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## Sex uncovered special issue: The ecology of sexual reproduction

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### Abstract

Sexual reproduction is widely regarded as one of the major unexplained phenomena in biology. Nonetheless, while a general answer may remain elusive, considerable progress has been made in the last few decades. Here we first review the genesis of, and support for, the major ecological hypotheses for biparental sexual reproduction. We then focus on the idea that host-parasite coevolution can favor cross fertilization over uniparental forms of reproduction, as this hypothesis currently has the most support from natural populations. We also review the results from experimental evolution studies, which tend to show that exposure to novel environments can select for higher levels of sexual reproduction, but that sex decreases in frequency after populations become adapted to the previously novel conditions. In contrast, experimental coevolution studies suggest that host-parasite interactions can lead to the long-term persistence of sex. Taken together, the evidence from natural populations and from laboratory experiments point to antagonistic coevolution as a potent and possibly ubiquitous force of selection favoring cross-fertilization and recombination.

### Keywords

antagonistic coevolution; experimental evolution; Hill-Robertson interference; parthenogenesis; recombination; Red Queen hypothesis

### Introduction

Long before sexual reproduction became a scandal in evolutionary biology, exactly the opposite was considered “scandalous:” parthenogenesis. The fusion of gametes was thought to be necessary for development (a biological law). Hence the development of unfertilized eggs (parthenogenesis), as observed by von Siebold (1856), led to considerable angst for some, particularly Rudolf Wagner (Churchill, 1979). In his 1857 review of von Siebold’s (1856) book on parthenogenesis, Wegner wrote (as quoted by Churchill, 1979):

“I must unfortunately say that one of the most unpleasant of facts, [Parthenogenesis] has been introduced into physiology, which for the hope of so-called general laws of animal life-phenomena is most distasteful. It is impossible,

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considering the glorification of our highly vaunted progress in the theoretical understanding of the life processes, for it to be welcomed or particularly encouraged; and sincerely speaking, I can be as little pleased about it as a physicist would be if suddenly one or more exceptions to the law of gravitation were discovered.”

Parthenogenesis was eventually widely accepted as a biological fact, and it became the subject of intense study in Europe (Vandel, 1928). But more than 100 years passed since the original discovery of parthenogenesis before its opposite, sexual reproduction, was presented by Maynard Smith as anomalous under evolutionary theory (see Meirmans, 2009). Maynard Smith (1978) originally became interested in the subject, as it seemed to him that sexual reproduction was the only trait that required a group-selection argument, as suggested by Fisher (1958).

Any characters ascribed to interspecific selection should of course characterize, not species, but whole genera or families, and it may be doubted if it would be possible to point to any such character, with the possible exception, as suggested in Chapter VI, of sexuality itself, which could be interpreted as evolved for the specific rather than for the individual advantage. (page 50 in Fisher, 1958)

However, Maynard Smith later changed his mind and began to consider possible advantages to sex at the individual level: “... I realized that it was illogical to reject Wynne-Edwards’s (1962) views as group selectionist, if at the same time I accepted a group selectionist explanation of sex” (page 2 in Maynard Smith, 1978). As Maynard Smith worked to understand the possible advantages to sex at the individual level, he found that sexual reproduction carries a rather extreme cost, at least in comparison to parthenogenetic reproduction (Maynard Smith, 1971, Maynard Smith, 1978). The cost is, in fact, at the level of the group, and it stems directly from the fact that the males produced by sexual reproduction do not contribute to the reproductive output of the group. Hence, the per-capita birth rate can be reduced by as much as one half in sexual populations with 1:1 sex ratios. This he called, “the cost of males.” (Note: in keeping with tradition, we use “sex” here to imply cross-fertilization.)

At about the same time, Williams (1975) also became interested in the individual-level advantages to sexual reproduction. He too recognized a cost of sex, which he called, “the cost of meiosis.” Here the cost of cross-fertilization between unrelated parents stems from the 50% reduction in relatedness between parent and offspring, when compared to self-fertilization (Lloyd, 1979, Charlesworth, 1980). Do both costs simultaneously apply? If not, which one is the relevant cost? A model by Lively and Lloyd (1990) showed that either one or the other cost applies, depending on the type of uniparental offspring produced; both costs do not simultaneously apply. A more recent model has further suggested that the cost of males is two-fold in annual populations (as assumed by Maynard Smith), but the cost of males per generation can be greater than two fold in iteroparous, sexual populations (Lively, 2010b).

