

RAPID PARASITE ADAPTATION DRIVES SELECTION FOR HIGH RECOMBINATION RATES

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The Red Queen hypothesis proposes that sex is maintained through selection pressure imposed by coevolving parasites: susceptible hosts are able to escape parasite pressure by recombining their genome to create resistant offspring. However, previous theoretical studies have shown that the Red Queen typically selects against sex unless selection is strong, arguing that high rates of recombination cannot evolve when parasites are of low virulence. Here we show that under the biologically plausible assumption of a severe fitness cost for parasites that fail to infect, the Red Queen can cause selection for high recombination rates, and that the strength of virulence is largely irrelevant to the direction of selection for increased recombination rates. Strong selection on parasites and short generation times make parasites usually better adapted to their hosts than vice versa and can thus favor higher recombination rates in hosts. By demonstrating the importance of host-imposed selection on parasites, our findings resolve previously reported conflicting results.

KEY WORDS: Evolution of sex, host–pathogen coevolution, parasites, recombination, Red Queen.

The Red Queen principle is one of the most important frameworks in the theory of evolution. It states that the adaptations and counteradaptations of competing species lead to cyclical coevolutionary dynamics (Van Valen 1973). The most fruitful applications of this principle have been on the question of the maintenance of sexual reproduction (Jaenike 1978; Hamilton 1980; Hamilton et al. 1990; Howard and Lively 1997; Peters and Lively 1999; Schmid-Hempel and Jokela 2002). Termed “the Red Queen hypothesis” (Bell 1982), it posits that coevolutionary interactions between hosts and parasites might explain the maintenance of sex and recombination in hosts as a means to reduce the risk of infection in offspring. Because parasitic infections often have a strong genetic basis (Woolhouse et al. 2002; Nimchuk et al. 2003), the hypothesis postulates that by shuffling the genes that influence susceptibility to infection, hosts can escape parasite pressure better than their asexual, clonal competitors.

Previous theoretical studies have found that parasites can select for higher rates of recombination (Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Peters and Lively 2007), but the generality of these results has been questioned. The key dif-

iculty with those studies is that they often only investigated a small part of the parameter space. In an attempt to resolve this problem, a recent study has derived the first general analytical conditions on the evolution of sex through species interactions (Otto and Nuismer 2004), and has conducted simulations over a wide range of parameters. The study reported that the Red Queen typically selects against sex unless selection is strong, corroborating earlier findings (May and Anderson 1983; Howard and Lively 1994; Peters and Lively 1999; Schmid-Hempel and Jokela 2002) that parasites must be highly virulent in order for the Red Queen hypothesis to work. Moreover, the study concluded that although the Red Queen may explain low levels of recombination, it fails to explain the high levels of recombination that are observed in so many species.

Although the Red Queen Principle can be applied to all kinds of species interactions, host–parasite interactions are an extreme form in the sense that one player, the parasite, has a constant evolutionary advantage over the other player, the host, because it can typically adapt much faster. A characteristic of parasites, and microparasites in particular, is that they usually have very short

generation cycles compared to their hosts (Anderson and May 1991), and that they often suffer from a high fitness cost if they fail to infect a host. Those two factors have a strong influence on how well the parasites are adapted to the next generation of hosts, which in turn determines the threat the parasite population poses to the host population. Despite the importance of this process as a driving force behind the Red Queen, it has received relatively little attention in the past. Previous studies have generally focused on the effect of different virulence strengths, but the effect of selection on the parasite has been ignored (most simulation studies have assumed that parasites that are unable to infect a host die (Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Peters and Lively 2007)).

To investigate whether selection on the parasite is crucial for understanding the evolution of high recombination rates, we used a simple deterministic simulation model similar to Otto and Nuismer (2004), which tracks the frequencies of haploid host and parasite genotypes. Both hosts and parasites have k interaction loci with two alleles (0 and 1) that determine the species interaction. Additionally, the host has a modifier locus with two possible alleles, m (wild-type) and M (mutant), that affect the recombination rate (thus, in a model with $k = 2$, the eight possible host genotypes are 00m, 00M, 01m, 01M, 10m, 10M, 11m, and 11M). The host population is initiated with random genotype frequencies, except that all hosts have the wild-type allele m at the modifier locus. The parasite population is also initiated with random genotype frequencies. At each time step, the following processes occur (in the given order): host reproduction, host selection, host mutation, pathogen reproduction, pathogen selection, and pathogen mutation. The latter three processes are iterated n_{pg} times before a new time step starts (i.e., n_{pg} denotes the number of pathogen generations per host generation).

