



**HAL**  
open science

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

Diala Abu Awad, Denis Roze

► **To cite this version:**

Diala Abu Awad, Denis Roze. Effects of partial selfing on the equilibrium genetic variance, mutation load, and inbreeding depression under stabilizing selection. *Evolution - International Journal of Organic Evolution*, 2018, 72 (4), pp.751-769. 10.1111/evo.13449 . hal-02621298

**HAL Id: hal-02621298**

**<https://hal.inrae.fr/hal-02621298v1>**

Submitted on 5 Jan 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



# Peer Community In Evolutionary Biology

---

Abu Awad D, Roze D. 2017. **Effects of partial selfing on the equilibrium genetic variance, mutation load and inbreeding depression under stabilizing selection.** *bioRxiv*, 180000,  
<https://doi.org/10.1101/180000>

**An article reviewed and recommended by *Peer Community In Evolutionary Biology*:**

<http://dx.doi.org/10.24072/pci.evolbiol.100041>

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

Diala Abu Awad\* and Denis Roze<sup>†,‡</sup>

\* INRA, UMR AGAP, 34060 Montpellier, France

† CNRS, UMI 3614 Evolutionary Biology and Ecology of Algae, 29688 Roscoff,  
France

‡ Sorbonne Universités, UPMC Université Paris VI, 29688 Roscoff, France

*Running title:* Selfing and stabilizing selection

*Keywords:* adaptive landscape, epistasis, evolutionary quantitative genetics, multi-locus population genetics, self-fertilization

*Address for correspondence:*

Denis Roze

Station Biologique de Roscoff

Place Georges Teissier, CS90074

29688 Roscoff Cedex

France

Phone: (+33) 2 56 45 21 39

Fax: (+33) 2 98 29 23 24

email: roze@sb-roscoff.fr

1 ABSTRACT

2 This preprint has been reviewed and recommended by Peer Community In Evo-  
3 lutionary Biology (<http://dx.doi.org/10.24072/pci.evolbiol.100041>).

4  
5 The mating system of a species is expected to have important effects on its ge-  
6 netic diversity. In this paper, we explore the effects of partial selfing on the equilibrium  
7 genetic variance  $V_g$ , mutation load  $L$  and inbreeding depression  $\delta$  under stabilizing se-  
8 lection acting on a arbitrary number  $n$  of quantitative traits coded by biallelic loci with  
9 additive effects. Overall, our model predicts a decrease in the equilibrium genetic vari-  
10 ance with increasing selfing rates; however, the relationship between self-fertilization  
11 and the variables of interest depends on the strength of associations between loci, and  
12 three different regimes are observed. When the  $U/n$  ratio is low (where  $U$  is the total  
13 haploid mutation rate on selected traits) and effective recombination rates are suffi-  
14 ciently high, genetic associations between loci are negligible and the genetic variance,  
15 mutation load and inbreeding depression are well predicted by approximations based  
16 on single-locus models. For higher values of  $U/n$  and/or lower effective recombi-  
17 nation, moderate genetic associations generated by epistasis tend to increase  $V_g$ ,  $L$  and  
18  $\delta$ , this regime being well predicted by approximations including the effects of pairwise  
19 associations between loci. For yet higher values of  $U/n$  and/or lower effective recom-  
20 bination, a different regime is reached under which the maintenance of coadapted gene  
21 complexes reduces  $V_g$ ,  $L$  and  $\delta$ . Simulations indicate that the values of  $V_g$ ,  $L$  and  $\delta$   
22 are little affected by assumptions regarding the number of possible alleles per locus.

23

## INTRODUCTION

24 Genetic diversity maintained within populations plays an important role in  
25 defining their adaptive potential (for a species to evolve, there must be heritable phe-  
26 notypic variation on which selection can act). The ultimate source of this diversity is  
27 mutation, with a substantial proportion of new mutations being of a slightly deleteri-  
28 ous nature (Eyre-Walker and Keightley, 2007): hence, a corollary to the maintenance  
29 of genetic diversity is the existence of a mutation load, defined as the reduction in  
30 mean fitness of a population relative to the fitness of an optimal genotype (Haldane,  
31 1937). Furthermore, the fact that most deleterious alleles are partially recessive causes  
32 inbred offspring to have a lower fitness (on average) than outbred ones, as they tend to  
33 carry higher numbers of homozygous mutations (inbreeding depression, Charlesworth  
34 and Charlesworth, 1987).

35 By affecting the average degree of homozygosity of individuals and the efficiency  
36 of recombination between loci, the reproductive system of a species is expected to have  
37 an important influence on the effect of selection against deleterious alleles, and thus on  
38 the mutation load, inbreeding depression and level of diversity maintained within popu-  
39 lations. One mating system that has received considerable attention is self-fertilization,  
40 a reproductive strategy occurring at various rates in an important proportion of plant  
41 and animal species (Jarne and Auld, 2006; Goodwillie et al., 2005; Iqbal and Kohn,  
42 2006). Self-fertilization, and inbreeding in general, may have different effects on ge-  
43 netic polymorphisms depending on the strength of selection acting on them (Glémin,  
44 2007). When directional selection against deleterious alleles is sufficiently strong rela-  
45 tive to drift ( $N_e s \gg 1$ ), the increased homozygosity caused by inbreeding is expected

46 to improve the efficiency of selection against those alleles (purging), reducing the mu-  
47 tation load and inbreeding depression (Lande and Schemske, 1985; Charlesworth et  
48 al., 1990). At the other extreme, polymorphism at neutrally-behaving loci ( $N_e s \ll 1$ )  
49 should also be lowered by inbreeding, as the effective population size is reduced by  
50 identity-by-descent within loci (Pollak, 1987) and by stronger interference effects be-  
51 tween loci — background selection, hitchhiking (Nordborg, 1997; Glémin and Ronfort,  
52 2013; Roze, 2016). In intermediate regimes ( $N_e s \sim 1$ ), however, the reduction in  $N_e$   
53 due to inbreeding may cause an increased frequency of deleterious alleles (because  
54 selection is less effective), which may explain the higher  $\pi_N/\pi_S$  ratio observed in var-  
55 ious selfing species compared with their outcrossing relatives (Brandvain et al., 2013;  
56 Burgarella et al., 2015, and other references listed in Table 1 of Hartfield, 2015).

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

70 effects in highly selfing populations, due to the fact that selfing reduces the efficiency  
71 of recombination between loci — recombination having no effect when it occurs in  
72 homozygous individuals (Kamran-Disfani and Agrawal, 2014; Hartfield and Glémin,  
73 2016). Epistatic interactions represent another possible source of linkage disequilib-  
74 rium between selected loci. Charlesworth et al. (1991) considered a model in which  
75 epistasis between deleterious alleles is fixed and synergistic (the effects of mutations  
76 alone being smaller than when combined with others), and showed that the effect of  
77 the selfing rate on the load and inbreeding depression may be non-monotonic under  
78 this form of epistasis, with an increase in both variables above a (high) self-fertilization  
79 threshold. However, although models with fixed epistasis have lead to important in-  
80 sights, epistatic interactions are known to vary across pairs of loci, and this variation  
81 may have important evolutionary consequences (Phillips et al., 2000; Martin et al.,  
82 2007). Interestingly, several aspects of the complexity of epistatic interactions (such  
83 as possible compensatory effects between deleterious alleles, *i.e.*, reciprocal sign epis-  
84 tasis) are captured by models of stabilizing selection acting on quantitative traits, such  
85 as Fisher’s geometric model (Fisher, 1930). Furthermore, the distributions of epistasis  
86 generated by this type of model seem compatible with our empirical knowledge on  
87 epistasis (Martin et al., 2007).

88         Only a few models have explored the effect of self-fertilization on genetic vari-  
89 ance for quantitative traits at equilibrium between mutation and stabilizing selection.  
90 Modeling a quantitative trait coded by additive loci, Wright (1951) showed that, in  
91 the absence of selection, the genetic variance for the trait is increased by a factor  
92  $1 + F$  (where  $F$  is the inbreeding coefficient), due to the increased homozygosity of  
93 the underlying loci. Selection will oppose this increase in variance, however, by elim-



inating 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 popula-  
tion. More recently, Lande and Porcher (2015) extended this model to multiple selected  
traits, and used 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),  
while assuming 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 dif-  
ferent 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

118 implicitly assumes an unrealistically high mutation rate per locus and/or very weak  
119 fitness effects of mutations (Turelli, 1984). Lande and Porcher (2015) also considered  
120 an infinitesimal model (in which traits are coded by an infinite number of loci, selec-  
121 tion having a negligible effect on allele frequencies at each locus), and showed that a  
122 similar threshold pattern emerges, although the effect of selfing on the genetic variance  
123 and inbreeding depression above the threshold differs between the two models (in par-  
124 ticular, outbreeding depression is not observed in the infinitesimal model). However,  
125 the effect of selfing on the genetic variance of quantitative traits under more general  
126 assumptions regarding the strength of selection at the underlying loci remains unclear.

127         In this paper, we introduce partial self-fertilization into previous models of sta-  
128 bilizing selection acting on quantitative traits coded by biallelic loci (Latter, 1960; Bul-  
129 mer, 1972; Barton, 1986, 1989; Turelli and Barton, 1990; Roze and Blanckaert, 2014).  
130 Charlesworth and Charlesworth (1995) had extended such models to take complete  
131 selfing into account, and found that the genetic variance under stabilizing selection  
132 should be lower under complete selfing than under random mating. The present paper  
133 generalizes these results to arbitrary selfing rates and multiple selected traits. Assum-  
134 ing additive effects of alleles on phenotypes (no dominance or epistasis on phenotypic  
135 traits), we develop approximations incorporating the effects of pairwise associations  
136 between selected loci, and compare these approximations with results from individual-  
137 based simulations. Our results indicate that different regimes are possible depending  
138 on the effect of genetic associations on the genetic variance, this effect increasing as the  
139 overall mutation rate  $U$  and selfing rate  $\sigma$  increase, and decreasing as the genome map  
140 length  $R$ , mean fitness effect of mutations  $\bar{s}$  and number of selected traits  $n$  increase.  
141 When  $U$  and  $\sigma$  are sufficiently low and  $R$ ,  $\bar{s}$  and  $n$  sufficiently high, the effect of associ-

142 ations is negligible and the mutation load, inbreeding depression and genetic variance  
143 are well predicted by classical expressions ignoring associations. As the strength of  
144 associations increases, a second regime is entered in which the overall effect of associa-  
145 tions is to reduce purging, thereby increasing the genetic variance, mutation load and  
146 inbreeding depression; this “weak association” regime is generally well predicted by our  
147 approximations which include the effects of pairwise associations between loci. For yet  
148 higher  $U$ ,  $\sigma$  and/or lower  $R$ ,  $\bar{s}$  or  $n$ , a third regime is reached in which strong associa-  
149 tions between loci caused by compensatory effects among mutations reduce the genetic  
150 variance, load and inbreeding depression. Although our approximations break down  
151 in this “strong association” regime, the approximation proposed by Charlesworth and  
152 Charlesworth (1995) provides accurate results under complete selfing when the mu-  
153 tation rate is sufficiently high and the mean fitness effect of mutations sufficiently  
154 low.

155

## MODEL

156 **Genotype-phenotype map.** The parameters and variables of our model are summa-  
157 rized in Table 1. We consider a diploid population of size  $N$  with discrete generations.  
158 Offspring are produced by self-fertilization with probability  $\sigma$ , and by random union  
159 of gametes with probability  $1 - \sigma$ . The fitness of an organism represents its overall  
160 relative fecundity (assumed very large for all individuals), and depends on the values  
161 of  $n$  quantitative phenotypic traits under stabilizing selection. In the following we use  
162 subscripts  $\alpha, \beta, \gamma\dots$  to denote phenotypic traits, while subscripts  $i, j, k\dots$  denote loci.  
163 The value of trait  $\alpha$  in a given individual is denoted  $z_\alpha$ , and can be decomposed into

164 a genetic and an environmental component:

$$z_\alpha = g_\alpha + e_\alpha \quad (1)$$

165 where the environmental component  $e_\alpha$  is sampled from a Gaussian distribution with  
166 mean zero and variance  $V_e$  (the same for all traits). The genetic component  $g_\alpha$  (“breed-  
167 ing value”) is controlled by a large number of biallelic loci with additive effects. The  
168 two alleles at each locus are denoted 0 and 1, while  $X_i^M$  and  $X_i^P$  are defined as indicator  
169 variables that equal zero if the individual carries allele 0 at locus  $i$  on its maternally  
170 ( $X_i^M$ ) or paternally ( $X_i^P$ ) inherited chromosome, while they equal 1 if allele 1 is present.  
171 We also assume that  $g_\alpha = 0$  in an individual homozygous for allele 0 at all loci, so  
172 that:

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

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

176 Following Chevin et al. (2010), Lourenço et al. (2011) and Roze and Blanckaert  
177 (2014), a parameter  $m$  measures the degree of pleiotropy of mutations: each locus  
178 affects a subset of  $m$  phenotypic traits, sampled randomly (and independently for  
179 each locus) among the  $n$  traits. Therefore,  $m = 1$  means that each locus affects a  
180 single trait, while  $m = n$  corresponds to full pleiotropy (each locus affecting all traits),  
181 as in Fisher’s geometric model (Fisher, 1930). We assume that the distribution of  
182 mutational effects  $r_{\alpha i}$  over all loci affecting trait  $\alpha$  has average zero and variance  $a^2$   
183 (the same for all traits); if locus  $i$  does not affect trait  $\alpha$ , then  $r_{\alpha i} = 0$ . For simplicity, we  
184 consider a fully isotropic model with no mutational covariance between traits. Finally,

185  $u$  denotes the mutation rate from allele 0 to allele 1 and from allele 1 to allele 0 at  
 186 each locus, while  $U = u\ell$  is the haploid mutation rate over all loci (per generation).

