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► **To cite this version:**

Denis Roze. Selection for sex in finite populations. *Journal of Evolutionary Biology*, 2014, 27, pp.1304-132. 10.1111/jeb.12344 . hal-01137482

HAL Id: hal-01137482

<https://hal.science/hal-01137482>

Submitted on 31 Mar 2015

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“SEX UNCOVERED” SPECIAL ISSUE:

Selection for sex in finite populations

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Running head: Drift and selection for sex

ABSTRACT

1
2 Finite population size generates interference between selected loci, which has
3 been shown to favour increased rates of recombination. In this paper, I present differ-
4 ent analytical models exploring selection acting on a “sex modifier locus” (that affects
5 the relative investment into asexual and sexual reproduction) in a finite population.
6 Two forms of selective forces act on the modifier: direct selection due to intrinsic costs
7 associated with sexual reproduction, and indirect selection generated by one or two
8 other loci affecting fitness. The results show that indirect selective forces differ from
9 those acting on a recombination modifier even in the case of a haploid population: in
10 particular, a single selected locus generates indirect selection for sex, while two loci are
11 required in the case of a recombination modifier. This effect stems from the fact that
12 modifier alleles increasing sex escape more easily from low-fitness genetic backgrounds
13 than alleles coding for lower rates of sex. Extrapolating the results from three-locus
14 models to a large number of loci at mutation-selection balance indicates that in the
15 parameter range where indirect selection is strong enough to outweigh a substantial
16 cost of sex, interactions between selected loci have a stronger effect than the sum of in-
17 dividual effects of each selected locus. Comparisons with multilocus simulation results
18 show that such extrapolations may provide correct predictions for the evolutionarily
19 stable rate of sex, unless the cost of sex is high.

20

21 *Keywords:* deleterious mutation, evolution of sex, genetic drift, modifier model, mul-
22 tilocus model, selection

24 Almost 50 years ago, Crow and Kimura (1965) published a mathematical treat-
25 ment of the idea previously proposed by Fisher (1930) and Muller (1932) that sex
26 increases the rate of adaptation of species by allowing different beneficial mutations to
27 be combined into the same genome. A controversy ensued shortly after, as a different
28 model analyzed by Maynard Smith (1968) led to a contradictory result: beneficial al-
29 leles at two different loci spread at the same rate in sexuals and asexuals. The debate
30 was finally settled by Felsenstein (1974), who showed that a critical difference between
31 the two models concerns population size: while Crow and Kimura assume that new
32 mutations arise as single copies, Maynard Smith's model considers an infinite popula-
33 tion, in which beneficial alleles are initially in linkage equilibrium. As demonstrated
34 by Hill and Robertson (1966) a few years before, stochastic effects occurring in any
35 finite population tend to generate negative associations between beneficial alleles (*i.e.*,
36 beneficial alleles tend to be found more often in different genetic backgrounds than
37 combined within the same background). In sexual populations, these negative associ-
38 ations are broken by recombination, which therefore increases the rate of adaptation.
39 The same type of mechanism allows sexuals to escape Muller's ratchet, the gradual ac-
40 cumulation of deleterious alleles that occurs in non-recombining populations (Muller,
41 1964; Felsenstein, 1974).

42 Since Crow and Kimura's paper, the question of the possible advantage of sex-
43 ual reproduction has been one of the most hotly debated topics in evolutionary biology.
44 The fact that sex is advantageous in the long term does not in principle prevent an
45 asexual mutant from invading a sexual population: indeed, many strong costs are

46 associated with sexual reproduction, in terms of energy required to find or court a
47 mate, increased risks of predation and disease transmission, or investment into the
48 male function — since the males of most species do not contribute to the next gener-
49 ation in terms of resources (e.g., Maynard Smith, 1971; Lewis, 1987; Lehtonen et al.,
50 2012). Strong benefits of sex are thus needed to counterbalance these costs. Insights
51 about the possible strength of indirect selection for sex (stemming from the reduc-
52 tion of negative genetic associations) can be obtained from recombination modifier
53 models, such as the one originally proposed by Nei (1967): these models represent a
54 “modifier” gene that affects recombination rates between other genes, at which bene-
55 ficial/deleterious alleles segregate. The direction and magnitude of indirect selection
56 acting at the modifier locus can then be explored mathematically under different sce-
57 narios. Using this approach, different conditions that may favour sexual recombination
58 have been described: selection acting independently at different loci within finite or
59 spatially structured populations (due to the Hill-Robertson effect described above,
60 e.g., Felsenstein and Yokohama, 1976; Otto and Barton, 1997, 2001; Iles et al., 2003;
61 Barton and Otto, 2005; Keightley and Otto, 2006; Martin et al., 2006; Roze and Bar-
62 ton, 2006; Gordo and Campos, 2008; Hartfield et al., 2010), negative epistasis between
63 selected loci (Feldman et al., 1980; Charlesworth, 1990, 1993a; Barton, 1995; Otto and
64 Feldman, 1997), fluctuating selection, generated for example by biotic interactions
65 (Charlesworth, 1976; Barton, 1995; Gandon and Otto, 2007), and spatially varying se-
66 lection within structured populations (Lenormand and Otto, 2000). In many of these
67 models, selection for recombination can be strong in non-recombining populations, but
68 decreases rapidly as the baseline recombination rate increases.

69 There are important differences between the evolution of sex and the evolution

70 of recombination, however: in particular, reproductive modes are probably far more
71 constrained than recombination rates within genomes. In many obligatory sexual
72 species, reproducing asexually may require a combination of several mutations which
73 may be individually deleterious: in mammals for example, parthenogenesis would re-
74 quire both the spontaneous development of an ovule without fertilization and the sup-
75 pression of genomic imprinting (which prevents normal development in the absence of
76 a paternally inherited genome), which may explain why it has never been observed.
77 Similarly, in cyclical parthenogenetic species such as aphids, cladocerans and rotifers,
78 overwintering eggs are typically produced by sexual reproduction (e.g., Simon et al.,
79 2002), and it has been argued that sex may be maintained for this reason — although
80 it is less clear why overwintering eggs could not be produced asexually, as this oc-
81 curs for example in some *Daphnia pulex* populations (Hebert and Crease, 1980; Innes
82 and Hebert, 1988). Based on this type of observation, several authors have proposed
83 that sex may be maintained by selection at the species level (Williams, 1975; Nunney,
84 1989; De Vienne et al., 2013): according to this hypothesis, only the lineages in which
85 viable asexual mutants cannot occur (due to some constraint) persist over evolution-
86 ary time, while asexual lineages eventually go extinct due to mutation accumulation
87 and/or failure to adapt. Although this type of process can certainly explain the main-
88 tenance of sex in some groups (such as mammals), it cannot explain evolution towards
89 higher rates of sex (and in the extreme, obligatory sex) within a lineage: for this, sex
90 must confer benefits on a sufficiently short timescale so that its direct costs can be
91 outweighed. Assessing whether this is possible or not requires obtaining quantitative
92 predictions on the possible strength of selection for sex under different scenarios.

93 In this paper, I explore the advantage of sex generated by selection acting in-

94 dependently at multiple loci (no epistasis) within finite populations. To date, most
95 analytical results on the effects of finite population size stem from haploid recombina-
96 tion modifier models representing selection acting at two loci (e.g., Otto and Barton,
97 1997; Barton and Otto, 2005; Martin et al., 2006; Roze and Barton, 2006). While
98 indirect selective pressures acting on sex have been shown to be different from those
99 acting on recombination in diploid organisms — since sex allows both recombination
100 and segregation (affecting homozygosity/heterozygosity at single loci, e.g., Uyenoyama
101 and Bengtsson, 1989; Otto, 2003; Agrawal, 2009a,b; Roze and Michod, 2010), in hap-
102 loids selection for recombination is often thought to be equivalent to selection for sex.
103 In the first part of the paper, however, I show that selective pressures acting on a sex
104 modifier locus (affecting the rate of sexual vs. asexual reproduction) are different from
105 those acting on a recombination modifier, even in the case of a haploid population:
106 in particular, while two selected loci are required to generate indirect selection on a
107 recombination modifier, a single selected locus can favour sex within a finite haploid
108 population. In a second part, I use individual-based simulations to explore how the
109 rate of sex evolves when deleterious mutations occur at a large number of loci (in the
110 presence of a direct cost of sex), and compare the results with analytical predictions
111 obtained by extrapolations from three-locus models. The results show that such ex-
112 trapolations give correct predictions for the equilibrium rate of sex in different cases (in
113 particular as long as the cost of sex is not too high) and capture the qualitative effects
114 of the different parameters of the model (population size, number of loci, strength of
115 selection against deleterious alleles).

117 **The sex modifier model.** The effects of one or two selected loci on the evolution of
118 a modifier gene affecting the relative investment into sexual vs. asexual reproduction
119 can be studied using analytical methods (Table 1 shows the parameters used in the
120 different models). The basic model represents a population of N haploid individuals
121 with discrete generations. As in previous models (Uyenoyama and Bengtsson, 1989;
122 Otto, 2003; Agrawal, 2009a,b; Roze and Michod, 2010; Roze and Otto, 2012) I assume
123 that each individual i invests a proportion σ_i of its resources into sexual reproduction
124 (producing both male and female gametes) and a proportion $1 - \sigma_i$ into clonal repro-
125 duction. A parameter c represents the overall effect of direct costs associated with sex:
126 the probabilities that individual i is the maternal parent of a given individual of the
127 next generation through asexual and sexual reproduction are proportional to $1 - \sigma_i$
128 and σ_i/c , respectively ($c = 1$ in the absence of a direct cost of sex). This cost may stem
129 from the fact that a fraction of resources invested into sex are used to produce male
130 gametes, which do not contribute to the next generation in terms of resources (“cost
131 of males”, $c = 2$ under equal investments into the sexual female and male functions)
132 and/or other costs such as additional resources that may be needed to facilitate gamete
133 encounter. Individuals produce asexual spores and gametes by mitosis; spores develop
134 directly into new (haploid) individuals, while gametes fuse at random to form zygotes,
135 which immediately undergo meiosis to produce new haploids. I assume that each par-
136 ent produces a very large (effectively infinite) number of juveniles, N individuals being
137 then sampled randomly among all juveniles to form the next adult generation.

138 Investment into sex is controlled by a single “modifier” locus with two alleles

139 m and M : the rates of sex of m and M individuals are σ and $\sigma + \delta\sigma$, respectively.
140 Either one or two selected loci control the overall fecundity (total investment into
141 reproduction) of individuals. In the one-locus case, the two alleles at the selected
142 locus are denoted a and A , the fecundities of a and A individuals being proportional
143 to 1 and $1 + s$. With two selected loci, I denote b and B the two alleles at the
144 second selected locus, and suppose for simplicity that allele B has the same selection
145 coefficient s as allele A (although the model is easily extended to the more general case
146 of different selection coefficients); the effects of the two loci on fecundity are supposed
147 to be multiplicative (no epistasis). Finally, r_{ij} denotes the recombination rate between
148 loci i and j .

149 **Quasi-linkage equilibrium (QLE) approximation.** Approximate expressions for
150 the expected change in allele frequency at the modifier locus in terms of the model
151 parameters and expected genetic variances at the different loci can be obtained using
152 a separation of timescales argument, which assumes that the different forces causing
153 changes in allele frequencies (selection, drift, modifier effect) are weak relative to “ef-
154 fective” rates of recombination (which depend on the rate of sex in the population)
155 breaking linkage disequilibria between loci. The analysis proceeds in two steps: the
156 first step corresponds to the calculation of the expected change in frequency at the
157 modifier locus over one generation, as a function of various moments of allele frequen-
158 cies and linkage disequilibria in the parental generation; during the second step, a QLE
159 approximation is used to express all moments involving linkage disequilibria in terms
160 of moments involving allele frequencies only. For this, recursions for these different
161 moments must be derived, and solved at equilibrium. A general method for deriving

162 recursions on moments under a diploid life cycle is given in Appendix A of Roze and
163 Michod (2010). Appendix A of the present article briefly sketches the method for the
164 case of a haploid life cycle, using the same general principles. Defining X_i an indicator
165 variable that equals 1 if allele i (M , A or B) is present in a given individual and 0
166 otherwise, the frequency of allele i in the population is given by $p_i = E[X_i]$, where E
167 stands for the average over all individuals. Pairwise linkage disequilibria are defined
168 as $D_{ij} = E[\zeta_i \zeta_j]$, where $\zeta_i = X_i - p_i$, while the three-locus linkage disequilibrium (e.g.,
169 Slatkin, 1972) is given by $D_{MAB} = E[\zeta_M \zeta_A \zeta_B]$. Throughout the paper, $\langle \mathcal{M} \rangle_t$ stands for
170 the expected value of the moment \mathcal{M} (such as $D_{MAB} D_{AB}$ or $p_M D_{MA}$) among individ-
171 uals of generation t . Appendix A sketches how the life cycle can be decomposed into
172 different steps in order to compute moments at generation $t+1$ in terms of moments at
173 generation t (these recursions are implemented in a *Mathematica* notebook, available
174 as Supplementary Material). When s , $\delta\sigma$ and $1/N$ are small relative to recombination
175 rates among loci multiplied by the rate of sex σ , one can show that moments involv-
176 ing linkage disequilibria quickly become small and change slowly over time (Nagylaki,
177 1993; Barton and Turelli, 1991; Barton and Otto, 2005; Roze and Michod, 2010); in
178 this case, these moments can be expressed in terms of the different parameters of the
179 model and moments of allele frequencies, such as $\langle p_M q_M \rangle_t$ or $\langle p_M q_M p_A q_A \rangle_t$ (where
180 $q_i = 1 - p_i$). This QLE approximation simplifies considerably the equations, but is
181 expected to break down when effective rates of recombination are small. However, we
182 will see that accurate approximations can be obtained when recombination rates and
183 the strength of selection s are of the same order of magnitude, in the situation where
184 deleterious alleles are maintained at mutation-selection balance at selected loci: indeed
185 in this case, changes in allele frequencies are only driven by the modifier effect and by

186 drift, and the QLE only requires that $\delta\sigma$ and $1/N$ are small relative to effective rates
187 of recombination.

