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Mutation rate evolution in partially selfing and partially asexual
organisms

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ABSTRACT

1
2 Different factors may influence the evolution of the mutation rate of a species:
3 costs associated with DNA replication fidelity, indirect selection caused by the mu-
4 tations produced (that should generally favor lower mutation rates, given that most
5 mutations affecting fitness are deleterious) and genetic drift, that may render selection
6 acting on weak mutators inefficient. In this paper, we use a two-locus model to compute
7 the strength of indirect selection acting on a modifier locus that affects the mutation
8 rate towards a deleterious allele at a second, linked locus, in a population undergoing
9 partial selfing or partial clonality. The results show that uniparental reproduction in-
10 creases the effect of indirect selection for lower mutation rates. Extrapolating to the
11 case of a whole genome with many deleterious alleles and introducing a direct cost a
12 DNA replication fidelity, the results can be used to compute the evolutionarily stable
13 mutation rate U . In the absence of mutational bias towards higher U , the analytical
14 prediction fits well with individual-based, multilocus simulation results. When such a
15 bias is added into the simulations, however, genetic drift may lead to the maintenance
16 of higher mutation rates, and this effect may be amplified in highly selfing or highly
17 clonal populations due to their reduced effective population size.

19 Rates of spontaneous mutation per nucleotide and per cell division span several
20 orders of magnitudes within eukaryotes (e.g., Sung et al., 2012; Lynch et al., 2016),
21 providing evidence that mutation rates evolve over long timescales. Furthermore,
22 mutation rate variation within a species has been documented in various groups of or-
23 ganisms including bacteria, green algae and fruit flies (e.g., Demerec, 1937; Woodruff
24 et al., 1984; Miller, 1996; Haag-Liautard et al., 2007; Ness et al., 2015), suggesting that
25 mutation rates may possibly change rapidly if natural selection can act upon this ge-
26 netic variation. Changes in mutation rates have indeed been observed during evolution
27 experiments (Sniegowski et al., 2000): for example, increased mutation rate in evol-
28 ving populations of bacteria due to the fixation of mutator genotypes (e.g., Sniegowski
29 et al., 1997), or decreased mutation rate in populations of *Drosophila* exposed to X-
30 irradiation during several generations (Nöthel, 1987).

31 Starting with Sturtevant (1937), a number of evolutionary forces that may influ-
32 ence the evolution of mutation rates have been identified (Drake et al., 1998; Sniegowski
33 et al., 2000; Baer et al., 2007; Lynch, 2010). Because most mutations affecting fitness
34 are deleterious (Eyre-Walker and Keightley, 2007), alleles coding for higher mutation
35 rates should be associated with less fit genetic backgrounds, thus favoring reduced mu-
36 tation rates. Using a two-locus modifier model in which one locus affects the mutation
37 rate between alleles at a linked locus directly affecting fitness, Kimura (1967) showed
38 that the strength of selection to reduce mutation in a panmictic, diploid population is
39 approximately $sh \delta u / (r + sh)$, where δu is the change in mutation rate caused by the
40 modifier locus, r the recombination rate between the two loci and sh the heterozygous

41 effect of the deleterious allele, assumed different from zero — see Karlin and McGregor
42 (1974) for the case of a fully recessive deleterious allele. This result was later general-
43 ized by Kondrashov (1995), Dawson (1998, 1999), Johnson (1999a) and Lynch (2008)
44 to the case of modifiers changing the deleterious mutation rate over a whole genome.
45 In asexual populations, this effect may be compensated by the higher rate of produc-
46 tion of beneficial alleles by mutator genotypes, which may lead to transient increases
47 in mutation rate when mutators hitchhike with the beneficial alleles they created (e.g.,
48 Leigh, 1970; Eshel, 1973; Taddei et al., 1997; Tenaillon et al., 1999; André and Godelle,
49 2006). In sexual populations, however, recombination destroys the association between
50 mutators and beneficial alleles, and selection for reduced mutation due to the effect of
51 deleterious alleles should generally prevail (Leigh, 1970; Johnson, 1999b).

52 The maintenance of nonzero mutation rates is often considered as the result of
53 two opposing forces: selection for reduced mutation rates due to the deleterious effect of
54 most mutations, and the intrinsic cost of DNA replication fidelity (e.g., Kimura, 1967;
55 Drake et al., 1998; Baer et al., 2007; Sniegowski et al., 2000). More recently, Lynch
56 (2008, 2011) proposed that the equilibrium value of the mutation rate may instead
57 result from a balance between indirect selection and genetic drift: indeed, once the
58 mutation rate has decreased to a very low level, the strength of selection for further
59 increases in replication fidelity may become weaker than genetic drift. The mutation
60 rate would thus reach higher values in populations with lower effective population
61 size N_e , due to less efficient selection acting on modifier alleles reducing mutation:
62 this agrees with the observation that the mutation rate is lower in species with larger
63 estimated N_e (Lynch, 2010; Sung et al., 2012; Lynch et al., 2016).

64 Based on Kimura (1967)'s result mentioned above, reproductive systems that

65 reduce effective recombination rates (such as selfing or clonality) should increase the
66 strength of selection for lower mutation rates (as mutators tend to stay longer associ-
67 ated with the deleterious alleles they produce). In the extreme case of full selfing or
68 full clonality, the strength of selection against a mutator allele becomes equivalent to
69 the increase in mutation load that it causes: neglecting drift, this corresponds to the
70 increase in mutation rate caused by the mutator (e.g., Sturtevant, 1937; Drake et al.,
71 1998). Using multilocus simulations incorporating a cost of replication fidelity, Sloan
72 and Panjeti (2010) showed that the equilibrium deleterious mutation rate is indeed
73 lower in asexual than in sexual populations, generating an indirect benefit for asexual-
74 ity. With selfing, selection for lower mutation rates should be further enhanced by the
75 increased fitness effect of deleterious alleles due to increased homozygosity. However,
76 background selection may strongly reduce the effective size of highly selfing or clonally
77 reproducing populations (Nordborg, 1997; Glémin and Ronfort, 2013; Agrawal and
78 Hartfield, 2016; Roze, 2016) which, according to Lynch’s (2010) hypothesis mentioned
79 above, may possibly increase the equilibrium mutation rate. The overall effect of self-
80 ing or clonality on the evolution of mutation rates thus remains unclear, and has been
81 little explored.

82 In this paper, we extend Kimura’s (1967) two-locus model to compute the
83 strength of indirect selection acting on a mutation modifier locus in a partially selfing
84 or partially clonal diploid population. The results confirm that uniparental repro-
85 duction increases selection against mutator alleles due to stronger associations with
86 deleterious alleles. Under partial selfing, the strength of indirect selection generated
87 by closely linked loci can be approximated by replacing r and h in Kimura (1967)’s re-
88 sult by effective recombination and dominance coefficients $r(1 - F)$ and $h(1 - F) + F$

89 (e.g., Glémin and Ronfort, 2013; Roze, 2016; Hartfield and Glémin, 2016). However,
90 this approximation underestimates the effect of more distant loci, which may become
91 important when the selfing rate is high. We then extrapolate from this two-locus model
92 to derive expressions for the genomic deleterious mutation rate at equilibrium between
93 indirect selection generated by deleterious alleles and the cost of replication fidelity,
94 and show that these expressions correctly predict the outcome of individual-based
95 multilocus simulations. Finally, using two different simulation models with different
96 assumptions on the genetic architecture of the mutation rate, we show that consistent
97 with Lynch’s (2010) hypothesis, populations with lower effective size may maintain
98 higher mutation rates, provided that mutations increasing replication fidelity (antimu-
99 tator alleles) occur less frequently than those decreasing it (mutator alleles). In some
100 cases, intermediate rates of outcrossing lead to lower mutation rates than obligate out-
101 crossing or obligate selfing/clonality, due to strong reductions in the effective size of
102 highly selfing or clonal populations caused by background selection.

103

METHODS

104 **Two-locus model.** Our analytical model represents a very large (effectively infinite)
105 population of diploid individuals with discrete generations. As in Kimura (1967),
106 we consider the evolution of a locus (denoted M) affecting the mutation rate at a
107 second locus (denoted A), which directly affects fitness. Two alleles (denoted 0 and
108 1) segregate at each locus; we assume that allele 1 at locus A is deleterious, reducing
109 fitness by a factor $1 - sh$ in heterozygotes and $1 - s$ in homozygotes. For simplicity,
110 we assume additivity at the mutation modifier locus (locus M), the mutation rate

111 at locus A being u_0 , $u_0 + \delta u$ and $u_0 + 2\delta u$ in individuals with genotype 00, 01 and
 112 11 at locus M (respectively). We assume that mutations from 0 to 1 and from 1 to
 113 0 occur at the same rate; however this hypothesis should not significantly affect the
 114 results, as the effect of back mutations will be negligible as long as the deleterious
 115 allele stays at low frequency in the population. We also introduce an intrinsic cost of
 116 DNA replication fidelity, so that individuals with lower mutation rates pay a fitness
 117 cost. For this, we will assume that the fitness of an individual is multiplied by a
 118 function f_c that increases with the mutation rate, and will consider different forms
 119 of cost function. Individuals contribute to the next generation in proportion to their
 120 fitness; under partial selfing a proportion α of juveniles is produced by selfing, while
 121 under partial asexuality a proportion γ is produced clonally (the remaining proportion
 122 $1 - \alpha$ or $1 - \gamma$ being produced by outcrossing with random union of gametes). Finally,
 123 r measures the recombination rate between the two loci. We assume that mutation
 124 occurs after selection, before recombination; however, assuming that mutation occurs
 125 just after recombination yields the same results (as long as the mutation rate depends
 126 on the genotype of the diploid parent).