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

$$\bar{z}_\alpha \approx \bar{g}_\alpha = 2 \sum_{i=1}^{\ell} r_{\alpha i} p_i \quad (3)$$

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

$$V_{p,\alpha} = V_{g,\alpha} + V_e \quad (4)$$

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

193

194 **Genetic associations and decomposition of the genetic variance.** Genetic

195 associations are defined as in Kirkpatrick et al. (2002). In particular, the centered

196 variables  $\zeta_{i,\emptyset}$  and  $\zeta_{\emptyset,i}$  are defined as:

$$\zeta_{i,\emptyset} = X_i^M - p_i, \quad \zeta_{\emptyset,i} = X_i^P - p_i. \quad (5)$$

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

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

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

$$\zeta_{i,i} = (X_i^M - p_i) (X_i^P - p_i) \quad (7)$$

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

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

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

$$D_{\mathbb{U},\mathbb{V}} = \text{E}[\zeta_{\mathbb{U},\mathbb{V}}] \quad (9)$$

202 where E stands for the average over all individuals in the population. We also define  
 203  $\tilde{D}_{\mathbb{U},\mathbb{V}}$  as  $(D_{\mathbb{U},\mathbb{V}} + D_{\mathbb{V},\mathbb{U}})/2$ , and write  $\tilde{D}_{\mathbb{U},\emptyset}$  as  $\tilde{D}_{\mathbb{U}}$  (for simplicity). In particular,  $D_{i,i}$  is  
 204 a measure of excess homozygosity (due, for example, to non-random mating) at locus  
 205  $i$  ( $D_{i,i} = 0$  at Hardy-Weinberg equilibrium). As shown in Supplementary File S1, it  
 206 can be written as  $D_{i,i} = F p_i q_i$ , where  $F$  is the inbreeding coefficient (probability of  
 207 identity by descent between two alleles present at the same locus in the same indi-  
 208 vidual). The association  $\tilde{D}_{i,j}$  corresponds to the linkage disequilibrium between loci  $i$   
 209 and  $j$  (association between alleles present on the same haplotype), while  $\tilde{D}_{i,j}$  is the  
 210 association between alleles at loci  $i$  and  $j$  present on different haplotypes of the same  
 211 individual. We will see that the association  $D_{ij,ij}$  also appears in the computations,  
 212 and can be expressed as  $\phi_{ij} p_i q_i p_j q_j$ , where  $\phi_{ij}$  is the probability of joint identity by  
 213 descent at loci  $i$  and  $j$ . The quantities  $\phi_{ij}$  and  $F$  enter into the definition of the identity  
 214 disequilibrium between loci  $i$  and  $j$ , given by  $G_{ij} = \phi_{ij} - F^2$  (Weir and Cockerham,  
 215 1973), which will appear in some of our results.

216 From these definitions, and using equations 2 and 3, the genetic variance for  
 217 trait  $\alpha$  can be written as:

$$\begin{aligned} V_{g,\alpha} &= \text{E}[(g_\alpha - \bar{g}_\alpha)^2] \\ &= \text{E}\left[\sum_{i,j} r_{\alpha i} r_{\alpha j} (\zeta_{i,\emptyset} + \zeta_{\emptyset,i}) (\zeta_{j,\emptyset} + \zeta_{\emptyset,j})\right] \end{aligned} \quad (10)$$

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

219 one obtains from equation 9:

$$V_{g,\alpha} = 2 \sum_{i=1}^{\ell} r_{\alpha i}^2 (p_i q_i + D_{i,i}) + 2 \sum_{i,j \neq i} r_{\alpha i} r_{\alpha j} (\tilde{D}_{ij} + \tilde{D}_{i,j}). \quad (11)$$

220 Following previous usage (e.g., Bulmer, 1985), we will call *genic variance* (denoted  
221  $V_{g,\alpha}^0$ ) the quantity  $2 \sum_{i=1}^{\ell} r_{\alpha i}^2 p_i q_i$ , corresponding to the genetic variance in a popula-  
222 tion with the same allele frequencies, but in the absence of genetic association (within  
223 and between loci). As shown by equation 11, excess homozygosity tends to increase  
224 the genetic variance through the term in  $D_{i,i}$ . The second term of equation 11 (the  
225 effect of between-locus associations) tends to be negative under stabilizing selection,  
226 since the allele increasing the value of trait  $\alpha$  at locus  $i$  tends to be associated with the  
227 allele decreasing its value at locus  $j$  (e.g., Bulmer, 1971, 1974; Lande, 1976; Turelli and  
228 Barton, 1990). However, below we show that that excess homozygosity and associa-  
229 tions between loci also affect equilibrium allele frequencies, and thus the genic variance.

230

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

$$W = \exp \left[ -\frac{d^2}{2\omega^2} \right] \quad (12)$$

233 where  $\omega^2$  measures the strength of selection, and  $d = \sqrt{\sum_{\alpha=1}^n z_{\alpha}^2}$  is the Euclidean  
234 distance (in phenotypic space) between the individual's phenotype and the optimum,  
235 which we assume is located at  $\mathbf{z} = (0, 0, \dots, 0)$ . From equation 12, the fitness associ-  
236 ated with a given genotype (obtained by averaging over environmental effects) is also  
237 Gaussian, and given by:

$$W_g = W_{g,\max} \exp \left[ -\frac{d_g^2}{2V_s} \right] \quad (13)$$

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

$$\bar{s} = \frac{ma^2}{2V_s} \quad (14)$$

242 (e.g., Martin and Lenormand, 2006b). Under our assumption of additivity of pheno-  
243 typic effects it is easy to show that the reduction in  $\log W_g$  caused by a homozygous  
244 deleterious allele (in an optimal genotype) is four times the reduction caused by the  
245 same allele in the heterozygous state. Provided that most mutations have weak fitness  
246 effects (so that  $\log(1-s) \approx -s$ ), the dominance coefficient of deleterious alleles is  
247 thus close to 0.25 at the fitness optimum (see Manna et al., 2011 for more general  
248 results on dominance in Fisher's geometric model).

249 The effect of the shape of the fitness peak will be explored using a generalized  
250 version of equation 13 (e.g., Martin and Lenormand, 2006a; Tenaillon et al., 2007):

$$W_g = W_{g,\max} \exp \left[ - \left( \frac{d_g}{\sqrt{2V_s}} \right)^Q \right]. \quad (15)$$

251 Gaussian fitness (equation 13) thus corresponds to  $Q = 2$ , while the fitness peak is  
252 sharper around the optimum when  $Q < 2$ , and flatter when  $Q > 2$ . Importantly,  
253  $Q$  affects the average dominance coefficient of deleterious alleles, making them more  
254 dominant for  $Q < 2$  and more recessive for  $Q > 2$  (Manna et al., 2011), as well as  
255 the average epistasis (on fitness) between alleles, positive for  $Q < 2$ , and negative  
256 for  $Q > 2$  (Gros et al., 2009). Approximations for the mutation load and inbreeding  
257 depression can be derived for  $Q \neq 2$  as long as the distribution of breeding values in  
258 the population is approximately Gaussian.



259 **Individual-based simulations.** In order to verify the analytical results obtained,  
260 individual-based simulations were run using a C++ program described in Supple-  
261 mentary File S5 (and available from Dryad), in which the genome of each individual  
262 consists of two copies of a linear chromosome carrying  $\ell$  equidistant biallelic loci affect-  
263 ing the  $n$  traits under selection. Another version of the program was used to consider  
264 a different genetic architecture, under which an infinite number of alleles are possible  
265 at each locus (see Supplementary File S5).

266

## RESULTS

267 **Neglecting associations between loci.** In the following section we show that  
268 genetic associations between loci may be neglected when the haploid genomic mutation  
269 rate  $U$  is sufficiently low. In this case, equation 11 simplifies to:

$$V_{g,\alpha} \approx 2 \sum_{i=1}^{\ell} r_{\alpha i}^2 (p_i q_i + D_{i,i}). \quad (16)$$

270 Expressions for  $p_i q_i$  and  $D_{i,i}$  at equilibrium, assuming weak selection ( $V_{g,\alpha} \ll V_s$ ) and  
271 neglecting associations among loci are derived in Supplementary File S1. To leading  
272 order,  $D_{i,i} \approx F p_i q_i$  where  $F = \sigma / (2 - \sigma)$  is the inbreeding coefficient. Neglecting  
273 associations between loci and assuming that mean phenotypes are at the optimum  
274 ( $\bar{g}_\alpha = 0$ ), the effect of selection on  $p_i q_i$  is given by:

$$\Delta_{\text{sel}} p_i q_i \approx -s_i (1 + 3F) (1 - 2p_i)^2 p_i q_i \quad (17)$$

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

$$\Delta_{\text{mut}} p_i q_i \approx u (1 - 2p_i)^2. \quad (18)$$

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

$$s_i p_i q_i \approx \frac{u}{1 + 3F}, \quad (19)$$

280 in agreement with results of previous biallelic models under random mating (e.g.,  
 281 Bulmer, 1972; Barton, 1986). A stability analysis indicates that the equilibrium given  
 282 by equation 19 is stable when  $p_i q_i < 1/4$  (that is, when  $s_i (1 + 3F) > 4u$ ), otherwise  
 283  $p_i = 1/2$  is stable. When all loci are at the equilibrium where  $p_i q_i < 1/4$ , summing  
 284 both sides of equation 19 over  $i$  yields, using  $s_i = \sum_{\alpha=1}^n r_{\alpha i}^2 / (2V_s)$ :

$$\sum_{\alpha=1}^n V_{g,\alpha}^0 \approx \frac{4V_s U}{1 + 3F} \quad (20)$$

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

$$V_{g,\alpha}^0 \approx \frac{4V_s U}{n(1 + 3F)} = \frac{2V_s U}{n} \frac{2 - \sigma}{1 + \sigma}. \quad (21)$$

287 From equations 16 and 21, the equilibrium genetic variance is:

$$V_{g,\alpha} \approx V_{g,\alpha}^0 (1 + F) \approx \frac{4V_s U}{n(1 + \sigma)}. \quad (22)$$

288 When  $\sigma = 0$  and  $n = 1$ , equation 22 is equivalent to the result of previous biallelic  
 289 models (e.g., Latter, 1960; Bulmer, 1972) and to Turelli's house-of-cards approximation  
 290 (Turelli, 1984).

291 Assuming that the variance in log-fitness is small, mean fitness is approximately  
 292  $\bar{W} \approx e^{\overline{\log W_g}}$ . Defining the mutation load  $L$  as the reduction in  $\bar{W}$  relative to the average  
 293 fitness of an optimal genotype, one obtains from equation 13:

$$L = 1 - \frac{\bar{W}}{W_{g,\text{max}}} \approx 1 - \exp \left[ -\frac{\sum_{\alpha=1}^n V_{g,\alpha}}{2V_s} \right]. \quad (23)$$

294 Equations 22 and 23 yield:

$$L \approx 1 - \exp \left[ -\frac{2U}{1 + \sigma} \right]. \quad (24)$$

295 Inbreeding depression  $\delta$  measures the mean fitness of selfed offspring, relative to the  
 296 mean fitness of outcrossed offspring. Under the same assumptions, it is given by:

$$\begin{aligned} \delta &= 1 - \frac{\overline{W}_{\text{self}}}{\overline{W}_{\text{out}}} \\ &\approx 1 - \exp \left[ -\frac{\sum_{\alpha=1}^n (V_{g,\alpha}^{\text{self}} - V_{g,\alpha}^{\text{out}})}{2V_s} \right] \end{aligned} \quad (25)$$

297 where  $V_{g,\alpha}^{\text{self}}$  and  $V_{g,\alpha}^{\text{out}}$  are the genetic variances for trait  $\alpha$  among selfed and out-  
 298 crossed offspring, respectively (e.g., Lande and Schemske, 1985). The intralocus as-  
 299 sociation  $D_{i,i}$  among selfed offspring is  $D_{i,i}^{\text{self}} = \frac{1}{2}(p_i q_i + D_{i,i})$  and therefore  $V_{g,\alpha}^{\text{self}} =$   
 300  $V_{g,\alpha}^0 \left[ 1 + \frac{1}{2}(1 + F) \right]$ , while  $V_{g,\alpha}^{\text{out}} = V_{g,\alpha}^0$ , yielding (using equation 21):

$$\delta \approx 1 - \exp \left[ -\frac{\sum_{\alpha=1}^n V_{g,\alpha}}{4V_s} \right] \approx 1 - \exp \left[ -\frac{U}{1 + \sigma} \right]. \quad (26)$$

301 Equations 24 and 26 are equivalent to the classical expressions obtained for the load and  
 302 inbreeding depression at mutation-selection balance when the dominance coefficient  $h$   
 303 of deleterious alleles is set to 0.25 (e.g., Charlesworth and Charlesworth, 1987), in  
 304 agreement with the fact that  $h \approx 0.25$  under Gaussian stabilizing selection when  
 305 mutations have additive effects on phenotypes (see previous section).

