The Evolutionary Enigma of Sex

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ABSTRACT: Sexual reproduction entails a number of costs, and yet the majority of eukaryotes engage in sex, at least occasionally. In this article, I review early models to explain the evolution of sex and why they failed to do so. More recent efforts have attempted to account for the complexities of evolution in the real world, with selection that varies over time and space, with differences among individuals in the tendency to reproduce sexually, and with populations that are limited in size. These recent efforts have clarified the conditions that are most likely to explain why sex is so common, as exemplified by the articles in this symposium issue of the *American Naturalist*.

Introduction

Sexual reproduction is a costly endeavor. In order to outcross, an individual has to find a potential partner, attract it, risk contracting sexually transmitted diseases, hazard predation while mating (sometimes by the mate itself), and forego opportunities to gather resources. For many facultatively sexual species, there is an additional cost involved in switching from mitotic to meiotic reproduction. For example, in *Saccharomyces cerevisiae*, mitotic replication occurs in ~90 min, but the induction of meiosis takes days.

All of this effort would make sense if sex were a more efficient means of transmitting genes to future generations, but it is not. A sexual parent transmits only 50% of its genes to the next generation, compared with 100% for an asexual parent. Thus, unless sexuals produce twice as many offspring per individual, sexuality suffers from a transmission disadvantage, a problem so acute that it has been labeled *the* cost of sex (Bell 1982).

Last, but not least, sexual reproduction breaks apart favorable combinations of genes built by past selection. To hammer this point home, consider an analogy. Imagine entering a poker hall after a game has been played. If you were to offer the winners (holding, say, a 3♣, 4♣, 5♣, 6♣, 7♣ straight at one table, a three-queen hand Q♦, Q♡, Q♠, 2♡, 8♦ at another, etc.) the opportunity to keep their hands or to shuffle their cards with those of another, everybody would hold his or her cards. Winning hands—those that have "survived" previous rounds—have cards that work well with one another. Shuffling these cards together produces descendant hands with no guarantee of success (creating, e.g., a lousy hand of 3♣, 4♣, Q♠, 2♡, 8♦). In all card games of interest, it is not enough to know the suit and number of each card in isolation; rather, the interactions among cards are what determine whether the card is in a winning hand or a losing hand. Similarly, genes do not work in isolation; the interactions among an individual's genes in the context of its environment are what determines whether that individual will successfully survive to reproduce or fail. Sexually mixing one's genes with those of another destroys the network of alleles that worked well in the parent, creating a new network that may or may not function.

In the face of such legendary costs, we might expect sexual reproduction to be rare. Yet, the vast majority of eukaryotic organisms reproduce sexually—at least occasionally. Among named animal species, only ~0.1% are considered to be exclusively asexual (Vrijenhoek 1998). While the ability to reproduce asexually is more widespread in plants, less than 1% of the approximately 250,000 angiosperm species are thought to be substantially asexual (Asker and Jerling 1992; Whitton et al. 2008). Virtually all of these asexual taxa are at the tips of the tree of life. For example, asexuality in the seed plants is confined to single species or to closely related species complexes (with the possible exception of a very small and poorly studied genus *Houttuynia* in the Saururaceae). Nevertheless, a large fraction of plants are capable of vegetative reproduction (via rhizomes, runners, tubers, bulbils, etc.) and/or the production of asexual seed (apomixis). Similarly, the majority of protists and fungi can reproduce asexually by fissioning, budding, or spore production.

Given the costs of sex and the widespread potential for asexual reproduction, why do so many species reproduce sexually? This question has been called the paradox of sex. Most biologists would answer that sex and recombination have evolved because they generate variation needed by selection. Indeed, this is one of the oldest explanations for sex, attributed to August Weismann (1889, p. 279):

> Sexual reproduction can also increase the differences between

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> individuals …. Such differences afford the material by means of which natural selection is able to increase or weaken each character according to the needs of the species.

That sex evolved to generate variation may very well be correct, but there are two holes in the argument that make it a much less obvious answer than it would at first seem. Because these holes are not widely appreciated, even among evolutionary biologists, they deserve some attention.

I. *Sex Need Not Increase Variation.* The first hole in Weismann's argument is that sex and recombination do not always produce more variable offspring. This problem is most easily appreciated in the case of a single gene subject to selection (fig. 1). Here selection favors *AA* individuals in a population that is initially in Hardy-Weinberg proportions. After selection, there is an excess of homozygotes because of the high fitness of homozygotes relative to heterozygotes. If the population were to reproduce asexually (fig. 1, *left arrow*), this genetic association would be retained among the offspring, and there would be a great deal of variation, with many low-fitness *aa* homozygotes and high-fitness *AA* homozygotes. If the population were to reproduce sexually (fig. 1, *right arrow*), it would return to Hardy-Weinberg proportions, increasing the frequency of heterozygotes of intermediate fitness and reducing the variation present.

This example illustrates a more general point. Whether at one locus or many, when extreme genotypes (i.e., the

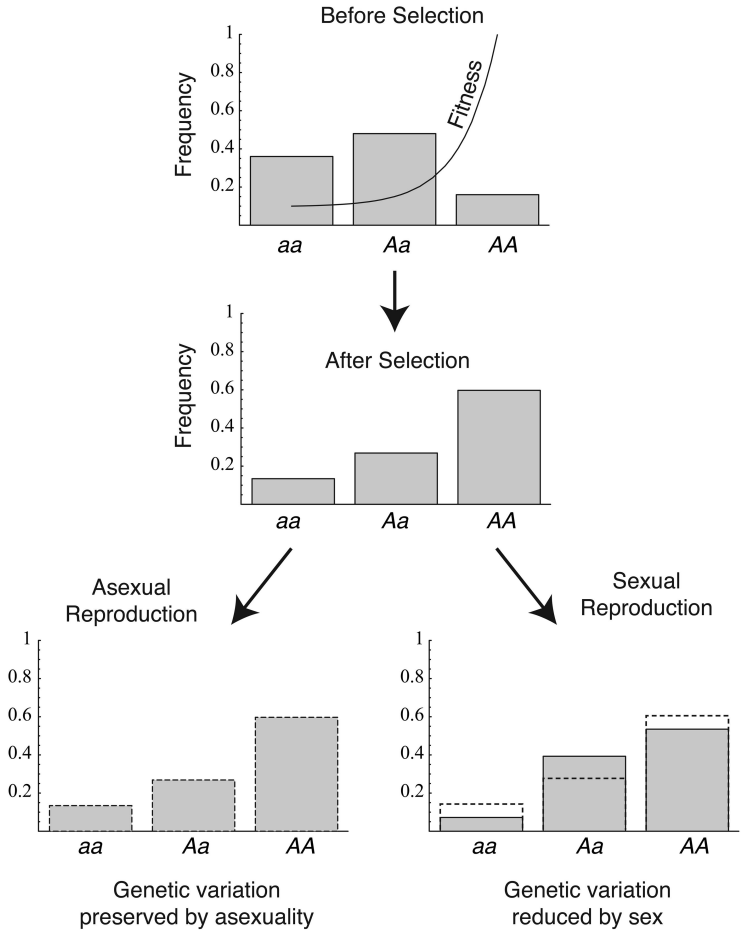

Figure 1: Variability built up by selection is decreased by sex. A population in Hardy-Weinberg proportions with a 40% frequency of allele *A* is subject to selection, with fitnesses given by the curve (*top*). Because the log-fitness surface is positively curved, the result of selection is a population with excess homozygosity and a greater degree of genetic variability than expected at Hardy-Weinberg (*middle*, *bottom*, *dashed lines*). Asexual reproduction in such a population preserves this variation (*bottom left*), but sexual reproduction with random mating brings the population back into Hardy-Weinberg proportions and reduces variation (*bottom right*). Specifically, the variance in number of *A* alleles is 0.517 after asexual reproduction but only 0.393 after sexual reproduction. This example illustrates the fact that sex does not always increase variation.

least fit and the most fit genotypes) have higher fitness, on average, than do intermediate genotypes, selection itself builds up genetic associations that enhance variation. At one locus, this genetic association is measured by Wright's F statistic, which is positive whenever homozygotes are more common than Hardy-Weinberg expectations. Selection drives F to become positive (excess homozygosity) when the fittest allele is partially recessive (measured on a multiplicative scale, such that the genotypic fitnesses obey $\ln(W_{Aa}) < (\ln(W_{AA}) + \ln(W_{aa}))/2$; Chasnov 2000). Similarly, between two loci, genetic associations are measured by linkage disequilibrium, D, which is positive whenever the most fit (say, $++$) and least fit (say, $--$) haplotypes are more common than expected from their component allele frequencies. Selection drives D to become positive when epistasis is positive (measured on a multiplicative scale, such that $(\ln(W_{+-}) + \ln(W_{-+}))/2 < (\ln(W_{++}) + \ln(W_{--}))/2$; Eshel and Feldman 1970; Barton 1995*a*). In short, whenever the fitness surface exhibits positive curvature, positive associations build up among beneficial alleles so that there is more genotypic variation than one would expect from the allele frequencies. Sex, in this case, destroys these genetic associations, with segregation breaking down departures from Hardy-Weinberg (F) and recombination breaking down disequilibrium (D), creating offspring with more intermediate genotypes than had the parents reproduced asexually.

