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Epistasis, inbreeding depression and the evolution of self-fertilization

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ABSTRACT

1
2 Inbreeding depression resulting from partially recessive deleterious alleles is
3 thought to be the main genetic factor preventing self-fertilizing mutants from spread-
4 ing in outcrossing hermaphroditic populations. However, deleterious alleles may also
5 generate an advantage to selfers in terms of more efficient purging, while the effects
6 of epistasis among those alleles on inbreeding depression and mating system evolution
7 remain little explored. In this paper, we use a general model of selection to disentangle
8 the effects of different forms of epistasis (additive-by-additive, additive-by-dominance
9 and dominance-by-dominance) on inbreeding depression and on the strength of se-
10 lection for selfing. Models with fixed epistasis across loci, and models of stabilizing
11 selection acting on quantitative traits (generating distributions of epistasis) are con-
12 sidered as special cases. Besides its effects on inbreeding depression, epistasis may
13 increase the purging advantage associated with selfing (when it is negative on aver-
14 age), while the variance in epistasis favors selfing through the generation of linkage
15 disequilibria that increase mean fitness. Approximations for the strengths of these
16 effects are derived, and compared with individual-based simulation results.

17

INTRODUCTION

18 Self-fertilization is a widespread mating system found in hermaphroditic plants
19 and animals (e.g., Jarne and Auld, 2006; Iqbal and Busch, 2013). In Angiosperms, the
20 transition from outcrossing to selfing occurred multiple times, leading to approximately
21 10–15% of species self-fertilizing at very high rates (Barrett et al., 2014). Two possible
22 benefits of selfing have been proposed to explain such transitions: the possibility for a
23 single individual to generate offspring in the absence of mating partner or pollinator
24 (“reproductive assurance”, Darwin, 1876; Stebbins, 1957; Porcher and Lande, 2005a;
25 Busch and Delph, 2012), and the “automatic advantage” stemming from the fact that,
26 in a population containing both selfers and outcrossers, selfers tend to transmit more
27 copies of their genome to the next generation if they continue to export pollen —
28 thus retaining the ability to sire outcrossed ovules (Fisher, 1941; Charlesworth, 1980;
29 Stone et al., 2014). The main evolutionary force thought to oppose the spread of self-
30 ing is inbreeding depression, the decreased fitness of inbred offspring resulting from
31 the expression of partially recessive deleterious alleles segregating within populations
32 (Charlesworth and Charlesworth, 1987). When selfers export as much pollen as out-
33 crossers (leading to a 50% transmission advantage for selfing), inbreeding depression
34 must be 0.5 to compensate for the automatic advantage of selfing (Lande and Schemske,
35 1985). However, observations from natural populations indicate that self-fertilizing in-
36 dividuals do not always export as much pollen as their outcrossing counterparts, as
37 some of their pollen production is used to fertilize their own ovules (see references
38 in Porcher and Lande, 2005a). This phenomenon, known as pollen discounting, de-
39 creases the automatic advantage of selfing (Nagyfalvi, 1976; Charlesworth, 1980), thus

40 reducing the threshold value of inbreeding depression above which outcrossing can be
41 maintained (e.g., Holsinger et al., 1984). It may also lead to evolutionarily stable
42 mixed mating systems (involving both selfing and outcrossing) under some models of
43 discounting such as the mass-action pollination model (Holsinger, 1991; Porcher and
44 Lande, 2005a).

45 Several models explored the evolution of mating systems while explicitly rep-
46 resenting the genetic architecture of inbreeding depression (e.g., Charlesworth et al.,
47 1990; Uyenoyama and Waller, 1991; Epinat and Lenormand, 2009; Porcher and Lande,
48 2005b; Gervais et al., 2014), and highlighted the importance of another genetic factor
49 (besides the automatic advantage and inbreeding depression) affecting the evolution of
50 selfing. This third factor stems from the fact that selection against deleterious alleles is
51 more efficient among selfed offspring (due to their increased homozygosity) than among
52 outcrossed offspring, generating positive linkage disequilibria between alleles increas-
53 ing the selfing rate and the better alleles at selected loci. Alleles increasing selfing thus
54 tend to be found on better purged genetic backgrounds, which may allow selfing to
55 spread even when inbreeding depression is higher than 0.5 (Charlesworth et al., 1990).
56 This effect becomes more important as the strength of selection against deleterious
57 alleles increases (so that purging occurs more rapidly), recombination decreases, and
58 as alleles increasing selfing have larger effects — so that linkage disequilibria can be
59 maintained over larger numbers of generations (Charlesworth et al., 1990; Uyenoyama
60 and Waller, 1991; Epinat and Lenormand, 2009). This corresponds to Lande and
61 Schemske’s (1985) verbal prediction that a mutant allele coding for complete selfing
62 may increase in frequency regardless of the amount of inbreeding depression.

63 Most genetic models on the evolution of selfing assume that deleterious alleles

64 have multiplicative effects (no epistasis). Charlesworth et al. (1991) considered a de-
65 terministic model including synergistic epistasis between deleterious alleles, showing
66 that this form of epistasis tends to flatten the relation between inbreeding depression
67 and the population's selfing rate, inbreeding depression sometimes increasing at high
68 selfing rates. Concerning the spread of selfing modifier alleles, the results were qual-
69 itatively similar to the multiplicative model, except that, for parameter values where
70 full outcrossing is not stable, the evolutionarily stable selfing rate tended to be slightly
71 below 1 under synergistic epistasis (whereas it would have been at exactly 1 in the
72 absence of epistasis). Other models explored the effect of partial selfing on inbreed-
73 ing depression generated by polygenic quantitative traits under stabilizing selection
74 (Lande and Porcher, 2015; Abu Awad and Roze, 2018). This type of model typically
75 generates distributions of epistatic interactions across loci, including possible compen-
76 satory effects between mutations. When effective recombination is sufficiently weak,
77 linkage disequilibria generated by epistasis may greatly reduce inbreeding depression,
78 and even generate outbreeding depression between selfing lineages carrying different
79 combinations of compensatory mutations. However, the evolution of the selfing rate
80 was not considered by these models.

81 In this paper, we use a general model of epistasis between pairs of selected loci
82 to explore the effects of epistasis on inbreeding depression and on the evolution of self-
83 ing. We derive analytical approximations showing that epistatic interactions affect the
84 spread of selfing modifiers through various mechanisms: by affecting inbreeding depres-
85 sion, the purging advantage of selfers and also through linkage disequilibria between
86 selected loci. Although the expressions obtained can become complicated for interme-
87 diate selfing rates, we will see that the condition determining whether selfing can spread

88 in a fully outcrossing population often remains relatively simple. Notably, our model
89 allows us to disentangle the effects of additive-by-additive, additive-by-dominance and
90 dominance-by-dominance epistatic interactions on inbreeding depression and selection
91 for selfing — while the models used by Charlesworth et al. (1991), Lande and Porcher
92 (2015) and Abu Awad and Roze (2018) impose certain relations between these quan-
93 tities. The cases of fixed, synergistic epistasis and of stabilizing selection acting on
94 quantitative traits (Fisher’s geometric model) will be considered as special cases, for
95 which we will also present individual-based simulation results. Overall, our results
96 show that, for a given level of inbreeding depression and average strength of selection
97 against deleterious alleles, epistatic interactions tend to facilitate the spread of selfing,
98 due to the fact that selfing can maintain beneficial combinations of alleles.

99 METHODS

100 **Life cycle.** Our analytical model represents an infinite, hermaphroditic population
101 with discrete generations. A proportion σ of ovules produced by a given individual
102 are self-fertilized, while its remaining ovules are fertilized by pollen sampled from the
103 population pollen pool (Table 1 provides a list of the symbols used throughout the
104 paper). A parameter κ represents the rate of pollen discounting: an individual with
105 selfing rate σ contributes to the pollen pool in proportion $1 - \kappa\sigma$ (e.g., Charlesworth,
106 1980). Therefore, κ equals 0 in the absence of pollen discounting, while κ equals 1
107 under full discounting (in which case complete selfers do not contribute to the pollen
108 pool). We assume that the selfing rate σ is genetically variable, and coded by ℓ_σ loci

109 with additive effects:

$$\sigma = \sum_{i=1}^{\ell_{\sigma}} (\sigma_i^{\text{M}} + \sigma_i^{\text{P}}) \quad (1)$$

110 where the sum is over all loci affecting the selfing rate, and where σ_i^{M} and σ_i^{P} represent
111 the effect of the alleles present respectively on the maternally and paternally inherited
112 genes at locus i (note that the assumption of additivity within and between loci may
113 not always hold, in particular when selfing rates are close to 0 or 1). The model does
114 not make any assumption concerning the number of alleles segregating at loci affecting
115 the selfing rate.

116 The fitness W of an organism is defined as its overall fecundity (that may depend
117 on its survival), so that the expected number of seeds produced by an individual is
118 proportional to W , while its contribution to the population pollen pool is proportional
119 to $W(1 - \kappa\sigma)$. We assume that W is affected by a possibly large number ℓ of biallelic
120 loci. Alleles at each of these loci are denoted 0 and 1; the quantity X_j^{M} (resp. X_j^{P})
121 equals 0 if the individual carries allele 0 on its maternally (resp. paternally) inherited
122 copy of locus j , and equals 1 otherwise. The frequencies of allele 1 at locus j on the
123 maternally and paternally inherited genes (averages of X_j^{M} and X_j^{P} over the whole
124 population) are denoted p_j^{M} and p_j^{P} . Finally, $p_j = (p_j^{\text{M}} + p_j^{\text{P}})/2$ is the frequency of
125 allele 1 at locus j in the whole population.

126 **Genetic associations.** Throughout the paper, index i will denote a locus affecting
127 the selfing rate of individuals, while indices j and k will denote loci affecting fitness.
128 Following Barton and Turelli (1991) and Kirkpatrick et al. (2002), we define the cen-
129 tered variables:

$$\zeta_i^{\text{M}} = \sigma_i^{\text{M}} - \overline{\sigma_i^{\text{M}}}, \quad \zeta_i^{\text{P}} = \sigma_i^{\text{P}} - \overline{\sigma_i^{\text{P}}}, \quad (2)$$

$$\zeta_j^M = X_j^M - p_j^M, \quad \zeta_j^P = X_j^P - p_j^P, \quad (3)$$

130 where $\overline{\sigma_i^M}$ and $\overline{\sigma_i^P}$ are the averages of σ_i^M and σ_i^P over the whole population. The
 131 genetic association between the sets \mathbb{U} and \mathbb{V} of loci present in the maternally and
 132 paternally derived genome of an individual is defined as:

$$D_{\mathbb{U},\mathbb{V}} = E[\zeta_{\mathbb{U},\mathbb{V}}] \quad (4)$$

133 where E stands for the average over all individuals in the population, and with:

$$\zeta_{\mathbb{U},\mathbb{V}} = \left(\prod_{x \in \mathbb{U}} \zeta_x^M \right) \left(\prod_{y \in \mathbb{V}} \zeta_y^P \right). \quad (5)$$

134 For example, $D_{j,j} = E[(X_j^M - p_j^M)(X_j^P - p_j^P)]$ is a measure of departure from Hardy-
 135 Weinberg equilibrium at locus j , while $D_{\emptyset,jk} = E[(X_j^P - p_j^P)(X_k^P - p_k^P)]$ measures the
 136 linkage disequilibrium between loci j and k on paternally derived haplotypes. Finally,
 137 $\tilde{D}_{\mathbb{U},\mathbb{V}}$ is defined as $(D_{\mathbb{U},\mathbb{V}} + D_{\mathbb{V},\mathbb{U}})/2$, and $\tilde{D}_{\mathbb{U},\emptyset}$ will be denoted $\tilde{D}_{\mathbb{U}}$.