306 Figure 1 shows that the mutation load is well predicted by equation 24 when  
 307  $N_e \bar{s}$  is sufficiently large (for  $U = 0.1$  and  $n = 50$ ), and generally decreases as selfing  
 308 increases — results for different numbers of loci  $\ell$  are shown in Supplementary Fig-  
 309 ure S1, while Supplementary Figures S2 and S3 show that the genetic variance and  
 310 inbreeding depression follow similar patterns. Drift may have significant effects on  
 311 genetic variation, however, when  $N_e \bar{s}$  is  $\approx 1$  or lower. Following Bulmer (1972), a

312 diffusion model can be used to compute the expected value of  $p_i q_i$  under selection, mu-  
313 tation and drift, provided that the effects of associations between loci are neglected.  
314 As explained in Supplementary File S2, the result can then be integrated over the  
315 distribution of  $s_i$  across loci to obtain the equilibrium genetic variance, inbreeding  
316 depression and mutation load. Figures 1 and S1 – S3 show that drift increases  $V_g$ ,  
317  $L$  and  $\delta$  in regimes where  $p_i q_i$  tends to stay small at most loci at the deterministic  
318 equilibrium ( $\bar{s} = 10^{-2}, 10^{-3}$  in Figure 1), and has the opposite effect in regimes where  
319  $p_i q_i$  is high ( $\bar{s} = 10^{-4}$  in Figure 1). Simple approximations can be obtained when the  
320 effect of selection is negligible at most loci (see Supplementary File S2), which provide  
321 accurate predictions when  $N_e \bar{s}$  is sufficiently low, or when  $\bar{s} \ll u$  so that  $p_i = 1/2$  at  
322 most loci at the deterministic equilibrium (Figures S1 – S4). In this mutation-drift  
323 regime,  $V_g$ ,  $L$  and  $\delta$  are nearly independent of  $\sigma$  when  $N_e u \ll 1$  (the increase in vari-  
324 ance caused by excess homozygosity being exactly compensated by the reduction in  
325 variance caused by the lower effective population size), or increase with  $\sigma$  for larger  
326 values of  $N_e u$ . The discrepancies between analytical and simulation results observed  
327 in Figure 1 at high selfing rates are partly due to the reduction in effective population  
328 size  $N_e$  caused by background selection, which is not accounted for in the diffusion  
329 model. An estimation of  $N_e$  using the equilibrium diversity at a neutral locus (with  
330 an infinite number of possible alleles) at the mid-point of the chromosome (as in Roze,  
331 2016) yielded an  $N_e$  of approximately 740, 300 and 200 for  $\bar{s} = 10^{-4}, 10^{-3}$  and  $10^{-2}$   
332 (respectively) for  $N = 5,000$  and  $\sigma = 1$  (right-most points in Figure 1B). Replacing  
333  $N$  by  $N_e(1 + F)$  in the diffusion model provides predictions that closely match the  
334 simulation results for  $\bar{s} = 10^{-4}$  and  $10^{-3}$ , suggesting that the initial discrepancy was  
335 indeed caused by background selection reducing  $N_e$  (results not shown). However, for

336  $\bar{s} = 10^{-2}$ , the diffusion model still performs poorly despite the corrected  $N_e$ . This im-  
337 plies that the discrepancy between analytical and simulation results is more likely due  
338 to interactions among loci, and possibly also to deviations of mean phenotypes from  
339 the optimum caused by genetic drift (that are not taken into account in the analysis).

340 In Supplementary File S3, we derive expressions for the genetic variance, muta-  
341 tion load and inbreeding depression (for both the mutation-selection and the mutation-  
342 drift regimes) under the generalized fitness function given by equation 15. In the  
343 mutation-selection regime ( $s_i \gg 1/N_e$ ,  $u$  at most loci), one obtains:

$$\frac{V_g}{V_s} \approx \left[ \frac{4U}{Q(1+\sigma)} \frac{\Gamma\left(\frac{n}{2}\right)}{\Gamma\left(\frac{Q+n}{2}\right)} \right]^{\frac{2}{Q}} \quad (27)$$

344 (where  $\Gamma$  is Euler's Gamma function), while

$$L \approx 1 - \exp \left[ -\frac{4U}{Q(1+\sigma)} \right] \quad (28)$$

345

$$\delta \approx 1 - \exp \left[ -\frac{4U}{Q(1+\sigma)} \left[ \left( \frac{3-\sigma}{2} \right)^{\frac{Q}{2}} - \left( \frac{2-\sigma}{2} \right)^{\frac{Q}{2}} \right] \right], \quad (29)$$

346 these equations being equivalent to equations 22, 24 and 26 when  $Q = 2$ . As shown  
347 by Figure 2, equations 27 – 29 provide good predictions of the simulation results when  
348 the population size and number of loci are sufficiently large (and selfing is not too  
349 high). As  $Q$  increases, the fitness peak becomes flatter around the optimum, and the  
350 equilibrium genetic variance increases (Figure 2B). However, despite increasing the  
351 genetic variance, higher values of  $Q$  lead to lower mutation loads due to the fact that  
352 deleterious alleles are more often eliminated when present in combination within the  
353 same genome: this corresponds to the classical result that negative epistasis reduces  
354 the mutation load in sexually reproducing populations (e.g., Kimura and Maruyama,  
355 1966; Kondrashov and Crow, 1988). Indeed, the average epistasis between deleterious

356 alleles equals zero for  $Q = 2$ , but becomes negative when  $Q > 2$ , and positive when  
357  $Q < 2$  (Gros et al., 2009). By contrast, inbreeding depression is less affected by  $Q$ ,  $\delta$   
358 slightly increasing or decreasing as  $Q$  increases, depending on the selfing rate.

359 Figure 3 shows the effects of the parameters  $m$  and  $n$  (for  $Q = 2$ ). The degree  
360 of pleiotropy  $m$  of mutations affects their distribution of fitness effects (e.g., Lourenço  
361 et al., 2011). In Figure 3A,  $\bar{s}$  is kept constant by decreasing the variance of mutational  
362 effects  $a^2$  as  $m$  increases (see equation 14). Increasing  $m$  (while keeping  $\bar{s}$  constant)  
363 decreases the variance in fitness effects of mutations: indeed, one can show that the  
364 variance of mutational effects on log fitness (at the optimum) is given by  $2\bar{s}^2/m$ . Figure  
365 3A shows that  $m = 5$  and  $m = 50$  yield very close results when  $\bar{s} = 10^{-4}$ , as selection  
366 has a negligible effect at most loci for both values of  $m$  (for the parameter values used  
367 here), and the genetic variance does not depend on  $m$  at mutation-drift equilibrium (see  
368 equation B8 in Supplementary File S2). When  $\bar{s} = 10^{-2}$ , most loci are at mutation-  
369 selection balance ( $s_i \gg 1/N, u$ ) for both  $m = 5$  and  $m = 50$ , and the genetic variance  
370 is again not affected by  $m$  (see equation 22). Slightly different results are obtained  
371 for  $m = 1$ , due to the higher variance in fitness effects of mutations, causing a larger  
372 fraction of loci to be substantially affected by both selection and drift (this effect being  
373 captured by the diffusion model). Similarly, the effect of  $m$  is more pronounced when  
374  $\bar{s} = 10^{-2}$  and  $\sigma = 1$ , as  $N_e$  is greatly reduced by background selection when selfing is  
375 high, causing higher proportions of loci to be substantially affected by drift.

376 As shown by Figure 3B, the number of selected traits  $n$  has only little effect on  
377 the load in the mutation-drift regime ( $\bar{s} = 10^{-4}$ ), in agreement with equation B9 in  
378 Supplementary File S2. However, while the diffusion model also predicts very little ef-  
379 fect of  $n$  in the mutation-selection regime ( $\bar{s} = 10^{-2}$ ), larger effects are observed in the

380 simulations, with larger deviations from the analytical predictions (and higher load)  
381 for lower values of  $n$ . These deviations are caused by associations between loci (which  
382 are neglected in equation 24 and in the diffusion model). In the next subsection, we  
383 show that the relative effect of these associations is indeed stronger when  $n$  is lower,  
384 and derive an approximation including the effect of pairwise genetic associations that  
385 better matches the simulation results.

386

387 **Effects of associations between loci.** In Supplementary File S1, we derive approx-  
388 imations for the effects of associations between pairs of loci on the genetic variance at  
389 mutation-selection balance, under a Gaussian fitness function ( $Q = 2$ ). For this, we  
390 assume that these associations remain weak, and neglect the effects of all associations  
391 involving more than two loci. As shown by equation 11, associations  $\tilde{D}_{ij}$ ,  $\tilde{D}_{i,j}$  (between  
392 alleles at loci  $i$  and  $j$ , either on the same or on different haplotypes) directly affect the  
393 genetic variance. At equilibrium, these associations are approximately given by:

$$\tilde{D}_{ij} \approx \frac{1}{1-F} \left( \frac{1}{\rho_{ij}} + 2F \right) \Delta_{\text{sel}} \tilde{D}_{ij} \quad (30)$$

394

$$\tilde{D}_{i,j} \approx \frac{F}{1-F} \left( \frac{1}{\rho_{ij}} + 2 \right) \Delta_{\text{sel}} \tilde{D}_{i,j}, \quad (31)$$

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

$$\Delta_{\text{sel}} \tilde{D}_{ij} \approx - \frac{\sum_{\alpha=1}^n r_{\alpha i} r_{\alpha j}}{V_s} [(1+F)^2 + G_{ij}] p_i q_i p_j q_j. \quad (32)$$

397 The term  $G_{ij}$  in equation 32 represents the identity disequilibrium between loci  $i$   
398 and  $j$ : the correlation in identity by descent between loci, generating a correlation  
399 in homozygosity (Weir and Cockerham, 1973, Supplementary File S1). Equation 32  
400 shows that stabilizing selection generates a positive association between alleles at loci

401  $i$  and  $j$  that tends to displace phenotypes in opposite directions (allele 1 with allele  
402 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  
403 locus  $i$  is then partially compensated by its associated allele at locus  $j$  (e.g., Bulmer,  
404 1974; Lande, 1976; Turelli and Barton, 1990). This effect of selection is strengthened  
405 by homozygosity (and correlations in homozygosity between loci) caused by selfing.  
406 As may be seen from equations 30 and 31,  $\tilde{D}_{i,j} \approx F \tilde{D}_{ij}$  when loci are tightly linked  
407 ( $\rho_{ij} \ll 1$ ), as expected from separation of timescales arguments (e.g., Nordborg, 1997;  
408 Roze, 2016). However, our approximations diverge as recombination tends to zero (or  
409 as the selfing rate tends to 1), due to the assumption that genetic associations remain  
410 weak.

411 We show in Supplementary File S1 how  $\tilde{D}_{ij}$  and  $\tilde{D}_{i,j}$  can be summed over all  
412 pairs of loci in order to compute their overall direct effect on the genetic variance (sec-  
413 ond term of equation 11). These associations depend on recombination rates through  
414 the terms in  $1/\rho_{ij}$  in equations 30 and 31, and also through the identity disequilibrium  
415  $G_{ij}$  in equation 32. However, because  $G_{ij}$  only weakly depends on the recombination  
416 rate, its average over all pairs of loci is often very close to the value obtained under  
417 free recombination, provided that the genome map length is not too small (see Sup-  
418 plementary Figure S5). In the following, we thus approximate  $G_{ij}$  by its expression  
419 for freely recombining loci, denoted  $G$ :

$$G = \frac{4\sigma(1-\sigma)}{(4-\sigma)(2-\sigma)^2}. \quad (33)$$

420 By contrast, linkage has more effect on the average of  $1/\rho_{ij}$  over all pairs of loci,  
421 corresponding to the inverse of the harmonic mean recombination rate between all  
422 pairs of loci (denoted  $\rho_H$  thereafter). Assuming that the number of loci is large,



423 one obtains for the direct effect of linkage disequilibria on the genetic variance (see  
424 Supplementary File S1):

$$2 \sum_{i,j \neq i} r_{\alpha i} r_{\alpha j} (\tilde{D}_{ij} + \tilde{D}_{i,j}) \approx -\frac{2}{V_s} \frac{2 + \sigma}{(1 - \sigma)(2 - \sigma)(4 - \sigma)} \left[ \frac{1}{\rho_H} + 2\sigma \right] (V_{g,\alpha}^0)^2 \quad (34)$$

425 where the genic variance  $V_{g,\alpha}^0$  may be replaced by its expression to leading order, given  
426 by equation 21. Equation 34 shows that the immediate effect of associations between  
427 alleles with compensatory phenotypic effects is to reduce the genetic variance (since this  
428 term is negative). The fraction in equation 34 is an increasing function of  $\sigma$ , which  
429 implies that self-fertilization increases the strength of associations, thus decreasing  
430  $V_{g,\alpha}$ . However, because the genic variance is expected to decrease with  $\sigma$  (equation  
431 21), the direct effect of linkage disequilibria on  $V_{g,\alpha}$  may remain approximately constant  
432 (or even slightly decrease) as  $\sigma$  increases from zero.