188 **Multilocus simulations.** As we will see in the next section, analytical results from
189 three-locus models can be extrapolated to predict the overall strength of selection on a
190 sex modifier when deleterious alleles segregate at a large number of loci; however, this
191 supposes that the effects of higher-order interactions (between three or more selected
192 loci) can be neglected, which is not guaranteed: even if the effect of each of these higher-
193 order interactions is small, the number of such interactions increases very rapidly as
194 the number of polymorphic loci increases. In order to test the predictions obtained
195 from three-locus models, I use individual-based simulations representing deleterious
196 mutations occurring at a large (quasi-infinite) number of possible loci. The simulation
197 program (written in C++, and available from Dryad) is very similar to the programs
198 used in previous papers (Roze and Michod, 2010; Roze and Otto, 2012). It represents
199 a population of N haploid individuals whose genome consists in a linear chromosome
200 with infinitely many loci. Every generation, the number of new deleterious mutations
201 per chromosome is sampled from a Poisson distribution with parameter U , and the
202 position of each mutation is sampled from a uniform distribution. The fecundity W_i of
203 an individual is given by $(1 - s)^n$, where n is the number of mutations in its genome.
204 When forming the next generation, each parental individual i contributes as a mother
205 (either through sexual or asexual reproduction) with a probability proportional to
206 $W_i [c(1 - \sigma_i) + \sigma_i]$ (where σ_i is the rate of sex of parent i). The new individual is
207 then produced asexually with probability $c(1 - \sigma_i) / [c(1 - \sigma_i) + \sigma_i]$ (in which case its
208 genotype is a copy of the parental genotype), and sexually with the complementary

209 probability. In this last case, a second individual is sampled to contribute as a father,
210 the probability of sampling parent j being proportional to $W_j \sigma_j$. The two parental
211 genomes are recombined to form a new haploid genome, the number of cross-overs being
212 sampled from a Poisson distribution with parameter R (genome map length), and the
213 position of each cross-over being sampled from a uniform distribution. During a given
214 number of preliminary generations (usually 2000), the rate of sex is the same for all
215 individuals (and is generally fixed to 1). Then, mutations are introduced (at rate 10^{-4}
216 per generation) at a sex modifier locus located at the midpoint of the chromosome.
217 Alleles at this locus take values between 0 and 1, corresponding to the rate of sex
218 of the individual (which is thus a quantitative trait). When a mutation occurs at
219 the modifier locus, with probability 0.5 the new value is sampled from a uniform
220 distribution between 0 and 1, while with probability 0.5 it equals the value of the
221 parent allele plus a random number between -0.1 and 0.1 (the new value being set
222 to 0 or 1 if it is negative or greater than 1, respectively); this mutation scheme allows
223 both large and small effect mutations to arise relatively frequently. The program runs
224 for 2 million generations and records the average value of alleles at the modifier locus
225 every 100 generations; the equilibrium rate of sex is obtained by averaging over the
226 last 1.9×10^6 generations. In some simulations I only considered two alleles at the
227 modifier locus, as will be explained in greater detail below.

229 All analytical results assume that selection is weak (s small) and are derived
 230 to the first order in $\delta\sigma$ and $1/N$ (weak modifier, large population size). The effect of
 231 relaxing these hypotheses will then be explored by multilocus simulations. Through
 232 the following, σ_{eff} denotes the effective rate of sex in the population (proportion of
 233 sexually produced progeny) which equals $\sigma/[c(1-\sigma) + \sigma]$ to leading order, while
 234 $\rho_{ij} = \sigma_{\text{eff}} r_{ij}$ denotes the effective recombination rate between loci i and j (proportion
 235 of recombinants per generation). Finally, $\delta\sigma_{\text{eff}} = \delta\sigma/[c(1-\sigma) + \sigma]$ denotes the effect
 236 of allele M on the effective rate of sex.

237 **Two-locus model.** Although the results shown in this section hold for both $s > 0$
 238 and $s < 0$, I will assume for clarity that $s > 0$ (A is the favoured allele) when
 239 discussing the results. Using the methods described in Appendix A (implemented in
 240 the Supplementary Material), one obtains for the expected change in frequency of the
 241 modifier over one generation:

$$\langle \Delta p_M \rangle_t = -\delta\sigma_{\text{eff}} (c-1) \langle p_M q_M \rangle_t^{\text{sel}} + s \langle D_{MA} \rangle_t - s^2 \langle p_A D_{MA} \rangle_t \quad (1)$$

242 where $\langle p_M q_M \rangle_t^{\text{sel}}$ is the expected genetic variance at the modifier locus among selected
 243 parents (weighting each parent by its relative fecundity, see Appendix A), given by:

$$\langle p_M q_M \rangle_t^{\text{sel}} = \langle p_M q_M \rangle_t - 2s \langle p_M D_{MA} \rangle_t - s^2 \langle D_{MA}^2 \rangle_t. \quad (2)$$

244 As we will see below, $\langle p_M D_{MA} \rangle_t$ is positive at QLE, and equation 2 represents the
 245 fact that the genetic variance at the modifier locus tends to be reduced by selection at
 246 the other locus (e.g., Maynard Smith and Haigh, 1974; Charlesworth, 1993b): $p_M q_M$

247 thus tends to be lower when measured among selected parents than when measured
 248 before selection. The first term of equation 1 represents the effect of the direct cost
 249 of sex, reducing the frequency of the allele coding for more sex (this reduction being
 250 proportional to the genetic variance at the modifier locus among selected parents). The
 251 second term of equation 1 represents the effect of genetic hitchhiking, favouring the
 252 modifier allele that tends to be positively linked (on average) with the better allele (A)
 253 at the selected locus. Finally, the last term of equation 1 represents the fact that for a
 254 given value of D_{MA} , the strength of hitchhiking tends to decrease when the beneficial
 255 allele is more frequent in the population; this stems from the fact that hitchhiking is
 256 proportional to the ratio s/\overline{W} (which determines the selection gradient at the selected
 257 locus), and that mean fecundity \overline{W} is an increasing function of p_A .

258 Further progress can be made by obtaining QLE expressions for the four mo-
 259 ments $\langle D_{MA}^2 \rangle$, $\langle p_M D_{MA} \rangle$, $\langle p_A D_{MA} \rangle$ and $\langle D_{MA} \rangle$ that appear in the equations above.
 260 The first of these moments is the variance in linkage disequilibrium, generated by finite
 261 population size. To leading order, it is given by:

$$\langle D_{MA}^2 \rangle_t = \frac{\langle p_M q_M p_A q_A \rangle_t}{N \rho_{MA} (2 - \rho_{MA})} \quad (3)$$

262 (see also eq. B3a in Barton and Otto, 2005). The moment $\langle p_M D_{MA} \rangle$ is generated by
 263 finite population size and selection for allele A . To the first order in s , its expression
 264 at QLE is:

$$\langle p_M D_{MA} \rangle_t = s \frac{1 - \rho_{MA}}{\rho_{MA}} \langle D_{MA}^2 \rangle_t \quad (4)$$

265 (see also eq. B3b in Barton and Otto, 2005). This result can be interpreted as follows:
 266 due to drift, allele M is sometimes associated with allele A ($D_{MA} > 0$), sometimes
 267 with allele a ($D_{MA} < 0$). Because A is beneficial, M tends to increase in frequency

268 when $D_{MA} > 0$, and decrease in frequency when $D_{MA} < 0$, thus generating a positive
 269 covariance between allele frequency p_M and linkage disequilibrium D_{MA} . The same
 270 mechanism generates a covariance between p_A and D_{MA} in the presence of a direct
 271 cost of sex ($c > 1$), that has the sign of $-\delta\sigma$. At QLE, it is given by:

$$\langle p_A D_{MA} \rangle_t = -\delta\sigma_{\text{eff}} (c - 1) \frac{1 - \rho_{MA}}{\rho_{MA}} \langle D_{MA}^2 \rangle_t. \quad (5)$$

272 Finally, the expected value of the linkage disequilibrium at QLE is:

$$\begin{aligned} \langle D_{MA} \rangle_t = \frac{1}{\rho_{MA}} \left[2(1 - \rho_{MA}) \left[\delta\sigma_{\text{eff}} (c - 1) \langle p_M D_{MA} \rangle_t^{\text{sel}} - s \langle p_A D_{MA} \rangle_t \right] \right. \\ \left. + \delta\sigma_{\text{eff}} [r_{MA} + (c - 1) \rho_{MA}] \langle p_M D_{MA} \rangle_t^{\text{sel}} \right] \end{aligned} \quad (6)$$

273 where $\langle p_M D_{MA} \rangle_t^{\text{sel}}$ is measured after selection, and at QLE is equal to $s \langle D_{MA}^2 \rangle_t / \rho_{MA}$.

274 The terms on the first line of equation 6 represent linkage disequilibrium generated by
 275 the Hill-Robertson effect between the modifier and the selected locus: finite population
 276 size tends to generate negative LD between deleterious alleles as different loci (Hill
 277 and Robertson, 1966). Therefore, when allele M is deleterious due to the cost of sex
 278 ($\delta\sigma > 0$), it tends to be associated with the better allele A at the second locus. This
 279 effect disappears in the absence of a direct cost of sex ($c = 1$). By contrast, the
 280 term on the second line of equation 6 does not vanish when $c = 1$, indicating that
 281 linkage disequilibrium is generated between the two loci even in the absence of direct
 282 selection at the modifier locus. Like the first term, this second term has the sign of $s\delta\sigma$,
 283 indicating that an allele increasing sex tends to be associated with the better allele (A)
 284 at the selected locus; furthermore, it is generated by the positive covariance between
 285 p_M and D_{MA} . This effect may be understood as follows: whenever D_{MA} is negative,
 286 it tends to reduce the frequency of M , in which case an M individual that reproduces
 287 sexually has higher chances to mate with an m individual, and thus to recombine onto a

288 better genome (carrying A , since m tends to be more associated with A). By contrast,
 289 a positive D_{MA} increases the frequency of M , in which case M individuals have greater
 290 chances to mate with other M individuals, and thus to stay associated with the better
 291 allele. Averaging over these different situations, the fraction of alleles M that become
 292 disassociated from the beneficial allele (and associated with the deleterious allele)
 293 when recombining with m individuals is thus lower than the fraction of alleles M that
 294 become disassociated from the deleterious allele (and associated with the beneficial
 295 one) when recombining with m (again because m tends to be less frequent when M is
 296 associated with A). Although both modifier alleles benefit from this effect, the allele
 297 that engages in sex more often (M if $\delta\sigma > 0$) benefits more, generating a positive
 298 association between this allele and the beneficial allele A . This mechanism should
 299 not work, however, when one of the modifier alleles never engages in sex ($\sigma = 0$).
 300 Although equation 6 does not capture this (as it is derived under the assumption
 301 that $\delta\sigma \ll \sigma$, which is necessary for the QLE approximation to hold), one can show
 302 that the recursion for $\langle D_{MA} \rangle_t$ becomes independent of $\delta\sigma$ when $\sigma = 0$ and $c = 1$,
 303 confirming that no linkage disequilibrium is generated (on average) when one of the
 304 modifier alleles codes for fully asexual reproduction.

305 From the equations above, the expected change in frequency of the modifier
 306 can be written as:

$$\begin{aligned}
 \langle \Delta p_M \rangle_t = & -\delta\sigma_{\text{eff}} (c - 1) \left[\langle p_M q_M \rangle_t - 2s^2 \frac{2 - \rho_{MA}}{\rho_{MA}^2} \langle D_{MA}^2 \rangle_t \right] \\
 & + \frac{\delta\sigma_{\text{eff}} s^2}{\rho_{MA} \sigma_{\text{eff}}} \langle D_{MA}^2 \rangle_t .
 \end{aligned} \tag{7}$$

307 The term on the first line indicates that interference between the two loci due to finite
 308 population size (through the variance in LD) tends to attenuate the effect of the direct
 309 cost of sex (Hill-Robertson effect). More interestingly, the second line shows that in

310 the absence of cost, a modifier increasing sex tends to increase in frequency, due to
 311 the effect described just above. Note that this effect does not operate in the case
 312 of a recombination modifier, which is only expressed during the diploid phase, once
 313 individuals have “decided” to engage in sex (because recombination only has a genetic
 314 effect in double heterozygotes, the average benefits gained by allele M should thus be
 315 exactly the same as those gained by allele m).

