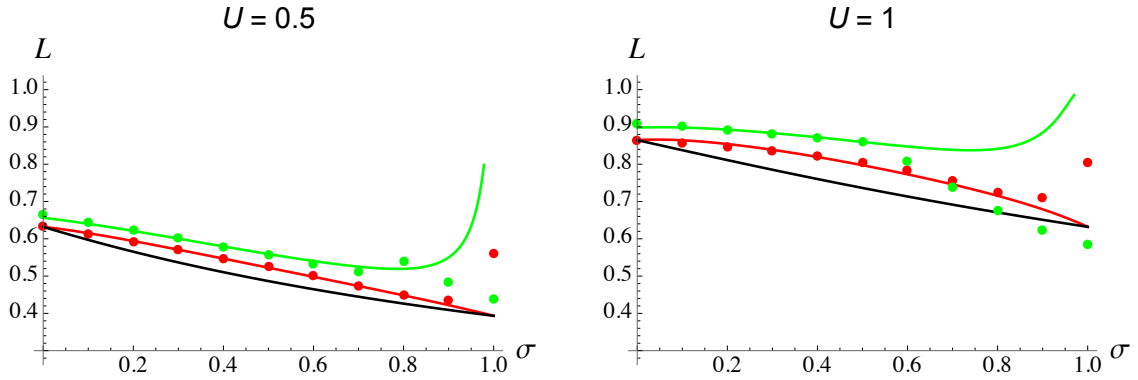

Figure 5. Mutation load L as a function of the selfing rate σ, for $\overline{s} = 0.01$, $n = 50$, $m = 5$, $U = 0.5$ (left) and 1 (right). The black curves correspond to the approximation for mutation-selection regime, neglecting genetic associations (equation 25). Green curves: approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45); red curves: approximation including the effects of identity disequilibria between loci, but not the effects of epistasis (obtained by removing the terms in U^2/n from equations 42, 44 and 45, equivalent to equation 11 in Roze, 2015). Green dots: simulation results; red dots: results from the simulation program used in Roze (2015) representing multiplicative selection (no epistasis), with $s = 0.04$ and $h = 0.25$. Other parameter values are $N = 5{,}000$, $\ell = 10{,}000$, $R = 20$ (yielding $\rho_{\mathrm{H}} \approx 0.38$).

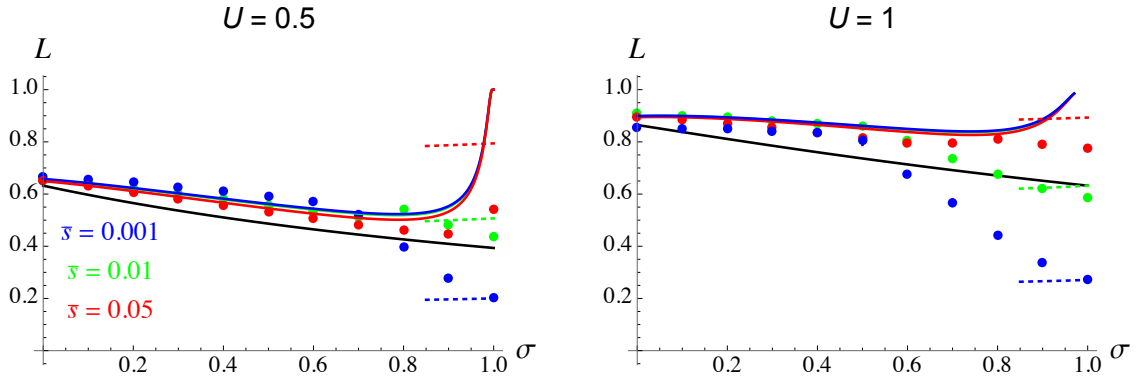

Figure 6. Mutation load L as a function of the selfing rate σ, for different values of the mutation rate U and average heterozygous effect of mutations $\overline{s}$; other parameter values are as in Figure 5. Dots: simulation results; black curves: approximation for mutation-selection regime, neglecting genetic associations (equation 25); solid colored curves: approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45); dotted colored curves: single-locus model with many alleles, assuming a Gaussian distribution of allelic values (equations 49 and 50).