433 Associations between loci do not only affect  $V_{g,\alpha}$  through equation 34, however,  
434 but also affect the equilibrium allele frequencies and the excess homozygosity  $D_{i,i}$   
435 at each locus. The effect on  $D_{i,i}$  is mainly driven by identity disequilibria: indeed,  
436 neglecting associations between 3 or more loci, one obtains (see Supplementary File  
437 S1):

$$D_{i,i} \approx F \left[ 1 - 2 \sum_{j \neq i} s_j G_{ij} p_j q_j \right] p_i q_i. \quad (35)$$

438 Equation 35 is equivalent to equation 5 in Roze (2015) (which is expressed to the first  
439 order in  $p_j$ ), as can be noted by replacing  $s$  and  $h$  in Roze (2015) by  $4s_j$  and  $1/4$ . It  
440 shows that identity disequilibria reduce the excess homozygosity at each locus: this  
441 is due to the fact that homozygotes at locus  $i$  are more likely to be also homozygous  
442 at locus  $j$ , while homozygotes at locus  $j$  have a lower fitness than heterozygotes when  
443 deleterious alleles are partially recessive. Identity disequilibria thus tend to reduce

444 the genetic variance through this effect on  $D_{i,i}$ , by an amount corresponding to the  
 445 sum of the term in  $G_{ij}$  in equation 35 over all pairs of loci. Approximating  $G_{ij}$  by its  
 446 expression for freely recombining loci (equation 33), one obtains that this effect reduces  
 447  $V_{g,\alpha}$  by approximately  $-n F G (V_{g,\alpha}^0)^2 / (2V_s)$ , where again  $V_{g,\alpha}^0$  may be replaced by the  
 448 expression given by equation 21, to leading order (see Supplementary File S1).

449 Finally, associations between loci affect equilibrium allele frequencies ( $p_i q_i$ ) at  
 450 each locus. As shown in Supplementary File S1, both the linkage disequilibria gen-  
 451 erated by epistasis and the identity disequilibria caused by partial selfing reduce the  
 452 efficiency of purging, thereby increasing  $p_i q_i$  and thus the genic variance. Indeed,  
 453 an expression for the effect of selection on  $p_i q_i$  that includes the effects of pairwise  
 454 associations is, to leading order:

$$\begin{aligned} \Delta_{\text{sel}} p_i q_i \approx & -s_i (1 - 2p_i)^2 \left[ p_i q_i + 3D_{i,i} - 6(1 + F) \sum_{j \neq i} s_j G_{ij} p_i q_i p_j q_j \right] \\ & + 2(1 - 2p_i)^2 \sum_{j \neq i} a_{ij} \left[ (1 + 2F) \tilde{D}_{ij} + \tilde{D}_{i,j} \right. \\ & \left. + a_{ij} \frac{16(1 + \sigma)(2 + \sigma)}{(2 - \sigma)^2(4 - \sigma)} p_i q_i p_j q_j \right] \end{aligned} \quad (36)$$

455 with  $a_{ij} = -\sum_{\alpha} r_{\alpha i} r_{\alpha j} / (2V_s)$ , and where  $\tilde{D}_{ij}$ ,  $\tilde{D}_{i,j}$  and  $D_{i,i}$  are given by equations 30,  
 456 31 and 35. The first line of equation 36 is equivalent to equation 6 in Roze (2015),  
 457 showing that identity disequilibria reduce the efficiency of purging by decreasing the  
 458 excess homozygosity ( $D_{i,i}$ ), and by two additional effects represented by the term in  
 459  $6(1 + F)$  (see Roze (2015) for interpretation of these effects). The term on the second  
 460 and third lines (proportional to  $a_{ij}^2$ ) represents the effect of epistasis between loci: this  
 461 term also reduces purging, since selection against deleterious alleles is less efficient  
 462 when these alleles are partially compensated by alleles at other loci.

463 An expression for the genic variance at mutation-selection balance is given by

464 equation A65 in Supplementary File S1. From this, one obtains for the genetic variance:

$$V_{g,\alpha} = \frac{4V_s U}{n(1+\sigma)} \left[ 1 + 2U \frac{\sigma(1-\sigma)[6+\sigma(2-\sigma)]}{(2-\sigma)(4-\sigma)(1+\sigma)^2} + \frac{4U}{n} \frac{(2-\sigma)(2+\sigma)}{(1-\sigma)(4-\sigma)(1+\sigma)} \left( \frac{1}{2\rho_H} + \frac{2+\sigma(1-\sigma)(2-\sigma)}{2+\sigma(1-\sigma)} \right) \right] \quad (37)$$

465 where the terms in  $U$  between the brackets correspond to the effect of between-locus  
 466 associations. The first of these terms (on the first line of equation 37) represents the  
 467 effect of identity disequilibria, while the term in  $U/n$  on the second line represents  
 468 the effect of epistasis (compensatory effects between alleles at different loci). Both  
 469 terms are positive, indicating that the overall effect of interactions between loci is  
 470 to increase the genetic variance, due to the fact that correlations in homozygosity  
 471 and compensatory effects between mutations both reduce the efficiency of purging  
 472 (equation 36). Furthermore, while the effect of identity disequilibria scales with  $U$ , the  
 473 effect of epistasis scales with  $U/n$ : indeed, it becomes less and less likely that alleles  
 474 at different loci have compensatory effects on all of the traits as the dimensionality of  
 475 the fitness landscape increases. Finally, the effect of epistasis is more strongly affected  
 476 by linkage between loci (through the term in  $1/\rho_H$ ); the effect of linkage on the term  
 477 in  $U$  representing the effect of linkage disequilibria is weaker, and has been neglected  
 478 in equation 37. Under random mating ( $\sigma = 0$ ), equation 37 simplifies to:

$$V_{g,\alpha} = \frac{4V_s U}{n} \left[ 1 + \frac{2U}{n} \left( \frac{1}{\rho_H} + 2 \right) \right] \quad (38)$$

479 which takes a similar form as equation 4.16 in Turelli and Barton (1990) in the case of  
 480 a single selected trait ( $n = 1$ ). Supplementary Figure S6 shows how the equilibrium  
 481 genetic variance and its different components vary with the selfing rate, in a regime  
 482 where both identity disequilibria and epistasis have significant effects ( $U = 1$ ).

483 Assuming that  $\overline{W} \approx e^{\overline{\log W_g}}$ , an approximation for the load at mutation-selection  
 484 balance is  $1 - \exp[-n V_g / (2V_s)]$ , where  $V_g$  is the genetic variance given by equation  
 485 37 (the same for all traits). A slightly better approximation can be obtained by using  
 486  $\overline{W} \approx e^{\overline{\log W_g}} (1 + \frac{1}{2} \text{Var}[\log W_g])$ , where  $\text{Var}[\log W_g]$  is the variance in log fitness in the  
 487 population (Roze, 2015). To leading order, it is given by (see Supplementary File S1):

$$\text{Var}[\log W_g] \approx 2\bar{s}U \frac{1+3\sigma}{1+\sigma} + 4U^2 \frac{\sigma(1-\sigma)}{(4-\sigma)(1+\sigma)^2} + \frac{8U^2}{n} \frac{(2-\sigma)(2+\sigma)}{(4-\sigma)(1+\sigma)^2}, \quad (39)$$

488 simplifying to  $2U(\bar{s} + 4U/n)$  in the absence of selfing. The first term of equation 39  
 489 represents the sum of single-locus contributions to the variance in log fitness, while the  
 490 second and third term correspond to the effects of identity disequilibria and epistasis  
 491 (respectively), both increasing the variance in fitness. The mutation load is then given  
 492 by:

$$L \approx 1 - \left(1 + \frac{1}{2} \text{Var}[\log W_g]\right) \exp\left[-\frac{nV_g}{2V_s}\right]. \quad (40)$$

493 Similarly, we show in Supplementary File S1 that an expression for inbreeding depres-  
 494 sion including the effects of pairwise associations between loci is:

$$\delta \approx 1 - \left(1 + \frac{1}{2} \Delta \text{Var}[\log W_g]\right) \exp\left[-\frac{nV_g}{4V_s}\right] \quad (41)$$

495 where  $\Delta \text{Var}[\log W_g]$  is the difference in variance in log fitness between selfed and  
 496 outcrossed offspring, given by:

$$\Delta \text{Var}[\log W_g] \approx \frac{7\bar{s}U}{1+\sigma} + U^2 \frac{\sigma(1-\sigma)}{(4-\sigma)(1+\sigma)^2} + \frac{2U^2}{n} \frac{(10-\sigma)(2-\sigma)}{(4-\sigma)(1+\sigma)^2} \quad (42)$$

497 (the terms in  $\text{Var}[\log W_g]$  and  $\Delta \text{Var}[\log W_g]$  in equations 40 and 41 are often small,  
 498 however, and may thus be neglected). After replacing  $V_g$ ,  $\text{Var}[\log W_g]$  and  $\Delta \text{Var}[\log W_g]$   
 499 by the expressions given by equations 37, 39 and 42, the approximations obtained for

500 the load and inbreeding depression include terms in  $U^2$  representing the effect of iden-  
501 tity disequilibria, and terms in  $U^2/n$  representing the effect of epistasis between loci.  
502 The terms in  $U^2$  are identical to the terms representing the effect of identity disequi-  
503 libria in a model with purely multiplicative selection against deleterious alleles (no  
504 epistasis) when setting the dominance coefficient  $h$  of deleterious alleles to  $1/4$  (equa-  
505 tions 11 and 14 in Roze, 2015). The novelty here thus corresponds to the effect of  
506 epistasis (compensatory effects between deleterious alleles), that tends to increase  $V_g$ ,  
507  $L$ ,  $\delta$  by reducing the efficiency of purging.

508 Figure 3B shows that equations 37, 39 and 40 capture the increase in load ob-  
509 served in the simulations as the number of traits  $n$  decreases (see Supplementary Figure  
510 S7 for the genetic variance and inbreeding depression). Note that the harmonic mean  
511 recombination rate  $\rho_H$  between pairs of loci under our simulated genetic architecture  
512 (linear chromosome with equally spaced loci) can be obtained from:

$$\frac{1}{\rho_H} = \frac{2}{\ell(\ell-1)} \sum_{i=1}^{\ell-1} \frac{2(\ell-i)}{1 - \exp\left[-2i\frac{R}{\ell-1}\right]} \quad (43)$$

513 (see Appendix 2 in Roze and Blanckaert, 2014), yielding  $\rho_H \approx 0.42$  for  $\ell = 1,000$  and  
514  $R = 20$ . Figure 4 shows that for low or moderate selfing rates, decreasing the genome  
515 map length from  $R = 20$  to  $R = 1$  increases the mutation load, by increasing the  
516 strength of linkage disequilibria caused by epistasis, that in turn reduce the efficiency  
517 of purging. In this regime, equations 37, 39 and 40 provide an accurate prediction for  
518 the load (see Supplementary Figure S8 for genetic variance and inbreeding depression).  
519 At high selfing rates, however, a different regime is entered, in which the assumption  
520 of weak genetic associations breaks down. As can be seen in Figure 4, in this regime  
521 (which spans a broader parameter range under tighter linkage) the load decreases more

522 rapidly as  $\sigma$  increases. Increasing linkage tends to reduce the mutation load when the  
523 selfing rate is high, although the effect of  $R$  vanishes when  $\sigma = 1$ . When linkage is  
524 extremely tight, the approximations given above break down for all values of  $\sigma$ : as  
525 shown by Figures 4 and S8, decreasing  $R$  has a non-monotonic effect on the genetic  
526 variance, load and inbreeding depression when selfing is small to moderate, the lowest  
527 values of  $V_g$ ,  $L$  and  $\delta$  being reached when  $R = 0$  (in which case selfing has no effect).  
528 An approximation for the genetic variance under complete linkage can be obtained by  
529 treating the whole genome as a single locus with a very large number of possible alleles,  
530 and assuming a Gaussian distribution of allelic effects in the population (Lande, 1977;  
531 Supplementary File S4). This yields:

$$\frac{V_g}{2V_s} \approx 2\sqrt{\frac{\bar{s}U}{2n} \frac{2}{2 + \sigma(1 - \sigma)}}, \quad (44)$$

532

$$L \approx 1 - \exp\left[-\frac{nV_g}{2V_s}\right], \quad \delta \approx 1 - \exp\left[-\frac{nV_g}{4V_s}\right]. \quad (45)$$

533 Note that equation 44 is equivalent to equation 3A in Charlesworth and Charlesworth  
534 (1995) when  $\sigma = 1$  and  $n = 1$ . As shown by Figures 4 and S8, equations 44 and 45  
535 only slightly overestimate  $V_g$ ,  $L$  and  $\delta$  when  $\sigma = 1$  and/or  $R = 0$ . As shown below,  
536 better predictions are observed for higher values of  $U/n$  and lower values of  $\bar{s}$ .