138 Using these notations, the variance in selfing rate in the population can be
 139 written as:

$$V_\sigma = E \left[\left(\sum_i (\zeta_i^M + \zeta_i^P) \right)^2 \right]. \quad (6)$$

140 Ignoring genetic associations between different loci affecting the selfing rate, this be-
 141 comes:

$$V_\sigma \approx 2 \sum_i (\tilde{D}_{ii} + D_{i,i}). \quad (7)$$

142 **General expression for fitness, and special cases.** The fitness of an individual
 143 divided by the population mean fitness \overline{W} can be expressed in terms of “selection
 144 coefficients” $a_{\mathbb{U},\mathbb{V}}$ representing the effect of selection acting on the sets \mathbb{U} and \mathbb{V} of loci

145 (Barton and Turelli, 1991; Kirkpatrick et al., 2002):

$$\frac{W}{\overline{W}} = 1 + \sum_{\mathbb{U}, \mathbb{V}} a_{\mathbb{U}, \mathbb{V}} (\zeta_{\mathbb{U}, \mathbb{V}} - D_{\mathbb{U}, \mathbb{V}}). \quad (8)$$

146 Throughout the paper, we assume no effect of the sex-of-origin of genes on fitness, so
 147 that $a_{\mathbb{U}, \mathbb{V}} = a_{\mathbb{V}, \mathbb{U}}$. The coefficient $a_{j, \emptyset} = a_{\emptyset, j}$ will be denoted a_j and represents selection
 148 for allele 1 at locus j . The coefficient $a_{j, j}$ represents the effect of dominance at locus j ,
 149 while $a_{jk, \emptyset}$ and $a_{j, k}$ represent cis and trans epistasis between loci j and k . Coefficients
 150 $a_{jk, j}$ and $a_{jk, jk}$ respectively correspond to additive-by-dominance and dominance-by-
 151 dominance epistatic interactions between loci j and k , measured as deviations from
 152 additivity.

153 We will consider different examples of fitness functions (for which approximate
 154 expressions for $a_{\mathbb{U}, \mathbb{V}}$ coefficients are given in Supplementary File S1). The first corre-
 155 sponds to the case where allele 1 at each fitness locus j is deleterious, with selection
 156 and dominance coefficients s and h . Epistatic interactions occur between pairs of loci,
 157 and are decomposed into additive-by-additive (e_{axa}), additive-by-dominance (e_{axd}) and
 158 dominance-by-dominance (e_{dxd}) epistasis. We assume multiplicative effects of epistatic
 159 components on fitness W (*i.e.*, additive effects on $\log W$), so that:

$$W = (1 - hs)^{n_{\text{he}}} (1 - s)^{n_{\text{ho}}} (1 + e_{\text{axa}})^{n_2} (1 + e_{\text{axd}})^{n_3} (1 + e_{\text{dxd}})^{n_4} \quad (9)$$

160 where n_{he} and n_{ho} are the numbers of loci at which a deleterious allele is present in the
 161 heterozygous (n_{he}) or homozygous (n_{ho}) state, while n_2 , n_3 and n_4 are the numbers of
 162 interactions between 2, 3 and 4 deleterious alleles at two different loci, given by:

$$n_2 = \frac{1}{2} n_{\text{he}} (n_{\text{he}} - 1) + 2n_{\text{he}} n_{\text{ho}} + 2n_{\text{ho}} (n_{\text{ho}} - 1), \quad (10)$$

163

$$n_3 = n_{\text{he}} n_{\text{ho}} + 2n_{\text{ho}} (n_{\text{ho}} - 1), \quad (11)$$

164

$$n_4 = \frac{1}{2}n_{ho}(n_{ho} - 1). \quad (12)$$

165 Note that epistatic interactions are the same for all pairs of deleterious alleles. In
166 such models, with fixed epistasis and possibly large numbers of loci, combinations of
167 mutations quickly become advantageous when epistasis is positive, in which case they
168 go to fixation and polymorphism is not maintained. We therefore focused on cases
169 where e_{axa} , e_{axd} and e_{dxd} are negative. Charlesworth et al. (1991) explored the effect
170 of synergistic epistasis (measured by a parameter β) on inbreeding depression, using a
171 fitness function that imposes relations between h , e_{axa} , e_{axd} and e_{dxd} . As explained in
172 Supplementary File S1, their fitness function (equation 2 in Charlesworth et al., 1991)
173 is equivalent to setting $e_{axa} = -\beta h^2$, $e_{axd} = -\beta h(1 - 2h)$ and $e_{dxd} = -\beta(1 - 2h)^2$ in
174 our equation 9.

175 Our second fitness function corresponds to stabilizing selection acting on an
176 arbitrary number n of quantitative traits, with a symmetrical, Gaussian-shaped fitness
177 function. The general model is the same as in Abu Awad and Roze (2018): $r_{\alpha j}$ denotes
178 the effect of allele 1 at locus j on trait α , and we assume that the different loci have
179 additive effects on traits:

$$g_{\alpha} = \sum_j r_{\alpha j} (X_j^M + X_j^P) \quad (13)$$

180 where g_{α} is the value of trait α in a given individual (note that $g_{\alpha} = 0$ for all traits
181 in an individual carrying allele 0 at all loci). We assume that the values of $r_{\alpha j}$ for all
182 loci and traits are sampled from the same distribution with mean zero and variance
183 a^2 . The fitness of individuals is given by:

$$W = \exp\left[-\frac{\sum_{\alpha=1}^n g_{\alpha}^2}{2V_s}\right] \quad (14)$$

184 where V_s represents the strength of selection. According to equation 14, the optimal
185 value of each trait is zero. This model generates distributions of fitness effects of
186 mutations and of pairwise epistatic effects on fitness (the average value of epistasis
187 being zero), while deleterious alleles have a dominance coefficient close to 1/4 in an
188 optimal genotype (Martin and Lenormand, 2006b; Martin et al., 2007; Manna et al.,
189 2011).

190 The last fitness function we examined is a generalization of the fitness function
191 given by equation 14, in order to introduce a coefficient Q affecting the shape of the
192 fitness peak:

$$W = \exp \left[- \left(\frac{d}{\sqrt{2V_s}} \right)^Q \right], \quad (15)$$

193 where $d = \sqrt{\sum_{\alpha=1}^n g_{\alpha}^2}$ is the Euclidean distance from the optimum in phenotypic space
194 (e.g., Martin and Lenormand, 2006a; Tenailon et al., 2007; Roze and Blanckaert, 2014;
195 Abu Awad and Roze, 2018). The fitness function is thus Gaussian when $Q = 2$, while
196 $Q > 2$ leads to a flatter fitness peak around the optimum. As shown by Gros et
197 al. (2009), the value of Q affects the average value of epistasis (on fitness) between
198 mutations, which becomes negative when $Q > 2$.

199 **Quasi-linkage equilibrium (QLE) approximation.** Using the general expression
200 for fitness given by equation 8, the change in the mean selfing rate per generation can
201 be expressed in terms of genetic associations between loci affecting the selfing rate
202 and loci affecting fitness. Expressions for these associations can then be computed us-
203 ing general methods to derive recursions on allele frequencies and genetic associations
204 (Barton and Turelli, 1991; Kirkpatrick et al., 2002). For this, we decompose the life cy-
205 cle into two steps: selection corresponds to the differential contribution of individuals

206 due to differences in overall fecundity and/or survival rates (W), while reproduction
207 corresponds to gamete production and fertilization (involving either selfing or out-
208 crossing). Associations measured after selection (that is, weighting each parent by its
209 relative fitness) will be denoted $D'_{\text{U,V}}$, while associations after reproduction (among
210 offspring) will be denoted $D''_{\text{U,V}}$. Assuming that “effective recombination rates” (that
211 is, recombination rates multiplied by outcrossing rates) are sufficiently large relative to
212 the strength of selection, genetic associations equilibrate rapidly relative to the change
213 in allele frequencies due to selection. In that case, associations can be expressed in
214 terms of allele frequencies by computing their values at equilibrium, for given allele
215 frequencies (e.g., Barton and Turelli, 1991; Nagylaki, 1993). Note that when allele fre-
216 quencies at fitness loci have reached an equilibrium (for example, at mutation-selection
217 balance), one does not need to assume that the selection coefficients $a_{\text{U,V}}$ are small rela-
218 tive to effective recombination rates for the QLE approximation to hold, but only that
219 changes in allele frequencies due to the variation in the selfing rate between individuals
220 are small. We will thus assume that the variance in the selfing rate in the population
221 V_σ stays small (and therefore, the genetic variance contributed by each locus affecting
222 the selfing rate is also small), and compute expressions to the first order in V_σ . This
223 is equivalent to the assumption that alleles at modifier loci have small effects, as is
224 commonly assumed in modifier models.

225 **Individual-based simulations.** In order to verify our analytical results, individual-
226 based simulations were run using two C++ programs, one with uniformly deleterious
227 alleles with fixed epistatic effects (equation 9) and the other with stabilizing selection
228 on n quantitative traits (equation 14). Both are described in Supplementary File S5

229 (and are available from Dryad). Both programs represent a population of N diploid
230 individuals with discrete generations, the genome of each individual consisting of two
231 copies of a linear chromosome with map length R Morgans. In the first program (fixed
232 epistasis), deleterious alleles occur at rate U per haploid genome per generation at an
233 infinite number of possible sites along the chromosome. A locus with an infinite number
234 of possible alleles, located at the mid-point of the chromosome controls the selfing rate
235 of the individual (given by averaging the selfing rate coded by the two alleles at this
236 locus). In the program representing stabilizing selection, each chromosome carries ℓ
237 equidistant biallelic loci affecting the n traits under selection (as in Abu Awad and
238 Roze, 2018). The selfing rate is controlled by 10 additive loci evenly spaced over the
239 chromosome, each with an infinite number of possible alleles (the selfing rate being
240 set to zero if the sum of allelic values at these loci is negative, and one if the sum
241 is larger than one). In both programs, mutations affecting the selfing rate occur at
242 rate $U_{\text{self}} = 10^{-3}$ per generation, the value of each mutant allele at a selfing modifier
243 locus being drawn from a Gaussian distribution with standard deviation σ_{self} centered
244 on the allele value before mutation. The selfing rate is set to zero during an initial
245 burn-in period (set to 20,000 generations) after which mutations are introduced at
246 selfing modifier loci.