Hosts reproduce by recombining their genotypes, whereas parasites reproduce clonally. Recombination of two host genomes occurs at a rate that depends on the allele at the modifier locus in the two recombining hosts. If both hosts have allele m , the recombination rate is r_{mm} (i.e., the wild-type recombination rate). If one host has allele m and the other has allele M , the recombination rate is r_{mM} . If both hosts have allele M , the recombination rate is r_{MM} . We allow a maximum of one recombination event per genome, and the probability of the crossing-over event is independent of its location on the genome. Selection is simulated by calculating the new genotype frequencies according to the fitness matrices \mathbf{w}_{ij}^H and \mathbf{w}_{ij}^P that define the host–parasite interactions: \mathbf{w}_{ij}^H denotes the fitness of a host genotype i interacting with a parasite genotype j and \mathbf{w}_{ij}^P denotes the fitness of the parasite-genotype i interacting with a host genotype j . Because the interaction probability for host i and parasite j is proportional to their frequencies, f_i^H and f_j^P , the fitness of the host genotype i reads

$$w_i^H = \sum_j w_{ij}^H f_j^P$$

and thus the frequency of the host-genotype i after selection is

$$f_i^H = f_i^H \frac{w_i^H}{\sum_k w_k^H f_k^H}$$

The parasite frequencies after selection are calculated analogously. Each interaction locus mutates independently with probability $\mu = 10^{-5}$ per generation, and forward and backward mutations occur with the same probability.

In all simulation runs, the initial host and parasite populations are allowed to coevolve for 1000 host generations, during which all hosts reproduce at a wild-type recombination rate r_{mm} . After that, the mutant allele M is introduced in 50% of the host population, and after another 1000 host generations, the frequency of M is recorded. First, we modeled the host–parasite interaction using the matching allele (MA) mechanism, a widely used paradigm in previous studies (Hamilton et al. 1990; Howard and Lively 1994; Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Peters and Lively 2007). Infected hosts have fitness $w_H = 1 - s_H$, whereas noninfecting parasites have fitness $w_P = 1 - s_P$. All others have fitness 1. This distinction between host and parasite selection coefficients allows us to simulate all possible combinations of fitness effects (i.e., s_H and s_P from 0 to 1 with a stepwise increase of 0.01).

Figure 1 shows whether the frequency of M increased at the end of the simulation runs, with $r_{mm} = 0.1$, $r_{mM} = 0.15$, $r_{MM} = 0.2$. One can easily see that given sufficiently strong selection on the parasite (s_P), the strength of selection on the host (s_H) becomes largely irrelevant. In other words, a modifier that increases recombination rate can spread even when parasite virulence is very low. The results of this figure are consistent with the results obtained in earlier studies that were restricted to either the horizontal line where $s_P = 1$ (Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Peters and Lively 2007) or to selection coefficients smaller or equal 0.5 (Otto and Nuismer 2004). Specifically, Figure 1 shows (1) that the evolution of increased recombination rates under the Red Queen hypothesis depends crucially on the strength of selection on the parasites and (2) that strong selection on the parasite is more important than strong selection on the host. Increasing the number of loci that determine the interaction between parasite and host reduces the parameter area where a higher recombination rate is selected for. The effect, however, is relatively weak (see Online Supplementary Fig. S1), especially in the area of strong selection on the parasite ($s_P > 0.5$). Although hosts may have a large number of genes involved in parasite interactions, the number of loci determining the interaction with any individual parasite species may be low. Extending the model to hosts with many interaction