537 The effects of identity disequilibria between loci remain negligible for the pa-  
538 rameter values used in Figures 3 and 4. As shown by Figure 5, identity disequilibria  
539 become more important for higher values of the mutation rate  $U$ . Indeed, the relative  
540 effects of identity disequilibria on the load can be deduced from the differences be-  
541 tween the three curves in each panel of Figure 5, the red curves showing the predicted  
542 mutation load in the absence of epistasis, but taking into account identity disequilibria  
543 (obtained by removing the terms in  $U^2/n$  from equations 37, 39 and 40, leading to an

544 expression equivalent to equation 11 in Roze, 2015). The difference between the black  
545 and red curves thus represents the predicted effect of identity disequilibria on the load,  
546 while the difference between the red and green curves corresponds to the additional  
547 effect of epistasis. Simulations indicate that the change in regime observed above a  
548 threshold selfing rate (around  $\sigma = 0.5$  for  $U = 1$  in Figure 5) is due to epistasis, since  
549 this threshold is not observed in simulations without epistasis (red dots). Supplemen-  
550 tary Figure S9 shows that this threshold pattern is little affected by population size  
551  $N$ , as long as the effects of drift remain small. Similarly, the results only weakly de-  
552 pend on the number of loci  $\ell$ , as long as the mutation rate per locus  $u = U/\ell$  is small  
553 enough so that  $p_i q_i < 1/4$  at most loci (see Supplementary Figure S10 for distribu-  
554 tions of allele frequencies in simulations with  $\ell = 1,000$  and  $\ell = 10,000$ ). Figure S9  
555 also shows that the results are little affected by the degree of pleiotropy of mutations  
556  $m$ , as long as  $\bar{s}$  remains constant. However,  $\bar{s}$  does affect  $V_g$ ,  $L$  and  $\delta$  in the regime  
557 where our approximations break down. As shown by Figure 6, decreasing  $\bar{s}$  lowers  
558 the threshold selfing rate above which our approximations are not valid and results in  
559 lower equilibrium mutation loads (see Supplementary Figure S11 for results on  $V_g$  and  
560  $\delta$ ). Figures 6 and S11 also show that, when  $\bar{s}$  is sufficiently small, the single-locus,  
561 Gaussian model (equations 44 and 45, dotted curves on the figures) provides accurate  
562 predictions for  $V_g$ ,  $L$  and  $\delta$  under complete selfing ( $\sigma = 1$ ).

563 In Figure 7 we show that decreasing the number of traits under selection  $n$   
564 decreases the threshold selfing rate above which our approximations break down (see  
565 Supplementary Figure S12 for inbreeding depression and scaled genetic variance). Be-  
566 low the threshold, the mutation load decreases as  $n$  increases, as predicted by our  
567 analytical results (although our approximations become less precise for low  $n$  and high

568  $U$ ), while  $n$  has the opposite effect above the threshold. Overall, we observe that in  
569 this second regime (in which interactions between loci have important effects), the  
570 mutation load generally increases with the number of selected traits, the fitness effects  
571 of mutations  $\bar{s}$ , the mutation rate  $U$  and recombination rate (through the parameter  
572  $R$ ). However, Figure 8 shows that the effects of these parameters on inbreeding de-  
573 pression are more complicated. In particular, outbreeding depression (negative  $\delta$ ) may  
574 occur in regimes where the effects of epistasis are particularly strong (high  $U$ , low  $n$ )  
575 and when the selfing rate is moderate to high (above 0.5 but below 1), outbreeding  
576 depression becoming stronger when  $\bar{s}$ ,  $U$  and  $R$  increase (the approximation derived  
577 from equation 37 fails for all values of  $\sigma$  for the parameter values used in Figure 8,  
578 and is not shown here). Supplementary Figures S13 and S14 show that for the same  
579 parameter values,  $V_g$  and  $L$  always increase when  $\bar{s}$ ,  $U$  and  $R$  increase.

580

## DISCUSSION

581 The response of a population to environmental change depends critically on its  
582 genetic diversity. Our results predict that the level of genetic variation maintained at  
583 equilibrium under stabilizing selection acting on quantitative traits is generally lower  
584 in more highly selfing population, due to more efficient purging (although increasing  
585 selfing may sometimes increase genetic variation, for example when mutations have  
586 weak fitness effects, as shown by Figure S3). This finding agrees with Charlesworth  
587 and Charlesworth's (1995) theoretical prediction that fully selfing populations should  
588 maintain lower genetic variance for quantitative traits under stabilizing selection than  
589 fully outcrossing ones, and with several empirical studies comparing levels of genetic



590 variation for morphological traits in closely related pairs of plant species with con-  
591 trasted mating systems (Charlesworth and Charlesworth, 1995; Geber and Griffen,  
592 2003; Bartkowska and Johnston, 2009 and references therein). We also show that the  
593 lower level of variation present in more highly selfing populations is associated with  
594 lower values of the mutation load and inbreeding depression. The meta-analysis carried  
595 out by Winn et al. (2011) showed that inbreeding depression is indeed lower in highly  
596 selfing plant species compared to species with lower selfing rates, while no significant  
597 difference is observed between species with low vs. intermediate selfing rates. It has  
598 been put forth that correlations in homozygosity between selected loci may suppress  
599 purging at moderate selfing rates (“selective interference”, Lande et al., 1994; Winn et  
600 al., 2011); this, however, would imply that a large number of segregating deleterious al-  
601 leles have very low dominance coefficients, generating very high inbreeding depression  
602 (Kelly, 2007; Roze, 2015), which seems unlikely. Another possible explanation for the  
603 lack of purging at intermediate selfing rates involves epistasis (compensatory effects  
604 between mutations coding for the same quantitative trait, Lande and Porcher, 2015).  
605 Our analysis of the effects of epistasis (under assumptions that differ from those made  
606 in Lande and Porcher’s model) shows that different regimes are possible, and outlines  
607 how the parameters affect transitions between these regimes.

608 In our model, the effect of epistasis on the equilibrium genetic variance  $V_g$  is  
609 inversely proportional to effective recombination rates between selected loci, and scales  
610 with  $U/n$  (where  $n$  is the number of selected traits and  $U$  the total mutation rate on  
611 those traits). Indeed,  $U/n$  determines the number of segregating “interacting” mu-  
612 tations, that is, mutations with epistatic fitness effects. As  $n$  tends to infinity, all  
613 mutations become orthogonal in phenotypic space (with independent fitness effects),

614 and our results converge to the results from previous population genetics models with-  
615 out epistasis (e.g., Charlesworth and Charlesworth, 1987; Roze, 2015). When  $U/n$   
616 is small and map length  $R$  is sufficiently large, associations between loci have little  
617 effect. Under Gaussian stabilizing selection ( $Q = 2$ ), the average coefficient of epista-  
618 sis between mutations (on fitness) is zero (Martin and Lenormand, 2006b) while the  
619 dominance coefficient of deleterious alleles (in an optimal genotype) is close to 0.25  
620 under the assumption of additive effects on phenotypes. In this case, we found that  
621 classical deterministic expressions based on single-locus models (hence neglecting the  
622 variance in epistatic interactions) provide accurate predictions for the mutation load  $L$   
623 and inbreeding depression  $\delta$ . Simple approximations are also obtained under the more  
624 general fitness function given by equation 15, confirming that the mutation load is an  
625 increasing function of the average coefficient of epistasis between mutations (Kimura  
626 and Maruyama, 1966; Kondrashov and Crow, 1988; Phillips et al., 2000; Roze and  
627 Blanckaert, 2014). Neglecting the effect of associations between loci also allowed us  
628 to explore the effects of drift using diffusion methods. As in previous studies (e.g.,  
629 Charlesworth, 2013; Roze and Blanckaert, 2014), we found that drift may lower the  
630 mutation load by reducing  $V_g$ . However, this result probably strongly depends on the  
631 assumption that mutations may increase or decrease phenotypic traits with the same  
632 probability (no mutational bias): indeed, previous works showed that drift may in-  
633 crease the load in the presence of a mutational bias by displacing mean phenotypes  
634 away from the optimum (Zhang and Hill, 2008; Charlesworth, 2013). Given that partial  
635 selfing reduces effective population size, it would be of interest to study the combined  
636 effects of drift and mutational bias in models with selfing.

637 The variance in epistasis has stronger effects as the  $U/n$  ratio increases and/or as

638 the effective recombination rate decreases (*i.e.* due to selfing). Our results showed that  
639 two different regimes are possible. (1) When genetic associations (linkage disequilibria)  
640 generated by epistasis stay moderate, the overall effect of epistasis is to increase  $V_g$ ,  $L$   
641 and  $\delta$  by decreasing the efficiency of selection against deleterious alleles. This regime  
642 is generally well described by our model taking into account the effects of associations  
643 between pairs of loci. This result bears some similarity with the result obtained by  
644 Phillips et al. (2000), showing that the variance in epistasis between deleterious alleles  
645 increases the mutation load. Equation 2.1 in Phillips et al. (2000) is not fully equivalent  
646 to our expression for the load under random mating, however, possibly due to different  
647 assumptions on the relative orders of magnitude of  $s_i$ ,  $s_j$  and  $e_{ij}$  (where  $s_i$  and  $s_j$  are  
648 the strength of selection at loci  $i$  and  $j$  and  $e_{ij}$  is epistasis between those loci) and  
649 how they covary. Nevertheless, it is interesting to note that both results become  
650 equivalent if  $\text{Var}[e_{ij}/(s_i s_j)]$  in Phillips et al. (2000) is replaced by  $\text{Var}[e_{ij}/\bar{s}^2]$  (where  
651  $\text{Var}$  stands for the variance across all pairs of loci), using the fact that  $\text{Var}[e_{ij}] = 4\bar{s}^2/n$   
652 in our model (with a Gaussian fitness function). (2) Increasing the value of  $U/n$   
653 and/or reducing effective recombination rates or  $\bar{s}$  generates a transition to a different  
654 regime in which the effect of the variance in epistasis switches, reducing  $V_g$ ,  $L$  and  $\delta$ .  
655 Because our analytical approach fails in this regime (presumably due to higher-order  
656 associations between loci), it is more difficult to obtain an intuitive understanding of  
657 the selective mechanisms involved. However, it is likely that selection operates on  
658 multilocus genotypes (comprising combinations of alleles with compensatory effects)  
659 that can be maintained over many generations due to high selfing rates and/or low  
660 recombination. A similar transition from genic to genotypic selection as recombination  
661 decreases was described by Neher and Shraiman (2009), using a haploid model in which

662 epistasis is randomly assigned to genotypes.

663         Although our results show some qualitative similarities with those obtained by  
664 Lande and Porcher (2015) — e.g., the same transition between regimes occurs in both  
665 models as selfing increases — several differences can be observed. In particular, Lande  
666 and Porcher’s model predict little or no effect of selfing on  $V_g$  below the threshold selfing  
667 rate corresponding to the change in regime, and an abrupt change in  $V_g$  at the threshold  
668 (except in their infinitesimal model). A step change such as this is never observed in  
669 our model, even for parameter values at which the effect of drift should be negligible  
670 at most loci. These differences between the models are not due to the different genetic  
671 architectures considered (biallelic vs. multiallelic): indeed, Supplementary Figures S15  
672 and S16 show that assuming biallelic loci or an infinite number of possible alleles per  
673 locus in our individual-based simulations yields very similar results (for  $\ell = 1,000$   
674 and  $\ell = 10,000$ ). Rather, they must be due to Lande and Porcher’s assumption of  
675 a Gaussian distribution of allelic effects maintained at each locus in each selfing age  
676 class, implicitly assuming a sufficiently high mutation rate per locus  $u$  and low fitness  
677 effect of mutations  $\bar{s}$  (Turelli, 1984). In our multiallelic simulations (with  $u = 10^{-5}$  to  
678  $10^{-3}$  and  $\bar{s} = 0.01$ ), the number of alleles maintained at each locus is not sufficiently  
679 large to generate a Gaussian distribution of segregating allelic effects (see Figures S15  
680 and S16). One may also note that the effect of the number of selected traits  $n$  seems  
681 different in both models (compare Lande and Porcher’s Figure 5 and 6 to our Figure  
682 7), but this is due to the fact that the overall mutation rate  $U$  is proportional to  $n$  in  
683 Lande and Porcher’s model (while  $U$  is fixed in Figure 7). Increasing both  $n$  and  $U$  in  
684 order to maintain a constant  $U/n$  ratio, we indeed observed that the transition between  
685 regimes occurs at lower selfing rates when  $n$  is larger, as in Lande and Porcher’s Figure

686 5 and 6 (results not shown). In general, whether  $U$  should scale with  $n$  depends on  
687 the degree of pleiotropy of mutations (Lande and Porcher assume no pleiotropy). Our  
688 model allowed us to explore the effects of pleiotropy through the parameter  $m$ , showing  
689 that pleiotropy mostly affects the results through its effect on  $\bar{s}$  (equation 14). The  
690 equilibrium genetic variance thus depends on  $m$  in regimes where  $V_g$  is affected by  $\bar{s}$ , in  
691 particular when  $N_e \bar{s} \approx 1$  or lower (Figures 1, S1 – S4), and when genetic associations  
692 are strong (Figure 6). However, pleiotropy may have stronger effects under different  
693 assumptions regarding the genetic architecture of traits, for example when different  
694 sets of traits are affected by different sets of loci (modular pleiotropy, Welch and  
695 Waxman, 2003). The effects of selective or mutational covariance among traits would  
696 also be interesting to explore: indeed, such covariances decrease the effective number of  
697 selected traits (Martin and Lenormand, 2006b), potentially increasing the importance  
698 of associations between loci.

