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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

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

*Keywords:* deleterious mutation, evolution of sex, genetic drift, modifier model, multilocus 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

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

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).

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

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  $\sigma$  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

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

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

**Multilocus simulations.** As we will see in the next section, analytical results from three-locus models can be extrapolated to predict the overall strength of selection on a sex modifier when deleterious alleles segregate at a large number of loci; however, this supposes that the effects of higher-order interactions (between three or more selected loci) can be neglected, which is not guaranteed: even if the effect of each of these higher-order interactions is small, the number of such interactions increases very rapidly as the number of polymorphic loci increases. In order to test the predictions obtained from three-locus models, I use individual-based simulations representing deleterious mutations occurring at a large (quasi-infinite) number of possible loci. The simulation program (written in C++, and available from Dryad) is very similar to the programs used in previous papers (Roze and Michod, 2010; Roze and Otto, 2012). It represents a population of  $N$  haploid individuals whose genome consists in a linear chromosome with infinitely many loci. Every generation, the number of new deleterious mutations per chromosome is sampled from a Poisson distribution with parameter  $U$ , and the position of each mutation is sampled from a uniform distribution. The fecundity  $W_i$  of an individual is given by  $(1 - s)^n$ , where  $n$  is the number of mutations in its genome. When forming the next generation, each parental individual  $i$  contributes as a mother (either through sexual or asexual reproduction) with a probability proportional to  $W_i [c(1 - \sigma_i) + \sigma_i]$  (where  $\sigma_i$  is the rate of sex of parent  $i$ ). The new individual is then produced asexually with probability  $c(1 - \sigma_i) / [c(1 - \sigma_i) + \sigma_i]$  (in which case its 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  $1.9 \times 10^6$  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,  $\sigma_{\text{eff}}$  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):  $p_M q_M$

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

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

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

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

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

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

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

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

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

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

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

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



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

As shown by Figure 1, two-locus simulations confirm that in the absence of a direct cost of sex ( $c = 1$ ), a modifier increasing sex tends to increase in frequency during the sweep of a beneficial allele at a second locus. In the simulations the beneficial allele  $A$  is initially in frequency  $p_{A,0} = 0.05$ , while the sex modifier  $M$  is initially in frequency  $p_{M,0} = 0.5$  and in linkage equilibrium with  $A$ . The program measures the final frequency of  $M$  at the end of the sweep, the whole process being repeated  $50 \times 10^6$  times. A prediction for the total increase in frequency of  $M$  over the sweep can be obtained by integrating equation 7 over time (treated as a continuous variable), and assuming that  $p_A$  remains close to a deterministic trajectory. In this case, using the 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 yields for the expected total increase in frequency of  $M$ :

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

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

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

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

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

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

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

QLE expressions for the different moments that appear in equations 9 and 10 are given in Appendix B. From these, it can be shown that all the different terms involving the selected loci generate selection for increased rates of sex. Although it is not possible for space reasons to provide an intuitive explanation for each of the moments involved, it is interesting to note that the extra benefits of sex that appear when introducing a second selected locus do not all stem from recombination between the selected loci (which again differs from the case of a recombination modifier). In the following I assume that allele  $M$  increases sex ( $\delta\sigma > 0$ ), and consider the effect of the three-locus 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

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

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

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

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

where  $pq_{AB} = p_A q_A p_B q_B$  (note that the factor  $1 - 4s$  was neglected in the previous 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  $\rho_{AB}$  are small. Appendix  
 416 C provides approximations for other moments when  $\rho_X$  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  $\sigma$  is of order  $\epsilon$ , 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

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

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

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

The first term of equation 15 represents the effect of the cost of sex, the second term is the sum of the individual effects of all selected loci, and the third term is the sum of all effects of interactions between pairs of loci. Presumably, interactions between three, four or more selected loci could also generate indirect selection for sex (through terms in  $(Us)^3$ ,  $(Us)^4$ ...), but the computation of these terms would be tedious. The terms  $\Theta_1$  and  $\Theta_2$  that appear in equation 15 are complicated functions of the effective rate of sex  $\sigma_{\text{eff}}$ , cost of sex  $c$ , strength of selection  $s$  and recombination rates, integrated over all possible genomic positions of deleterious alleles (which requires performing two numerical integrations over the genetic map). When effective recombination rates are large relative to  $s$  (which requires  $\sigma_{\text{eff}} \gg s$ ),  $\Theta_1$  and  $\Theta_2$  become approximately 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  $\sigma_{\text{eff}}$  (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  $\Theta_1$  and  $\Theta_2$   
 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