316 As shown by Figure 1, two-locus simulations confirm that in the absence of a
 317 direct cost of sex ($c = 1$), a modifier increasing sex tends to increase in frequency during
 318 the sweep of a beneficial allele at a second locus. In the simulations the beneficial
 319 allele A is initially in frequency $p_{A,0} = 0.05$, while the sex modifier M is initially in
 320 frequency $p_{M,0} = 0.5$ and in linkage equilibrium with A . The program measures the
 321 final frequency of M at the end of the sweep, the whole process being repeated 50×10^6
 322 times. A prediction for the total increase in frequency of M over the sweep can be
 323 obtained by integrating equation 7 over time (treated as a continuous variable), and
 324 assuming that p_A remains close to a deterministic trajectory. In this case, using the
 325 fact that $dp_A/dt = sp_Aq_A$ we have $\int_0^\infty p_Aq_A dt = \int_{p_{A,0}}^1 dp_A/s = (1 - p_{A,0})/s$, which
 326 yields for the expected total increase in frequency of M :

$$\langle \Delta p_M \rangle_{\text{total}} \approx \frac{\delta \sigma s (1 - p_{A,0}) p_{M,0} (1 - p_{M,0})}{N \rho_{MA}^2 \sigma (2 - \rho_{MA})} \quad (8)$$

327 assuming no direct cost of sex ($c = 1$). Figure 1B shows that this prediction fits well
 328 with the simulation results as long as the baseline rate of sex σ in the population is not
 329 too small — note that with a single selected locus, the expected change in frequency of
 330 the modifier stays very small. Furthermore, Figure 1A confirms that this benefit of sex
 331 vanishes when the rate of sex of allele m tends to zero; however, even a small baseline

332 rate of sex generates an advantage for a mutant increasing sex (the total change in
 333 frequency of the modifier has a maximum at around $\sigma \approx 0.01$, for the parameter values
 334 used in Figure 1).

335 **Three-locus model.** In the presence of a second selected locus (where B is the
 336 beneficial allele), the expected change in frequency of the modifier becomes:

$$\begin{aligned}
 \langle \Delta p_M \rangle_t &= -\delta\sigma_{\text{eff}}(c-1) \langle p_M q_M \rangle_t^{\text{sel}} + s(\langle D_{MA} \rangle_t + \langle D_{MB} \rangle_t) \\
 &\quad + s^2(\langle D_{MAB} \rangle_t - \langle p_A D_{MA} \rangle_t - \langle p_B D_{MB} \rangle_t) \\
 &\quad - s^3(\langle D_{MA} D_{AB} \rangle_t + \langle D_{MB} D_{AB} \rangle_t + \langle p_A D_{MAB} \rangle_t + \langle p_B D_{MAB} \rangle_t) \\
 &\quad - s^4 \langle D_{MAB} D_{AB} \rangle_t
 \end{aligned} \tag{9}$$

337 where the genetic variance at the modifier locus among selected parents is given by:

$$\begin{aligned}
 \langle p_M q_M \rangle_t^{\text{sel}} &= \langle p_M q_M \rangle_t - 2s(\langle p_M D_{MA} \rangle_t + \langle p_M D_{MB} \rangle_t) \\
 &\quad - s^2(\langle D_{MA}^2 \rangle_t + \langle D_{MB}^2 \rangle_t + 2\langle D_{MA} D_{MB} \rangle_t + 2\langle p_M D_{MAB} \rangle_t) \\
 &\quad - 2s^3(\langle D_{MAB} D_{MA} \rangle_t + \langle D_{MAB} D_{MB} \rangle_t) - s^4 \langle D_{MAB}^2 \rangle_t.
 \end{aligned} \tag{10}$$

338 QLE expressions for the different moments that appear in equations 9 and 10 are given
 339 in Appendix B. From these, it can be shown that all the different terms involving the
 340 selected loci generate selection for increased rates of sex. Although it is not possible
 341 for space reasons to provide an intuitive explanation for each of the moments involved,
 342 it is interesting to note that the extra benefits of sex that appear when introducing
 343 a second selected locus do not all stem from recombination between the selected loci
 344 (which again differs from the case of a recombination modifier). In the following I
 345 assume that allele M increases sex ($\delta\sigma > 0$), and consider the effect of the three-locus
 346 disequilibrium $\langle D_{MAB} \rangle_t$. As we will see, this disequilibrium is positive on average,

347 meaning that allele M tends to be more often associated with the extreme genotypes
 348 ab and AB than allele m . This positive $\langle D_{MAB} \rangle$ favors M through two effects: the
 349 first corresponds to the fact that under multiplicative selection, the mean fitness of
 350 extreme genotypes ($1 + s + s^2/2$) is higher than the fitness of intermediate genotypes
 351 ($1 + s$): this corresponds to the term in $\langle D_{MAB} \rangle_t$ on the second line of equation 9.
 352 The second effect (which is often much stronger) is the fact that the larger variance in
 353 fitness present in the sub-population carrying M increases the efficiency of selection:
 354 the fitter alleles A and B tend to increase in frequency within this sub-population
 355 (through the increase of the AB genotype), generating positive pairwise associations
 356 D_{MA} , D_{MB} (equation B15). Allele M thus tends to be associated with the fitter
 357 alleles A and B , and therefore increases in frequency (term in $\langle D_{MA} \rangle_t + \langle D_{MB} \rangle_t$ on
 358 the first line of equation 9). Where does the positive $\langle D_{MAB} \rangle$ come from? As shown
 359 by equation B11, different mechanisms are involved, of which I will only discuss two.
 360 A first source of $\langle D_{MAB} \rangle$ is the negative linkage disequilibrium D_{AB} generated by the
 361 Hill-Robertson effect (first line of eq. B11). This corresponds to the often described
 362 benefit of sex/recombination in a finite population: increasing recombination tends to
 363 break negative associations between selected loci, and thereby increases the efficiency of
 364 selection. A different source of positive $\langle D_{MAB} \rangle$ (second line of equation B11), however,
 365 does not involve recombination between the selected loci. This second mechanism
 366 stems from a positive correlation between p_M and D_{MAB} , which can be explained as
 367 follows. Finite population size generates random fluctuations in D_{MAB} ; when $D_{MAB} >$
 368 0 , extreme genotypes (ab , AB) are more frequent on the M background and AB
 369 increases in frequency, generating positive associations D_{MA} , D_{MB} (by contrast, when
 370 $D_{MAB} < 0$, AB increases in frequency on the m background, generating negative

371 D_{MA}, D_{MB}): drift and selection thus generate a positive correlation between D_{MAB}
 372 and D_{MA} (eq. B4), and also between D_{MAB} and D_{MB} . When D_{MA}, D_{MB} are positive,
 373 M tends to increase in frequency by hitchhiking, which in turn produces a positive
 374 correlation between D_{MAB} and p_M (eq. B10). This positive correlation generates a
 375 positive $\langle D_{MAB} \rangle$, in the same way as the positive correlation between p_M and D_{MA}
 376 generated a positive $\langle D_{MA} \rangle$ in the two-locus model: during sex, alleles at the modifier
 377 locus tend to move more often from Ab, aB backgrounds to ab, AB backgrounds
 378 than the opposite, and allele M (which engages in sex more often) benefits more from
 379 this effect. Note that this last source of positive $\langle D_{MAB} \rangle$ would operate even in the
 380 absence of recombination between the selected loci, and would not appear in the case
 381 of a recombination modifier. Indeed, using the same method to derive an expression
 382 for the expected change in frequency of a neutral recombination modifier (changing
 383 r_{AB} to $r_{AB} + \delta r_{AB}$) yields the same expressions as in Appendix B for $c = 1$ (no direct
 384 selection) and replacing $\delta\sigma_{\text{eff}} r_{AB}$ by δr_{AB} , except that the terms involving $\langle p_M D_{MAB} \rangle_t^{\text{sel}}$
 385 and $\langle p_M D_{MA} \rangle_t^{\text{sel}}$ in equations B11 and B15 disappear.

386 **Mutation-selection balance.** The expressions shown in the previous section and in
 387 Appendix B were derived under the assumption that $\delta\sigma, 1/N \ll s \ll \rho_X$ (where again
 388 ρ_X is the effective rate of recombination between loci in the set X): indeed, all results
 389 were expressed to the first order in $\delta\sigma$ and $1/N$ (assuming that these parameters are
 390 much smaller than all other parameters), while the QLE approximation requires that
 391 selection is much weaker than recombination ($s \ll \rho_X$). However, this last condition
 392 becomes less stringent when selected loci are at mutation-selection balance (equilib-
 393 rium between mutation generating deleterious alleles and selection removing these

394 alleles): indeed, in that case all changes in allele frequencies are due to drift and to
 395 the modifier effect, and the QLE therefore only requires that $\delta\sigma, 1/N \ll \rho_X$. More
 396 accurate results can thus be obtained for the case where effective recombination rates
 397 are small (of order s). As can be seen from Appendix B, all moments (such as $\langle D_{AB}^2 \rangle$,
 398 $\langle D_{AB} \rangle$, $\langle p_M D_{MA} \rangle$...) generated by selection and drift become of the same order of
 399 magnitude when s and ρ_X are of the same order; similarly, moments involving the
 400 modifier effect $\delta\sigma$ (such as $\langle D_{MAB} D_{AB} \rangle$, $\langle D_{MAB} \rangle$, $\langle D_{MA} \rangle$...) all become of the same
 401 order. Extra terms must be added to the recursions for these different moments when
 402 ρ_X coefficients are of order s , however the changes are relatively minor if we assume
 403 that deleterious alleles remain at low frequency, so that we can neglect all moments
 404 involving p_i^2 , where p_i is the frequency of the deleterious allele at locus i (“rare alleles
 405 approximation”). Because it is more convenient to work with moments involving the
 406 frequencies of deleterious alleles (rather than the frequencies of favoured alleles), I as-
 407 sume from now on that A and B are the deleterious alleles, and denote s the selection
 408 coefficient against these alleles (ab , Ab , aB and AB genotypes thus have fitnesses 1,
 409 $1 - s$, $1 - s$ and $(1 - s)^2$, where $s > 0$). Using the methods described in Appendix A
 410 and assuming that effective recombination rates may be of order s yields the follow-
 411 ing recursion for the squared linkage disequilibrium between selected loci $\langle D_{AB}^2 \rangle$, to
 412 leading order:

$$\langle D_{AB}^2 \rangle_{t+1} = \frac{\langle pq_{AB} \rangle_t}{N} + (1 - \rho_{AB})^2 (1 - 4s) \langle D_{AB}^2 \rangle_t \quad (11)$$

413 where $pq_{AB} = p_A q_A p_B q_B$ (note that the factor $1 - 4s$ was neglected in the previous
 414 analysis). At equilibrium, we thus have:

$$\langle D_{AB}^2 \rangle_t = \frac{\langle pq_{AB} \rangle_t}{N [1 - (1 - \rho_{AB})^2 (1 - 4s)]} \quad (12)$$

415 which is approximately $\langle pq_{AB} \rangle_t / [2N(\rho_{AB} + 2s)]$ when s and ρ_{AB} are small. Appendix
 416 C provides approximations for other moments when ρ_X coefficients are of order s . In
 417 particular, the linkage disequilibrium $\langle D_{AB} \rangle$ generated by the Hill-Robertson effect
 418 becomes:

$$\langle D_{AB} \rangle_t \approx -\frac{2s^2 \langle pq_{AB} \rangle_t}{N(\rho_{AB} + 2s)^2(\rho_{AB} + 3s)}. \quad (13)$$

419 Assuming $\langle pq_{AB} \rangle_t \approx (u/s)^2$, where u is the per-locus mutation rate towards deleterious
 420 alleles, one obtains:

$$\langle D_{AB} \rangle_t \approx -\frac{2u^2}{N(\rho_{AB} + 2s)^2(\rho_{AB} + 3s)}. \quad (14)$$

421 Figure 2A shows that this prediction fits well with two-locus simulation results: as long
 422 as $s > 0.001$ (for the parameters used in Figure 2A), the linkage disequilibrium between
 423 deleterious alleles at mutation-selection balance becomes weaker as s increases, which
 424 is not predicted by the result obtained assuming $s \ll \rho_{AB}$, as it neglects the terms in s
 425 in the denominator of equation 14 — note that the discrepancy between equation 14
 426 and the simulation results observed for $s < 0.001$ stems from the fact that equation 14
 427 assumes $1/N \ll s$. Selection for a modifier increasing sex through its effect in breaking
 428 the linkage disequilibrium $\langle D_{AB} \rangle$ is proportional to $s^2 \langle D_{AB} \rangle$ (Appendices B, C) and
 429 should thus be maximised for intermediate values of s , as shown by Figure 2B.

430 From the expressions derived in Appendices B and C and assuming that the
 431 baseline rate of sex σ is of order ϵ , one obtains that the strength of selection for sex
 432 generated by each selected locus i is of order $\delta\sigma s^2 p_i / [N\epsilon^3]$, where p_i is the frequency
 433 of the deleterious allele at locus i , while selection for sex generated by the interaction
 434 between loci i and j is of order $\delta\sigma s^4 p_i p_j / [N\epsilon^5]$. Because p_i, p_j are small at mutation-
 435 selection balance (assuming $u \ll s$), the effect of between-locus interactions may thus

436 seem negligible relative to the individual effect of each locus. However, we will see in
 437 the next section that this is no longer true when deleterious alleles segregate at many
 438 loci, so that the number of between-locus interactions becomes very large.