699 In the regime where genetic associations generated by epistasis reduce  $V_g$  (regime  
700 (2) mentioned above), outbreeding depression may occur due to the lower fitness of  
701 recombinants between selfing lineages maintaining coadapted gene complexes (Figure  
702 8), a result shared with Lande and Porcher’s (2015) Gaussian Allele Model. In our  
703 additive model of phenotypic effects, outbreeding depression should only be expressed  
704 in F2 individuals (that is, among the offspring of an individual produced by a cross  
705 between different selfing lineages), once recombination has disrupted compensatory as-  
706 sociations between alleles at different loci. This explains why outbreeding depression is  
707 not observed under complete (or nearly complete) selfing in Figure 8, as all outcrossed  
708 individuals are F1 hybrids between selfing lineages. Outbreeding depression between  
709 lineages collected from the same geographical location has been observed in highly

710 selfing plants (Parker, 1992; Volis et al., 2011) and *Caenorhabditis* nematodes (Dolgin  
711 et al., 2007; Gimond et al., 2013). In all cases, estimated selfing rates are higher than  
712 those leading to  $\delta < 0$  in our simulations, however, and outbreeding depression was  
713 observed in F1 offspring of crosses between inbred lines of nematodes. The occurrence  
714 of outbreeding depression at higher selfing rates may be partly explained by the fact  
715 that experimental crosses were often performed between genetically different lines; by  
716 contrast, in our simulations the parents of an outcrossed individual may share the  
717 same genotype (in particular when the number of genetically different selfing lineages  
718 is reduced due to the low effective size of highly selfing populations), reducing the  
719 magnitude of outbreeding depression. However, the occurrence of outbreeding depres-  
720 sion in F1 individuals must involve dominance effects which are absent from our model.  
721 Exploring the effects of dominance/recessivity of mutations on phenotypic traits would  
722 be an interesting extension of this work.

723         Due to the lower genetic diversity of self-fertilizing populations, it has been  
724 suggested that they should be less able to adapt to a changing environment (e.g.,  
725 Stebbins, 1957; Williams, 1992; Takebayashi and Morrell, 2001). In the absence of  
726 epistasis, existing models indeed predict that selfing populations should have lower  
727 rates of adaptation than outcrossing ones (Glémin and Ronfort, 2013; Hartfield and  
728 Glémin, 2016). When compensatory effects between mutations are possible, however, a  
729 substantial amount of genetic variance may be hidden by genetic associations between  
730 loci in highly selfing populations (Lande and Porcher, 2015, the present study). After  
731 a change in environment, this variance may be liberated by rare outcrossing events,  
732 increasing the short-term evolutionary response of highly (but not fully) selfing popu-  
733 lations. Exploring how selfing affects adaptation under directional selection, and more

734 generally how the variability of epistatic interactions between loci may influence the  
735 evolution of mating systems represents a natural next step of this work.

736

737 **Acknowledgements.** We thank Aneil Agrawal, Patrice David, Sylvain Glémin,  
738 Frédéric Guillaume, Thomas Lenormand, Emmanuelle Porcher, Ophélie Ronce, Joëlle  
739 Ronfort and an anonymous reviewer for helpful discussions and comments, and the  
740 bioinformatics and computing service of Roscoff's Biological Station (Abims platform)  
741 for computing time. This work was supported by the French Agence Nationale de  
742 la Recherche (project SEAD, ANR-13-ADAP-0011 and project SexChange, ANR-14-  
743 CE02-0001).

744

## LITERATURE CITED

745 Bartkowska, M. P. and M. O. Johnston. 2009. Quantitative genetic variation in pop-  
746 ulations of *Amsinckia spectabilis* that differ in rate of self-fertilization. *Evolution*  
747 63:1103–1117.

748 Barton, N. H. 1986. The maintenance of polygenic variation through a balance between  
749 mutation and stabilizing selection. *Genet. Res.* 47:209–216.

750 ———. 1989. The divergence of a polygenic system subject to stabilizing selection,  
751 mutation and drift. *Genet. Res.* 54:59–77.

752 Brandvain, Y., T. Slotte, K. M. Hazzouri, S. I. Wright, and G. Coop. 2013. Ge-  
753 nomic identification of founding haplotypes reveals the history of the selfing species  
754 *Capsella rubella*. *PLoS Genetics* 9:e1003754.

755 Bulmer, M. G. 1971. The effect of selection on genetic variability. *Am. Nat.* 105:201–  
756 211.

757 ———. 1972. The genetic variability of polygenic characters under optimizing selec-  
758 tion, mutation and drift. *Genet. Res.* 19:17–25.

759 ———. 1974. Linkage disequilibrium and genetic variability. *Genet. Res.* 23:281–289.

760 ———. 1985. *The Mathematical Theory of Quantitative Genetics*, 2nd edition. Oxford  
761 University Press, Oxford.

762 Burgarella, C., P. Gayral, M. Ballenghien, A. Bernard, P. David, P. Jarne, A. Correa,  
763 S. Hurtrez-Boussès, J. Escobar, N. Galtier, and S. Glémin. 2015. Molecular evolution  
764 of freshwater snails with contrasting mating systems. *Mol. Biol. Evol.* 32:2403–2416.



765 Charlesworth, B. 2013. Why we are not dead one hundred times over. *Evolution*  
766 67:3354–3361.

767 Charlesworth, B., M. T. Morgan, and B. Charlesworth. 1990. Inbreeding depression,  
768 genetic load, and the evolution of outcrossing rates in a multilocus system with no  
769 linkage. *Evolution* 44:1469–1489.

770 Charlesworth, B., M. T. Morgan, and D. Charlesworth. 1991. Multilocus models of  
771 inbreeding depression with synergistic selection and partial self-fertilization. *Genet.*  
772 *Res.* 57:177–194.

773 Charlesworth, D. and B. Charlesworth. 1987. Inbreeding depression and its evolution-  
774 ary consequences. *Ann. Rev. Ecol. Syst.* 18:237–268.

775 ———. 1995. Quantitative genetics in plants: the effect of the breeding system on  
776 genetic variability. *Evolution* 49:911–920.

777 Chevin, L.-M., G. Martin, and T. Lenormand. 2010. Fisher’s model and the genomics  
778 of adaptation: restricted pleiotropy, heterogenous mutation, and parallel evolution.  
779 *Evolution* 64:3213–3221.

780 Dolgin, E. S., B. Charlesworth, S. E. Baird, and A. D. Cutter. 2007. Inbreeding and  
781 outbreeding depression in *Caenorhabditis* nematodes. *Evolution* 61:1339–1352.

782 Eyre-Walker, A. and P. D. Keightley. 2007. The ditribution of fitness effects of new  
783 mutations. *Nat. Rev. Genet.* 8:610–618.

784 Fisher, R. A. 1930. *The genetical theory of natural selection*. Clarendon Press, Oxford.

785 Geber, M. A. and L. R. Griffen. 2003. Inheritance and natural selection on functional  
786 traits. *Int. J. Plant Sci.* 164:S21–S42.

787 Gimond, C., R. Jovelin, S. Han, C. Ferrari, A. D. Cutter, and C. Braendle. 2013. Out-  
788 breeding depression with low genetic variation in selfing *Caenorhabditis* nematodes.  
789 *Evolution* 67:3087–3101.

790 Glémin, S. 2007. Mating systems and the efficacy of selection at the molecular level.  
791 *Genetics* 177:905–916.

792 Glémin, S. and J. Ronfort. 2013. Adaptation and maladaptation in selfing in outcross-  
793 ing species: new mutations versus standing variation. *Evolution* 67:225–240.

794 Goodwillie, C., S. Kalisz, and C. G. Eckert. 2005. The evolutionary enigma of mixed  
795 mating systems in plants: occurrence, theoretical explanations, and empirical evi-  
796 dence. *Ann. Rev. Ecol. Evol. Syst.* 36:47–79.

797 Gros, P.-A., H. Le Nagard, and O. Tenaillon. 2009. The evolution of epistasis and  
798 its links with genetic robustness, complexity and drift in a phenotypic model of  
799 adaptation. *Genetics* 182:277–293.

800 Haldane, J. B. S. 1937. The effect of variation on fitness. *Am. Nat.* 71:337–349.

801 Hartfield, M. 2015. Evolutionary genetic consequences of facultative sex and outcross-  
802 ing. *J. Evol. Biol.* 29:5–22.

803 Hartfield, M. and S. Glémin. 2016. Limits to adaptation in partially selfing species.  
804 *Genetics* 203:959–974.

- 805 Igic, B. and J. R. Kohn. 2006. The distribution of plant mating systems: study bias  
806 against obligately outcrossing species. *Evolution* 60:1098–1103.
- 807 Jarne, P. and J. R. Auld. 2006. Animals mix it up too: the distribution of self-  
808 fertilization among hermaphroditic animals. *Evolution* 60:1816–1824.
- 809 Kamran-Disfani, A. and A. F. Agrawal. 2014. Selfing, adaptation and background  
810 selection in finite populations. *J. Evol. Biol.* 27:1360–1371.
- 811 Kelly, J. K. 2007. Mutation-selection balance in mixed mating populations. *J. Theor.*  
812 *Biol.* 246:355–365.
- 813 Kimura, M. and T. Maruyama. 1966. The mutational load with epistatic gene inter-  
814 actions in fitness. *Genetics* 54:1337–1351.
- 815 Kirkpatrick, M., T. Johnson, and N. H. Barton. 2002. General models of multilocus  
816 evolution. *Genetics* 161:1727–1750.
- 817 Kondrashov, A. S. and J. F. Crow. 1988. King’s formula for the mutation load with  
818 epistasis. *Genetics* 120:853–856.
- 819 Lande, R. 1976. The maintenance of genetic variability by mutation in a polygenic  
820 character with linked loci. *Genet. Res.* 26:221–235.
- 821 ———. 1977. The influence of the mating system on the maintenance of genetic  
822 variability in polygenic characters. *Genetics* 86:485–498.
- 823 Lande, R. and E. Porcher. 2015. Maintenance of quantitative genetic variance un-  
824 der partial self-fertilization, with implications for the evolution of selfing. *Genetics*  
825 200:891–906.

- 826 Lande, R. and D. W. Schemske. 1985. The evolution of self-fertilization and inbreeding  
827 depression in plants. I. Genetic models. *Evolution* 39:24–40.
- 828 Lande, R., D. W. Schemske, and S. T. Schultz. 1994. High inbreeding depression,  
829 selective interference among loci, and the threshold selfing rate for purging recessive  
830 lethal mutations. *Evolution* 48:965–978.
- 831 Latter, B. D. H. 1960. Natural selection for an intermediate optimum. *Aust. J. Biol.*  
832 *Sci.* 13:30–35.
- 833 Lourenço, J., N. Galtier, and S. Glémin. 2011. Complexity, pleiotropy and the fitness  
834 effect of mutations. *Evolution* 65:1559–1571.
- 835 Manna, F., G. Martin, and T. Lenormand. 2011. Fitness landscapes: an alternative  
836 theory for the dominance of mutation. *Genetics* 189:923–937.
- 837 Martin, G., S. F. Elena, and T. Lenormand. 2007. Distributions of epistasis in microbes  
838 fit predictions from a fitness landscape model. *Nat. Genet.* 39:555–560.
- 839 Martin, G. and T. Lenormand. 2006a. The fitness effect of mutations across environ-  
840 ments: a survey in light of fitness landscape models. *Evolution* 60:2413–2427.
- 841 ———. 2006b. A general multivariate extension of Fisher’s geometrical model and the  
842 distribution of mutation fitness effects across species. *Evolution* 60:893–907.
- 843 Neher, R. A. and B. I. Shraiman. 2009. Competition between recombination and  
844 epistasis can cause a transition from allele to genotype selection. *Proc. Natl. Acad.*  
845 *Sci. U. S. A.* 106:6866–6871.

