Chapter 7
Sex and the Red Queen

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The essence of sex in our theory is that it stores genes that are currently bad but have promise for reuse. It continually tries them in new combination, waiting for the time when the focus of disadvantage has moved elsewhere – Hamilton et al. (1990).

Abstract Negative frequency-dependent selection exerted by parasites and pathogens can generate a selective advantage for rare host genotypes. This mechanism, known as the Red Queen, is currently considered to be one of the most likely explanations for the predominance of sexual reproduction in natural populations. Even so, the extent to which the Red Queen can and does provide an advantage to sex in nature is fiercely debated. Here, we survey the history of the development of the Red Queen hypothesis as applied to the maintenance of sex and discuss its theoretical underpinnings. We then review and synthesize the current body of theory and empirical data relevant to assessing whether Red Queen dynamics are likely to contribute to any general explanation for why sex is so common. We conclude that while there are many independent lines of evidence in support of a role for the Red Queen, important theoretical and empirical gaps remain. In particular, there is a need for theory addressing the breadth of conditions under which the Red Queen can favor sex, predictions for the patterns of molecular evolution expected for loci under negative frequency-dependent selection, and empirical research evaluating the strength of parasite-mediated selection in nature and the genetics of susceptibility and infection.

7.1 Sex and the Red Queen – Introduction

Negative frequency-dependent selection exerted by parasites such that rare host genotypes are favored is now considered to be one of the most likely selective

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forces underlying the persistence of sex and outcrossing[1] in natural systems. Disproportionately high infection in common host genotypes can create a short-term advantage to sex, because sex results in the production of offspring with variable genotypes.

A more general version of this mechanism originated with Van Valen's (1973) observation that species within a taxonomic group tend to go extinct at a constant rate. Van Valen argued that this pattern could be due to "stochastically constant" deterioration of environmental conditions (caused by either biotic or abiotic forces, though he emphasized antagonistic biotic interactions) from the perspective of species adapted to earlier conditions, and termed this mechanism "The Red Queen's hypothesis." While Van Valen left the origin of the name unstated in the main body of the paper, he did cite Lewis Carroll's *Through the Looking Glass*; *"Now here, you see, it takes all the running you can do, to keep in the same place."* This was the Red Queen's explanation to a confused Alice as to why she could run as fast as she could in Wonderland but never get anywhere, a situation analogous to the constant evolutionary pressure exerted by a changing environment. Bell (1982) recognized the parallels between Van Valen's view of extinction rates and the constant adaptation that should characterize host-parasite coevolution and applied the Red Queen moniker to a new hypothesis that invoked pressure from coevolving parasites to generate an advantage for sex.

Conceptual development of the Red Queen hypothesis ultimately began, as noted by Hamilton (1980), with Haldane (1949), and was revisited by Clarke (1976), both of whom identified disproportionately high attack of common host or prey genotypes as a potential explanation for surprisingly high levels of allelic polymorphism. Haldane (1949) was also the first to argue that disease is likely to be a selective force of profound importance for the maintenance of genetic diversity in many species. While selection imposed by biotic factors was increasingly implicated in the persistence of sex and outcrossing in the 1970's (e.g. Levin 1975, Glesener and Tilman 1978), the explicit coupling of the Red Queen with sex originated with Jaenike (1978; also see Bell 1982). He responded to Williams's (1966, 1975) assertion that the maintenance of sex requires immediate, individual advantages by building on models (Maynard Smith 1971; Charlesworth 1976) showing that recombination can persist if environments change rapidly enough to favor different combinations of alleles from one generation to the next (also see Lewontin 1974). In this case, sex is beneficial because it allows for the production of genetically variable offspring and increases the probability of producing offspring with the combination of alleles that happen to be favored at the time. While this mechanism can provide an individual-level advantage to sex, both Maynard Smith and Charlesworth assumed that the agent of selection was abiotic and unlikely to change rapidly enough to allow sex to persist (also see Maynard Smith 1978).

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[1] Since sex and outcrossing are similar phenomena, and since Red Queen dynamics may contribute to favoring both in a similar manner, "outcrossing" is also included when "sex" is mentioned, and vice versa, unless stated otherwise.

Jaenike's innovation was to provide "biological realism" for these previously-developed models by postulating that the mechanism of selection was biotic in origin (see also Levin 1975; Glesener and Tilman 1978; Bell 1982). Specifically, he pointed out that if parasites preferentially attack common genotypes to which they are adapted, sex will produce novel or rare genotypes that are temporarily free from infection. Although Levin (1975) suggested that pressure from pests could favor *novel* genotypes and thus recombination in plants, Jaenike's idea was an important step forward in that it provided an advantage to rareness, not just novelty, and provided a more general, intrinsic advantage to sexual reproduction.

These ideas were formalized by Hamilton (1980) (also see Glesener 1979, Hamilton 1982), who provided a model verifying that negative frequency-dependent selection exerted by parasites can create cycles in host and parasite genotypic fitness and, under certain conditions, favor sex. Hutson and Law (1981) obtained a similar result with regard to the frequency of recombination, while Price and Waser (1982) found that an allele for sex will spread under stable conditions when there is strong selection for rare genotypes and when offspring dispersal is limited. The Red Queen gained additional credibility from models presented by Hamilton et al. (1990) that, unlike previous models, demonstrated how the Red Queen can still provide an advantage to sexual reproduction under "challenging" but "realistic" conditions (e.g., with repeated mutations to parthenogenesis and when the full two-fold cost of sex is realized). Despite these major theoretical advances, however, the broad applicability of the Red Queen hypothesis remains a contentious issue due to the potentially restrictive conditions under which sex evolves and is maintained (May and Anderson 1983; Howard and Lively 1994; Otto and Nuismer 2004; Agrawal and Otto 2006; Gandon and Otto 2007). A particular focus of this controversy has been the assumed requirements for high virulence, tight linkage, and rapidly fluctuating epistasis, as discussed below.

7.2 Assumptions and Predictions of the Model

The primary assumption of the Red Queen hypothesis is that parasites that are able to infect common host genotypes achieve a significant selective advantage, which thus favors rare hosts. The theory of negative frequency-dependent selection by parasites predicts that loci involved in host infectivity should be polymorphic both within and between natural populations and that genotypic combinations of alleles at these loci should oscillate in frequency over time as local parasites continually adapt to their host population. The implications are that common host genotypes in natural populations should be or become over-infected by parasites relative to their frequency in the population. This type of "over-reactive" frequency-dependent selection has been shown to lead to cyclical dynamics, where parasites eventually track common host genotypes and, assuming there is a fitness cost associated with infection, drive them to lower frequency (Hamilton 1980). The constant cycle of adaptation predicts that only a subset of common genotypes is expected to be over-infected at any one time. This means that interpretation of data relating infection

and genotype frequency can be misleading unless data are collected across many populations and/or across time.

The occurrence and characteristics of the predicted oscillatory cycles have been the focus of numerous theoretical and empirical studies (e.g., Jaenike 1978; Bell 1982; Seger 1988; Hamilton et al. 1990; Dybdahl and Lively 1998; Koskella and Lively 2007). For example, computer simulations of host-parasite coevolution have shown that the period of oscillations (i.e., how quickly parasites drive common clones down in frequency) is determined primarily by parasite generation time, while the amplitude of the oscillations (i.e., the degree of change of individual genotypes over time) is driven mainly by the virulence of the parasite (Lively 1999; Gandon 2002).

A key feature of these dynamics is the time lag between the rise in frequency of a recently rare and resistant host genotype and the subsequent chance introduction of a matching parasite genotype via migration, mutation, or recombination. This means that there will also be a time lag prior to over-infection of the newly common host by the local parasites. This time lag (or phase difference) is essential for driving oscillatory dynamics and has therefore been the focus of much theoretical work (Hutson and Law 1981). For example, host recombination rate, parasite migration rate between host populations, the level of parasite specificity, and the degree of parasite virulence (i.e. the fitness cost of infection for the host) have all been predicted to affect the phase difference (Gandon 2002). These findings suggest that parasite populations that are able to respond more quickly to selection, e.g., more genetically variable populations, will more closely track common host genotypes and more quickly drive changes in the genetic makeup of local host populations.

Where present, these negative frequency-dependent dynamics are predicted to lead to local adaptation of parasites to host populations since parasites are more likely to successfully infect common host genotypes in populations with which they are coevolving. Specifically, if parasites are driving genetic changes in host populations and if geographically distinct populations are evolving independently, each parasite population should be better at infecting hosts from local, sympatric populations than hosts from allopatric populations.

7.2.1 Population Genetics

Population genetic models that explore the Red Queen hypothesis are based on the premise that sex can be advantageous in the face of a changing environment because recombination disrupts non-random association between alleles, i.e., linkage disequilibrium (LD). The idea here is that recombination acts to re-randomize genotypes by breaking up any genotypes that are more frequent in a population than would be expected by random assortment.

