# Spatial Heterogeneity and the Evolution of Sex in Diploids

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ABSTRACT: Much of the theoretical work on the evolution of sex has focused on the effects of recombination. In diploids, segregation also occurs during sexual reproduction. Segregation breaks down some types of genetic associations that are not affected by recombination and thus influences the evolution of sex in ways that are not apparent from studying the evolution of recombination as a surrogate for sex. Here I examine the evolution of sex in diploids experiencing spatially heterogeneous selection. If divergent selection causes genetic differentiation, then migration can be a powerful force generating genetic associations that may not be favored by selection. An advantage to sex can arise from breaking down these associations. By examining modifiers of both sex and recombination, the model allows for a direct comparison of the forces acting on these related but different processes, illuminating the role of segregation. The model also includes inbreeding, which has been shown to be important for both segregation and recombination. I find that inbreeding affects the evolution of sex through segregation, not recombination. Several suggestions for empirical experiments are given.

*Keywords:* spatial heterogeneity, segregation, recombination, sexual reproduction, migration.

## Introduction

Alleles in real populations are unlikely to be independently distributed with respect to one another. Instead, alleles are statistically associated in various ways. Sexual reproduction changes the distribution of alleles among individuals by breaking down genetic associations. The evolution of sex is thought to be driven by the benefit of altering these associations, but identifying that benefit has proven challenging. Nonetheless, the theoretical issues have become much clearer in the past two decades. We have a better understanding of how different evolutionary forces (selection, drift, and migration) build associations and the consequences of breaking them down (Otto and Lenormand 2002; Agrawal 2006*a*). Although gaps remain, we have a much better framework for identifying areas of weakness and relating new work to existing theory.

The sexual process of recombination erodes associations between alleles at different loci (i.e., linkage or gametic disequilibrium). Much of the theory for the evolution of sex has focused on identifying the conditions under which these effects of recombination are beneficial. In diploids, associations also occur between alleles on homologous chromosomes, including associations between alleles at the same locus (i.e., an excess of either homozygotes or heterozygotes). Segregation is the sexual process by which associations between alleles on homologous chromosomes are broken down, and thus segregation will also affect whether or not sex is advantageous in diploids. Although the consequences of recombination have received considerably more attention than those of segregation, it is not yet clear what the relative importance of these two processes are.

Sex is usually thought to be beneficial because it shuffles gene combinations; that is, it changes associations among alleles. Of course, there can be no genetic associations if there is no genetic variation (i.e., alleles cannot covary if they do not vary). Consequently, most models for the evolution of sex invoke some means of maintaining genetic variation in fitness. In the evolution-of-sex literature, deleterious mutations and host-parasite coevolution have been the two most intensely studied factors in the past two decades. While most of the attention has focused on the effects of recombination, the effects of segregation have been studied recently in both mutation-selection balance and coevolution models. These results provide some insights into selection on genetic mixing and allow for some comparison of the effects of segregation and recombination.

In a deterministic mutation-selection balance model, Otto (2003) showed that the conditions favoring segregation were exactly analogous to the conditions favoring recombination when sexual reproduction involved random mating. Classic theory predicts that recombination is favored only under a very stringent requirement: epistasis must be weak and negative (Barton 1995; Otto and Feldman 1997). Analogously, Otto (2003) showed that dominance must be weak and negative, meaning that deleterious mutations must be slightly but not excessively recessive. (Similar conditions are required in both recombination [Barton 1995] and segregation [Otto 2003] for adaptive sweep scenarios, as with mutation-selection balance, when selection is weak.) The conditions favoring recombination and segregation are so restrictive because in these models selection is the only force building asso-

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ciations. If associations are built entirely by selection, there will typically be an excess of good allele combinations. Rearranging these combinations through segregation or recombination will produce bad combinations, causing selection against genetic mixing.

There are several possible solutions to this apparent paradox. One solution is that associations are built by forces other than selection. In this case, there may be an excess of some allele combinations, even though alternative combinations are more fit. For example, Otto (2003) showed that it was much easier to find conditions favoring segregation if there were even low levels of inbreeding, because inbreeding generates associations that are broken down by segregation. Moreover, her model indicated that the effects of segregation on the evolution of sex may be much larger than those of recombination. However, more recent work on the evolution of recombination in finite populations shows that an interaction between drift and selection can be very important in generating associations between deleterious alleles and allows recombination to be strongly favored (Keightley and Otto 2006). It remains unclear how the inclusion of drift affects the conditions favoring segregation. Regardless, the theoretical work on recombination in finite populations provides another example in which a force other than selection (in this case, a drift × selection interaction) plays an important role in shaping associations (Felsenstein and Yokoyama 1976; Barton and Otto 2005; Martin et al. 2006).

A second possible solution to the paradox is that selection may vary such that combinations favored at one point in time are disfavored in the future. Even if selection produces an excess of combinations that are good under the current conditions, it may be beneficial to mix these combinations if conditions in the future are likely to favor alternative combinations. This is the idea behind most models of the Red Queen hypothesis, which posits that sex is advantageous when hosts are constantly challenged by coevolving parasites. Much of the theoretical work has involved models with haploid hosts, and so any advantage to sex must arise from the effects of recombination (Parker 1994; Peters and Lively 1999, 2007; Otto and Nuismer 2004; Salathé et al. 2008). These models show that parasites can select for increased recombination under certain conditions. In some cases, it has been shown that this advantage arises because parasites generate selection for some host haplotypes at one point in time and for alternative haplotypes in the near future (Peters and Lively 1999, 2007).

However, these models exclude the effects of segregation because they assume that hosts are haploid. Recent diploid models indicate that parasites often select against segregation. These negative effects of segregation often overwhelm any benefits of recombination, so that parasites usually select against sex even when recombination is favored (Agrawal 2006*b*, forthcoming; Agrawal and Otto 2006). Parasite pressure affects selection on recombination and segregation differently because while parasites can cause rapid fluctuations in the epistatic selection experienced by hosts (selecting for recombination), they often cause no or only slow fluctuations in dominance (selecting against segregation).

The situation can change dramatically if encounters between hosts and parasites are not completely random, as is typically assumed. If hosts are slightly biased toward encountering parasites transmitted by their mothers, parasites can generate selection for sex through the effects of segregation (Agrawal 2006*b*). Selection for sex in this case is through a mechanism very different from that in most Red Queen models. With maternal-transmission bias, sex is favored because segregation reduces the genetic association between mothers and offspring. In contrast, the benefits of recombination observed in earlier haploid models resulted from the reduction in linkage disequilibrium, which is beneficial when the sign of epistasis fluctuates rapidly (Barton 1995; Peters and Lively 1999; Gandon and Otto 2007).

These previous studies on mutation-selection balance and the Red Queen illustrate two important points. First, forces other than selection can be important in generating associations. Second, recombination and segregation are not always selected in the same direction. Because sex in diploids involves both processes, one cannot assume that sex will be favored simply because recombination is. One of the main goals of the work described here is to directly compare, within the context of the same modeling framework, the forces acting on the evolution of recombination versus those acting on the evolution of sex.

It is well known that spatial heterogeneity in selection can maintain genetic variance in fitness (Felsenstein 1976). Consequently, some or many of the genetic associations affected by sex may involve loci that are polymorphic because of spatial heterogeneity in selection. The model presented here examines how migration between locally differentiated populations affects the evolution of sex. Previous authors have studied the evolution of recombination in models with spatial heterogeneity (Pylkov et al. 1998; Lenormand and Otto 2000), and my work is closely related to these papers. Here I model the evolution of a gene that modifies either sex or recombination in a population that receives migrants from a second population that is genetically differentiated with respect to either one or two other loci that determine local adaptation. As has been shown in recombination models (Pylkov et al. 1998; Lenormand and Otto 2000), migration can create an excess of particular combinations even when alternative combinations have higher fitness within patches. That result is extended here to include associations that are affected

by segregation. Inbreeding is also included in the model because it has been shown to be of importance for both segregation (Otto 2003) and recombination (Roze and Lenormand 2005).

## The Model

Here I present a diploid model for the evolution of sex in the context of population differentiation and inbreeding that provides some insights into the roles of segregation and recombination. I consider two populations, connected by migration, that are divergently selected with respect to two loci (i.e., local adaptation genes). The purpose of this model is to study the gradual evolution of sex in organisms that are capable of both reproductive modes (i.e., evolving from some amount of sex to more sex). Alternative alleles at a modifier gene create quantitative variation in the degree of investment in sexual versus asexual reproduction. Although related, the case of an obligately sexual group competing against an obligately asexual group is in some sense a different problem (Agrawal 2006*a*). Some advantages to segregation in that context have been reported (Kirkpatrick and Jenkins 1989; Agrawal and Chasnov 2001; Haag and Roze 2007), but that situation is not discussed further here. In the remainder of the article, I focus exclusively on results from modifier models in which the amount of sex or recombination changes by a small amount.

