Segregation and the Evolution of Sex Under Overdominant Selection

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ABSTRACT

The segregation of alleles disrupts genetic associations at overdominant loci, causing a sexual population to experience a lower mean fitness compared to an asexual population. To investigate whether circumstances promoting increased sex exist within a population with heterozygote advantage, a model is constructed that monitors the frequency of alleles at a modifier locus that changes the relative allocation to sexual and asexual reproduction. The frequency of these modifier alleles changes over time as a correlated response to the dynamics at a fitness locus under overdominant selection. Increased sex can be favored in partially sexual populations that inbreed to some extent. This surprising finding results from the fact that inbred populations have an excess of homozygous individuals, for whom sex is always favorable. The conditions promoting increased levels of sex depend on the selection pressure against the homozygotes, the extent of sex and inbreeding in the population, and the dominance of the invading modifier allele.

ONE of the most enduring questions in evolutionary biology is why sexual reproduction has evolved and maintained itself in so many species (Bell 1982; Michod and Levin 1988). Numerous studies have proposed models to identify the conditions most favorable to the evolution and maintenance of sex and genetic mixing (see reviews by Barton and Charlesworth 1998; Otto and Michalakis 1998; West *et al.* 1999; Otto and Lenormand 2002). Most of these theoretical models have focused exclusively on the consequences of recombination to the evolution of sex. Recombination has generally been considered the primary benefit of sexual reproduction since it can counter many of the disadvantages of asexuality such as the inability to combine favorable mutations that arise in separate individuals (Fisher 1930; Muller 1932), the difficulty in regenerating fit genotypes that are lost by drift (Muller 1964), and the reduced efficacy of selection at linked loci (Hill and Robertson 1966). However, sex involves both segregation of alleles at each locus and recombination between alleles at different loci. Relatively little attention has been given to the segregation of alleles during meiosis, possibly because of Muller's (1932) claim that segregation is of no evolutionary value. More recently it has been shown that segregation contributes significantly to the evolution of sex. Segregation in a diploid sexual organism allows a single favorable mutation to become fixed in double dosage at a given locus (*i.e.*, as a homozygote), whereas two separate mutations are required in an asexual organism (Kirkpatrick and Jenkins 1989). In diploids, segregation alone can strongly decelerate the accumulation of deleterious mutations through Muller's ratchet (Antezana and Hudson 1997). Furthermore, segregation acts to purge deleterious mutations from the genome, reducing the mutation load (Chasnov 2000; Agrawal and Chasnov 2001). Otto (2003, this issue) investigated the circumstances favoring increased sex and genetic mixing due to selection for segregation rather than for recombination by constructing a modifier model where alleles at a modifier locus altered the degree of sex under conditions of purifying and directional selection. This article builds on this previous work by determining the conditions under which segregation favors an increased frequency of sex when there is overdominant selection.

Segregation breaks down one-locus genetic associations between alleles on homologous chromosomes. In fact, a fully sexually reproductive population with nonoverlapping generations will achieve Hardy-Weinberg equilibrium frequencies after one generation of random mating, completely breaking down one-locus genetic associations.

However, one-locus genetic associations can accumulate over time within asexual or partially sexual populations. When these genetic associations affect fitness, indirect selection will act on any property that influences their accumulation, including the level of sexual reproduction. The genetic associations at a locus (**A**) between two alleles (A and a) can be measured by the inbreeding coefficient, F,

$$F = \frac{p_{AA} - p_A^2}{p_A p_a} = \frac{p_{AA}p_{aa} - (p_{Aa}/2)^2}{p_A p_a}, \quad (1)$$

where p_{ij} and p_k are the frequencies of genotype ij and allele k, respectively. F is a measure of the discrepancy between the observed genotypic frequency and the ex-

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pected frequency at Hardy-Weinberg proportions. It also identifies whether homozygotes are more frequent ($F > 0$) or less frequent ($F < 0$) than expected.

One-locus genetic associations can be advantageous or not, depending on the form of selection (see Weiner *et al.* 1992). In the case of overdominant selection, heterozygotes are fitter than homozygotes, and the fitness of a diploid individual measured relative to the heterozygote is

$$\text{Fitness}(AA) = 1 - s, \quad \text{Fitness}(Aa) = 1, \quad \text{Fitness}(aa) = 1 - t, \qquad (2)$$

where s and t are positive selection coefficients less than or equal to one. With heterozygote advantage, one would expect the frequency of heterozygotes to rise to fixation within a fully asexual population, producing a strong negative one-locus genetic association ($F = -1$). On the other hand, within a sexual population, meiosis disrupts this genetic association forming the less fit homozygotes. Therefore, with overdominant selection, a sexual population experiences a lower mean fitness compared to an asexual population, a fitness cost known as the segregation load (Crow 1970; Peck and Waxman 2000). We would thus expect that heterozygote advantage would select against sexual reproduction to preserve advantageous one-locus genetic associations.

This article addresses the expectation that sex is not favored under overdominant selection due to the segregation load by investigating whether circumstances promoting increased sex exist within a population that is capable of both sexual and asexual reproduction, as is common among fungi, protists, algae, plants, and various invertebrate animal groups (Bell 1982). To determine how the level of sex evolves within a population, we monitor the frequency of alleles at a modifier locus, **M**, that change the relative allocation to sexual and asexual reproduction. The frequency of these modifier alleles can change over time as a correlated response to the dynamics at a fitness locus, **A**, subject to overdominance in viability. Contrary to the hypothesis that sex would never be favored, we find that modifier alleles that increase the frequency of sex can spread under a range of biologically reasonable parameters in a partially sexual population that inbreeds to some extent. This result is due to genetic associations between the modifier locus and the fitness locus that are formed upon introduction of the rare modifier allele, causing double heterozygotes and double homozygotes to be more common than expected. Because it is always advantageous under overdominant selection for homozygotes to reproduce sexually, the advantages of a modifier that increases levels of sex among homozygotes can outweigh the costs of an increased segregation load among heterozygotes.