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

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

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

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

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

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

**Evolutionarily stable rate of sex.** The analytical model can be used to predict the evolutionarily stable rate of sex, corresponding to the value of  $\sigma$  towards which the population should evolve in the long term (assuming that evolution proceeds by small steps, since the model supposes that  $\delta\sigma$  is small): this corresponds to the value at which the curves cross the  $x$ -axis in Figure 3A, that is, the value of  $\sigma$  for which  $s_M = 0$ . Such predictions can then be compared with the results of simulations representing 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  $\sigma_{\text{eff}}$  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  $\sigma_{\text{eff}}$  (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  $\sigma_{\text{eff}}$   
 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  $\pm 0.03$ , and gave very  
 548 similar results (not shown). Finally, Figure 4 also shows that integrating numerically

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

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

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

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

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

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



size.

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

Overall, the results presented in this paper show that deleterious mutations tend to favour small rates of sex in the presence of strong direct costs of sex, but are unlikely to explain the evolution of obligate sex (again, due to the fact that indirect selection decreases very rapidly as the baseline rate of sex in the population increases). Note however that population spatial structure should enhance indirect selection due to stochastic effects (while also slowing the spread of asexual mutants) and therefore allow higher rates of sex to be maintained (Peck et al., 1999; Martin et al., 2006; Salathé et al., 2006; Hartfield et al., 2012). Generally, the magnitude of indirect selection depends critically on the deleterious mutation rate  $U$  and selection coefficient against deleterious alleles  $s$ , for which the few estimates available typically have rather large variances. In particular, estimates of the distribution of fitness effects (DFE) of 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 eficial 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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## APPENDIX A: DERIVING RECURSIONS FOR MOMENTS OF ALLELE

### FREQUENCIES AND LINKAGE DISEQUILIBRIA

In the following, different superscripts denote moments measured at different steps of the life cycle:  $\langle \mathcal{M} \rangle_t^{\text{sel}}$  denote the expected value of  $\mathcal{M}$  after selection (weighting each parent by its relative fecundity), while  $\langle \mathcal{M} \rangle_t^{\text{juv}}$  stands for the expected value of  $\mathcal{M}$  among juveniles (after reproduction, before drift). Three different systems of recursions represent the effects of selection (computing  $\langle \mathcal{M} \rangle_t^{\text{sel}}$  in terms of  $\langle \mathcal{M} \rangle_t$ ), reproduction (computing  $\langle \mathcal{M} \rangle_t^{\text{juv}}$  in terms of  $\langle \mathcal{M} \rangle_t^{\text{sel}}$ ) and drift (computing  $\langle \mathcal{M} \rangle_{t+1}$  in terms of  $\langle \mathcal{M} \rangle_t^{\text{juv}}$ ). Note that allele frequencies may change during each of these steps (due to differential fecundities, the direct cost of sex, and drift). The recursions describing the effects of these three events (selection, reproduction, drift) are in turn divided into two steps. A first step corresponds to the calculation of the expectation of moment  $\mathcal{M}$  after the event, but using the values of allele frequencies before the event: in particular,  $\langle \mathcal{M} \rangle_t'$  corresponds to the expected value of  $\mathcal{M}$  after selection, but where the allele frequencies that appear in  $\mathcal{M}$  (note that allele frequencies also appear in the definitions of LDs) are replaced by their values before selection. For 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  $E_{\text{sel}}$  stands for the average over individuals after selection (weighting each individual by its relative fecundity), and  $p_M, p_A$  are the frequencies of  $M$  and  $A$  before selection. Similarly,  $\langle \mathcal{M} \rangle_t''$  and  $\langle \mathcal{M} \rangle_t'''$  correspond to the expected values of  $\mathcal{M}$  after reproduction and drift (respectively), but using the values of allele frequencies before reproduction (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 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  $\langle \Delta_{\text{r}p_M} \rangle_t$ ). 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:

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

855 where  $p_M$  and  $p_A$  are allele frequencies before selection. Expanding in terms of  $\Delta_{\text{s}} p_M$ ,  
856  $\Delta_{\text{s}} p_A$  (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:

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

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  $\overline{W}$  the average fecundity in the population. These can be written as