The cost of males led Maynard Smith to conclude that, all else equal, obligate sexual reproduction would be replaced by asexual reproduction, leading to the question, what

maintains sex in the short term? The “all-else-equal” assumption is simply that sexuals and asexuals have very similar, if not identical, niche widths, and that sexual and asexual females are equally fecund. Thus, in the absence of some countervailing selection against asexual reproduction, cross-fertilization would be rapidly eliminated. Hence, a ploidy difference between sexuals and asexuals is not by itself a violation of the all-else-equal assumption, unless changes in ploidy alter the fundamental niche, or reduce the fecundity, of the asexuals. In other words, ploidy differences by themselves are not a sufficient explanation for the maintenance of sexual diploids in direct competition with polyploid asexuals.

## Contrasting the ecological hypotheses using natural populations

One of the earliest traditions for ecological studies of sex focused on elucidating the distribution of parthenogenesis. The patterns in nature could be highly informative if there were general patterns across clades for the distribution of the two reproductive modes. Bell (1982) neatly summarized the data for a wide variety of eukaryotic organisms in his book, *The masterpiece of nature: the evolution and genetics of sexuality*. But he also did much more. He laid out the existing ecological hypotheses and then squeezed different predictions out of each of them. With these predictions in hand, he used the distributional data in an attempt to falsify one or more of the alternatives, giving an excellent example of the strong inference method (Platt, 1964) and the value of contrasting multiple working hypothesis (Chamberlin, 1890, Chamberlin, 1897).

One of the prevailing ecological explanations for sex at the time of Bell’s book was William’s “lottery model.” The gist of Williams’ idea was that the production of genetically variable offspring could be favored in changing abiotic environments, even with a two-fold cost (Williams, 1975). Under the lottery model, sex is a bet-hedging strategy, where the production of variable offspring is associated with a higher geometric mean fitness (Stearns, 2000). Hence, the lottery model predicted that sexual reproduction would be more common in temporally variable environments, and that asexual reproduction would be more common in stable environments. Bell (1982) found exactly the opposite. The distributional data showed that it was asexual reproduction, not sex, that was associated with unpredictable and temporary habitats. Under the weight of the evidence, the lottery model began to fade as an explanation for sex. Nonetheless, the idea that sex is a bet-hedging strategy is still appealing, although the driving mechanism could be different than originally envisioned by Williams. In other words, the sources of environmental change could be biotic, rather than abiotic.

In contrast to the prediction of the lottery model, Bell (1982) found that sex is associated with constant environments, like the tropics. This finding was consistent with two other alternatives that he considered. One of these alternatives he called the tangled bank hypothesis. The conceptual roots of the tangled bank hypothesis stem from Levine’s model on multiple niche polymorphism (Levene, 1953). The basic idea is that genetic polymorphism could be favored in spatially heterogeneous environments if different genetically determined morphs were favored in the different habitat types. The tangled bank idea also had support from similar arguments put forth by Vrijenhoek (1979) in his construction of the frozen niche variation hypothesis, and by formal ecological models

constructed by Case and Taper (1986). In these models, clones have a narrower niche width than sexuals; and, as such, a single clone cannot completely exclude the sexuals, leading to coexistence of sexual and asexual forms. Vrijenhoek's data on the distribution of sexual and asexual fish was clearly consistent with this view (Vrijenhoek, 1979). On the other hand, the ecological conditions for the maintenance of genetic polymorphism in this way can be narrow (Maynard Smith & Hoekstra, 1980, Lively, 1986). In addition, canalized morphs are subject to invasion by conditional (plastic) strategies if reliable cues exist for the different patches (Lively, 1986, Hazel *et al.*, 2004).

Bell's distributional data were also consistent with a fledging idea, which he named the Red Queen hypothesis. The genesis of the Red Queen idea came from multiple authors at about the same time, in particular Hamilton, Levin, Jaenike, Bell, and Lloyd (Hamilton, 1975, Levin, 1975, Jaenike, 1978, Hamilton, 1980, Lloyd, 1980). The idea here is that parasites would be under strong selection to infect the most common host genotypes. Hence, assuming that some kind of genetic match is required for successful infection, parasites that match the most common host genotype would be favored by natural selection. Thus, a clonally propagated host genotype could have a two-fold advantage when rare, but would likely suffer disproportionately high levels of infection once it became common. Bell reasoned that the potential for this kind of host-parasite coevolution would be more often realized in stable environments where disease transmission is more likely. Hence, parasites might drive selection for sex in stable environments. The parasite idea also had early empirical support from the distribution of asexual reproduction in terrestrial animals (Glesener & Tilman, 1978).