127 Following previous works (e.g., Barton and Turelli, 1991; Kirkpatrick et al.,
 128 2002; Roze, 2015, 2016), genetic associations within and between loci are defined as
 129 follows. We define $X_{i,1}$ and $X_{i,2}$ as indicator variables that equal 1 if a given individual
 130 carries allele 1 at locus i on its first or second haplotype (respectively), and 0 otherwise.
 131 The frequency of allele 1 at locus i in the whole population is thus given by $p_i =$
 132 $E[(X_{i,1} + X_{i,2})/2]$, where E stands for the average over all individuals. Defining the
 133 centered variables $\zeta_{i,1}$ and $\zeta_{i,2}$ as

$$\zeta_{i,1} = X_{i,1} - p_i, \quad \zeta_{i,2} = X_{i,2} - p_i, \quad (1)$$

134 the genetic association between the sets \mathbb{S} and \mathbb{T} of loci present on the two haplotypes
 135 of the same individual is given by:

$$D_{\mathbb{S},\mathbb{T}} = \text{E}[\zeta_{\mathbb{S},\mathbb{T}}] \quad (2)$$

136 where

$$\zeta_{\mathbb{S},\mathbb{T}} = \frac{\zeta_{\mathbb{S},1} \zeta_{\mathbb{T},2} + \zeta_{\mathbb{S},2} \zeta_{\mathbb{T},1}}{2}, \quad (3)$$

$$\zeta_{\mathbb{S},1} = \prod_{i \in \mathbb{S}} \zeta_{i,1}, \quad \zeta_{\mathbb{T},2} = \prod_{i \in \mathbb{T}} \zeta_{i,2}$$

137 (note that $D_{\mathbb{S},\mathbb{T}} = D_{\mathbb{T},\mathbb{S}}$), and where sets \mathbb{S} and \mathbb{T} may be the empty set \emptyset , M , A
 138 or MA . Associations between genes present on the same haplotype of an individual
 139 ($D_{\mathbb{S},\emptyset}$) will be simply denoted $D_{\mathbb{S}}$. For example, $D_{M,M} = \text{E}[(X_{M,1} - p_M)(X_{M,2} - p_M)]$
 140 is a measure of the departure from Hardy-Weinberg equilibrium at locus M , while
 141 D_{MA} represents the linkage disequilibrium between loci M and A (genetic association
 142 between alleles present on the same haplotype). Similarly, $D_{M,A}$ measures the asso-
 143 ciation between alleles at loci M and A present on different haplotypes of the same
 144 individual.

145 In the following, we assume that both loci have weak effects (s , δu small) and
 146 derive an expression for the change in p_M (the frequency of allele 1 at locus M) to
 147 the first order in s and δu . We will see that this expression includes different forms of
 148 genetic associations. Assuming that the effective recombination rate is large relative
 149 to δu , we will then use a quasi-linkage equilibrium approximation (QLE) to express
 150 these associations in terms of allele frequencies and of the different parameters of the
 151 model. Finally, the result will be extrapolated to compute the overall strength of
 152 selection on a modifier allele affecting the mutation rate at a large number of selected
 153 loci, assuming that genetic associations between those loci can be neglected.

154 **Multilocus simulations.** Our simulation program (written in C++ and available
155 from Dryad) is modified from Roze (2015, 2016), and represents a finite population
156 of N diploid individuals whose genome consists in a linear chromosome along which
157 deleterious mutations occur every generation. For simplicity, all mutations have the
158 same selection and dominance coefficients (s, h). A mutation modifier locus is located
159 at the mid-point of the chromosome, and controls the deleterious mutation rate (the
160 mutation rate of an individual being the average of the values coded by its two modifier
161 alleles). At the start of each generation, the fitness of every individual is computed as

$$W = f_c(U) (1 - sh)^i (1 - s)^j \quad (4)$$

162 where U is the deleterious mutation rate of the individual (per haploid genome), f_c
163 the function representing the cost of replication fidelity, i, j are the number of het-
164 erozygous and homozygous deleterious alleles present in the genome of the individual.
165 In general, we will use the cost function $f_c(U) = e^{-\frac{c}{U}}$, but different functions will also
166 be considered (as explained in the Results section). To form each of the N juveniles of
167 the next generation, an individual is sampled randomly to serve as a maternal parent.
168 If the fitness of the individual (divided by the maximal fitness in the population) is
169 higher than a random number sampled from a uniform distribution between 0 and 1,
170 the individual is retained, otherwise another individual is sampled until the test is sat-
171 isfied. Under partial selfing, the mother self-fertilizes with probability α , in which case
172 the new individual is formed by two recombinant chromosomes from the same parent.
173 Under partial asexuality, the mother reproduces clonally with probability γ , in which
174 case the genome of the new individual is a copy of the maternal genome. If the mother
175 reproduces by outcrossing (with probability $1 - \alpha$ or $1 - \gamma$), a second individual is

176 sampled using the same procedure as above to serve as a father, and the genome of
177 the new individual is generated from recombinant chromosomes from both parents.
178 During meiosis, the number of cross-overs is sampled from a Poisson distribution with
179 parameter R (genome map length, in Morgans), and the position of each cross-over is
180 sampled from a uniform distribution. The parameter R will typically take large values
181 ($R = 20$) in order to mimic a whole genome with multiple chromosomes. Deleterious
182 mutations occur once the parents have been selected, before recombination (note
183 that different offspring from the same parent will carry different new mutations). The
184 number of new deleterious mutations on each chromosome is sampled from a Poisson
185 distribution whose parameter corresponds to the mutation rate of the parent, and the
186 position of each new mutation is sampled from a uniform distribution along the chro-
187 mosome. Back mutations do not occur, and any deleterious allele that has reached
188 fixation is removed from the population in order to increase execution speed.

189 During a number of preliminary generations (usually 2000), the deleterious
190 mutation rate of each individual (per haploid genome) is set to $U_{\text{init}} = 0.1$. Then,
191 new alleles coding for different mutation rates can appear at the modifier locus (at
192 rate $\mu_M = 10^{-3}U$ per generation, where U is the deleterious mutation rate of the
193 individual). When a mutation occurs at the modifier locus, the mutation rate coded
194 by the new allele is sampled from a Gaussian distribution centered on the value of
195 the allele before mutation, with variance $\sigma_M^2 = 10^{-4}$ (if the new value is negative, it
196 is set to zero). As explained in the Results section, different mutational models were
197 also considered, including a bias towards higher values of U and scaling of σ_M^2 with U .
198 The program generally runs for 10^6 generations, the equilibrium mutation rate being
199 computed by averaging over the last 8×10^5 generations.

200 A second simulation program considers a different genetic architecture for the
201 mutation rate: instead of being coded by a single locus, U depends on 1000 biallelic
202 loci evenly spaced along the chromosome. Alleles at each of these loci are denoted
203 0 and 1; genotypes carrying alleles 0 at all loci have mutation rate $U_{\min} = 0.01$. At
204 each locus, allele 1 increases the mutation rate, by an amount that is sampled (in-
205 dependently for each locus) from an exponential distribution with parameter λ . The
206 effects of alleles 1 at the same or at different loci are additive. During the first 2000
207 generations, all loci affecting the mutation rate are fixed for allele 0; then, during 10^6
208 generations mutations occur at rate $10^{-5} U$ at each of these loci (mutations and back
209 mutations occur at the same rate). Selection and recombination are implemented as
210 in the previous program.

211

212 ***Data availability.*** The authors state that all data necessary for confirming the
213 conclusions presented in the article are represented fully within the article. Data
214 available from the Dryad Digital Repository: <http://dx.doi.org/10.5061/dryad.1j6b0>.

215

RESULTS

216 **Change in frequency at the mutation modifier locus.** In the Appendix, we
217 show that an expression for the change in frequency of allele 1 at locus M , to the first
218 order in δu and s is given by:

$$\begin{aligned} \Delta p_M \approx \delta u \frac{d \ln f_c}{du} (1 + F) p_M q_M \\ - s h (D_{MA} + D_{M,A}) - s (1 - 2h) D_{MA,A}. \end{aligned} \quad (5)$$

219 The term on the first line of equation 5 represents the effect of the cost of replication
220 fidelity, favoring alleles that increase the mutation rate. This direct selective pressure

221 increases with the rate of inbreeding ($1 + F$ factor), due to increased homozygosity
 222 at locus M . The term on the second line represents the effect of indirect selection
 223 disfavoring mutator alleles, as these alleles tend to be more often associated with the
 224 deleterious allele at the second locus. Indeed, D_{MA} and $D_{M,A}$ represent the association
 225 between allele 1 at locus M and the deleterious allele at locus A on the same or on
 226 the other haplotype, while $D_{MA,A}$ represents the association between allele 1 at locus
 227 M and homozygotes for the deleterious allele at locus A . We now derive expressions
 228 for these associations at QLE.

229

230 **Expressions for genetic associations.** In the following, $D_{S,T}^{\text{sel}}$, $D_{S,T}^{\text{mut}}$ and $D'_{S,T}$ denote
 231 genetic associations measured after selection, mutation and recombination/segregation
 232 (respectively). Recursions for genetic associations over each step of the life cycle are
 233 computed to the first order in s and δu . We will also assume that the deleterious allele
 234 stays at low frequency and neglect terms in p_A . Under high effective recombination,
 235 it is sufficient to express associations to the first order in δu , neglecting terms in s .
 236 However, these expressions diverge when the effective recombination rate tends to zero
 237 (due to terms $r(1 - \alpha)$ or $r(1 - \gamma)$ in their denominators). In order to obtain more
 238 accurate expressions for the case where the effective recombination rate is of order s
 239 (assuming that the deleterious allele stays at mutation-selection balance and that δu
 240 is sufficiently small, so that the QLE approximation holds), we include terms in s in
 241 the recursions for genetic associations, by computing the effect of selection on these
 242 associations.