Linkage disequilibrium caused by epistasis for fitness can be disadvantageous under two scenarios; first, if there is directional selection and epistasis for fitness is negative; or second, if there is fluctuating selection in which the sign of epistasis

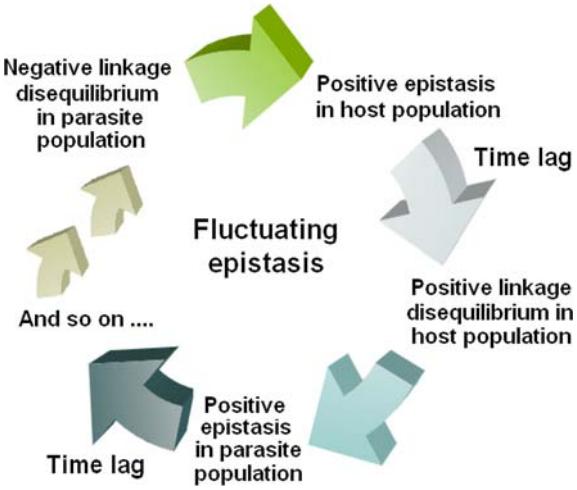

Fig. 7.1 Diagram depicting fluctuating epistasis in which the sign of epistasis in host populations changes in response to the sign of linkage disequilibrium ("LD") in the parasite population, and vice versa. For example, negative LD in the parasite causes positive epistasis in the host population whereby host genotypes that are rare and currently resistant have a disproportionately high fitness. This positive epistasis in the host population then leads to positive LD in the host population after a time lag (as the uninfected host genotype increases in frequency and, eventually, becomes more common than would be predicted based on the individual frequencies of each allele). This positive LD in the host creates positive epistasis in the parasite population since any parasite genotype able to infect this now-common host genotype will have a significant fitness advantage. This would then, after a time lag, lead to positive LD in the parasite population and negative epistasis in the host population, and the cycle continues (Peters and Lively 1999)

changes frequently (Barton 1995; Peters and Lively 1999, 2007; Gandon and Otto 2007). Under the first scenario, negative epistasis is generated any time that the fitness of an individual with two beneficial alleles is less than the product of the fitness for two separate individuals carrying only one of the two alleles. Under weak selection, the build-up of negative epistasis in a population allows for the increased spread of advantageous alleles via recombination and is therefore thought to confer an advantage to sex (Lythgoe 2000). Under the second scenario, the signs of both epistasis and linkage disequilibrium fluctuate over time in a genotype-specific manner (see Fig. 7.1; Maynard Smith 1978; Seger and Hamilton 1988; Barton 1995). This scenario requires that the fluctuations occur over a short and precise time-scale such that epistasis and LD are of opposite signs for a large portion of coevolutionary time (Barton 1995).

While the ability of fluctuating epistasis (see Fig. 7.1) to maintain sex was initially viewed with skepticism because fluctuations had to be so rapid (e.g. Maynard Smith 1978; Barton 1995), new theory has suggested that this particular criticism may be unwarranted (see below). Moreover, the assumption of genotype-specific fluctuations in linkage disequilibrium and epistasis is likely often met during host-parasite coevolution since there is strong evidence for genotype-specific infection

patterns and since rare genotypes are favored via negative frequency-dependent selection (i.e., epistasis and LD are of opposite signs).

A good example of theory that supports the case for fluctuating epistasis is presented in Peters and Lively (1999). They used a series of numerical simulations of host-parasite coevolution to show that tight genetic specificity for infection points to fluctuating epistasis rather than directional selection as the more likely candidate for the maintenance of recombination. The same model was later used under a wider range of parameters to show that recombination spreads in a population due to both short-term benefits in the face of fluctuating epistasis and long-term benefits in response to directional selection (Peters and Lively 2007). Lythgoe (2000) used a deterministic model of parasites with acquired immunity and was also able to implicate fluctuating epistasis as a likely mechanism for the maintenance of sex. Furthermore, Gandon and Otto (2007) used a series of deterministic models to isolate the effects of fluctuating epistasis in large populations. They showed that higher levels of host recombination are favored when LD and epistasis are more often out of phase, which happens when parasites are better adapted to their hosts (see also Fig. 7.2).

The amount of time that LD and epistasis are of opposite signs is also a function of the strength of selection, such that the signs differ more often under strong selection when the period of fluctuations is small (Barton 1995). For example, under a model incorporating highly virulent parasites, negative frequency-dependent selection is predicted to result in a time lag of only 1–2 generations between a given change in the sign of epistasis and the corresponding change in LD (Peters and Lively 1999).

However, even with appropriately rapid fluctuating epistasis, the theory remains restricted by requirements of tight linkage (Gandon and Otto 2007; Peters and Lively 2007) and high virulence (Peters and Lively 2007, but see Salathé et al. 2007). Furthermore, recent theoretical work by Kouyos et al. (2007) suggests that small modifications of the standard Red Queen model can lead to dampening of the LD cycles that are critical to the Red Queen. The authors go on to show that the amplitude of the LD oscillations is inversely correlated with population size and that drift counteracts the dampening of the cycles. In light of the current theory, the ability of host-parasite interactions to single-handedly maintain oscillations in natural populations remains unclear.

The strong selection required to maintain sex in many models has also been a source of concern for many theoreticians, because it implies that only very virulent and/or highly prevalent parasites will be able to maintain sex and outcrossing (e.g., Otto and Nuismer 2004). This problem has been circumvented in some models through the incorporation of further parameters in an attempt to more closely approximate biological realism. For example, Hutson and Law (1981) determined that a recombination modifier allele will spread under relatively weak selection if the coevolutionary time lag is relatively long. More recent models found an increased advantage to sex under larger numbers of interacting loci (Hamilton et al. 1990), when there is some vertical transmission of parasites (Agrawal 2006), when recombination is present but infrequent (Peters and Lively 2007), and when

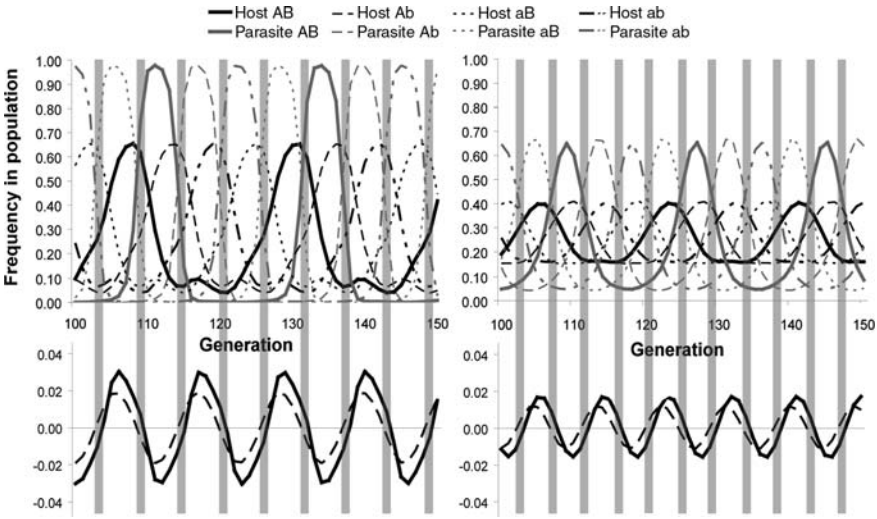

Fig. 7.2 Simulation results using the model of Lively (1999), in which population genetic recursion equations are used to track changes in allele frequencies over time in response to selection, as determined by infection success. The model assumes two diallelic loci with infection of hosts determined through a matching-alleles (MA) framework. The MA model of infection assumes that parasites infect hosts in a genotype-specific manner, such that an Ab parasite is only able to infect Ab hosts. The *top panel* of the figure shows genotype-specific changes in frequency of hosts (*black lines*) and parasites (*grey lines*) over 50 generations of coevolution. The *bottom panels* show the corresponding changes in linkage disequilibrium ("LD") (*solid line*) and epistasis (*dashed line*) over the same period of time. The *grey bars* highlight the periods of time in which epistasis and LD have opposite signs. The *left-hand panels* represent a low rate of parasite migration (0.001), while the *right-hand panels* represent a higher rate of migration (0.05) where parasites are quicker to respond to changes in host genotype frequencies. Because fluctuations in genotype frequencies are occurring more rapidly in the *right-hand panels*, the proportion of time that epistasis and LD are of opposite signs is greater (Barton 1995)

segregation in diploids (as opposed to just recombination in haploids) is considered as a mechanism generating novel combinations of alleles (Agrawal and Otto 2006).

One important consideration is that certain characteristics of parasite community dynamics are likely to play an important role in the realized selective pressure for sex, but are rarely included in laboratory estimates of parasite virulence. As a result, the strength of parasite-mediated selection in nature may often be underestimated. For example, parasite prevalence in a given host population directly influences the strength of parasite-mediated selection, and is thus a critical determinant of the evolutionary response of the host population (Otto and Nuismer 2004). A recent model also shows that virulence may be greater when host condition is density-dependent (Lively 2006). Furthermore, it is rare that only a single parasite species is exerting pressure on a given host population. This means that, to the extent that it is possible, the combined effects of all parasite species in a given community should be considered (Hamilton et al. 1990).

Another way to circumvent the assumption of high parasite virulence was introduced by Salathé et al. (2007), who turn the tables by highlighting the importance of host-mediated selection on parasite populations. The authors created a model that incorporates a biologically realistic fitness cost to parasites that are unable to infect a host in the next generation. They found that when parasites are well-adapted to host populations, as would occur under strong selection for successful infection, recombination in the host population is more likely to create novel and resistant genotypes than to break up currently resistant genotypes. The authors interpreted this result as a consequence of the strong selection for parasites to match local hosts, which results in a greater frequency of susceptible host genotypes. In this case, the primary outcome of recombination would be to break these susceptible host genotypes up and to create rare or novel genotypes, which are temporarily resistant. In addition to the theoretical advances discussed in the previous paragraph, this work is an example of how the incorporation of more biological realism into current working models can uncover the robustness of the Red Queen hypothesis.

7.2.2 Infection Dynamics

One important assumption underlying many host-parasite models is tight genetic specificity for infection such that certain host genotypes are susceptible to a subset of parasite genotypes and resistant to others. Computer simulations have shown that high specificity for infection can lead to oscillations in genotype frequencies and the long-term maintenance of genetic diversity (e.g., Seger 1988). As discussed previously, these oscillatory dynamics are central to many theories regarding host-parasite coevolution, including both local adaptation and the maintenance of sexual reproduction (Hamilton 1980; Bell 1982; Price and Waser 1982; Hamilton et al. 1990).