The issue of whether intraspecific competition or host-parasite coevolution better explains the distribution patterns elucidated by Bell is still not completely resolved. However, experimental studies of the tangled bank hypothesis (and its relative, the sib-competition model) have not been supportive of the idea (Schmitt & Ehrhardt, 1987, Willson *et al.*, 1987, Garcia & Toro, 1992). In his book, *Natural selection: the mechanism of evolution*, published 15 years after *The masterpiece of nature*, Bell (1997) (page 541) wrote,

“The Tangled Bank is an attractive explanation for the prevalence of sex in relatively stable and saturated communities in tropical and marine environments where competition for resources is likely to be continual and intense. Nevertheless, the evidence from crops and *Chlamydomonas* has persuaded me that it is unlikely to be correct. Arbitrary mixtures do indeed seem to be more productive than the average of their components, but the effect is too slight at the scale of offspring within a single sexual brood to overcome the manifest inefficiency of sex.”

Other authors, however, have pointed out that the basic idea might hold with some modification (Song *et al.*, 2011), so further empirical tests may be required. There is also the possibility that density-dependent selection, in concert with other factors (including parasites), might have explanatory power (Lively, 2010a).

On empirical grounds, direct contrast of the Red Queen and the tangled bank hypotheses have been more aligned with the Red Queen. Ellstrand and Antonovics published two key studies in the mid-1980s on the effects of density and frequency on the fitness of tillers from

sweet vernal grass (Antonovics & Ellstrand, 1984, Ellstrand & Antonovics, 1985). They found no effect of density per se, as required by the tangled bank; but they did find an advantage to being a rare genotype, as required by the parasite model. Although the mechanism underlying the rare advantage was not known at the time, subsequent studies of the system identified possible disease agents (Kelley *et al.*, 1988, Kelley, 1993, Kelley, 1994).

In 1987, Burt and Bell published a compelling study on recombination rates in mammals (Burt & Bell, 1987). They reasoned that, under the tangled bank hypothesis, recombination would be favored in species having large broods as a way to diversify offspring and reduce competition among them. But under the Red Queen hypothesis, recombination would be favored in long-lived species as a way to produce offspring that were relatively resistant to rapidly evolving parasites. Interestingly, long-lived species tend to have smaller broods, so higher recombination rates in long-lived species would be consistent with the Red Queen, while higher recombination rates in short-lived (large clutches) species would favor the tangled bank. The results were unambiguous. The correlation between longevity and recombination rates was positive and highly statistically significant. Thus, the data lent support to the Red Queen, and further undermined the tangled bank hypothesis.

In the same year, Lively (1987) published a comparative study on the distributions of sexual and parthenogenetic reproduction in a freshwater snail. The goal was to conduct strong-inference tests contrasting the lottery model, the tangled bank model, and the Red Queen hypothesis. The results were only consistent with the predictions of the Red Queen hypothesis. More specifically, the results were consistent with the prediction offered by Lloyd (1980) that asexual reproduction would dominate in populations where the strength of selection caused by antagonistic coevolution is low. Specifically, regarding antagonistic coevolution, Lloyd (1980) stated that,

“If this proves to be so, we will then be able to examine whether the occurrence of asexual reproduction is correlated with relaxation of the biological hostility of the environment.”

The snail study showed that asexual reproduction dominated in regions where sterilization by larval trematodes was low, suggesting that sexual reproduction had been replaced by asexual reproduction where parasite-mediated selection was weak.

## Tests of the Red Queen Hypothesis using natural populations

This section covers work that subsequently focused on testing the predictions of, and the necessary conditions for, the Red Queen hypothesis in natural populations. First, it might be useful to distill out the different ways that the Red Queen has been discussed.

The original use of the Red Queen character comes from Van Valen (1973). He used the idea that “you have to run as fast as you can to stay in the same place” (Carroll, 1872) as an explanation for the constant rates of extinction observed in marine organisms. He hypothesized that extinction would occur, independent of lineage age, if there were a constant probability of species interactions becoming unstable, as might happen when a prey

species evolves protection against an obligate predator. However, following *The masterpiece of nature*, the Red Queen hypothesis took on a new meaning in microevolutionary studies. Bell (1982) saw that the idea could also be used as a heuristic to understand the population genetics of rapid host-parasite coevolution.

Two usages of the “Red Queen hypothesis” seem to be common at the present time in microevolutionary studies: (1) the first is that there may be parasite-mediated selection for host genetic diversity (and vice versa) that can lead to oscillations in genotype frequencies, and (2) the second, related use, is that there may be parasite-mediated selection for sex. The first is a necessary, but not sufficient, condition for the second: parasite-mediated, frequency-dependent selection against common genotypes could maintain genetic polymorphism in host resistance, but selection could nonetheless be insufficiently strong to overcome the cost of sex.