243

244 *Selection.* To leading order, the effect of selection on D_{MA} can be written as:

$$D_{MA}^{\text{sel}} \approx \text{E} \left[\frac{W}{\overline{W}} \frac{\zeta_{MA,\emptyset} + \zeta_{\emptyset,MA}}{2} \right]. \quad (6)$$

245 Note that equation 6 is an approximation, as it neglects the change due to selection of
 246 allele frequencies p_M and p_A that appear in $\zeta_{MA,\emptyset}$ and $\zeta_{\emptyset,MA}$ (see equation 1). However,
 247 taking this change in allele frequencies into account would introduce a term $\Delta_{\text{sel}} p_M \times$
 248 $\Delta_{\text{sel}} p_A$ of order $\delta u s$ (e.g., equation 23 in Barton and Turelli, 1991) that can be neglected
 249 here. From equations 6 and A6, neglecting terms in $(\delta u)^2$ and terms proportional to
 250 p_A , one obtains:

$$D_{MA}^{\text{sel}} \approx (1 - sh) D_{MA} - s(1 - h) D_{MA,A}. \quad (7)$$

251 Similarly, one arrives at:

$$D_{M,A}^{\text{sel}} \approx (1 - sh) D_{M,A} - s(1 - h) D_{MA,A} \quad (8)$$

252

$$D_{MA,A}^{\text{sel}} \approx (1 - s) D_{MA,A}. \quad (9)$$

253 Equations 7 – 9 show that selection tends to decrease genetic associations between the
 254 two loci, as it reduces the frequency of the deleterious allele in the population.

255

256 *Mutation.* The effect of genotype-dependent mutation on genetic associations can
 257 be computed as follows. Mutation changes the frequency of allele 1 at locus A to
 258 $p_A^{\text{mut}} = \bar{u}(1 - p_A) + (1 - \bar{u})p_A$ (where \bar{u} is the average mutation rate at locus A), while
 259 in a given individual, $X_{A,i}$ changes to $1 - X_{A,i}$ with probability u (the mutation rate of
 260 the individual at locus A), and remains unchanged with probability $1 - u$. Therefore,
 261 D_{MA} after mutation is given by:

$$D_{MA}^{\text{mut}} = \frac{1}{2} \text{E} \left[(X_{M,1} - p_M) \left[u(1 - X_{A,1}) + (1 - u)X_{A,1} - p_A^{\text{mut}} \right] \right. \\ \left. + (X_{M,2} - p_M) \left[u(1 - X_{A,2}) + (1 - u)X_{A,2} - p_A^{\text{mut}} \right] \right] \quad (10)$$

262 where E is the average over all individuals before mutation. Replacing $X_{i,j}$ by $\zeta_{i,j} + p_i$
 263 and u by $\bar{u} + \delta u (\zeta_{M,1} + \zeta_{M,2})$, equation 10 yields (after neglecting terms of order $(\delta u)^2$
 264 and terms in p_A):

$$\begin{aligned} D_{MA}^{\text{mut}} &\approx (1 - 2\bar{u}) D_{MA}^{\text{sel}} + \delta u (p_M q_M + D_{M,M}) \\ &\approx (1 - 2\bar{u}) D_{MA}^{\text{sel}} + \delta u (1 + F) p_M q_M . \end{aligned} \quad (11)$$

265 Similarly, one obtains:

$$D_{M,A}^{\text{mut}} \approx (1 - 2\bar{u}) D_{M,A}^{\text{sel}} + \delta u (1 + F) p_M q_M, \quad (12)$$

266

$$D_{MA,A}^{\text{mut}} \approx (1 - 4\bar{u}) D_{MA,A}^{\text{sel}} \quad (13)$$

267 (indeed, one can show that the term in δu of $D_{MA,A}^{\text{mut}}$ is of order p_A). Equations 11 and
 268 12 show that the modifier effect generates an association between the allele increasing
 269 mutation and the deleterious allele at the other locus, either on the same or on the
 270 other haplotype. The buildup of D_{MA} and $D_{M,A}$ is stronger under inbreeding (term
 271 $1 + F$ in equations 11 and 12), due to increased homozygosity at the modifier locus: the
 272 probability that a deleterious allele is present in the same genome as an allele coding
 273 for higher mutation is increased when the high-mutation allele is also present on the
 274 other haplotype.

275

276 *Recombination/segregation.* The effects of recombination and segregation depend on
 277 the reproductive system. Under partial selfing, we have:

$$D'_{MA} = (1 - r) D_{MA}^{\text{mut}} + r D_{M,A}^{\text{mut}} \quad (14)$$

278

$$D'_{M,A} = \frac{\alpha}{2} (D_{MA}^{\text{mut}} + D_{M,A}^{\text{mut}}) \quad (15)$$

279

$$D'_{MA,A} \approx \frac{\alpha}{2} [D_{MA,A}^{\text{mut}} + (1 - r) D_{MA}^{\text{mut}} + r D_{M,A}^{\text{mut}}], \quad (16)$$

280 equation 16 assuming that p_A is small. Under partial asexuality:

$$D'_{MA} = [1 - r(1 - \gamma)] D_{MA}^{\text{mut}} + r(1 - \gamma) D_{M,A}^{\text{mut}} \quad (17)$$

281

$$D'_{M,A} = \gamma D_{M,A}^{\text{mut}}, \quad D'_{MA,A} = \gamma D_{MA,A}^{\text{mut}}. \quad (18)$$

282

283 *QLE expressions.* The expressions given above can be used to compute solutions for
 284 D_{MA} , $D_{M,A}$ and $D_{MA,A}$ at QLE, corresponding to the equilibrium values of genetic as-
 285 sociations for given values of allele frequencies (under the assumption that associations
 286 equilibrate fast relative to changes in allele frequencies). For the case of a partially
 287 selfing population, one obtains (assuming $\bar{u} \ll s$, and thus neglecting terms in \bar{u}):

$$D_{MA} \approx \frac{\delta u (1 + F) (1 + 2Fr) p_M q_M}{s h_e + r [1 - F - s [h_e (1 - 2F) - F (2 - F)]]} \quad (19)$$

288

$$D_{M,A} \approx \frac{\delta u (1 + F) F (1 + 2r) p_M q_M}{s h_e + r [1 - F - s [h_e (1 - 2F) - F (2 - F)]]} \quad (20)$$

289

$$D_{MA,A} \approx F D_{MA} \quad (21)$$

290 with $h_e = h(1 - F) + F$, and $F = \alpha / (2 - \alpha)$. Equations 19 – 21 can be used to
 291 obtain the strength of indirect selection acting on the modifier locus, given by $s_{\text{ind}} =$
 292 $-s [h(D_{MA} + D_{M,A}) + (1 - 2h) D_{MA,A}] / (p_M q_M)$ (from equation 5):

$$s_{\text{ind}} \approx -\frac{\delta u (1 + F) s [h_e - 2F(F - 2h_e)r]}{s h_e + r [1 - F - s [h_e (1 - 2F) - F (2 - F)]]} \quad (22)$$

293 In the absence of selfing ($\alpha = 0$), s_{ind} simplifies to:

$$s_{\text{ind}} \approx -\frac{\delta u s h}{1 - (1 - s h)(1 - r)} \quad (23)$$

294 which agrees with the result obtained by Kimura when the modifier effect is weak
 295 (equation 2 in Kimura, 1967). Under complete selfing ($\alpha = 1$), s_{ind} simplifies to $-2\delta u$.

296 When linkage is tight (small r), a separation of timescales argument yields
 297 $D_{M,A} \approx F D_{MA}$ (Nordborg, 1997; Roze, 2016): this may also be seen from equations
 298 19 and 20, neglecting terms in r in the numerators. From this, one obtains that s_{ind}
 299 is equivalent to the result obtained under random mating (equation 23), replacing δu
 300 by $\delta u (1 + F)$, h by h_e and r by $r_e = r (1 - F)$. This can also be obtained directly by
 301 neglecting the term in r in the numerator of equation 22, and the term in rs in the
 302 denominator. Figure 1A compares the prediction from equation 22 and the prediction
 303 obtained by replacing δu , h and r in equation 23 by effective parameters: both yield
 304 undistinguishable results when linkage is sufficiently tight, but discrepancies appear
 305 when loci are loosely linked.

306 Under partial asexuality, genetic associations at QLE are given by:

$$D_{MA} \approx \frac{\delta u [1 + \gamma r] p_M q_M}{sh + r [1 - \gamma + sh (1 + \gamma)]} \quad (24)$$

307

$$D_{M,A} \approx \frac{\delta u \gamma p_M q_M}{1 - \gamma + sh \gamma}, \quad D_{MA,A} = 0. \quad (25)$$

308 As shown by Figure 1B, the strength of indirect selection s_{ind} is roughly equivalent
 309 to the expression obtained under random mating, replacing r by $r (1 - \gamma)$, as long
 310 as the rate of clonal reproduction γ stays moderate. This is not the case for higher
 311 values of γ , however, due to the extra contribution of the association $D_{M,A}$ (mutations
 312 generated on the other haplotype, that remain associated to the modifier allele due to
 313 clonal reproduction). As under complete selfing, one obtains that $s_{\text{ind}} = -2\delta u$ under
 314 full asexuality ($\gamma = 1$). In both cases, the strength of indirect selection in the absence
 315 of recombination corresponds to the increase in mutation load caused by the modi-
 316 fier (as the modifier allele stays associated with the deleterious alleles it generates).
 317 Under selfing, the increase in load equals the increase in haploid mutation rate (since

318 $L = u$ under full selfing), which is $2\delta u$ as individuals quickly become homozygous at
 319 the modifier locus. Under clonality, the increase in load is twice the increase in haploid
 320 mutation rate (since $L = 2u$, assuming h is significantly greater than zero), which is
 321 δu as individuals stay heterozygous at the modifier locus.