II. *Generating Variation through Sex Often Reduces Fitness.* Even when sex does act to increase variation, this variation need not be favorable. Again, the easiest case to visualize is that of a single locus subject to selection, this time with heterozygous advantage (fig. 2). Now, the fitness surface is negatively curved (so much so that it is hump shaped), and after selection, there is an excess of heterozygotes ($F < 0$). If the population were to reproduce sexually (fig. 2, *right arrow*) rather than asexually (*left arrow*), it is true that the resulting offspring would be more variable, with more genotypic variation and more variance in fitness. But this variation does not help the process of natural selection. Instead, sex creates the very genotypes (more *AA* and *aa* individuals) that are selected against.

Again, this simple example illustrates a more general point. Sexual reproduction might produce more variable offspring, but this does not necessarily increase average fitness. Indeed, by breaking down the genetic combinations built by past selection, sex almost always creates offspring of lower average fitness than asexual reproduction. The reduction in offspring fitness caused by sex is known as the "segregation load" or the "recombination load," depending on whether associations within or between loci are broken down. When genetic associations have been built by past selection, breaking down these associations causes an immediate fitness improvement in only a narrow sliver of parameter space involving dominance (Otto 2003) or epistasis (Barton 1995*a*), where the fitness surface is negatively curved on a multiplicative scale (causing $F < 0$ or $D < 0$) but positively curved on an additive scale (so that fitness would be increased if $F > 0$ or $D > 0$).

As a concrete example, for sexually produced offspring to have an average fitness higher than that of asexually produced offspring at a locus with fitnesses $W_{AA} = 1$, $W_{Aa} = 1 - hs$, and $W_{aa} = 1 - s$, dominance must satisfy

$$\frac{1}{2} < h < \frac{1 - \sqrt{1 - s}}{s} \tag{1}$$

(e.g., $0.5 < h < 0.513$ when $s = 0.1$). Within these limits, selection causes heterozygotes to become more common than expected on the basis of Hardy-Weinberg proportions ($F < 0$), but heterozygotes actually have a lower fitness than the average of the homozygotes' fitnesses. Below the lower limit, however, heterozygotes become more common than expected and are more fit than the average of the homozygotes, while above the upper limit, heterozygotes become less common than expected and are less fit; in either case, sex would reduce fitness by returning the population to Hardy-Weinberg proportions. Populations at equilibrium under heterozygote advantage (as in fig. 2) never satisfy condition (1), and segregation and recombination then cause a particularly acute reduction in fitness.

Early Models of the Evolution of Sex

In short, sex need not increase variability, and even when it does so, the variation generated by sex need not improve fitness. Given these problems, are there any types of fitness surfaces that do allow sex to evolve?

To address this question, a number of theoretical studies have investigated the evolutionary dynamics at genes that alter the amount of genetic mixing within a population, either by changing the relative allocation of resources to sexual and asexual reproduction or by altering the number and position of crossover events. Such genes are known as "modifier genes," in that they modify a characteristic of interest. That modifiers of genetic mixing exist is clear from studies demonstrating genetic variation in levels of recombination (e.g., Brooks 1988; Williams et al. 1995; Kong et al. 2002), sporulation and mating rates in fungi (e.g., Xu 2002; Zeyl et al. 2005; Gerke et al. 2006; Hill and Otto 2007), and the ability to produce asexual seed (see Whitton et al. 2008). Furthermore, genomic studies are producing more and more specific examples of loci that modify levels of mixing, including local hot spots of recombination (e.g., Winckler et al. 2005), modifiers of ge-

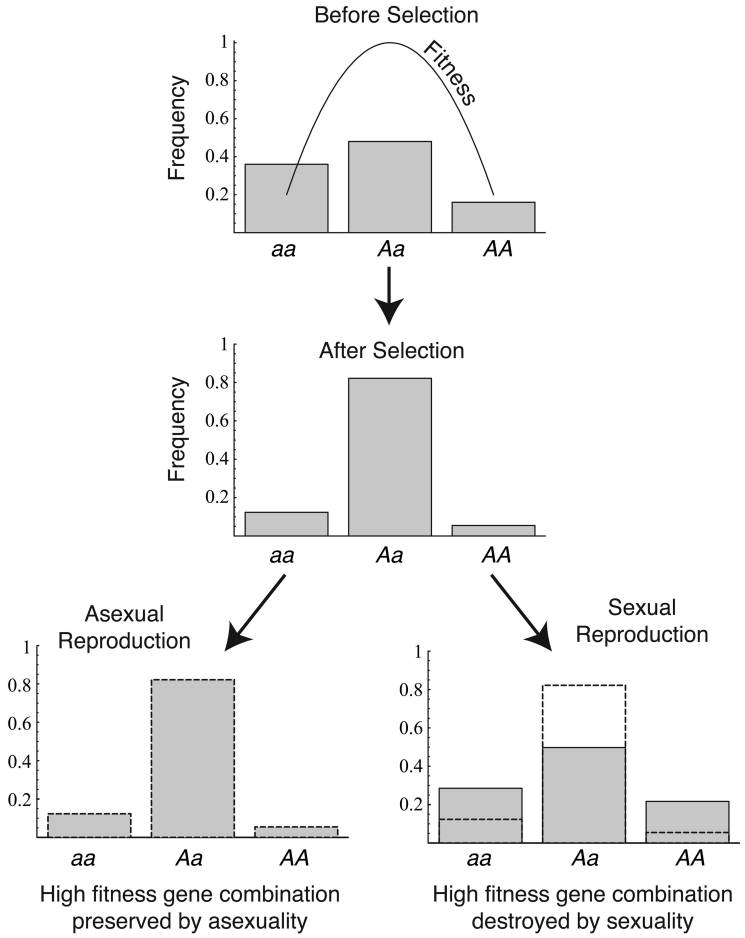

Figure 2: Variability when increased by sex need not be advantageous. A population in Hardy-Weinberg proportions with a 40% frequency of allele *A* is subject to selection, with fitnesses given by the curve (*top*). Because the log-fitness surface is negatively curved, the result of selection is a population with excess heterozygosity and less genetic variability than expected at Hardy-Weinberg (*middle*; *bottom*, *dashed lines*). While asexual reproduction preserves this genetic association, sexual reproduction brings the population back into Hardy-Weinberg proportions and reintroduces the genetic variation hidden in the heterozygotes (*bottom right*). This variation, however, destroys the fittest gene combination (*Aa*) and reduces mean fitness.

nomewide rates of recombination (e.g., Ji et al. 1999; Kong et al. 2008), and genes controlling meiosis (Ravi et al. 2008).

Theoretical models examining the dynamics of modifier genes were first discussed by Kimura (1956) and Nei (1967). In general terms, modifier models consider the fate of any mutant modifier allele within any possible resident population, for example, the fate of an allele changing recombination from r_1 to r_2. As a special case, such modifier models can also be used to describe the evolution of two separate groups of individuals that never mix genetically, as long as one of the modifier alleles completely suppresses recombination or avoids sex (as discussed in Felsenstein and Yokoyama 1976). This is an important special case because increasing variation is often thought to provide a group-level advantage favoring sexual populations over asexual populations. Thus, modifier models can be used to see when this group advantage favors sex and recombination and whether this advantage persists even when the groups recombine with one another and are not genetically isolated.