## Parasites and genetic diversity

Running in-order-to-stay-in-the-same place is an apt analogy for host-parasite coevolution leading to selection for genetic diversity. Any host genotype that becomes common should eventually be selected against by virulent, coevolving parasites (assuming that a genetic match is required for infection). Such selection can lead to oscillations of genotypes in both the host and parasites, especially if parasite-mediated selection is strong enough to be destabilizing (e.g., Hamilton *et al.*, 1990). Hence it would seem that host and parasites are running just to stay in the same place. In other words, genotypes (and alleles) oscillate over time, but averaged over thousands of generations, they appear to remain constant.

There are now data directly supporting the idea that parasites provide selection against common clonal genotypes. For example, field studies (Dybdahl & Lively, 1998, Lively & Dybdahl, 2000, Jokela *et al.*, 2009) and a controlled laboratory experiment (Koskella & Lively, 2009) have shown that initially resistant, common clones of a freshwater snail (*Potamopyrgus antipodarum*) decrease in frequency after becoming disproportionately infected by a co-evolving trematode worm (*Microphallus sp.*). Interestingly, one of these studies examined a mixed population of sexual and asexual snails, so the selection against the common clone should have temporally favored rare clones as well as the sexual population to some degree (Jokela *et al.*, 2009). Field studies of clonal populations of *Daphnia* have similarly demonstrated parasite-mediated selection against common host clones (Duncan & Little, 2007, Wolinska & Spaak, 2009). Moreover, field studies of gynogenetic fish have shown that the most common clones were more heavily infected with trematode larvae than coexisting sexual populations, unless the sexual population was highly inbred (Lively *et al.*, 1990). However, following restoration of genetic diversity into the inbred population, the sexuals were observed to be less infected than the common clone. Therefore, sex alone was not responsible for the observed effect, as it provided no escape from infection in the absence of genetic diversity (Lively *et al.*, 1990). Similar findings were recently reported in a partially self-fertilizing fish: outcrossed offspring were more genetically diverse, and they had a lower prevalence of infection than self-fertilized fish (Ellison *et al.*, 2011).



The evidence for parasite-mediated selection against common host genotypes strongly implies that some kind of genetic match of the host is required by the parasite for successful infection. This is a wide-open area for more research, but recent studies on *Daphnia* strongly imply the existence of a matching-alleles interaction between host and parasites (Luijckx *et al.*, 2011, Luijckx *et al.*, 2013). Similarly, line-cross experiments between different populations of locally adapted trematode worms were highly suggestive of epistatic interactions among loci involved in infecting their snail hosts (Dybdahl *et al.*, 2008). There is also now direct experimental evidence of epistasis among loci in flour beetles (*Tribolium*) that are involved in resistance to microsporidian parasites (Wegner *et al.*, 2008). Finally, susceptibility to infection in a freshwater snail appears to be driven by highly polymorphic, matching-type interaction with a medically important trematode worm (review in Mitta *et al.*, 2012).

Parasite-mediated selection against common genotypes should lead to the maintenance of clonal diversity, even if the clones are not all equally fecund. Two recent studies are consistent with this idea. King *et al.* (2011b) found that clonal diversity was significantly correlated with the prevalence of the most common trematode species infecting stream populations of a fresh-water snail, *P. antipodarum*, in New Zealand. Dagan *et al.* (2013) similarly found that clonal diversity was significantly correlated with trematode prevalence in another species of freshwater snail in Israel, *Melanoides tuberculata*. On the other hand, the accumulation of clonal diversity via frequency-dependent selection could undermine the advantages of sexual reproduction (Howard & Lively, 1994, Howard & Lively, 1998, Park *et al.*, 2010).

## Parasites and sexual reproduction

Can antagonistic coevolution provide an advantage to sexual reproduction in natural populations? A recent long-term study of a mixed (sexual and asexual) population of freshwater snails in New Zealand examined the prevalence of infection in sexual and asexual females at four sites over five years (Vergara *et al.*, 2014). The results showed that, averaged over all sites, the asexual population (which was composed of multiple clones) was significantly more infected than the sexual population for four of five years. In addition, the results showed that, at some sites and years, sexual females were more than twice as likely to be *uninfected* as compared to asexual females. Given that infection by this parasite (a trematode) is invariably sterilizing, these results demonstrate a large periodic advantage to sexual reproduction over asexual reproduction. The results also demonstrate that parasites can periodically select against the sexual subpopulation. Finally, the geometric mean fitnesses of the sexual and asexual subpopulations (as estimated from the change in their frequencies over time) were approximately equal, which suggests that parasite-mediated selection contributes to the stable coexistence of sexual and asexual females.