846 Nordborg, M. 1997. Structured coalescent processes on different time scales. *Genetics*  
847 146:1501–1514.

848 Parker, M. A. 1992. Outbreeding depression in a selfing annual. *Evolution* 46:837–841.

849 Phillips, P. C., S. P. Otto, and M. C. Whitlock. 2000. Beyond the average: the evolu-  
850 tionary importance of gene interactions and variability of epistatic effects. Pp. 20–38  
851 *in* J. B. Wolf, E. D. Brodie, and M. J. Wade, eds. *Epistasis and the Evolutionary*  
852 *Process*. Oxford University Press, New York.

853 Pollak, E. 1987. On the theory of partially inbreeding finite populations. I. Partial  
854 selfing. *Genetics* 117:353–360.

855 Roze, D. 2015. Effects of interference between selected loci on the mutation load,  
856 inbreeding depression and heterosis. *Genetics* 201:745–757.

857 ———. 2016. Background selection in partially selfing populations. *Genetics* 203:937–  
858 957.

859 Roze, D. and A. Blanckaert. 2014. Epistasis, pleiotropy and the mutation load in  
860 sexual and asexual populations. *Evolution* 68:137–149.

861 Scofield, D. G. and S. T. Schultz. 2006. Mitosis, stature and evolution of plant mating  
862 systems: low- $\Phi$  and high- $\Phi$  plants. *Proc. Roy. Soc. (Lond.) B* 273:275–282.

863 Stebbins, G. L. 1957. Self fertilization and population variability in higher plants. *Am.*  
864 *Nat.* 91:337–354.

865 Takebayashi, N. and P. L. Morrell. 2001. Is self-fertilization an evolutionary dead

866 end? Revisiting an old hypothesis with genetic theories and a macroevolutionary  
867 approach. *Am. J. Bot.* 88:1143–1150.

868 Tenaillon, O., O. K. Silander, J.-P. Uzan, and L. Chao. 2007. Quantifying organismal  
869 complexity using a population genetic approach. *PLoS One* 2:e217.

870 Turelli, M. 1984. Heritable genetic variation via mutation-selection balance: Lerch's  
871 zeta meets the abdominal bristle. *Theor. Popul. Biol.* 25:138–193.

872 Turelli, M. and N. H. Barton. 1990. Dynamics of polygenic characters under selection.  
873 *Theor. Popul. Biol.* 38:1–57.

874 Vitalis, R. and D. Couvet. 2001. Two-locus identity probabilities and identity disequi-  
875 librium in a partially selfing subdivided population. *Genet. Res.* 77:67–81.

876 Volis, S., I. Shulgina, M. Zaretsky, and O. Koren. 2011. Epistasis in natural populations  
877 of a predominantly selfing plant. *Heredity* 106:300–309.

878 Weir, B. S. and C. C. Cockerham. 1973. Mixed self and random mating at two loci.  
879 *Genet. Res.* 21:247–262.

880 Welch, J. J. and D. Waxman. 2003. Modularity and the cost of complexity. *Evolution*  
881 57:1723–1734.

882 Williams, G. C. 1992. *Natural Selection: Domains, Levels, and Challenges*. Oxford  
883 University Press, New York, NY.

884 Winn, A. A., E. Elle, S. Kalisz, P.-O. Cheptou, C. G. Eckert, C. Goodwillie, M. O.  
885 Johnston, D. A. Moeller, R. H. Ree, R. D. Sargent, and M. Vallejo-Marín. 2011.

886 Analysis of inbreeding depression in mixed-mating plants provides evidence for se-  
887 lective interference and stable mating systems. *Evolution* 65:3339–3359.

888 Wright, S. 1951. The genetical structure of populations. *Ann. Eugen.* 15:323–354.

889 Zhang, X.-S. and W. G. Hill. 2008. The anomalous effects of biased mutation revis-  
890 ited: mean-optimum deviation and apparent directional selection under stabilizing  
891 selection. *Genetics* 179:1135–1141.

892 **Table 1:** Parameters and variables of the model.

893

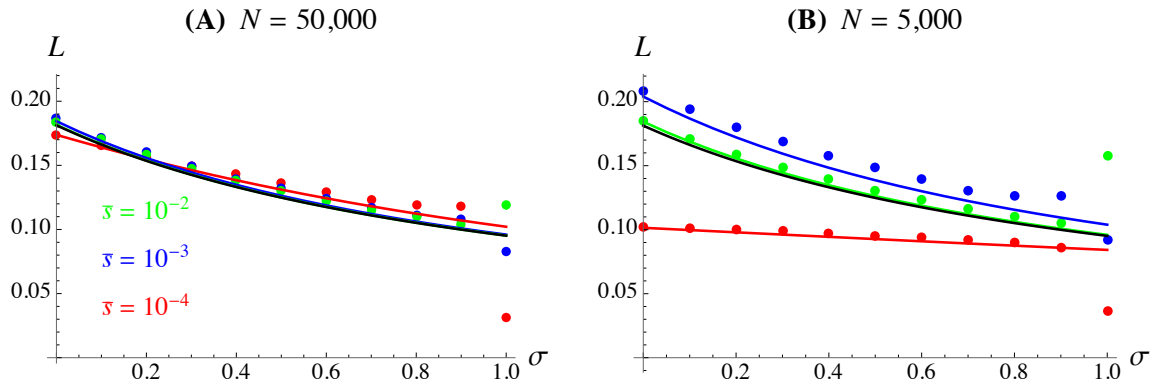
$N$	Population size
$\sigma$	Selfing rate
$n$	Number of selected traits
$m$	Degree of pleiotropy of mutations
$a^2$	Variance of mutational effects on selected traits
$V_e$	Environmental variance (on selected traits)
$\omega^2$	Strength of stabilizing selection on phenotypic traits
$V_s = \omega^2 + V_e$	Strength of stabilizing selection on breeding values $g_\alpha$
$Q$	Shape of the fitness peak (equation 15)
$\ell$	Number of loci affecting selected traits
$u$	Mutation rate per locus
$U = u\ell$	Mutation rate (per haploid genome) on loci affecting selected traits
$R$	Genome map length
$\rho_H$	Harmonic mean recombination rate between pairs of loci affecting selected traits
$\bar{s}$	Average heterozygous effect of mutations on log fitness (in an optimal genotype)
$z_\alpha$	Value of phenotypic trait $\alpha$ (in a given individual)
$g_\alpha, e_\alpha$	Genetic and environmental components of trait $\alpha$

894



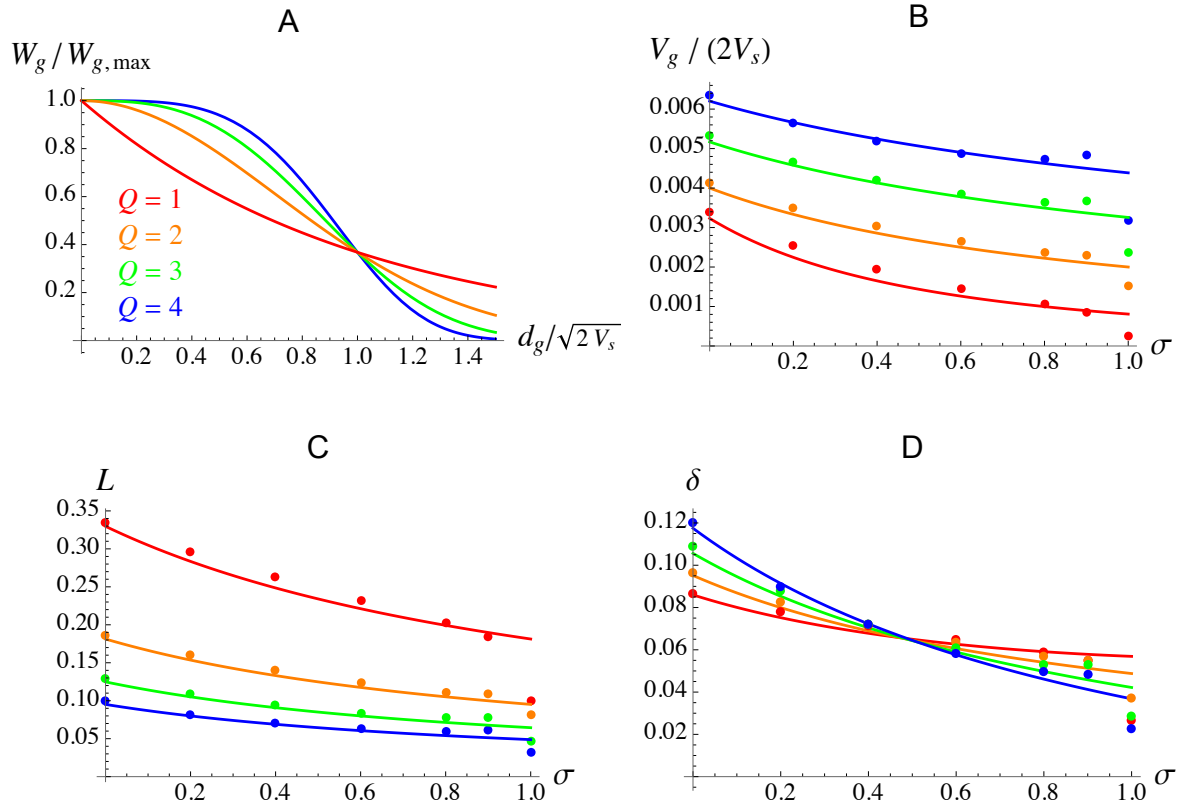
895

$r_{\alpha i}$	Effect of allele 1 at locus $i$ on trait $\alpha$
$p_i, q_i$	Frequencies of alleles 1 and 0 at locus $i$
$D_{i,i}$	Excess homozygosity at locus $i$
$\tilde{D}_{ij}$	Association between alleles 1 at loci $i$ and $j$ on the same haplotype (linkage disequilibrium)
$\tilde{D}_{i,j}$	Association between alleles 1 at loci $i$ and $j$ on different haplotypes
896 $V_{g,\alpha}$	Genetic variance for trait $\alpha$ (variance of $g_\alpha$ )
$V_{g,\alpha}^0$	Genic variance for trait $\alpha$ ( $2 \sum_i r_{\alpha i}^2 p_i q_i$ )
$F$	Inbreeding coefficient
$G_{ij}$	Identity disequilibrium between loci $i$ and $j$
$G$	Identity disequilibrium between freely recombining loci
$L$	Mutation load
$\delta$	Inbreeding depression



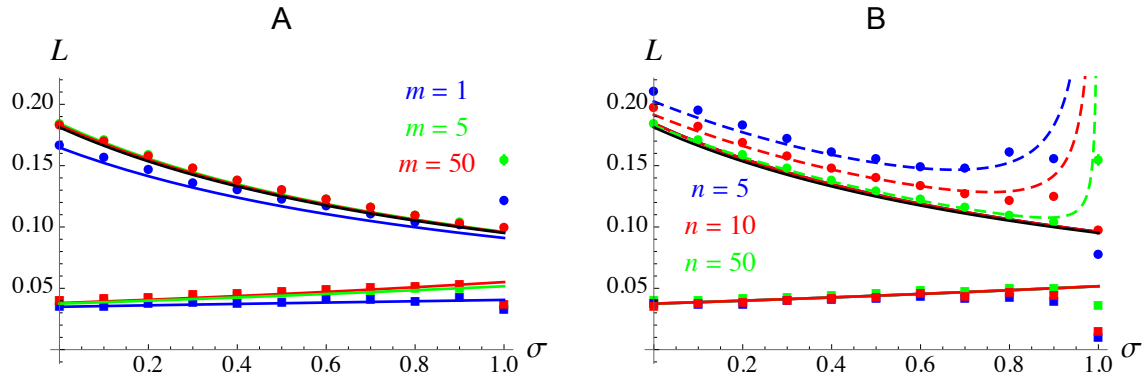
897

898 **Figure 1.** Mutation load  $L$  as a function of the selfing rate  $\sigma$ . Black curve: approx-  
899 imation for mutation-selection regime neglecting genetic associations (equation 24).  
900 The different colors correspond to different values of  $\bar{s}$  as shown in A. Colored solid  
901 curves: results from the diffusion model (Supplementary File S2). Dots correspond to  
902 simulation results; in this and the following figures, error bars (computed by splitting  
903 the last 70,000 generations into 7 batches of 10,000 generations and calculating the  
904 standard error over batches) are smaller than the size of symbols in most cases. Other  
905 parameter values are  $U = 0.1$ ,  $R = 20$ ,  $n = 50$ ,  $m = 5$ ,  $\ell = 10,000$ .