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

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

and the ratio  $W/\overline{W}$  can be expanded in a Taylor series in  $s$ , allowing one to compute  $D'_{\mathbb{U}}$  in terms of allele frequencies and linkage disequilibria before selection. For example,  $W/\overline{W} = 1 + s(\zeta_A + \zeta_B)$  to the first order in  $s$ , yielding  $\langle p_A D_{MA} \rangle'_t = \langle p_A D_{MA} \rangle_t + s(\langle p_A D_{MAA} \rangle_t + \langle p_A D_{MAB} \rangle_t) + o(s)$ . Linkage disequilibria with repeated indices (such 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. 5 in Barton and Turelli, 1991). For example,  $\langle p_A D_{MAA} \rangle_t = \langle p_A D_{MA} \rangle_t - 2 \langle p_A^2 D_{MA} \rangle_t$ , 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) equals zero.

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

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

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

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

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

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 method is readily extended to more complex moments (e.g., Roze and Michod, 2010). Throughout the paper, I assume that population size is large and calculate all recursions to the first order in  $1/N$ .

## APPENDIX B: EXPRESSIONS FOR MOMENTS IN THE THREE-LOCUS

### MODEL

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

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

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

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

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

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

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

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

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

Moments before selection are given by the same expressions multiplied by  $(1 - \rho_{MA}) \times (1 - \rho_{MAB})$  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  $s \delta \sigma$ :

$$\langle D_{MA}D_{AB} \rangle_t = \frac{(1 - \rho_{MA}) \left[ s(1 - \rho_{AB}) \langle D_{MAB}D_{AB} \rangle_t - \delta \sigma_{\text{eff}} (r_{AB} + c - 1) \langle D_{MAB}D_{MA} \rangle_t^{\text{sel}} \right]}{1 - (1 - \rho_{MA})(1 - \rho_{AB})} \quad (\text{B6})$$

$$\begin{aligned} \langle p_A D_{MAB} \rangle_t &= \frac{1}{\rho_{MAB}} \left[ -\delta \sigma_{\text{eff}} [r_{AB} + (c - 1) \rho_{AB}] \langle p_M q_M p_A D_{AB} \rangle_t^{\text{sel}} \right. \\ &\quad \left. + (1 - \rho_{MAB}) \left[ s \langle D_{MAB}D_{AB} \rangle_t - \delta \sigma_{\text{eff}} (c - 1) \langle D_{MAB}D_{MA} \rangle_t^{\text{sel}} \right] \right] \end{aligned} \quad (\text{B7})$$

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:

$$\langle p_M q_M D_{AB} \rangle_t^{\text{sel}} = -2s \frac{\langle p_M q_M p_A D_{AB} \rangle_t + \langle p_M q_M p_B D_{AB} \rangle_t + s \langle p_M q_M D_{AB}^2 \rangle_t}{\rho_{AB}} \quad (\text{B8})$$

$$\langle D_{MA}D_{MB} \rangle_t^{\text{sel}} = s \frac{\langle D_{MAB}D_{MA} \rangle_t + \langle D_{MAB}D_{MB} \rangle_t + s \langle D_{MAB}^2 \rangle_t}{1 - (1 - \rho_{MA})(1 - \rho_{MB})} \quad (\text{B9})$$

$$\langle p_M D_{MAB} \rangle_t^{\text{sel}} = s \frac{\langle D_{MAB}D_{MA} \rangle_t + \langle D_{MAB}D_{MB} \rangle_t + s \langle D_{MAB}^2 \rangle_t}{\rho_{MAB}} \quad (\text{B10})$$

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  $s^2$ :

$$\begin{aligned} \langle D_{MAB} \rangle_t &= \frac{1}{\rho_{MAB}} \left[ -\delta \sigma_{\text{eff}} [r_{AB} + (c - 1) \rho_{AB}] \langle p_M q_M D_{AB} \rangle_t^{\text{sel}} \right. \\ &\quad + \delta \sigma_{\text{eff}} [r_{MAB} + (c - 1) (2 - \rho_{MAB})] \langle p_M D_{MAB} \rangle_t^{\text{sel}} \\ &\quad + \delta \sigma_{\text{eff}} [r_{AB} + (c - 1) (2 - \rho_{MA} - \rho_{MB})] \langle D_{MA}D_{MB} \rangle_t^{\text{sel}} \\ &\quad \left. - (1 - \rho_{MAB}) \left[ 2s (\langle D_{MA}D_{AB} \rangle_t + \langle D_{MB}D_{AB} \rangle_t + \langle p_A D_{MAB} \rangle_t \right. \right. \\ &\quad \left. \left. + \langle p_B D_{MAB} \rangle_t) + 4s^2 \langle D_{MAB}D_{AB} \rangle_t \right] \right]. \end{aligned} \quad (\text{B11})$$

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,

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

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

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.