All of the symbols used in the model are defined in table 1. The model is based on a diploid organism with three loci in the order **M**, **A**, **B**. The first locus affects reproductive mode but has no direct effect on fitness. The **A** and **B** loci affect fitness. I assume a two-population model with divergent selection in the two populations (i.e., *A* and *B* are favored in population 1, but *a* and *b* are favored in population 2). In population *i*, the fitness of an individual is given by

$$\begin{aligned} W_{G,i} = {} & (1 - s_{\mathrm{A},i})^{X_{G,\mathrm{A},i}}(1 - s_{\mathrm{B},i})^{X_{G,\mathrm{B},i}} \\ & + \frac{1}{2}X_{G,\mathrm{A},i}(X_{G,\mathrm{A},i} - 1)\iota_{\mathrm{A},i} \\ & + \frac{1}{2}X_{G,\mathrm{B},i}(X_{G,\mathrm{B},i} - 1)\iota_{\mathrm{B},i} \\ & + X_{G,\mathrm{A},i}X_{G,\mathrm{B},i}\varepsilon_{\mathrm{a}\times\mathrm{a},i} \\ & + \frac{1}{2}X_{G,\mathrm{A},i}X_{G,\mathrm{B},i}(X_{G,\mathrm{B},i} - 1)\varepsilon_{\mathrm{a}\times\mathrm{d},i} \\ & + \frac{1}{2}X_{G,\mathrm{B},i}X_{G,\mathrm{A},i}(X_{G,\mathrm{A},i} - 1)\varepsilon_{\mathrm{d}\times\mathrm{a},i} \\ & + \frac{1}{4}X_{G,\mathrm{A},i}(X_{G,\mathrm{A},i} - 1)X_{G,\mathrm{B},i}(X_{G,\mathrm{B},i} - 1)\varepsilon_{\mathrm{d}\times\mathrm{d},i}, \end{aligned} \tag{1}$$

where $X_{G,\mathrm{A},i}$ and $X_{G,\mathrm{B},i}$ are the number of alleles carried by genotype $G$ at the **A** and **B** loci, respectively, that are maladaptive in population $i$ (e.g., for genotype $AB/Ab$, $X_{\mathrm{A},1} = 0$, $X_{\mathrm{A},2} = 2$, $X_{\mathrm{B},1} = 1$, and $X_{\mathrm{B},2} = 1$). This model of fitness assumes no cis-trans epistasis (i.e., $AB/ab$ individuals have the same fitness as $Ab/aB$ individuals) but is otherwise quite general. Loosely speaking, the parameters $s_{\mathrm{A},i}$ and $s_{\mathrm{B},i}$ represent selection on the maladapted alleles in population $i$ at the **A** and **B** loci, respectively, when each locus is in the heterozygous state. The parameters $\iota_{\mathrm{A},i}$ and $\iota_{\mathrm{B},i}$ represent fitness interactions in population $i$ between maladapted alleles within the **A** and **B** loci, respectively. This is an alternative way of representing dominance similar to that used in other modifier models of segregation (Otto 2003). Negative values for $\iota_{\mathrm{A},i}$ and $\iota_{\mathrm{B},i}$ indicate that the maladapted alleles ($a$ and $b$) are partially to fully recessive with respect to their effects on fitness. The remaining parameters represent epistatic interactions in population $i$ between maladapted alleles at different loci. Specifically, $\varepsilon_{\mathrm{a}\times\mathrm{a},i}$, $\varepsilon_{\mathrm{a}\times\mathrm{d},i}$, $\varepsilon_{\mathrm{d}\times\mathrm{a},i}$, and $\varepsilon_{\mathrm{d}\times\mathrm{d},i}$ represent additive × additive, additive × dominance, dominance × additive, and dominance × dominance epistasis, respectively. (Technically, parameters such as $\varepsilon_{\mathrm{a}\times\mathrm{a},i}$ might more accurately be referred to as multiplicative × multiplicative epistasis, since these interaction effects are measured here as deviations from multiplicativity. Nonetheless, I use the more traditional terminology for ease of understanding and because the quantitative difference between multiplicative and additive models is negligible when selection is weak.)

The life cycle proceeds as follows. At the beginning of a generation, the frequency of genotype $G$ in population $i$ ($i \in \{1, 2\}$) is given by $F_{\mathrm{b},G,i}$. Selection occurs within each population using the fitness functions above. The frequency of genotype $G$ in population $i$ after selection is $F_{\mathrm{s},G,i} = F_{\mathrm{b},G,i}W_{G,i}/\overline{W}_i$ where $\overline{W}_i$ is the mean fitness in population $i$. Migration between populations occurs after selection. The migration rates into populations 1 and 2 are $m_1$ and $m_2$, respectively. The frequency of genotype $G$ in population $i$ after migration is $F_{\mathrm{m},G,i} = F_{\mathrm{s},G,i}(1 - m_i) + F_{\mathrm{s},G,j}m_i$, where $i \neq j$.

Reproduction, which can be sexual or asexual, occurs after migration. Individuals invest a fraction of their resources into sexual reproduction and the remainder into asexual reproduction; this division of resources is dependent on an individual's genotype with respect to the modifier (**M**) locus. This gene does not directly affect fitness; that is, there are no intrinsic costs of sex. The fraction of resources invested in sexual reproduction for individuals of genotypes $m/m$, $M/m$, and $M/M$ is $\sigma$, $\sigma + h_\sigma\delta_\sigma$, and $\sigma + \delta_\sigma$, respectively. To clarify the presentation, I assume that the $M/m$ heterozygote has an intermediate level of sex ($0 \le h_\sigma \le 1$) and that the $M$ allele causes more sex ($\delta_\sigma > 0$). When organisms reproduce sexually, they are assumed

**Table 1:** Definition of symbols

| Symbol | Definition |
|---|---|
| $X_{G,\,\mathrm{L},\,i}$ | Number of alleles in genotype $G$ at locus **L** that are locally maladaptive in population $i$ |
| $p_{\mathrm{L},\,i}$ | Frequency of uppercase allele (e.g., $M$, $A$, $B$) at locus **L** in population $i$ |
| $q_{\mathrm{L},\,i}$ | $1 - p_{\mathrm{L},\,i}$ |
| $C_{\mathbf{H1/H2},\,i}$ | Association among loci in sets **H1** and **H2** in population $i$, where **H1** and **H2** refer to loci in the first and second haplotypes of a diploid, respectively |
| $F_{l,\,G,\,i}$ | Frequency of genotype $G$ in population $i$ at life stage $l$ |
| $m_i$ | Migration rate into population $i$ |
| $\Delta_{\mathrm{L}} = (p_{\mathrm{L},\,1} - p_{\mathrm{L},\,2})$ | Degree of population differentiation in allele frequency at locus **L** |
| $\sigma$ | Baseline level of sex (fraction of resources invested into sexual reproduction by $m/m$ genotypes) |
| $f$ | Fraction of sexual offspring produced through selfing |
| $r_{\mathrm{MA}}$ | Recombination rate between **M** and **A** |
| $r_{\mathrm{AB}}$ | Recombination rate between **A** and **B** |
| $r_{\mathrm{MB}} = r_{\mathrm{MA}}(1 - r_{\mathrm{AB}}) + (1 - r_{\mathrm{MA}})r_{\mathrm{AB}}$ | Probability that **M** and **B** are separated by recombination |
| $r_{\mathrm{MAB}} = 1 - (1 - r_{\mathrm{MA}})(1 - r_{\mathrm{AB}})$ | Probability that a recombination event will disrupt the **MAB** complex |
| $R_1 = r_{\mathrm{MA}}^2 + (1 - r_{\mathrm{MA}})^2$ | Twice the probability that two independent gametes produced independently by an **MA** double heterozygote will be the same with respect to these loci; note that $R_1 > 0$ |
| $R_2 = r_{\mathrm{MB}}^2 + (1 - r_{\mathrm{MB}})^2$ | Same as for $R_1$ but with respect to the **M** and **B** loci; note that $R_2 > 0$ |
| $R_3 = r_{\mathrm{AB}}^2 + (1 - r_{\mathrm{AB}})^2$ | Same as for $R_1$ but with respect to the **A** and **B** loci; note that $R_3 > 0$ |
| $\delta_\sigma$ | Amount by which the $M$ allele increases the investment into sexual reproduction when homozygous |
| $\delta_{\mathrm{r}}$ | Amount by which the $M$ allele increases the recombination in the **A**-**B** interval when homozygous |
| $h_\sigma$ | Traditional dominance measure for the effect of the $M$ allele on investment into sexual reproduction |
| $h_{\mathrm{r}}$ | Traditional dominance measure for the effect of the $M$ allele on recombination |
| $H_{\sigma 1} = p_{\mathrm{M},\,1}(1 - h_\sigma) + (1 - p_{\mathrm{M},\,1})h_\sigma$ | $0 \le H_{\sigma 1} \le 1$, assuming $0 \le h_\sigma \le 1$ |
| $H_{\sigma 2} = p_{\mathrm{M},\,1}h_\sigma + (1 - p_{\mathrm{M},\,1})(1 - h_\sigma)$ | $0 \le H_{\sigma 2} \le 1$, assuming $0 \le h_\sigma \le 1$ |
| $H_{\mathrm{r}1} = p_{\mathrm{M},\,1}(1 - h_{\mathrm{r}}) + (1 - p_{\mathrm{M},\,1})h_{\mathrm{r}}$ | $0 \le H_{\mathrm{r}1} \le 1$, assuming $0 \le h_{\mathrm{r}} \le 1$ |
| $s_{\mathrm{L},\,i}$ | Selection against the maladapted allele (in heterozygous state) at locus **L** in population $i$ |
| $\iota_{\mathrm{L},\,i}$ | Dominance selection on locus **L** in population $i$ |
| $\varepsilon_{\mathrm{a}\times\mathrm{a},\,i}$ | Additive × additive epistasis in population $i$ |
| $\varepsilon_{\mathrm{a}\times\mathrm{d},\,i}$ | Additive × dominance epistasis in population $i$ |
| $\varepsilon_{\mathrm{d}\times\mathrm{a},\,i}$ | Dominance × additive epistasis in population $i$ |
| $\varepsilon_{\mathrm{d}\times\mathrm{d},\,i}$ | Dominance × dominance epistasis in population $i$ |
| $I_1 = \iota_{\mathrm{A},\,1} + 2q_{\mathrm{B},\,1}\varepsilon_{\mathrm{d}\times\mathrm{a},\,1} + q_{\mathrm{B},\,1}^2\varepsilon_{\mathrm{d}\times\mathrm{d},\,1}$ | Average fitness effect of converting heterozygotes to homozygotes at the **A** locus ($A/a$, $A/a \to A/A$, $a/a$) |
| $I_2 = \iota_{\mathrm{B},\,1} + 2q_{\mathrm{A},\,1}\varepsilon_{\mathrm{a}\times\mathrm{d},\,1} + q_{\mathrm{A},\,1}^2\varepsilon_{\mathrm{d}\times\mathrm{d},\,1}$ | Average fitness effect of converting heterozygotes to homozygotes at the **B** locus ($B/b$, $B/b \to B/B$, $b/b$) |
| $I_3 = \varepsilon_{\mathrm{a}\times\mathrm{a},\,1} + q_{\mathrm{A},\,1}\varepsilon_{\mathrm{d}\times\mathrm{a},\,1} + q_{\mathrm{B},\,1}\varepsilon_{\mathrm{a}\times\mathrm{d},\,1} + q_{\mathrm{A},\,1}q_{\mathrm{B},\,1}\varepsilon_{\mathrm{d}\times\mathrm{d},\,1}$ | Average fitness effect of converting intermediate diallelic combinations to extreme combinations ($Ab$, $aB \to AB$, $ab$) |
| $I_4 = \varepsilon_{\mathrm{a}\times\mathrm{d},\,1} + q_{\mathrm{A},\,1}\varepsilon_{\mathrm{d}\times\mathrm{d},\,1}$ | Average fitness effect of converting triallelic genotypes involving both copies of the **B** locus into alternative types ($ab/\_b$, $aB/\_B$, $AB/\_b$, $Ab/\_B \to AB/\_B$, $Ab/\_b$, $aB/\_b$, $ab/\_B$) |
| $I_5 = \varepsilon_{\mathrm{d}\times\mathrm{a},\,1} + q_{\mathrm{B},\,1}\varepsilon_{\mathrm{d}\times\mathrm{d},\,1}$ | Average fitness effect of converting triallelic genotypes involving both copies of the **A** locus into alternative types ($ab/a\_$, $Ab/A\_$, $AB/a\_$, $aB/A\_ \to aB/a\_$, $AB/A\_$, $Ab/a\_$, $ab/A\_$) |