METHODS

A two-locus model, based on that of Otto (2003, this issue), was designed with a modifier locus, **M**, and a fitness locus, **A**, within a diploid population with nonoverlapping generations and without mutation. Allele frequencies were monitored by first censusing at the juvenile stage, followed by selection and reproduction. We label haplotypes as 1 for *MA*, 2 for *Ma*, 3 for *mA*, and 4 for *ma*, and let x_{ij} equal the frequency of juveniles with haplotypes i and j. No selection occurs at the haploid stage, and all loci are assumed to be autosomal with selection acting irrespective of the sex of the parent. Therefore, we assume that $x_{ij} = x_{ji}$ and monitor only x_{ij} for $j \geq i$, such that, for example, the frequency of *MM Aa* individuals is $2x_{12}$. At this point, selection occurs according to Equations 2. Let $\tilde{x}_{ij}$ equal the frequency of adults with haplotypes i and j after selection such that, for example, the frequency of *MM AA* adults is $\tilde{x}_{11} = x_{11}(1 - s)/\overline{W}$, where $\overline{W}$ is the mean fitness within the population. Reproduction then occurs, and the probability that an individual undergoes sexual reproduction depends on its genotype at the modifier locus, **M**:

Genotype:	*MM*	*Mm*	*mm*
Probability of sex:	σ_1	σ_2	σ_3

(3)

Recombination occurs between the **M** and **A** loci during meiosis of a sexual individual at a rate r. We assume that meiosis produces haploid individuals where y_i denotes the frequency of haplotype i such that, for example, the frequency of *MA* haploids would be

$$y_1 = \frac{\sigma_1(\tilde{x}_{11} + \tilde{x}_{12}) + \sigma_2(\tilde{x}_{13} + \tilde{x}_{14}(1 - r) + \tilde{x}_{23}r)}{\overline{\sigma}}, \qquad (4)$$

where $\overline{\sigma}$ is the average proportion of the diploid population that reproduces sexually,

$$\overline{\sigma} = \sigma_1(\tilde{x}_{11} + 2\tilde{x}_{12} + \tilde{x}_{22}) + \sigma_2(2\tilde{x}_{13} + 2\tilde{x}_{14} + 2\tilde{x}_{23} + 2\tilde{x}_{24}) + \sigma_3(\tilde{x}_{33} + 2\tilde{x}_{34} + \tilde{x}_{44}). \qquad (5)$$

Haploid individuals of genotype i then produce gametes, which mate with other gametes from the same haploid parent with probability f or undergo random union with probability $1 - f$. Thus, inbreeding is included in our model in the form of gametophytic selfing (intragametophytic selfing in the terminology of Klekowski 1969), which produces only homozygous diploids of genotype ii. In contrast, random union results in diploids of genotypes ii and ij in proportion to their component haplotype frequencies. We refer to f as the selfing rate to avoid confusion with the inbreeding coefficient, F, although we expect that other forms of inbreeding would yield similar results (see Discussion). If an individual reproduces asexually, which occurs at a probability of $1 - \sigma_i$, then it contributes directly to the frequency of its genotype in the next generation. Thus, one can derive the frequency of diploid juveniles in the next generation. For example, the frequencies of *MM AA* (x'_{11}) and *MM Aa* ($2x'_{12}$) juveniles equal

$$x'_{11} = (1 - \sigma_1)\tilde{x}_{11} + \overline{\sigma}(y_1^2(1 - f) + y_1 f),$$
$$2x'_{12} = (1 - \sigma_2)2\tilde{x}_{12} + \overline{\sigma}(2y_1y_2(1 - f)). \qquad (6)$$

To test whether a modifier for increased sex could invade and spread within a population, the recursions (6) and similar recursions for the remaining genotypes are used in the following analyses. First, we determine the stable polymorphism at the **A** locus with the *M* allele fixed at the modifier locus. We then determine the conditions under which a new modifier allele, *m*, that alters the degree of sexual reproduction could spread within a population. Mathematica 4.1 (Wolfram 1991) packages are available for additional details regarding the construction and analyses of the model.

RESULTS

The equilibrium: With the *M* allele fixed at the modifier locus, a stable polymorphism is attained that depends on the level of sexual reproduction, the selfing rate, and the strength of selection within the population. At equilibrium, the frequencies of the fitness-locus alleles, *A* and *a*, equal

$$p_A = \frac{(t - Fs)}{(1 - F)(s + t)}, \quad p_a = \frac{(s - Ft)}{(1 - F)(s + t)}, \quad (7)$$

where *F*, the inbreeding coefficient, equals

$$F = \frac{\sigma_1(s + t - st(1 - f)) - \sqrt{\sigma_1^2(s + t - st(1 - f))^2 + 4st(st(1 - \sigma_1) - \sigma_1 f(s + t - st))}}{2st}. \quad (8)$$

The frequency of both alleles must lie between 0 and 1, and the two must sum to 1. Because the denominator of (7) is nonnegative, we require that $t > Fs$ and $s > Ft$ for both p_A and p_a to be positive. If these conditions are not met, either because the selfing rate is too high or because one homozygote is much fitter than the other, then there is no polymorphic equilibrium.

With *M* fixed, the equilibrium genotypic frequencies, denoted by $\hat{x}_{ij}$, are

$$\hat{x}_{11} = \frac{t(1 + F)(t - Fs)}{(1 - F)(s + t)^2}, \quad \hat{x}_{12} = \frac{(t - Fs)(s - Ft)}{(1 - F)(s + t)^2}, \quad \hat{x}_{22} = \frac{s(1 + F)(s - Ft)}{(1 - F)(s + t)^2}. \quad (9)$$

If the population is initially asexual such that $\sigma_1 = 0$, we can see that $F = -1$ by Equation 8, indicating a strong negative one-locus genetic association where the frequency of the homozygotes is 0. However, if some small amount of sex is present, and if $t > Fs$ and $s > Ft$, then a polymorphism with all three genotypes exists. Increased levels of sex, higher selfing rates, and weaker selection coefficients generate a lower frequency of the heterozygotes at equilibrium.

One can prove that, as long as the polymorphism exists, the equilibrium mean fitness is a decreasing function of the level of sex, σ_1, regardless of the level of selfing, *f*. Mean fitness considerations would thus predict the evolution of asexuality for all relevant values of *f*. As we shall see, however, genotypic associations create individual differences in the fitness effects of sex that can drive the spread of modifier alleles that increase the frequency of sex under certain conditions.