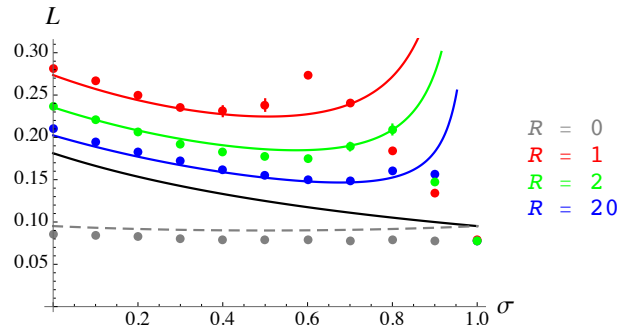
906

907 **Figure 2.** A: fitness as a function of the (scaled) distance from the optimum, for  
 908 different values of the parameter  $Q$  (from equation 15). B, C, D: scaled genetic vari-  
 909 ance, mutation load and inbreeding depression as a function of the selfing rate  $\sigma$ , for  
 910 different values of  $Q$ . The curves represent the analytical results (neglecting associa-  
 911 tions between loci) at mutation-selection balance (equations 27 – 29), while the dots  
 912 correspond to simulation results. Parameter values:  $N = 50,000$ ,  $\ell = 10,000$ ,  $U = 0.1$ ,  
 913  $R = 20$ ,  $n = 50$ ,  $m = 5$ ,  $a^2 / (2V_s) = 0.0002$  (yielding  $\bar{s} = 0.001$  for  $Q = 2$ ).



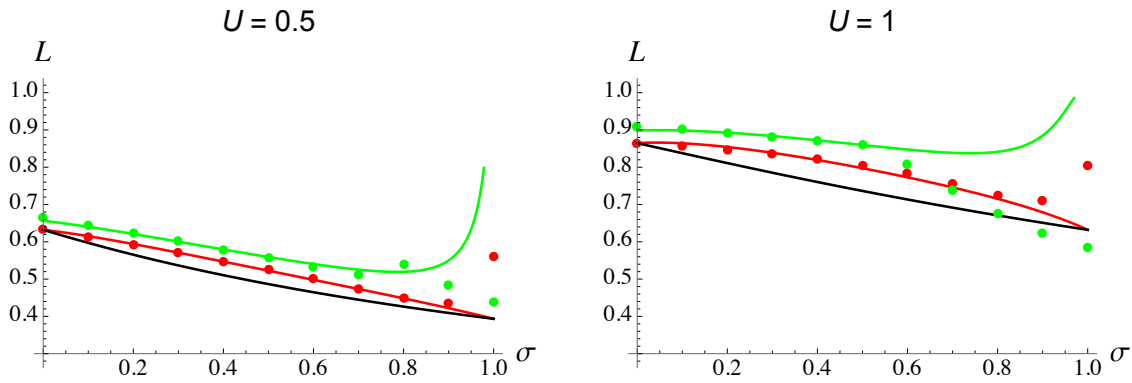
914

915 **Figure 3.** Mutation load  $L$  as a function of the selfing rate  $\sigma$  for  $\bar{s} = 10^{-2}$  (top, filled  
 916 circles) and  $\bar{s} = 10^{-4}$  (bottom, filled squares). A: the different colors correspond to  
 917 different values of  $m$  (degree of pleiotropy of mutations); B: the different colors corre-  
 918 spond to different values of  $n$  (number of selected traits). Black curve: approximation  
 919 for mutation-selection regime, neglecting genetic associations (equation 24). Colored  
 920 solid curves: results from the diffusion model (Supplementary File S2). Colored dashed  
 921 curves (in B): approximation including the effect of pairwise interactions among loci  
 922 (equations 37, 39 and 40). Other parameter values are  $U = 0.1$ ,  $R = 20$ ,  $N = 5,000$ ,  
 923  $\ell = 1,000$ ,  $n = 50$  (in A),  $m = 5$  (in B).



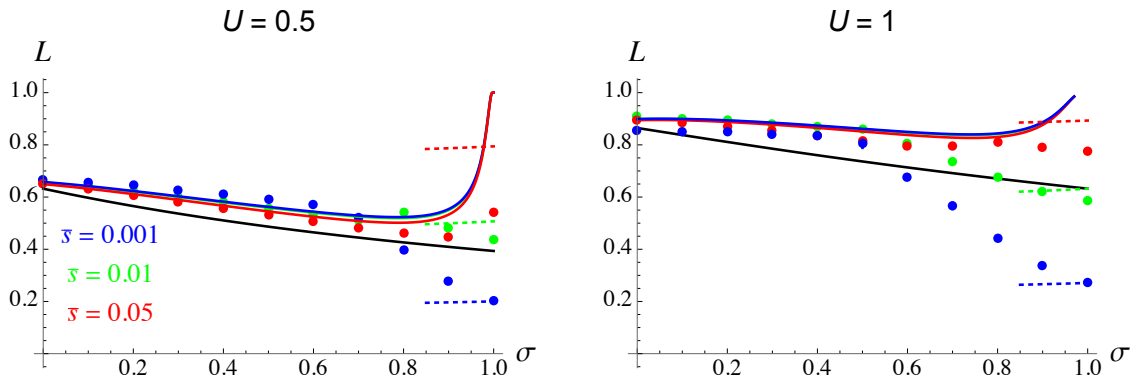
924

925 **Figure 4.** Mutation load  $L$  as a function of the selfing rate  $\sigma$ , for  $\bar{s} = 0.01$ ,  $n =$   
926  $m = 5$  and different values of the genome map length  $R$ , yielding (using equation 43)  
927  $\rho_H \approx 0.07, 0.13$  and  $0.42$  for  $R = 1, 2, 20$  (respectively). Dots: simulation results;  
928 black curve: approximation for mutation-selection regime neglecting genetic associ-  
929 ations (equation 24); colored curves: approximation including the effect of pairwise  
930 interactions among loci (equations 37, 39 and 40); dashed grey curve: single-locus  
931 model with many alleles, assuming a Gaussian distribution of allelic values (equations  
932 44 and 45). Other parameter values are as in Figure 3.



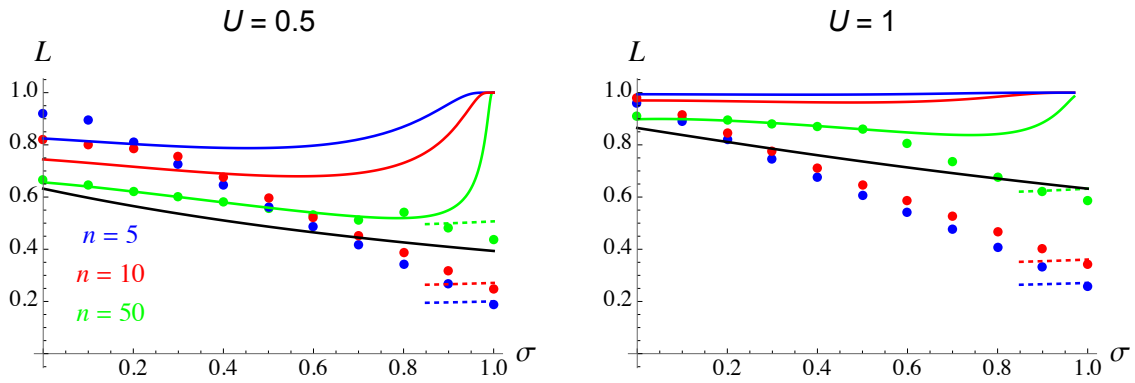
933

934 **Figure 5.** Mutation load  $L$  as a function of the selfing rate  $\sigma$ , for  $\bar{s} = 0.01$ ,  $n = 50$ ,  $m =$   
935  $5$ ,  $U = 0.5$  (left) and  $1$  (right). The black curves correspond to the approximation for  
936 mutation-selection regime, neglecting genetic associations (equation 24). Green curves:  
937 approximation including the effect of pairwise interactions among loci (equations 37,  
938 39 and 40); red curves: approximation including the effects of identity disequilibria  
939 between loci, but not the effects of epistasis (obtained by removing the terms in  $U^2/n$   
940 from equations 37, 39 and 40, equivalent to equation 11 in Roze, 2015). Green dots:  
941 simulation results; red dots: results from the simulation program used in Roze (2015)  
942 representing multiplicative selection (no epistasis), with  $s = 0.04$  and  $h = 0.25$ . Other  
943 parameter values are  $N = 5,000$ ,  $\ell = 10,000$ ,  $R = 20$  (yielding  $\rho_H \approx 0.38$ ).



944

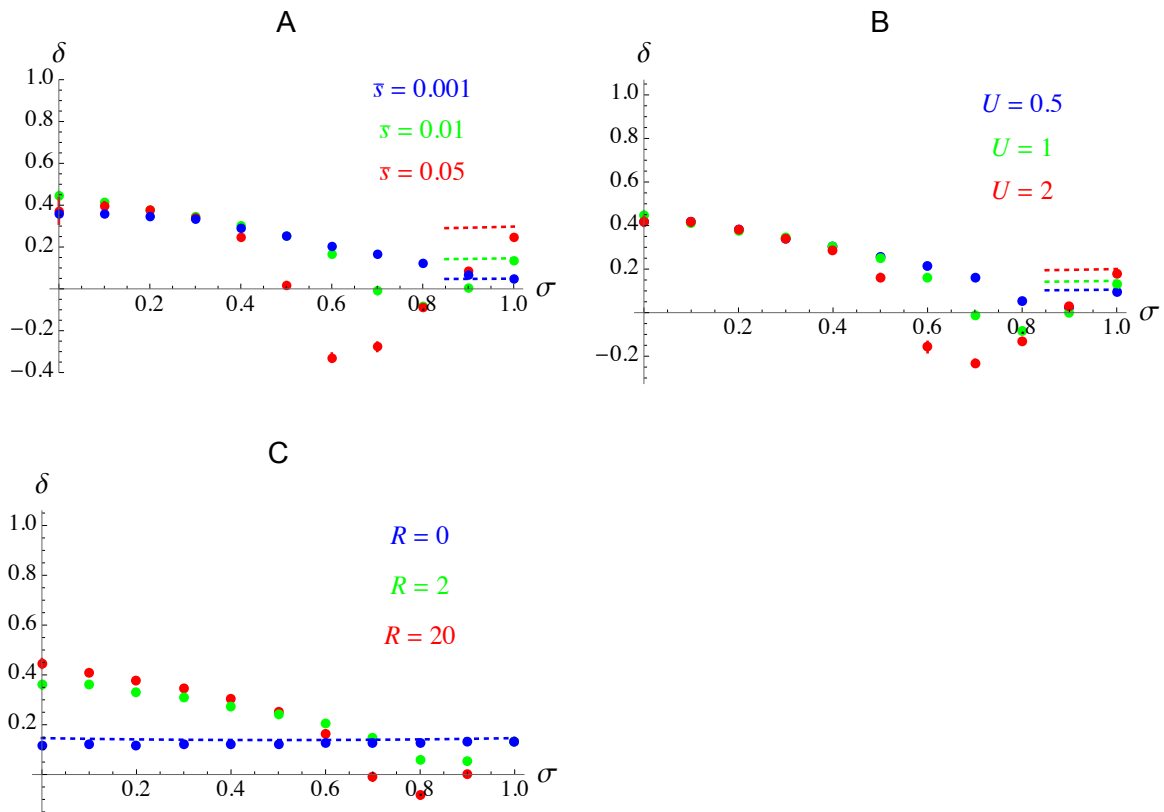
945 **Figure 6.** Mutation load  $L$  as a function of the selfing rate  $\sigma$ , for different values of the  
946 mutation rate  $U$  and average heterozygous effect of mutations  $\bar{s}$ ; other parameter values  
947 are as in Figure 5. Dots: simulation results; black curves: approximation for mutation-  
948 selection regime, neglecting genetic associations (equation 24); solid colored curves:  
949 approximation including the effect of pairwise interactions among loci (equations 37,  
950 39 and 40); dotted colored curves: single-locus model with many alleles, assuming a  
951 Gaussian distribution of allelic values (equations 44 and 45).



952

953 **Figure 7.** Mutation load  $L$  as a function of the selfing rate  $\sigma$ , for different values  
954 of the mutation rate  $U$  and number of selected traits  $n$ ; other parameter values are  
955 as in Figure 5. Dots: simulation results; black curves: approximation for mutation-  
956 selection regime, neglecting genetic associations (equation 24); solid colored curves:  
957 approximation including the effect of pairwise interactions among loci (equations 37,  
958 39 and 40); dotted colored curves: single-locus model with many alleles, assuming a  
959 Gaussian distribution of allelic values (equations 44 and 45).





960

961 **Figure 8.** Inbreeding depression  $\delta$  as a function of the selfing rate  $\sigma$ , for  $n = m = 5$   
 962 and different values of  $\bar{s}$  (A),  $U$  (B) and  $R$  (C). Dots: simulation results; dotted curves:  
 963 single-locus model with many alleles, assuming a Gaussian distribution of allelic values  
 964 (equations 44 and 45). Other parameter values are  $N = 5,000$ ,  $\ell = 10,000$ ,  $R = 20$ ,  
 965  $U = 1$  and  $\bar{s} = 0.01$ .