247

RESULTS

248 **Effects of epistasis on inbreeding depression.** We first explore the effects of
249 epistasis on inbreeding depression, assuming that the selfing rate is fixed. Throughout

250 the paper, inbreeding depression δ is classically defined as:

$$\delta = 1 - \frac{\overline{W}^{\text{self}}}{\overline{W}^{\text{out}}} \quad (16)$$

251 where $\overline{W}^{\text{self}}$ and $\overline{W}^{\text{out}}$ are the mean fitnesses of offspring produced by selfing and by
 252 outcrossing, respectively (e.g., Lande and Schemske, 1985). In Supplementary File
 253 S2, we show that a general expression for δ in terms of one- and two-locus selection
 254 coefficients, in a randomly mating population ($\sigma = 0$) is given by:

$$\delta \approx -\frac{1}{2} \sum_j a_{j,j} p_j q_j - \frac{1}{2} \sum_{j < k} a_{jk,jk} [1 - 2\rho_{jk} (1 - \rho_{jk})] p_j q_j p_k q_k - \sum_{j < k} c_{jk} \tilde{D}_{jk} \quad (17)$$

255 where the sums are over all loci affecting fitness, and with:

$$c_{jk} = a_{j,k} + [a_{jk,j} (1 - 2p_j) + a_{jk,k} (1 - 2p_k)] (1 - \rho_{jk}), \quad (18)$$

256 ρ_{jk} being the recombination rate between loci j and k . With arbitrary selfing, and
 257 assuming all $\rho_{jk} \approx 1/2$, equation 17 generalizes to:

$$\delta \approx -\frac{1}{2} \sum_j a_{j,j} (1 + F) p_j q_j - \frac{1}{4} \sum_{j < k} a_{jk,jk} [(1 + F)^2 + G_{jk}] p_j q_j p_k q_k \quad (19)$$

258 with several higher-order terms depending on genetic associations between loci gen-
 259 erated by epistatic interactions (\tilde{D}_{jk} , $\tilde{D}_{j,k}$, $\tilde{D}_{jk,j}$, see equation B17 in Supplementary
 260 File S2 for the complete expression). The term F in equation 19 corresponds to the
 261 inbreeding coefficient (probability of identity by descent between the maternal and
 262 paternal copy of a gene), given by:

$$F = \frac{\sigma}{2 - \sigma} \quad (20)$$

263 at equilibrium, while G_{jk} is the identity disequilibrium between loci j and k (Weir and
 264 Cockerham, 1973), given by:

$$G_{jk} = \phi_{jk} - F^2, \quad \text{with} \quad \phi_{jk} = \frac{\sigma}{2 - \sigma} \frac{2 - \sigma - 2(2 - 3\sigma) \rho_{jk} (1 - \rho_{jk})}{2 - \sigma [1 - 2\rho_{jk} (1 - \rho_{jk})]} \quad (21)$$

265 (ϕ_{jk} is the joint probability of identity by descent at loci j and k). Under free recom-
 266 bination ($\rho_{jk} = 1/2$), it simplifies to:

$$G_{jk} = \frac{4\sigma(1-\sigma)}{(4-\sigma)(2-\sigma)^2}, \quad (22)$$

267 which will be denoted G hereafter.

268 In the case of unconditionally deleterious alleles with fixed epistasis (equation
 269 9), equation 19 and the expressions for $a_{U,V}$ coefficients given in Supplementary File
 270 S1 yield:

$$\delta \approx 1 - \exp \left[-\frac{1}{2} [s(1-2h) - 2e_{\text{axd}} n_d] (1+F) n_d + \frac{e_{\text{dxd}}}{8} [(1+F)^2 + G] n_d^2 \right] \quad (23)$$

271 where $n_d = \sum_j p_j$ is the average number of deleterious alleles per haploid genome.
 272 Equation 23 assumes that deleterious alleles stay rare in the population (so that terms
 273 in p_j^2 may be neglected) and that the different terms of equation 19 contribute multi-
 274 plicatively to δ (which often yields better approximations than the additive expression).
 275 The equilibrium value of n_d can be obtained by solving

$$\Delta_{\text{sel}} n_d + U = 0 \quad (24)$$

276 where $\Delta_{\text{sel}} n_d = \sum_j \Delta_{\text{sel}} p_j$ is the change in n_d due to selection and U is the deleterious
 277 mutation rate per haploid genome. From equation B26 in Supplementary File S2, we
 278 have to the first order in the selection coefficients:

$$\begin{aligned} \Delta_{\text{sel}} p_j \approx & a_j (1+F) p_j + a_{j,j} F p_j + \sum_{k \neq j} a_{j,k,k} [F(1+F) + G_{jk}] p_j p_k \\ & + \sum_{k \neq j} a_{j,k,jk} [F^2 + G_{jk}] p_j p_k. \end{aligned} \quad (25)$$

279 Summing over loci and using the expressions for $a_{U,V}$ coefficients given in Supplemen-

280 tary File S1, one obtains:

$$\begin{aligned} \Delta_{\text{sel}} n_{\text{d}} \approx & -s [h + (1 - h) F] n_{\text{d}} + 2e_{\text{axa}} (1 + F) n_{\text{d}}^2 \\ & + e_{\text{axd}} [F (3 + F) + G] n_{\text{d}}^2 + e_{\text{dxd}} (F^2 + G) n_{\text{d}}^2 \end{aligned} \quad (26)$$

281 that can be used with equation 24 to obtain the equilibrium value of n_{d} . Equation
282 26 shows that, for non-random mating, negative values of e_{axa} , e_{axd} or e_{dxd} reduce
283 the mean number of deleterious alleles at equilibrium, thereby reducing inbreeding
284 depression (the effects of e_{axd} and e_{dxd} on the equilibrium value of n_{d} vanish when
285 mating is random, as $F = G = 0$ in this case). As shown by equation 23, negative
286 values of e_{axd} and e_{dxd} also directly increase inbreeding depression (even under random
287 mating), by decreasing the fitness of homozygous offspring. Figures 1A–C compare
288 the predictions obtained from equations 23 and 26 with simulation results, testing
289 the effect of each epistatic component separately. Negative e_{axa} reduces inbreeding
290 depression by lowering the frequency of deleterious alleles in the population (equation
291 26, Figure 1A); furthermore, it reduces the purging effect of selfing, so that inbreeding
292 depression may remain constant or even slightly increase as the selfing rate increases.
293 When the selfing rate is low, e_{axd} and e_{dxd} have little effect on the mean number of
294 deleterious alleles n_{d} , and the main effect of negative e_{axd} and e_{dxd} is to increase in-
295 breeding depression by decreasing the fitness of homozygous offspring (equation 23,
296 Figures 1B–C). As selfing increases, this effect becomes compensated by the enhanced
297 purging caused by negative e_{axd} and e_{dxd} (equation 26). Figure 1D shows the results
298 obtained using Charlesworth et al.’s (1991) fitness function, yielding $e_{\text{axa}} = -\beta h^2$,
299 $e_{\text{axd}} = -\beta h (1 - 2h)$ and $e_{\text{dxd}} = -\beta (1 - 2h)^2$. Remarkably, the increased purging
300 caused by negative epistasis almost exactly compensates the decreased fitness of ho-
301 mozygous offspring, so that inbreeding depression is only weakly affected by epistasis

302 in this particular model, for the parameter values used in Figure 1.

303 An expression for inbreeding depression under Gaussian stabilizing selection
304 (equation 14) is given in Abu Awad and Roze (2018). As shown in Supplementary
305 File S2, this expression can be recovered from our general expression for δ in terms of
306 $a_{U,V}$ coefficients. Because the average epistasis is zero under Gaussian selection (e.g.,
307 Martin et al., 2007), inbreeding depression is only affected by the variance in epista-
308 sis, whose main effect is to generate linkage disequilibria that increase the frequency
309 of deleterious alleles (see also Phillips et al., 2000) and thus increase δ . As shown
310 by Abu Awad and Roze (2018), a different regime is entered above a threshold selfing
311 rate when the mutation rate U is sufficiently large, in which epistatic interactions lower
312 inbreeding depression (see also Lande and Porcher, 2015). Selection coefficients $a_{U,V}$
313 under the more general fitness function given by equation 15 are derived in Supple-
314 mentary File S1, showing that a “flatter-than-Gaussian” fitness peak ($Q > 2$) generates
315 negative dominance-by-dominance epistasis ($a_{jk,jk} < 0$), increasing inbreeding depres-
316 sion (by contrast, the first term of equation 17 representing the effect of dominance
317 is not affected by Q). In the absence of selfing, and neglecting the effects of genetic
318 associations among loci, one obtains (see Supplementary File S2 for derivation):

$$\delta \approx 1 - \exp \left[-U \left(1 + \frac{Q-2}{8} \right) \right] \quad (27)$$

319 where the term in $(Q-2)/8$ is generated by the term in $a_{jk,jk}$ in equation 17. Although
320 this expression differs from equation 29 in Abu Awad and Roze (2018) — that was
321 obtained using a different method — both results are quantitatively very similar as
322 long as Q is not too large (roughly, $Q < 6$). Generalizations of equation 27 to arbitrary
323 σ , and including the effects of pairwise associations between loci (for $\sigma = 0$) are given

324 in Supplementary File S2 (equations B40 and B54).

325 **Evolution of selfing in the absence of epistasis.** In Supplementary File S3, we
326 derive an expression for the change in the mean selfing rate $\bar{\sigma}$ per generation, neglecting
327 the effects of epistatic interactions and associations between loci affecting fitness. This
328 expression can be decomposed into three terms:

$$\Delta\bar{\sigma} = \Delta_{\text{auto}}\bar{\sigma} + \Delta_{\text{depr}}\bar{\sigma} + \Delta_{\text{purge}}\bar{\sigma} \quad (28)$$

329 with:

$$\Delta_{\text{auto}}\bar{\sigma} \approx \frac{1 - \kappa}{1 - \kappa\bar{\sigma}} \frac{V'_{\sigma}}{2}, \quad (29)$$

330

$$\Delta_{\text{depr}}\bar{\sigma} = 2 \sum_{i,j} a_{j,j} \tilde{D}_{i,j,j}, \quad (30)$$

331

$$\Delta_{\text{purge}}\bar{\sigma} = 2 \sum_{i,j} a_j \left(\tilde{D}_{ij} + \tilde{D}_{i,j} \right) \quad (31)$$

332 where the sums are over all loci i affecting the selfing rate and all loci j affecting fitness.

333 The term $\Delta_{\text{auto}}\bar{\sigma}$ represents selection for increased selfing rates due to the automatic

334 transmission advantage associated with selfing (Fisher, 1941). It is proportional to

335 the variance in selfing rate after selection V'_{σ} , and vanishes when pollen discounting is

336 complete ($\kappa = 1$). The second term corresponds to the effect of inbreeding depression.

337 It depends on coefficients $a_{j,j}$ representing the effect of dominance at loci affecting

338 fitness; in particular, $a_{j,j} < 0$ when the average fitness of the two homozygotes at

339 locus j is lower than the fitness of heterozygotes (which is the case when the deleterious

340 allele at locus j is recessive or partially recessive). It also depends on associations $\tilde{D}_{i,j,j}$

341 that are shown to be positive at QLE, reflecting the fact that alleles increasing the

342 selfing rate tend to be present on more homozygous backgrounds. Finally, the last

343 term depends on coefficients a_j representing directional selection for allele 1 at locus

344 j , and associations \tilde{D}_{ij} and $\tilde{D}_{i,j}$ which are positive when alleles increasing the selfing
 345 rate at locus i tend to be associated with allele 1 at locus j , either on the same or
 346 on the other haplotype. This term is generally positive (favoring increased selfing
 347 rates), representing the fact that alleles coding for higher selfing increase the efficiency
 348 of selection at selected loci (by increasing homozygosity), and thus tend to be found
 349 on better purged genetic backgrounds, as explained in the Introduction (we show in
 350 Supplementary File S3 that \tilde{D}_{ij} and $\tilde{D}_{i,j}$ are also generated by other effects involving
 351 the identity disequilibrium between loci i and j , when $0 < \bar{\sigma} < 1$).