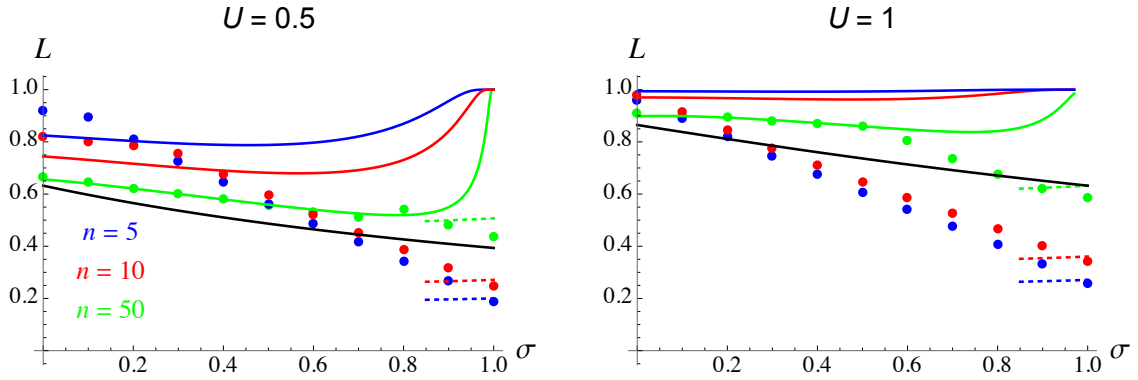

Figure 7. Mutation load L as a function of the selfing rate σ, for different values of the mutation rate U and number of selected traits n; other parameter values are as in Figure 5. Dots: simulation results; black curves: approximation for mutation-selection regime, neglecting genetic associations (equation 25); solid colored curves: approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45); dotted colored curves: single-locus model with many alleles, assuming a Gaussian distribution of allelic values (equations 49 and 50).