Conditions for modifier spread: We performed a local stability analysis of the recursions near the equilibrium polymorphism (9) to determine whether a rare modifier allele, *m*, that changes the reproductive allocation of an organism between sexual and asexual reproduction (σ) will invade or disappear within a population. If all the eigenvalues (λ) of the local stability matrix are less than one in magnitude, the rare modifier allele declines in frequency, whereas if at least one eigenvalue is greater than one, then the *m* allele will spread within the population over time. The strength of indirect selection acting on a modifier due to segregation can be defined as $\phi = \lambda - 1$, where λ is the leading eigenvalue. If selection is weak and the modifier is rare, ϕ describes the asymptotic rate at which the modifier spreads:

$$\phi \approx \frac{p'_m - p_m}{p_M p_m}. \quad (10)$$

Because each fitness locus has a small effect on the frequency of the modifier, the genome-wide strength of selection (Φ) can be calculated by summing ϕ over all overdominant fitness loci, assuming that these loci are in linkage equilibrium.

One eigenvalue of the local stability matrix equals $(1 - \sigma_3)/\overline{W}$. This result indicates that a modifier allele that causes an almost complete loss of sex in the homozygous condition ($\sigma_3 < 1 - \overline{W}$) can invade. Thus, sexual populations are always prone to invasion by primarily asexual offshoots, within which the most-fit *Aa* genotype rises to near fixation.

To solve for the remaining eigenvalues, we assumed that the effect of the modifier on the frequency of sexual reproduction is weak. That is, we determined the eigenvalue as a linear function of $\Delta\sigma_2$ and $\Delta\sigma_3$, where $\Delta\sigma_2 = (\sigma_2 - \sigma_1)$ and $\Delta\sigma_3 = (\sigma_3 - \sigma_1)$ represent the change in the frequency of sex among *Mm* and *mm* individuals, respectively. As a check, this leading eigenvalue does simplify to one when the modifier is neutral and has no effect on the frequency of sex ($\Delta\sigma_2 = \Delta\sigma_3 = 0$). Unfortunately, the leading eigenvalue is too long and complicated to report (available upon request), and so we focus on cases of special interest, assuming throughout that the modifier is weak ($\Delta\sigma$ is small).

Nonselfing populations: When selfing is absent ($f = 0$), the only other eigenvalue that is ever the leading eigenvalue and greater than one simplifies to

$$\lambda_{f=0} = 1 - \frac{\Delta\sigma_2(F(st - s - t) + st)^2}{(s + t - st(1 + F))((s + t)(1 + F^2) - st(1 + F)^2)} + O(\Delta\sigma^2). \quad (11)$$

If the new modifier allele, *m*, increases the frequency of sex ($\sigma_2 > \sigma_1$), $\lambda_{f=0}$ is always less than one, indicating that modifier alleles that increase the frequency of sex are never expected to invade in the absence of selfing or other forms of inbreeding.

Primarily asexual populations: With inbreeding, we first consider populations in which sex is extremely rare. If a population is fully asexual ($\sigma_1 = 0$), the eigenvalue simplifies to

$$\lambda(\sigma_1 = 0) = 1 - \frac{1}{2}\Delta\sigma_2(1 + f) + O(\Delta\sigma^2), \qquad (12)$$

which is always less than one for a new modifier allele that increases the frequency of sex. In this case, selection acts strongly against sex, with the equivalent of an indirect selection coefficient, ϕ, one-half times greater than the effect of the modifier. Therefore, a modifier for increased sex can never invade a completely asexual population. However, even if some small amount of sexual reproduction is initially present, then parameters do exist for which the eigenvalue is greater than one. A Taylor series approximation of the leading eigenvalue around $\sigma_1 = 0$ simplifies to

$$\lambda(\sigma_1 \approx 0) = 1 - [\Delta\sigma_2(\sigma_1(st(3 + f^2) - (s + t)(1 - f)) + 2st(1 + f)) - \Delta\sigma_3(\sigma_1 f(1 - f)(s + t - 2st))]/4st + O(\sigma_1^2\Delta\sigma, \Delta\sigma^2). \qquad (13)$$

Equation 13 indicates that sex is able to invade ($\lambda \geq 1$) when the modifier is completely recessive ($\Delta\sigma_2 = 0$). In this case, the strength of indirect selection is proportional to $(s + t)/st$, implying that selection for sex strengthens as s and t become smaller. The range of selection coefficients promoting sex decreases rapidly, however, as the effect of the modifier in heterozygous individuals ($\Delta\sigma_2$) increases. Equation 13 also indicates that sex can spread if selection against one homozygote is much weaker than selection against the other homozygote ($s \gg t$ or $s \ll t$) or if both selection coefficients are small ($s, t \ll 1$). While Equation 13 is derived assuming that the frequency of sex (σ_1) is small relative to the selection coefficients, a numerical analysis of the eigenvalues demonstrates that, indeed, there is always a range of weak selection coefficients in which sex is favored (see Equations 16 and 17), unless the modifier is fully dominant.

Primarily sexual populations: Next, we consider a population that is nearly fully sexual with inbreeding. Taking the Taylor series of the eigenvalue around $\sigma_1 = 1$, the leading-order term simplifies to

$$\lambda(\sigma_1 \approx 1) = 1 - [(t - fs)(s - ft)(\Delta\sigma_2(f(s(1 - s) + t(1 - t)) + st(1 + f)) - \Delta\sigma_3 f(s(1 - s) + t(1 - t)))]/[(1 - f)(s + t - st(1 + f))^2] + O((1 - \sigma_1)\Delta\sigma, \Delta\sigma^2). \qquad (14)$$

As σ_1 approaches 1, the equilibrium inbreeding coefficient, F (8), approaches f. Thus, as stipulated by Equations 7, the polymorphic equilibrium exists only when $t > fs$ and $s > ft$ (*i.e.*, $t/f > s > ft$ must hold). With this restriction, Equation 14 indicates that dominant modifiers ($\Delta\sigma_2 = \Delta\sigma_3$) invade only if they decrease the frequency of sex. Conversely, recessive modifiers ($\Delta\sigma_2 = 0$) invade whenever they increase the frequency of sex (recall that recessive modifiers can also invade if they cause the loss of sex, $\sigma_3 < 1 - \overline{W}$). According to (14), the strength of indirect selection, ϕ, is proportional to $st/(s + t)$ for a fully recessive modifier under weak selection, indicating that selection for sex weakens as s and t become smaller, in contrast to the case of a primarily asexual population.