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

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

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

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

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

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

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

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

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

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

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

Moments generated by the modifier effect are given by:

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



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

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

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

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

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

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

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

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  $\Theta_1$  and  $\Theta_2$  are functions of recombination rates, the effective rate of sex  $\sigma_{\text{eff}}$ , 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

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

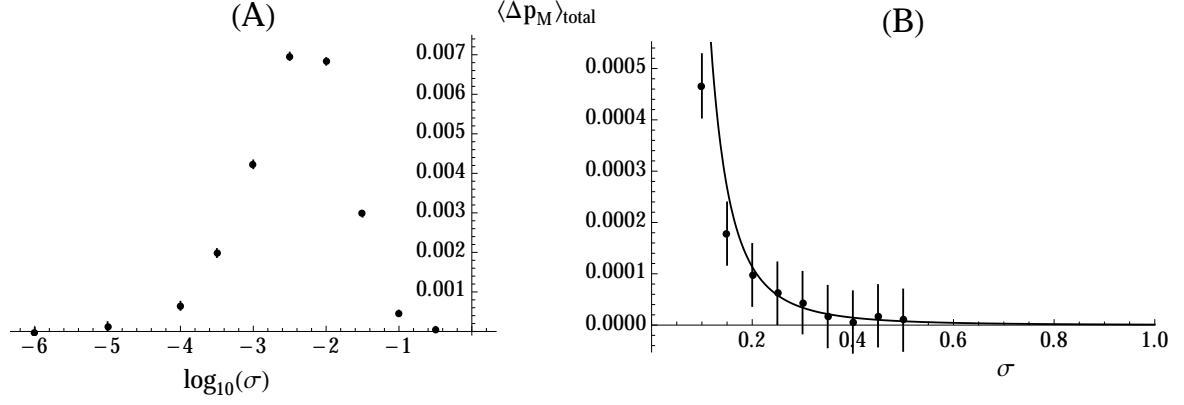
968 with:

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

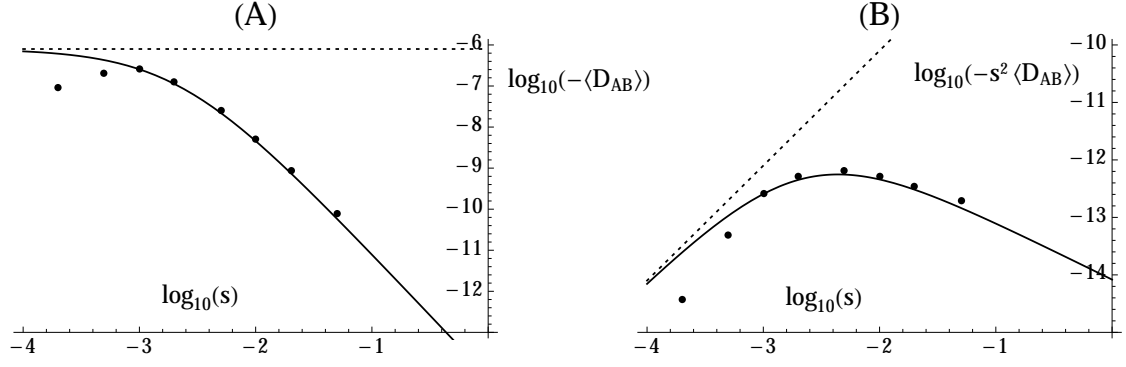
969

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

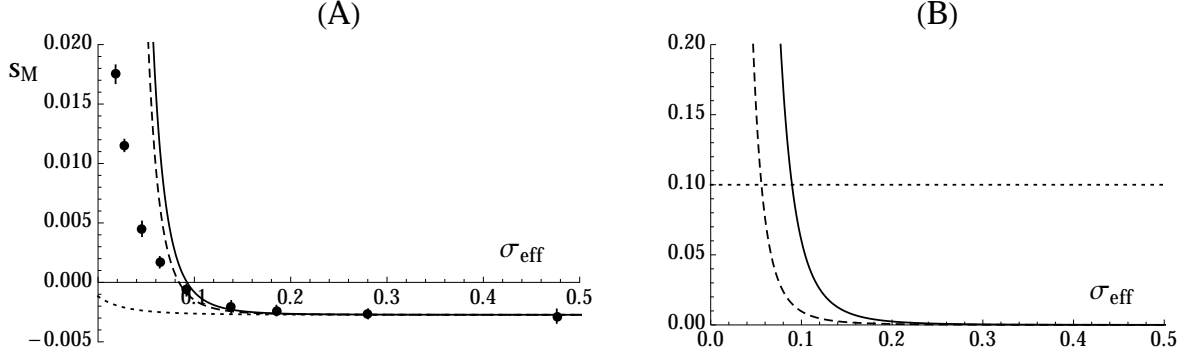
970 Expressions for arbitrary recombination rates between the three loci can be obtained  
971 from equations C1 to C17. Extrapolating these results to the case where deleterious  
972 alleles occur over a whole genome can be done by summing equation C18 over all loci  
973  $A$  and  $B$ , which yields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



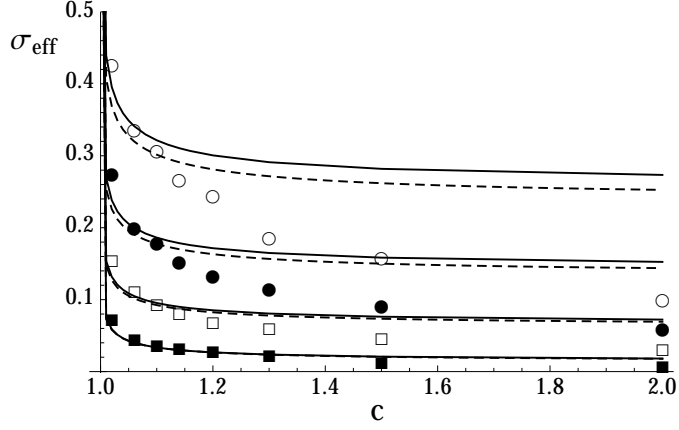
**Figure 1.** Average increase in frequency of allele  $M$  during the sweep of the beneficial allele  $A$ , as a function of the baseline rate of sex  $\sigma$  in the population (measured on a log scale in A). Dots show results from two-locus simulations (error bars measure  $\pm 1.96$  S.E.); the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



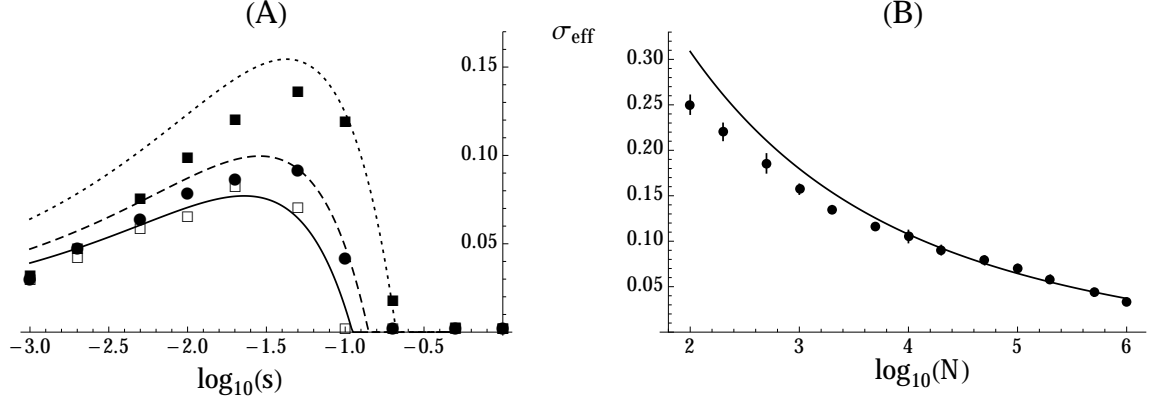
**Figure 2.** Average value of the linkage disequilibrium between two deleterious alleles at mutation-selection balance (multiplied by  $s^2$  in B), as a function of the strength of selection against those alleles  $s$  (on a log scale). Solid curves: predictions from equation 14; dotted curves: predictions 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:  $N = 2000$ ,  $\rho_{AB} = 0.005$ ,  $u = 10^{-5}$ .