Two models describing the genetics of host-parasite interactions have received the vast majority of theoretical and empirical attention, though many others exist. The first model described was the "gene-for-gene" model (GFG), which predicts that the interaction between parasite virulence loci and host resistance loci determines successful infection (Flor 1956). The matching alleles model (MA), on the other hand, is based upon a system of self/nonself recognition molecules such that hosts can successfully defend against any parasite genotype that does not match their own (Hamilton 1980; Bell 1982; Peters and Lively 1999).

Agrawal and Lively (2002, 2003) have shown that both GFG and MA models of infection can lead to genotypic oscillations, but that the resulting dynamics are often very different. For example, under the GFG model, the possibility of universally virulent parasites and/or universally resistant hosts exists. In this case, with any migration or mutation, a universally virulent parasite would quickly sweep to fixation and genetic polymorphism within the host and parasite populations would not be maintained. GFG can result in oscillatory dynamics if the model incorporates a fitness cost to resistant host genotypes in an avirulent parasite environment

or to virulent parasite genotypes in a mainly susceptible host population (May and Anderson 1983). Polymorphism can also be maintained under the GFG model in the absence of costs if genetic drift is incorporated (Salathé et al. 2005)

A model incorporating a combination of GFG and MA-type interactions led to sustained oscillations, suggesting that movement away from the strict genetic models might more often lead to dynamic cycling (Agrawal and Lively 2003). This result is particularly interesting since many host-parasite systems do not conform to the predictions of any one proposed infection genetic model (e.g., Rolff and Siva-Jothy 2003; Nidelet and Kaltz 2007; Wegner et al. 2007). In other words, it is likely that the true infection genetics of any given system act more as a combination of the current models than as predicted under any one model. The dynamics observed under GFG conditions, however, have been shown to have more damped and less frequent oscillations, which are less likely to favor sex (but see Agrawal and Lively 2002). Thus, while models incorporating GFG can favor sex under certain conditions, negative frequency-dependent selection leading to the maintenance of polymorphism, and perhaps sex, occurs more readily in MA-based models (Frank 1992, 2000; Brunet and Mundt 2000; Agrawal and Lively 2002).

7.3 Does It Work?

While theory suggests that Red Queen dynamics can maintain sex under certain conditions, direct empirical tests incorporating even several of the integral components of the hypothesis are rare (Lively and Apanius 1995; Apanius et al. 1997; Meirmans and Neiman 2006). This is largely due to the complexity of the Red Queen, which involves (but is not excluded to) host-parasite coevolution, local adaptation, negative frequency-dependent selection, risk of infection, and time-lagged oscillations in host and parasite genotype frequency and in the frequency of infection of rare vs. common genotypes (Wuethrich 1998; Lively 2001; Meirmans and Neiman 2006).

As a result, empirical work relevant to evaluating whether the Red Queen contributes widely to the maintenance of sex has focused on examining at best a few of its components (Apanius et al. 1997; Meirmans and Neiman 2006). This means that the majority of these studies are limited in their ability to exclude other potential explanations for results that fit the predictions of the Red Queen (Wuethrich 1998). As reviewed below, while there is mounting empirical evidence for each of the basic components of the theory, several key questions remain unanswered.

7.3.1 Geographical Distribution of Sex and Outcrossing

There is a well-documented pattern of high frequency of outcrossing and sex in undisturbed, biologically complex habitats (Levin 1975; Glesener and Tilman 1978; Barrett and Eckert 1990; Hamilton et al. 1990) where disease and other “natural enemies” are prevalent (Levin 1975; Glesener and Tilman 1978; Lloyd 1980; Bell

1982). In fact, the recognition of the predominance of sex in stable communities led to the devaluing of models hypothesizing that sex is common because it provides a selective advantage when abiotic conditions are unpredictable (Glesener and Tilman 1978; Maynard Smith 1978; Price and Waser 1982). Levin (1975) was the first to propose that the ecological association between sex and stability may result from pathogen-mediated selection for outcrossing in natural populations. The documentation of these patterns set the stage for more direct exploration of the role of Red Queen dynamics in the maintenance of sex.

7.3.2 Frequency of Sex vs Frequency of Infection

If Red Queen dynamics contribute to the maintenance of sex within species, and if variance in the risk of infection is high, primarily sexual/outcrossing populations and species should be found where the risk and prevalence of infection is high, and vice versa (Lively and Apanius 1995; Lively 2001). As noted above, the geographical distribution of sex broadly fits these predictions.

Whether the Red Queen explains the distribution of sex and outcrossing within and between species was first explicitly addressed in two studies from 1987 that employed comparative approaches to determine whether variables assumed to be associated with the intensity of parasite pressure could explain variation in the frequency of sex or recombination. In a study aimed at identifying the determinants of recombination frequency amongst 40+ mammal species, Burt and Bell (1987) showed that ~75% of the variance in recombination above the level required for normal meiosis was explained by variance in generation time. They argued that this result was in line with the expectations of the Red Queen, since longer generation times should favour higher levels of recombination because parasites would have more time to adapt to a particular host genotype prior to host reproduction. Lively (1987) found that a large fraction of the variation in the relative frequency of sexual vs. asexual *Potamopyrgus antipodarum*, a New Zealand snail, was explained by variation in the frequency of infection by virulent parasites. In other words, highly sexual populations were also heavily infected, as expected if sex can only gain an advantage in the face of intense pressure from coevolving parasites (also see Lively 1992; Lively and Jokela 2002; King and Lively 2009). Importantly, later studies established that this link between the frequency of sex and infection was not due to increased susceptibility of sexual *P. antipodarum* (Lively and Jokela 1996; Jokela et al. 1997). Positive associations between parasitism and outcrossing in two other hermaphroditic freshwater snail species have also been documented (Schrag et al. 1994, reviewed in Johnson et al. 1997), but are not a ubiquitous feature of snail species with mixed sexual/asexual populations (Ben-Ami and Heller 2005, 2008).

Covariance between the relative frequency of sex/outcrossing and the frequency of parasitism is now established in a wide range of taxa, providing broad but indirect support for a role for the Red Queen in the maintenance of sex. For example, Kumpulainen et al. (2004) showed that the variation in the relative frequency of

parasitoids explained a large fraction of the variance in the relative frequency of sexual psychid moths, while asexual moths tend to predominate in locations that are relatively parasitoid-free. Outcrossing has also been shown to be more prevalent in plant species subject to attack by multiple pathogen and parasite species (Busch et al. 2004).

Associations between the frequency of recombination within a species and the presence of virulent parasites are also expected if the Red Queen can provide a short-term advantage to sex and recombination. Such a pattern was documented in a recent selection experiment conducted by Fischer and Schmid-Hempel (2005). They found evidence for increased frequency of recombination in populations of the flour beetle, *Tribolium castaneum*, after only 8 generations of exposure to a microsporidian parasite, *Nosema whitei*, relative to parasite-free control populations. The results from this experimental coevolution study are a major contribution to the body of empirical data relevant to the Red Queen in that they suggest that parasite-mediated selection can quickly facilitate the spread of recombination in a population.

7.3.3 Susceptibility to Infection

If sex/outcrossing are favored by Red Queen dynamics, individuals that are the product of asexual reproduction or selfing should be, *on average,* easier to infect with local, coevolving parasites than individuals that are the product of outcrossed sex (Lively and Apanius 1995; Agrawal and Lively 2001). Empirical assessment of this prediction is complicated by a number of factors including the likelihood of periodic maladaptation of coevolving parasites (Morand et al. 1996), the extent to which selection for particular mating systems relies upon the genetics of infection and resistance (e.g., Agrawal and Lively 2001, 2002), and the difficulty of accurately measuring the risk of infection in natural populations (Lively 2001).

Direct support for this element of the Red Queen also requires that higher levels of infection in asexuals, relative to sympatric sexuals, are due to increased mean susceptibility of asexuals to infection by coevolving, local parasites. Indirect evidence for this pattern comes from observational studies finding that asexual or selfed individuals have higher rates of infection or more enemy damage than sympatric sexually-produced individuals, though other explanations for this pattern cannot be rejected with such data alone (Mee and Rowe 2006). A good early example of this type of study comes from Burt and Bell (1991), who found that asexually produced American beech (*Fagus grandifolia*) seedlings suffered more herbivore damage when very young than did sympatric sexually-produced seedlings. Similar patterns have since been documented in asexual vs. sexual lizards (Moritz et al. 1991; see also Chapter 21), fish (Hakoyama et al. 2001; Mee and Rowe 2006; see also Chapter 19), flatworms (Michiels et al. 2001; see also Chapter 18), and inbred vs. outbred sheep (Coltman et al. 1999).

A few studies have directly compared the susceptibility of asexual vs. sexual taxa to infection by parasites and pathogens. Hakoyama et al. (2001) examined the

metacercarial load and immunocompetence in sexual vs. asexual *Carassius* (crucian carp) living sympatrically in a Japanese river. They found that sexual *Carassius* had a significantly lower load of metacercarian parasites and ~50% higher immune activity than their asexual counterparts. Hakoyama et al. concluded that the reduced immune activity of asexuals could underpin their higher parasite load, but that more data are needed to understand whether this phenomenon actually helps to maintain sex in this species. Another recent study showed that asexual lineages of a freshwater snail (*Potamopyrgus antipodarum*) had ~ 30% lower count of a particular type of immune defense cells than sexuals (Osnas and Lively 2006), though whether this plays a role in the persistence of sexual *P. antipodarum* is unclear.