For intermediate levels of dominance, modifiers that increase the frequency of sex are able to invade as long as selection is weak enough (s and t small enough). We define the dominance coefficient of the modifier, h_M, as $(\sigma_2 - \sigma_1) = h_M(\sigma_3 - \sigma_1)$; h_M ranges from zero for a fully recessive modifier to one for a dominant modifier. To obtain the boundary between the region where the modifier allele would spread and where it would disappear, we used Equation 14 to solve $\lambda = 1$ for s, yielding

$$s_{(\lambda=1)} = \frac{1}{2} + \frac{\sqrt{4(1 - h_M)^2 f^2 t(1 - t) + (f - h_M(f + t + ft))^2} - th_M(1 + f)}{2(1 - h_M)f}. \qquad (15)$$

In a population that is nearly fully sexual, increased sex is favored below the value of s given by (15). Figure 1 illustrates this condition for an additive modifier ($h_M = \frac{1}{2}$) when $f = 0.05$ (Figure 1A) and when $f = 0.25$ (Figure 1B). The figures illustrate our main result: sex with some degree of selfing tends to be favored when there is weak selection against one or both of the homozygotes. We can also see that increasing the selfing rate increases the range of selection coefficients at which increased sex is favored. However, increasing f also diminishes the range of selection coefficients that sustain a biologically reasonable polymorphism, as demonstrated by the expansion of the shaded regions.

General results: Although it is not possible to describe the boundary between when sex is and is not favored for an arbitrary initial frequency of sex (σ_1), we can determine the approximate position of the boundary by focusing on the points, α and β, depicted in Figure 1. α represents the point along the $s = t$ line where the eigenvalue equals one, and β represents the point along the $Fs = t$ line (or the $Ft = s$ line) where the eigenvalue equals one. In other words, α defines the maximum selection coefficient value with fully symmetric overdominance under which increased sex is favored, while β defines the maximum selection coefficient value under asymmetric overdominance under which increased sex is favored. Therefore, larger α or β values would lead to a greater range of selection coefficients favoring increased sex.

The cutoff value of α for which increased sex is favored is

$$s_\alpha = t_\alpha = \frac{2\sigma_1(1 - h_M)f(f(1 - f) + h_M(1 + f^2))}{(2f + h_M(1 - f))(h_M(1 + f) + \sigma_1(1 - h_M)f(1 - f))}, \qquad (16)$$

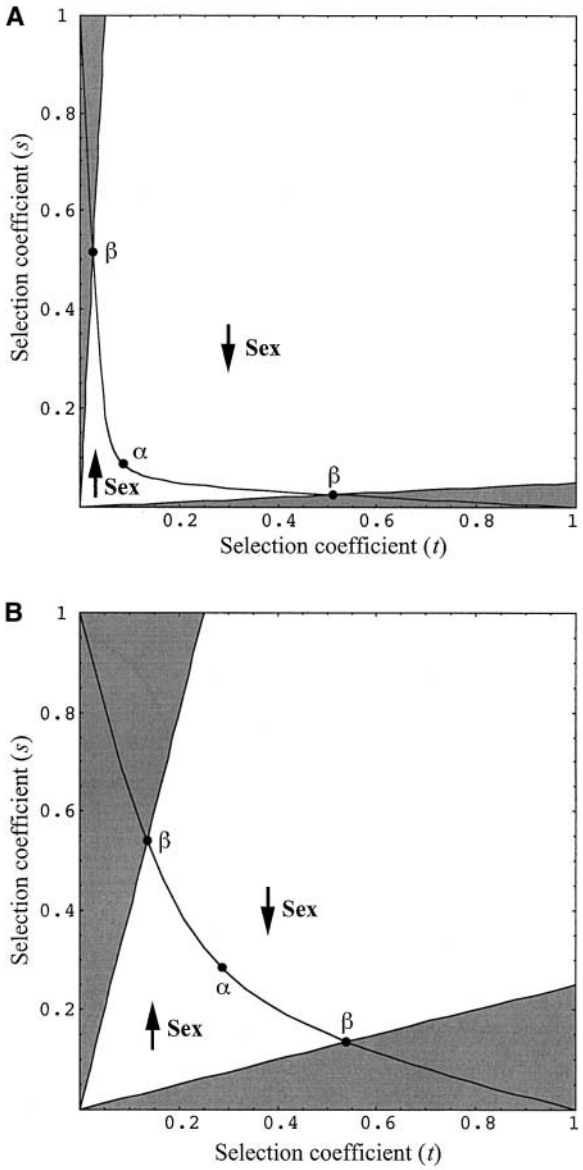

FIGURE 1.—Conditions under which an additive modifier that changes the frequency of sex spreads within a population that is nearly fully sexual. The shaded regions define combinations of s and t values that do not support a biologically reasonable polymorphism. Using Equation 14, the curve in A delimits the parameter space in which sex is favored when $f = 0.05$, and B illustrates the case with $f = 0.25$. These curves were confirmed by an exact numerical analysis of the eigenvalues for every combination of s and t between 0 and 1 in 0.01 increments (using $\sigma_1 = 0.99$, $\sigma_2 = 0.9925$, $\sigma_3 = 0.995$); virtually identical curves were obtained. Point α is the value along the $s = t$ line where the eigenvalue equals one, indicating the cutoff under symmetric overdominance between where increased sex is favored and disfavored. β is the point along the $Fs = t$ line or along the $Ft = s$ line where the eigenvalue equals one, indicating the maximum selection coefficient value under asymmetric overdominance for which increased sex is favored.