In addition, recent biogeographic studies of this snail have been consistent with earlier work, suggesting that asexual forms of the snail are more likely to occur in lakes and streams where parasites are rare (Lively, 1992, Lively & Jokela, 2002, King & Lively, 2009, King *et al.*, 2011b). This pattern could, of course, be generated if males or sexual snails are, in general, inherently more susceptible to infection, but this is not the case (Vergara *et al.*,

2014). Moreover, the pattern has been found to hold within lakes. Sexual snails are more common in shallow-water habitats where infection is common, while asexuals snails are more common in deeper habitats where infection is rare (Jokela & Lively, 1995, Lively & Jokela, 1996, Krist *et al.*, 2000). Experimental studies showed that field-collected parasites from these lakes were strongly adapted to infect the shallow-water snails from their “home” (sympatric) lake, but they were not adapted to infect the deep-water snails from their home lake (King *et al.*, 2009, King *et al.*, 2011a). Hence, sexual reproduction in these snails is associated with coevolutionary hotspots, as expected under the Red Queen hypothesis. The hotspots appear to be generated by the foraging patterns of the final host (ducks) for this trophically transmitted trematode. As the ducks forage primarily in the shallow-water, the recycling of parasite genotypes, and hence coevolution, would be expected to be more common in the shallow-water habitats. Consistent with this idea, a recent study has shown a more rapid turnover of clonal genotypes in the shallow regions of the lake than in the deep regions of the lake (Paczesniak *et al.*, 2014).

There is also recent evidence that geographical parthenogenesis in dandelions (*Taraxacum officinale*) could result (at least in part) from coevolutionary interactions with biological antagonists (Verhoeven & Biere, 2013). Dandelions exhibit the classic pattern of geographical parthenogenesis, with diploid sexual plants and triploid apomicts co-occurring in south-central Europe, but only apomictic plants extending into Northern Europe. The study showed that asexual populations at higher latitudes were subject to less infection by rusts and weevils than the sexual populations in the more southern latitudes. In addition, soils from southern latitudes contained significantly more pathogenic microbes than soils from northern latitudes. Hence, at a broad geographic scale, asexual plants were associated with reduced biological antagonism. On the other hand, as Verhoeven & Biere (2013) point out, not all studies that have looked for this kind of association (between biological hostility and sexual reproduction) have found it (see for example Meirmans *et al.*, 2006, Killick *et al.*, 2008, Dagan *et al.*, 2013).

### The exception that proves the rule?

Under the Red Queen, sex is maintained by parasite-mediated selection against common clonal genotypes. How then does the Red Queen explain the existence of ancient asexual lineages? Wilson and Sherman (2010, 2013) showed that ancient asexuality may be possible in rotifers, because the rotifers can eliminate infections by entering into a desiccated resting stage. In addition, the resting stage is wind-dispersed, independent of parasites, thus breaking the coevolutionary loop that is critical to the maintenance of sex under the Red Queen (Wilson & Sherman, 2010, Wilson & Sherman, 2013).

Conceptually similar results were found in *Potamopyrgus* snails. Although the oldest asexual lineages for this snail fall way short of being considered “ancient asexuals” (Neiman *et al.*, 2009), the study nonetheless found that the oldest clonal lineages (500,000 years old) were restricted to populations where parasites were rare (Neiman *et al.*, 2005). Taken together, these studies suggest that asexual reproduction can persist in the absence of selection imposed by biological enemies, as anticipated by theoretical studies (Ladle *et al.*, 1993, Judson, 1997).



## Genetic underpinnings of the Red Queen

The data discussed above are consistent with the idea that host-parasite coevolution can favor cross-fertilization over uniparental forms of reproduction. Nonetheless, it is not yet clear whether the genetic architecture envisioned under the Red Queen is generally met. With respect to recombination, a strict interpretation of the Red Queen would require that two or more loci are under parasite-mediated, frequency-dependent selection, and that the linkage disequilibrium among alleles at these loci is produced by fluctuating epistasis for fitness (Barton, 1995a, Peters & Lively, 1999, Gandon & Otto, 2007, Peters & Lively, 2007, Salathé *et al.*, 2008). This is in contrast with the Hill-Robertson effect (discussed below), where alleles under directional selection become associated with relatively deleterious alleles by chance (Hill & Robertson, 1966, Felsenstein, 1974). It remains possible that sex is generally favored by parasite-mediated selection driving directional, rather than fluctuating selection, and that recombination is indirectly selected to break up linkage disequilibrium between favorable alleles and deleterious alleles at other loci. However, directional selection resulting in periodic selective sweeps would not be expected to produce the high levels of (sometimes trans-specific) polymorphism observed in immune-defense genes (Figuroa *et al.*, 1988, Stahl *et al.*, 1999, Tian *et al.*, 2002, Mitta *et al.*, 2012, Thrall *et al.*, 2012, Barribeau *et al.*, 2014). It also remains possible that polymorphic, disease-defense loci generally exist on separate chromosomes, in which case host-parasite coevolution by itself could not explain the evolution of meiotic crossing over; but it could nonetheless be involved in selection for cross-fertilization as a method to diversify offspring (Wilfert & Schmid-Hempel, 2008).