to produce a fraction $f$ of their offspring through selfing and the remainder, $1 - f$, through outcrossing. Selfing is assumed to be sporophytic selfing (i.e., gametes combine at random with other gametes from the same parent). Outcrossing is modeled as the random union of gametes within populations.

During sexual reproduction, gametes are produced according to the standard rules of segregation and recombination during meiosis. The recombination rate between the **M** and **A** loci is $r_{MA}$. I allow the recombination rate between the fitness loci to depend on the modifier so that this model may also be used to study the evolution of recombination, permitting a direct comparison of the effects of recombination and sex (which involves both segregation and recombination). Specifically, the recombination rate between the **A** and **B** loci is $r_{AB}$, $r_{AB} + h_r\delta_r$, and $r_{AB} + \delta_r$ for individuals of genotypes $m/m$, $M/m$, and $M/M$, respectively. (Setting $\delta_\sigma = 0$ or $\delta_r = 0$ means that the modifier will affect only recombination or only sex, respectively.) Let $\gamma_{h,G}$ be the frequency of haplotype $h$ among the gametes produced by an individual of genotype $G$ ($\sum_h \gamma_{h,G} = 1$). The $\gamma_{h,G}$ values are determined according to the standard rules of meiosis, given the recombination rates (as determined by the **M** locus) and assuming no interference.

From the information above, the distribution of offspring genotypes can be calculated as follows. Let $z_D$ be the fraction of resources invested in sexual reproduction by an individual of genotype $D$ (as determined by its alleles at the modifier locus). The frequency of haplotype $h$ in the entire gamete pool for population $i$ is $g_{h,i} = \sum_D F_{m,D,i}\gamma_{h,D}z_D/Z_i$, where $Z_i = \sum_D F_{m,D,i}z_D$ is the relative sexual output of population $i$ (i.e., $Z_i$ is the fraction of offspring that are produced through sexual reproduction in population $i$). Let $K_{h1,h2,G}$ be an indicator variable that denotes whether the combination of gametic haplotypes $h1$ and $h2$ forms the diploid zygote of genotype $G$. The frequency of $G$ among the offspring is

$$\begin{aligned} F_{o,G,i} = {} & F_{m,G,i}(1 - z_G) \\ & + Z_i(1 - f)\sum_{h1}\sum_{h2} g_{h1}g_{h2}K_{h1,h2,G} \\ & + Z_i f\sum_D \sum_{h1}\sum_{h2} F_{m,D,i} \\ & \times \frac{z_D}{Z_i}\gamma_{h1,D}\gamma_{h2,D}K_{h1,h2,G}. \end{aligned} \tag{2}$$

The three terms represent offspring produced through asexual reproduction, through outcrossing, and through (sporophytic) selfing, from left to right. I assume nonoverlapping generations so that $F_{o,G,i}(t) = F_{b,G,i}(t + 1)$. (More generally, one may interpret survival for an extra generation as a form of asexual reproduction, ignoring issues of senescence.)

As an alternative to using genotype frequencies, it is useful to describe the population by the allele frequencies and the pattern of associations among these alleles (Barton and Turelli 1991; Kirkpatrick et al. 2002). This diploid model with three loci is described by three allele frequencies, nine two-way associations, 10 three-way associations, nine four-way associations, three five-way associations, and one six-way association. The symbol $C_{\mathbf{H1/H2},i}$ represents the association among loci in sets **H1** and **H2** in population $i$, where **H1** and **H2** refer to loci in the first and second haplotypes of a diploid, respectively. Momentarily ignoring $i$, $C_{AB/\varnothing}$ measures the linkage disequilibrium between alleles at the **A** and **B** loci on the same chromosome; $C_{A/A}$ measures the intralocus association at the **A** locus (a measure of the excess of homozygosity); $C_{AB/AB}$ measures the four-way associations among alleles at the **A** and **B** loci on both chromosomes (a measure of identity disequilibrium), etc. In this model, there is symmetry such that $C_{\mathbf{H1/H2}} = C_{\mathbf{H2/H1}}$, because at all life stages the frequency of the diploid genotype consisting of haplotypes $h1$ and $h2$ is the same as the frequency of the diploid genotypes $h2$ and $h1$ (e.g., the frequency of *MAB*/*mab* individuals is the same as the frequency of *mab*/*MAB* individuals). The associations are measured as

$$\begin{aligned} C_{\mathbf{H1/H2},i} = {} & \sum_G F_{b,G,i}\left(\prod_{\mathbf{L}\in\mathbf{H1}} Q_{G,L/\varnothing} - p_{L,i}\right) \\ & \times \left(\prod_{\mathbf{L}\in\mathbf{H2}} Q_{G,\varnothing/L} - p_{L,i}\right), \end{aligned} \tag{3}$$

where $Q_{G,L/\varnothing}$ and $Q_{G,\varnothing/L}$ are indicator variables that denote whether an individual of genotype $G$ carries an uppercase allele (e.g., *M*, *A*, *B*) at its first and second copy (respectively) of locus **L**. The symbol $p_{L,i}$ represents the frequency of the uppercase allele at locus **L** in population $i$. It is calculated as

$$p_{L,i} = \sum_G F_{G,i}\frac{Q_{G,L/\varnothing} + Q_{G,\varnothing/L}}{2}. \tag{4}$$

To simplify the analysis, I assume that most of the parameters are small in absolute value. Specifically, I assume $s_{A,i}$, $s_{B,i}$, $\iota_{A,i}$, $\iota_{B,i}$, $\varepsilon_{a\times a,i}$, $\varepsilon_{a\times d,i}$, $\varepsilon_{d\times a,i}$, $\varepsilon_{d\times d,i}$, $m_i$, $f$, $\delta_\sigma$, and $\delta_r$ are $O(\xi)$, where $0 < \xi \ll 1$. As in other related modifier models (Barton 1995; Lenormand and Otto 2000; Otto 2003; Roze and Lenormand 2005), I assume that associations have reached their quasi-linkage equilibrium (QLE) values (Kimura 1965). This involves a separation of time-

scales in which associations are assumed to obtain their steady state values quickly relative to the rate of allele frequency change. This assumption is reasonable, provided that associations are not too large in magnitude (i.e., the forces building associations, such as dominance, epistasis, migration, and selfing, are not too strong relative to the forces breaking them down, segregation and recombination). Therefore, the analytical results are expected to be most quantitatively accurate when the baseline levels of sex ($\sigma$) and recombination ($r_{MA}$, $r_{AB}$) are not too low.

## Results

To simplify the presentation, I provide the results for several special cases in order to emphasize particular points. Throughout, I assume that the frequency of the modifier locus is the same in both populations, so that the modifier frequency within each population is not directly influenced by migration. For simplicity, I have presented results only as they pertain to population 1. Population 2 results can be obtained simply by changing the subscripts referring to population. To begin, I assume that the modifier affects only the rate of sex ($\delta_r = 0$).

### *Single Fitness Locus*

The simplest case to consider is where mating is random within populations ($f = 0$) and only the **A** locus affects fitness (i.e., the **B** locus is neutral: $s_{B,i} = \iota_{B,i} = \varepsilon_{a\times a,i} = \varepsilon_{a\times d,i} = \varepsilon_{d\times a,i} = \varepsilon_{d\times d,i} = 0$). Because there is only a single locus affecting fitness, the consequences of sex are entirely due to segregation. As shown below, two types of associations are of importance in this model. The association $C_{A/A,1}$ measures the intralocus association at the **A** locus. A positive value means that there is an excess of homozygotes, and a negative value indicates that there is an excess of heterozygotes. The second critical association is that between the modifier locus and homozygosity at the **A** locus, as quantified by $C_{MA/A,1}$. A positive value indicates that the modifier allele *M* is more likely to be found in **A**-locus homozygotes than is the *m* allele; a negative value indicates that the *M* allele is more likely to be found in **A**-locus heterozygotes than is the *m* allele.