There still remains no clear and generalizable relationship between mating system and susceptibility to parasites (e.g., Stevens et al. 1997; Haag et al. 2003; Puurtinen et al. 2004); there are systems where parasite prevalence is statistically indistinguishable in sexuals and asexuals (e.g., Tobler and Schlupp 2005) and in selfing vs. outcrossing individuals (e.g., Puurtinen et al. 2004), or even higher in sexuals than in asexuals (e.g., Hanley et al. 1994; Brown et al. 1995). Such results are difficult to interpret definitively in light of potentially complicating factors such as differences in ploidy level between sexual and asexuals (Osnas and Lively 2006) and high among-clone variance in asexual lineage susceptibility (Brown et al. 1995). A meta-analysis that takes these phenomena into account could be quite illuminating. Either way, it is clear that more research into the genetics and physiology of infection and resistance in sexuals vs. asexuals and selfers vs. outcrossers is needed to fully evaluate the role of parasite pressure in the predominance of sex and outcrossing.

7.3.4 Rare Advantage

Antonovics and Ellstrand (1984) used sweet vernal grass (*Anthoxanthum odoratum*) to perform the first empirical study explicitly aimed at testing the Red Queen. Although their research did not focus upon parasites per se, it did test a key component of the Red Queen: that minority genotypes would realize a fitness advantage simply as a function of being rare. Minority *A. odoratum* genotypes did in fact experience a two-fold advantage, leading Antonovics and Ellstrand to conclude that negative frequency-dependent selection by a biotic agent could facilitate the maintenance of sex in natural populations (also see Ellstrand and Antonovics 1985). A follow-up study by Schmitt and Antonovics (1986) found no minority-genotype advantage for *A. odoratum* with regard to probability of infection by aphids, suggesting that negative frequency-dependent selection was not prominent in this particular parasite. They did observe, however, that infected plants had ~30% higher survivorship when surrounded by unrelated vs. related neighbors, which indicates that aphid infection could interact with other mechanisms to favor sex and outcrossing. Kelley (1994) summarized data from this system in order to determine whether an aphid-transmitted virus that infects *A. odoratum* might favor sexually-produced genotypes.

He determined that the virus provided a weak advantage for rare and/or sexually produced *A. odoratum* genotypes, but concluded that more study was needed to clarify the role of this and other pathogens in favoring rare *A. odoratum* genotypes species.

A 1990 study of parasite load in sexual vs. asexual topminnows (*Poeciliopsis* spp.) in several natural populations provided particularly compelling support for negative frequency-dependent selection exerted by parasites favoring rare hosts (Lively et al. 1990). One population, Sandal Pool, contained members of two topminnow clones along with sexual individuals, while another population, Log Pool, contained sexuals but only one of the two Sandal Pool clones. The clone present in both populations was at low frequency relative to the other clone in Sandal Pool. Lively et al. (1990) found that the single Log Pool clone had a significantly higher load of trematode parasites than the coexisting sexuals, while the other, more common clone was more infected than both the other clone and the sexuals in Sandal Pool. This result indicated that the frequency of infection was a function of clonal frequency rather than among-clone variance in susceptibility. This inference was bolstered by a superficially contradictory finding from a third population, where sexual topminnows were infected at higher levels than their sympatric clonal counterparts. However, this pool had recently experienced a drought that resulted in the loss of nearly all of the genetic diversity of the sexual topminnow population. Consequently, the sexual individuals in the pool were very homozygous relative to the asexuals, which maintained permanent high heterozygosity due to their apomictic reproduction (Vrijenhoek and Lerman 1982). Once the genetic diversity of the sexuals was supplemented by an introduction of sexual fish from a different population, the common clone was found to have significantly higher frequency of infection than the sexuals only 2 years following the transplant. The latter result also demonstrates that parasites can respond rapidly to changes in host genotypic frequency, a key component of the Red Queen hypothesis (Lively and Apanius 1995; Peters and Lively 1999).

It is clear, however, that not all interactions between hosts and their coevolving parasites involve negative frequency-dependence. For example, Strauss and Karban (1994) found that, counter to the predictions of the Red Queen, genetic diversity (or rareness, per se) provided no advantage for *Erigeron glaucas* (seaside daisy) subject to infection by a herbivorous thrip, *Apterothrips apteris*. Similar results were documented in another plant species, *Allium vineale*, by Ronsheim (1996), and in a freshwater bryozoan (Vernon et al. 1996). The negative results from plants are perhaps not surprising given that plant-parasite interactions are often characterized by GFG infection genetics that are less likely to provide a direct advantage to sex (Kover and Caicedo 2001).

Clay and Kover (1996) concluded that there were still not sufficient data to determine whether negative frequency-dependent selection against common genotypes is widespread enough to provide a general explanation for the predominance of sex. More than a decade later, there is now evidence for negative frequency-dependent selection exerted by parasites in a diverse array of taxa (e.g. Carius et al. 2001; Bruvo et al. 2007; Mundt et al. 2008), suggesting that this particular

component of the Red Queen is a relatively common feature of host-parasite interactions.

7.3.5 Parasitic Tracking of Common Host Genotypes

The Red Queen requires not just rare advantage but also evolutionary tracking of common parasite genotypes, or so-called "reciprocal entrainment" (Lively and Apanius 1995). A good example of this comes from Dybdahl and Lively (1998), who found that clonal genotype frequencies of the New Zealand freshwater snail, *Potamopyrgus antipodarum,* were correlated with time-lagged changes in infection by the sterilizing trematode, *Microphallus*. By examining genotype-specific infection rates in natural populations over a period of five years they found that clones that had been rare and under-infected in samples from previous generations tended to become over-infected after they became common. In a follow-up study, Lively and Dybdahl (2000) showed that common clones were infected at ~30% higher levels than sympatric rare clones by local parasites, but that levels of infection between rare and common clones did not differ when exposed to allopatric parasites. This result showed that common genotypes were specifically being targeted by coevolving parasites and were not just inherently more susceptible. Jokela et al. (2009) took this approach a step further by showing that clones from a mixed sexual/asexual population that were both common and resistant 7–10 years ago had since become extremely rare and more susceptible to infection. This is a key finding because it provides definitive evidence that key elements of the Red Queen can operate on the short time scale required to maintain sex, and in a population where sexuals and asexuals compete.

Lythgoe and Read (1998) highlighted the *Potamopyrgus-Microphallus* system, and pointed out that one can test the predictions of Red Queen models by looking backward in time to determine which host genotypes were common and which were rare prior to the infection data at the time of the study. They called this method the "Advice of the Rose" after Lewis Carroll's novel in which Alice is told by the rose to walk backwards in order to find the Red Queen.

This idea was recently tested using experimental coevolution methods comparing infectivity of *Microphallus* populations that were coevolving directly with *Potamopyrgus antipodarum* with infectivity of *Microphallus* populations on hosts that were lagged behind by one generation (Koskella and Lively 2007). After only three generations of experimental coevolution, the coevolving parasites were ~65% more infective to their own, coevolving hosts than to the control hosts, which had not received parasites since the start of the experiment. Furthermore, the experimental host populations were ~32% less susceptible than control hosts to parasites from their original population, indicating that the host populations had responded to selection imposed by the coevolving parasites. These results are indicative of just how powerful such experiments can be for detecting the effects of parasite-mediated selection. Furthermore, the results showed that the lagged host treatment

had a consistently higher rate of infection than the coevolving host treatment. Parasites were therefore tracking their host populations in a time-lagged manner such that parasites from any given generation were better able to infect hosts that were lagged behind by one generation than contemporaneous hosts that already had an opportunity to respond to selection by the parasite.

Data examining the ubiquity of parasite-mediated, frequency-dependent selection has focused on uncovering its two major components; time-lagged dynamics in parasite tracking and genotype-specific tracking of host genotypes. However, it is important to note that, although over-infection of common clones is a direct prediction of the Red Queen hypothesis, it is only predicted to be found in roughly half of the cases. This is because the time lag dynamics allow hosts to remain common and under-infected until a suitable parasite genotype arises in the population via either migration or mutation (Dybdahl and Lively 1995; Morand et al. 1996). This means that absence of infection in a common host genotype is not sufficient to reject the Red Queen. Therefore, future studies examining parasite-mediated, negative frequency-dependent dynamics should follow multiple common host genotypes and should test for over- or under-infection in a genotype-specific manner over time.

7.3.6 Parasite Local Adaptation

As mentioned previously, empirical data on parasite local adaptation has been viewed as a key piece of the Red Queen puzzle. Whether a parasite is better able to infect members of its local, sympatric host population than allopatric hosts depends in part upon the degree of genetic specificity for infection and the dynamics of coevolution.

A distinct alternative to the Red Queen is the hypothesis of Arms Race coevolution (Dawkins and Krebs 1979), which describes a situation in which hosts continually build up their armory of resistance to parasitism while parasites respond by becoming more virulent or evolving ever-changing mechanisms of evading host immunity. This form of unidirectional coevolution is characterized by repeated selective sweeps (Woolhouse et al. 2002) and, unlike the Red Queen, does not generate a rare advantage per se. Rather, hosts and parasites are continually evolving novel adaptations in response to one another which, once defeated, will never again incur resistance/virulence against the other player. In addition, the adaptations resulting in resistance of hosts and virulence of parasites are an inherent property of the individual genotype, such that some hosts are more resistant overall and some parasites are more virulent overall. Thus, another major demarcation between Arms Race and Red Queen coevolution is that under the Red Queen, a genotype which is susceptible to one parasite genotype may be resistant to another and vice versa. Since populations with highly virulent parasites would most likely also contain highly resistant hosts, parasite local adaptation is not predicted to be universal because virulent parasites would be more infective to any allopatric hosts that have not yet

evolved a similarly high level of resistance. The implication of these differences between the two mechanisms is that Arms Race dynamics are less likely to favor sexual reproduction. Distinguishing between these two theories, and thus, the extent to which parasite pressure is likely to favor sex, requires insight into how host and parasite populations change over time and whether directional selection or negative frequency-dependent selection explains the antagonistic interaction between the species.