## Hill-Robertson interference

As indicated above, the disruption of Hill-Robertson interference is another possible mechanism for explaining the potential benefits of sex and recombination. Hill-Robertson interference occurs when, by chance, advantageous alleles become associated with deleterious alleles at linked loci. This linkage reduces the efficacy of natural selection (Hill & Robertson, 1966, Barton, 1995b, Otto & Barton, 1997, Roze & Barton, 2006). The loss of fitness or curbed evolutionary potential under Hill-Robertson interference may be manifested through several related processes, including clonal interference among asexuals, genetic hitchhiking, background selection, and Muller's Ratchet (Charlesworth *et al.*, 2009). Each of these phenomena and their relationship to Hill-Robertson interference were recently reviewed by Hartfield and Keightley (2012).

Sex and recombination are predicted to alleviate the problems caused by Hill-Robertson interference by breaking apart groups of linked loci, thereby increasing the strength of selection relative to drift (Barton, 1995b, Otto & Barton, 1997, Roze & Barton, 2006). As such, sex/recombination is predicted to reduce the probability of fixing deleterious mutations (Muller, 1964, Felsenstein, 1974, Lande & Schemske, 1985, Charlesworth *et al.*, 1993, Lynch *et al.*, 1995), unite beneficial alleles from different lineages to facilitate adaptation (Fisher-Muller hypothesis (Fisher, 1930, Muller, 1932)), reduce genetic hitchhiking associated with selective sweeps (Maynard Smith & Haigh, 1974, Hartfield &

Otto, 2011), and ultimately permit selection to operate on smaller portions of genomes (Felsenstein, 1974, Peck, 1994, Barton, 1995b, Otto & Barton, 1997).

The Hill-Robertson effect is not a mutually exclusive alternative to the Red Queen hypothesis. Indeed, directional selection could be impeded by Red Queen dynamics (and *vice versa*), which could result in selection for recombination between immune-defense loci and non-immune defense loci (Hodgson & Otto, 2012). In addition, parasite-mediated selection against common genotypes may aid the accumulation of deleterious mutations in clones, which would facilitate their removal from the population (Howard & Lively, 1994, Howard & Lively, 1998, Howard & Lively, 2002, Park *et al.*, 2010).

## Experimental evolution

Several recent studies employing experimental evolution have investigated the role of genetic and ecological factors in driving the evolution and maintenance of sex and/or recombination (reviewed by Hartfield & Keightley, 2012, Kawecki *et al.*, 2012, Roze, 2012). These studies have mainly focused on the benefits of genetic exchange and recombination under: (1) the accumulation of deleterious mutations, (2) persistent migration into different environments, (3) adaptation to novel conditions, (4) and coevolution with pathogens and parasites. Some of the studies contrasted cross-fertilization with self-fertilization, which, though a form of sexual reproduction, has consequences similar to those of asexual reproduction (Heller & Maynard Smith, 1979, Lande & Schemske, 1985, Charlesworth *et al.*, 1993, Lynch *et al.*, 1995).

## Deleterious mutations

Deleterious mutations have long been invoked as a potential explanation for the maintenance of sex (Muller, 1964, Kondrashov, 1988). Sex and recombination are predicted to reduce the probability of fixing deleterious mutations, relative to uniparental reproduction, by preventing Muller's ratchet and/or reducing genetic hitchhiking (Heller & Maynard Smith, 1979).

The nematode *Caenorhabditis elegans* has provided a useful model organism for studying the evolution and maintenance of outcrossing in response to the influx of deleterious mutations. *Caenorhabditis elegans* populations are composed of hermaphrodites and males (Brenner, 1974). Hermaphrodites can reproduce either through self-fertilization or through cross-fertilization, resulting in a mixed mating system in which outcrossing is inherently costly (Stewart & Phillips, 2002, Katju *et al.*, 2008). Several studies have demonstrated, as predicted, that outcrossing rates increase in *C. elegans* populations under experimentally elevated mutation rates (Cutter, 2005, Manoel *et al.*, 2007, Morran *et al.*, 2009). However, deleterious mutations alone do not seem to be a sufficient source of selection to favor the evolution of high levels of outcrossing. Although each study reported greater outcrossing rates in response to elevated mutation rates, the increase in outcrossing was either modest or temporary. Mutation is therefore not a likely explanation for the high frequency of obligate outcrossing exhibited by many taxa across the tree of life.