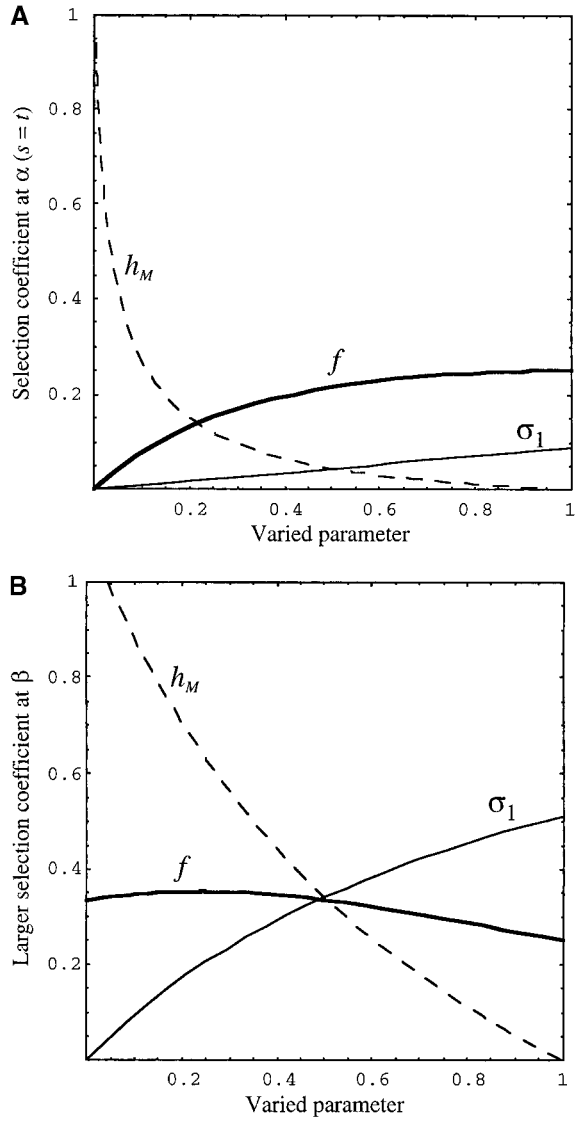

FIGURE 2.—The effect of varying the initial degree of sex, the amount of inbreeding, and the dominance of the modifier on the boundary between when sex is and is not favored at points α and β (see Figure 1). A shows how α changes and B shows how the larger selection coefficient at β changes. The x-axis is the varied parameter: the current level of sex (σ_1) for the thin curve, the level of selfing (f) for the bold curve, and the dominance level of the modifier (h_M) for the dashed curve. The parameters that are not changing are under standard conditions of $\sigma_1 = 0.5$, $f = 0.05$, with an additive modifier of $\sigma_2 = \sigma_1 + 0.005$ and $\sigma_3 = \sigma_1 + 0.01$.

which was determined by solving for $\lambda = 1$ when $s = t$. Note that (16) goes to 0 as σ_1 goes to 0, which confirms the previous finding that sex is not favored in a fully asexual population in this model. Figure 2A shows how the cutoff, α, changes when we let one parameter, σ_1, f, or the dominance coefficient of the modifier, h_M, vary when the remaining parameters are held at arbitrary standard conditions. Here we define the standard conditions as $\sigma_1 = 0.5$, $f = 0.05$, with an additive modifier of $\sigma_2 = \sigma_1 + 0.005$ and $\sigma_3 = \sigma_1 + 0.01$. As σ_1 increases, α marginally increases (Figure 2A, thin curve). Therefore, for increased sex to be favored, selection against the homozygotes can be slightly stronger the greater the initial level of sex. Increasing f causes α to increase more

substantially (Figure 2A, thick curve). This implies that increased levels of selfing increase the range of selection coefficients that promote sex. We can see that a fully recessive modifier can always invade since the cutoff value, (16), equals one when $h_M = 0$, but that as h_M increases, α decreases rapidly such that a fully dominant modifier can never invade (Figure 2A, dashed curve). By definition, at the cutoff value, β, the inbreeding coefficient, F, equals either s/t or t/s. Here we deal with the case when $F = s/t$ although the s and t values can be reversed to find the complementary β point. We solve for when the eigenvalue equals one with $F = s/t$ and use the equilibrium F value (8), which must also hold true to solve for s and t, such that at β,

$$s_\beta = \frac{\sigma_1(1 - h_M)f(1 + f)}{1 + h_M f + f^2(1 - h_M)}$$

$$t_\beta = \frac{\sigma_1(1 - h_M)(1 + f)((1 - f) + 2h_M f)}{(\sigma_1(1 - h_M)(1 - f^2) + (1 + f)h_M - (1 - h_M)f(1 - f))(1 + h_M f + f^2(1 - h_M))}. \quad (17)$$

Figure 2B shows how the larger selection coefficient value at β (t_β in Equations 17) changes when we let one parameter vary at a time from the standard conditions. As σ_1 increases, t_β increases (Figure 2B, thin curve). Thus, a modifier for increased sex can invade a population with stronger asymmetric selection against the homozygotes with greater initial levels of sex. As f increases, t_β initially increases slightly and then decreases (Figure 2B, thick curve). This trend is due to the fact that at larger f values, the range of selection coefficients that support a polymorphism diminishes, effectively reducing the t_β value. While the cutoff curve that defines where increased levels of sex are favored is moving away from the origin, the curve that defines selection coefficients supporting a biologically reasonable polymorphism is increasing at a faster rate, and thus t_β is observed to decrease at large f values while s_β continues to increase. As the modifier becomes more dominant, t_β decreases (Figure 2B, dashed curve), indicating again that recessive modifiers that increase the frequency of sex are most likely to spread.

Taking into account points α and β, we can see that sex is most likely to be favored when selection against the homozygotes is weak such that the segregation load is low. Furthermore, the conditions favoring increased sex become less restrictive when the modifier is more recessive, when the initial amount of sex is greater, and when the selfing rate is higher, as long as a polymorphism can be maintained. Indeed, it is possible to show that, as long as there is some amount of sex within the population, a fully recessive modifier that increases the frequency of sex will always spread ($\lambda \geq 1$, with equality holding when $s = t = 1$ or $f = 1$). In contrast, a fully dominant modifier can never invade ($\lambda < 1$). The proof involves showing that the boundary curve does not lie within the region where $0 < s, t < 1$ for selection coefficients that support a polymorphism. Uyenoyama and Waller (1991) studied a model for the evolution of outcrossing *vs.* inbreeding under overdominant viability selection and similarly concluded that conditions of full dominance of the modifier locus are least conducive to the evolution of increased outcrossing.