As outlined above, one important type of evidence in favor of Red Queen dynamics is parasite tracking of common host genotypes. Systems where dormant stages of both host and parasite are occasionally preserved present a promising avenue for direct empirical tests of parasite tracking. Decaestecker et al. (2007) used this approach to show that *Daphnia magna* were consistently more susceptible to contemporaneous parasites than those from past generations (see also Chapter 15). Since this type of data is very difficult if not impossible to collect for most systems, reciprocal cross-infection experiments testing for local adaptation can provide indirect support for parasite tracking (Lively and Apanius 1995; Johnson et al. 1997, Lively et al. 2004), as well as for tight genetic specificity for infection (e.g., Carius et al. 2001). Assessment of the presence and extent of local adaptation is complicated by the expectation that the time-lag characterizing host-parasite coevolution under negative frequency-dependent selection should result in periodic "local maladaptation" (Morand et al. 1996). Hence, it not surprising that while local adaptation has been documented in many taxa, it does not characterize all host-parasite systems (as reviewed in Greischar and Koskella 2007).

Among the many studies documenting a strong degree of local adaptation is Shykoff and Schmid-Hempel (1991). They exposed uninfected groups of bumblebees (*Bombus terrestris*) to *B. terrestris* infected with a horizontally-transmitted trypanosome parasite, and found that the prevalence of infection following exposure was more than twice as high when the source and target hosts were related. A more recent study examining infection dynamics of the freshwater crustacean, *Daphnia magna,*and its bacterial parasite, *Pasteuria ramosa,* found that host clone/parasite combinations that had been isolated together from natural populations resulted in successful new infections nearly twice as often as novel host-parasite combinations (Carius et al. 2001). This study further showed that no single host clone was more resistant to every parasite genotype, which is suggestive of matching-allele type dynamics rather than gene-for-gene, as discussed previously. There is also strong evidence for local adaptation in the *Microphallus-Potamopyrgus antipodarum* system (Lively et al. 2004; Jokela et al. 2009), and from several other snail-parasite systems (reviewed in Lively 1996; Johnson et al. 1997; Webster and Davies 2001).

Local adaptation has also been demonstrated within experimental coevolution studies. For example, Nidelet and Kaltz (2007) compared the frequency of infection in three lineages of the protozoan *Paramecium caudatum* by "resident," coevolving lines of a bacterial parasite (*Holospora undulata*) to infection by novel, non-coevolving *H. undulata* lines. In all three *P. caudatum* lineages, there was a small but significant increase in infection prevalence for resident vs. novel parasites following ~30 bacterial generations of host-parasite sympatry. These types of laboratory

experiments offer a powerful tool for investigating both genotypic specificity for infection and patterns of coevolution.

7.3.7 Molecular Evolution in Disease Resistance Loci

Haldane (1949) was the first to suggest that selection by parasites might favor rare hosts and explain the high intraspecific allelic diversity of vertebrate cell-surface molecules. This possibility remained an abstract concept for decades, requiring the elucidation of the molecular structure of immunological factors and the ability to generate and analyze DNA sequence data. Since then, there has been a growing body of empirical research in support of the idea that negative frequency-dependent selection may underlie evolution at many genes associated with immune function (e.g. Stahl et al. 1999; Bergelson et al. 2001; Tiffin et al. 2004; Lazarro 2005; Bakker et al. 2006; Dionne et al. 2007; Schwensow et al. 2007; reviewed in Bernatchez and Landry 2003; Charlesworth 2006; Piertney and Oliver 2006).

The most compelling data come from studies of the major histocompatibility complex (MHC), a multi-gene region that is the main source of immunological self/non-self recognition in vertebrates. Its unusual structure, co-dominant expression, and high allelic diversity led Bodmer (1972) and Doherty and Zinkernagel (1975) to suggest that heterozygosity or rareness at MHC might confer a fitness advantage mediated by coevolutionary interactions with pathogens (also see Hamilton 1982). Doherty and Zinkernagel (1975) provided initial empirical support for this hypothesis by showing that mice heterozygous for one component of MHC had enhanced immunological surveillance relative to homozygous mice.

Whether MHC diversity is actually maintained by negative frequency-dependent selection exerted by pathogens has been controversial and attracted much attention (e.g., Hughes and Nei 1988, 1992; Takahata and Nei 1990; Slade and McCallum 1992; Potts et al. 1994; Apanius et al. 1997; Edwards and Hedrick 1998; Hughes and Yeager 1998; Wedekind et al. 2005; Milinski 2006; Piertney and Oliver 2006; Knapp 2007), though there is little doubt that some form of selection is involved (Apanius et al. 1997; Bernatchez and Landry 2003; Piertney and Oliver 2006). This subject has been the focus of recent reviews (e.g. Bernatchez and Landry 2003; Milinski 2006; Piertney and Oliver 2006), so we provide only a brief overview.

Hughes and Nei were the first to use DNA sequence data to study MHC evolution by conducting a series of comparisons of the relative amounts of synonymous and non-synonymous polymorphism in class I and class II MHC (Hughes and Nei 1988, 1989a, b). Non-synonymous polymorphism is predicted to be low relative to synonymous polymorphism in genetic regions that are subject to purifying selection (as most genetic regions are assumed to be) because non-synonymous mutations change protein structure. However, if rareness per se is favored, as hypothesized in the antigen recognition site (ARS) of MHC, non-synonymous polymorphisms are predicted to accumulate at relatively high rates.

Hughes and Nei found that this prediction was met in both Classes I and II MHC, with high non-synonymous polymorphism in the ARS relative to other parts of

MHC and to other protein-coding genes not directly involved in pathogen recognition (Hughes and Nei 1988, 1989a, 1989b; also see Schaschl and Wegner). While Hughes and Nei (1988) attributed this result to overdominance, Hughes et al. (1994) concluded that MHC polymorphism is maintained by selection favoring diversity in the ARS, and noted that the association of MHC haplotypes with resistance to malaria implicates pathogens as an important selective agent. Since then, other researchers have documented similar patterns of sequence evolution in other taxa, and have come to similar conclusions (e.g., Bernatchez and Landry 2003; Mayer and Brunner 2007).

The results of Hughes and Nei inspired research more directly aimed at disentangling the selective force(s) underlying the unique pattern of evolution at MHC. An important body of work comes from studies that address whether particular MHC genotypes are more resistant to infection than others. Some studies find that certain MHC genotypes are associated with higher susceptibility to infectious disease (e.g. Briles et al. 1977; Todd et al. 1990; Hill et al. 1991, 1994; Apanius et al. 1997; Ameisen et al. 2002; Wegner et al. 2004; Westerdahl et al. 2004; Milinski 2006; Wedekind et al. 2005; Knapp 2007), or that MHC heterozygotes are more resistant to infection (e.g. Penn et al. 2002; McClelland et al. 2003; Wegner et al. 2004), while other studies find no consistent link between heterozygosity and resistance to infection (e.g. Wedekind et al. 2005; Schwensow et al. 2007; reviewed in Bernatchez and Landry 2003; Milinski 2006). A small body of data (e.g., Schwensow et al. 2007) does find that rare MHC genotypes are infected at low levels relative to more common genotypes, as expected under negative frequency-dependent selection (reviewed in Knapp 2007).

Potts et al. (1994) reviewed the state of the empirical data relevant to whether pathogens directly mediate MHC diversity, and concluded that more data were needed to address this question. Recent reviews have come to the same conclusion (Wedekind et al. 2005; Milinski 2006; Piertney and Oliver 2006; Knapp 2007). One complicating factor is that, as for many complex biological phenomena (West et al. 1999; Meirmans and Neiman 2006), multiple, non-mutually exclusive mechanisms are likely to be involved in the selective maintenance of MHC diversity (Apanius et al. 1997; Piertney and Oliver 2006). A complication that applies more generally is that there are still no clear expectations for the pattern of molecular evolution that will definitively allow identification of negative frequency-dependent selection (Bernatchez and Landry 2003; Tiffin et al. 2004; Nordborg et al. 2005; Bakker et al. 2006; Charlesworth 2006; Piertney and Oliver 2006; Tiffin and Moeller 2006).

7.4 Pluralism

As noted by Kondrashov (1993), there exist at least 20 potential explanations for the predominance of sex (e.g., Kondrashov 1993). However, none of these hypotheses (including the Red Queen) has found sufficient empirical support to consider the sex problem solved. In particular, single mechanisms seem to be limited by narrow applicability; each model can only favor sex/outcrossing under a set of strict, often unrealistic assumptions (West et al. 1999; Meirmans and Neiman 2006). The

inability to explain sex via single mechanisms has resulted in a recent shift in focus away from discrimination between mechanistically simple hypotheses towards more complex approaches that can potentially be applied under a broader rage of conditions (Barton and Charlesworth 1998; West et al. 1999; Burt 2000; Meirmans and Neiman 2006; de Visser and Elena 2007). Several recent studies have theoretically explored pluralistic mechanisms for sex, incorporating the Red Queen along with other mechanisms such as mutation accumulation (Howard and Lively 1994, 1998) and mate choice (Howard and Lively 2003).

7.4.1 The Red Queen and Pluralism

As detailed above, the extent to which the assumptions underlying the Red Queen hold is the subject of much controversy. Even if the many requirements for Red Queen are in place, simulations show that when asexual assemblages are diverse, the Red Queen will not drive individual lineages to extinction due to the selective advantage that accrues to a rare asexual genotype under conditions of coevolving virulent parasitism (Howard and Lively 1994, 1998). Furthermore, the host-parasite coevolutionary dynamics that are required for operation of the Red Queen select for genetic diversity rather than sex per se (Lively and Howard 1994). This means that if all else is equal, a genetically diverse array of asexual lineages is as well-equipped to deal with parasitism as a sexual population (Glesener and Tilman 1979; Lively and Howard 1994; Lythgoe 2000).