322

323 **Multilocus extrapolation and simulation results.** These two-locus results can be
 324 extrapolated to the case of a modifier affecting the mutation rate in the whole genome
 325 by integrating s_{ind} over the genetic map. If the map length is sufficiently large, the
 326 overall effect can be approximated by assuming free recombination among all loci, re-
 327 placing r by $1/2$ and δu by δU (the increase in haploid mutation rate caused by allele
 328 1 at the modifier locus) in the expressions above. The evolutionarily stable mutation
 329 rate (at which indirect selection to reduce the mutation rate exactly balances the cost
 330 of replication fidelity) can then be obtained by solving $s_{\text{direct}} + s_{\text{ind}} = 0$ for U , where
 331 the strength of direct selection is given by $s_{\text{direct}} \approx \delta U (1 + F) d \ln f_c / dU$, assuming
 332 δU is small (see equation 5). Under partial selfing and assuming free recombination,
 333 this yields

$$U_{\text{ESS}} \approx \sqrt{\frac{c [2 - \alpha (3 - \alpha) (1 - s)]}{2s [\alpha + h (2 - \alpha (1 + \alpha))]}}, \quad (26)$$

334 when the cost function is given by $f_c(U) = e^{-\frac{c}{U}}$, so that $d \ln f_c / dU = c/U^2$. Equation
 335 26 simplifies to $\sqrt{c/(2sh)}$ when $\alpha = 0$, and to \sqrt{c} when $\alpha = 1$. The equivalent
 336 expression for partial asexuality is given by:

$$U_{\text{ESS}} \approx \sqrt{\frac{c [1 - \gamma + sh \gamma] [1 - \gamma + sh (1 + 2\gamma)]}{sh (1 + \gamma) [2 (1 - \gamma) + 3sh \gamma]}}, \quad (27)$$

337 simplifying to $\sqrt{c/2}$ under full asexuality ($\gamma = 1$).

338 Figure 2 shows that the predicted value for the evolutionarily stable mutation

339 rate obtained by integrating equations 22 and 24–25 over the genetic map (see *Math-*
340 *ematica* notebook in Supplementary Material for the integration) generally fits well
341 with the multilocus simulation results (using our first simulation program, with a sin-
342 gle modifier locus). With a genome map length of 20 Morgans, the simpler expressions
343 obtained assuming free recombination (equations 26 and 27) also provide accurate pre-
344 dictions: discrepancies appear for lower values of s , due to the fact that deleterious
345 alleles segregate at higher numbers of loci, increasing the number of deleterious alleles
346 that are closely linked to the mutation modifier locus. Figures 2C and 2D show that
347 integrating equations 22 and 24–25 over the genetic map also provides accurate predic-
348 tions for lower values of map length R . As shown by Figure 2E, discrepancies between
349 analytical and simulation results appear for low values of h and intermediate selfing
350 rates ($h = 0.1, \alpha = 0.2, 0.4$ in Figure 2E): these discrepancies are possibly generated
351 by identity disequilibria between selected loci (correlations in homozygosity), which
352 are neglected in the analytical model (the discrepancies observed for $s = 0.01$ in Figure
353 2A may also be caused by identity disequilibria).

354 Supplementary Figure S1 shows the approximations obtained for U_{ESS} when
355 replacing h and r by the effective parameters $h(1 - F) + F$ and $r(1 - F)$ (under par-
356 tial selfing) and r by $r(1 - \gamma)$ (under partial clonality) in the expression for indirect
357 selection under random mating (equation 23). Although these approximations tend
358 to overestimate U_{ESS} by underestimating the strength of indirect selection generated
359 by distant loci, they often stay relatively close to the more exact expressions given
360 above, the discrepancy being stronger for intermediate selfing or clonality rates and
361 for weaker strength of selection against deleterious alleles.

362

363 **Effects of population size and mutational bias.** Figures 3A and 3B show that
 364 changing population size N from 10^4 to 10^3 or to 10^5 has little effect on the average
 365 mutation rate at equilibrium (although the variance of U around its average value
 366 increases as N decreases). This may seem at odds with the prediction of Lynch (2010)
 367 mentioned in the Introduction, which states that the mutation rate should be lower
 368 in populations with larger N_e , in regimes where a substantial proportion of muta-
 369 tions changing U are significantly affected by genetic drift. Indeed, averaging over
 370 the distribution of mutational effects at the modifier locus, the mean value of $2|\delta U|sh$
 371 (corresponding to the average strength of indirect selection acting on a new modifier
 372 allele under random mating and free recombination) is close to 10^{-4} in the simulations,
 373 and thus of the same order of magnitude as the strength of genetic drift (at least for
 374 $N = 10^3$ and 10^4). Nevertheless, decreasing N from 10^{-4} to 10^{-3} does not significantly
 375 affect the average value of U at equilibrium (see Figure 3). Similar results are obtained
 376 when using different forms of cost function f_c . In Figures 3C and 3D, $f_c(U) = U^c$,
 377 where c is set to ≈ 0.007 so that $U_{\text{ESS}} \approx 0.2$ under random mating for the parameter
 378 values used in Figure 3, according to our approximations: as illustrated by Figure 4,
 379 the selection gradient obtained ($d \ln f_c / dU = c/U$) is less steep around U_{ESS} than with
 380 the exponential cost function used in Figures 2 and 3A, 3B. Finally, $f_c = e^{aU + \frac{b}{2}U^2}$ in
 381 Figures 3E and 3F, yielding a linear selection gradient ($d \ln f_c / dU = a + bU$). Param-
 382 eters a and b were set to $a \approx 0.10$ and $b \approx -0.35$ so that $U_{\text{ESS}} \approx 0.2$ under random
 383 mating for the parameter values used in Figure 3, while the slope of the selection
 384 gradient at U_{ESS} is the same as with the $e^{-\frac{c}{U}}$ cost function used in Figures 2 and 3A,
 385 3B (see Figure 4). Because the mutation rate evolves to very low levels for these pa-
 386 rameter values at sufficiently high selfing or clonality rates, we maintained a minimum

387 mutation rate of $\mu_M = 10^{-4}$ at the modifier locus in the simulation program in order
388 to prevent that the population remains stuck in the absorbing state of perfect replica-
389 tion fidelity ($U = 0$). Supplementary Figure S2 shows the same simulation results as
390 Figures 3E and 3F, displayed on a log scale.

391 The reason for the limited effect of drift on the average value of U observed in
392 Figure 3 is the absence of mutational bias at the modifier locus: indeed, mutations
393 increase or decrease U with the same probability. Drift may have stronger effects when
394 mutations affecting U tend to occur more often in a particular direction (Zhang and
395 Hill, 2008; Lynch, 2011; Charlesworth, 2013): most likely in the direction of increased
396 values of U , as it should be easier to impair DNA replication fidelity than to improve
397 it. Indeed, when such a mutational bias is added in the simulation program (by intro-
398 ducing a parameter β such that a fraction $\beta > 0.5$ of mutations at the modifier locus
399 tend to increase U), the mutation rate evolves towards higher values when population
400 size is sufficiently small. When this is the case, U keeps increasing unless one assumes
401 that the average size of mutational steps δU is proportional to U , so that fewer muta-
402 tions may fix by drift as U reaches higher values (e.g., Lynch, 2011). Figure 5 shows
403 the results of simulations in which δU is sampled in a half-Gaussian distribution with
404 standard deviation $\sigma_M U$ (for both $\delta U > 0$ and $\delta U < 0$), where U is the mutation rate
405 coded by the modifier allele before mutation. For the parameter values used in Figure
406 5, the equilibrium mutation rate is slightly higher for $N = 10^4$ than for $N = 10^5$,
407 but generally remains close to the ESS value (see Supplementary Figure S3 for the
408 same results shown on a log scale). Genetic drift has a much stronger effect on the
409 equilibrium value of U when $N = 10^3$, however. As expected, increasing the degree of
410 mutational bias (by increasing β) or decreasing the average size of mutational steps

411 δU (by reducing σ_M^2) amplifies the effects of drift, causing higher values of U to evolve.
 412 Intermediate selfing or clonality rates bring U closer to its ESS value (by increasing the
 413 strength of indirect selection), but U may increase again as α or γ approach 1, due to
 414 background selection amplifying the effect of drift. In some simulations, background
 415 selection caused a runaway process in which the reduction in N_e leads to elevated
 416 mutation rate, further reducing N_e . When this is the case, U reaches very high val-
 417 ues and the program has to be stopped manually: this happened for clonality rates
 418 higher than the right-most points in Figure 6B, D, F, and for $\alpha = 0.2$, $\alpha = 0.3$ and
 419 $0.93 \leq \alpha \leq 0.99$ in Figure 6E (while an equilibrium was reached for $\alpha = 1$). As shown
 420 by Supplementary Figures S4 – S7, qualitatively similar results were obtained under
 421 the different cost functions shown in Figure 4.

422 Similar results were also obtained using our second simulation program, repre-
 423 senting a more realistic genetic architecture in which U is controlled by L biallelic loci.
 424 Since the minimal mutation rate (corresponding to the mutation rate of a genotype
 425 carrying allele 0 at each mutation modifier locus) is U_{\min} , and since the heterozy-
 426 gous effect of each modifier locus is sampled from an exponential distribution with
 427 parameter λ (whose average is $1/\lambda$), the average value of U should thus be close to
 428 $U_{\text{drift}} = U_{\min} + L/\lambda$ in regimes where the evolution of U is mainly controlled by drift
 429 (assuming large L , and additivity within and between modifier loci). Below U_{drift} ,
 430 mutations at modifier loci thus tend to increase U (mutational bias). Figure 6 shows
 431 simulation results for $L = 1000$, $\lambda = 500$ and $U_{\min} = 0.01$ (so that $U_{\text{drift}} \approx 2$). As can
 432 be seen on the figure, U becomes closer to its mutation-drift equilibrium value U_{drift}
 433 as N decreases. Again, increasing the selfing rate or the clonality rate tends to reduce
 434 U by increasing the strength of indirect selection; however, above a given threshold

435 for α or γ (that depends on population size), U increases as the selfing or clonality
436 rate increases (due to background selection effects). Note that we could not obtain
437 estimates for the equilibrium mutation rate under high clonality rates (Figure 6B, on
438 the right of the right-most points) because deleterious alleles tend to accumulate in
439 the heterozygous state in the population, causing the program to become increasingly
440 slow.