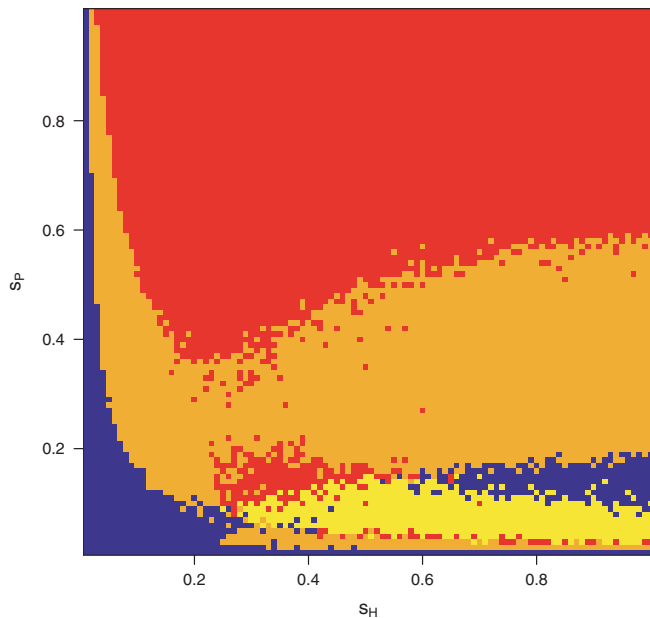


Figure 1. Selection on a modifier increasing the recombination rate ($r_{mm} = 0.1$, $r_{mM} = 0.15$, $r_{MM} = 0.2$) for different selection pressures on hosts (s_H) and parasites (s_P) with $k = 2$. Both $n_{pg} = 1$ and $n_{pg} = 5$ were tested. The selection coefficients s_H and s_P range from 0 to 1 with 0.01 gradation, and each of the 10,000 points on the graph shows the average result of 20 simulation runs (10 for each value of n_{pg}) with different random initial conditions. The graph shows whether the allele M increases or decreases in frequency, using the following color code: red (increase when $n_{pg} = 1$ or $n_{pg} = 5$), blue (decrease when $n_{pg} = 1$ or $n_{pg} = 5$), orange (increase when $n_{pg} = 5$, decrease when $n_{pg} = 1$), and yellow (decrease when $n_{pg} = 5$ and increase when $n_{pg} = 1$). No change from the initial frequency is graphically displayed as a decrease (e.g., when s_H or $s_P = 0$). Selection for higher recombination occurs in the majority of selection coefficient combinations, particularly when selection on the parasite is strong.

loci and multiple parasite populations with a few loci shows selection for increased recombination (see Online Supplementary S2) for most of the parameter space.

If a modifier that increases the recombination rate can spread, what levels of recombination rate can be supported? To tackle this question, we ran simulations with various combinations of wild-type (r_{mm}) and mutant (r_{MM}) recombination rates, where $r_{mM} = (r_{mm} + r_{MM}) / 2$. Previous studies have shown that high levels of recombination cannot evolve when selection is weak. Our simulations confirm these results (Fig. 2A, B). However, the simulations also show that this effect is specifically due to weak selection on the parasite only. Indeed, high levels of recombination can evolve for weak selection on the host, provided selection on the parasite is strong (Fig. 2C, D).

An important simplification in many models concerns the type of genetic interaction and its resulting fitness landscape. In

the simulations discussed above, we have used the matching allele (MA) mechanism, a widely used interaction type that models hosts as resistant unless the parasite “matches” all alleles of the host it tries to infect, modeling a system of self/nonself recognition (Klein and O’huigin 1994). The MA mechanism imposes strong epistasis, and natural host–parasite interactions are likely to deviate from the exact rules underlying the MA mechanism. Figure 3 shows the selection for increased recombination rate on various fitness landscapes. The vertical line $s_1 = 0$, for example, represents the pure MA model. As expected, increased recombination is selected against when selection is weak on both host and parasite. The line $s_2 = 2s_1$ represents the additive matching allele (AMA) model in which the match of only one allele translates in an exactly intermediate fitness on an additive scale. The results show that deviations from models such as the MA or AMA can change the outcome qualitatively. Importantly, however, most areas on the plot show selection for increased recombination rates, specifically when selection on the parasite is stronger than on the host (Fig. 3B–D).

The basic mechanism of the Red Queen hypothesis is the escape from parasite pressure by turning susceptible into resistant genotypes. Yet, recombination has also the potential to break up resistant genotypes. Which process predominates strongly depends on how well the parasites are adapted to infect the next generation of hosts: If the parasites are well adapted, the frequency of susceptible genotypes increases, and therefore the chance of recombination to generate resistant genotypes by breaking up susceptible genotypes increases. The state of adaptation within the parasite population in turn depends on both the selection coefficient s_P and on the number of parasite generations per host generation, n_{pg} . Therefore, decreasing n_{pg} results in less selection for higher recombination. Earlier simulation studies (Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Peters and Lively 2007) have focused on the case in which $n_{pg} = 1$, which deprives the parasite of its ability to adapt faster than the host because there is no other difference between the host and parasite except the one specified by the fitness matrices. Still, our conclusions hold even with such a conservative assumption: strong selection on the parasite is sufficient to cause selection for increased recombination rates (Fig. 1). Another way to model differing generations times is to simulate iteroparity in the host (Otto and Nuismer 2004). Assuming overlapping host generations may change the evolutionary advantage of short-lived parasites, but does not affect our results qualitatively (results not shown).