Recognizing some of these difficulties, Howard and Lively (1994) pointed out that the Red Queen may apply more broadly if it is operating in concert with other mechanisms. For example, they used computer simulations to show that bottlenecking of host lineages caused by intense, coevolving parasitism targeting common host genotypes could accelerate the rate of deleterious mutation accumulation by decreasing the efficacy of purifying selection (Howard and Lively 1994, 1998), posing a further challenge to asexuals. These simulations found that extinction of asexual lineages due to interaction between the Red Queen and mutation accumulation can happen within several hundred generations of the origin of the asexual lineage, rapidly enough to allow sex to persist (Howard and Lively 1994). In contrast, their models suggest that neither the Red Queen nor mutation accumulation alone can give sex enough of a short-term advantage to explain its widespread persistence.

7.4.2 Empirical Tests

Authors have increasingly implicated pluralistic mechanisms such as the model described above as potential explanations for the persistence of sex (e.g. Jokela et al. 2003; Bruvo et al. 2007), though empirical tests remain scarce (West et al. 1999; Meirmans and Neiman 2006). In fact, to the best of our knowledge, no direct empirical tests of pluralist hypotheses for sex exist in mixed sexual/asexual systems in which sex requires an explanation. While two recent studies in asexual

bacterial model systems (*Escherichia* and *Pseudomonas*) have documented interactions between parasite pressure and mutations in a manner that is consistent with that postulated in pluralist models (Cooper et al. 2005; Buckling et al. 2006; also see Coltman et al. 1999), widespread empirical application of pluralist models has been hampered by the common perception that these models may be effectively untestable in non-model eukaryotic systems (Meirmans and Neiman 2006).

Instead, early attempts to empirically test pluralistic hypotheses for sex have largely been indirect, investigating whether readily measurable phenomena (e.g., low fertility) that may be linked to an expected direct consequence of asexuality that itself is difficult to measure, high mutation load, are associated with higher rates or more severe consequences of disease (e.g. Bruvo et al. 2007). Other tests have used sexual model eukaryotic systems (e.g. Peters 1999; Haag et al. 2003; Salathé and Ebert 2003; Killick et al. 2006). Many of these studies obtain results consistent with those expected under particular pluralist mechanisms (e.g. Killick et al. 2006; Bruvo et al. 2007), paving the way for more direct and powerful tests of these ideas (Meirmans and Neiman 2006).

7.5 Conclusions

There is increasingly strong empirical support for many of the key elements of the Red Queen hypothesis for sex. However, whether Red Queen dynamics play an important role in the maintenance of sex and outcrossing in many natural populations remains unresolved. While recent theoretical advances have emphasized that host-parasite interactions can favor sex under a broader range of conditions than originally envisioned (especially if pluralism is considered), reasonable doubts remain. In general, the complexity of the mechanisms involved means that a definitive verdict on the utility of the Red Queen as an explanation for sex requires both more theory (e.g., Gandon and Otto 2007) and more data (Peters and Lively 2007). We believe that in particular, data evaluating the strength and extent of parasite-mediated selection in natural populations and studies directed at elucidating the genetics of infection/ resistance and whether/why there are differences in susceptibility to infection in sexual vs. asexuals are needed to give the Red Queen a fair and full test.

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References

Agrawal AF (2006) Similarity selection and the evolution of sex: revisiting the Red Queen. PLoS Biol 4: 1364–1371

Agrawal AF, Lively CM (2001) Parasites and the evolution of self fertilization. Evolution 55: 869–879

Agrawal AF, Lively CM (2002) Infection genetics: gene-for-gene versus matching-allele models, and all points in between. Evol Ecol Res 4: 79–90
Agrawal AF, Lively CM (2003) Modeling infection genetics as a two-step process combining gene-for-gene and matching-allele genetics. Proc R Soc Lond B 270: 323–334
Agrawal AF, Otto SP (2006) Host-parasite coevolution and selection on sex through the effects of segregation. Am Nat 168: 617–629
Ameisen JC, Lelièvre JD, Pleskoff O (2002) HIV/host interactions: new lessons from the Red Queen's country. AIDS 16: S25–S31
Antonovics J, Ellstrand NC (1984) Experimental studies of the evolutionary significance of sexual reproduction. I. A test of the frequency-dependent selection hypothesis. Evolution 38: 103–115
Apanius V, Penn D, Slev PR, Ruff LR, Potts WK (1997) The nature of selection on the major histocompatibility complex. Crit Rev Immunol 17: 179–224
Bakker EG, Toomajian C, Kreitman M, Bergelson J (2006) A genome-wide survey of *R* gene polymorphisms in *Arabidopsis*. Plant Cell 18: 1803–1818
Barrett SCH, Eckert CG (1990) Variation and evolution of mating system in seed plants. In: Kawano S (ed) Biological approaches and evolutionary trends in plants. Acad Press, London, pp. 229–254
Barton NH (1995) A general model for the evolution of recombination. Genet Res 65: 123–144.
Barton NH, Charlesworth B (1998) Why sex and recombination? Science 281: 1985–1990
Bell G (1982) The masterpiece of nature. Croon Helm, London
Ben-Ami F, Heller J (2005) Spatial and temporal patterns of parthenogenesis and parasitism in the freshwater snail *Melanoides tuberculata*. J Evol Biol 18: 138–146
Ben-Ami, F, Heller J (2008) Sex versus parasitism versus density. Biol J Linn Soc 93: 527–544.
Bergelson J, Kreitman M, Stahl EA, Tian D (2001) Evolutionary dynamics of plant *R*-genes. Science 292: 2281–2285
Bernatchez L, Landry C (2003) MHC studies in nonmodel vertebrates: what have we learned about natural selection in 15 years? J Evol Biol 16: 363–377
Bodmer WF (1972) Evolutionary significance of the HL-A system. Nature 237: 139–145
Briles WE, Stone HA, Cole RK (1977) Marek's disease: effects of B histocompatibility alloalleles in resistant and susceptible chickens. Science 195: 193–195
Brown SG, Kwan S, Shero S (1995) The parasitic theory of sexual reproduction: parasitism in unisexual and bisexual geckos. Proc R Soc Lond B 260: 317–320
Brunet J, Mundt CC (2000) Disease, frequency-dependent selection, and genetic polymorphisms: experiments with stripe rust and wheat. Evolution 54: 406–415.
Bruvo R, Schulenburg H, Storhas M, Michiels NK (2007) Synergism between mutational meltdown and Red Queen in parthenogenetic biotypes of the freshwater planarian *Schmidtea polychroa*. Oikos 116: 313–323
Buckling A, Wei Y, Massey RC, Brockhurst MA, Hochberg ME (2006) Antagonistic coevolution with parasites increases the cost of host deleterious mutations. Proc R Soc Lond B 273: 45–49
Burt A (2000) Perspective: sex, recombination, and the efficacy of selection: was Weismann right? Evolution 54: 337–351
Burt A, Bell G (1987) Mammalian chiasma frequencies as a test of two theories of recombination. Nature 326: 803–805
Burt A, Bell G (1991) Seed reproduction is associated with a transient escape from parasite damage in American beech. Oikos 61: 145–148
Busch J, Neiman M, Koslow JM (2004) Evidence for maintenance of sex by pathogens in plants. Evolution 58: 2584–2590
Carius HJ, Little TJ, Ebert D (2001) Genetic variation in a host-parasite association: potential for coevolution and frequency-dependent selection. Evolution 55: 1136–1145
Charlesworth B (1976) Recombination modification in a fluctuating environment. Genetics 83: 181–195
Charlesworth D (2006) Balancing selection and its effects on sequences in nearby genome regions. PLoS Genet 2: 0379–0384