352 The variance in the selfing rate after selection V'_σ , and the associations $\tilde{D}_{ij,j}$,
 353 \tilde{D}_{ij} and $\tilde{D}_{i,j}$ can be expressed in terms of V_σ and of allele frequencies using the QLE
 354 approximation described in the Methods. The derivations and expressions obtained
 355 for arbitrary values of $\bar{\sigma}$ can be found in Supplementary File S3 (equations C31, C47,
 356 C48, C55 and C64), and generalize the results given by Epinat and Lenormand (2009)
 357 in the case of strong discounting ($\kappa \approx 1$). When the mean selfing rate in the population
 358 approaches zero, one obtains:

$$V'_\sigma \approx V_\sigma, \quad \tilde{D}_{ij,j} \approx \frac{1}{2} \tilde{D}_{ii} p_j q_j, \quad (32)$$

$$\tilde{D}_{ij} \approx \frac{1}{2} \frac{a_j + a_{j,j} (1 - 2p_j)}{\rho_{ij} - a_j (1 - 2p_j) (1 - \rho_{ij})} \tilde{D}_{ii} p_j q_j, \quad \tilde{D}_{i,j} \approx 0. \quad (33)$$

360 Using the fact that $V_\sigma = 2 \sum_i \tilde{D}_{ii}$ under random mating (equation 7), equations 29 –
 361 33 yield, for $\bar{\sigma} \approx 0$:

$$\Delta_{\text{auto}} \bar{\sigma} \approx \frac{1 - \kappa}{2} V_\sigma, \quad \Delta_{\text{depr}} \bar{\sigma} \approx -\delta V_\sigma, \quad (34)$$

362 where $\delta = - \left(\sum_j a_{j,j} p_j q_j \right) / 2$ is inbreeding depression, neglecting the effect of inter-
 363 actions between selected loci (see equation 17), while

$$\Delta_{\text{purge}} \bar{\sigma} \approx \sum_j \left[\mathcal{E} \left[\frac{1}{\rho_{ij} - a_j (1 - 2p_j) (1 - \rho_{ij})} \right] a_j [a_j + a_{j,j} (1 - 2p_j)] p_j q_j \right] \frac{V_\sigma}{2} \quad (35)$$

364 where the sum is over all loci j affecting fitness, and where \mathcal{E} is the average over all
365 loci i affecting the selfing rate. Because $\Delta_{\text{purge}}\bar{\sigma}$ is of second order in the selection
366 coefficients $(a_j, a_{j,j})$, it will generally be negligible relative to $\Delta_{\text{depr}}\bar{\sigma}$ (which is of first
367 order in $a_{j,j}$), in which case selfing can increase if $\delta < (1 - \kappa)/2$ (Charlesworth, 1980).
368 When $\bar{\sigma} > 0$, $\Delta_{\text{depr}}\bar{\sigma}$ is not simply given by δV_σ (in particular, it also depends on the
369 rate of pollen discounting and on identity disequilibria between loci affecting the selfing
370 rate and loci affecting fitness, as shown by equation C31 in Supplementary File S3),
371 but it is possible to show that $\Delta_{\text{depr}}\bar{\sigma}$ tends to decrease in magnitude as $\bar{\sigma}$ increases
372 (while $\Delta_{\text{auto}}\bar{\sigma}$ becomes stronger as $\bar{\sigma}$ increases), leading to the prediction that $\bar{\sigma} = 0$
373 and $\bar{\sigma} = 1$ should be the only evolutionarily stable selfing rates (Lande and Schemske,
374 1985).

375 As shown by equation 35, the relative importance of $\Delta_{\text{purge}}\bar{\sigma}$ should increase
376 when the strength of directional selection (a_j) increases, when deviations from addi-
377 tivity $(a_{j,j})$ are weaker and when linkage among loci is tighter. In the case where
378 allele 1 at each fitness locus is deleterious with selection and dominance coefficients s
379 and h (and assuming that $p_j \ll 1$) we have $a_j \approx -sh$ and $a_{j,j} \approx -s(1 - 2h)$, while
380 $p_j q_j \approx u/(sh)$ at mutation-selection balance (where u is the per locus mutation rate
381 towards allele 1). In that case, equation 35 simplifies to:

$$\Delta_{\text{purge}}\bar{\sigma} \approx \mathcal{E} \left[\frac{1}{\rho_{ij} + sh(1 - \rho_{ij})} \right] s(1 - h) U \frac{V_\sigma}{2} \quad (36)$$

382 where U is the deleterious mutation rate per haploid genome and \mathcal{E} is now the average
383 over all pairs of loci i and j . Figure 2A compares the prediction obtained from equa-
384 tions 34 and 36 with simulation results, in the absence of pollen discounting ($\kappa = 0$),
385 and when alleles affecting the selfing rate have weak effects ($\sigma_{\text{self}} = 0.01$). Simulations

386 confirm that selfing may evolve when inbreeding depression is higher than 0.5 (due to
387 the effect of $\Delta_{\text{purge}}\bar{\sigma}$), provided that the fitness effect of deleterious alleles is sufficiently
388 strong. The prediction for the case of unlinked loci (obtained by setting $\rho_{ij} = 0.5$ in
389 equation 36) actually gives a closer match to the simulation results than the result
390 obtained by integrating equation 36 over the genetic map. This may stem from the
391 fact that equation 36 overestimates the effect of tightly linked loci. The effect of the
392 size of mutational steps at the modifier locus does not affect the maximum value of
393 inbreeding depression for which selfing can spread, as long as mutations tend to have
394 small effects on the selfing rate (compare Figure 2A and 2B). However, the relative
395 effect of purging (observed for high values of s) becomes more important when selfing
396 evolves by mutations of larger size ($\sigma_{\text{self}} = 0.3$ in Figure 2C, while mutations directly
397 lead to fully selfing individuals in Figure 2D), in agreement with the results obtained
398 by Charlesworth et al. (1990) — note that our approximations break down when selfing
399 evolves by large-effect mutations.

400 In the case of multivariate Gaussian stabilizing selection acting on n traits
401 coded by biallelic loci with additive effects (equation 14) we have (to the first order
402 in the strength of selection $1/V_s$): $a_j = -\varsigma_j (1 - 2p_j)$ and $a_{j,j} = -2\varsigma_j$, where $\varsigma_j =$
403 $\sum_{\alpha=1}^n r_{\alpha j}^2 / (2V_s)$ is the fitness effect of a heterozygous mutation at locus j in an optimal
404 genotype. Assuming that polymorphism stays weak at loci coding for the traits under
405 stabilizing selection, so that $(1 - 2p_j)^2 \approx 1$, and using the fact that $p_j q_j \approx u/\varsigma_j$ under
406 random mating (when neglecting interactions between loci), one obtains from equation
407 35:

$$\Delta_{\text{purge}}\bar{\sigma} \approx \mathcal{E} \left[\frac{3\varsigma_j}{\rho_{ij} + \varsigma_j (1 - \rho_{ij})} \right] U \frac{V_\sigma}{2} \quad (37)$$

408 which is equivalent to equation 36 when introducing differences in s among loci, with

409 $h = 1/4$ (note that the homozygous effect of mutation at locus j in an optimal genotype
410 is $\approx 4\zeta_j$). When neglecting the term in ζ_j in the denominator of equation 37, this
411 simplifies to:

$$\Delta_{\text{purge}}\bar{\sigma} \approx \frac{3}{2} \frac{\bar{\zeta} U V_{\sigma}}{\rho_{h,\sigma z}} \quad (38)$$

412 where $\bar{\zeta}$ is the mean heterozygous effect of mutations on fitness in an optimal genotype,
413 and where $\rho_{h,\sigma z}$ is the harmonic mean recombination rate over all pairs of loci i and
414 j , where i affects the selfing rate and j affects the traits under stabilizing selection.
415 Using the fitness function given by equation 15 (where Q describes the shape of the
416 fitness peak), equation 38 generalizes to:

$$\Delta_{\text{purge}}\bar{\sigma} \approx \frac{3U^2}{\rho_{h,\sigma z}} \left(\frac{4U}{Q\bar{\zeta}} \right)^{-\frac{2}{Q}} V_{\sigma} \quad (39)$$

417 (see Supplementary File S1), which increases as Q increases in most cases. Therefore,
418 for a given value of inbreeding depression, a flatter fitness peak tends to increase
419 the relative importance of purging on the spread of selfing mutants in an outcrossing
420 population.

421 **Effects of epistasis on the evolution of selfing.** Expressions for the change
422 in mean selfing rate $\bar{\sigma}$, including the effects of epistasis between pairs of selected
423 loci are derived in Supplementary File S4. Because the expressions quickly become
424 cumbersome under partial selfing, we restrict our analysis to the initial spread of selfing
425 in an outcrossing population ($\bar{\sigma} \approx 0$). The change in mean selfing rate per generation
426 now writes:

$$\Delta\bar{\sigma} = \Delta_{\text{auto}}\bar{\sigma} + \Delta_{\text{depr}}\bar{\sigma} + \Delta_{\text{LD}}\bar{\sigma} + \Delta_{\text{purge}}\bar{\sigma}. \quad (40)$$

427 As above, $\Delta_{\text{auto}}\bar{\sigma}$ represents the direct transmission advantage of selfing and is still

428 given by equation 34 as $\bar{\sigma}$ tends to zero. The term $\Delta_{\text{depr}}\bar{\sigma}$ corresponds to the effect of
 429 inbreeding depression; taking into account epistasis between selected loci, it writes:

$$\begin{aligned} \Delta_{\text{depr}}\bar{\sigma} = & 2 \sum_{i,j} a_{j,j} \tilde{D}_{ij,j} + 2 \sum_{i,j < k} a_{jk,jk} \tilde{D}_{ijk,jk} \\ & + 2 \sum_{i,j < k} a_{j,k} \left(\tilde{D}_{ij,k} + \tilde{D}_{ik,j} \right) + 2 \sum_{i,j,k} a_{jk,j} \left(\tilde{D}_{ijk,j} + \tilde{D}_{ij,jk} \right) \end{aligned} \quad (41)$$

430 As shown in Supplementary File S4, expressing the different associations that appear
 431 in equation 41 at QLE, to leading order (and when $\bar{\sigma}$ tends to zero) yields $\Delta_{\text{depr}}\bar{\sigma} =$
 432 $-\delta' V_{\sigma}$, where δ' is inbreeding depression measured after selection, that is, when the
 433 parents used to produce selfed and outcrossed offspring contribute in proportion
 434 to their fitness (an expression for δ' in terms of allele frequencies and associations
 435 between pairs of loci is given by equation B9 in Supplementary File S2). Indeed, what
 436 matters for the spread of selfing is the ratio between the mean fitnesses of selfed and
 437 outcrossed offspring, taking into account the differential contributions of parents due
 438 to their different fitnesses. With epistasis, inbreeding depression is affected by genetic
 439 associations between selected loci, and δ' thus depends on the magnitude of those
 440 associations after selection. Note that epistasis may also affect inbreeding depression
 441 through the effective dominance $a_{j,j}$ and equilibrium frequency p_j of deleterious alleles
 442 (as described earlier), and these effects are often stronger than effects involving genetic
 443 associations when epistasis differs from zero on average.