In this single-fitness-locus model, the per-generation change in frequency of the modifier allele is

$$\Delta p_{M,1} = {}_{Q}C_{MA/A,1}\iota_{A,1} + o(\xi^3). \tag{5}$$

The presubscript "Q" denotes the QLE value of the association. Because the modifier does not affect fitness directly, it evolves only through its association with other genes. Equation (5) shows that the modifier evolves through its association with homozygosity at the **A** locus, ${}_{Q}C_{MA/A,1}$. The modifier becomes associated with homozygosity at the **A** locus through the action of segregation. For example, if there is an excess of **A**-locus homozygotes before reproduction, then *M* alleles, by inducing higher rates of sex, will be more likely than *m* alleles to be found in heterozygotes after reproduction (e.g., *MA*/*MA* and *Ma*/*Ma* individuals are more likely to reproduce sexually, creating *MA*/*Ma* offspring, whereas *mA*/*mA* and *ma*/*ma* individuals are more likely to reproduce asexually, giving *mA*/*mA* and *ma*/*ma* offspring). Because the modifier breaks down the intralocus association by inducing sex, we expect the sign of the association involving the modifier ${}_{Q}C_{MA/A,1}$ to be opposite that of the intralocus association (${}_{Q}C_{A/A,1}$), and we expect ${}_{Q}C_{MA/A,1}$ to depend in magnitude on the extent to which the modifier causes more sex than the alternative allele. A QLE analysis confirms these expectations:

$${}_{Q}C_{MA/A,1} = -\frac{\delta_\sigma H_{\sigma 1}}{\sigma(1-\sigma)} V_{M,1}\,{}_{Q}C_{A/A,1} + o(\xi^2), \tag{6}$$

where $V_{M,1} = p_{M,1}(1 - p_{M,1})$ is the genic variance at the **M** locus in population 1 at the beginning of a generation. The symbol $H_{\sigma 1} = p_{M,1}(1 - h_\sigma) + (1 - p_{M,1})h_\sigma$ is positive, provided that $0 \le h_\sigma \le 1$. Consequently, the sign of ${}_{Q}C_{MA/A,1}$ is always opposite that of ${}_{Q}C_{A/A,1}$, assuming that the modifier increases the rate of sex ($\delta_\sigma > 0$).

Combining equations (5) and (6), we see that the modifier is favored when dominance and the intralocus association are of opposite signs (i.e., $\Delta p_{M,1} > 0$ when ${}_{Q}C_{A/A,1}\iota_{A,1} < 0$). The required condition ${}_{Q}C_{A/A,1}\iota_{A,1} < 0$ occurs when either (i) there is an excess of homozygotes (${}_{Q}C_{A/A,1} > 0$) but heterozygotes are more fit than homozygotes ($\iota_{A,1} < 0$) or (ii) there is an excess of heterozygotes (${}_{Q}C_{A/A,1} < 0$) but homozygotes are more fit ($\iota_{A,1} > 0$). In both cases, sex is advantageous because it converts the overrepresented type to the underrepresented type in a situation where the underrepresented type is more fit. This is analogous to the result that there is a short-term advantage to recombination when epistasis and linkage disequilibrium are of opposite signs (Barton 1995).

As described above, much hinges on the sign of the intralocus association relative to that of dominance. The steady state value for this association is

$${}_{Q}C_{A/A,1} = (V_{A,1}^2\iota_{A,1} + m_1\Delta_A^2)\frac{1-\sigma}{\sigma} + o(\xi), \tag{7}$$

where $\Delta_A = (p_{A,1} - p_{A,2})$ is the genetic differentiation between the two populations with respect to the **A** locus.

The two terms in the first set of parentheses indicate that there are two forces, dominance selection ($V_{A,1}^2\iota_{A,1}$) and migration ($m_1\Delta_A^2$), affecting the sign of this association

(i.e., the direction of departure from Hardy-Weinberg genotype frequencies). The first term represents the influence of dominance in fitness on variation within the population. A positive value for the dominance coefficient $\iota_{A,1}$ means that the (geometric) average fitness of the two homozygotes is greater than that of the heterozygote; this form of nonlinear selection will tend to create an excess of homozygotes. Conversely, a negative value for $\iota_{A,1}$ means that the (geometric) average fitness of the two homozygotes is less than that of the heterozygote; this form of dominance selection will tend to create an excess of heterozygotes.

If dominance were the only force affecting the association, it would be difficult to select for sex. Consider the case where heterozygotes are more fit than homozygotes ($\iota_{A,1} < 0$). In this case, dominance will tend to generate an excess of heterozygotes. Segregation will convert these heterozygotes into homozygotes, which are less fit on average. This is an example of the classic problem underlying the evolution of sex discussed in the introduction. Selection creates an excess of good allele combinations, and sex shuffles these genotypes and creates worse combinations in the process. Thus, sex typically results in an immediate reduction in fitness, in this case creating a "segregation load." (By including second-order terms, it can be shown that a segregation load is expected unless the dominance coefficient falls in the narrow region of parameter space where the geometric mean but not the arithmetic mean fitness of the two homozygotes is less than that of the heterozygote; see appendix.)

In this model, selection is not the only force affecting the intralocus association. The term $m_1\Delta_A^2$ in equation (7) represents the effect of migration. This term is always positive, indicating that migration between genetically differentiated populations always tends to build an excess of homozygotes. If $A$ is common in population 1 and $a$ is common in population 2, then migration of diploid individuals imports $a/a$ genotypes into population 1. Consequently, there may be an excess of homozygotes even if heterozygotes are more fit on average. This creates an immediate advantage to sex if heterozygotes are relatively more fit, because segregation converts the excess of homozygotes into heterozygotes, $A/A \times a/a \rightarrow A/a$. Note that heterozygotes do not need to be more fit than the best homozygote, just more fit than the average of the two homozygotes (i.e., overdominance is not required).

In the above results, I have not quantified the degree of differentiation between populations, $\Delta_A$. Instead, I have simply assumed that spatial heterogeneity in selection causes the difference in allele frequency to be large ($\Delta_A$ is $O(1)$). In general, $\Delta_A$ will be large at migration-selection balance if divergent selection between populations is strong relative to migration. If this is not the case, then $\Delta_A$ will be small and the intralocus association will be determined by dominance selection, resulting in a situation where the segregation load is likely to prevent the spread of the modifier allele promoting sex.

The value of $\Delta_A$ is easy to quantify when migration is weak relative to selection ($m_1, m_2 \ll s_{A,1}, s_{A,2} \ll 1$). At migration-selection balance, $p_{A,1} \approx 1 - m_1/s_{A,1}$ and $p_{A,2} \approx m_2/s_{A,2}$. With these values in $V_{A,1}$ and $\Delta_A$, the intralocus association becomes

$$
\begin{aligned}
{}_{Q}C_{A/A,1} = \Bigg\{ & m_1\left[1 - (2s_{A,1} - \iota_{A,1})\frac{(1-\sigma)}{\sigma}\right] \\
& - m_1^2\frac{2s_{A,1} - \iota_{A,1}}{s_{A,1}^2} - \frac{2m_1m_2}{s_{A,2}}\Bigg\} \\
& \times \frac{(1-\sigma)}{\sigma} + o(\xi^3),
\end{aligned}
\tag{8}
$$

which is positive under the specified assumptions ($m \ll s \ll 1$). The negative quadratic term indicates that the association is maximized at intermediate levels of migration when maladaptive alleles are recessive ($\iota_{A,1} < 0$). When migration rates are very low, there is very little variation within populations, so dominance selection has a relatively small effect; migration causes a net excess of homozygotes (i.e., a positive association), but the association is small in magnitude because there is so little variation. As migration becomes more frequent, there is more variation within populations, allowing a larger covariance between alleles (i.e., a larger intralocus association). However, if migration provides high levels of variation within the population, dominance selection plays a larger role, making the association negative when $\iota_{A,1} < 0$. Lenormand and Otto (2000) observed an analogous relationship when studying linkage disequilibrium evolving under the joint forces of migration and epistasis.

It should be noted that the approximation above is derived under the assumption that migration is weak relative to selection. The approximation above will not be accurate when this assumption is violated, but the qualitative predictions are robust. In figure 1, I present simulation results showing the region of parameter space in a symmetric model ($m_1 = m_2 = m$, $s_{A,1} = s_{A,2} = s$, $\iota_{A,1} = \iota_{A,2} = \iota$) where a short-term advantage to sex exists because migration creates an excess of homozygotes even when heterozygotes are more fit. The parameter space where sex is favored is large when migration is small because populations are strongly differentiated, so that migration is the major determinant of the intralocus association. As migration increases, populations are less well differentiated unless selection is strong, so it is only with respect to strongly selected loci that sex is favored.