Clarke B (1976) The ecological genetics of host-parasite relationships. In: Taylor AER, Muller R (eds) Genetic aspects of host-parasite relationships. Blackwell Scientific, Oxford, pp. 87–103
Clay K, Kover PX (1996) The Red Queen hypothesis and plant/pathogen interactions. Annu Rev Phytopathol 34: 29–50
Coltman DW, Pilkington JG, Smith JA, Pemberton JM (1999) Parasite-mediated selection against inbred Soay sheep in a free-living island population. Evolution 53: 1259–1267
Cooper TF, Lenski RE, Elena SF (2005) Parasites and mutational load: an experimental test of a pluralistic theory for the evolution of sex. Proc R Soc Lond B 272: 311–317
Dawkins R, Krebs JR (1979) Arms races between and within species. Proc R Soc Lond B 205: 489–511
Decaestecker E, Gaba S, Raeymaekers JAM, Stocks R, Van Kerckhoven L, Ebert D, De Meester L (2007) Host-parasite 'Red Queen' dynamics archived in pond sediment. Nature 450: 870–873
de Visser JAGM, Elena SF (2007) The evolution of sex: empirical insights into the roles of epistasis and drift. Nat Rev Genet 8: 139–149
Dionne M, Miller KM, Dodson JJ, Caron F, Bernatchez L (2007) Clinal variation in MHC diversity with temperature: evidence for the role of host-pathogen interaction on local adaptation in Atlantic salmon. Evolution 61: 2154–2164
Doherty PC, Zinkernagel RM (1975) Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. Nature 256: 50–52
Dybdahl MF, Lively CM (1995) Host-parasite interactions: infection of common clones in natural populations of a freshwater snail (*Potamopyrgus antipodarum*). Proc R Soc Lond B 260: 99–103
Dybdahl MF, Lively CM (1998) Host-parasite coevolution: evidence for rare advantage and time-lagged selection in a natural population. Evolution 52: 1057–1066
Edwards SV, Hedrick PW (1998) Evolution and ecology of MHC molecules: from genomics to sexual selection. Trends Ecol Evol 13: 305–311
Ellstrand NC, Antonovics J (1985) Experimental studies on the evolutionary significance of sexual reproduction. II. A test of the density-dependent selection hypothesis. Evolution 39: 657–666
Fischer OM, Schmid-Hempel P (2005) Selection by parasites may increase host recombination frequency. Biol Lett 1: 193–195
Flor HH (1956) The complementary genic systems in flax and flax rust. Adv Genet 8: 275–296
Frank SA (1992) Models of plant–pathogen coevolution. Trends Genet 8: 213–219
Frank SA (2000) Specific and non-specific defense against parasitic attack. J Theor Biol 202: 283–304
Gandon S (2002) Local adaptation and the geometry of host-parasite coevolution. Ecol Lett 5: 246–256
Gandon S, Otto SP (2007) The evolution of sex and recombination in response to abiotic or coevolutionary fluctuations in epistasis. Genetics 175: 1835–1853
Glesener RR (1979) Recombination in a simulated predator-prey interaction. Am Zool 19: 763–771
Glesener RR, Tilman D (1978) Sexuality and the components of environmental uncertainty: clues from geographic parthenogenesis in terrestrial animals. Am Nat 112: 659–673
Greischar M, Koskella B (2007) A synthesis of experimental work on parasite local adaptation. Ecol Lett 10: 418–434
Haag CR, Sakwiska O, Ebert D (2003) Test of synergistic interaction between infection and inbreeding in *Daphnia magna*. Evolution 57: 777–783
Hakoyama H, Nishimura T, Matsubara N, Iguchi K (2001) Difference in parasite load and non-specific immune reaction between sexual and gynogenetic forms of *Carassius auratus*. Biol J Linnean Soc 72: 401–407
Haldane JBS (1949) Disease and evolution. Ric Sci 19 (Suppl): 68–76
Hamilton WD (1980) Sex vs. non-sex vs. parasite. Oikos 35: 282–290
Hamilton WD (1982) Pathogens as causes of genetic diversity in their host populations, In: Anderson RM, May RM (eds) Population biology of infectious diseases. Springer, Berlin, pp. 269–296

Hamilton WD, Axelrod R, Tanese R (1990) Sexual reproduction as an adaptation to resist parasites (A review). Proc Natl Acad Sci USA 87: 3566–3573
Hanley KA, Bolger DT, Case TJ (1994) Comparative ecology of sexual and asexual gecko species (*Lepidodactylus*) in French Polynesia. Evol Ecol 8: 438–454
Hill AVS, Allsopp CEM, Kwiatkowski D, Anstey NM, Twumasi P, Rowe PA, Bennett S, Brewster D, McMichael AJ, Greenwood BM (1991) Common West African HLA antigens are associated with protection from severe malaria. Nature 352: 595–600
Hill AVS, Yates SNR, Allsopp CM, Gupta S, Gilbert SC, Lalvani A, Aidoo M, Davenport M, Plebanski M (1994) Human leukocyte antigens and natural selection by malaria. Philos Trans R Soc Lond B 346: 379–385
Howard RS, Lively CM (1994) Parasitism, mutation accumulation, and the maintenance of sex. Nature 367: 554–557
Howard RS, Lively CM (1998) The maintenance of sex by parasitism and mutation accumulation under epistatic fitness functions. Evolution 52: 604–610
Howard RS, Lively CM (2003) Opposites attract? Mate choice for parasite evasion and the evolutionary stability of sex. J Evol Biol 16: 681–689
Hughes AL, Hughes MK, Howell CY, Nei M, Howard JC, Higgs P (1994) Natural selection at the class II major histocompatibility complex loci of mammals. Philos Trans R Soc Lond B 345: 359–367
Hughes AL, Nei M (1988) Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection. Nature 335: 167–170
Hughes AL, Nei M (1989a) Evolution of the major histocompatibility complex: independent origin of non-classical class I genes in different groups of mammals. Mol Biol Evol 6: 559–579
Hughes AL, Nei M (1989b) Nucleotide substitution at major histocompatibility complex class II loci: evidence for overdominant selection. Proc Natl Acad Sci USA 86: 958–962
Hughes AL, Nei M (1992) Models of host-parasite interaction and MHC polymorphism. Genetics 132: 863–864
Hughes AL, Yeager M (1998) Natural selection at major histocompatibility complex loci of vertebrates. Annu Rev Genet 32: 415–435
Hutson V, Law R (1981) Evolution of recombination in populations experiencing frequency-dependent selection with time delay. Proc R Soc Lond B 213: 345–359
Jaenike J (1978) An hypothesis to account for the maintenance of sex within populations. Evol Theor 3: 191–194
Johnson SG, Lively CM, Schrag SJ (1997) Evolution and ecological correlates of uniparental and biparental reproduction in freshwater snails, In: Streit B, Städler T, Lively CM (eds) Evolutionary ecology of freshwater animals. Birkhäuser Verlag, Basel, pp. 263–291
Jokela J, Dybdahl MF, Lively CM (2009) The maintenance of sex, clonal dynamics, and host-parasite coevolution in a mixed population of sexual and asexual snails. Am Nat 174: S43–S53
Jokela J, Lively CM, Dybdahl MF, Fox JA (2003) Genetic variation in sexual and clonal lineages of a freshwater snail. Biol J Linn Soc 79: 165–181
Jokela J, Lively CM, Fox JA, Dybdahl MF (1997) Flat reaction norms and 'frozen' phenotypic variation in clonal snails (*Potamopyrgus antipodarum*). Evolution 51: 1120–1129
Kelley SE (1994) Viral pathogens and the advantage of sex in the perennial *Anthoxanthum odoratum*. Philos Trans R Soc Lond B 346: 295–302
Killick SC, Carlsson AM, West SA, Little TJ (2006) Testing the pluralist approach to sex: the influence of environment on synergistic interactions between mutation load and parasitism in *Daphnia magna*. J Evol Biol 19(5): 1603–1611
King KC, Lively CM (2009) Geographic variation in sterilizing parasite species and the Red Queen. Oikos: in press (DOI 10.1111/j.1600-0706.2009.17476.x)
Knapp LA (2007) Selection on MHC? A matter of form over function. Heredity 99: 241–242
Kondrashov AS (1993) Classification of hypotheses on the advantage of amphimixis. J Hered 84: 372–387

Koskella B, Lively CM (2007) Advice of the Rose: experimental coevolution of a trematode parasite and its snail host. Evolution 62: 152–159

Kouyos RD, Salathé M, Bonhoeffer S (2007) The Red Queen and the persistence of linkage-disequilibrium oscillations in finite and infinite populations. BMC Evol Biol 7: 211–219

Kover PX, Caicedo AL (2001) The genetic architecture of disease resistance in plants and the maintenance of recombination by parasites. Mol Ecol 10: 1–16

Kumpulainen T, Grapputo A, Mappes J (2004) Parasites and sexual reproduction in psychid moths. Evolution 58: 1511–1520

Lazarro BP (2005) Elevated polymorphism and divergence in the class C scavenger receptors of *Drosophila melanogaster* and *D. simulans*. Genetics 169: 2023–2034

Levin DA (1975) Pest pressure and recombination systems in plants. Am Nat 109: 437–451

Lewontin RC (1974) The genetic basis of evolutionary change. Columbia University Press, New York

Lively CM (1987) Evidence from a New Zealand snail for the maintenance of sex by parasitism. Nature 328: 519–521

Lively CM (1992) Parthenogenesis in a freshwater snail: reproductive assurance versus parasitic release. Evolution 46: 907–913.

Lively CM (1996) Host-parasite coevolution and sex. Bioscience 46: 107–114

Lively CM (1999) Migration, virulence, and the geographic mosaic of adaptation by parasites. Am Nat 153: S34–S47

Lively CM (2001) Trematode infection and the distribution and dynamics of parthenogenetic snail populations. Parasitology 123: S19–S26

Lively CM (2006) The ecology of virulence. Ecol Lett 9: 1089–1095

Lively CM, Apanius V (1995) Genetic diversity in host-parasite interactions. In: Grenfell BT, Dobson AP (eds) Ecology of infectious diseases in natural populations. Cambridge University Press, Cambridge, UK, pp. 421–449

Lively CM, Craddock C, Vrijenhoek RC (1990) The Red Queen hypothesis supported by parasitism in sexual and clonal fish. Nature 344: 864–866

Lively CM, Dybdahl MF (2000) Parasite adaptation to locally common host genotypes. Nature 405: 679–681

Lively CM, Dybdahl MF, Jokela J, Osnas EE, Delph LF (2004) Host sex and local adaptation by parasites in a snail-trematode interaction. Am Nat 164: S6–S18

Lively CM, Howard RS (1994) Selection by parasites for clonal diversity and mixed mating. Philos Trans R Soc Lond B 346: 271–281

Lively CM, Jokela J (1996) Clinal variation for local adaptation in a host-parasite interaction. Proc R Soc Lond B 263: 891–897

Lively CM, Jokela J (2002) Temporal and spatial distributions of parasites and sex in a freshwater snail. Evol Ecol Res 4: 219–226

Lloyd DG (1980) Demographic factors and mating patterns in angiosperms. In: Solbrig OT (ed) Demography and evolution in plant populations. Botanical Monographs. University of California Press, Berkeley, pp. 67–88

Lythgoe KA (2000) The coevolution of parasites with host-acquired immunity and the evolution of sex. Evolution 54: 1142–1156