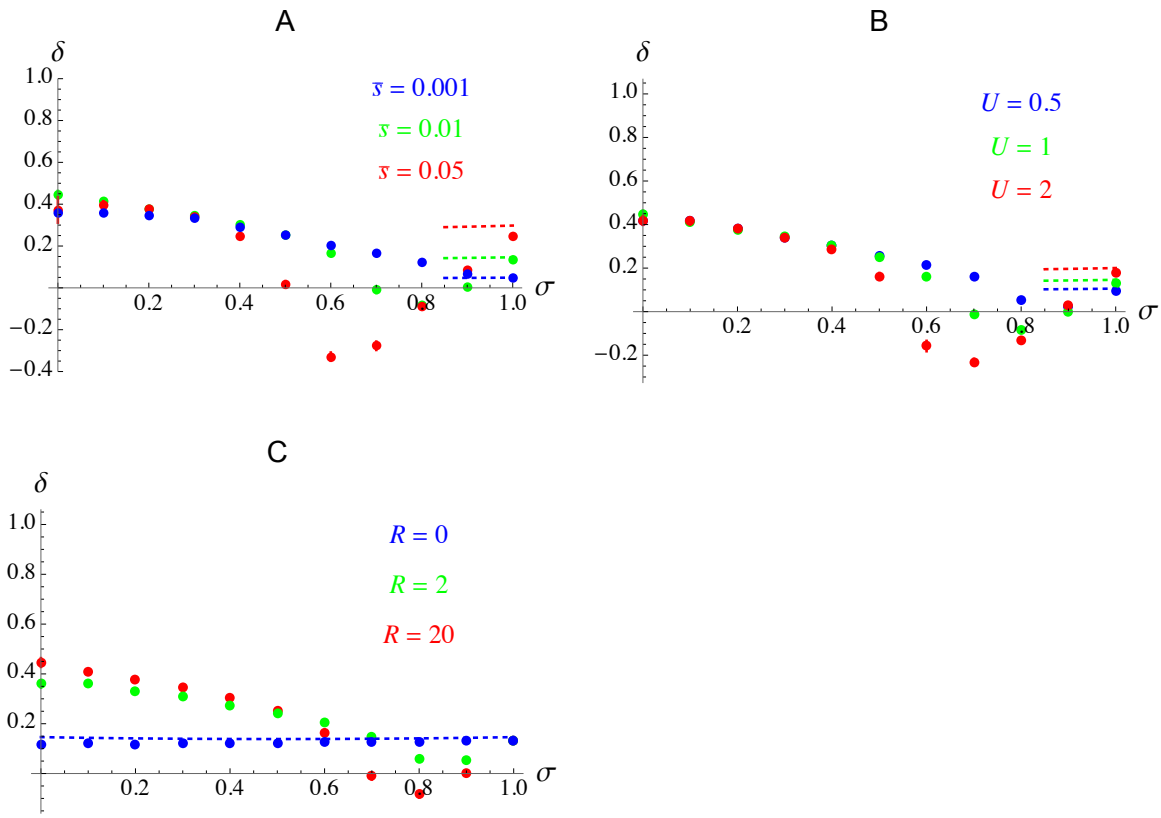

Figure 8. Inbreeding depression δ as a function of the selfing rate σ, for $n = m = 5$ and different values of $\overline{s}$ (A), u (B) and R (C). Dots: simulation results; dotted blue curve: single-locus model with many alleles, assuming a Gaussian distribution of allelic values (equations 49 and 50). Other parameter values are $N = 5{,}000$, $\ell = 10{,}000$, $R = 20$, $U = 1$ and $\overline{s} = 0.01$.

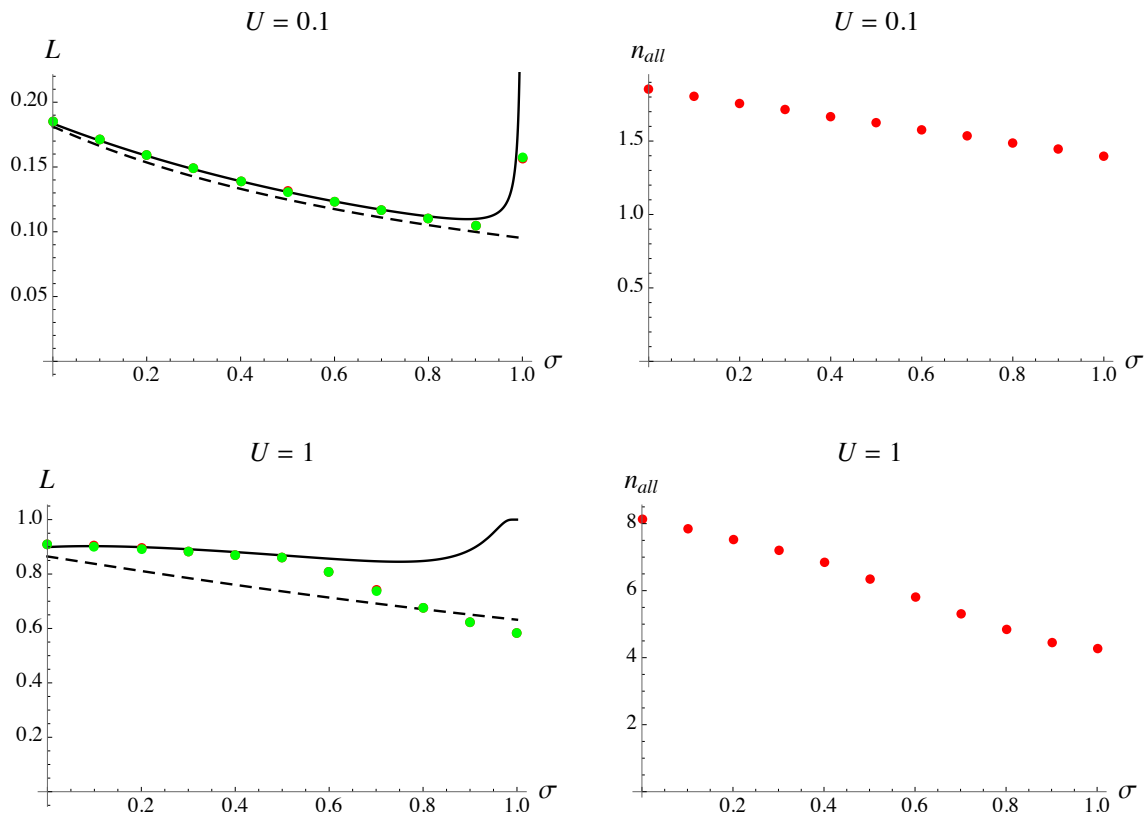

Figure 9. Left: mutation load L as a function of the selfing rate σ, for $U = 0.1$ and 1, and other parameter values as in Figure 5 ($\overline{s} = 0.01$, $n = 50$, $m = 5$, $N = 5{,}000$, $\ell = 10{,}000$, $R = 20$). Simulation results: green dots: biallelic model, red dots: model with an infinite number of possible alleles per locus (green and red dots are nearly undistinguishable). Solid curve: approximation including the effect of pairwise interactions among loci (equations 42, 44 and 45); dashed curve: approximation ignoring the effect of genetic associations (equation 25). Right: average number of allele per locus at equilibrium in the simulations with an infinite number of possible alleles per locus.