Previous work on the Red Queen hypothesis has led to a diverse and often inconsistent set of results. The reasons for these discrepancies are most likely due to different assumptions in the models, different regions in parameter space investigated, and different questions asked. For example, while some studies have examined whether parasites can pay for the twofold cost induced by

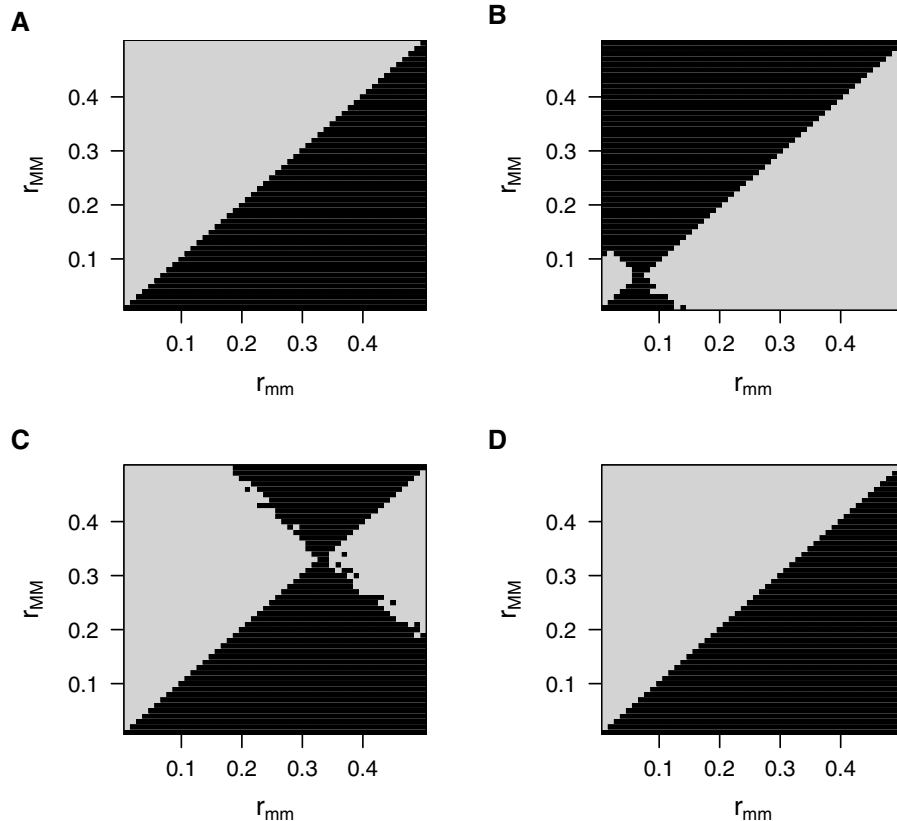


Figure 2. Selection on a modifier under various selection strengths with $k = 2$, $n_{pg} = 5$. The intermediate recombination rate is $r_{mM} = (r_{mm} + r_{MM})/2$. The graph shows whether the allele M increases (gray) or decreases (black) in frequency. The recombination rates r_{mm} and r_{MM} range from 0 to 0.5 with 0.01 gradation, and each of the 2500 points on a graph shows the average result of 10 simulation runs with different random initial conditions. (A) Strong selection on both host and parasite, $s_H = s_P = 0.5$. The modifier allele M can spread as long as it increases the wild-type recombination rate. (B) Weak selection on both host and parasite, $s_H = s_P = 0.05$. For high wild-type recombination rates, the modifier allele M can generally spread only as long as it decreases the recombination rate, stabilizing at a recombination rate around 0.08. (C, D) Weak selection on the host, but strong selection on the parasite, $s_H = 0.05$, $s_P = 0.7$ in (C), $s_H = 0.05$, $s_P = 1.0$ in (D). For most (C) or all (D) wild-type recombination rates, a modifier M can spread provided it increases the recombination rate.