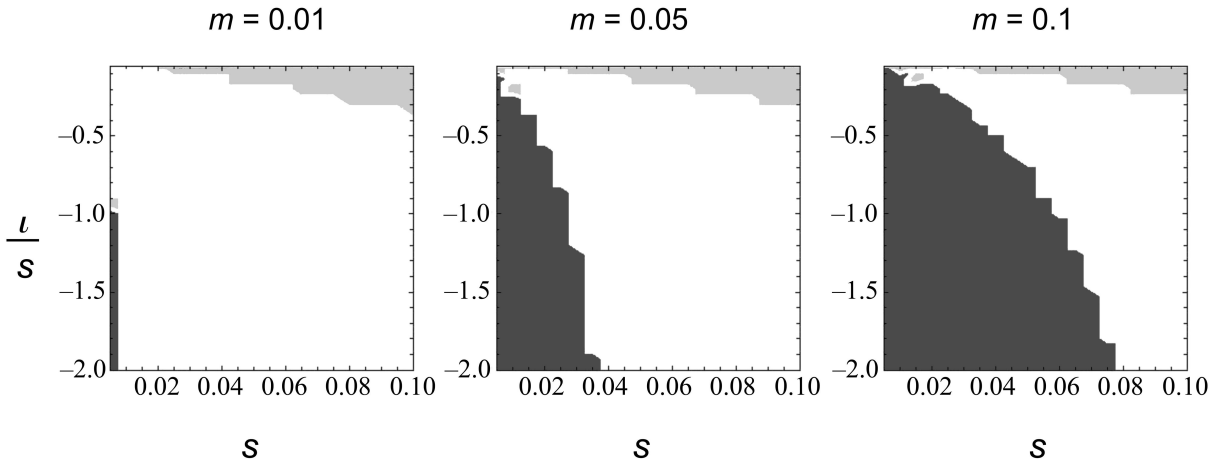


**Figure 1:** Conditions favoring sex in a model with a single fitness locus. Results from a deterministic symmetric model ($m_1 = m_2 = m$, $s_{A,1} = s_{A,2} = s$, $\iota_{A,1} = \iota_{A,2} = \iota$) are shown as a function of the strength of divergent selection $s$ and the relative strength of dominance $\iota/s$. Note that only negative dominance values are shown. Regions in dark gray show parameter combinations where there is a short-term disadvantage to sex and a modifier of sex is disfavored. In these regions, dominance selection within populations is the primary determinant of the intralocus association, and sex is disfavored because it destroys the association favored by selection. Regions in white and light gray depict parameter combinations where there is a short-term advantage to sex because migration creates an excess of homozygotes even though heterozygotes are more fit. The three panels show results for different migration rates ($m = 0.01$, 0.05, and 0.1). When migration rates are low, populations are strongly genetically differentiated and migration is the major determinant of intralocus associations. As migration rates increase, stronger selection is required to maintain high levels of differentiation, so only genes with sufficiently high $s$ provide a short-term advantage to sex. In the white regions, a sex modifier increases in frequency, as expected from the short-term advantage. In the light-gray regions, a sex modifier decreases in frequency because the long-term disadvantage of sex outweighs the short-term advantage (see appendix). Theory predicts that long-term effects are most important when $|\iota|$ is weak relative to $s^2$ (see eq. [A1]), which occurs in the upper right-hand corner of each plot. In these simulations, the baseline levels of sex and recombination are $\sigma = 0.75$ and $r_{MA} = 0.3$, respectively. Consistent with theoretical expectations, the light-gray region in the upper right-hand corner of each plot shrinks if the baseline level of genetic mixing is higher (not shown). Note that the symmetric model used here is peculiar in that it generates marginal overdominance so that polymorphisms remain stable even when selection is weak and migration is strong. Thus, the region in which sex is disfavored is larger than it would be in other models.

### *Single-Fitness-Locus Model with Inbreeding*

Otto (2003) showed that low levels of inbreeding can dramatically affect the conditions favoring segregation. This is because inbreeding directly generates various types of associations between alleles on homologous chromosomes. I include inbreeding by allowing a fraction of sexually produced offspring to self-fertilize with probability $f$. (Note that I have included inbreeding here as the random union of gametes from the same individual [sporophytic selfing] rather than the union of like gametes [gametophytic selfing], as in Otto 2003.) I assume that the rate of inbreeding is low; that is, that $f$ is $O(\xi)$. Although inbreeding has been explicitly modeled as selfing, here, as in other modifier models (Otto 2003; Roze and Lenormand 2005), it is hoped that these results will provide insight into inbreeding that may arise in other ways (e.g., population subdivision within each of the two main populations).

Assuming that dominance is not too weak (i.e., that $\iota_{A,1}$ is $O(\xi)$), the change in the modifier is given by equation (5). However, with inbreeding the association between the modifier and homozygosity at the **A** locus becomes

$$
{}_{Q}C_{MA/A,1} = -\frac{\delta_\sigma H_{\sigma 1}}{\sigma(1-\sigma)} V_{M,1}\left({}_{Q}C_{A/A,1} - \frac{1}{2} V_{A,1} f\right) - \frac{\delta_\sigma H_{\sigma 2}}{\sigma} {}_{Q}C_{MA/MA,1} + o(\xi^2), \tag{9}
$$

where $H_{\sigma 2} = p_{M,1} h_\sigma + (1 - p_{M,1})(1 - h_\sigma)$. When $f = 0$, equation (9) collapses to equation (6) because ${}_{Q}C_{MA/MA,1} = 0$ when $f = 0$ (see below). The intralocus association at QLE for locus **A** is

$$
{}_{Q}C_{A/A,1} = (V_{A,1}^2 \iota_{A,1} + m_1 \Delta_{A,1}^2) \times \frac{(1-\sigma)}{\sigma} + \frac{1}{2} V_{A,1} f + o(\xi). \tag{10}
$$

As expected, inbreeding increases homozygosity. However, the main effect of inbreeding with respect to the evolution of the modifier comes through its effect on the four-way association between homozygosity at the **M** locus and homozygosity at the **A** locus:

$$ {}_{\mathrm{Q}}C_{\mathrm{MA/MA,1}} = \frac{1}{2} V_{\mathrm{M,1}} V_{\mathrm{A,1}} R_1 f + o(\xi), \tag{11} $$

where $R_1 = r_{\mathrm{MA}}^2 + (1 - r_{\mathrm{MA}})^2$. We see from equation (11) that ${}_{\mathrm{Q}}C_{\mathrm{MA/MA,1}}$ is always positive. This association exists because individuals who are the product of inbreeding are more likely to be homozygous at both loci than expected by chance based on the frequency of homozygotes at each individual locus. This is known as the Bennett-Binet effect (Bennett and Binet 1956). As shown by equation (9), an overabundance of double homozygotes (${}_{\mathrm{Q}}C_{\mathrm{MA/MA,1}} > 0$) reduces the association between *M* and homozygosity at the **A** locus. As discussed elsewhere (Dolgin and Otto 2003; Otto 2003; Agrawal and Otto 2006), this counterintuitive result occurs because double homozygotes involving the *M* allele (*MA*/*MA* and *Ma*/*Ma*) are more likely to engage in sex and create heterozygotes than are double homozygotes involving the *m* allele (*mA*/*mA* and *ma*/*ma*).

When equations (9)–(11) are combined with equation (5), the total change in the modifier is given by

$$ \Delta p_{\mathrm{M,1}} = -\frac{\delta_\sigma H_{\sigma 1}}{\sigma^2} V_{\mathrm{M,1}} (V_{\mathrm{A,1}}^2 \iota_{\mathrm{A,1}} + m_1 \Delta_{\mathrm{A,1}}^2) \iota_{\mathrm{A,1}} $$

$$ - \frac{\delta_\sigma H_{\sigma 2}}{2\sigma} V_{\mathrm{M,1}} V_{\mathrm{A,1}} R_1 f \iota_{\mathrm{A,1}} + o(\xi^3). \tag{12} $$

The first term is unrelated to inbreeding and shows the result described in the previous section (eqq. [5]–[7]): sex can be favored if migration causes an excess of homozygotes when heterozygotes are relatively more fit. The second term represents the effect of inbreeding. Inbreeding creates an excess of double homozygotes, and the modifier can gain an advantage through sex if heterozygotes are more fit. Both terms require locally maladapted alleles to be recessive ($\iota_{\mathrm{A,1}} < 0$) to favor sex. The first term also requires that migration be a more important determinant of the intralocus association than dominance selection. In the absence of population differentiation, the first term is always negative, so it is more difficult to select for sex. In contrast, the effect of inbreeding expressed in the second term does not depend on population differentiation.

As a point of technical interest, the results provide some insight into the conjecture of Otto (2003) that modeling inbreeding as selfing may serve as a useful proxy for inbreeding resulting from population subdivision. In my model, there are two forms of nonrandom mating. First, matings occur within but not between the two ecologically differentiated populations (i.e., subdivision). Second, individuals self-fertilize at rate *f*. These two forms of nonrandom mating affect the evolution of sex quite differently. The main effect of selfing on sex arises because selfing generates an excess of double homozygotes, for example, ${}_{\mathrm{Q}}C_{\mathrm{MA/MA,1}} > 0$. This association would likely arise in a standard island model of population subdivision, because drift would cause variation among populations in the frequencies of both *M* and *A* alleles, so that different haplotypes (*MA*, *Ma*, *mA*, and *ma*) would be overrepresented in different populations, resulting in an excess of double homozygotes at the metapopulation level. However, in my model, population subdivision does not generate an excess of double homozygotes, because we have assumed that the frequency of *M* is equal across populations; divergent ecological selection generates strong differentiation between populations with respect to **A**, but migration homogenizes the populations with respect to **M**. It is worth noting that even though an excess of double homozygotes might exist in a standard island model, it is not obvious that this would reduce the association between *M* and homozygosity at the **A** locus, as described above for the selfing model. Recall that this reduction occurs in the selfing model because *MA*/*MA* and *Ma*/*Ma* are more likely than *mA*/*mA* and *ma*/*ma* individuals to engage in sex with each other and create **A**-locus heterozygotes. In an explicit island model, it is unclear whether this would happen, because *MA*/*MA* individuals would tend to be in different demes than *Ma*/*Ma* individuals. To clarify these and other issues (e.g., soft vs. hard selection; Haag and Roze 2007), spatially explicit modeling is required to understand how population structure affects the evolution of sex. Note that Roze (2009, this issue) presents a recombination model that is spatially explicit and can be compared to a model involving selfing (Roze and Lenormand 2005).