Several additional studies support this conclusion. A recent study in yeast showed that elevated mutation rates increased the rate of adaptation in sexual populations relative to asexual populations (Gray & Goddard, 2012b). However, this increase in fitness only occurred under selection imposed by a stressful environment, and not under benign conditions. Similarly, *Chlamydomonas reinhardtii*, exhibited no signs of deleterious mutation purging relative to asexual populations when maintained under benign conditions (Renaut *et al.*, 2006). In both systems, deleterious mutation alone again appears to be an insufficient source of selection for the maintenance of sex. This conclusion is further supported by evidence that genomic mutation rates are too low to favor sex via recurrent deleterious mutations (Keightley & Eyre-Walker, 2000). Nonetheless, deleterious mutations may act together with other forms of selection to favor sex (Howard & Lively, 1994, West *et al.*, 1999, Park *et al.*, 2010).

## Migration

Hill-Robertson interference may also favor sex and recombination under conditions in which there is spatial heterogeneity in selection, coupled with migration between the different environments (Lenormand & Otto, 2000, Agrawal, 2009). By breaking down genetic associations, sex and recombination may increase the efficacy of selection on immigrant genotypes that are poorly suited for the novel environment, while also promoting the preservation and spread of incoming beneficial alleles. Therefore, sex and recombination could either maintain or enhance local adaptation in the different environments, and the benefit could outweigh the associated costs. However it is also possible for such migration and sex to disrupt locally adapted allelic combinations, which would select against sex (Agrawal, 2009). Nonetheless, there is some empirical support from studies by Becks and Agrawal (2010) and Gray and Goddard (2012a) that demonstrate migration as a factor capable of selecting for sex.

Gray and Goddard (2012a) found that the combination of sex and migration between yeast populations evolving in two different environments allowed simultaneous adaptation to each environment. Asexual populations adapted to the two environments, but at a much slower rate. Moreover, sexual populations without migration did not exhibit the high levels of adaptation as shown by sexual population with migration. Therefore, the combination of sex and migration can facilitate the assembly of adaptive genotypes across different environments.

Becks and Agrawal (2010) studied populations of rotifers with the ability to reproduce either asexually or sexually in two different environments. In one treatment, they allowed frequent migration between populations; in the other (control) treatment, the populations were maintained in the absence of migration. They found that the propensity to reproduce sexually increased in populations experiencing migration, but decreased in the absence of migration. Therefore, selection for local adaptation coupled with frequent migration was strong enough to overcome the inherent costs of sex. This work also establishes migration between different environments as a potential factor favoring the evolution and maintenance of sex. However, it remains unclear if migration is capable of selecting for obligate sex, as sexual reproduction did not evolve to fixation under the migration treatment. It is also

unclear at present whether migration among locally adapted populations represents a general explanation for sex in natural populations.

## Adaptation to novel conditions

The Fisher-Muller hypothesis predicts that sex/recombination should facilitate rapid adaptation to novel or changing environments (Fisher, 1930, Muller, 1932). Sex and recombination are thought to do so by uniting beneficial mutations from different lineages, separating them from their initial genetic background and then recombining them into the same genome (Felsenstein, 1974, Peck, 1994). When the fitness costs induced by a novel environment are severe, the ability to rapidly adapt may more than overcome the fitness deficits associated with sex. Therefore novel environmental conditions necessitating rapid adaptation are thought to select for the evolution of greater levels of genetic mixing (Weissmann, 1889, Crow, 1992, Peck, 1993, Peck, 1994).

In experimental evolution studies, the Fisher-Muller hypothesis is perhaps the most empirically supported hypothesis concerning the advantages of outcrossing. Outcrossing has often been found to increase the rate of adaptation to a novel environment relative to asexual reproduction (Colegrave, 2002, Kaltz & Bell, 2002, Goddard *et al.*, 2005, Grimberg & Zeyl, 2005, Becks & Agrawal, 2012, Gray & Goddard, 2012a, Gray & Goddard, 2012b, Lachapelle & Bell, 2012, Masri *et al.*, 2013). Outcrossing is also capable of facilitating greater rates of adaptation relative to self-fertilization, indicating that the genetic exchange between lineages associated with outcrossing facilitates more rapid adaptation (Lopes *et al.*, 2008, Morran *et al.*, 2009, Anderson *et al.*, 2010, Morran *et al.*, 2011, Teotonio *et al.*, 2012, Morran *et al.*, 2013). Overall, it seems that outcrossing is generally favored over asexual reproduction and self-fertilization in novel environments.