What did the first generation of modifier models find? In a nutshell, genetic mixing never evolved. Only modifiers that reduced the amount of recombination spread (Kimura 1956; Nei 1967; Feldman 1972; Feldman et al. 1983). These models considered populations at equilibrium under selection with various forms of heterozygote advantage, and they assumed that no other processes besides individual-level selection were acting (no mutation, no inbreeding, no sexual selection, no drift). While early models focused

on the fate of modifiers of recombination, similar results hold for modifiers of the amount of sex: lower levels of segregation evolve at an equilibrium with only selection present (Dolgin and Otto 2003). Why? At an equilibrium, there is no benefit to variation. Instead, it behooves the reproductive system to preserve whatever genetic combinations are most fit. Genetic mixing tends, on average, to produce less fit offspring, which die and take along with them the modifiers that promote recombination and segregation. The tendency for sex and recombination to decline at equilibria under selection became known as the "reduction principle" (Feldman et al. 1997).

This first generation of models exacerbated the paradox of sex by formally demonstrating that it is difficult for genetic mixing to evolve, even without costs. At the time, the most obvious resolution was that real populations are not at equilibrium. Perhaps the benefits of sex and recombination would become apparent only in models that considered nonequilibrium situations, with either environmental change or a steady influx of mutations providing an ongoing opportunity for natural selection to act.

The next generation of models considered evolving populations and met with greater success. In populations subject to directional selection, modifiers increasing levels of recombination could spread if fitness surfaces were negatively curved on a multiplicative scale (Charlesworth 1993; Barton 1995*a*). The same was found at mutation-selection balance (Feldman et al. 1980; Kondrashov 1984; Charlesworth 1990; Barton 1995*a*; Otto and Feldman 1997), where the negative fitness curvature among deleterious mutations was called synergistic epistasis. Again, similar results were found with modifiers of sex rather than modifiers of recombination (Otto 2003). The requirement for negatively curved fitness surfaces makes sense because selection then builds genetic associations where intermediate genotypes are more common than expected (Wright's $F < 0$ and $D < 0$). That is, such selection causes beneficial alleles to be hidden in genomes with deleterious alleles at other sites more often than would be expected by chance. Sex can then restore variation by breaking down these associations, thus improving the response to directional selection and facilitating the elimination of deleterious alleles.

But the success of these models was limited. The curvature of the fitness surfaces cannot be too negative or else the fitness load caused by segregation and recombination would be so severe that modifiers promoting genetic mixing decline in frequency at a faster rate than can be overcome by the benefits of enhanced variation (fig. 3). This particular limitation is not too severe in populations that are almost exclusively asexual because the modifier alleles that increase mixing remain associated with the novel combinations that they produce for many

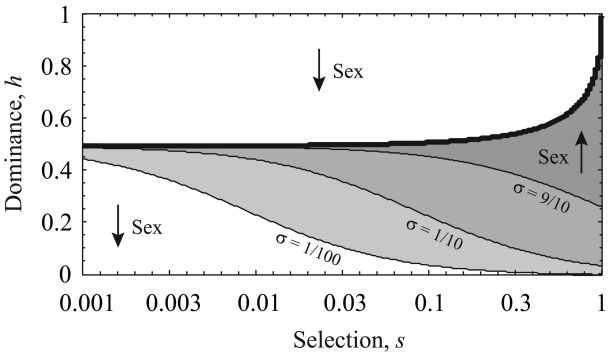

Figure 3: Fitness surfaces must be negatively curved but only moderately so for sex to evolve. With selection acting on a diploid gene, modifiers that increase the allocation to sexual reproduction are favored in the gray regions because of the benefits of segregation (using eq. [11] of Otto 2003). The fitness surface is negatively curved on a multiplicative scale below the thick curve (where $1 - hs$ equals $(1 - s)^{1/2}$). Dominance must lie below this curve and above the lower curves for increased sex to be favored (lower curves are illustrated for different levels of sex, σ). Equivalent results are found with mutation-selection balance or directional selection (Otto 2003) and with epistasis between two haploid loci (see fig. 1 in Otto and Gerstein 2006). The modifier increases sex by a small amount and is unlinked to the selected locus. Mating, when sexual, is random.

generations. But in populations that have high levels of genetic mixing, only negatively and modestly curved fitness surfaces allow sex and recombination to evolve to and be maintained at appreciable levels. For example, when sexual reproduction is prevalent within a diploid population, modifiers that maintain or increase the frequency of sex are favored over modifiers that lower the frequency of sex only when dominance obeys

$$\frac{2}{4 + 3s} < h < \frac{1 - \sqrt{1 - s}}{s} \tag{2}$$

(e.g., $0.46 < h < 0.513$ when $s = 0.1$; from eq. [11] in Otto 2003). Similarly, modifiers maintaining high frequencies of recombination between two selected loci in a haploid population are favored only when epistasis, ε, obeys

$$-\frac{s^2(3 - s)}{1 - s} < \varepsilon < 0 \tag{3}$$

(e.g., $-0.03 < \varepsilon < 0$ when $s = 0.1$, where fitness is defined as $W_{++} = 1$, $W_{+-} = W_{-+} = 1 - s$, and $W_{--} = (1 - s)^2 + \varepsilon$; from eq. [3] in Otto and Feldman 1997). Thus, epistasis must be negative ($\varepsilon < 0$) and not very strong. Even without accounting for costs of sex, these ranges are a slim fraction of the parameter space, implying that directional selection and mutation-selection balance are un-

likely to account for the evolution of high rates of sex and recombination.

These models inspired a flurry of empirical studies attempting to estimate the curvature of the fitness surface. As discussed in recent reviews (Rice 2002; de Visser and Elena 2007; Kouyos et al. 2007*a*), the evidence is mixed, with some studies finding negative epistasis but other studies finding no epistasis or positive epistasis, on average. What these studies do find, however, is a great deal of variation in how genes interact, depending on the exact genes in question, including cases where alleles that are deleterious in some genetic backgrounds become beneficial in others (see fitness landscapes measured by de Visser et al. [2009], in this issue). This variability is not surprising, but it makes it harder for sex and recombination to evolve (Otto and Feldman 1997). Those gene pairs that exhibit positive fitness interactions select against sex and recombination, as do those gene pairs that exhibit strong negative fitness interactions (because of the substantial load imposed by genetic mixing). Thus, only when the majority of gene pairs exhibit negatively and moderately curved fitness interactions is sex favored. Essentially, to account for the evolution and maintenance of high levels of sex and recombination, the majority of dominance interactions must obey condition (2), and the majority of epistatic interactions must obey condition (3). Unfortunately, evidence is not consistent with a preponderance of negatively and moderately curved fitness interactions (Rice 2002; de Visser and Elena 2007; Kouyos et al. 2007*a*).

Recent Models of the Evolution of Sex

The above results left theoreticians in an uncomfortable place. While models had identified some conditions under which sex and recombination could evolve, these conditions were fiddly and not well supported by empirical evidence. Evolutionary theory seemed to be resting on a rather shaky foundation, where we could not even explain something as commonplace as sexual reproduction.

Yet it was also clear that the models were overly simplified. In the real world, selection varies over time and space, rates of sex vary, and populations are not infinitely large, as is assumed in all of the above models. As exemplified by the contributions to this issue of the *American Naturalist*, the past decade has seen a strong push to clarify how including greater realism impacts the conditions under which sex can evolve and be maintained. In this section, I provide an overview of these recent developments.

Selection Varies over Time. When the environment changes rapidly over time, genetic associations built up by past selection can become detrimental. In this case, rather than causing a load, segregation and recombination increase the fitness of offspring either immediately or in the near future (Salathé et al. 2009, in this issue). Using the poker analogy, if we change the rules of the game often enough, winners might well decide to shuffle their cards. Models allowing for fluctuating environments have found that sex can be favored but only if the fluctuations occur rapidly enough. In particular, for high rates of recombination to evolve in haploid models, epistasis must change sign on a timescale of two to five generations, although low levels of recombination are favored with slower cycles (Peters and Lively 1999; Gandon and Otto 2007).