Incorporating a cost of sex: A cost of sex was added to the model by reducing the reproductive output resulting from sex by $(1 - \delta)$, where δ would be $\frac{1}{2}$ in the classic case of a twofold cost of sex (see details in Otto 2003, this issue). For a new modifier allele that increases the frequency of sex to spread, a local stability analysis indicates that $\Psi + \Phi$ must be positive, where Ψ represents selection acting directly against the modifier as a result of the cost of sex and Φ represents selection acting indirectly as a result of the modifier's effects on segregation at overdominant polymorphisms throughout the genome. As in Otto (2003), Ψ equals

$$\Psi = \frac{-\delta((1 - f)\Delta\sigma_2 + f\Delta\sigma_3)}{1 - \delta\sigma_1}. \quad (18)$$

Note that Ψ equals the difference in the cost of sex paid by the new and old modifier alleles; thus, it is small for weak modifiers that only slightly change the frequency of sex. The amount of indirect selection acting on the modifier as a result of one overdominant locus is defined as $\phi = \lambda - 1 - \Psi$. Focusing on the case of weak selection [s and t are $O(\varepsilon)$, where ε is small],

$$\phi = \frac{(\Delta\sigma_3 - \Delta\sigma_2)(t - fs)(s - ft)\, f(1 + \delta)}{\sigma_1(1 - f)(s + t)(1 - \delta)} + O(\varepsilon^2\Delta\sigma, \Delta\sigma^2). \quad (19)$$

If sex is infrequent and the modifier is weak and almost completely recessive, even a single overdominant locus can generate enough selection to favor the evolution of sex in the face of a twofold cost of sex (verified by a numerical analysis of the eigenvalues).

For most parameter combinations, however, the modifier is selected against when there is only one overdominant locus and a substantial cost of sex. The indirect effects of selection rise, however, with the number of loci, L, subject to overdominant selection, while the direct cost of sex remains constant. Assuming linkage equilibrium among selected loci (so that $\Phi \approx L\phi$) and ignoring variation in the parameters among loci, the number of overdominant loci required to pay for a cost of sex is

$$L > \frac{\sigma_1(1 - f)(s + t)(1 - \delta)\delta((1 - f)h_M + f)}{(1 - h_M)(t - fs)(s - ft)f(1 + \delta)(1 - \delta\sigma_1)}. \quad (20)$$

If, for example, $f = 0.05$ and $s = t$ in a population that reproduces sexually and asexually in approximately equal amounts ($\sigma_1 = \frac{1}{2}$), a twofold cost of sex ($\delta = \frac{1}{2}$) can be paid by the indirect effects of a modifier on overdominant polymorphisms at, roughly, $0.23/t$ loci for a recessive modifier or $4.91/t$ loci for an additive modifier. Although sensitive to the degree of dominance of the modifier, (20) is insensitive to the strength of the modifier (confirmed by numerical analysis). It

should be remembered, however, that these calculations assume that selection is weak enough (s and t small enough) that sex is favored in the absence of a cost of sex (see Figures 1 and 2).

DISCUSSION

Sexual reproduction involves segregation of alleles at diploid loci, allowing the formation of offspring genotypes that differ from parental genotypes, whereas asexual reproduction produces offspring with conserved parental genotypes. This creates differences in fitness that are the basis of indirect selection on the mode of reproduction that is tracked in our modifier model. With overdominance in viability, the heterozygote genotype has the highest fitness. A fully outcrossing heterozygous individual will produce half homozygous offspring, who are less fit than the parental genotype, whereas asexually produced offspring will retain the fittest heterozygous genotype. Due to this segregation load, it was expected that selection would always favor the evolution of asexuality rather than of sexuality. We found, however, that increased sex can be favored under biologically reasonable parameters (weak selection and some degree of inbreeding) due to genetic associations that arise between the modifier and fitness loci.

In inbreeding populations, genetic associations develop between genotypes at different loci (Haldane 1949; Bennett and Binet 1956; Weir and Cockerham 1973). Double heterozygotes and double homozygotes become more common and single heterozygotes less common than expected from the product of respective genotypic frequencies (Holsinger 1988). This is because homozygotes at one locus are more likely than expected to be derived from inbreeding at random. Such individuals are more likely to be homozygous at other loci as well. This tendency of homozygosity to arise at multiple loci more often than expected from one-locus genotypic frequencies is known as the Bennett-Binet effect (Bennett and Binet 1956), and the departure of two-locus genotypic frequencies from the product of one-locus genotypic frequencies is known as identity disequilibrium (Hartl and Clark 1989). With respect to our model, the presence of inbreeding generates positive identity disequilibria, which implies that if an individual is homozygous at the modifier locus, it is more likely to be homozygous at fitness loci. A recessive modifier increases the frequency of sex only in individuals that are homozygous at the modifier locus. Under inbreeding, these individuals are also more likely to be homozygous at the fitness locus, and because selection always favors sex in homozygotes at the fitness locus, the spread of recessive modifiers is promoted. Conversely, a dominant modifier for increased sex acts fully in individuals that are heterozygous at the modifier locus and thus also tends to disrupt the advantageous heterozygous genotype at fitness loci, which are found to be associated with the heterozygous modifier more often than expected at random. As a result, a fully dominant modifier is selected against and can never invade. For modifiers of intermediate dominance ($0 < h_M < 1$), identity disequilibria within inbred populations continue to favor the evolution of sex as long as selection at the fitness locus, and hence the segregation load, is sufficiently weak (see Figure 2). Following this logic, the modifier that would be most strongly favored in the presence of overdominant viability selection would be one that was underdominant at the modifier locus, thereby decreasing sex in the double heterozygotes and increasing sex in the double homozygotes.

Counterintuitively, sex is more often favored when sex is least likely to produce the fittest genotypes (the heterozygotes), that is, when inbreeding is stronger (higher f; assuming a polymorphism is maintained). This surprising result is due to the fact that inbreeding facilitates the production of identity disequilibrium between the modifier and fitness loci. Higher selfing rates make it more likely that modifier alleles that act more strongly in homozygotes at the modifier locus will also tend to act more strongly in homozygotes at the fitness loci, among which sex is always favored with overdominant selection.