439 **Extrapolation to many loci.** The results shown in the previous sections (and in
 440 Appendices B and C) can be extrapolated to predict the overall strength of indirect
 441 selection acting on a sex modifier when deleterious mutations occur over a whole
 442 genome (with a genomic deleterious mutation rate U , and assuming for simplicity that
 443 all deleterious alleles have the same selection coefficient s). Neglecting the effects of
 444 interactions between more than two selected loci, one obtains the following expression
 445 for the selection gradient at the modifier locus (see Appendix C):

$$s_M \equiv \frac{\langle \Delta p_M \rangle_t}{\langle p_M q_M \rangle_t} = \delta \sigma_{\text{eff}} \left[-(c-1) + \frac{Us}{N} \Theta_1 + \frac{(Us)^2}{2N} \Theta_2 \right] \quad (15)$$

446 The first term of equation 15 represents the effect of the cost of sex, the second term is
 447 the sum of the individual effects of all selected loci, and the third term is the sum of all
 448 effects of interactions between pairs of loci. Presumably, interactions between three,
 449 four or more selected loci could also generate indirect selection for sex (through terms
 450 in $(Us)^3$, $(Us)^4$...), but the computation of these terms would be tedious. The terms
 451 Θ_1 and Θ_2 that appear in equation 15 are complicated functions of the effective rate
 452 of sex σ_{eff} , cost of sex c , strength of selection s and recombination rates, integrated
 453 over all possible genomic positions of deleterious alleles (which requires performing
 454 two numerical integrations over the genetic map). When effective recombination rates
 455 are large relative to s (which requires $\sigma_{\text{eff}} \gg s$), Θ_1 and Θ_2 become approximately
 456 independent of s , and can be derived from the expressions given in Appendix B: in

457 this case, equation 15 indicates that the strength of indirect selection for sex depends
 458 on the Us product (independently of the individual values of U and s) which is also the
 459 variance in fitness in the population at mutation-selection balance. However, this is no
 460 longer true when effective recombination rates are of order s , as terms in s appear in the
 461 denominator of expressions for genetic moments at QLE (Appendix C). In general, the
 462 results obtained assuming small σ_{eff} (Appendix C) are still approximately valid when
 463 $\sigma_{\text{eff}} \gg s$, as they often closely match those obtained from Appendix B in the regime
 464 where $\sigma_{\text{eff}} \gg s$. Finally, relatively simple expressions can be obtained for Θ_1 and Θ_2
 465 assuming free recombination among all loci (equations C19 to C22); as we will see,
 466 these are often close to the results obtained by integrating numerically over the genetic
 467 map, as long as the mean number of deleterious alleles per genome is not too large,
 468 and map length R not too small (so that most loci segregating for deleterious alleles
 469 are loosely linked).

470 Figure 3A compares the prediction from equation 15 with multilocus simula-
 471 tions (in which deleterious alleles segregate at a large number of loci). Only two alleles
 472 segregate at the modifier locus in the simulations, the allele coding for more sex (say
 473 allele M) being introduced in frequency $p_M = 0.05$ once the population has reached
 474 mutation-selection balance for deleterious alleles. The population evolves until one of
 475 the modifier allele reaches a frequency higher than 0.98, after which the frequency of
 476 M is set back to 0.05 (by switching alleles at the modifier locus in randomly sampled
 477 individuals), and the process is repeated again. The selection gradient s_M is estimated
 478 from the average change in frequency of M over one generation (measured every 50
 479 generations), divided by the average variance at the modifier locus ($p_M q_M$). As can
 480 be seen on Figure 3A, the selection gradient s_M is negative when the baseline rate of

sex in the population is high: in that case, indirect selection is weaker than the cost of sex, and the allele coding for less sex (m) is favoured. The pattern reverses for lower values of σ_{eff} , however, due to the fact that the strength of indirect selection increases rapidly as σ_{eff} decreases. Figure 3A also shows that equation 15 (dotted curve) greatly underestimates selection for sex in the parameter range where indirect selection is strong enough to compensate for the cost of sex (low values of σ_{eff}). Note that the dotted curve in Figure 3A corresponds to the result obtained assuming free recombination between all loci (equations C19 - C22). However, integrating equations C1 to C17 over the genetic map leads to almost undistinguishable results (a C++ program performing the numerical integration is available from Dryad), while simulating freely recombining loci leads to very similar results as those shown in Figure 3A (results not shown). A possible explanation for the discrepancy between the QLE model and the simulations is the fact that the model neglects higher-order interactions between selected loci, which may have two types of effects: (i) breaking associations between three or more selected loci (such as D_{ABC} , D_{ABCD} , ...) may generate additional benefits to sexual reproduction, and (ii) background selection may amplify two-locus associations (such as D_{AB}) by increasing the magnitude of stochastic effects. Computing the effect of background selection on the different moments that appear in Appendices B and C may be feasible using the methods shown in Appendix A, but exceeds the scope of the present paper; however, we will see below that replacing population size N by the effective population size N_e (derived from the computation of average coalescence time at a neutral locus) in equation 15 often yields correct predictions of the strength of indirect selection at the modifier locus. Following Hudson and Kaplan (1995), an expression for the effective population size under background selection, assuming free

505 recombination between all loci is given by (see Online Appendix S1):

$$N_e \approx N \exp \left[-\frac{4Us}{(\sigma_{\text{eff}} + 2s)^2} \right]. \quad (16)$$

506 In a linear genome with restricted recombination, N_e is given by a more complicated
 507 expression which depends on the position of the locus and on map length R . At the
 508 modifier locus (mid-point of the chromosome), one obtains:

$$N_e \approx N \exp \left[-\frac{2Us}{R\alpha^2} \left(2 \log \left[\frac{\beta}{2s} \right] + \frac{(e^R - 1) \sigma_{\text{eff}} \alpha}{s\beta} \right) \right], \quad (17)$$

509 with $\alpha = 2s + \sigma_{\text{eff}}$, $\beta = \alpha e^R - \sigma_{\text{eff}}$. As can be seen on Figure 3A, replacing N by N_e
 510 in equation 15 (either using 16 or 17) provides a better prediction of the strength of
 511 indirect selection for sex, as long as the effective rate of sex is not too small; we will
 512 see below that this generalises to other parameter values. Finally, Figure 3B shows
 513 the three components of selection on the sex modifier that appear within the brackets
 514 of equation 15 (after replacing N by N_e). As can be seen on the figure, the sum of
 515 the individual effects of all loci is small relative to the effects of pairwise interactions
 516 among loci, in the parameter range where indirect selection becomes important relative
 517 to the cost of sex.

518 **Evolutionarily stable rate of sex.** The analytical model can be used to predict
 519 the evolutionarily stable rate of sex, corresponding to the value of σ towards which
 520 the population should evolve in the long term (assuming that evolution proceeds by
 521 small steps, since the model supposes that $\delta\sigma$ is small): this corresponds to the value at
 522 which the curves cross the x -axis in Figure 3A, that is, the value of σ for which $s_M = 0$.
 523 Such predictions can then be compared with the results of simulations representing
 524 deleterious alleles occurring at a large number of loci, and where the rate of sex is free

525 to evolve (as described in the Methods). Figure 4 shows the equilibrium value of the
526 effective rate of sex σ_{eff} in the population as a function of the cost of sex, for differ-
527 ent values of the deleterious mutation rate U . Simulation started from purely sexual
528 populations, but additional simulations starting from purely asexual populations (for
529 the same parameter values) led to the same results. Multilocus simulations confirm
530 that the evolutionarily stable rate of sex first drops rapidly as the cost of sex increases
531 from $c = 1$ (no cost), but then much more slowly as c reaches higher values. This is
532 expected from the analytical results shown in the previous subsections, as the strength
533 of indirect selection for sex increases very sharply below a given value of σ_{eff} (see Figure
534 3): when the baseline rate of sex is low, indirect selection for sex can be substantial
535 and compensate for strong direct costs. Overall, extrapolations from three-locus QLE
536 models (equation 15, replacing N by N_e as described in the previous subsection) pro-
537 vide correct predictions for the equilibrium rate of sex as long as the cost of sex is not
538 too large, the fit being less good for higher values of the deleterious mutation rate U .
539 This likely stems from the fact that replacing N by N_e does not adequately describe
540 the effect of background selection on two and three-locus moments, in particular when
541 the effective rate of sex is low (as was already apparent on Figure 3A): the discrepancy
542 thus becomes more important for higher values of c (since the effective rate of sex σ_{eff}
543 is a decreasing function of c) and for higher values of U (since background selection is
544 stronger when U is high). Note that the differences observed between the analytical
545 predictions and the simulations is not due to the fact that large effect mutations occur
546 at the modifier locus in the simulations: indeed, additional simulations were run in
547 which mutations at the modifier locus had a maximum effect of ± 0.03 , and gave very
548 similar results (not shown). Finally, Figure 4 also shows that integrating numerically

549 the QLE results over the genetic map (in order to take genetic linkage into account)
550 gives results which are often similar to those obtained in the case of unlinked loci,
551 unless U is high (compare dashed and solid lines).

552 As shown by Figure 5, smaller populations have higher rates of sex at equilib-
553 rium: this is expected from the analytical model, since all the different mechanisms
554 favouring sex rely on finite population size, and become stronger in smaller popula-
555 tions. Different results were obtained by Iles et al. (2003), Keightley and Otto (2006)
556 and Gordo and Campos (2008), who found that the strength of selection for recombina-
557 tion or sex (measured either by the relative fixation probability or by the increase
558 in frequency of an allele increasing sex/recombination) increases with population size.
559 However, these studies considered very low baseline rates of sex/recombination, for
560 which the approximations used in the present paper break down. As shown by Fig-
561 ure 6, simulations indicate that the selection gradient at the modifier locus (measured
562 from simulations representing only two alleles at the modifier locus, as described pre-
563 viously) is lower for $N = 20000$ than for $N = 2000$ when σ_{eff} is higher than about
564 0.005, while the pattern is opposite for lower values of σ_{eff} (in agreement with Iles et
565 al., 2003, Keightley and Otto, 2006 and Gordo and Campos, 2008). Understanding
566 why selection for sex is stronger in larger populations when sex is rare would deserve
567 more investigation; although Keightley and Otto (2006) explained this result from the
568 fact that larger populations maintain more polymorphic loci, this is not the case in
569 the simulations shown here: the overall genetic variance at selected loci (measured by
570 the sum of $p_j q_j$ over all loci) is always higher when $N = 2000$ than when $N = 20000$,
571 due to the fact that drift allow deleterious alleles to reach higher frequencies (results
572 not shown). Figure 5A also shows that the strength of selection against deleterious

573 alleles (s) has a non-monotonic effect on selection for sex (the equilibrium rate of sex
574 being close to zero when mutations have very strong fitness effects). This effect is
575 captured by the QLE model, and is due to the fact that the different genetic associa-
576 tions (such as D_{AB}) generating selection for sex are decreasing functions of s (see also
577 Figure 2); a similar, non-monotonic effect of s on the relative fixation probability of
578 a recombination modifier was observed by Gordo and Campos (2008). Overall, the
579 analytical model provides more accurate predictions for larger values of population
580 size, and higher values of s ; Figure 7 shows that this remains true for different values
581 of the deleterious mutation rate, up to $U = 4$ (as can be seen on Figure 7B, the effect
582 of genetic linkage becomes more visible at higher values of U , since deleterious alleles
583 are more abundant within genomes). Figure 8 shows that when s is sufficiently small,
584 the equilibrium rate of sex is only weakly dependent on the values of U and s , as long
585 as Us remains constant: indeed, the equilibrium rate of sex seems to reach a plateau as
586 U increases, decreasing s so that Us remains constant. This effect is not well predicted
587 by the QLE model, which tends to overestimate selection for sex for lower values of s .

588 According to the analytical model, the number of selected loci should have little
589 effect on the results (for a fixed value of the genomic mutation rate U), as long as it is
590 sufficiently large so that sums over all loci can be approximated by integrals, and that
591 the mutation rate per locus is small ($u \ll s$, so that deleterious alleles remain at low
592 frequency). A modified version of the program in which deleterious alleles occur at
593 discrete locations along the chromosome was used to explore the effect of the number
594 of loci: as shown by Figure S1, the results confirm that the equilibrium rate of sex does
595 not depend on the number of loci, as long as it is higher than 10^3 (for the parameter
596 values used in Figure S1). Finally, Figure S2 explores the effect of map length R

597 (average number of cross-overs along the genome at meiosis): R has little effect on
598 the results as long as it is not too small (roughly, $R > 5$ in Figure S2), while tighter
599 linkage increases selection for sex by amplifying interference effects among selected loci
600 and hitchhiking of modifier alleles increasing sex. As shown by Figure S2, integrating
601 the QLE results over the genetic map overestimates selection for sex when R is small,
602 which again is probably due to the fact that higher-order interactions among loci are
603 not adequately represented by replacing N by N_e .