A particularly likely mechanism inducing rapid oscillations in the fitness of gene combinations is interactions among antagonistic species, such as hosts and parasites (Jaenike 1978; Hamilton 1980; Lloyd 1980; Jokela et al. 2009, in this issue). This mechanism of fluctuating selection is known as the "Red Queen" hypothesis for the evolution of sex (Bell 1982) because species must continually evolve as fast as they can to remain in place with respect to other species, much like the Red Queen and Alice must run just to stay in place in Lewis Carroll's *Through the Looking Glass*.

One limitation of the Red Queen hypothesis is that for the sign of linkage disequilibria to cycle rapidly in haploid models, selection must be quite strong (May and Anderson 1983; Howard and Lively 1994; Otto and Nuismer 2004). Selection does not necessarily have to be strong in both species, however; strong selection in the parasites and moderately weak selection in the host can generate rapid cycles that favor the evolution of sex (Salathé et al. 2008). That said, previous results have focused on cases where all loci contribute equally to the host-parasite interaction. In many cases, however, parasites have evolved mechanisms to express only one antigen locus at a time (Donelson 1995; Barbour and Restrepo 2000; Kusch and Schmidt 2001). If we assume that genes differ in their importance to the outcome of host-parasite interactions, with one gene as the main determinant of whether infection occurs (a major antigen locus, say, in a parasite) and a second locus as a minor determinant, then the Red Queen hypothesis again runs into difficulties (fig. 4).

A second limitation to the Red Queen hypothesis arises in diploid populations. In many models of host-parasite interactions, heterozygous individuals have either universally high fitness (e.g., heterozygous hosts can recognize multiple types of parasites) or universally low fitness (e.g., heterozygous parasites are more readily detected by hosts), and the form of selection does not cycle over time (with respect to whether selection generates $F > 0$ or $F < 0$). Because genetic associations built up by past selection never become detrimental, segregation gains no short-term benefit from breaking them apart (Agrawal and Otto 2006). Higher levels of segregation might still evolve if segregation increases variation and improves the response to selection

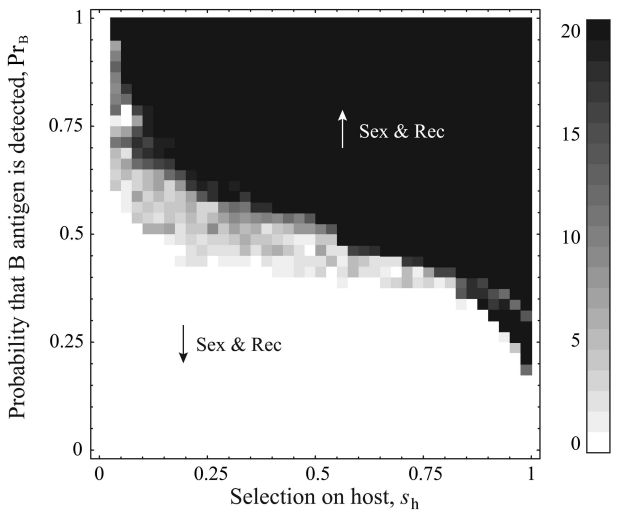

Figure 4: Haploid model of host-parasite interactions with differences in selection among loci. Following the notation of Salathé et al. (2008), we assume that infection is required for parasite survival (maximally strong selection: $s_p = 1$), while infected hosts suffer a fitness reduction of s_h (*X*-axis). Locus A is the major antigen locus of the parasite, which must match locus A in the host for infection to occur. Locus B in the parasite has a secondary effect; if there is a match at locus A but not at locus B, the host can detect and clear the parasite with probability Pr_B (*Y*-axis). Each locus has two alleles, with initial frequencies chosen at random and no initial disequilibria. Recursions were run for 1,000 generations before allowing the modifier to affect recombination. Each cell reports the number of replicates out of 20 in which a modifier increasing host recombination between loci A and B rose in frequency over the next 1,000 generations (recombination rate while in the transient diploid phase: $r_{mm} = 0.05$, $r_{Mm} = 0.075$, $r_{MM} = 0.1$; initial frequency of modifier allele $M = 0.5$). Like locus A, locus B must be a strong determinant of infection (Pr_B sufficiently high) for increased recombination to evolve. Other parameters: recombination between modifier and A locus in host = 0.075; recombination in parasite = 0.

(within the shaded regions of fig. 3), but this requires intermediate dominance, which is not typically observed in host-parasite interactions (Flor 1956; Burdon 1997; Crute et al. 1997; Li and Cowling 2003).

Thus, while genetic associations between loci may cycle (favoring increased recombination), genetic associations within loci tend not to cycle (favoring reduced segregation). Modifiers that increase the frequency of sex in diploid organisms affect the prevalence of both recombination and segregation, but simulations of the Red Queen with both processes have found that segregation dominates, favoring declines in the frequency of sex in many cases (Agrawal and Otto 2006).

Despite the above, the Red Queen can play an important role in the evolution of sex in two other contexts. The first is if individuals are exposed to parasites carried by their parents or other relatives. In this case, sex can readily evolve because families infected with parasites benefit from producing genetically diverse offspring who have some chance of resisting their relatives' diseases (Rice 1983; Agrawal 2006). This is a promising explanation for the empirical pattern that sexuality is more prevalent than asexuality in locations where parasites are common (reviewed in Neiman and Koskella 2009; Jokela et al. 2009). A second context in which the Red Queen might play an important role is as a source of ongoing selection in drift-based explanations for the evolution of sex (see below).

Selection Varies over Space. When selection varies over space, genetic associations created by migration can be locally detrimental. Breaking down these associations rather than causing a fitness load can increase the fitness of offspring and benefit modifiers that increase the frequency of sex and recombination. Consider two loci A and B that contribute to drought tolerance, where alleles A_1 and B_1 are more fit than alleles A_2 and B_2 in dry patches but the reverse holds in wet patches. Migration will tend to carry A_1B_1 and A_2B_2 chromosomes between these two patch types, generating positive linkage disequilibrium. If, however, individuals with intermediate degrees of drought tolerance (with A_1B_2 and A_2B_1 chromosomes) have reasonably high fitness (i.e., there is negative epistasis), then modifiers increasing recombination will produce fitter offspring, on average, selecting for high rates of recombination (Pylkov et al. 1998; Lenormand and Otto 2000). A similar mechanism acts on within-locus associations (see Agrawal 2009, in this issue). Migration among heterogeneous patches often generates excess homozygosity, which benefits modifiers that increase the frequency of segregation via sex if heterozygotes have higher fitness, on average, than homozygotes. Thus, if locally beneficial alleles tend to be dominant, we would expect sex to evolve to break down associations created by migration. Qualitatively similar results are observed when excess homozygosity is produced by other mechanisms, such as selfing (Otto 2003; Agrawal 2009).

This mechanism, whereby sex is favored in a spatially heterogeneous environment, predicts that sex and recombination should immediately increase offspring fitness, so empirical measurements demonstrating that recombination and segregation loads can be reversed in natural populations would be extremely valuable (for an example, see Kelley et al. 1988). Whether migration creates the sorts of genetic associations that lead to a reversal of the load can be tested by comparing the fitness of offspring produced by crossing local and migrant individuals (see also Agrawal 2009). For sex to be explained by segregation breaking deleterious associations within loci, the average fitness of offspring from local × migrant crosses should be greater than that observed, on average, among local × local crosses and migrant × migrant crosses in the local en-

vironment. Here, because diploid individuals from each population are used as parents (local parents and migrant parents), recombination only shuffles alleles already present within each population, while segregation should have a stronger effect by mixing together alleles from the two populations. For sex to be explained by recombination breaking down deleterious associations among loci, a different design is needed; now, the average fitness of offspring from local × F_1 crosses should be greater than that observed, on average, among local × local crosses and local × migrant crosses. At loci where the locals carry allele *A* while the migrants carry allele *a*, the local × F_1 cross will generate half *AA* and half *Aa* offspring, and the same is true when averaging offspring across local × local crosses and local × migrant crosses. Thus, this second design controls the within-locus associations but allows recombination to act in the F_1 individuals to break down between-locus associations. Results from such experiments would clarify just how often selection varies over the spatial scale relevant to migration in a way that favors the evolution of sex.