In our model, inbreeding was included in the form of gametophytic selfing. Other forms of inbreeding, such as sporophytic selfing (*i.e.*, mating among gametes produced by a diploid individual), mating among relatives, or spatial population structure, should also lead to an overabundance of double homozygotes and double heterozygotes. On the other hand, these other forms of inbreeding are less effective at generating identity disequilibrium, which drives the evolution of sex in our model. Consider, for example, the case of sporophytic selfing, which has two major differences compared with gametophytic selfing. First of all, sporophytic selfing can produce single heterozygotes. Second, with recombination between the fitness and modifier loci, inbreeding in double heterozygotes can form every genotypic combination. We explored the effect of these differences in a modifier model in which gametophytic selfing was replaced with sporophytic selfing. Because sporophytic selfing generates weaker genotypic associations, sex is less often favored. Furthermore, the effect of the dominance of the modifier is diminished, such that a fully recessive modifier that increases reproductive allocation to sex is not always favored. In the case of absolute linkage ($r = 0$), sporophytic selfing produces 50% double homozygous offspring. Consistent with this, a graphical analysis showed that for a nearly fully sexual population under symmetric overdominance, sporophytic selfing requires double the selfing rate compared to gametophytic selfing to produce the same α value (see Figure 1). The greater the rate of recombination, r, between the modifier and fitness loci, however, the greater the sporophytic selfing rate that is required to achieve the same α value as gametophytic selfing because inbreeding is even less effective at creating double

homozygotes. Even if the two loci are unlinked ($r = \frac{1}{2}$), however, the identity disequilibrium is positive, indicating that the genotypic associations that allow the evolution of sex are still produced. Indeed, as long as selection against homozygotes is sufficiently weak, increased levels of sex are again favored in the presence of sporophytic selfing. We conjecture that this result would continue to hold with overdominant selection regardless of the form of inbreeding.

This article is the first to track evolutionary changes at genetic loci controlling the rate of sexual reproduction under overdominant selection and thus fills an important gap in the literature. As expected, when inbreeding is absent, increased asexuality is always favored. Our results are thus consistent with the "reduction principle," which states that in randomly mating populations at equilibrium in the absence of perturbational forces such as mutation, selection always favors perfect transmission, where offspring genotypes are identical to parental genotypes (Altenberg and Feldman 1987). However, when the assumption of random mating is violated, imperfect transmission can be favored. Indeed, we found that increased sex is favored when there is some degree of inbreeding and when selection is sufficiently weak. This result is similar to the finding that increased recombination rates can be favored within partially selfing populations (Charlesworth *et al.* 1979; Holsinger and Feldman 1983).

Recently, Peck and Waxman (2000) showed that under overdominant selection sexually produced offspring are, on average, less fit than asexually produced offspring. Furthermore, they noted that this mean difference in fitness intensifies as a population becomes more asexual. While most theoretical studies suggest that the greatest benefits of sex arise when only a small proportion of the population reproduces sexually (see reviews by Green and Noakes 1995; Hurst and Peck 1996), Peck and Waxman argue that populations with low levels of sex may not be evolutionarily stable due to the comparatively low fitness of sexually produced offspring at overdominant loci. Conversely, they argued that high levels of sex may be evolutionarily favored because the difference between the mean fitness of sexually and asexually produced offspring at overdominant loci diminishes as the population becomes more sexual. In their mean fitness analysis, which assumed no inbreeding, overdominant selection never directly favored sex, and their argument relied on the presence of other benefits of sex. In contrast, our results indicate that overdominant selection alone can drive the evolution of increased levels of sex in the presence of inbreeding. Our results are consistent with the arguments of Peck and Waxman (2000), however, in that we found that the more common sex is within a population, the broader the range of conditions under which more sex is favored (Figure 2), in contrast to most previous models of the evolution of sex. Even though the parameter range favoring the spread of sexual modifiers is largest when sex is common, the strength of the force favoring the modifier tends to be greater when sex is rare. As long as selection is weak enough, modifiers that increase the frequency of sex have a larger eigenvalue when sex is rare than when sex is common (see Equation 19). Consequently, when a cost of sex is added to the model, fewer overdominant loci are required to compensate for the cost of sex and to allow the spread of modifier alleles that increase sex when sex is rare than when sex is common. In more asexual populations, the genetic associations that drive the spread of the modifier tend to rise to higher levels and exert more of an influence on the modifier. Our results indicate that, for weak selection, these genetic associations play a more important role in the evolution of sex than do the immediate effects of sex on the mean fitness of offspring.

Of course, the relevance of this model to the evolution of sex depends on the extent to which there is overdominant selection in natural populations, which has been a matter of long-standing debate (Charlesworth and Charlesworth 1987). Some early estimates of dominance coefficients from *Drosophila melanogaster* indicated that mutations were, on average, overdominant (Wallace 1957; Mukai *et al.* 1964; Mukai 1969). Attention later turned away from overdominance and toward mutation-selection balance as a source of fitness variation, partly as a result of studies on inbreeding depression. Inbreeding depression can be caused by production of less fit homozygotes at loci subject to overdominant selection and/or by the production of homozygous mutants at loci segregating for partially recessive deleterious mutations. The two sources of inbreeding depression can be disentangled by several techniques (Charlesworth and Charlesworth 1987). For example, if two inbred lines are crossed, information concerning the average dominance coefficient can be obtained from an analysis of variation among F_2 individuals. Such studies in maize have failed to support overdominance as the major determinant of inbreeding depression (Charlesworth and Charlesworth 1987). Similarly, because overdominance fails to maintain polymorphisms in populations that have been highly selfing for long periods of time (see Equation 7), the existence of high levels of inbreeding depression in predominantly selfing species has been taken as evidence for partially recessive mutations (Charlesworth *et al.* 1994). These studies show that overdominant selection is typically not the main source of inbreeding depression (see also Deng *et al.* 1998; Roff 2002), but they do not show that overdominant selection does not contribute to inbreeding depression and fitness variation *alongside* partially recessive mutations. Indeed, recent analyses suggest that deleterious mutations alone appear incapable of explaining the high levels of fitness variation and inbreeding depression observed in *D. melanogaster* and that some form of balancing selection, such as overdominance, must also act (Charlesworth and Charlesworth 1999). To resolve this issue fully requires the careful

analysis of dominance coefficients of individual mutations. A recent study of EMS-induced mutations in *Caenorhabditis elegans* suggests that ~10% of mutations that are deleterious when homozygous are beneficial in heterozygotes (Peters *et al.* 2003). Taking into account the fact that such mutations are expected to remain polymorphic within a population for much longer periods of time than unconditionally deleterious mutations, this study implies that a large fraction of segregating alleles affecting fitness might experience overdominant selection. Further research is necessary to obtain more quantitative estimates of the relative importance of overdominant selection and directional selection, as it is fairly clear that both factors contribute to fitness variation.