604 DISCUSSION

605 Because every population is finite in size, drift-based explanations for the evo-
606 lution of sex seem particularly compelling (e.g., Otto, 2009); however, few previous
607 papers derived quantitative results on the possible strength of indirect selection for
608 sex generated by this type of mechanism. As we have seen in introduction, the ma-
609 jority of analytical results on the subject are based on recombination modifier models,
610 considering the spread of a mutant allele affecting recombination between two selected
611 loci in haploid organisms. However, the questions of the evolution of sex and the
612 evolution of recombination differ by several important aspects. A first (that was men-
613 tioned earlier) concerns the fact that it is probably easier to modify recombination
614 rates than to switch to a different reproductive mode. Although this is certainly true
615 in most obligate sexuals, this type of constraint may be less important in organisms
616 that alternate between reproductive modes and become sexual in response to an envi-
617 ronmental stimulus, as in cladocerans or rotifers (Hebert and Crease, 1980; Innes and
618 Hebert, 1988; Becks and Agrawal, 2012). A second difference is that strong intrinsic

619 costs are often associated with sexual reproduction (cost of males, costs generated by
620 the mating process...), while increasing or decreasing recombination should have less
621 direct effect on fitness (although many or too few cross-overs per chromosome may
622 result in aneuploidy). Finally, a third difference is that increasing sex may not yield
623 the same indirect benefits as increasing recombination. While this has been shown
624 previously in the case of diploid organisms, where a single selected locus may generate
625 indirect selection for sex through segregation (Uyenoyama and Bengtsson, 1989; Otto,
626 2003; Agrawal, 2009a,b; Roze and Michod, 2010), we have seen in this paper that this
627 is also true in haploids, as a single locus under selection tends to favour any mutation
628 increasing sex in a finite population. This effect (which does not occur in the case of a
629 recombination modifier) stems from the fact that alleles coding for more frequent sex
630 escape more easily from low-fitness genetic backgrounds than alleles coding for lower
631 rates of sex; the same type of benefit is also produced by interactions between selected
632 loci, in addition to the benefits gained by breaking negative associations between those
633 loci. This mechanism (which had not been described before) cannot provide an ad-
634 vantage to sexuals when competing against pure asexuals (since asexuals never “share”
635 their genetic background), but is susceptible to select for increased rates of occurrence
636 of sex in organisms using both reproductive modes. It is interesting to note that this
637 mechanism presents some similarities with the concept of condition-dependent sex or
638 recombination (Agrawal et al., 2005; Hadany and Otto, 2007, 2009), in which alleles
639 that increase the rate of sex or recombination when present in low-fitness individuals
640 benefit from a deterministic advantage due to the possibility of escaping from these
641 low-fitness genotypes; however, an important difference is that the effect described in
642 the present paper does not require condition-dependent rates of sex.

643 Can indirect selection generated by stochastic forces compensate for strong
644 direct costs of sexual reproduction? This requires that sufficiently many selected loci
645 are polymorphic at the same time, as the effect of a single selected locus (or a pair of
646 interacting loci) is rather weak. As we have seen, predictions from analytical models
647 can be extrapolated to situations where selection occurs at many loci (under certain
648 conditions), but this neglects the effect of higher-order interactions (between three or
649 more selected loci) which are difficult to explore analytically due to the large number of
650 variables involved. Although the effect of each of these higher-order interactions should
651 be relatively weak, the number of such possible interactions becomes very large rapidly
652 as the number of selected loci increases. The multilocus simulation results presented in
653 this paper show that extrapolations from three-locus models may nevertheless provide
654 correct predictions for the evolutionarily stable rate of sex in some cases, once the
655 overall effect of selection occurring in the background is accounted for by replacing
656 population size by the effective population size N_e , derived from background selection
657 models. This suggests that selection on a sex modifier mainly stems from its effect on
658 pairwise associations between selected loci, at least as long as the baseline rate of sex
659 is not too low; however, effect of higher-order interactions should be explored more
660 rigorously in order to obtain a better understanding of the different effects involved
661 (and more accurate predictions for low rates of sex). Multilocus simulations also
662 confirm several qualitative predictions from the analytical model, in particular the
663 fact that indirect selection increases very sharply as the baseline rate of sex in the
664 population decreases (causing a relatively slow decrease of the equilibrium rate of sex
665 as the cost of sex increases), and the fact that the strength of indirect selection is
666 maximized for intermediate values of s , and is a decreasing function of population

667 size.

668 While the present model only considers haploid individuals, QLE results for
669 diploids were derived in Roze and Michod (2010) using two and three-locus models
670 (equivalent to Appendix B in the present paper). Analytical and multilocus simula-
671 tion results indicate that the different parameters (N , c , U , s) have similar qualitative
672 effects in haploids and diploids in the absence of dominance (additive deleterious al-
673 leles: $h = 0.5$). When deleterious alleles are partially recessive, however, sex is often
674 disfavoured due to segregation load (generated by dominance within loci and associa-
675 tive overdominance between loci), and multilocus simulations indicate that populations
676 may evolve towards complete asexuality when sex is costly (see Figures 6 and 7 in Roze
677 and Michod, 2010). In general, conditions favouring sex thus seem more restricted in
678 diploids than in haploids.

679 Overall, the results presented in this paper show that deleterious mutations
680 tend to favour small rates of sex in the presence of strong direct costs of sex, but are
681 unlikely to explain the evolution of obligate sex (again, due to the fact that indirect
682 selection decreases very rapidly as the baseline rate of sex in the population increases).
683 Note however that population spatial structure should enhance indirect selection due
684 to stochastic effects (while also slowing the spread of asexual mutants) and therefore
685 allow higher rates of sex to be maintained (Peck et al., 1999; Martin et al., 2006;
686 Salathé et al., 2006; Hartfield et al., 2012). Generally, the magnitude of indirect se-
687 lection depends critically on the deleterious mutation rate U and selection coefficient
688 against deleterious alleles s , for which the few estimates available typically have rather
689 large variances. In particular, estimates of the distribution of fitness effects (DFE) of
690 mutations obtained from DNA polymorphism data (e.g., Keightley and Eyre-Walker,

691 2007; Boyko et al., 2008) often suggest much lower values of s (on average) than those
692 obtained from mutation accumulation experiments or direct measurements of the fit-
693 ness effects of individual mutations (Eyre-Walker and Keightley, 2007; Halligan and
694 Keightley, 2009). Because each method has its own drawbacks and limitations, it is
695 still difficult to know what should be a realistic value for the average s . In general,
696 deleterious mutations may have stronger effects when acting in combination with ben-
697 efcial alleles spreading through the population (Hartfield et al., 2010), or with loci
698 under fluctuating selection. Ultimately, more detailed knowledge about the magni-
699 tude and causes of heritable variation in fitness within populations will be needed to
700 assess the potential strength of indirect selection for sexual reproduction.

701

702 **Acknowledgements.** I thank Aneil Agrawal, Nick Barton and an anonymous re-
703 viewer for helpful comments, and the bioinformatics and computing service of Roscoff's
704 Biological Station for computing time. This work was supported by the French Agence
705 Nationale de la Recherche (ANR-11-BSV7-013-03).

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826 In the following, different superscripts denote moments measured at different
827 steps of the life cycle: $\langle \mathcal{M} \rangle_t^{\text{sel}}$ denote the expected value of \mathcal{M} after selection (weighting
828 each parent by its relative fecundity), while $\langle \mathcal{M} \rangle_t^{\text{juv}}$ stands for the expected value
829 of \mathcal{M} among juveniles (after reproduction, before drift). Three different systems of
830 recursions represent the effects of selection (computing $\langle \mathcal{M} \rangle_t^{\text{sel}}$ in terms of $\langle \mathcal{M} \rangle_t$),
831 reproduction (computing $\langle \mathcal{M} \rangle_t^{\text{juv}}$ in terms of $\langle \mathcal{M} \rangle_t^{\text{sel}}$) and drift (computing $\langle \mathcal{M} \rangle_{t+1}$
832 in terms of $\langle \mathcal{M} \rangle_t^{\text{juv}}$). Note that allele frequencies may change during each of these
833 steps (due to differential fecundities, the direct cost of sex, and drift). The recursions
834 describing the effects of these three events (selection, reproduction, drift) are in turn
835 divided into two steps. A first step corresponds to the calculation of the expectation
836 of moment \mathcal{M} after the event, but using the values of allele frequencies before the
837 event: in particular, $\langle \mathcal{M} \rangle_t'$ corresponds to the expected value of \mathcal{M} after selection,
838 but where the allele frequencies that appear in \mathcal{M} (note that allele frequencies also
839 appear in the definitions of LDs) are replaced by their values before selection. For
840 example, $\langle p_A D_{MA} \rangle_t'$ is the expected value of $p_A E_{\text{sel}} [(X_M - p_M)(X_A - p_A)]$, where E_{sel}
841 stands for the average over individuals after selection (weighting each individual by
842 its relative fecundity), and p_M, p_A are the frequencies of M and A before selection.
843 Similarly, $\langle \mathcal{M} \rangle_t''$ and $\langle \mathcal{M} \rangle_t'''$ correspond to the expected values of \mathcal{M} after reproduction
844 and drift (respectively), but using the values of allele frequencies before reproduction
845 (for $\langle \mathcal{M} \rangle_t''$) and before drift (for $\langle \mathcal{M} \rangle_t'''$). Note that $\langle D_M \rangle_t' = \langle E_{\text{sel}} [X_M - p_M] \rangle_t$ is the
846 expected change in frequency of M during selection (also denoted $\langle \Delta_s p_M \rangle_t$), while

847 $\langle D_M \rangle_t''$ is the expected change in frequency of M during reproduction (also denoted
848 $\langle \Delta_r p_M \rangle_t$). Although $\langle D_M \rangle_t'''$ (the expected change in frequency of M due to drift)
849 equals zero, higher-order moments (such as $\langle D_M^2 \rangle_t''''$) are different from zero. Finally,
850 the second step of the recursions corresponds to the update of allele frequencies, and is
851 identical for the three life cycle events. Although this second step can be represented by
852 a general expression (e.g., eq. A43 in Roze and Michod, 2010), here I simply show the
853 derivation of $\langle p_A D_{MA} \rangle_t^{\text{sel}}$ as an example (which is easily generalized to other moments).
854 We have:

$$\langle p_A D_{MA} \rangle_t^{\text{sel}} = \langle (p_A + \Delta_s p_A) E_{\text{sel}} [(X_M - p_M - \Delta_s p_M)(X_A - p_A - \Delta_s p_A)] \rangle_t \quad (\text{A1})$$

855 where p_M and p_A are allele frequencies before selection. Expanding in terms of $\Delta_s p_M$,
856 $\Delta_s p_A$ (written as D_M, D_A) yields:

$$\langle p_A D_{MA} \rangle_t^{\text{sel}} = \langle p_A D_{MA} \rangle_t' + \langle D_{MA} D_A \rangle_t' - \langle p_A D_M D_A \rangle_t' - \langle D_M D_A^2 \rangle_t'. \quad (\text{A2})$$

857 $\langle p_A D_{MA} \rangle_t^{\text{juv}}$ and $\langle p_A D_{MA} \rangle_{t+1}$ are given by the same expression, replacing moments
858 $\langle \mathcal{M} \rangle_t'$ by $\langle \mathcal{M} \rangle_t''$ and $\langle \mathcal{M} \rangle_t'''$, respectively. A general expression that allows one to
859 compute the effect of updating allele frequencies on any moment can be implemented
860 in *Mathematica* (see Supplementary Material).

861 Similarly, the calculation of $\langle \mathcal{M} \rangle_t'$ in terms of $\langle \mathcal{M} \rangle_t$ (selection), $\langle \mathcal{M} \rangle_t''$ in terms
862 of $\langle \mathcal{M} \rangle_t^{\text{sel}}$ (reproduction) and $\langle \mathcal{M} \rangle_t'''$ in terms of $\langle \mathcal{M} \rangle_t^{\text{juv}}$ (drift) can be automated in
863 *Mathematica*. The general principles are the following. To compute moments $\langle \mathcal{M} \rangle_t'$ in
864 terms of moments before selection $\langle \mathcal{M} \rangle_t$, one uses the fact that D_i, D_{ij} and D_{ijk} after
865 selection (but using allele frequencies before selection) are given by:

$$D_{\mathbb{U}}' = E \left[\frac{W}{\overline{W}} \zeta_{\mathbb{U}} \right] \quad (\text{A3})$$

866 where \mathbb{U} is any set of loci, $\zeta_{\mathbb{U}} = \prod_{i \in \mathbb{U}} \zeta_i$, W is the fecundity of an individual and \overline{W}
 867 the average fecundity in the population. These can be written as

$$W = (1 + s p_A + s \zeta_A) (1 + s p_B + s \zeta_B) \quad (\text{A4})$$

$$\overline{W} = (1 + s p_A) (1 + s p_B) + s^2 D_{AB}$$

868 and the ratio W/\overline{W} can be expanded in a Taylor series in s , allowing one to compute $D'_{\mathbb{U}}$
 869 in terms of allele frequencies and linkage disequilibria before selection. For example,
 870 $W/\overline{W} = 1 + s(\zeta_A + \zeta_B)$ to the first order in s , yielding $\langle p_A D_{MA} \rangle'_t = \langle p_A D_{MA} \rangle_t +$
 871 $s(\langle p_A D_{MAA} \rangle_t + \langle p_A D_{MAB} \rangle_t) + o(s)$. Linkage disequilibria with repeated indices (such
 872 as D_{MAA}) can be rewritten using the relation: $D_{\mathbb{U}ii} = p_i q_i D_{\mathbb{U}} + (1 - 2p_i) D_{\mathbb{U}i}$ (e.g., eq.
 873 5 in Barton and Turelli, 1991). For example, $\langle p_A D_{MAA} \rangle_t = \langle p_A D_{MA} \rangle_t - 2 \langle p_A^2 D_{MA} \rangle_t$,
 874 since any moment $\langle \mathcal{M} \rangle_t$, $\langle \mathcal{M} \rangle_t^{\text{sel}}$ or $\langle \mathcal{M} \rangle_t^{\text{juv}}$ involving D_i (where i is a single locus)
 875 equals zero.