441 DISCUSSION

442 It is widely accepted that mutation rates are maintained at low levels in order
443 to avoid producing an overly strong burden of deleterious alleles. In this paper, we
444 confirm that this deterministic force favoring lower mutation rates is increased by
445 uniparental reproduction, and compute the strength of this effect in populations with
446 intermediate selfing rates or clonality rates. In agreement with previous separation
447 of timescales arguments (Nordborg, 1997; Roze, 2016), when linkage between loci is
448 sufficiently tight the result obtained under partial selfing becomes equivalent to the
449 expression obtained under random mating (Kimura, 1967), replacing the dominance
450 coefficient of deleterious alleles and recombination rates by the effective parameters
451 $h(1 - F) + F$ and $r(1 - F)$; however, this expression underestimates the strength
452 of indirect selection generated by loosely linked loci. Introducing a direct fitness cost
453 associated with DNA replication fidelity, we could obtain simple approximations for the
454 evolutionarily stable mutation rate, which were confirmed by multilocus, individual-
455 based simulations, in the absence of mutational bias at the mutation modifier locus.

456 When a mutational bias towards lower fidelity of DNA replication (*i.e.*, higher

457 mutation rate) is added into the model, the average value of the mutation rate at
458 equilibrium becomes more sensitive to genetic drift, in agreement with general results
459 on the evolution of quantitative traits under mutation, selection and drift (Zhang and
460 Hill, 2008; Charlesworth, 2013). In that case, the mutation rate U may reach high
461 values when mutations affecting U have a weak effect, so that the effect of indirect
462 selection acting on these mutations becomes weaker than the strength of genetic drift:
463 this is the essence of the argument proposed by Lynch to explain the observed negative
464 correlation between estimated effective population size N_e and the mutation rate (e.g.,
465 Lynch, 2010; Sung et al., 2012; Lynch et al., 2016). However, the mutational bias by
466 itself is not a sufficient condition for U to stabilize around a value that depends on
467 N_e . This will occur under the extra assumption that the average size of mutational
468 steps at mutation modifier loci increases with the mutation rate, so that the relative
469 effect of drift at these loci becomes weaker as U increases (Lynch, 2011, Figure 5 of the
470 present article). Alternatively, when U is affected by a sufficiently large number of loci
471 with a distribution of effects, the fraction of loci at which indirect selection is weaker
472 than drift will decrease as N_e increases, which may also generate a negative relation
473 between the average value of U and N_e (Figure 6). After adding these ingredients
474 into our simulation programs, we observed three possible types of outcomes: either
475 drift has only a limited effect, and U stays close to its deterministic equilibrium (at
476 which indirect selection generated by deleterious alleles exactly balances the cost of
477 replication fidelity), or U stabilizes around a higher value that depends on N_e , or a
478 runaway process occurs, under which drift causes the evolution of higher U , in turn
479 reducing N_e through background selection effects, causing further increase in U (which
480 should eventually lead to population extinction through mutational meltdown).

481 Given that per-nucleotide mutation rates are very low in most species, the
482 hypothesis of a mutational bias towards higher mutation rates seems reasonable. Very
483 little is known on the distribution of the effects of mutations affecting U , however,
484 or on how this distribution may change as U evolves. Interactions between mutations
485 affecting DNA repair pathways have been demonstrated in bacteria and yeast. In some
486 cases, positive epistasis (on the mutation rate) has been shown between mutations in
487 genes with partially redundant effects, such as *MutM* and *MutY* in *E. coli* (Michaels
488 et al., 1992; Fowler et al., 2003), or *MSH3* and *MSH6* in *S. cerevisiae* (Marsischky
489 et al., 1996). These examples provide possible scenarios under which the effect of a
490 modifier allele would increase with the baseline mutation rate. However, examples of
491 negative epistasis also exist, for example when a repair pathway involves the combined
492 activity of two proteins (such as *MSH2* and *MSH6* in yeast, Marsischky et al., 1996).
493 Overall, we still lack a clear picture of how the average effect of mutator/antimutator
494 alleles should change with the baseline mutation rate. Furthermore, these studies
495 generally focus on mutators with large effects, which may not be representative of the
496 majority of mutations affecting U . Obtaining more detailed information on the genetic
497 architecture of mutation rate variation within natural populations would represent an
498 important progress, but remains a formidable task.

499 While our results show that the effects of partial selfing and partial clonality are
500 very similar in regimes where drift has only a limited effect, differences appear when
501 drift is stronger and may lead to mutation accumulation. Muller’s ratchet occurred in
502 some of our simulations with partial or complete selfing: for $s = 0.01$ and $\alpha = 1$ in
503 Figure 2, and in different cases with $N = 1000$ in Figure 5 (for $\alpha = 1$ in 5A, $\alpha = 0.98$
504 and 1 in 5B, $\alpha = 0.2, 0.3$ and $0.93 \leq \alpha \leq 1$ in 5E). It also occurred for $N = 1000$,

505 2000, 3000 and high α (≥ 0.9) in Figure 6. Because our simulation program removes
506 fixed mutations, it could still continue to run and U generally stabilized, except for
507 $\alpha = 0.2, 0.3$ and $0.93 \leq \alpha \leq 0.99$ in Figure 5E, where U increased to very high values
508 and the program had to be stopped when $U > 30$. However, in all these cases any
509 real population would eventually reach extinction due to mutation accumulation. By
510 contrast, at high clonality rates mutations tend to accumulate in the heterozygous state
511 (even when $\gamma < 1$), an effect already observed in previous studies by Charlesworth et
512 al. (1993a,b) and Roze and Michod (2010). Because these mutations could in principle
513 still be removed from the population by rare segregation events, the simulation program
514 does not eliminate them and becomes increasingly slow. This occurred in nearly all
515 cases with $\gamma = 1$ in Figures 2 and 3, although the mutation rate reached an equilibrium
516 before the program had to be stopped. It also occurred for values of γ higher than the
517 right-most points in Figures 5 and 6 (at a faster rate as γ increased), in which case
518 the program had to be stopped before U had reached equilibrium. Again, in all these
519 situations the population would eventually go extinct by mutational meltdown. These
520 results outline two important differences between partial selfing and partial clonality:
521 (1) the mutation accumulation regime is reached sooner under partial clonality than
522 under partial selfing as the rate of uniparental reproduction increases (due to the
523 absence of segregation), and (2) a runaway process leading to very high mutation
524 rates may occur at moderate selfing rates ($\alpha = 0.2, 0.3$ in Figure 5E, see also Figures
525 S2 and S3), while it does not occur at higher selfing rates. This last effect is not
526 observed under partial clonality, and could possibly be due to identity disequilibria
527 between selected loci reducing the efficiency of selection (e.g., Roze, 2015).

528 Provided that mutation rate polymorphism exists within populations, the evo-

529 lution of U could in principle interact with the evolution of different aspects of re-
530 productive systems, such as reproductive modes or mating systems. In regimes where
531 the effect of drift on the evolution of U stays negligible, this should favor the evo-
532 lution of uniparental reproduction, as it should be associated with lower mutation
533 rates (Sloan and Panjeti, 2010). However, the evolution of U may have opposite ef-
534 fects in regimes where it is more strongly affected by drift, and where high rates of
535 uniparental reproduction may trigger the evolution of higher mutation rates, through
536 stronger background selection effects. Whether the evolution of the mutation rate
537 would occur on a sufficiently fast timescale to significantly affect the evolution of re-
538 productive systems should in principle depend on the genetic architecture of U and
539 of the reproductive system; however, this should be explored more rigorously using
540 theoretical approaches. Even if mutation rate evolution is not fast enough to have a
541 significant impact on evolutionary transitions between mating systems, U may change
542 in response to a switch in reproductive system. This may affect the species-level se-
543 lection component acting on the evolution of reproductive systems, for example by
544 accelerating the extinction of selfing or asexual lineages by mutational meltdown if U
545 reaches higher levels due to stronger drift. More generally, it may affect the long-term
546 evolutionary potential of selfing or asexual species, or the relation between the selfing
547 rate and level of inbreeding depression across species. It would thus be of particular
548 interest to obtain mutation rate estimates from different pairs of closely related species
549 with contrasted reproductive systems, in order to see if a general pattern emerges.

550 Finally, our model makes a number of assumptions on selection against deleteri-
551 ous alleles: in particular, all deleterious alleles have the same selection and dominance
552 coefficient, while drift has no significant effect on their equilibrium frequency. Given

553 the concave shape of the relation between the selection coefficient of deleterious alleles
554 s and the strength of indirect selection acting on the mutation rate, introducing vari-
555 ability in s across loci (while keeping the average constant) should in principle reduce
556 the overall strength of selection for lower mutation rates. However, our deterministic
557 model cannot be used to predict the effect of deleterious alleles for which $N_e s \sim 1$
558 (whose frequency is significantly affected by drift), while our infinite sites simulation
559 program cannot deal with very low s values as individuals then carry very large num-
560 bers of mutations, causing the program to become extremely slow. Given that an
561 important proportion of mutations may possibly fall in the $N_e s \sim 1$ parameter region
562 (e.g., Eyre-Walker and Keightley, 2007), it would be important to explore the effect
563 of such weakly selected deleterious alleles on the evolution of mutation rate modifiers.
564 This may introduce new effects of reproductive systems on mutation rate evolution,
565 as the reproductive system may affect the proportion of mutations on which natural
566 selection is effective (by affecting N_e). Our model also assumes that all mutations
567 affecting fitness are deleterious: while previous theoretical work has shown that ben-
568 efiticial mutations should only have a minor role on the evolution of mutation rates in
569 sexual, outcrossing populations (Leigh, 1970; Johnson, 1999b), their effect should be-
570 come more important in populations undergoing high rates of selfing or clonality (since
571 mutator alleles can stay associated with the beneficial alleles they produced), and may
572 increase the equilibrium mutation rate in such populations. Last, as in most theoreti-
573 cal studies of mutation rate evolution, we have neglected epistatic interactions between
574 selected mutations: in particular, our model does not take into account possible com-
575 pensatory effects between deleterious alleles (*e.g.*, reciprocal sign epistasis). Allowing
576 the sign of the fitness effect of mutations to depend on the genetic background (which

577 typically occurs in models of directional selection acting on quantitative traits) may
578 affect the selective forces acting on mutation modifier loci. Exploring the evolution
579 of the mutation rate under more realistic assumptions on the genetic architecture of
580 fitness will be the subject of future work.