444 The new term $\Delta_{\text{LD}}\bar{\sigma}$ appearing in equation 40 represents an additional effect of
 445 epistasis (besides its effects on inbreeding depression δ'), and is given by:

$$\Delta_{\text{LD}}\bar{\sigma} = 2 \sum_{i,j < k} a_{jk} \tilde{D}_{ijk}. \quad (42)$$

446 The association \tilde{D}_{ijk} represents the fact that the linkage disequilibrium D_{jk} between
 447 loci j and k (generated by epistasis among those loci) tends to be stronger on hap-

lotypes that also carry an allele increasing the selfing rate at locus i . Indeed, the magnitude of D_{jk} depends on the relative forces of selection generating D_{jk} and recombination breaking it, and selfing affects both processes: by increasing homozygosity, selfing reduces the effect of recombination (e.g., Nordborg, 1997), but it also increases “effective” epistasis, given that when a beneficial combination of alleles is present on one haplotype of an individual, it also tends to be present on the other haplotype due to homozygosity, enhancing the effect of fitness differences between haplotypes.

An expression for \tilde{D}_{ijk} at QLE is given in Supplementary File S4, showing that \tilde{D}_{ijk} is generated by all epistatic components (a_{jk} , $a_{j,k}$, $a_{j,k,j}$, $a_{j,k,k}$ and $a_{j,k,jk}$). In the case of uniformly deleterious alleles with fixed epistasis (equation 9), one obtains:

$$\Delta_{\text{LD}}\bar{\sigma} \approx \mathcal{E} \left[\frac{e_{\text{axa}} (2 + \rho_{jk}^2) + e_{\text{axd}} + (e_{\text{axd}} + \frac{1}{2}e_{\text{dxd}}) [1 - 2\rho_{jk} (1 - \rho_{jk})]}{\rho_{ijk} - (1 - \rho_{ijk}) (a_j + a_k + e_{\text{axa}})} \right] e_{\text{axa}} n_{\text{d}}^2 \frac{V_{\sigma}}{2} \quad (43)$$

where \mathcal{E} is the average over all triplets of loci i , j and k , ρ_{ijk} is the probability that at least one recombination event occurs between the three loci i , j and k during meiosis (note that the denominator is approximately ρ_{ijk} when recombination rates are large relative to selection coefficients), and where n_{d} is the mean number of deleterious alleles per haploid genome. Assuming free recombination among all loci ($\rho_{jk} = 1/2$, $\rho_{ijk} = 3/4$), equation 43 simplifies to:

$$\Delta_{\text{LD}}\bar{\sigma} \approx \frac{e_{\text{axa}}}{6} (9e_{\text{axa}} + 6e_{\text{axd}} + e_{\text{dxd}}) n_{\text{d}}^2 V_{\sigma}. \quad (44)$$

Using Charlesworth et al.’s (1991) fitness function, equation 44 yields:

$$\Delta_{\text{LD}}\bar{\sigma} \approx [\beta h (1 + h) n_{\text{d}}]^2 \frac{V_{\sigma}}{6}. \quad (45)$$

Finally, under stabilizing selection acting on quantitative traits (and assuming that

466 recombination rates are not too small), one obtains:

$$\Delta_{\text{LD}}\bar{\sigma} \approx \mathcal{E} \left[\frac{2 + \rho_{jk}^2}{\rho_{ijk}} \right] \frac{2U^2}{n} V_{\sigma}, \quad (46)$$

467 (where n is the number of selected traits) independently of the shape of the fitness
 468 peak Q , simplifying to $(6U^2/n) V_{\sigma}$ under free recombination (see Supplementary File
 469 S4).

470 As in the previous section, the term $\Delta_{\text{purge}}\bar{\sigma}$ equals $2 \sum_{i,j} a_j \tilde{D}_{ij}$ under random
 471 mating and represents indirect selection for selfing due to the fact that selfing increases
 472 the efficiency of selection against deleterious alleles. At QLE and to the first order in
 473 $a_{\text{U,V}}$ coefficients, the linkage disequilibrium \tilde{D}_{ij} is given by (see Supplementary File S4
 474 for derivation):

$$\begin{aligned} \tilde{D}_{ij} \approx & \frac{1}{2} \frac{\tilde{D}_{ii} p_j q_j}{\rho_{ij} - a_j (1 - 2p_j) (1 - \rho_{ij})} \left[a_j + a_{j,j} (1 - 2p_j) \right. \\ & \left. + \sum_k [a_{jk,k} + [a_{jk,k} + a_{jk,jk} (1 - 2p_j)] [1 - 2\rho_{jk} (1 - \rho_{jk})]] p_k q_k \right]. \end{aligned} \quad (47)$$

475 The term on the first line of equation 47 is the same as in equation 33, representing
 476 the fact that increased homozygosity at locus j improves the efficiency of selection act-
 477 ing at this locus. Note that epistatic interactions may affect this term (in particular
 478 when the average epistasis between selected loci differs from zero) through the selec-
 479 tion coefficients a_j and $a_{j,j}$ as well as equilibrium allele frequencies p_j . The term in the
 480 second line of equation 47 shows that negative additive-by-dominance or dominance-
 481 by-dominance epistasis between deleterious alleles increase the benefit of selfing, by
 482 increasing the efficiency of selection against deleterious alleles in homozygous individ-
 483 uals. In the case of unconditionally deleterious alleles with fixed epistasis, one obtains

484 (to the first order in epistatic coefficients):

$$\Delta_{\text{purge}}\bar{\sigma} \approx \mathcal{E} \left[\frac{h[s(1-h) - 3e_{\text{axd}}n_{\text{d}} - [1 - 2\rho_{jk}(1 - \rho_{jk})](e_{\text{axd}} + e_{\text{dxd}})n_{\text{d}}] - 2e_{\text{axa}}n_{\text{d}}}{\rho_{ij} - (1 - \rho_{ij})a_j} \right] \times sn_{\text{d}} \frac{V_{\sigma}}{2}. \quad (48)$$

485 Under free recombination, this simplifies to:

$$\Delta_{\text{purge}}\bar{\sigma} \approx [h[2s(1-h) - (7e_{\text{axd}} + e_{\text{dxd}})n_{\text{d}}] - 4e_{\text{axa}}n_{\text{d}}] sn_{\text{d}} \frac{V_{\sigma}}{4}. \quad (49)$$

486 Under Gaussian stabilizing selection, the coefficients $a_{jk,j}$ and $a_{jk,jk}$ are small relative
 487 to the other selection coefficients (as shown in Supplementary File S1), and the term
 488 on the second line of equation 47 may thus be neglected (in which case $\Delta_{\text{purge}}\bar{\sigma}$ is still
 489 given by equation 38). With a flatter fitness peak (equation 15 with $Q > 2$), using the
 490 expressions for $a_{jk,j}$ and $a_{jk,jk}$ given by equations A54 and A55 in Supplementary File
 491 S1 yields:

$$\Delta_{\text{purge}}\bar{\sigma} \approx \frac{U^2}{\rho_{h,\sigma z}} \left[3 + \frac{7(Q-2)}{4} \right] \left(\frac{4U}{Q\bar{\sigma}} \right)^{-\frac{2}{Q}} V_{\sigma} \quad (50)$$

492 where the term in $Q-2$ between brackets corresponds to the term on the second line of
 493 equation 47 (effects of additive-by-dominance and dominance-by-dominance epistasis).

494 Figure 3 shows the parameter space (in the $\kappa - \delta'$ plane) in which an initially
 495 outcrossing population ($\bar{\sigma} = 0$) evolves towards selfing, in the case of uniformly dele-
 496 terious alleles (fixed epistasis, equation 9). Note that when selfing increased in the
 497 simulations (green dots), we always observed that the population evolved towards self-
 498 ing rates close to 1. Figures 3A–C show that negative e_{axd} or e_{dxd} (the other epistatic
 499 components being set to zero) slightly increase the parameter range under which selfing
 500 evolves: in particular, selfing can invade for values of inbreeding depression δ' slightly
 501 higher than 0.5 in the absence of pollen discounting ($\kappa = 0$). Epistasis has stronger

502 effects when negative e_{axd} and/or e_{dxd} are combined with negative e_{axa} , as shown by
503 Figures 3D–F (we did not test the effect of negative e_{axa} alone, as δ' is greatly reduced
504 in this case unless e_{axa} is extremely weak). The QLE model (dashed and solid curves)
505 correctly predicts the maximum inbreeding depression δ' for selfing to evolve, as long
506 as this maximum is not too large: high values of δ' indeed imply high values of U , for
507 which the QLE model overestimates the strength of indirect effects (in particular, the
508 model predicts that selfing may evolve under high depression, above the upper parts
509 of the curves in Figures 3D–F, but this was never observed in the simulations). In
510 all cases shown in Figure 3, the increased parameter range under which selfing can
511 evolve is predicted to be mostly due to the effect of negative epistasis on $\Delta_{\text{purge}}\bar{\sigma}$, the
512 effect of $\Delta_{\text{LD}}\bar{\sigma}$ remaining negligible. Finally, one can note that the maximum δ' for
513 selfing to evolve is lower with $e_{axa} = -0.005$, $e_{axd} = e_{dxd} = -0.01$ (Figure 3E) than
514 with $e_{axa} = -0.005$, $e_{axd} = -0.01$, $e_{dxd} = 0$ (Figure 3D). This is due to the fact that
515 negative e_{axd} and e_{dxd} have two opposite effects: they increase the effect of selection
516 against homozygous mutations (which increases $\Delta_{\text{purge}}\bar{\sigma}$), but they also increase the
517 strength of inbreeding depression for a given mutation rate U (see Figure 1), decreas-
518 ing the mean number of deleterious alleles per haplotype n_d associated with a given
519 value of δ' (which decreases $\Delta_{\text{purge}}\bar{\sigma}$).

520 Supplementary Figure S1 shows the effect of the size of mutational steps at
521 the selfing modifier locus, in the absence of epistasis (corresponding to Figure 3A),
522 and with all three components of epistasis being negative (corresponding to Figure
523 3E). Increasing the size of mutational steps has more effect in the presence of negative
524 epistasis, since negative epistasis increases the purging advantage of alleles coding for
525 more selfing ($\Delta_{\text{purge}}\bar{\sigma}$), whose effect becomes stronger relative to $\Delta_{\text{auto}}\bar{\sigma}$ and $\Delta_{\text{depr}}\bar{\sigma}$

526 when modifier alleles have larger effects (as previously shown in Figure 2).

527 Figure 4 shows the results obtained under Gaussian stabilizing selection (equa-
528 tion 14) acting on different numbers of traits n , keeping the mean deleterious effect
529 of mutations $\bar{\varsigma}$ constant. Under stabilizing selection, inbreeding depression reaches an
530 upper limit as the mutation rate U increases (this upper limit being lower for lower
531 values of n), explaining why high values of δ' could not be explored in Figure 4. Again,
532 epistasis increases the parameter range under which selfing can invade (the effect of
533 epistasis being stronger when the number of selected traits n is lower), and the QLE
534 model yields correct predictions as long as inbreeding depression (and thus U) is not
535 too large. In contrast with the fixed epistasis model discussed above, the model pre-
536 dicts that $\Delta_{\text{purge}}\bar{\sigma}$ stays negligible, the difference between the dotted and solid/dashed
537 curves in Figure 4 being mostly due to $\Delta_{\text{LD}}\bar{\sigma}$: selfers thus benefit from the fact that
538 they can maintain beneficial combinations of alleles (mutations with compensatory
539 effects) at different loci. Interestingly, for $n = 5$ and sufficiently high rates of pollen
540 discounting κ , selfing can invade if inbreeding depression is lower than a given thresh-
541 old, or is very high. The latter case corresponds to a situation where polymorphism is
542 important (high U) and where large numbers of compensatory combinations of alleles
543 are possible. Although the model predicts that the same phenomenon should occur
544 for higher values of n , it was not observed in simulations with $n = 15$ and $n = 30$,
545 except for $n = 15$ and $\kappa = 0.4$. However, Supplementary Figures S2 and S3 show
546 that the evolution of selfing above a threshold value of δ' occurs more frequently when
547 the fitness peak is flatter ($Q > 2$), and when mutations affecting the selfing rate have
548 larger effects.