### *Model with Two Loci Affecting Fitness*

I now consider a second locus affecting fitness (i.e., the **B** locus is not neutral). Just as we saw migration affecting the intralocus association by importing maladapted alleles at the **A** locus in pairs (e.g., *a*/*a*), it also affects other associations in a similar way. For example, migration imports chromosomes containing maladapted alleles at two loci (*ab*), generating positive linkage disequilibrium. Migration also affects the association between homozygosity at the two fitness loci because migration often brings these maladapted chromosomes in as pairs (*ab*/*ab*). These (and other) associations are broken down by sex, causing the modifier allele to become associated with these associations (e.g., $C_{\mathrm{MAB/\varnothing}}$, $C_{\mathrm{MAB/AB}}$). Various forms of epistasis determine the fitness consequences of breaking down associations involving alleles at different loci. The change in the frequency of the modifier is given by

$$\begin{aligned}\Delta p_{M,1} = {}& {}_{Q}C_{MA/A,1}I_1 + {}_{Q}C_{MB/B,1}I_2 \\ & + ({}_{Q}C_{MAB/\varnothing,1} + {}_{Q}C_{M/AB,1} \\ & \quad + {}_{Q}C_{MA/B,1} + {}_{Q}C_{MB/A,1})I_3 \\ & - ({}_{Q}C_{MAB/B,1} + {}_{Q}C_{MB/AB,1})I_4 \\ & - ({}_{Q}C_{MAB/A,1} + {}_{Q}C_{MA/AB,1})I_5 \\ & + {}_{Q}C_{MAB/AB,1}\varepsilon_{d\times d} + o(\xi^3),\end{aligned} \tag{13}$$

where the $I$ terms are the average fitness consequences of disrupting different types of allele combinations (see table 1).

Assuming no selfing ($f = 0$) and substituting in the appropriate QLE values for the associations, the equation above becomes

$$\begin{aligned}\Delta p_{M,1} = {}& -\frac{\delta_\sigma H_{\sigma 1} V_{M,1}}{\sigma^2} \\ & \times \Bigg[(V_{A,1}^2 I_1 + m_1\Delta_A^2)I_1 + (V_{B,1}^2 I_2 + m_1\Delta_B^2)I_2 \\ & \quad + \left(4 + \frac{1}{r_{MAB}}\right)(V_{A,1}V_{B,1}I_3 + m_1\Delta_A\Delta_B)I_3 \\ & \quad + 2(V_{A,1}V_{B,1}^2 I_4 + m_1\Delta_A\Delta_B^2)I_4 \\ & \quad + 2(V_{A,1}^2 V_{B,1} I_5 + m_1\Delta_A^2\Delta_B)I_5 \\ & \quad + 2(V_{A,1}^2 V_{B,1}^2\varepsilon_{d\times d,1} + m_1\Delta_A^2\Delta_B^2)\varepsilon_{d\times d,1}\Bigg] \\ & + o(\xi^3),\end{aligned} \tag{14}$$

where $r_{MAB} = 1 - (1 - r_{MA})(1 - r_{AB})$. If there is no genetic differentiation between populations ($\Delta_A = \Delta_B = 0$), then each of the terms in the square brackets is positive (i.e., all are positive functions of squared $I$ or $\varepsilon$ terms), indicating that selection acts against sex. This is because, in the absence of genetic differentiation between populations, migration has no effect and associations are built only by selection. Eroding these associations through sex undoes the work of selection and is detrimental. When there is genetic differentiation among populations, migration can cause some allele combinations to be overrepresented even if alternative combinations would be more fit. This provides an opportunity for sex to be favored. This is exactly the same logic as was used to understand the single-fitness-locus model. In the two-locus model, there are many more types of associations that can occur, but the principle is the same. Migration causes maladapted alleles to enter a population in clusters rather than as independent alleles (because they enter a population packaged in individual diploid organisms). If having several maladapted alleles simultaneously is worse than expected on the basis of their individual effects, then sex can be favored because sex redistributes these alleles more evenly through the population.

If organisms self at rate $f$, then the change in the modifier is given by

$$\begin{aligned}\Delta p_{M,1} = {}& \Delta p_{f=0} - \frac{\delta_\sigma H_{\sigma 2} V_{M,1} f}{2\sigma} \\ & \times (V_{A,1}R_1 I_1 + V_{B,1}R_2 I_2 \\ & \quad + V_{A,1}V_{B,1}R_1 R_3\varepsilon_{d\times d,1}) + o(\xi^3),\end{aligned} \tag{15}$$

where $\Delta p_{f=0}$ is the right-hand side of equation (14) and $R_2$ and $R_3$ are given in table 1. The second term of equation (15) is the effect of selfing. The first two terms in the parentheses are equivalent to the effect of selfing that was observed in the single-locus model (see eq. [12]), but $I_1$ (and $I_2$) replace $\iota_{A,1}$ (and $\iota_{B,1}$) and account for epistatic effects when homozygotes are converted to heterozygotes. These two selfing terms select for sex if heterozygotes are more fit, on average, than homozygotes. The third selfing term exists because selfing creates not only an excess of double homozygotes (e.g., *MA*/*MA*), which drive the first two terms, but also an excess of triple homozygotes (*Mab*/*Mab*, *MAb*/*MAb*, *mab*/*mab*, *mAb*/*mAb*, etc.). Triple homozygotes carrying the *M* allele are more likely to engage in sex with one another, producing offspring that are not doubly homozygous for maladapted alleles (e.g., *Mab*/*Mab* × *MAb*/*MAb* → *MAb*/*Mab*). This provides a benefit to sex if individuals that are doubly homozygous for maladapted alleles are relatively unfit ($\varepsilon_{d\times d,1} < 0$).

### *Evolution of Recombination*

We can also investigate the evolution of recombination in this model with two fitness loci by allowing the modifier to increase the recombination rate ($\delta_r > 0$) but not sex ($\delta_\sigma = 0$). In this case, the change in the modifier is given by

$$\Delta p_{M,1} = {}_{Q}C_{MAB/\varnothing,1}I_3 + {}_{Q}C_{MAB/AB,1}\varepsilon_{d\times d,1} + o(\xi^3), \tag{16}$$

where the second term exists only if there is inbreeding, $f \neq 0$. Note that this approximation assumes that epistasis is strong, $O(\xi)$. If epistasis is weak, $O(\xi^2)$, then other types of associations (${}_{Q}C_{MA/\varnothing}$, ${}_{Q}C_{MB/\varnothing,}$) become important (Barton 1995).

After substitution of the appropriate values for the associations, equation (16) becomes

$$\Delta p_{M,1} = -\frac{\delta_r H_{r1} V_{M,1}}{r_{MAB}} \frac{(V_{A,1} V_{B,1} I_3 + m_1 \Delta_A \Delta_B)}{r_{AB}\sigma} I_3 - \delta_r H_{r1} V_{M,1} V_{A,1} V_{B,1} f(1 - 2r_{AB}) \varepsilon_{d\times d,1} + o(\xi^3). \quad (17)$$

When there is no selfing ($f = 0$), the first term shows that, in the absence of genetic differentiation between populations ($\Delta_A = \Delta_B = 0$), selection acts against recombination. This is for the same reason as was discussed with respect to sex. If selection is the only force building linkage disequilibrium, then it creates an excess of good allele combinations. Recombination shuffles these combinations, often creating types that are less fit.

When there is genetic differentiation, migration can be an important source of linkage disequilibrium. In particular, we expect migration to generate positive linkage disequilibrium because migrants will tend to have maladapted alleles at both loci. If the effect of migration is large relative to epistatic selection, then there will be an excess of extreme haplotypes (*AB*, *ab*) even if the intermediate haplotypes (*Ab*, *aB*) are more fit ($I_3 < 0$). This effect of migration on the evolution of recombination has been studied in detail by Pylkov et al. (1998) and Lenormand and Otto (2000).

Inbreeding also affects the evolution of recombination. As shown by Roze and Lenormand (2005; see also Roze 2009, this issue), inbreeding can favor the evolution of recombination when double homozygotes are relatively unfit ($\varepsilon_{d\times d,1} < 0$). Recombination is favored because it reduces the frequency of double homozygotes among the selfed offspring of double heterozygotes (*AB*/*ab*, *Ab*/*aB*). This is advantageous because individuals doubly homozygous for maladaptive alleles are particularly unfit when $\varepsilon_{d\times d,1} < 0$. In other words, recombinant selfed offspring are more fit than nonrecombinant selfed offspring when $\varepsilon_{d\times d,1} < 0$.

## Discussion

The benefits of sex are thought to arise from the rearrangement of genetic variants, yet it is unclear why genetic variation for fitness persists in populations. A number of possible explanations exist (Falconer and Mackay 1996; Roff 1997), but one strong candidate is spatial heterogeneity in selection. Theoretically, spatial heterogeneity is effective at maintaining variation (Felsenstein 1976). Moreover, there are countless empirical examples of local adaptation (Hedrick et al. 1976; Hedrick 1986; Linhart and Grant 1996), indicating that selection varies over space, allowing populations to become differentiated. Here I have explored how migration between two differentiated populations affects the evolution of sex in diploids.

Most evolution-of-sex models have considered other forces maintaining variation (e.g., deleterious mutation, host-parasite coevolution). It is difficult to compare the strength of selection on sex arising from different sources of variation. It is not obvious that deleterious-mutations models are more important simply because all genes experience mutation. Only a small fraction of genes experience spatially divergent selection, but the levels of polymorphism for such genes may be very high. The amount of genetic variation in fitness due to a particular factor (spatial heterogeneity, mutation, host-parasite coevolution, etc.) can be thought of as the potential for that factor to affect the evolution of sex. Unfortunately, determining the relative contribution of these factors to the maintenance of genetic variance remains one of the classic unsolved problems in evolutionary biology (Falconer and Mackay 1996; Roff 1997). The goal here was to evaluate the conditions under which sex would be favored, given the existence of variation maintained by spatially divergent selection. In this way, assessing the likelihood of those conditions helps in evaluating the importance of spatial heterogeneity relative to deleterious mutation and other sources of variation.