876 To compute the effect of reproduction on linkage disequilibria, I call σ_{ind} the
 877 rate of sex of a given individual (equal to σ or $\sigma + \delta\sigma$ depending on its genotype at
 878 the modifier locus) and $\overline{\sigma}$ the average rate of sex in the population. We then have:

$$D_{\mathbb{U}}'' = \mathbb{E}_{\text{sel}} \left[\frac{c(1 - \sigma_{\text{ind}})}{c(1 - \overline{\sigma}) + \overline{\sigma}} \zeta_{\mathbb{U}} \right] + \sum_{\mathbb{S}, \mathbb{T} = \mathbb{U}} r_{\mathbb{S}, \mathbb{T}} \mathbb{E}_{\text{sel}} \left[\frac{\sigma_{\text{ind}}}{c(1 - \overline{\sigma}) + \overline{\sigma}} \zeta_{\mathbb{S}} \right] \mathbb{E}_{\text{sel}} \left[\frac{\sigma_{\text{ind}}}{\overline{\sigma}} \zeta_{\mathbb{T}} \right]. \quad (\text{A5})$$

879 The first and second terms of equation A5 correspond to the effects of asexual and
 880 sexual reproduction on $D_{\mathbb{U}}''$; the second term involves a sum over all possible partitions
 881 of the set \mathbb{U} into two subsets \mathbb{S} and \mathbb{T} , $r_{\mathbb{S}, \mathbb{T}}$ being the probability that among the
 882 loci in the set \mathbb{U} present in a haploid juvenile (after meiosis), loci in the subset \mathbb{S}
 883 are inherited from the maternal gamete, and loci in the subset \mathbb{T} from the paternal
 884 gamete. To compute $D_{\mathbb{U}}''$ as a function of linkage disequilibria and allele frequencies
 885 after selection, one can replace σ_{ind} and $\overline{\sigma}$ by $\sigma + \delta\sigma p_M + \delta\sigma \zeta_M$ and $\sigma + \delta\sigma p_M$ in
 886 equation A5, and compute all fractions to the first order in $\delta\sigma$.

887 Finally, the effect of drift on moments involving linkage disequilibria is obtained
888 using the following reasoning. $\langle D_{\mathbb{U}} \rangle_t'''$ is the expected value of $\zeta_{\mathbb{U}} = \prod_{i \in \mathbb{U}} (X_i - p_i)$
889 (where p_i 's are allele frequencies before drift, among juveniles) in an individual sampled
890 randomly in the population after drift. Because drift corresponds to the random
891 sampling of N juveniles, this is the same as the average value of $\zeta_{\mathbb{U}}$ among juveniles;
892 therefore, $\langle D_{\mathbb{U}} \rangle_t''' = \langle D_{\mathbb{U}} \rangle_t^{\text{juv}}$. Likewise, $\langle D_{\mathbb{U}} D_{\mathbb{V}} \rangle_t'''$ is the expected value of the product
893 $\zeta_{\mathbb{U}} \zeta_{\mathbb{V}}$, each ζ being measured in an individual sampled with replacement from the
894 population after drift. With probability $1/N$ the same individual is sampled twice, in
895 which case the expectation becomes the average value of $\zeta_{\mathbb{UV}}$ among juveniles, while
896 with probability $1 - 1/N$ two different individuals are sampled, in which case the
897 expectation becomes the average of the product $\zeta_{\mathbb{U}} \zeta_{\mathbb{V}}$ when each ζ is measured in a
898 randomly sampled juvenile. Therefore, we have:

$$\langle D_{\mathbb{U}} D_{\mathbb{V}} \rangle_t''' = \frac{1}{N} \langle D_{\mathbb{UV}} \rangle_t^{\text{juv}} + \left(1 - \frac{1}{N}\right) \langle D_{\mathbb{U}} D_{\mathbb{V}} \rangle_t^{\text{juv}}. \quad (\text{A6})$$

899 In particular, $\langle D_M^2 \rangle_t''' = \langle D_{MM} \rangle_t^{\text{juv}} / N = \langle p_M q_M \rangle_t^{\text{juv}} / N$ (since $\langle D_M^2 \rangle_t^{\text{juv}} = 0$). This
900 method is readily extended to more complex moments (e.g., Roze and Michod, 2010).
901 Throughout the paper, I assume that population size is large and calculate all recur-
902 sions to the first order in $1/N$.

904 MODEL

905 The three-locus model involves different moments of allele frequencies and LD,
 906 which are of different order in s and $\delta\sigma$. In the following, r_{MAB} is the probability that
 907 at least one recombination event occurs between the three loci, while $\rho_{MAB} = r_{MAB} \sigma_{\text{eff}}$.
 908 All moments are expressed at QLE to the first order in $1/N$ and $\delta\sigma$, and to leading
 909 order in s ; derivations can be found in the Supplementary Material. The variance in
 910 the three-locus linkage disequilibrium D_{MAB} is generated by finite population size:

$$\langle D_{MAB}^2 \rangle_t = \frac{\langle pq_{MAB} \rangle_t}{N \rho_{MAB} (2 - \rho_{MAB})}. \quad (\text{B1})$$

911 where $\langle pq_{MAB} \rangle_t = \langle p_M q_M p_A q_A p_B q_B \rangle_t$. Similarly, we have:

$$\langle p_M q_M D_{AB}^2 \rangle_t = \frac{\langle pq_{MAB} \rangle_t}{N \rho_{AB} (2 - \rho_{AB})}. \quad (\text{B2})$$

912 The moment $\langle D_{MAB} D_{AB} \rangle$ is generated by the modifier effect and drift:

$$\langle D_{MAB} D_{AB} \rangle_t = -\delta\sigma_{\text{eff}} \frac{T_1 \langle p_M q_M D_{AB}^2 \rangle_t + T_2 \langle D_{MAB}^2 \rangle_t}{1 - (1 - \rho_{AB})(1 - \rho_{MAB})} \quad (\text{B3})$$

913 with $T_1 = (1 - \rho_{AB}) [r_{AB} + (c - 1) \rho_{AB}]$ and $T_2 = (1 - \rho_{MAB}) (r_{AB} + c - 1)$. Moments
 914 $\langle D_{MAB} D_{MA} \rangle$, $\langle D_{MAB} D_{MB} \rangle$, $\langle p_M q_M p_A D_{AB} \rangle$ and $\langle p_M q_M p_B D_{AB} \rangle$ are generated by selec-
 915 tion and drift, and are of order s ; when measured after selection, they are given by:

$$\langle D_{MAB} D_{MA} \rangle_t^{\text{sel}} = s \frac{\langle D_{MAB}^2 \rangle_t}{1 - (1 - \rho_{MA})(1 - \rho_{MAB})} \quad (\text{B4})$$

$$\langle p_M q_M p_A D_{AB} \rangle_t^{\text{sel}} = s \frac{\langle p_M q_M D_{AB}^2 \rangle_t}{\rho_{AB}}. \quad (\text{B5})$$

917 Moments before selection are given by the same expressions multiplied by $(1 - \rho_{MA}) \times$
 918 $(1 - \rho_{MAB})$ and by $1 - \rho_{AB}$ (respectively), while $\langle D_{MAB} D_{MB} \rangle$ and $\langle p_M q_M p_B D_{AB} \rangle$ are

919 given by symmetrical expressions. The moments $\langle D_{MA}D_{AB} \rangle$, $\langle D_{MB}D_{AB} \rangle$, $\langle p_A D_{MAB} \rangle$

920 and $\langle p_B D_{MAB} \rangle$ are of order $s \delta\sigma$:

$$\langle D_{MA}D_{AB} \rangle_t = \frac{(1 - \rho_{MA}) \left[s(1 - \rho_{AB}) \langle D_{MAB}D_{AB} \rangle_t - \delta\sigma_{\text{eff}} (r_{AB} + c - 1) \langle D_{MAB}D_{MA} \rangle_t^{\text{sel}} \right]}{1 - (1 - \rho_{MA})(1 - \rho_{AB})}$$

921 (B6)

$$\langle p_A D_{MAB} \rangle_t = \frac{1}{\rho_{MAB}} \left[-\delta\sigma_{\text{eff}} [r_{AB} + (c - 1) \rho_{AB}] \langle p_M q_M p_A D_{AB} \rangle_t^{\text{sel}} \right. \\ \left. + (1 - \rho_{MAB}) \left[s \langle D_{MAB}D_{AB} \rangle_t - \delta\sigma_{\text{eff}} (c - 1) \langle D_{MAB}D_{MA} \rangle_t^{\text{sel}} \right] \right]$$

922 (B7)

922 while $\langle D_{MB}D_{AB} \rangle_t$ and $\langle p_B D_{MAB} \rangle_t$ are given by symmetrical expressions. Moments

923 $\langle p_M q_M D_{AB} \rangle$, $\langle D_{MA}D_{MB} \rangle$ and $\langle p_M D_{MAB} \rangle$ are generated by selection and drift, and are

924 of order s^2 . After selection, they are given by:

$$\langle p_M q_M D_{AB} \rangle_t^{\text{sel}} = -2s \frac{\langle p_M q_M p_A D_{AB} \rangle_t + \langle p_M q_M p_B D_{AB} \rangle_t + s \langle p_M q_M D_{AB}^2 \rangle_t}{\rho_{AB}}$$

925 (B8)

$$\langle D_{MA}D_{MB} \rangle_t^{\text{sel}} = s \frac{\langle D_{MAB}D_{MA} \rangle_t + \langle D_{MAB}D_{MB} \rangle_t + s \langle D_{MAB}^2 \rangle_t}{1 - (1 - \rho_{MA})(1 - \rho_{MB})}$$

926 (B9)

$$\langle p_M D_{MAB} \rangle_t^{\text{sel}} = s \frac{\langle D_{MAB}D_{MA} \rangle_t + \langle D_{MAB}D_{MB} \rangle_t + s \langle D_{MAB}^2 \rangle_t}{\rho_{MAB}}$$

927 (B10)

927 while the same moments before selection are obtained by multiplying the previous

928 expressions by $1 - \rho_{AB}$, $(1 - \rho_{MA})(1 - \rho_{MB})$ and $1 - \rho_{MAB}$ (respectively). The three-

929 locus linkage disequilibrium is generated by selection, drift and the modifier effect, and

930 is of order s^2 :

$$\langle D_{MAB} \rangle_t = \frac{1}{\rho_{MAB}} \left[-\delta\sigma_{\text{eff}} [r_{AB} + (c - 1) \rho_{AB}] \langle p_M q_M D_{AB} \rangle_t^{\text{sel}} \right. \\ + \delta\sigma_{\text{eff}} [r_{MAB} + (c - 1)(2 - \rho_{MAB})] \langle p_M D_{MAB} \rangle_t^{\text{sel}} \\ + \delta\sigma_{\text{eff}} [r_{AB} + (c - 1)(2 - \rho_{MA} - \rho_{MB})] \langle D_{MA}D_{MB} \rangle_t^{\text{sel}} \\ \left. - (1 - \rho_{MAB}) \left[2s(\langle D_{MA}D_{AB} \rangle_t + \langle D_{MB}D_{AB} \rangle_t + \langle p_A D_{MAB} \rangle_t \right. \right. \\ \left. \left. + \langle p_B D_{MAB} \rangle_t) + 4s^2 \langle D_{MAB}D_{AB} \rangle_t \right] \right].$$

931 (B11)

931 Finally, the two-locus moments involving the modifier and a single selected locus are
 932 also affected by selection at the third locus. One obtains:

$$\langle D_{MA}^2 \rangle_t^{\text{sel}} = \frac{1}{\rho_{MA} (2 - \rho_{MA})} \left[\frac{\langle p q_{MA} \rangle_t}{N} + s (2 \langle D_{MAB} D_{MA} \rangle_t + s \langle D_{MAB}^2 \rangle_t) \right] \quad (\text{B12})$$

933 $\langle D_{MA}^2 \rangle_t$ (before selection) being obtained by multiplying the term in s by $(1 - \rho_{MA})^2$
 934 in the previous expression,

$$\begin{aligned} \langle p_A D_{MA} \rangle_t = \frac{1 - \rho_{MA}}{\rho_{MA}} & \left[s (\langle p_A D_{MAB} \rangle_t + \langle D_{MA} D_{AB} \rangle_t) + s^2 \langle D_{MAB} D_{AB} \rangle_t \right. \\ & \left. - \delta \sigma_{\text{eff}} (c - 1) \langle D_{MA}^2 \rangle_t^{\text{sel}} \right] \end{aligned} \quad (\text{B13})$$

935

$$\begin{aligned} \langle p_M D_{MA} \rangle_t^{\text{sel}} = \frac{1}{\rho_{MA}} & \left[s (\langle D_{MA}^2 \rangle_t + \langle D_{MA} D_{MB} \rangle_t + \langle p_M D_{MAB} \rangle_t) \right. \\ & \left. + s^2 (2 \langle D_{MAB} D_{MA} \rangle_t + \langle D_{MAB} D_{MB} \rangle_t) + s^3 \langle D_{MAB}^2 \rangle_t \right] \end{aligned} \quad (\text{B14})$$

936 (which has to be multiplied by $1 - \rho_{MA}$ to obtain the same moment before selection),

937 and

$$\begin{aligned} \langle D_{MA} \rangle_t = \frac{1}{\rho_{MA}} & \left[\delta \sigma_{\text{eff}} [(c - 1) (2 - \rho_{MA}) + r_{MA}] \langle p_M D_{MA} \rangle_t^{\text{sel}} \right. \\ & + (1 - \rho_{MA}) \left[s (\langle D_{MAB} \rangle_t - 2 \langle p_A D_{MA} \rangle_t) - 2s^3 \langle D_{MAB} D_{AB} \rangle_t \right. \\ & \left. \left. - s^2 (2 \langle p_A D_{MAB} \rangle_t + 2 \langle D_{MA} D_{AB} \rangle_t + \langle p_B D_{MAB} \rangle_t + \langle D_{MB} D_{AB} \rangle_t) \right] \right]. \end{aligned} \quad (\text{B15})$$

938 Moments $\langle D_{MB}^2 \rangle_t$, $\langle p_B D_{MB} \rangle_t$, $\langle p_M D_{MB} \rangle_t$ and $\langle D_{MB} \rangle_t$ are given by symmetrical ex-
 939 pressions.