549 Finally, Figure 5 provides additional results on the effect of the number of se-

550 lected traits n , for fixed values of the overall mutation rate U . Inbreeding depression
551 is little affected by epistatic interactions when n is large, while low values of n tend
552 to decrease inbreeding depression, explaining the shapes of the dotted curves showing
553 the maximum level of pollen discounting for selfing to spread, when only taking into
554 account the effects of the automatic advantage and inbreeding depression. The differ-
555 ence between the dotted and solid/dashed curves shows the additional effect of linkage
556 disequilibria generated by epistasis ($\Delta_{LD}\bar{\sigma}$), whose relative importance increases as the
557 number of traits n decreases, and as the mutation rate U increases. Because U stays
558 moderate ($U = 0.2$ or 0.5), the analytical model provides accurate predictions of the
559 parameter range in which selfing is favored.

560 DISCUSSION

561 The automatic transmission advantage associated with selfing and inbreeding
562 depression are the two most commonly discussed genetic mechanisms affecting the
563 evolution of self-fertilization. When these are the only forces at play, a selfing mutant
564 arising in an outcrossing population is expected to increase in frequency as long as
565 inbreeding depression is weaker than the automatic advantage, whose magnitude de-
566 pends on the level of pollen discounting (Lande and Schemske, 1985; Holsinger et al.,
567 1984). However, because selfers also tend to carry better purged genomes due to their
568 increased homozygosity, several models showed that selfing mutants may invade under
569 wider conditions than those predicted solely based on these two aforementioned forces
570 (Charlesworth et al., 1990; Uyenoyama and Waller, 1991; Epinat and Lenormand, 2009;
571 Porcher and Lande, 2005b; Gervais et al., 2014). Our analytical and simulation results

572 confirm that the advantage procured through purging increases with the strength of
573 selection against deleterious alleles and with the degree of linkage within the genome.
574 The simulation results also indicate that the verbal prediction, according to which mu-
575 tations causing complete selfing may invade a population independently of its level of
576 inbreeding depression (Lande and Schemske, 1985, p. 33), only holds when deleterious
577 alleles have strong fitness effects, so that purging occurs rapidly (Figure 2D).

578 Whether purging efficiency should significantly contribute to the spread of self-
579 ing mutants depends on the genetic architecture of inbreeding depression. To date,
580 experimental data point to a small contribution of strongly deleterious alleles to in-
581 breeding depression: for example, Baldwin and Schoen (2019) recently showed that
582 in the self-incompatible species *Leavenworthia alabamica*, inbreeding depression is not
583 affected by three generations of enforced selfing (which should have led to the elimina-
584 tion of deleterious alleles with strong fitness effects). Previous experiments on different
585 plant species also indicate that inbreeding depression is probably generated mostly by
586 weakly deleterious alleles (Dudash et al., 1997; Willis, 1999; Carr and Dudash, 2003;
587 Charlesworth and Willis, 2009). Data on the additive variance in fitness within pop-
588 ulations are also informative regarding the possible effect of purging: indeed, using
589 our general expression for fitness (equation 8) and neglecting linkage disequilibria,
590 one can show that the additive component of the variance in fitness in a randomly
591 mating population (more precisely, the variance in W/\bar{W}) is given by the sum over
592 selected loci of $2a_j^2 p_j q_j$ (see also eq. A3b in Charlesworth and Barton, 1996), a term
593 which also appears in the effect of purging on the strength of selection for selfing
594 (equation 35). Although estimates of the additive variance in fitness in wild popula-
595 tions remain scarce, the few estimates of the “evolvability” parameter (corresponding

596 to the additive component of the variance in W/\overline{W}) available from plant species are
597 small, of the order of a few percents (Hendry et al., 2018). Note that strictly, the
598 effect of purging on the strength of selection for selfing is proportional to the quan-
599 tity $\sum_j a_j [a_j + a_{j,j} (1 - 2p_j)] p_j q_j$ (equation 35), which may be larger than $\sum_j a_j^2 p_j q_j$
600 (for example, in the case of deleterious alleles with fixed s and h , the first quantity
601 is approximately $s(1 - h)U$ and the second shU). However, the small values of the
602 available estimates of $\sum_j a_j^2 p_j q_j$, together with the experimental evidence mentioned
603 above on the genetics of inbreeding depression, indicate that selfing mutants probably
604 do not benefit greatly from purging. Nevertheless, it remains possible that the strength
605 of selection against deleterious alleles (a_j) increases in harsher environments (Cheptou
606 et al., 2000; Agrawal and Whitlock, 2010), leading to stronger purging effects in such
607 environments.

608 The effects of epistasis between deleterious alleles on inbreeding depression and
609 on the evolution of mating systems have been little explored (but see Charlesworth et
610 al., 1991). In this paper, we derived general expressions for the effect of epistasis be-
611 tween pairs of loci on inbreeding depression and on the strength of selection for selfing,
612 that can be applied to more specific models. Our results show that different compo-
613 nents of epistasis have different effects on inbreeding depression: in particular, while
614 negative additive-by-additive epistasis tends to lower inbreeding depression by reducing
615 the frequency of deleterious alleles, negative additive-by-dominance and dominance-by-
616 dominance epistasis increase inbreeding depression by lowering the fitness of homozy-
617 gous offspring. Very little is known on the average sign and relative magnitude of these
618 different forms of epistasis. In principle, the overall sign of dominance-by-dominance
619 effects can be deduced from the shape of the relation between the inbreeding coefficient

620 of individuals (F) and their fitness (Crow and Kimura, 1970, p. 80), an accelerating
621 decline in fitness as F increases indicating negative e_{dxd} . The relation between F and
622 fitness-related traits was measured in several plant species; the results often showed
623 little departure from linearity (e.g., Willis, 1993; Kelly, 2005), but the experimental
624 protocols used may have generated biases against finding negative e_{dxd} (Falconer and
625 Mackay, 1996; Lynch and Walsh, 1998; Sharp and Agrawal, 2016).

626 Most empirical distributions of epistasis between pairs of mutations affecting
627 fitness have been obtained from viruses, bacteria and unicellular eukaryotes (e.g., Mar-
628 tin et al., 2007; Kouyos et al., 2007; de Visser and Elena, 2007). While no clear con-
629 clusion emerges regarding the average coefficient of epistasis (some studies find that
630 it is negative, other positive and other close to zero), a general observation is that
631 epistasis is quite variable across pairs of loci. This variance of epistasis may slightly
632 increase inbreeding depression when it remains small (by reducing the efficiency of
633 selection against deleterious alleles, Phillips et al., 2000; Abu Awad and Roze, 2018),
634 or decrease inbreeding depression when it is larger and/or effective recombination is
635 sufficiently weak, so that selfing can maintain beneficial multilocus genotypes (Lande
636 and Porcher, 2015; Abu Awad and Roze, 2018). Besides this “short-term” effect on in-
637 breeding depression, the variance of epistasis also favors selfing through the progressive
638 buildup of linkage disequilibria that increase mean fitness (associations between alleles
639 with compensatory effects at different loci). Interestingly, this effect may allow selfers
640 to spread above a threshold value of the rate of mutation on traits under stabilizing
641 selection (Figures 4, S3). Is the variance of epistasis typically large enough, so that
642 this benefit of maintaining beneficial combinations of alleles may significantly help
643 selfing mutants to spread? Answering this question is difficult without better knowl-

644 edge on the importance of epistatic interactions on fitness in natural environments.
645 Nevertheless, some insights can be gained from our analytical results: for example,
646 neglecting additive-by-dominance and dominance-by-dominance effects, equations 42
647 and D7 indicate that the effect of linkage disequilibria on the strength of selection for
648 selfing should scale with the sum over pairs of selected loci of $a_{jk}^2 p_j q_j p_k q_k$, which also
649 corresponds to the epistatic component of the variance in fitness in randomly mating
650 populations. Although estimates of epistatic components of variance remain scarce,
651 they are typically not larger than additive components (e.g., Hill et al., 2008), suggest-
652 ing that the benefit of maintaining beneficial multilocus genotypes may be generally
653 limited (given that the additive variance in fitness seems typically small, as discussed
654 previously).

655 A mixed mating system was never stably maintained in our simulations: the
656 selfing rate always evolved towards a value either close to zero or one. Using a de-
657 terministic model, Charlesworth et al. (1991) showed that in the presence of negative
658 epistasis between deleterious alleles, and when outcrossing is not stable, a selfing rate
659 slightly below one corresponds to the evolutionarily stable strategy (ESS). This can be
660 understood from the fact that negative epistasis favors non-zero rates of recombination
661 (e.g., Barton, 1995), while recombination becomes ineffective under complete selfing.
662 Similarly, Kamran-Disfani and Agrawal (2014) showed that selfing rates slightly below
663 one are selectively favored over complete selfing in finite populations, when deleterious
664 alleles occur at multiple loci: again, this probably results from selection for recom-
665 bination, generated by Hill-Robertson effects between selected loci (e.g., Barton and
666 Otto, 2005). Similar effects must have occurred in our simulations, although we did
667 not check that selfing rates slightly below one resulted from selection to maintain low

668 rates of outcrossing, rather than from the constant input of mutations at selfing modi-
669 fier loci (this could be done by comparing the probabilities of fixation of alleles coding
670 for different selfing rates, as in Kamran-Disfani and Agrawal, 2014). It is possible that
671 mixed mating systems may be more easily maintained under changing environmental
672 conditions (for example, under directional selection acting on quantitative traits) than
673 under the stable conditions considered in the present paper; this represents an inter-
674 esting avenue for future research.