Migration between genetically differentiated populations can create an excess of homozygotes. This occurs because genes are imported as diploid individuals (e.g., *a*/*a* migrants into a population of mostly *A*/*A* residents). This type of effect would not be expected if migration occurred at the gametic stage, for example, pollen dispersal. (Note that other complications arise if dispersal is through gametes, because then migration is linked to reproductive mode; i.e., only the products of sexual reproduction migrate.) If migration of diploids is assumed, migration between genetically differentiated populations can result in an excess of homozygotes even when heterozygotes are more fit than the average of the homozygotes, $W_{A/a} > (1/2)(W_{A/A} + W_{a/a})$. Under these conditions, there is an immediate fitness advantage to sex because segregation will convert these homozygotes to heterozygotes. However, it is not immediately obvious that these conditions will often be met, and some discussion is warranted.

It is a necessary, though not sufficient, condition that maladapted alleles be recessive. Sex will evolve most readily if maladapted alleles are recessive in all environments ($\iota_{A,1}, \iota_{A,2} < 0$), which requires that alleles are dominant in the environment where they are favored but recessive where they are not. If the same allele is dominant across environments, sex may be favored in one population but not in the other, and the net result at the metapopulation level will depend on the quantitative differences in selection. However, there are several reasons why the domi-

nance of an allele with respect to fitness may switch across environments in the manner that is favorable to the evolution of sex. Imagine two populations that experience stabilizing selection for different optimal body size and that a single gene controls the difference in body size between the two demes. With stabilizing selection in each environment, the heterozygote will be more fit than the average of the two homozygotes in both environments, if it is assumed that the fitness surface has negative curvature over the realized range of phenotypes (fig. 2). This logic also works even if the gene is only one of many genes that contribute to the difference between the optimal phenotypes of the two populations. A second reason that dominance relationships for fitness may not be consistent across environments is that most mutations affect two (or more) phenotypes (i.e., pleiotropy), and dominance relationships may differ across phenotypes, which is important if the relative strength of selection on the two phenotypes changes across environments. For example, alleles conferring resistance to insecticides are often dominant, but the pleiotropic costs of these alleles can be recessive (Roush and Plapp 1982; Roush and McKenzie 1987). Third, locally favored alleles may evolve to be dominant (Otto and Bourguet 1999). Finally and most importantly, loci that have the most favorable type of dominance pattern (i.e., alleles that are dominant where they are favored) are the most likely to be maintained in a polymorphic state by migration-selection balance (Nagylaki 1975).

Fortunately, reasonably simple experiments can provide important insights into whether gene interactions are of the correct form to favor sex. The key issue is whether $F_1$ hybrids will be more or less fit than the average of the parental types. Ideally, fitnesses from both parental types and the hybrids should be measured in both environments. If maladapted alleles are recessive, then the hybrids will be more fit then the average of the parents. Of course, experiments of this kind will likely measure the effects of multiple genes that differentiate the parental populations. Thus, the observed results reflect not only dominance but also components of epistasis. However, these same epistatic effects are relevant to selection on sex, as reflected by the $I$ terms in the model with two fitness loci (eq. [14]). For example, in fitness measurements in population 1, the difference in fitness between the average of the two parental populations and the $F_1$ hybrids is

$$\begin{aligned}\frac{1}{2}(\overline{W}_{\text{pop1}} - \overline{W}_{\text{pop2}}) - \overline{W}_{\text{F}_1} = {} & \frac{1}{2}\Delta_{\text{A}}^2 I_1 + \frac{1}{2}\Delta_{\text{B}}^2 I_2 \\ & + \Delta_{\text{A}}\Delta_{\text{B}} I_3 - \Delta_{\text{A}}\Delta_{\text{B}}^2 I_4 \\ & - \Delta_{\text{A}}^2\Delta_{\text{B}} I_5 \\ & + \frac{1}{2}\Delta_{\text{A}}^2\Delta_{\text{B}}^2 \varepsilon_{\text{d}\times\text{d},1} + o(\xi).\end{aligned} \tag{18}$$

The right-hand side of equation (18) is similar to the term in square brackets in equation (14), provided that differentiation among populations is large relative to variation within populations ($|\Delta_{\text{A}}| \gg V_{\text{A},1}$, that is, that migration is more important than selection within demes in shaping associations). Even when this condition is met, equation

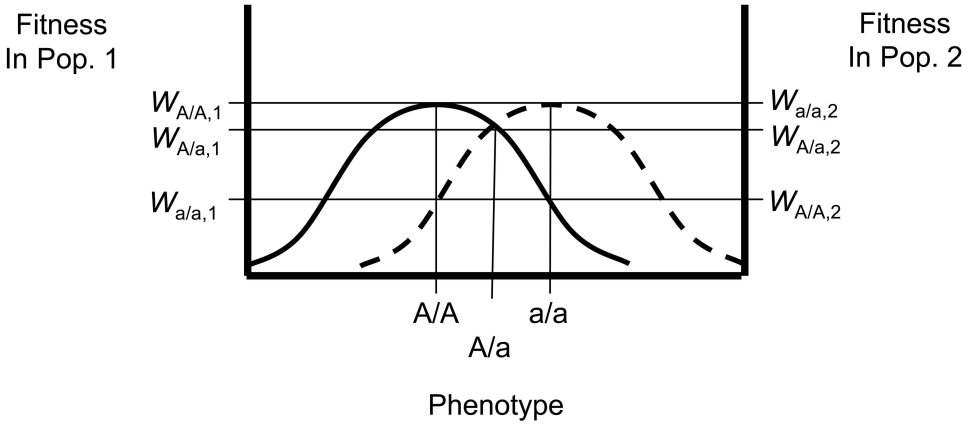


**Figure 2:** Dominance of locally adapted alleles. The figure illustrates a hypothetical scenario where a trait is under stabilizing selection for different optima in population 1 (*solid curve*) and population 2 (*dashed curve*). A single locus **A** with additive effects on the phenotype differentiates the two populations. Because of the negative curvature of fitness surfaces, the heterozygote is more fit than the average of the two homozygotes in both environments ($W_{A/a,i} > (W_{A/A,i} + W_{a/a,i})/2$ for $i = 1, 2$). In the context of this model, this would mean that dominance is negative in both environments: $\iota_{\text{A},1}, \iota_{\text{A},2} < 0$. The argument described above would not apply if optima for the two environments were too far apart, because the curvature for each of these fitness surfaces becomes positive far from the optimum.

(18) differs from the bracketed term in equation (14) with respect to the effect of $I_3$ because recombination in future generations also affects the modifier. Nonetheless, a finding that $F_1$ hybrids are more fit than the average of the parents indicates that nonlinear selection patterns (dominance and epistasis) tend to be in the direction that is conducive to sex. To some extent, the model simply confirms intuition: if hybrids are more fit than the average of the parents, then sex will tend to be good because it produces hybrids.

The type of experiment described above does not provide individual estimates of actual dominance and epistasis parameters ($\iota_{A,1}$, $\varepsilon_{a \times d,1}$, etc.), for which a more detailed genetic analysis would be required. Such parameter estimates are necessary for understanding the relative contributions of segregation and recombination to selection on sex. However, a simple comparison of the fitnesses of parental types and $F_1$ hybrids provides a coarse, yet informative, view of the net effect of segregation on selecting for sex in a subdivided populations.

Although the required experimental design is similar to what is reported in a number of experiments, most of these studies were inappropriate for the current purpose for a variety of reasons (e.g., hybrids were compared only to the local parent type, $F_2$ hybrids were used rather than $F_1$ hybrids, fitness was not assayed in the selected environment). The one study I found with the appropriate data involved aphids from populations adapted to alfalfa and populations adapted to clover. Via et al. (2000) measured the fitness of both parental types as well as of the $F_1$ hybrids on both host plants. They found that while hybrids were less fit than the local parental type, they were more fit than the average of the two parental types. This was true on both host plants, a result that is consistent with the scenario that is most likely to select for sex. It would be very useful to have more data of this kind from other organisms.

It is worth noting that the pattern reported by Via et al. (2000) may not be due to locally adapted alleles. If populations differ in frequency with respect to "standard" unconditionally deleterious alleles, then $F_1$ hybrids would be more fit than parental types because parental types will be homozygous at more loci than hybrids (Whitlock et al. 2000). The consequence for sex should be the same regardless of the type of genes that are responsible, but this deleterious-mutation scenario would change how we perceive the importance of spatial heterogeneity versus mutation. Ideally, crosses could be done between populations in similar habitats versus those in different habitats to provide insights into this issue.

The other requirement for sex to be favored is that migration play a dominant role in determining the sign of intralocus associations within populations (i.e., migration must generate a net excess of homozygotes even though heterozygotes are more fit). This condition is met most easily when populations are strongly differentiated genetically (e.g., one population is nearly fixed for *A* and the other population is nearly fixed for *a*). Strong differentiation is expected to occur when selection is strong relative to migration ($s \gg m$; reviewed by Felsenstein [1976]). If the migration rate is held constant, loci under strongly divergent selection between populations will become strongly differentiated and are the most likely to select for sex (fig. 1). However, if selection is very strong, there will be little variation, so genetic associations will be small in magnitude, and such loci will only weakly favor sex. Thus, genes with moderately high levels of selection will generate the strongest selection for sex. Less strongly selected loci will show less differentiation and be more variable within populations, and the intralocus associations will be more likely to reflect dominance selection acting within populations than migration between populations. Under these conditions, sex will not be favored, because it will be destroying associations created by selection. However, loci under weak selection are less likely to be maintained in a stable polymorphic state (Felsenstein 1976; Pylkov et al. 1998) and will tend to become fixed for one allele, thus not affecting the evolution of sex. It remains a theoretical challenge to assess what the net effect on sex would be under a realistic distribution of selective effects for various metapopulation scenarios.