941 The following expressions for moments of allele frequencies and linkage disequi-
 942 libria are derived for the case where alleles A and B are deleterious and maintained at
 943 mutation-balance (at equilibrium frequency $p_A = p_B \approx u/s$, where u is the per-locus
 944 deleterious mutation rate), and for weak effective recombination rates ρ_X (of order
 945 s); derivations can be found in the Supplementary Material. Moments generated by
 946 selection and drift are given by:

$$\frac{\langle pq_M D_{AB}^2 \rangle_t}{\langle pq_M \rangle_t} \approx \frac{p_A p_B}{2N (\rho_{AB} + 2s)} \quad (C1)$$

947

$$\frac{\langle D_{MAB}^2 \rangle_t}{\langle pq_M \rangle_t} \approx \frac{p_A p_B}{2N (\rho_{MAB} + 2s)} \quad (C2)$$

948

$$\frac{\langle pq_M p_A D_{AB} \rangle_t}{\langle pq_M \rangle_t} \approx -\frac{s p_A p_B}{2N (\rho_{AB} + 2s) (\rho_{AB} + 3s)} \quad (C3)$$

949

$$\frac{\langle D_{MAB} D_{MA} \rangle_t}{\langle pq_M \rangle_t} \approx -\frac{s p_A p_B}{2N (\rho_{MAB} + 2s) (\rho_{MA} + \rho_{MAB} + 3s)} \quad (C4)$$

950

$$\frac{\langle pq_M D_{AB} \rangle_t}{\langle pq_M \rangle_t} \approx -\frac{2s^2 p_A p_B}{N (\rho_{AB} + 2s)^2 (\rho_{AB} + 3s)} \quad (C5)$$

951

$$\frac{\langle D_{MA} D_{MB} \rangle_t}{\langle pq_M \rangle_t} \approx \frac{s^2 X p_A p_B}{2N (\rho_{MAB} + 2s) (\rho_{MA} + \rho_{MB} + 2s)} \quad (C6)$$

952

$$\frac{\langle p_M D_{MAB} \rangle_t}{\langle pq_M \rangle_t} \approx \frac{s^2 X p_A p_B}{2N (\rho_{MAB} + 2s)^2} \quad (C7)$$

953

$$\text{with } X = \frac{6s + 2\rho_{MAB} + \rho_{MA} + \rho_{MB}}{(\rho_{MAB} + \rho_{MA} + 3s) (\rho_{MAB} + \rho_{MB} + 3s)}, \quad (C8)$$

954

$$\frac{\langle D_{MA}^2 \rangle_t}{\langle pq_M \rangle_t} \approx \frac{p_A}{2N (\rho_{MA} + s)} \left[1 + \frac{s^2 p_B}{(\rho_{MAB} + 2s) (\rho_{MAB} + \rho_{MA} + 3s)} \right] \quad (C9)$$

955

$$\langle p_M D_{MA} \rangle_t \approx -\frac{s}{(\rho_{MA} + s)} \left[\langle D_{MA}^2 \rangle_t + \langle D_{MA} D_{MB} \rangle_t + \langle p_M D_{MAB} \rangle_t \right]. \quad (C10)$$

956 Moments generated by the modifier effect are given by:

$$\frac{\langle D_{MAB} D_{AB} \rangle_t}{\langle pq_M \rangle_t} \approx -\delta\sigma_{\text{eff}} \frac{2s (c - 1 + 2r_{AB}) + \rho_{AB} (c - 1 + r_{AB} + r_{MAB})}{2N (\rho_{AB} + 2s) (\rho_{MAB} + 2s) (\rho_{MAB} + \rho_{AB} + 4s)} p_A p_B \quad (C11)$$

$$\langle D_{MA}D_{AB} \rangle_t \approx -\frac{s \langle D_{MAB}D_{AB} \rangle_t + \delta\sigma_{\text{eff}}(c-1+r_{AB}) \langle D_{MAB}D_{MA} \rangle_t}{\rho_{MA} + \rho_{AB} + 3s} \quad (\text{C12})$$

$$\langle p_A D_{MAB} \rangle_t \approx -\frac{s \langle D_{MAB}D_{AB} \rangle_t + \delta\sigma_{\text{eff}} [r_{AB} \langle pqM p_A D_{AB} \rangle_t + (c-1) \langle D_{MAB}D_{MA} \rangle_t]}{\rho_{MAB} + 3s} \quad (\text{C13})$$

$$\begin{aligned} \langle D_{MAB} \rangle_t \approx \frac{1}{\rho_{MAB} + 2s} & \left[-\delta\sigma_{\text{eff}} r_{AB} \langle pqM D_{AB} \rangle_t \right. \\ & + \delta\sigma_{\text{eff}} [2(c-1) + r_{MAB}] \langle p_M D_{MAB} \rangle_t \\ & + \delta\sigma_{\text{eff}} [2(c-1) + r_{AB}] \langle D_{MA}D_{MB} \rangle_t \\ & \left. + 2s (\langle D_{MA}D_{AB} \rangle_t + \langle D_{MB}D_{AB} \rangle_t + \langle p_A D_{MAB} \rangle_t + \langle p_B D_{MAB} \rangle_t) \right] \end{aligned} \quad (\text{C14})$$

$$\langle p_A D_{MA} \rangle_t \approx -\frac{s (\langle D_{MA}D_{AB} \rangle_t + \langle p_A D_{MAB} \rangle_t) + \delta\sigma_{\text{eff}}(c-1) \langle D_{MA}^2 \rangle_t}{\rho_{MA} + 2s} \quad (\text{C15})$$

$$\langle D_{MA} \rangle_t \approx \frac{s (2 \langle p_A D_{MA} \rangle_t - \langle D_{MAB} \rangle_t) + \delta\sigma_{\text{eff}} [2(c-1) + r_{MA}] \langle p_M D_{MA} \rangle_t}{\rho_{MA} + s} \quad (\text{C16})$$

Under the same assumptions, the selection gradient at the modifier locus is given by:

$$s_M \equiv \frac{\langle \Delta p_M \rangle_t}{\langle p_M q_M \rangle_t} \approx -\delta\sigma_{\text{eff}}(c-1) - s \frac{\langle D_{MA} \rangle_t + \langle D_{MB} \rangle_t}{\langle pqM \rangle_t} \quad (\text{C17})$$

From equations C1 to C17, the selection gradient can be written under the form:

$$s_M \approx \delta\sigma_{\text{eff}} \left[-(c-1) + \frac{s^2}{N} \Theta_1 (p_A + p_B) + \frac{s^4}{N} \Theta_2 p_A p_B \right] \quad (\text{C18})$$

where Θ_1 and Θ_2 are functions of recombination rates, the effective rate of sex σ_{eff} , the cost of sex c and strength of selection s . Assuming free recombination between all loci, one obtains:

$$\Theta_1 = \frac{2}{(\sigma_{\text{eff}} + 2s)^3} \left[1 + \frac{8(c-1)(\sigma_{\text{eff}} + 3s)}{\sigma_{\text{eff}} + 4s} \right] \quad (\text{C19})$$

and

$$\Theta_2 = \frac{32 [(5\sigma_{\text{eff}} + 16s) X_1 + 8(c-1)(\sigma_{\text{eff}} + 6s) X_2]}{3(\sigma_{\text{eff}} + 2s)^3 (\sigma_{\text{eff}} + 3s) (\sigma_{\text{eff}} + 4s)^2 (\sigma_{\text{eff}} + 6s) (\sigma_{\text{eff}} + 8s)^3 (5\sigma_{\text{eff}} + 12s) (5\sigma_{\text{eff}} + 16s)} \quad (\text{C20})$$

968 with:

$$\begin{aligned} X_1 = & 1133568 s^6 + 2412288 s^5 \sigma_{\text{eff}} + 2142144 s^4 \sigma_{\text{eff}}^2 + 1016320 s^3 \sigma_{\text{eff}}^3 \\ & + 271780 s^2 \sigma_{\text{eff}}^4 + 38848 s \sigma_{\text{eff}}^5 + 2319 \sigma_{\text{eff}}^6 \end{aligned} \quad (\text{C21})$$

969

$$\begin{aligned} X_2 = & 921600 s^6 + 1920000 s^5 \sigma_{\text{eff}} + 1660672 s^4 \sigma_{\text{eff}}^2 + 763280 s^3 \sigma_{\text{eff}}^3 \\ & + 196622 s^2 \sigma_{\text{eff}}^4 + 26917 s \sigma_{\text{eff}}^5 + 1530 \sigma_{\text{eff}}^6 . \end{aligned} \quad (\text{C22})$$

970 Expressions for arbitrary recombination rates between the three loci can be obtained
971 from equations C1 to C17. Extrapolating these results to the case where deleterious
972 alleles occur over a whole genome can be done by summing equation C18 over all loci
973 A and B , which yields equation 15 in the main text.

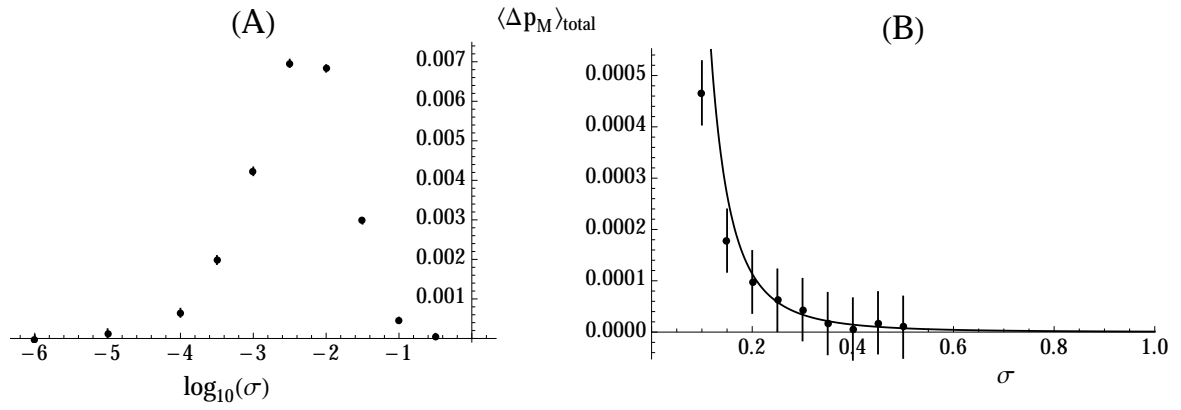


Figure 1. Average increase in frequency of allele M during the sweep of the beneficial allele A , as a function of the baseline rate of sex σ in the population (measured on a log scale in A). Dots show results from two-locus simulations (error bars measure ± 1.96 S.E.); the curve in B corresponds to the prediction from equation 8. Parameter values: $N = 2000$, $r_{MA} = 0.2$, $s = 0.02$, $\delta\sigma = 0.03$, $c = 1$.