581

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Using the definitions given in the main text, the fitness of an individual can be written as:

$$W = f_c(u) [1 - sh(X_{A,1} + X_{A,2}) - s(1 - 2h)X_{A,1}X_{A,2}] \quad (\text{A1})$$

where f_c represents the cost of replication fidelity and u is the mutation rate of the individual, given by:

$$u = u_0 + \delta u (X_{M,1} + X_{M,2}). \quad (\text{A2})$$

Replacing $X_{M,j}$ by $\zeta_{M,j} + p_M$ and noting that $\bar{u} = u_0 + 2\delta u p_M$ is the average mutation rate at locus A , we have $u = \bar{u} + \delta u (\zeta_{M,1} + \zeta_{M,2})$, and a Taylor series of $f_c(u)$ to the first order in δu yields:

$$f_c(u) = f_c(\bar{u}) \left[1 + \delta u \frac{1}{f_c(\bar{u})} \frac{df_c}{du} (\zeta_{M,1} + \zeta_{M,2}) \right] + o(\delta u). \quad (\text{A3})$$

Since $f_c(u) = f_c(\bar{u})$ when $\delta u = 0$, equation A4 may also be written as:

$$f_c(u) = f_c(\bar{u}) \left[1 + \delta u \frac{d \ln f_c}{du} (\zeta_{M,1} + \zeta_{M,2}) \right] + o(\delta u). \quad (\text{A4})$$

Replacing $X_{A,j}$ by $\zeta_{A,j} + p_A$ in equation A1, one then obtains (to the first order in δu):

$$W \approx f_c(\bar{u}) (1 - T_A) \left[1 + \delta u \frac{d \ln f_c}{du} (\zeta_{M,1} + \zeta_{M,2}) \right] \times \left[1 - \frac{sh}{1 - T_A} (\zeta_{A,1} + \zeta_{A,2}) - \frac{s(1 - 2h)}{1 - T_A} (\zeta_{A,A} - D_{A,A}) \right] \quad (\text{A5})$$

with $T_A = 2sh p_A + s(1 - 2h)(p_A^2 + D_{A,A})$. Denoting \bar{W} the average fitness in the

703 population, this yields (to the first order in δu and s):

$$\begin{aligned}
\frac{W}{\bar{W}} &\approx 1 + \delta u \frac{d \ln f_c}{du} (\zeta_{M,1} + \zeta_{M,2}) \\
&- sh (\zeta_{A,1} + \zeta_{A,2}) - s(1 - 2h) (\zeta_{A,A} - D_{A,A}) \\
&- \delta u \frac{d \ln f_c}{du} sh (\zeta_{MA,\emptyset} + \zeta_{\emptyset,MA} + \zeta_{M,A} + \zeta_{A,M} - 2D_{MA} - 2D_{M,A}) \\
&- \delta u \frac{d \ln f_c}{du} s(1 - 2h) [\zeta_{MA,A} + \zeta_{A,MA} - (\zeta_{M,1} + \zeta_{M,2}) D_{A,A} - 2D_{MA,A}].
\end{aligned} \tag{A6}$$

704 The change in frequency of allele 1 at locus M (over one generation) is given by:

$$\begin{aligned}
\Delta p_M &= \text{E} \left[\frac{W}{\bar{W}} \frac{X_{M,1} + X_{M,2}}{2} \right] - p_M \\
&= \text{E} \left[\frac{W}{\bar{W}} \frac{\zeta_{M,1} + \zeta_{M,2}}{2} \right]
\end{aligned} \tag{A7}$$

705 where E is the average over all individuals just before selection. From equations 2 and

706 A6, and using the fact that repeated indices appearing in genetic associations can be

707 eliminated using the relation $D_{Sii,\mathbb{T}} = p_i q_i D_{S,\mathbb{T}} + (1 - 2p_i) D_{Si,\mathbb{T}}$ (with $q_i = 1 - p_i$, e.g.,

708 equation 5 in Kirkpatrick et al., 2002), one arrives at:

$$\begin{aligned}
\Delta p_M &\approx \delta u \frac{d \ln f_c}{du} (p_M q_M + D_{M,M}) \\
&- sh (D_{MA} + D_{M,A}) - s(1 - 2h) D_{MA,A} \\
&- \delta u \frac{d \ln f_c}{du} sh [(1 - 2p_M) (D_{MA} + D_{M,A}) + 2D_{MA,M}] \\
&- \delta u \frac{d \ln f_c}{du} s(1 - 2h) (D_{MA,MA} - D_{M,M} D_{A,A}).
\end{aligned} \tag{A8}$$

709 The first term of equation A8 represents the effect of direct selection acting at locus

710 M (due to the cost of replication fidelity), while the other terms (involving genetic

711 associations) correspond to indirect selection. Associations D_{MA} , $D_{M,A}$ and $D_{MA,A}$

712 are of order δu , and the term on the second line of equation A8 is thus of order $\delta u s$.

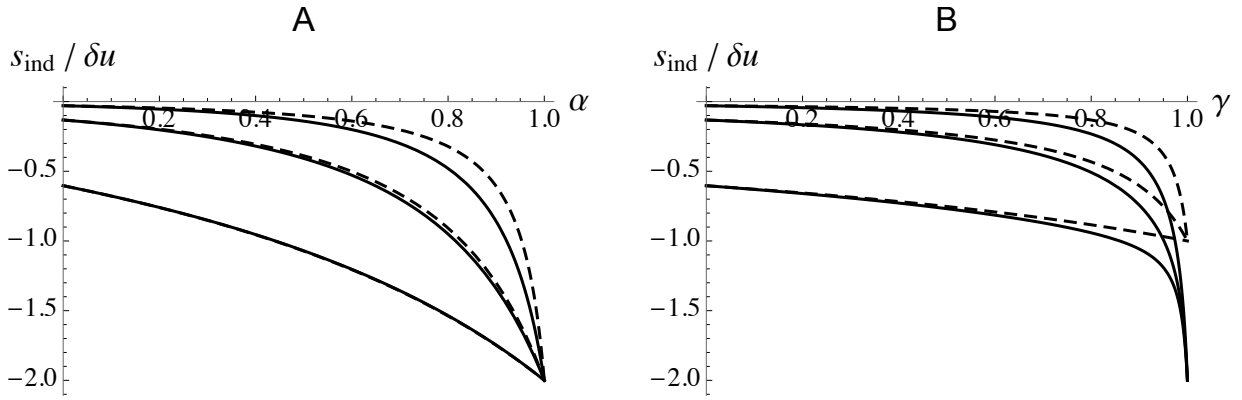
713 Furthermore, one can show that the association $D_{MA,M}$ is of order s (e.g., Roze, 2015),

714 and the third line of equation A8 can thus be neglected (terms of order $(\delta u)^2 s$ and

715 $\delta u s^2$). Finally, the term $D_{MA,MA} - D_{M,M} D_{A,A}$ that appears on the last line of equation

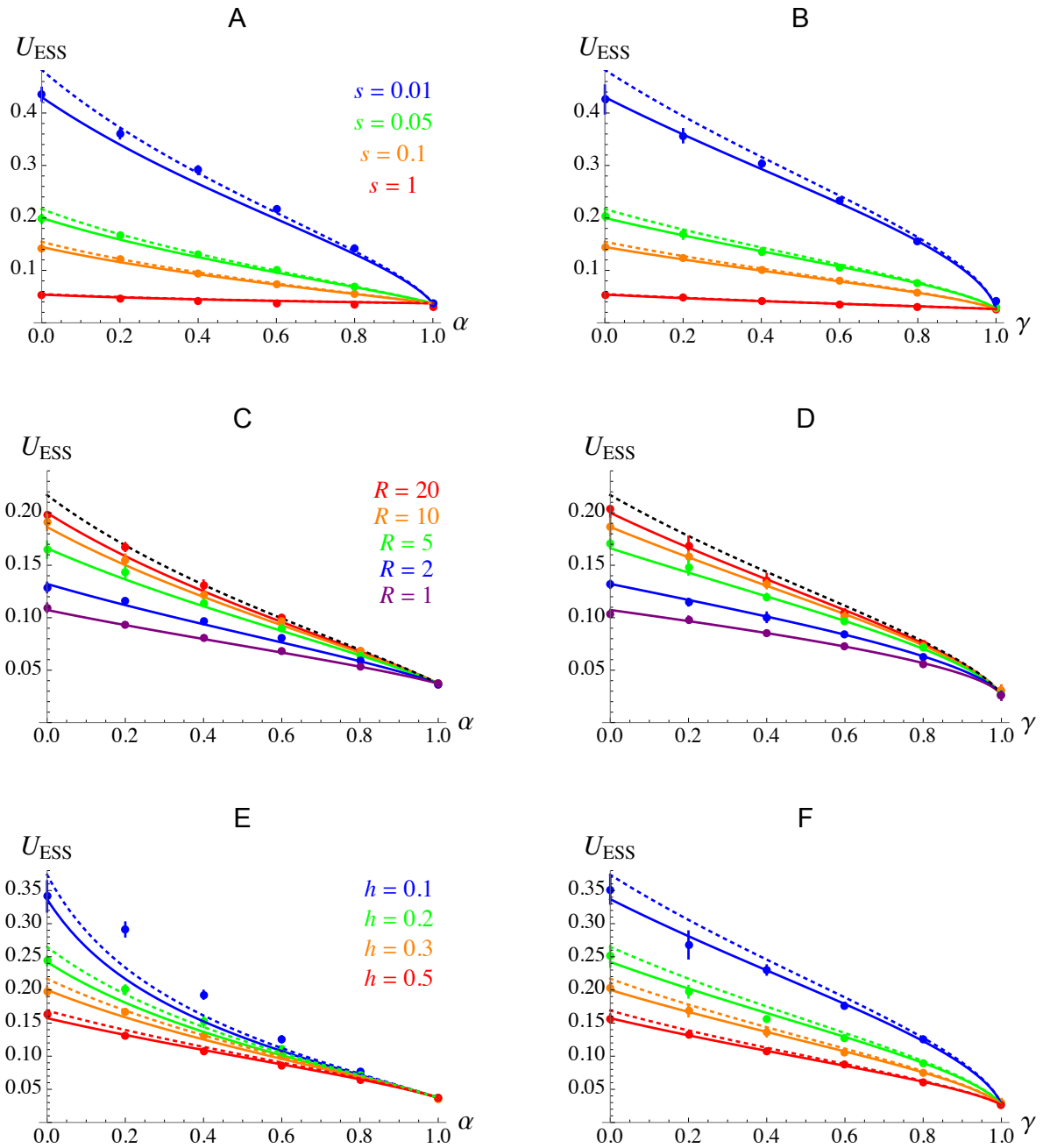
716 A8 can also be written $G_{MA} p_M q_M p_A q_A$, where G_{MA} is the identity disequilibrium
 717 between loci M and A , generated by partial selfing (Roze, 2015). Similarly, one can
 718 show that the association $D_{M,M}$ (measuring the excess homozygosity at locus M)
 719 that appears on the first line of equation A8 is affected by the identity disequilibrium
 720 through a term proportional to $s(1-2h)(D_{MA,MA} - D_{M,M}D_{A,A})$ — see equation 5 in
 721 Roze, 2015. However, we show in the main text that contrarily to $D_{MA,MA} - D_{M,M}D_{A,A}$,
 722 the expressions for D_{MA} , $D_{M,A}$ and $D_{MA,A}$ at QLE do not tend to zero when the
 723 frequency of the deleterious allele p_A tends to zero. Therefore, assuming that the
 724 deleterious allele stays at low frequency (p_A small), we may neglect terms proportional
 725 to p_A , and thus neglect terms involving the identity disequilibrium. In this case, $D_{M,M}$
 726 can be written as $F p_M q_M$, where F is the inbreeding coefficient (e.g., Roze, 2015),
 727 and equation A8 simplifies to:

$$\begin{aligned}
 \Delta p_M \approx \delta u \frac{d \ln f_c}{du} (1 + F) p_M q_M & \\
 - s h (D_{MA} + D_{M,A}) - s (1 - 2h) D_{MA,A} & .
 \end{aligned}
 \tag{A9}$$



728

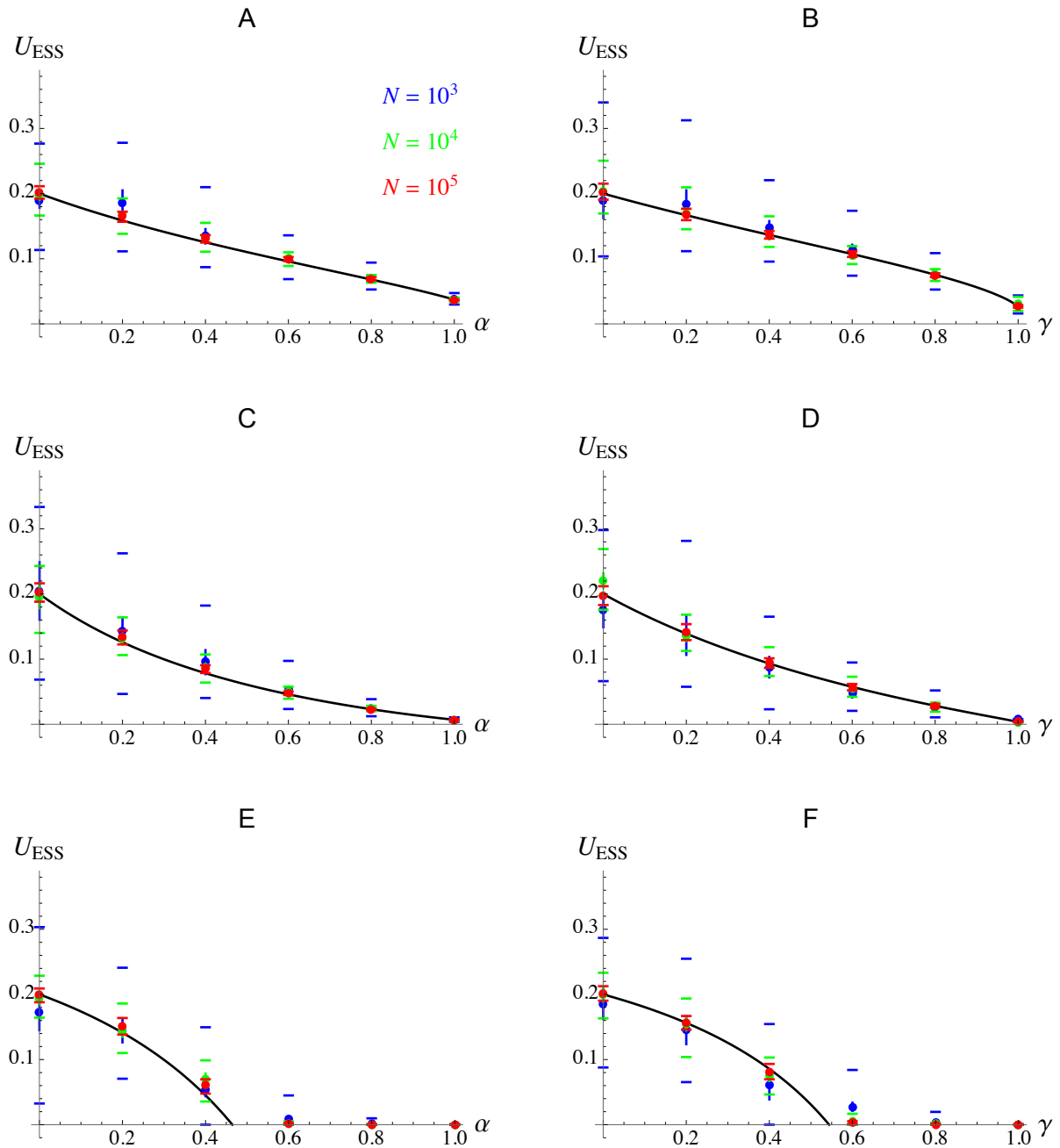
729 **Figure 1.** Strength of indirect selection acting on a mutation modifier locus (scaled
730 by δu) as a function of the selfing rate (A) and the clonality rate (B). Solid curves:
731 predictions from equations 22 and 24–25. Dashed curves, A: predictions obtained by
732 replacing δu by $\delta u (1 + F)$, h by $h_e = h (1 - F) + F$ and r by $r_e = r (1 - F)$ in the ex-
733 pression obtained under random mating (equation 23). Dashed curves, B: predictions
734 obtained by replacing r by $r (1 - \gamma)$ in the expression obtained under random mating.
735 Parameter values: $s = 0.05$, $h = 0.3$, $r = 0.01, 0.1$ and 0.5 from bottom to top.



736

737 **Figure 2.** Evolutionarily stable mutation rate (per haploid genome) as a function of
 738 the selfing rate (A, C, E) and the clonality rate (B, D, F), for different values of the
 739 strength of selection against deleterious alleles s (A, B), genome map length R (C,
 740 D) and dominance coefficient of deleterious alleles h (E, F). Solid curves: analytical
 741 predictions obtained by integrating equations 22 and 24–25 over the genetic map (see

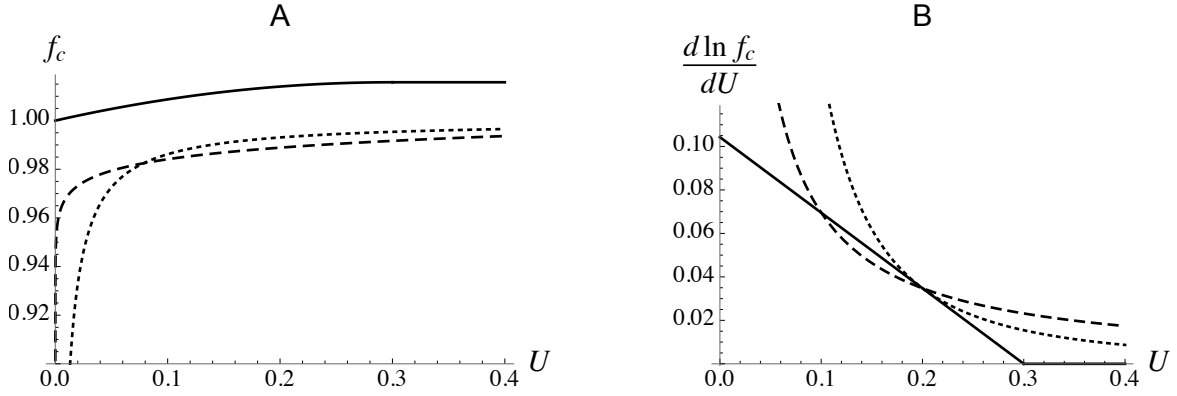
742 *Mathematica* notebook). Dashed curves: approximations for freely recombining loci
743 (equations 26 and 27). Dots: multilocus simulation results. Parameter values (unless
744 specified otherwise): $s = 0.05$, $h = 0.3$, $R = 20$, $N = 10^4$ (in the simulations). The cost
745 function is $f_c = e^{-\frac{c}{\bar{v}}}$, c being set to ≈ 0.0014 so that $U_{\text{ESS}} \approx 0.2$ under random mating
746 when $s = 0.05$, $h = 0.3$ and $R = 20$ according to our analytical results. In this and the
747 next figures, error bars are computed by splitting the results from each simulation into
748 batches of 10^5 generations and computing the variance between batches. Error bars
749 show ± 1.96 SE, and are smaller than the size of symbols in most cases. Simulations
750 with $s = 0.01$ (A, B) lasted 10^7 generations (instead of 10^6) in order to better estimate
751 the average mutation rate.