Lythgoe KA, Read AF (1998) Catching the Red Queen? The advice of the rose. Trends Ecol Evol 13: 473–474

May RM, Anderson RM (1983) Epidemiology and genetics in the coevolution of parasites and hosts. Proc R Soc Lond B 219: 291–313

Mayer F, Brunner A (2007) Non-neutral evolution of the major histocompatibility complex class II gene DRB1 in the sac-winged bat *Saccopteryx bilineata*. Heredity 99: 257–264

Maynard Smith J (1971) What use is sex? J Theor Biol 30: 319–355

Maynard Smith J (1978) The evolution of sex. Cambridge University Press, Cambridge, UK

McClelland EE, Penn DJ, Potts WK (2003) Major histocompatibility complex heterozygote superiority during coinfection. Infect Immun 71: 2079–2086
Mee JA, Rowe L (2006) A comparison of parasite loads on asexual and sexual *Phoxinus*(Pisces: Cyprinidae). Can J Zool 84: 808–816
Meirmans S, Neiman M (2006) Methodologies for testing a pluralist idea for the maintenance of sex. Biol J Linn Soc 89: 605–613
Michiels NK, Beukeboom LW, Pongratz N, Zeitlinger J (2001) Parthenogenetic flatworms have more symbionts than their coexisting, sexual conspecifics, but does this support the Red Queen? J Evol Biol 14: 110–119
Milinski M (2006) The major histocompatibility complex, sexual selection, and mate choice. Annu Rev Ecol Evol Syst 37: 159–186
Morand S, Manning SD, Woolhouse MEJ (1996) Parasite-host coevolution and geographic patterns of parasite infectivity and host susceptibility. Proc R Soc Lond B 263: 119–128
Moritz C, McCallum H, Donnellan S, Roberts JD (1991) Parasite loads in parthenogenetic and sexual lizards (*Heteronotia binoei*): support for the Red Queen hypothesis. Proc R Soc Lond B 244: 145–149
Mundt CC, Brunet J, Sackett KE (2008) Impact of density and disease on frequency-dependent selection and genetic polymorphism: experiments with stripe rust and wheat. Evol Ecol 22: 637–657.
Nidelet T, Kaltz O (2007) Direct and correlated responses to selection in a host-parasite system: testing for the emergence of genotype specificity. Evolution 61: 1803–1811
Nordborg M, Hu TT, Ishino Y, Jhaveri J, Zheng H, Bakker E, Calabrese P, Gladstone J, Goyal R, Jakobsson M, Kim S, Morozov Y, Padhukasahasram B, Plagnol V, Rosenberg NA, Shah C, Wall JD, Wang J, Zhao K, Kalbfleisch T, Schulz V, Kreitman M, Bergelson J (2005) The pattern of polymorphism in *Arabidopsis thaliana*. PLoS Biol 3: 1289–1299
Osnas EE, Lively CM (2006) Host ploidy, parasitism and immune defense in a coevolutionary snail-trematode system. J Evol Biol 19: 42–48
Otto SP, Nuismer SL (2004) Species interactions and the evolution of sex. Science 304: 1018–1020
Penn DJ, Damjanovich K, Potts WK (2002) MHC heterozygosity confers a selective advantage against multiple-strain infections. Proc Natl Acad Sci USA 99: 11260–11264.
Peters AD (1999) The effects of pathogen infection and mutation on life-history characters in *Arabidopsis thaliana*. J Evol Biol 12: 460–470
Peters AD, Lively CM (1999) The Red Queen and fluctuating epistasis: a population genetic analysis of antagonistic coevolution. Am Nat 154: 393–405
Peters AD, Lively CM (2007) Short- and long-term benefits and detriments to recombination under antagonistic coevolution. J Evol Biol 20: 1206–1217
Piertney SB, Oliver MK (2006) The evolutionary ecology of the major histocompatibility complex. Heredity 96: 7–21
Potts WK, Manning CJ, Wakeland EK (1994) The role of infectious disease, inbreeding and mating preferences in maintaining MHC genetic diversity: an experimental test. Philos Trans R Soc Lond B 346: 369–378
Price MV, Waser NM (1982) Population structure, frequency-dependent selection, and the maintenance of sexual reproduction. Evolution 36: 35–43
Puurtinen M, Hytönen M, Knott KE, Taskinen J, Nissinen K, Kaitala V (2004) The effects of mating system and genetic variability on susceptibility to trematode parasites in a freshwater snail, *Lymnaea stagnalis*. Evolution 58: 2747–2753
Rolff J, Siva-Jothy MT (2003) Invertebrate ecological immunology. Science 301: 472
Ronsheim ML (1996) Evidence against a frequency-dependent advantage for sexual reproduction in *Allium vineale*. Am Nat 147: 718–734
Salathé M, Ebert D (2003) The effects of parasitism and inbreeding on the competitive ability in *Daphnia magna*: evidence for synergistic epistasis. J Evol Biol 16: 976–985
Salathé M, Kouyos RD, Regoes RR, Bonhoeffer S (2007) Rapid parasite adaptation drives selection for high recombination rates. Evolution 62: 295–300

Salathé M, Scherer A, Bonhoeffer S (2005) Neutral drift and polymorphism in gene-for-gene systems. Ecol Lett 8: 925–932
Schmitt J, Antonovics J (1986) Experimental studies of the evolutionary significance of sexual reproduction. VI. Effect of neighbor relatedness and aphid infestation on seedling performance. Evolution 40: 830–836
Schrag SJ, Mooeres AO, Ndifon GT, Read AF (1994) Ecological correlates of male outcrossing ability in a simultaneous hermaphrodite snail. Am Nat 143: 636–655
Schwensow N, Fietz J, Dausmann KH, Sommer S (2007) Neutral versus adaptive genetic variation in parasite resistance: importance of major histocompatibility complex supertypes in a free-ranging primate. Heredity 99: 265–277
Seger J (1988) Dynamics of some simple host parasite models with more than two genotypes in each species. Philos Trans R Soc Lond B 319: 541–555
Seger J, Hamilton WD (1988) Parasites and sex. In: Michod RE, Levin BR (eds) The evolution of sex. Sinauer, Sunderland, pp. 176–193
Shykoff JA, Schmid-Hempel P (1991) Parasites and the advantage of genetic-variability within social insect colonies. Proc R Soc Lond B 243: 55–58
Slade RW, McCallum HI (1992) Overdominant vs. frequency-dependent selection at MHC loci. Genetics 132: 861–862
Stahl EA, Dwyer G, Mauricio R, Kreitman M, Bergelson J (1999) Dynamics of disease resistance polymorphism at the *Rpm1* locus of *Arabidopsis*. Nature 400: 667–671
Stevens L, Yan G, Pray LA (1997) Consequences of inbreeding on invertebrate host susceptibility to parasitic infection. Evolution 51: 2032–2039
Strauss SY, Karban R (1994) The significance of outcrossing in an intimate plant-herbivore relationship. I. Does outcrossing provide an escape from herbivores adapted to the parent plant? Evolution 48: 454–464
Takahata N, Nei M (1990) Allelic genealogy under over-dominant and frequency-dependent selection and polymorphism of major histocompatibility complex loci. Genetics 124: 967–978
Tiffin P, Moeller DA (2006) Molecular evolution of plant immune genes. Trends Genet 22: 662–670
Tiffin P, Hacker R, Gaut BS (2004) Population genetic evidence for rapid changes in intraspecific diversity and allelic cycling of a specialist defense gene in *Zea*. Genetics 168: 425–434
Tobler M, Schlupp I (2005) Parasites in sexual and asexual mollies (*Poecilia*, Poeciliidae, Teleostei): a case for the Red Queen? Biol Lett 1: 166–168
Todd JR, West BC, McDonald JC (1990) Human leukocyte antigen and leprosy: study in northern Louisiana and review. Rev Infect Dis 12: 63–74
Van Valen L (1973) A new evolutionary law. Evol Theor 1: 1–30
Vernon JG, Okamura B, Jones CS, Noble LR (1996) Temporal patterns of clonality and parasitism in a population of freshwater bryozoans. Proc R Soc Lond B 263: 1313–1318
Vrijenhoek RC, Lerman S (1982) Heterozygosity and developmental stability under sexual and asexual breeding systems. Evolution 36: 768–776.
Webster JP, Davies CM (2001) Coevolution and compatibility in the snail-schistosome system. Parasitology 123: S41–S56
Wedekind C, Walker M, Little TJ (2005) Major histocompatibility complex (MHC) effects, but no general MHC heterozygote advantage in single-strain infections. Genetics 170: 1427–1430
Wegner KM, Kalbe M, Reusch TBH (2007) Innate versus adaptive immunity in sticklebacks: evidence for trade-offs from a selection experiment. J Evol Ecol 21: 473–483
Wegner KM, Kalbe M, Schaschl H, Reusch TBH (2004) Parasites and individual major histocompatibility complex diversity – an optimal choice? Microbes Infect 6: 1110–1116
West SA, Lively CM, Read AF (1999) A pluralistic approach to sex and recombination. J Evol Biol 12: 1003–1012
Westerdahl H, Hansson B, Bensch S, Hasselquist D (2004) Between-year variation of MHC allele frequencies in great reed warblers: selection or drift? J Evol Biol 17: 485–492
Williams GC (1966) Adaptation and natural selection. Princeton University Press, Princeton

Williams GC (1975) Sex and evolution. Princeton University Press, Princeton
Woolhouse MEJ, Webster JP, Domingo E, Charlesworth B, Levin BR (2002) Biological and biomedical implications of the coevolution of pathogens and their hosts. Nat Genet 32: 569–577
Wuethrich B (1998) Evolution of sex: putting theory to the test. Science 281: 1980–1982