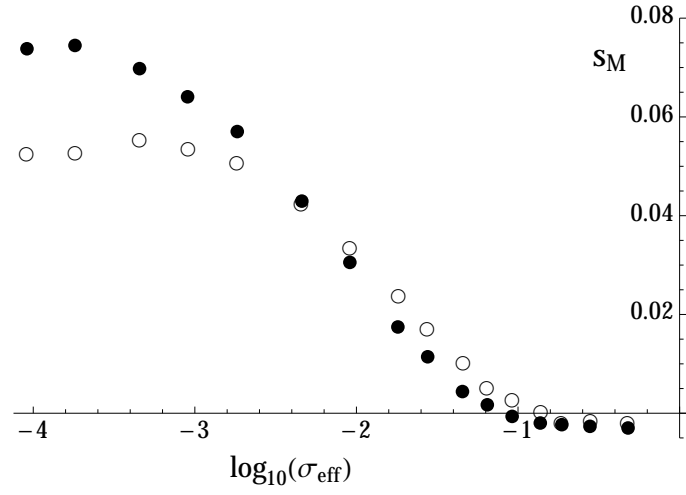
**Figure 3.** (A): selection gradient at the modifier locus  $s_M$ , as a function of the baseline rate of sex in the population  $\sigma_{\text{eff}}$ . Dots: multilocus simulation results (see text for more explanations); dotted curve: prediction from equation 15, using expressions for  $\Theta_1$  and  $\Theta_2$  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:  $N = 20000$ ,  $s = 0.05$ ,  $R = 10$ .

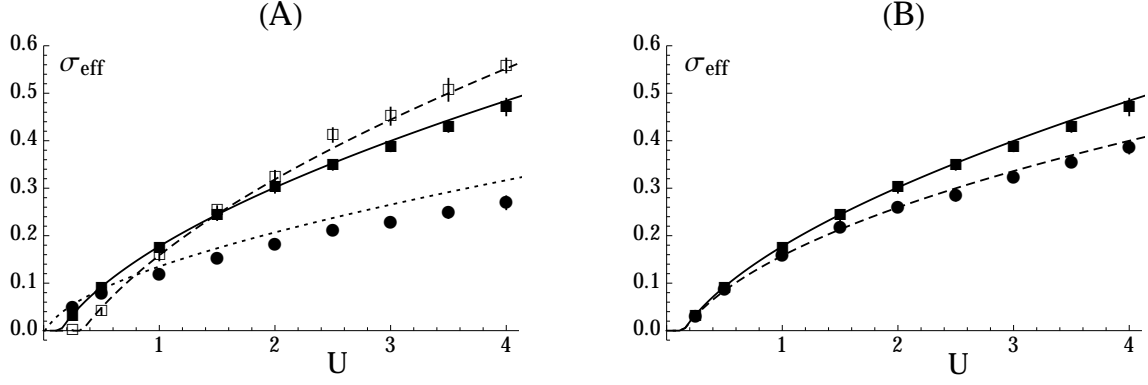


**Figure 5.** Effective rate of sex in the population at equilibrium as a function of the strength of selection against deleterious alleles  $s$  (A) and of population size ( $N$ ), both on a log scale. Dots show simulation results, while the curves correspond to predictions from the QLE model: equations 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 ( $\sigma = 1$ ).

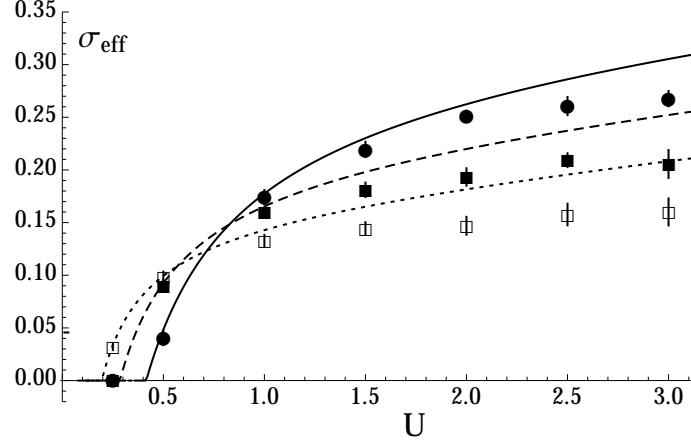


**Figure 6.** Selection gradient at the modifier locus  $s_M$ , as a function of the baseline rate of sex in the population  $\sigma_{\text{eff}}$  (on a log scale), for two values of population size:  $N = 2000$  (empty circles) and  $N = 20000$  (filled circles); other parameter values are as in Figure 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
$\sigma$	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)