Rates of Sex Vary among Individuals. Most models of the evolution of sex assume that individuals are equally likely to engage in sex, regardless of their condition in the current environment. Many organisms, however, are more likely to engage in sex when they are in poor condition (e.g., in yeast, *Chlamydomonas*, monogonont rotifers, *Daphnia*, aphids, and other cyclical parthenogens; see Hadany and Otto 2009, in this issue). Poor condition is most likely to be experienced at the end of the growing season, when resource competition is severe or when key nutrients, such as nitrogen, are lacking. More generally, poor condition will be experienced when an organism's genotype does not match the requirements of its current environment. Models that have investigated the evolution of condition-dependent sex have found it much easier for sex to evolve if individuals in worse condition allocate more resources to sexual reproduction than do individuals in good condition (Redfield 1988; Gessler and Xu 2000; Hadany and Beker 2003; Hadany and Otto 2007). Modifiers that cause individuals of low fitness to engage in sex are able to escape from genotypes that have little chance of long-term persistence; these modifiers effectively "abandon ship" when times are tough. Such modifiers also protect favorable gene combinations by promoting asexual reproduction in individuals with a high fitness in the current environment and so do not suffer as substantial a load. For both of these reasons, modifiers that increase the relative allocation to sexual reproduction when carried by low-fitness individuals are able to spread under a broad array of conditions, even when sex is costly (Hadany and Otto 2007).

While capable of explaining the evolution of sex in haploids or diploids, the abandon-ship mechanism is ineffective at selecting for recombination in diploid individuals (Agrawal et al. 2005). Even if a diploid individual is in poor condition, there is no cue to indicate whether recombination would improve the genetic background of a modifier. That is, there is no information available to a modifier allele to determine whether it is currently on the better or the worse of the two homologous chromosomes. Metaphorically, modifiers cannot assess whether recombination between homologous chromosomes allows them to abandon ship or causes them to jump onto a sinking ship.

As a mechanism accounting for the evolution of sex, the abandon-ship hypothesis predicts that stress should often induce sex, which is consistent with the pattern observed in many organisms that are facultatively sexual (see Hadany and Otto 2009). It further predicts that locally adapted individuals should allocate relatively more resources to growth or asexual reproduction, while locally maladapted individuals should invest more in sexual reproduction. This prediction can be tested in the lab or in the field by taking lines adapted to different conditions and comparing the relative allocation to sexual reproduction by using a reciprocal transplantation design.

Selection in Finite Populations. All of the models described above are deterministic, assuming infinitely large populations, which is clearly not realistic. There are two reasons for the preponderance of deterministic models of the evolution of sex. The first is that such models are mathematically more tractable because the full probability distribution of chromosome frequencies need not be tracked. The second is that evolutionary biologists perceive random genetic drift as a process that adds noise to evolutionary phenomena, not a process that qualitatively changes the expected outcome. A recent push to incorporate drift in models of the evolution of sex has demonstrated, however, that this perception is unwarranted; the conditions under which sex evolves are fundamentally different in finite populations.

Although the importance of drift to the question of sex may not be immediately obvious, many of the oldest arguments for the evolution of sex rely on the finiteness of population size. For example, Fisher (1930, p. 104) wrote that

> for, unless advantageous mutations occur so seldom that each has had time to become predominant before the next appears, they can only come to be simultaneously in the same gamete by means of recombination.

(See also Morgan 1913; Muller 1932.) The scenario envisioned by Fisher must have been of a finite population. In an infinite population, all possible combinations of mutations would arise instantaneously, so recombination

would not be necessary to bring together advantageous mutations. Similarly, Muller (1964) recognized that the best genotype could be lost by drift in finite populations; once lost, this genotype could be rapidly regenerated by recombining the remaining chromosomes in sexual populations, but an asexual population would have to await the right back mutations, leading to the decay of fitness in asexuals (Muller's ratchet). These arguments were originally envisioned as providing a group-level advantage to sexual populations over asexual populations, but they can also explain the evolution of higher rates of sex within a population by individual-level selection (Felsenstein 1974; Felsenstein and Yokoyama 1976). This is because modifier alleles that promote sexual reproduction in their carriers are more likely to bring together advantageous alleles currently carried by different individuals into the same offspring; such modifiers can then hitchhike up in frequency along with the favorable gene combinations that they produced.

It is not immediately obvious, however, why advantageous alleles should be carried by different individuals. When mutations first appear, they will often arise in different individuals, favoring sex and recombination, but they will also occasionally arise in the same individual, selecting against sex and recombination. Only with a model can the net effect be determined. Averaged over these possibilities, it has been shown that modifiers of sex and recombination are selectively favored (Otto and Barton 1997; Roze and Barton 2006). Intuitively, when beneficial mutations arise together, the resulting genetic variation is readily accessible to selection (e.g., involving $--$ and $++$ chromosome combinations); selection rapidly depletes this accessible variation by fixing the best combination. By contrast, when beneficial mutations arise in different individuals, the resulting genetic variation is somewhat hidden from selection by linkage to deleterious mutations (e.g., involving $+-$ and $-+$ chromosome combinations); selection then proceeds less rapidly, with these alternative chromosomes competing with one another. Thus, over a period of time, the genetic variation that persists tends to involve beneficial alleles hidden within deleterious genetic backgrounds. This process, whereby genetic associations that impede selection accumulate within finite populations, is known as the Hill-Robertson effect (Hill and Robertson 1966; Barton 1995*b*). Another way to view this process is that the population size is effectively limited to the subset of chromosomes that have reasonably high fitness (Hill and Robertson 1966; Rice 2002). This bottleneck reduces the efficacy of selection but can be relaxed by sex and recombination because the fate of an allele is not inexorably tied to the fate of its initial genetic background.

The accumulation of genetic associations that impede selection results not only from the appearance of new mutations but also from random genetic drift within finite populations subject to selection. When, by chance, drift causes an overproduction of extreme genotypes (e.g., $--$ with low fitness and $++$ with high fitness), the genetic variation is made more accessible to selection and so is more easily depleted. When, by chance, drift causes an overproduction of intermediate genotypes (e.g., $+-$ and $-+$), the genetic variation becomes more hidden from selection, stalling evolution. Thus, after a period of time, drift in the presence of selection leads to the accumulation of chromosomes where beneficial alleles are linked to deleterious alleles. Consequently, modifiers that increase the frequency of sex and recombination are able to bring together beneficial alleles (converting hidden variation into accessible variation), and these modifiers spread along with the favorable gene combinations that they helped to produce (Felsenstein and Yokoyama 1976; Otto and Barton 2001; Barton and Otto 2005).

There are three aspects of a drift-based explanation for the evolution of sex that are particularly compelling. The first is that the results are less sensitive to the form of epistasis than are the earlier models assuming an infinite population. Indeed, sex and recombination can evolve when epistasis is negative, absent, or positive (Otto and Barton 2001; Keightley and Otto 2006). Interestingly, this means that the very direction in which we predict sex to evolve is altered by drift; when epistasis is positive, modifiers that increase the level of sex would not be able to spread if populations were infinitely large, but they can spread in finite populations. Epistasis still matters to some extent, and strong fitness interactions can still select against sex and recombination (including dominance interactions, as described by Roze [2009], in this issue), but the fact that sex and recombination are favored over a broader range of epistatic interactions is promising in light of the empirical finding that epistasis is not predominantly weak and negative (Rice 2002; de Visser and Elena 2007).

The second compelling aspect of a drift-based explanation is that it does not require a particularly small population size. Drift drives the evolution of sex and recombination even in very large populations if there are many loci under selection (so that there can still be a substantial amount of hidden genetic variation; Iles et al. 2003; Keightley and Otto 2006) or if populations are spatially structured (so that drift and selection acting on a local scale deplete accessible variation; Martin et al. 2006). Indeed, with spatial structure, the size of the metapopulation could even be infinitely large, and yet local drift can drive the evolution of sex and recombination, even with a twofold cost of sex (Martin et al. 2006).