Our results demonstrate that overdominant selection is most likely to favor the spread of a modifier that increases sex when selection against homozygotes is weak (Figures 1 and 2). Although the best-known cases of overdominant selection (for example, involving sickle cell anemia and thalassemia in humans) involve strong selection against homozygotes, this undoubtedly reflects a detection bias against overdominant loci under weak selection. Indeed, the classic study of Mukai (1964) found the average reduction in fitness of homozygous mutants under purifying selection in *D. melanogaster* to be 0.03 or less. More recently, Keightley (1994) reported a maximum estimate of mean mutant effect on viablility of 0.004–0.01, with the majority of mutations having much smaller effects on fitness. While these studies do not pertain specifically to overdominant selection or to a species with a mixed-mating strategy, it seems likely that the majority of overdominant loci also have very weak selection. In fact, the segregation load would be intolerably large if selection were strong at several overdominant loci throughout the genome. Therefore, with inbreeding, overdominant loci may often satisfy the conditions necessary for the evolution of increased sex (selection weaker than Equations 15–17).

We now consider the long-term evolutionary consequences of overdominant selection. In our model, we assumed a fixed level of dominance of the new modifier allele. However, it is likely that the dominance of the modifier varies as different alleles arise that modify the frequency of sex. Let us first assume that the dominance coefficient, h_M, is fixed and that modifiers are weak. If a population is in a state where increased sex is favored and a modifier allele that increases the frequency of sex invades, then the range of selection coefficients for which further sex is favored becomes greater. Assuming that the selection coefficients and selfing rate do not change, then the population remains in a state favoring increased levels of sex, and the population eventually becomes fully sexual. The same argument can be made for a population that is in a state favoring decreased levels of sex, and selection should act to make this population fully asexual. If the population is in a state with partial sexuality at which the leading eigenvalue equals one, any slight perturbation in the selection pressure against the homozygotes or a small change in any of the parameters (including h_M of the modifier) would shift the system into a region favoring either increased or decreased sex and the population progresses to full sexuality or asexuality, respectively. This assumes, however, that there is no cost of sex. Because the strength of indirect selection on a modifier tends to be stronger when sex is rare (Equation 19), increased sex can be favored as long as the number of loci subject to overdominant selection satisfies (20), until the level of sex is reached at which the cost of sex overwhelms the benefits of segregation, and (20) no longer holds. Thus, a mixed sexual-asexual mating system would be expected in the presence of a cost of sex, assuming weak modifiers with a fixed dominance coefficient.

Let us now consider varying dominance to determine whether there is a level of sex that is resistant to invasion by any modifier allele altering the frequency of sex. This level of sex denotes the evolutionary stable state (ESS; Maynard Smith 1982). If a population were ever fully asexual, our model indicates that a modifier promoting sex can never invade (12). That is, a fully asexual population is an ESS under overdominant selection. In contrast, if a population were ever fully sexual, then it would be prone to invasion by a modifier that is sufficiently dominant (Equation 14 without a cost of sex and Equation 20 with a cost of sex) or sufficiently strong (causing a nearly complete loss of sex; $\sigma_3 < 1 - \overline{W}$). Thus, such a fully sexual population is not an ESS, although it may take a long time before a modifier arises that can invade. For populations with intermediate levels of sex (specifically, for σ_1 low enough that 20 is satisfied when $h_M = 0$), modifiers can invade that either increase the frequency of sex (for h_M small enough) or decrease the frequency of sex (for h_M large enough or σ_3 small enough), suggesting that the level of sex would fluctuate over evolutionary time, depending on the recent history of the modifier alleles.

Because inbreeding is a requirement to promote increased levels of sex in our model, combining this study with research on the evolution of inbreeding is necessary to form a complete theoretical framework of mating-system evolution under overdominant selection. Over long periods of evolutionary time, modifier alleles that alter the selfing rate, f, as well as modifiers that alter the level of sex, σ, would arise, and the fate of each would depend on the current mating system. A model of the evolution of selfing rates in fully sexual populations was analyzed by Uyenoyama and Waller (1991), who found that overdominance can lead to the evolution of increased or decreased selfing rates depending on the degree of dominance of the modifier, the extent of pollen discounting, the strength of selection, and the rate of recombination (Uyenoyama and Waller 1991). Although asexuality was not included in their model, it is likely that the level of sex, σ, would also influence the evolution of the selfing rate, f. If increasing σ favors

increased f, the two types of modifiers would tend to act synergistically, with more sexual populations becoming more inbred, which tends to increase the selective force promoting the evolution of sex. Alternatively, the selfing rate may evolve to such a high level that overdominant selection would no longer sustain a polymorphism (Charlesworth and Charlesworth 1990). If increasing σ favors decreased f, however, the two types of modifiers would act antagonistically, with more sexual populations becoming less inbred, which would reduce the parameter range in which sex is favored. Therefore, if we consider the level of sex and the selfing rate to be coevolving with modifiers of varying dominance, there are three possible outcomes: (1) the fixation of asexuality; (2) the evolution of high rates of selfing, resulting in the loss of polymorphism at overdominant loci; or (3) a dynamic evolutionary state with intermediate levels of sex. We need to gather more empirical data on overdominant selection and to model explicitly the coevolution of sex and inbreeding to determine which outcome is most likely.

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