675

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681

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

814

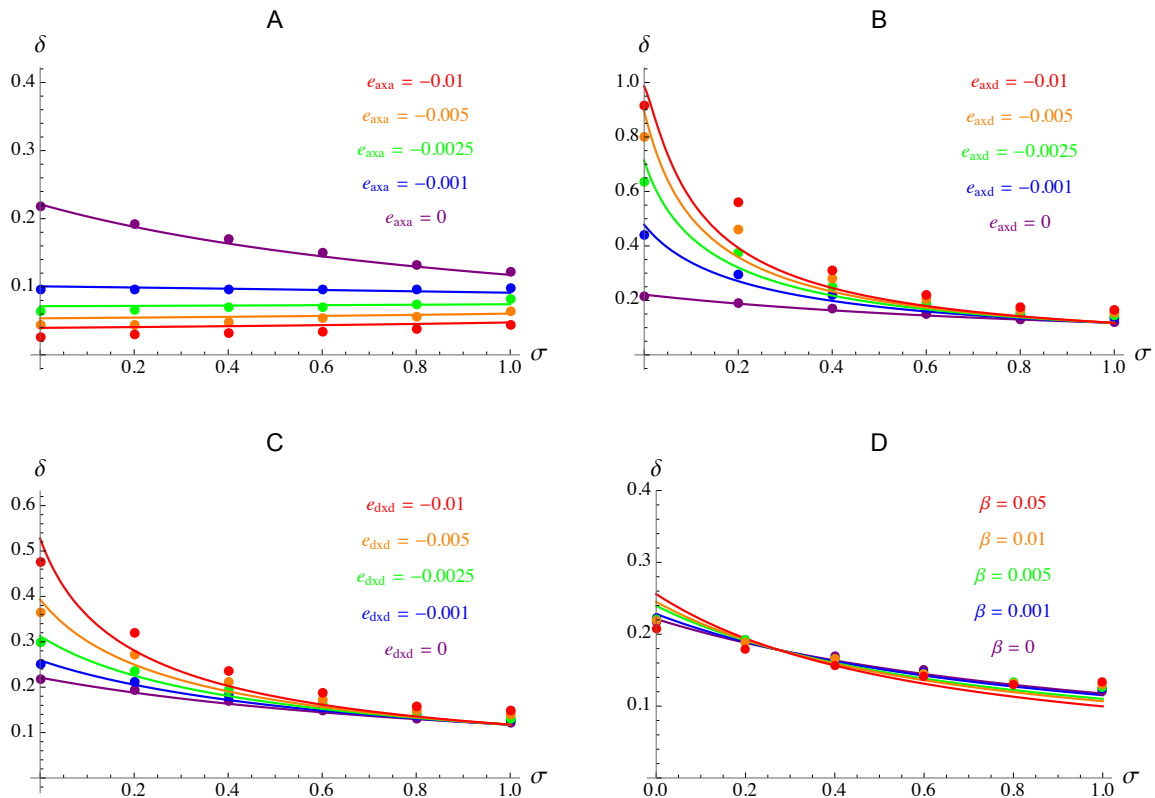
σ	Selfing rate
$\bar{\sigma}, V_{\sigma}$	Mean and variance in the selfing rate in the population
κ	Rate of pollen discounting
ℓ_{σ}	Number of loci affecting the selfing rate
W, \bar{W}	Fitness of an individual, and average fitness
ℓ	Number of loci affecting fitness
U	Overall (haploid) mutation rate at loci affecting fitness
p_j, q_j	Frequencies of alleles 1 and 0 at loci affecting fitness
ℓ	Number of loci affecting selected traits
n_d	Mean number of deleterious alleles per haploid genome
s, h	Selection and dominance coefficients of deleterious alleles
$e_{axa}, e_{axd}, e_{dxd}$	Additive-by-additive, additive-by-dominance and dominance-by-dominance epistasis between deleterious alleles
β	Strength of synergistic epistasis in Charlesworth et al.'s (1991) model
n	Number of quantitative traits under stabilizing selection
V_s	Strength of stabilizing selection
$r_{\alpha j}$	Effect of allele 1 at locus j on trait α

815

816

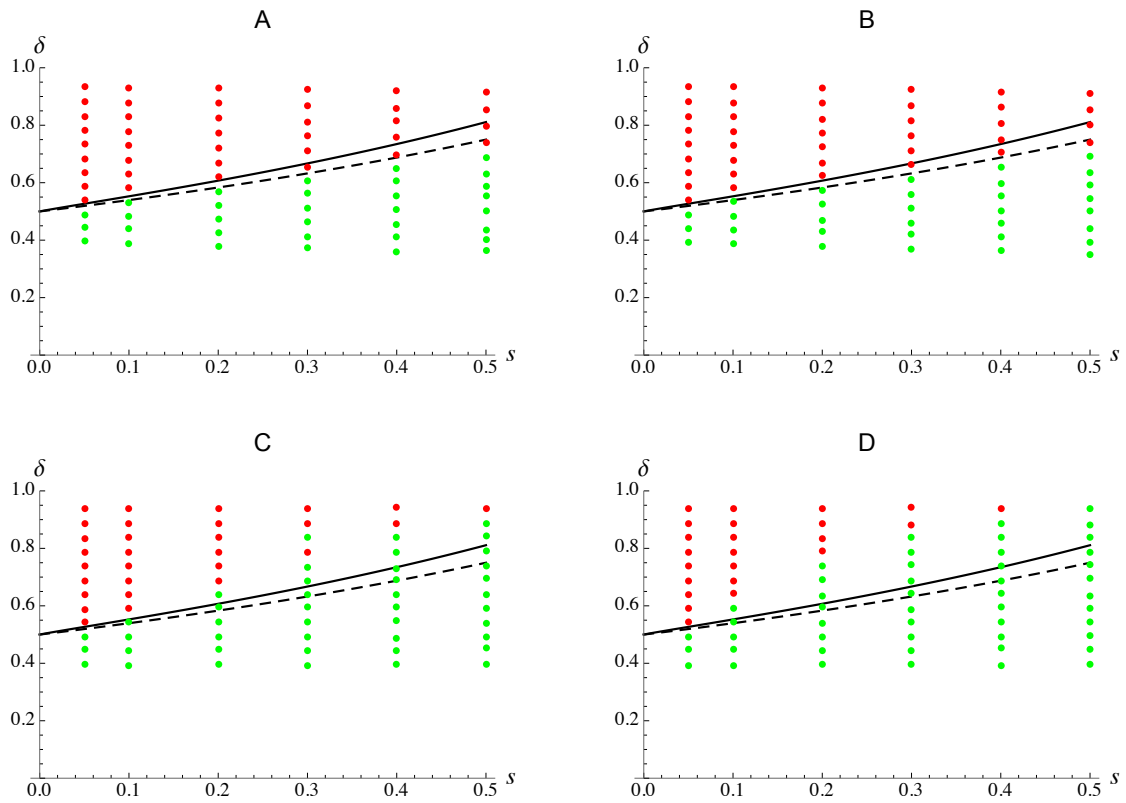
a^2	Variance of mutational effects on traits under stabilizing selection
Q	Shape of the fitness peak (equation 15)
$a_{\mathbb{U},\mathbb{V}}$	Effect of selection on the sets \mathbb{U} and \mathbb{V} of loci present on the maternally and paternally inherited haplotypes of an individual (equation 8)
$D_{\mathbb{U},\mathbb{V}}$	Genetic association between the sets \mathbb{U} and \mathbb{V} of loci present on the maternally and paternally inherited haplotypes of an individual (equation 4)
ρ_{jk}	Recombination rate between loci j and k
U_{self}	Mutation rate at loci affecting the selfing rate
σ_{self}^2	Variance of mutational effects at loci affecting the selfing rate
δ	Inbreeding depression
δ'	Inbreeding depression measured after selection
F	Inbreeding coefficient
G_{jk}	Identity disequilibrium between loci j and k
G	Identity disequilibrium between freely recombining loci

817



818

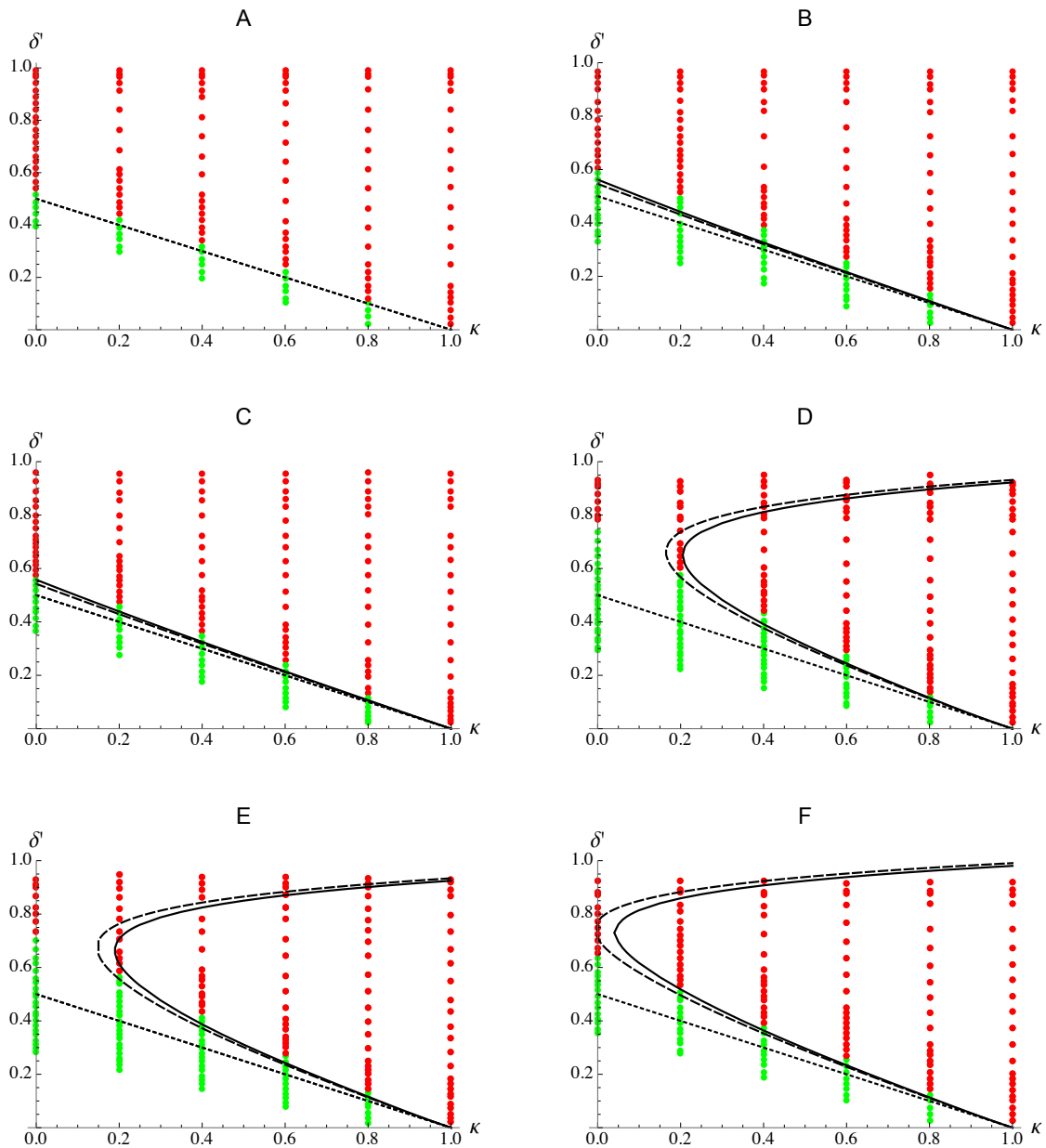
819 **Figure 1.** Inbreeding depression δ as a function of the selfing rate σ . A–C: effects of
 820 the different components of epistasis between deleterious alleles, additive-by-additive
 821 (e_{ava}), additive-by-dominance (e_{axd}) and dominance-by-dominance (e_{dxd}) — in each
 822 plot, the other two components of epistasis are set to zero. D: results obtained using
 823 Charlesworth et al.’s (1991) fitness function, where β represents synergistic epistasis
 824 between deleterious alleles (slightly modified as explained in Supplementary File S1).
 825 Dots correspond to simulation results (error bars are smaller than the size of symbols),
 826 and curves to analytical predictions from equations 23 and 26. Parameter values:
 827 $U = 0.25$, $s = 0.05$, $h = 0.25$. In the simulations $N = 20,000$ (population size)
 828 and $R = 20$ (genome map length); simulations lasted 10^5 generations and inbreeding
 829 depression was averaged over the last 5×10^4 generations.