The third compelling aspect of a drift-based explanation for sex and recombination is that it does not require a

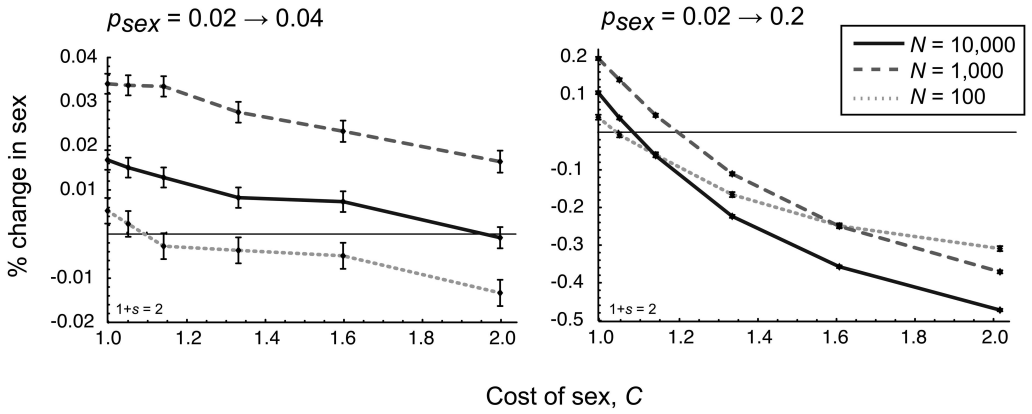

Figure 5: Costly sex can evolve in finite populations subject to selection. Selection was simulated at two loci, with beneficial alleles that doubled fitness. Changes in the frequency of a modifier allele, *M*, over 50 generations were monitored as by Otto and Barton (2001), except that the modifier altered the frequency of sex (*Y*-axis) rather than the rate of recombination and a cost of sex was incorporated (*X*-axis). Specifically, sexuals transmitted *C* times fewer genes to the next generation as did asexuals ($C = 2$ with a twofold cost of sex). The probability that two haploids that encountered one another engaged in sex was 0.02 if they both carried the *m* allele and was incremented for each *M* allele carried by the pair by 0.01 (*left*) or 0.09 (*right*). Epistasis was absent, and yet the modifier allele increasing sex rose in frequency as long as the cost of sex was not too severe. Because the cost of sex rises in proportion to the level of sex but the advantage of bringing together fit alleles declines when they are already likely to be together, low levels of sex (*left*) were more strongly favored than high levels (*right*). A smaller population size (e.g., $N = 100$) is not necessarily more conducive to the evolution of sex because genetic variation can be lost too quickly. The initial population was sampled from a distribution of chromosomes with the *M* allele at frequency 0.5, the beneficial alleles at frequency 0.1, and no linkage disequilibrium.

single form of selection. Directional selection works (Otto and Barton 2001; Barton and Otto 2005), as does selection against deleterious mutations (Keightley and Otto 2006). Red Queen dynamics can also work, although simulations suggest that drift matters more when multiple parasites interact with different host genes (Hamilton et al. 1990) than when a host interacts with a single parasite via a pair of genes (Kouyos et al. 2007*b*). Of course, in the real world, organisms experience all forms of selection (Rice 1999), and combinations of these selective forces have also been shown to benefit sex in finite populations, involving beneficial and deleterious mutations (Peck's [1994] "Ruby in the Rubbish"), beneficial mutations and the Red Queen (Peck 1993), or deleterious mutations and the Red Queen (Howard and Lively 1994).

Multiple lines of empirical evidence support the drift hypothesis for the evolution of sex. Several studies have demonstrated that asexual populations are unable to adapt as rapidly as sexual populations (Malmberg 1977; Colegrave 2002; Colegrave et al. 2002; Kaltz and Bell 2002; Poon and Chao 2004; Goddard et al. 2005; Cooper 2007). In an experiment with clonal *Escherichia coli* that varied the supply of mutations, the rate of adaptation did not rise as fast as would be expected from the rate of production of beneficial alleles, implying that these beneficial alleles were often arising in different individuals and competing with one another, an example of Hill-Robertson interference in asexual populations called "clonal interference" (de Visser et al. 1999). A similar result was observed with asexual *Chlamydomonas reinhardtii* when the mutation supply rate was altered by changing the population size (Colegrave 2002). In cases where the level of genetic variation is equalized among populations of different sizes, the advantage of sex was found to be strongest in smaller populations, where drift is more substantial (Poon and Chao 2004). In a recent experiment in *E. coli*, recombination increased the probability that a specific beneficial mutation fixed and increased its fixation rate, presumably because the mutant could be recombined away from linked deleterious mutations and into fitter lines (Cooper 2007). In addition to experiments showing an advantage to sex and recombination, there is some evidence that recombination rates rise following periods of strong selection (reviewed in Otto and Barton 2001). Because these studies come predominantly from laboratory experiments in the absence of parasites and with limited initial genetic variation, it is likely that the key role played by recombination is to bring together selectively favorable alleles that are present in different individuals. Finally, phylogenetic analyses have provided evidence that selection is less effective at eliminating deleterious nonsynonymous mutations in asexual lineages than in related sexual lineages of *Daphnia pulex* (Paland and Lynch 2006) and the freshwater snail *Campelona* (Johnson and Howard 2007), as expected from Hill-Robertson interference among loci.

An open question is whether the drift-based explanation

is strong enough to account for the evolution of sex in the face of substantial costs of sex. In figure 5, costs of sex were added to the program used by Otto and Barton (2001) to investigate the evolution of sex at a modifier locus in the presence of strong directional selection at two other loci. Even though epistasis was absent and the costs of sex were substantial (e.g., twofold), modifier alleles causing the frequency of sex to rise to moderately low levels were able to spread over the course of the 50 generations. With only two selected loci, however, modifiers causing the frequency of sex to rise to higher levels (fig. 5, *right*) did not spread unless costs were much less than twofold. Results similar to those in figure 5 were observed for modifiers of sex introduced into structured populations (Martin et al. 2006) and into populations at mutation-selection-drift balance with genomewide deleterious mutations occurring at a rate of one per generation (Keightley and Otto 2006). It remains to be demonstrated but seems plausible that high levels of sex could evolve, given a combination of selective forces acting across the genome, even in the face of substantial costs of sex.

Discussion

In a homogeneous and static world, where populations remain at stable equilibria under selection, there would almost certainly be no sex. In a dynamic world with selection but with infinitely large populations, there is also a good chance that there would be no sex or at least that sex would be restricted to those species whose fitness surfaces exhibit the right sort of negative curvature.

But the world is neither homogeneous nor static, and populations are never infinitely large. In accounting for more realistic scenarios, evolutionary models have established the following conditions allowing for the evolution of sex.

Selection Varies over Time. When genetic associations built by past selection are no longer favorable, sex and recombination can break apart these associations and improve the fitness of offspring.

Selection Varies over Space. When genetic associations created by migration are locally disadvantageous, sex and recombination can break apart these associations and improve the fitness of descendants.

Rates of Sex Vary among Individuals. If individuals in good condition reproduce asexually while less fit individuals reproduce sexually, sex—even costly sex—readily evolves.

Populations Are Finite. With drift and selection, populations rapidly use up accessible variation, where beneficial alleles are found together on the same chromosomes, but hidden variation, where beneficial alleles are found on chromosomes with deleterious alleles, persists over time. Sex and recombination are then favored to bring together fit alleles that tend to be found in different individuals.

So why do so many species reproduce sexually, given the costs of sex and the widespread potential for asexual reproduction? The answer may very well be to reintroduce variation, as suggested by Weismann (1889) more than a century ago. Indeed, the drift-based hypothesis for sex emphasizes that selection in finite populations rapidly exhausts accessible variation, leaving populations with an excess of chromosomes carrying a mixture of high-fitness and low-fitness alleles. In this case, sex and recombination can bring together beneficial alleles carried by different individuals, restoring variation and allowing selection to proceed further. Alternatively, sex may have evolved not to reintroduce variation but to eliminate genetic associations that arose at other times or locations and that are not favorable under the current conditions (causing the segregation or recombination loads to switch signs and become favorable). It is even possible that sex evolved for the simple reason that genetic elements that have the ability to cause their carriers to engage in sex when condition is poor will spread—not because they enhance variation, not because they break apart unfavorable gene combinations, but because they are selfish and can escape bad genetic backgrounds via sex. There is likely to be some truth in each of these explanations, depending on the organism in question.