When the conditions are met with respect to population differentiation and dominance, the mean fitness of sexual offspring should be greater than that of asexual offspring (and the variance in fitness of sexual offspring should be lower). This is a testable prediction in systems where sexual and asexual offspring can be generated from the same parents or from random samples of parents from the same population. Given that local selection is key, fitness must be assayed under the conditions in which the organisms have evolved (i.e., in the field or in the lab after experimental lab evolution with spatially heterogeneous selection). The only study to compare the average fitness of sexual and asexual offspring in the field found that the mean fitness of sexual offspring was higher (Kelley et al. 1988), consistent with the prediction from this modifier model. Of course, these data alone do not prove that migration among heterogeneous sites is the reason behind this result, as some other theories make a similar prediction (e.g., the Red Queen; see Peters and Lively 1999 and Agrawal 2006*b*). In fact, all modifier theories make predictions regarding the difference in the mean and/or variance of fitness of offspring produced sexually versus asexually, but, unfortunately, these important empirical data are rare (Charlesworth and Charlesworth 1975; Kelley et

al. 1988; Colegrave et al. 2002; Allen and Lynch 2008; see Agrawal 2006*a* for discussion).

The potential benefit to segregation that arises from migration between genetically differentiated populations is closely related to a benefit to recombination described in earlier models. In fact, when there is no inbreeding, the conditions under which segregation is favored in the single-fitness-locus diploid model are exactly analogous to those conditions favoring recombination identified by previous authors (Pylkov et al. 1998; Lenormand and Otto 2000). Specifically, a short-term advantage can exist if migration creates an excess of extreme haplotypes, *AB* and *ab* (analogous to an excess of homozygotes) when intermediate haplotypes, *Ab* and *aB*, are more fit. This fitness condition requires that there be negative epistasis ($I_3 < 0$), which is analogous to the requirement of negative dominance in the segregation model.

Here I have explicitly modeled both sex and recombination modifiers in the same diploid framework, allowing a direct comparison for the first time. While the sex result is analogous to the recombination result, they are not the same (i.e., eq. [14] does not equal eq. [17]), implying the obvious though oft-neglected point that segregation also affects the evolution of sex. Because of segregation, a number of associations that do not affect the evolution of recombination are relevant to the evolution of sex ($C_{A/A}$, $C_{AB/A}$, $C_{AB/AB}$, etc.). Even the key associations that drive the evolution of recombination ($C_{AB/\varnothing}$, $C_{A/B}$) differ quantitatively (though not qualitatively) between how they contribute to the evolution of sex versus recombination (compare the $I_3$ terms in eqq. [14] and [17]). This is because these associations are affected differently by sex and recombination and so develop different associations with sex modifiers (${}_{Q}C_{MAB/\varnothing,1}$, ${}_{Q}C_{M/AB,1}$, ${}_{Q}C_{MA/B,1}$, and ${}_{Q}C_{MB/A,1}$) than with recombination modifiers (only ${}_{Q}C_{MAB/\varnothing,1}$).

Finally, sex and recombination modifiers are both affected by inbreeding, but for different reasons. In her single-locus sex model, Otto (2003) showed that inbreeding creates an excess of double homozygotes (*MA*/*MA*, *Ma*/*Ma*, *mA*/*mA*, *ma*/*ma*). Those double homozygotes containing the *M* allele are more likely to engage in sex and restore heterozygosity (*MA*/*MA* × *Ma*/*Ma* → *MA*/*Ma*), providing an advantage to the modifier if heterozygotes are relatively more fit. Equation (15) extends that result to two fitness loci, showing that, in addition to the single-locus effects, there is an additional effect from converting the triple homozygotes (e.g., *MAB*/*MAB*, *Mab*/*Mab*) created by inbreeding to other genotypes through sex. There is an extra advantage to eliminating individuals doubly homozygous for maladapted alleles (*ab*/*ab*) when dominance × dominance epistasis is negative ($\varepsilon_{d\times d} < 0$).

Roze and Lenormand (2005) showed that this form of dominance also selects for more recombination when there is selfing. However, the reason is quite different. Double heterozygotes (*AB*/*ab* and *Ab*/*aB*) will produce fewer double homozygotes through selfing if recombination is higher. The benefit to the recombination modifier arises because selfed recombinant offspring are more fit than selfed nonrecombinant offspring. This benefit is not expected to extend to modifiers of sex because a sex modifier does not change the ratio of these two classes of offspring (Agrawal 2006*a*). Nonetheless, it is noteworthy that this form of epistasis is favorable to both sex and recombination (but see Roze 2009, this issue), although we have almost no data on it (see Roze and Lenormand 2005 for discussion).

In conclusion, the theoretical results presented here illustrate the importance of segregation in understanding selection on sex. As has been illustrated with respect to the evolution of recombination, migration between heterogeneous habitats can be an important factor affecting the evolution of sex—and many of these effects arise through segregation. Inbreeding also affects the evolution of sex and recombination, but its effects on sex seem to be driven primarily through segregation rather than recombination. As a field, our understanding of the theoretical issues affecting sex and recombination has developed considerably in the past two decades. As it continues to do so, there is an increasing need for empirical studies to measure the relevant properties. The main empirical issues that have emerged from the model presented here are as follows. To assess the likelihood that spatial heterogeneity is important for the evolution of sex, it is essential to empirically determine whether hybrids made from populations adapted to different habitats are better than the average of the parents. In addition, it would be very useful to measure the mean and variance in fitness of sexually versus asexually produced offspring to evaluate almost any model of sex (Agrawal 2006*a*). The model presented here predicts that sexually produced offspring will have a higher mean fitness and lower variance in fitness than asexual offspring. Finally, inbreeding affects the evolution of both sex and recombination. However, the form of epistasis that is most important in this context, dominance × dominance epistasis, has received little attention to date.

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## APPENDIX

### Single Fitness Locus with Weak Dominance

The analytical approximation given in equation (5) assumes that dominance selection is not very weak. As implied by equation (5), the immediate fitness consequence of breaking down the intralocus association is determined by dominance. If dominance is very weak, these immediate consequences are small, and longer-term consequences are relatively more important in the evolution of the modifier and cannot be ignored. When the analysis is performed assuming that dominance and migration are weak (i.e., $\iota_{A,1}$ and $m_1$ are $O(\xi^2)$), the change in the modifier becomes

$$\Delta p_{M,1} = {}_{Q}C_{MA/A,1}(\iota_{A,1} + s_{A,1}^2) + ({}_{Q}C_{MA/\varnothing,1} + {}_{Q}C_{M/A,1})s_{A,1} + o(\xi^5). \tag{A1}$$

The first term above is the same as in equation (5) and represents the immediate fitness consequences of converting the overrepresented types to the underrepresented types through sexual reproduction. (The first term is weighted by $\iota_{A,1} + s_{A,1}^2$ because this is the difference in fitness between the arithmetic average of the homozygotes, $A/A$ and $a/a$, and the fitness of the heterozygote, $A/a$. In eq. [5], $\iota_{A,1}$ serves as good approximation to $\iota_{A,1} + s_{A,1}^2$ because it was assumed that $|\iota_{A,1}| \gg s_{A,1}^2$.)

The second term in equation (A1) represents the longer-term effect of sex. This effect is driven by the association of the $M$ allele with the $A$ allele, either on its own chromosome (${}_{Q}C_{MA/\varnothing,1}$) and or its homolog (${}_{Q}C_{M/A,1}$). The steady state values for these associations are

$${}_{Q}C_{MA/\varnothing,1} = \left(\frac{1}{\sigma} + \frac{1}{\sigma r_{MA}} - 1\right){}_{Q}C_{MA/A,1}s_{A,1} + o(\xi^4), \tag{A2}$$

$${}_{Q}C_{M/A,1} = \left(\frac{1}{\sigma} - 1\right){}_{Q}C_{MA/A,1}s_{A,1} + o(\xi^4). \tag{A3}$$

These equations show that the $M$ allele develops an association with the $A$ allele because of the association of the $M$ allele with homozygosity at the **A** locus. Through sex, the $M$ allele changes its tendency to be found in **A**-locus homozygotes versus heterozygotes (as represented by ${}_{Q}C_{MA/A,1}$). In doing so, the $M$ allele changes whether it is found in a more variable ($A/A$ and $a/a$) or less variable ($A/a$) background relative to $m$. Whichever **M**-locus allele is found in the more variable background will experience a stronger response to selection on $A$; that is, the **M**-locus allele that is more often found in homozygotes will hitchhike more strongly with directional selection for $A$. As is always true with hitchhiking effects, the magnitude of the hitchhiking effect is strongly mediated by the extent to which the hitchhiking allele is linked to the selected allele; here, linkage depends on how much sex ($\sigma$) and recombination ($r_{MA}$) occur. This is called a long-term effect of sex because it is not the immediate consequence of changing the distribution of alleles but rather results from subsequent selection.

In the single-locus model presented in the main text, I emphasized that a short-term advantage to sex could occur if migration created an excess of homozygotes (${}_{Q}C_{MA/A,i} > 0$) but heterozygotes were relatively more fit ($\iota_{A,i} < 0$). By converting homozygotes to heterozygotes through sex, the modifier gained an immediate fitness advantage. However, we now see that there is a long-term disadvantage to sex that counters the short-term advantage. By converting homozygotes to heterozygotes, the $M$ allele becomes associated with less variance in fitness and thus responds less well than its alternative ($m$) to selection for the best genotype, $A/A$.

These types of long-term effects on modifier evolution are well known in recombination (Barton 1995) and segregation (Otto 2003) models when nonadditive components of selection (i.e., epistasis, dominance) are weak relative to the amount of genetic mixing. However, short-term effects of sex are relatively more important than the long-term effects when the degree of genetic mixing is reasonably high (see discussion in Agrawal 2006*a*). In the main text, I focus on short-term effects of sex, and thus those results apply best to understanding the evolution of sex in species that already have moderate to high levels of sex. The evolution of moderate levels of sex from very low levels of sex is probably driven by long-term (or variance) effects. For example, Keightley and Otto (2006) have shown that negative disequilibrium between deleterious mutations resulting from Hill-Robertson effects can easily select for low to moderate

levels of sex; the evolution of the sex modifier is driven by the long-term advantage from reducing the negative disequilibrium and increasing the variance in fitness.

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