But, what happens to outcrossing after organisms become well adapted to their novel environment? After a population is sufficiently adapted to a once novel environment, sex and recombination can act to disassemble the adaptive genotypes (Wright, 1931, Lynch & Deng, 1994). Thus asexual reproduction and self-fertilization are predicted to be favored over outcrossing after adaptation to the previously new environment. This temporary benefit of sex has empirical support. Becks and Agrawal (2012) found that rates of outcrossing increased as rotifer populations adapted to a novel environment, but then decreased as fitness plateaued. Further, they found that outcrossing generated more beneficial genotypes during adaptation, while asexual reproduction produced more beneficial genotypes after adaptation. Similarly, Morran and colleagues (2009, 2011) found that outcrossing rates increased to nearly 100% as *C. elegans* populations became adapted to a novel, non-evolving pathogenic bacteria (*Serratia marcescens*). Outcrossing then rapidly declined, presumably due to a fitness plateau following adaptation to the non-evolving pathogen. Therefore, frequent changes in the environment may be a key factor in the long-term maintenance of sex. In addition, multiple environmental factors may act in unison or sequentially to favor and maintain sex.

## Host-parasite coevolution

The Red Queen hypothesis predicts that coevolving parasites can provide a constantly changing environment and maintain outcrossing in spite of its inherent costs. Although Morran et al. (2011) found that exposure to a non-evolving bacterial pathogen was unable to maintain high outcrossing rates, exposure to coevolving pathogens resulted in the evolution and maintenance of high outcrossing rates in *C. elegans* populations. Therefore, coevolving pathogens provided the changing environment required to maintain high rates of outcrossing, despite the costs of outcrossing relative to self-fertilization. Masri et al. (2013) demonstrated a similar phenomenon in a coevolving, experimental *C. elegans/Bacillus thuringiensis* host/pathogen system. Despite the fact that male nematodes were more susceptible to *B. thuringiensis* infection than hermaphrodite nematodes, outcrossing was maintained in coevolving host populations throughout forty-eight host generations. Further experiments showed that outcrossed offspring exhibited greater survival rates in the presence of the pathogen than did selfed offspring. Again, coevolving pathogens favored the maintenance of outcrossing, despite the associated costs, which in this case comprised both the cost of outcrossing as well as elevated male susceptibility to the pathogen.

Selection to produce genetically variable offspring may also select for greater rates of recombination in the rapidly changing environment presented by coevolving parasites. Kerstes et al. (2012) studied recombination rates in the flour beetle, *Tribolium castaneum*, in response to exposure to the coevolving parasite, *Nosema whitei*. They found that the hosts evolved greater recombination rates and maintained greater levels of genetic diversity in response to exposure to the coevolving parasite. Therefore, it appears that antagonistic coevolution favored more frequent genomic shuffling.

## Conclusions

Taken together, the results of laboratory experiments on model organisms have shown that sexual reproduction can be favored in novel environments, but that sex is selected against following adaptation to the new environment. Hence, as anticipated by Maynard Smith, some kind of continual environmental change seems to be required for the long-term maintenance of sex (Maynard Smith, 1978). Antagonistic coevolution with parasites could provide a source of constant environmental change, as well as a source of negative frequency-dependent selection that could favor sexual over asexual reproduction, at least when clonal genotypes are common.

The results of recent laboratory experiments have been consistent with the basic tenets of the Red Queen hypothesis. High levels of outcrossing in *C. elegans* evolved and were maintained only in the presence of coevolving parasites (Morran et al., 2011). In addition, the rate of recombination was observed to increase in flour beetles that were experimentally coevolving with a microsporidian parasite (Kerstes et al., 2012). The results of field studies and experiments using natural populations across a wide range of organisms have also been largely consistent with the Red Queen hypothesis. Hence, at the present time, the Red Queen model is the best supported among the alternative ecological theories for sex, but it remains to be seen whether antagonistic coevolution is part of a very general explanation for sex.

Much also remains to be discovered regarding the genetic details of host-parasite interactions and the mode of selection required to favor the evolution and maintenance of sex. Such details will be critical to determining whether the Hill-Robertson effect is crucial to understanding these interactions, whether they can be understood as fluctuating epistasis among loci involved in defense, or whether both genetic mechanisms are key to the evolution and maintenance of sex. Finally, much remains to be discovered regarding the fitness effects of parasites in natural populations.

Is it possible, or even probable, that coevolving parasites, perhaps in the presence of other pathogens or in concert with the demands of life in saturated environments, are sufficiently common and virulent to select for sex even in the face of its many costs? Finding the answer will require more studies of both model organisms and natural populations.

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