Fairly strong empirical evidence has now amassed that selection is less effective in finite populations when sex is absent (due to Hill-Robertson effects) so that the conditions exist for the evolution of at least some sex, even costly sex. Too little evidence is currently available from natural populations, however, regarding the sign of the recombination and segregation loads, which are needed to determine whether and how often genetic associations present in a population are currently detrimental. Experiments are also needed to determine the degree to which organisms use their condition—their fit to the current environment—to alter their relative allocation to sexual reproduction versus asexual reproduction. This empirical data, alongside the evolutionary theory that has been developed, will provide us with the solid foundation needed to settle the paradox of sex.

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Literature Cited

Agrawal, A. F. 2006. Similarity selection and the evolution of sex: revisiting the Red Queen. PLoS Biology 4:e265.

———. 2009. Spatial heterogeneity and the evolution of sex in diploids. American Naturalist 174(suppl.):S54–S70.

Agrawal, A. F., and S. P. Otto. 2006. Host-parasite coevolution and selection on sex through the effects of segregation. American Naturalist 168:617–629.

Agrawal, A. F., L. Hadany, and S. P. Otto. 2005. The evolution of plastic recombination. Genetics 171:803–812.

Asker, S. E., and L. Jerling. 1992. Apomixis in plants. CRC, Boca Raton, FL.

Barbour, A. G., and B. I. Restrepo. 2000. Antigenic variation in vector-borne pathogens. Emerging Infectious Diseases 6:449–457.

Barton, N. H. 1995*a*. A general model for the evolution of recombination. Genetical Research 65:123–144.

———. 1995*b*. Linkage and the limits to natural selection. Genetics 140:821–841.

Barton, N. H., and S. P. Otto. 2005. Evolution of recombination due to random drift. Genetics 169:2353–2370.

Bell, G. 1982. The masterpiece of nature: the evolution and genetics of sexuality. University of California Press, Berkeley.

Brooks, L. 1988. The evolution of recombination rates. Pages 87–105 *in* R. E. Michod and B. R. Levin, eds. The evolution of sex: an examination of current ideas. Sinauer, Sunderland, MA.

Burdon, J. J. 1997. The evolution of gene-for-gene interactions in natural pathosystems. Pages 245–262 *in* I. R. Crute, E. B. Holub, and J. J. Burdon, eds. The gene-for-gene relationship in plant-parasite interactions. CAB International, Wallingford.

Charlesworth, B. 1990. Mutation-selection balance and the evolutionary advantage of sex and recombination. Genetical Research 55:199–221.

———. 1993. Directional selection and the evolution of sex and recombination. Genetical Research 61:205–224.

Chasnov, J. R. 2000. Mutation-selection balance, dominance and the maintenance of sex. Genetics 156:1419–1425.

Colegrave, N. 2002. Sex releases the speed limit on evolution. Nature 420:664–666.

Colegrave, N., O. Kaltz, and G. Bell. 2002. The ecology and genetics of fitness in *Chlamydomonas*. VIII. The dynamics of adaptation to novel environments after a single episode of sex. Evolution 56: 14–21.

Cooper, T. F. 2007. Recombination speeds adaptation by reducing competition between beneficial mutations in populations of *Escherichia coli*. PLoS Biology 5:e225, doi:10.1371/journal.pbio .0050225.

Crute, I. R., E. B. Holub, and J. J. Burdon, eds. 1997. The gene-for-gene relationship in plant-parasite interactions. CAB International, Wallingford.

de Visser, J. A. G. M., and S. F. Elena. 2007. The evolution of sex: empirical insights into the roles of epistasis and drift. Nature Review Genetics 8:139–149.

de Visser, J. A. G. M., C. Zeyl, P. Gerrish, J. Blanchard, and R. E. Lenski. 1999. Diminishing returns from mutation supply rate in asexual populations. Science 283:404–406.

de Visser, J. A. G. M., S.-C. Park, and J. Krug. 2009. Exploring the effect of sex on empirical fitness landscapes. American Naturalist 174(suppl.):S15–S30.

Dolgin, E. S., and S. P. Otto. 2003. Segregation and the evolution of sex under overdominant selection. Genetics 164:1119–1128.

Donelson, J. E. 1995. Mechanisms of antigenic variation in *Borrelia hermsii* and African trypanosomes. Journal of Biological Chemistry 270:7783–7786.

Eshel, I., and M. W. Feldman. 1970. On the evolutionary effect of recombination. Theoretical Population Biology 1:88–100.

Feldman, M. W. 1972. Selection for linkage modification. I. Random mating populations. Theoretical Population Biology 3:324–346.

Feldman, M. W., F. B. Christiansen, and L. D. Brooks. 1980. Evolution of recombination in a constant environment. Proceedings of the National Academy of Sciences of the USA 77:4838–4841.

Feldman, M. W., F. B. Christiansen, and U. Liberman. 1983. On some models of fertility selection. Genetics 105:1003–1010.

Feldman, M. W., S. P. Otto, and F. B. Christiansen. 1997. Population genetic perspectives on the evolution of recombination. Annual Review of Genetics 30:261–295.

Felsenstein, J. 1974. The evolutionary advantage of recombination. Genetics 78:737–756.

Felsenstein, J., and S. Yokoyama. 1976. The evolutionary advantage of recombination. II. Individual selection for recombination. Genetics 83:845–859.

Fisher, R. A. 1930. The genetical theory of natural selection. Oxford University Press, Oxford.

Flor, H. H. 1956. The complementary genic systems in flax and flax rust. Advances in Genetics 8:29–54.

Gandon, S., and S. P. Otto. 2007. The evolution of sex and recombination in response to abiotic or coevolutionary fluctuations in epistasis. Genetics 175:1835–1853.

Gerke, J. P., C. T. L. Chen, and B. A. Cohen. 2006. Natural isolates of *Saccharomyces cerevisiae* display complex genetic variation in sporulation efficiency. Genetics 174:985–997.

Gessler, D. D. G., and S. Z. Xu. 2000. Meiosis and the evolution of recombination at low mutation rates. Genetics 156:449–456.

Goddard, M. R., H. C. J. Godfray, and A. Burt. 2005. Sex increases the efficacy of natural selection in experimental yeast populations. Nature 434:636–640.

Hadany, L., and T. Beker. 2003. On the evolutionary advantage of fitness-associated recombination. Genetics 165:2167–2179.

Hadany, L., and S. P. Otto. 2007. The evolution of condition-dependent sex in the face of high costs. Genetics 176:1713–1727.

———. 2009. Condition-dependent sex and the rate of adaptation. American Naturalist 174(suppl.):S71–S78.

Hamilton, W. D. 1980. Sex vs. non-sex vs. parasite. Oikos 35:282–290.

Hamilton, W. D., R. Axelrod, and R. Tanese. 1990. Sexual reproduction as an adaptation to resist parasites: a review. Proceedings of the National Academy of Sciences of the USA 87:3566–3573.

Hill, J. A., and S. P. Otto. 2007. The role of pleiotropy in the maintenance of sex in yeast. Genetics 175:1419–1427.

Hill, W. G., and A. Robertson. 1966. The effect of linkage on the limits to artificial selection. Genetical Research 8:269–294.

Howard, R. S., and C. M. Lively. 1994. Parasitism, mutation accumulation and the maintenance of sex. Nature 367:554–557.

Iles, M. M., K. Walters, and C. Cannings. 2003. Recombination can

evolve in large finite populations given selection on sufficient loci. Genetics 165:333–337.

Jaenike, J. 1978. An hypothesis to account for the maintenance of sex in populations. Evolutionary Theory 3:191–194.

Ji, Y. F., D. M. Stelly, M. De Donato, M. M. Goodman, and C. G. Williams. 1999. A candidate recombination modifier gene for *Zea mays* L. Genetics 151:821–830.