830

831 **Figure 2.** Evolution of selfing in the absence of epistasis. The solid curve shows
832 the maximum value of inbreeding depression δ for selfing to spread in an initially
833 outcrossing population, as a function of the strength of selection s against deleterious
834 alleles (obtained from equations 34 and 36, after integrating equation 36 over the
835 genetic map), while the dashed curve corresponds to the same prediction in the case
836 of unlinked loci (obtained by setting $\rho_{ij} = 1/2$ in equation 36). Dots correspond to
837 simulation results (using different values of U for each value of s , in order to generate a
838 range of values of δ). In the simulations the population evolves under random mating
839 during the first 20,000 generations (inbreeding depression is estimated by averaging
840 over the last 10,000 generations); mutation is then introduced at the selfing modifier
841 locus. A red dot means that the selfing rate stayed below 0.05 during the 2×10^5

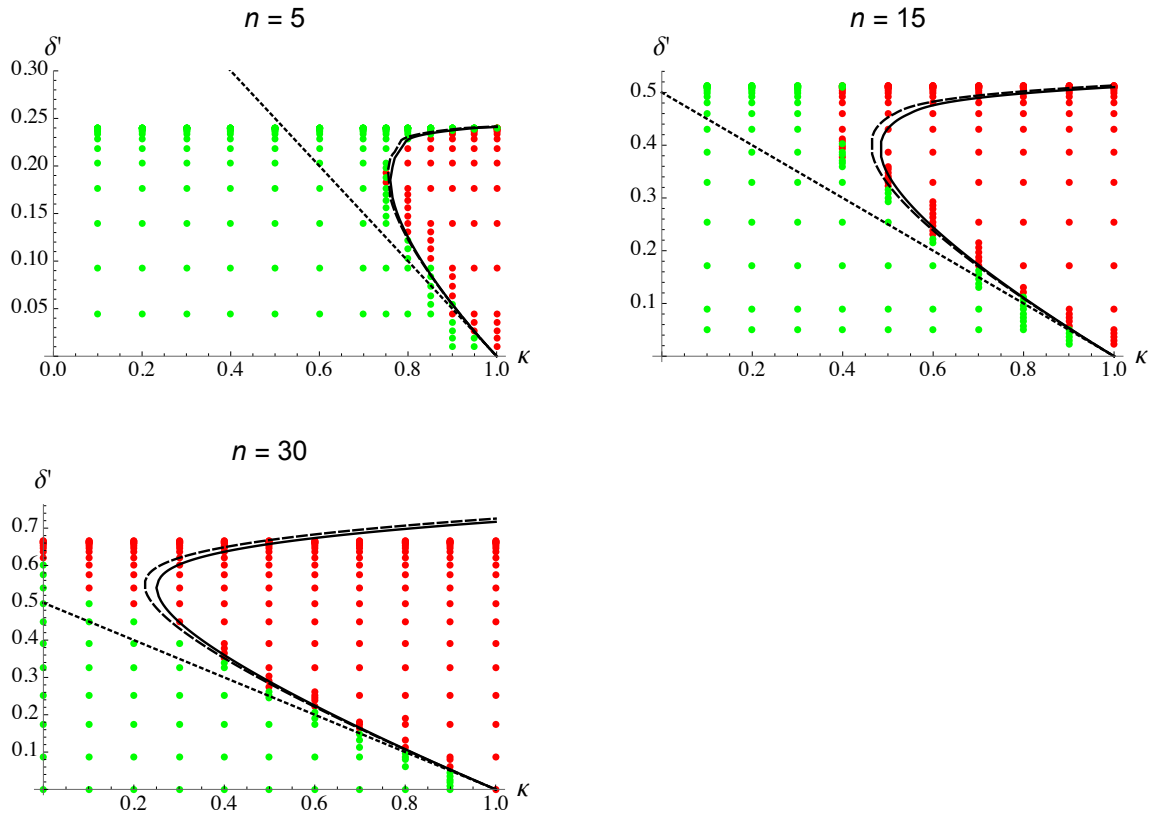
842 generations of the simulation, while a green dot means that selfing increased (in which
843 case the population always evolved towards nearly complete selfing). Parameter values:
844 $\kappa = 0$, $h = 0.25$, $R = 10$; in the simulations $N = 20,000$, $U_{\text{self}} = 0.001$ (mutation rate
845 at the selfing modifier locus). In A, the standard deviation of mutational effects at the
846 modifier locus is set to $\sigma_{\text{self}} = 0.01$, while it is set to $\sigma_{\text{self}} = 0.03$ in B, and to $\sigma_{\text{self}} = 0.3$
847 in C. In D, only two alleles are possible at the modifier locus, coding for $\sigma = 0$ or 1,
848 respectively.



849

850 **Figure 3.** Evolution of selfing with fixed, negative epistasis. The different plots
851 show the maximum value of inbreeding depression δ' (measured after selection) for
852 selfing to spread in an initially outcrossing population, as a function of the rate of
853 pollen discounting κ . Green and red dots correspond to simulation results and have
854 the same meaning as in Figure 2 (δ' was estimated by averaging over the last 10,000
855 generations of the 20,000 preliminary generations without selfing, simulations lasted

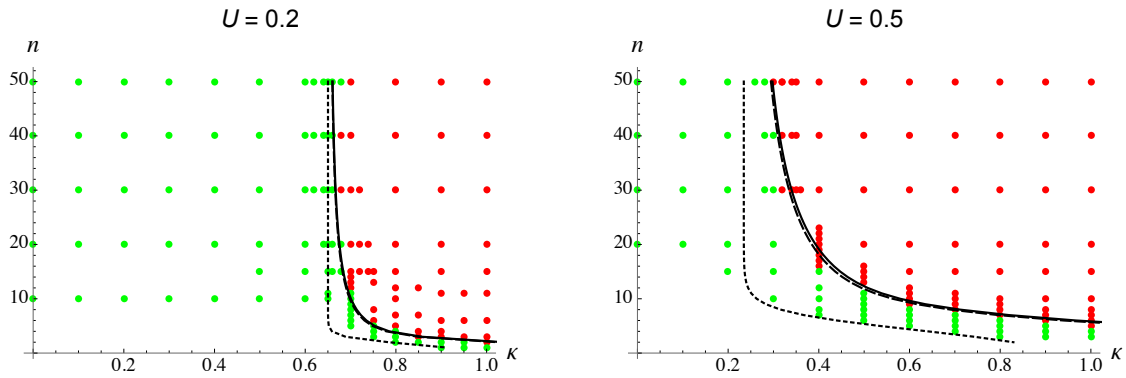
856 2×10^5 generations). The dotted lines correspond to the predicted maximum inbreeding
857 depression for selfing to increase obtained when neglecting $\Delta_{LD}\bar{\sigma}$ and $\Delta_{purge}\bar{\sigma}$ (that is,
858 $\delta' = (1 - \kappa)/2$), the dashed curves correspond to the prediction obtained using the
859 expressions for $\Delta_{LD}\bar{\sigma}$ and $\Delta_{purge}\bar{\sigma}$ under free recombination (equations 44 and 49),
860 while the solid curves correspond to the predictions obtained by integrating equations
861 43 and 48 over the genetic map (the effect of $\Delta_{LD}\bar{\sigma}$ is predicted to be negligible relative
862 to the effect of $\Delta_{purge}\bar{\sigma}$ in all cases). To obtain these predictions, the relation between
863 the mean number of deleterious alleles per haplotype n_d (that appears in equations
864 43–44 and 48–49) and δ' was obtained from a fit of the simulation results. A: $e_{axa} =$
865 $e_{axd} = e_{dxd} = 0$; B: $e_{axa} = e_{dxd} = 0$, $e_{axd} = -0.01$; C: $e_{axa} = e_{axd} = 0$, $e_{dxd} = -0.01$;
866 D: $e_{axa} = -0.005$, $e_{axd} = -0.01$, $e_{dxd} = 0$; E: $e_{axa} = -0.005$, $e_{axd} = e_{dxd} = -0.01$; F:
867 Charlesworth et al.'s (1991) model with $\beta = 0.05$. Other parameter values: $s = 0.05$,
868 $h = 0.25$, $R = 20$; in the simulations $N = 20,000$, $U_{self} = 0.001$ (mutation rate at the
869 selfing modifier locus), $\sigma_{self} = 0.03$ (standard deviation of mutational effects at the
870 modifier locus).



871

872 **Figure 4.** Evolution of self-fertilization under Gaussian stabilizing selection. The
 873 three plots show the effects of inbreeding depression δ' (measured after selection) and
 874 pollen discounting (parameter κ) on the evolution of self-fertilization, for different
 875 numbers of traits under selection ($n = 5, 15$ and 30). Green and red dots correspond to
 876 simulation results and have the same meaning as in Figures 2 and 3 (δ' was estimated
 877 by averaging over the last 10,000 generations of the 20,000 preliminary generations
 878 without selfing, simulations lasted 5×10^4 generations). The fact that inbreeding
 879 depression reaches a plateau as U increases (at lower values of δ' for lower values of
 880 n) sets an upper limit to the values of δ' that can be obtained in the simulations. The
 881 dotted lines correspond to the predicted maximum inbreeding depression for selfing
 882 to increase obtained when neglecting $\Delta_{LD}\bar{\sigma}$ and $\Delta_{\text{purge}}\bar{\sigma}$ (that is, $\delta' = (1 - \kappa)/2$), the

883 dashed curves correspond to the prediction obtained using the expression for $\Delta_{LD}\bar{\sigma}$
884 under free recombination (that is, $6U^2V_\sigma/n$, see equation 46), while the solid curves
885 correspond to the predictions obtained by integrating equation 46 over the genetic
886 map (the effect of $\Delta_{\text{purge}}\bar{\sigma}$ is predicted to be negligible relative to the effect of $\Delta_{LD}\bar{\sigma}$).
887 To obtain these predictions, the relation between U and δ' was obtained from a fit of
888 the simulation results. Other parameter values: $\bar{\zeta} = 0.01$, $R = 20$; in the simulations
889 $N = 5,000$, $U_{\text{self}} = 0.001$ (overall mutation rate at selfing modifier loci), $\sigma_{\text{self}} = 0.01$
890 (standard deviation of mutational effects on selfing).



891

892 **Figure 5.** Evolution of self-fertilization under Gaussian stabilizing selection. The two
 893 plots show the effect of the number of traits under selection n and pollen discounting
 894 (parameter κ) on the evolution of self-fertilization for two values of the mutation rate
 895 on traits under stabilizing selection ($U = 0.2$ and 0.5). Green and red dots correspond
 896 to simulation results and have the same meaning as in the previous figures. The dotted
 897 curves show the maximum value of pollen discounting κ for selfing to increase obtained
 898 when neglecting $\Delta_{LD}\bar{\sigma}$ and $\Delta_{purge}\bar{\sigma}$ (that is, $\delta' = (1 - \kappa)/2$), while the dashed and
 899 solid curves correspond to the predictions including the term $\Delta_{LD}\bar{\sigma}$ (from equation
 900 46) under free recombination (dashed) or integrated over the genetic map (solid). To
 901 obtain these predictions, the relation between n and δ' was obtained from a fit of the
 902 simulation results. Other parameter values: $\bar{\varsigma} = 0.01$, $R = 20$; in the simulations
 903 $N = 5,000$, $U_{self} = 0.001$ (overall mutation rate at selfing modifier loci), $\sigma_{self} = 0.01$
 904 (standard deviation of mutational effects on selfing).