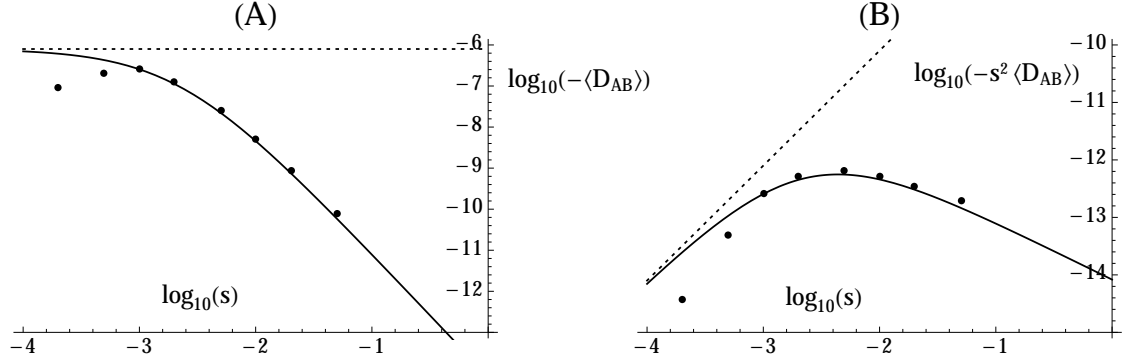


Figure 2. Average value of the linkage disequilibrium between two deleterious alleles at mutation-selection balance (multiplied by s^2 in B), as a function of the strength of selection against those alleles s (on a log scale). Solid curves: predictions from equation 14; dotted curves: predictions obtained assuming $s \ll \rho_{AB}$; dots: two-locus simulation results (averages over 10^{11} to 10^{12} points; error bars are small relative to the size of points). Parameter values: $N = 2000$, $\rho_{AB} = 0.005$, $u = 10^{-5}$.

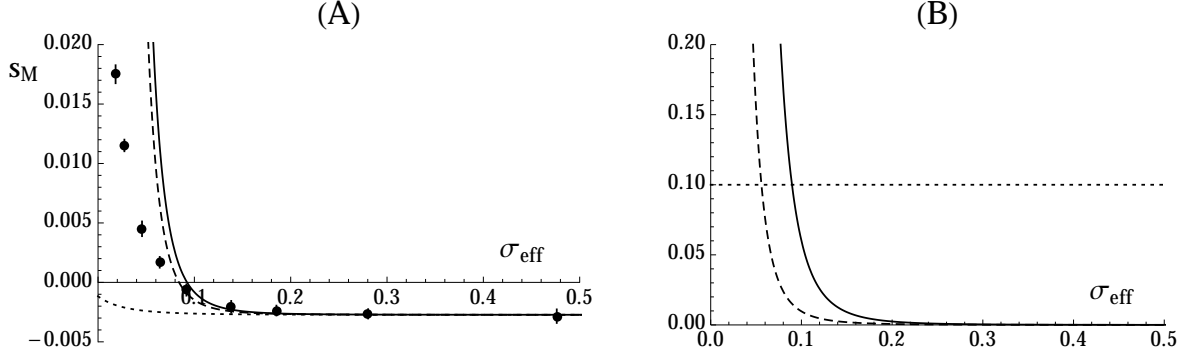


Figure 3. (A): selection gradient at the modifier locus s_M , as a function of the baseline rate of sex in the population σ_{eff} . Dots: multilocus simulation results (see text for more explanations); dotted curve: prediction from equation 15, using expressions for Θ_1 and Θ_2 under free recombination (equations C19 – C22); dashed, solid curves: predictions obtained by replacing N by N_e in these expressions (dashed: using the expression for N_e under free recombination, given by equation 16; solid: using the expression for N_e at the mid-point of a linear genome of genetic length R , given by equation 17). Parameter values: $N = 20000$, $U = 0.5$, $s = 0.05$, $R = 10$, $\delta\sigma = 0.03$. (B): three components of selection on the sex modifier, as a function of the baseline rate of sex in the population. The curves correspond to the three terms that appear within the brackets of equation 15, for the same parameter values as in (A). The dotted curve shows the opposite of the first term (cost of sex), that is, $c - 1$, while the dashed and solid curves show the second and third term, respectively (replacing N by N_e at the mid-point of the chromosome).

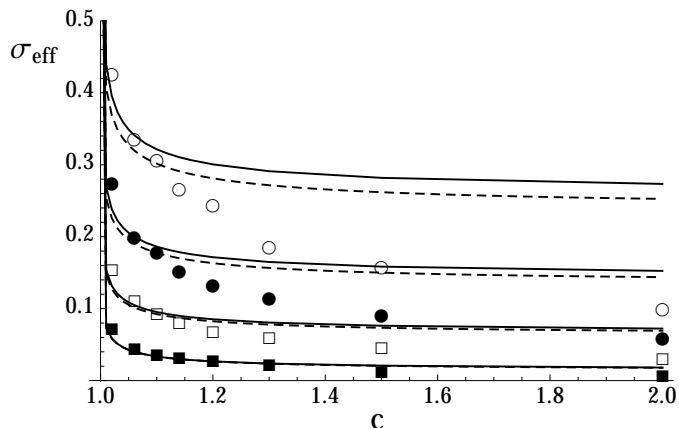


Figure 4. Effective rate of sex in the population at equilibrium as a function of the cost of sex c , and for different values of the deleterious mutation rate per genome U . Dots correspond to multilocus simulation results for $U = 0.25$ (filled squares), $U = 0.5$ (empty squares), $U = 1$ (filled circles) and $U = 2$ (empty circles). Error bars (obtained by splitting the results from each simulation into batches of 10^5 generations and calculating the variance over batches) are smaller than the size of symbols. Dashed curves correspond to predictions from equations C19 – C22 (assuming free recombination among all loci), replacing N by the effective population size at the modifier locus, while solid curves have been obtained by integrating the equations of appendix C over the genetic map (also replacing N by the effective population size at the modifier locus). Parameter values: $N = 20000$, $s = 0.05$, $R = 10$.

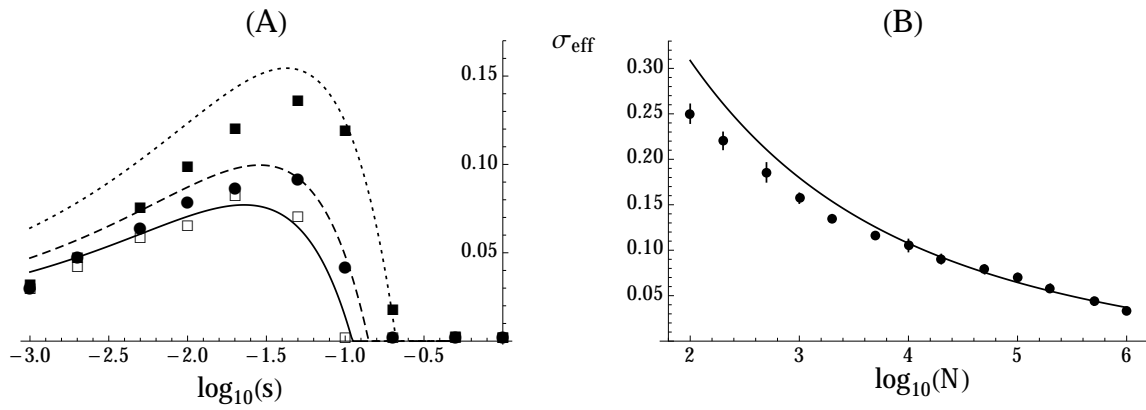


Figure 5. Effective rate of sex in the population at equilibrium as a function of the strength of selection against deleterious alleles s (A) and of population size (B), both on a log scale. Dots show simulation results, while the curves correspond to predictions from the QLE model: equations 15 and C19 – C22, replacing N by the effective population size at the modifier locus. (A): filled squares, dotted curve: $N = 2000$; circles, dashed curve: $N = 20000$; empty squares, solid curve: $N = 10^5$. (B): $s = 0.05$. Other parameter values: $U = 0.5$, $R = 10$, $c = 1.1$. Simulations started from purely sexual populations ($\sigma = 1$).

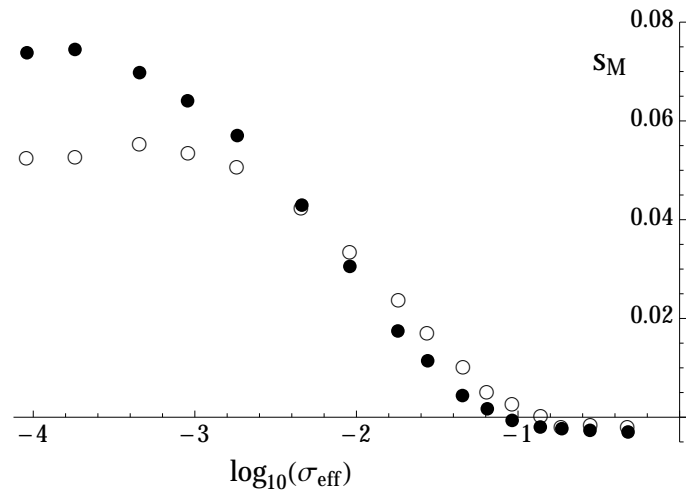


Figure 6. Selection gradient at the modifier locus s_M , as a function of the baseline rate of sex in the population σ_{eff} (on a log scale), for two values of population size: $N = 2000$ (empty circles) and $N = 20000$ (filled circles); other parameter values are as in Figure 3. Error bars are smaller than the size of symbols.

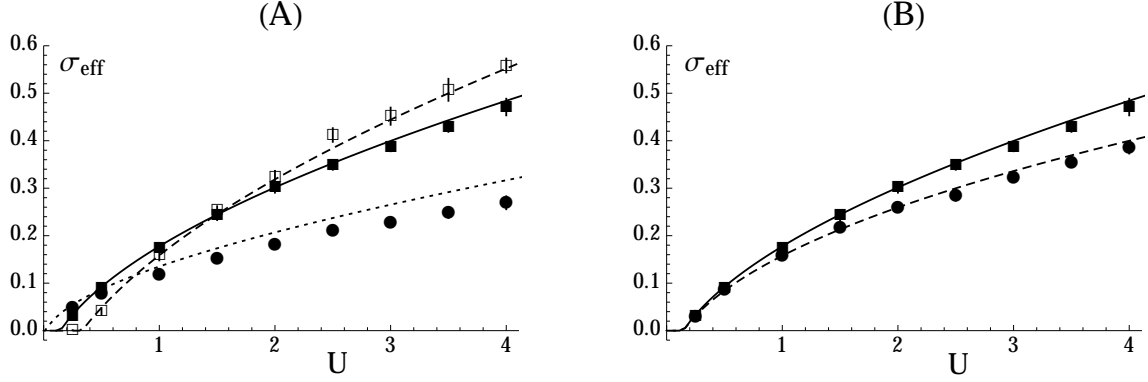


Figure 7. Effective rate of sex in the population at equilibrium as a function of the deleterious mutation rate U . Dots correspond to multilocus simulation results, and curves to the prediction obtained from the QLE model: equations 15 and C19 – C22, replacing N by the effective population size at the modifier locus. (A): circles, dotted curve: $s = 0.01$; filled squares, solid curve: $s = 0.05$; empty squares, dashed curve: $s = 0.1$. Other parameter values: $N = 20000$, $R = 10$, $c = 1.1$. (B): comparing the results obtained with a linear genetic map and with freely recombining loci, for $s = 0.05$: the squares and solid curve are the same as in A (linear map), while circles correspond to simulation results with freely recombining loci, and the dashed curve is the QLE prediction using the expression of N_e for unlinked loci (equation 16).

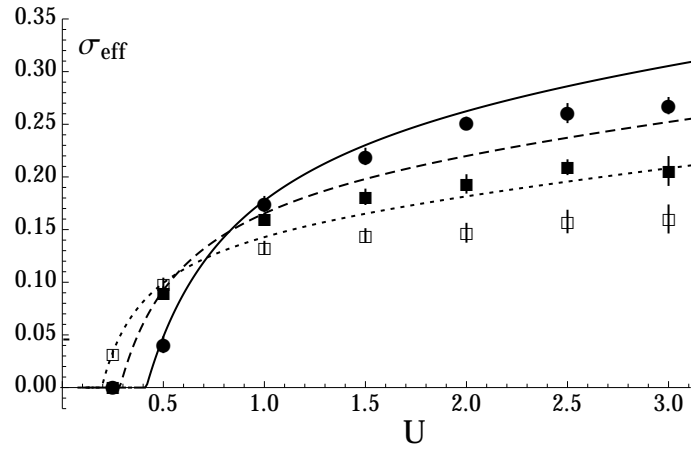


Figure 8. Effective rate of sex in the population at equilibrium as a function of the deleterious mutation rate U , adjusting s so that the Us product remains constant: $Us = 0.05$ (circles, solid curve), 0.025 (filled squares, dashed curves) and 0.0125 (empty squares, dotted curves). Curves correspond to the prediction obtained from the QLE model: equations 15 and C19 – C22, replacing N by the effective population size at the modifier locus. Parameter values: $N = 20000$, $R = 10$, $c = 1.1$.

Table 1: Model parameters.

N	population size
c	cost of sex
σ	investment into sexual reproduction
$\sigma_{\text{eff}} = \frac{\sigma}{c(1-\sigma)+\sigma}$	effective rate of sex (proportion of sexually produced offspring)
$\delta\sigma$	effect of allele M on investment into sex
r_{MA}	recombination rate between M and A (probability that a recombination occurs at meiosis)
$\rho_{MA} = r_{MA} \sigma_{\text{eff}}$	effective recombination rate between M and A (frequency of recombinants per generation)
s	selection coefficient of alleles A, B
u	rate of deleterious mutation per locus
U	rate of deleterious mutation per genome
R	genome map length (in Morgans)