Johnson, S. G., and R. S. Howard. 2007. Contrasting patterns of synonymous and nonsynonymous sequence evolution in asexual and sexual freshwater snail lineages. Evolution 61:2728–2735.

Jokela, J., M. F. Dybdahl, and C. M. Lively. 2009. The maintenance of sex, clonal dynamics, and host-parasite coevolution in a mixed population of sexual and asexual snails. American Naturalist 174(suppl.):S43–S53.

Kaltz, O., and G. Bell. 2002. The ecology and genetics of fitness in *Chlamydomonas*. XII. Repeated sexual episodes increase rates of adaptation to novel environments. Evolution 56:1743–1753.

Keightley, P. D., and S. P. Otto. 2006. Interference among deleterious mutations favours sex and recombination in finite populations. Nature 443:89–92.

Kelley, S. E., J. Antonovics, and J. Schmitt. 1988. A test of the short-term advantage of sexual reproduction. Nature 331:714–716.

Kimura, M. 1956. A model of a genetic system which leads to closer linkage by natural selection. Evolution 10:278–287.

Kondrashov, A. S. 1984. Deleterious mutations as an evolutionary factor. I. The advantage of recombination. Genetical Research 44: 199–217.

Kong, A., D. F. Gudbjartsson, J. Sainz, G. M. Jonsdottir, S. A. Gudjonsson, B. Richardsson, S. Sigurdardottir, et al. 2002. A high-resolution recombination map of the human genome. Nature Genetics 31:241–247.

Kong, A., G. Thorleifsson, H. Stefansson, G. Masson, A. Helgason, D. F. Gudbjartsson, G. M. Jonsdottir, et al. 2008. Sequence variants in the *RNF212* gene associate with genome-wide recombination rate. Science 319:1398–1401.

Kouyos, R. D., O. K. Silander, and S. Bonhoeffer. 2007*a*. Epistasis between deleterious mutations and the evolution of recombination. Trends in Ecology & Evolution 22:308–315.

Kouyos, R. D., M. Salathé, and S. Bonhoeffer. 2007*b*. The Red Queen and the persistence of linkage-disequilibrium oscillations in finite and infinite populations. BMC Evolutionary Biology 7:211–220.

Kusch, J., and H. J. Schmidt. 2001. Genetically controlled expression of surface variant antigens in free-living protozoa. Journal of Membrane Biology 180:101–109.

Lenormand, T., and S. P. Otto. 2000. The evolution of recombination in a heterogeneous environment. Genetics 156:423–438.

Li, C.-X., and W. A. Cowling. 2003. Identification of a single dominant allele for resistance to blackleg in *Brassica napus* "Surpass 400." Plant Breeding 122:485–488.

Lloyd, D. G. 1980. Benefits and handicaps of sexual reproduction. Evolutionary Biology 13:69–111.

Malmberg, R. L. 1977. The evolution of epistasis and the advantage of recombination in populations of bacteriophage T4. Genetics 86: 607–623.

Martin, G., S. P. Otto, and T. Lenormand. 2006. Selection for recombination in structured populations. Genetics 172:593–609.

May, R. M., and R. M. Anderson. 1983. Epidemiology and genetics in the coevolution of parasites and hosts. Proceedings of the Royal Society B: Biological Sciences 219:281–313.

Morgan, T. H. 1913. Heredity and sex. Columbia University Press, New York.

Muller, H. J. 1932. Some genetic aspects of sex. American Naturalist 66:118–138.

———. 1964. The relation of recombination to mutational advance. Mutation Research 1:2–9.

Nei, M. 1967. Modification of linkage intensity by natural selection. Genetics 57:625–641.

Neiman, M., and B. Koskella. 2009. Sex and the Red Queen. Forthcoming. *In* I. Schön, K. Martens, and P. Van Dijk, eds. Lost sex. Springer, Berlin.

Otto, S. P. 2003. The advantages of segregation and the evolution of sex. Genetics 164:1099–1118.

Otto, S. P., and N. H. Barton. 1997. The evolution of recombination: removing the limits to natural selection. Genetics 147:879–906.

———. 2001. Selection for recombination in small populations. Evolution 55:1921–1931.

Otto, S. P., and M. W. Feldman. 1997. Deleterious mutations, variable epistatic interactions, and the evolution of recombination. Theoretical Population Biology 51:134–147.

Otto, S. P., and A. C. Gerstein. 2006. Why have sex? the population genetics of sex and recombination. Biochemical Society Transactions 34:519–522.

Otto, S. P., and S. L. Nuismer. 2004. Species interactions and the evolution of sex. Science 304:1018–1020.

Paland, S., and M. Lynch. 2006. Transitions to asexuality result in excess amino acid substitutions. Science 311:990–992.

Peck, J. R. 1993. Frequency-dependent selection, beneficial mutations, and the evolution of sex. Proceedings of the Royal Society B: Biological Sciences 125:87–92.

———. 1994. A ruby in the rubbish: beneficial mutations, deleterious mutations and the evolution of sex. Genetics 137:597–606.

Peters, A. D., and C. M. Lively. 1999. The Red Queen and fluctuating epistasis: a population genetic analysis of antagonistic coevolution. American Naturalist 154:393–405.

Poon, A., and L. Chao. 2004. Drift increases the advantage of sex in RNA bacteriophage Phi6. Genetics 166:19–24.

Pylkov, K. V., L. A. Zhivotovsky, and M. W. Feldman. 1998. Migration versus mutation in the evolution of recombination under multilocus selection. Genetical Research 71:247–256.

Ravi, M., M. P. A. Marimuthu, and I. Siddiqi. 2008. Gamete formation without meiosis in *Arabidopsis*. Nature 451:1121–1125.

Redfield, R. J. 1988. Evolution of bacterial transformation: is sex with dead cells ever better than no sex at all? Genetics 119:213–221.

Rice, W. R. 1983. Parent-offspring pathogen transmission: a selective agent promoting sexual reproduction. American Naturalist 121: 187–203.

———. 1999. Genetic polarization: unifying theories for the adaptive significance of recombination. Journal of Evolutionary Biology 12: 1047–1049.

———. 2002. Experimental tests of the adaptive significance of sexual recombination. Nature Reviews Genetics 3:241–251.

Roze, D. 2009. Diploidy, population structure, and the evolution of recombination. American Naturalist 174(suppl.):S79–S94.

Roze, D., and N. H. Barton. 2006. The Hill-Robertson effect and the evolution of recombination. Genetics 173:1793–1811.

Salathé, M., R. D. Kouyos, R. R. Regoes, and S. Bonhoeffer. 2008. Rapid parasite adaptation drives selection for high recombination. Evolution 62:295–300.

Salathé, M., R. D. Kouyos, and S. Bonhoeffer. 2009. On the causes

of selection for recombination underlying the Red Queen hypothesis. American Naturalist 174(suppl.):S31–S42.

Vrijenhoek, R. C. 1998. Animal clones and diversity. BioScience 48: 617–628.

Weismann, A. 1889. The significance of sexual reproduction in the theory of natural selection. Pages 251–332 *in* E. B. Poulton, S. Schönland, and A. E. Shipley, eds. Essays upon heredity and kindred biological problems. Clarendon, Oxford.

Whitton, J., C. J. Sears, E. J. Baack, and S. P. Otto. 2008. The dynamic nature of apomixis in the angiosperms. International Journal of Plant Sciences 169:169–182.

Williams, C. G., M. M. Goodman, and C. W. Stuber. 1995. Comparative recombination distances among *Zea mays* L. inbreds, wide crosses and interspecific hybrids. Genetics 141:1573–1581.

Winckler, W., S. R. Myers, D. J. Richter, R. C. Onofrio, G. J. McDonald, R. E. Bontrop, G. A. McVean, et al. 2005. Comparison of fine-scale recombination rates in humans and chimpanzees. Science 308:107–111.

Xu, J. 2002. Estimating the spontaneous mutation rate of loss of sex in the human pathogenic fungus *Cryptococcus neoformans*. Genetics 162:1157–1167.

Zeyl, C., C. Curtin, K. Karnap, and E. Beauchamp. 2005. Antagonism between sexual and natural selection in experimental populations of *Saccharomyces cerevisiae*. Evolution 59:2109–2115.