752

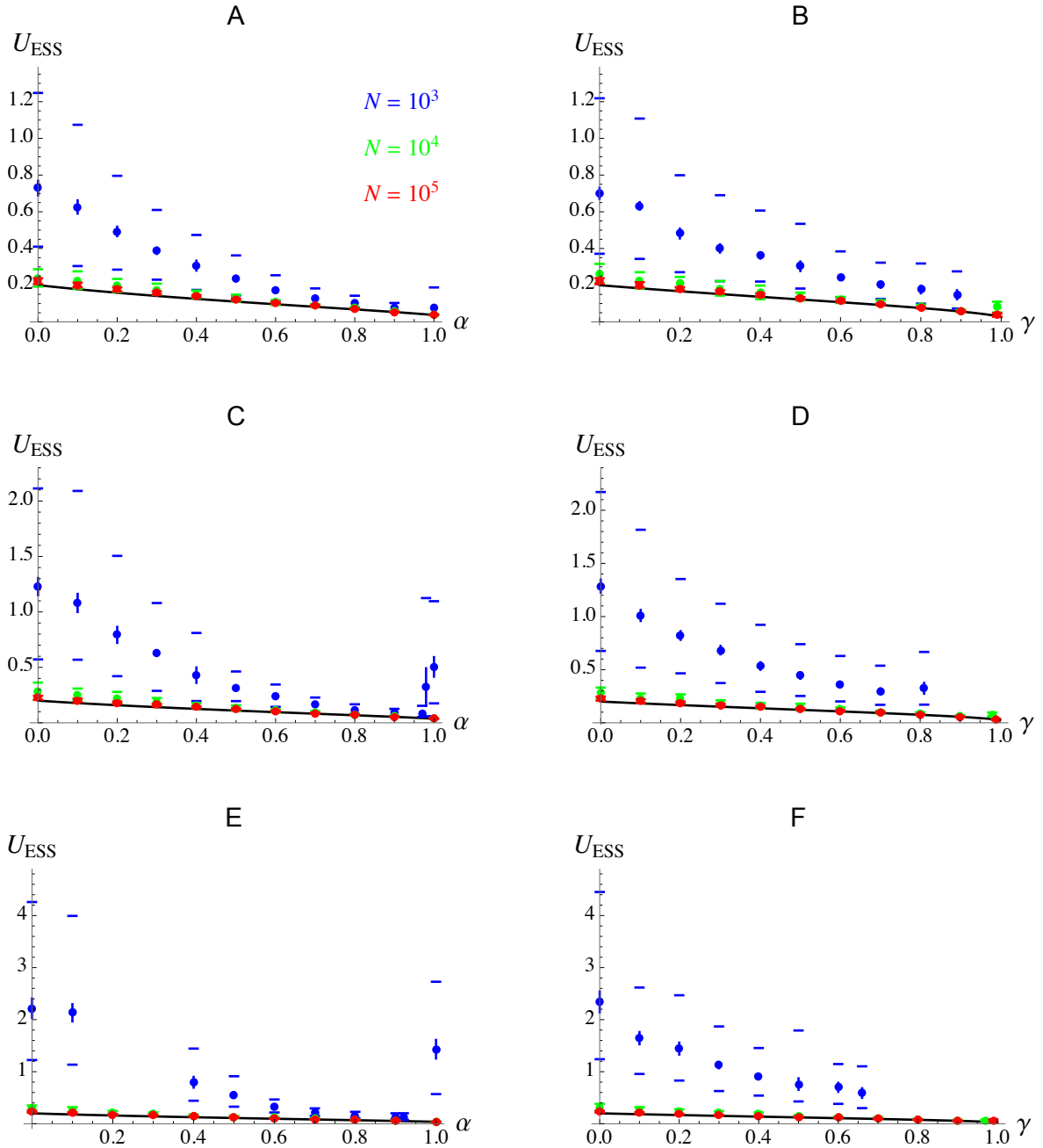
753 **Figure 3.** A, B: same as Figure 2 for different values of population size N (in the
 754 simulations), and with $s = 0.05$, $R = 20$, $h = 0.3$, cost function $f_c = e^{-\frac{c}{v}}$. The colored
 755 horizontal bars show the top and bottom 98th percentiles of the distribution of U over
 756 the last 8×10^5 generations of the simulation (once equilibrium has been reached).
 757 Black curves: analytical predictions obtained by integrating equations 22 and 24–25

758 over the genetic map. C, D: cost function $f_c = U^c$, with $c \approx 0.007$. E, F: cost function
759 $f_c = e^{aU + \frac{b}{2}U^2}$, with $a \approx 0.10$ and $b \approx -0.35$ (see Figure 4). Simulations with $N = 10^3$
760 lasted 10^7 generations (instead of 10^6) in order to better estimate the average mutation
761 rate.



762

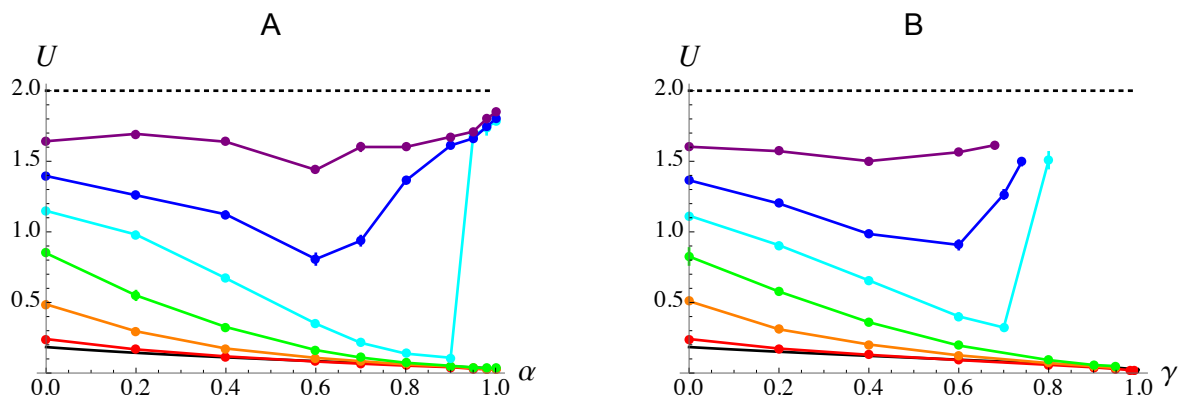
763 **Figure 4.** A: the different cost functions used in Figure 3: dotted: $f_c = e^{-\frac{c}{U}}$ (with
764 $c \approx 0.0014$); dashed: $f_c = U^c$ (with $c \approx 0.007$); solid: $f_c = e^{aU + \frac{b}{2}U^2}$ (with $a \approx 0.10$,
765 $b \approx -0.35$). In the last case, we assumed that f_c stays equal to its maximum value
766 of $e^{-\frac{a^2}{2b}}$ (obtained for $U_{\max} = -a/b$, here 0.3) when $U > U_{\max}$ (*i.e.*, direct selection
767 vanishes when $U > U_{\max}$). B: selection gradients generated by these cost functions. In
768 all cases, direct selection exactly balances indirect selection when $s = 0.05$, $h = 0.3$,
769 $R = 20$ and $U = 0.2$ under random mating, according to equation 23.



770

771 **Figure 5.** Equilibrium mutation rate as a function of the selfing rate (A, C, E) and
 772 the clonality rate (B, D, F) for different values of population size N , with mutational
 773 bias at the modifier locus. Mutations at the modifier locus increase U with probability
 774 β , and decrease U otherwise. In both cases, the mutational effect δU is drawn from
 775 a half-Gaussian distribution with standard deviation $\sigma_M U$ (where U is the mutation

776 rate coded by the modifier allele before mutation). A, B: $\beta = 0.9$, $\sigma_M^2 = 0.01$; C,
777 D: $\beta = 0.95$, $\sigma_M^2 = 0.01$; E, F: $\beta = 0.9$, $\sigma_M^2 = 0.0025$. Other parameter values:
778 $s = 0.05$, $h = 0.3$, $R = 20$, $c = 0.0014$ ($f_c = e^{-\frac{c}{\bar{v}}}$). Black curves: analytical predictions
779 obtained by integrating equations 22 and 24–25 over the genetic map. For clonality
780 rates higher than the right-most points (in B, D, F), deleterious alleles accumulate and
781 the simulation has to be stopped before U has reached its equilibrium value. Under
782 partial selfing, a runaway leading to very high values of U occurred for $N = 10^3$ and
783 $\alpha = 0.2$, $\alpha = 0.3$ and $0.93 \leq \alpha \leq 0.99$ in E.



784

785 **Figure 6.** Equilibrium mutation rate as a function of the selfing rate (A) and the
786 clonality rate (B). Colored dots and lines: results from the second simulation program,
787 in which U is coded by 1000 biallelic loci (evenly spaced along the chromosome) whose
788 effects are sampled from an exponential distribution with parameter $\lambda = 500$. Pop-
789 ulation size: $N = 1000, 2000, 3000, 5000, 10^4$ and 10^5 from top to bottom. Other
790 parameters: $s = 0.05, h = 0.3, R = 20, c = 0.001$ ($f_c = e^{-\frac{c}{\bar{v}}}$). Black curves: analytical
791 predictions under free recombination (equations 26 and 27); dotted lines: $U_{\text{drift}} \approx 2$.
792 In B, for clonality rates higher than the right-most points (for each population size),
793 deleterious alleles accumulate in the heterozygous state, and the program has to be
794 stopped before U has reached its equilibrium value.