the production of males (Maynard-Smith 1971) given a fixed recombination rate (Hamilton et al. 1990; Howard and Lively 1994), others have examined whether increased recombination can be selected for, without including the potential cost of producing males (Peters and Lively 1999; Schmid-Hempel and Jokela 2002; Otto and Nuismer 2004; Peters and Lively 2007). Additionally, the effects of other factors such as population structure (Ladle et al. 1993; Schmid-Hempel and Jokela 2002), similarity selection (Agrawal 2006), segregation in diploids (Agrawal and Otto 2006), and mutation accumulation (Howard and Lively 1994) can have a profound effect on the selective fate of a modifier changing the recombination rate. Given the complexity of the ecology of species interactions, taking these processes into account is important. Yet, if the Red Queen hypothesis would typically fail to explain high recombination rates in its most simple form (Otto and Nuismer 2004), this would strongly reduce its potential as an explanation for the widespread abundance of sex. As shown

above, this previously reported weakness of the Red Queen is limited to the assumption that the selective pressure on parasites is of moderate strength.

The results reported here challenge the widespread notion that the Red Queen cannot select for substantial recombination rates when selection on hosts is weak, that is, when parasites are of low virulence. We argue that host-imposed selection on parasites is of central relevance, because it results in a rapid adaptation of the parasite population to the current host population. This in turn increases the chance that recombination generates resistant genotypes. Given a sufficiently high fitness cost of failing to infect, virulence turns out to be largely irrelevant when assessing the direction of selection for increased recombination rates. An interesting future direction would be to develop an analytical understanding for the effects of host-imposed selection on the parasite. This could be done, for example, on the basis of analytically tractable Red Queen models (Barton 1995; Gandon

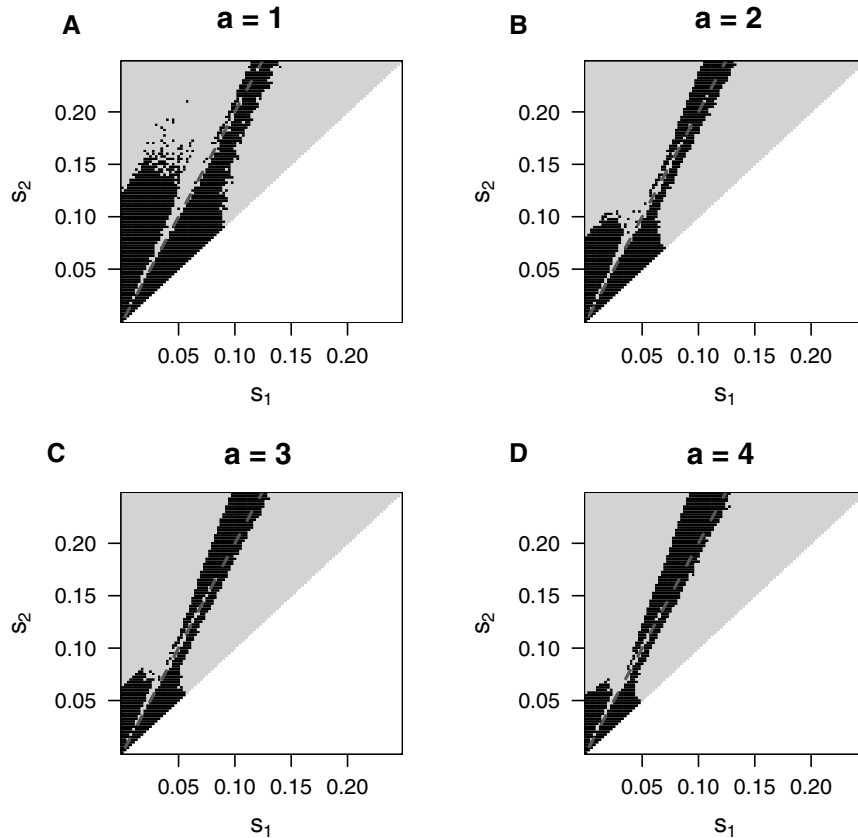


Figure 3. Selection on a modifier increasing the recombination rate ($r_{mm} = 0.1$, $r_{mM} = 0.15$, $r_{MM} = 0.2$) on different fitness landscapes with $k = 2$, $n_{pg} = 5$. The graph shows whether the allele M increases (gray) or decreases (black) in frequency. The number of host alleles, n , matched by the parasite determines the corresponding fitness w_n in the following way: for hosts, $w_2 = 1 - s_2$, $w_1 = 1 - s_1$, $w_0 = 1$, for parasites $w_2 = 1$, $w_1 = 1 - a(s_2 - s_1)$, $w_0 = 1 - as_2$. The parameter a defines how the strength of selection on parasites relates to that on hosts ($a > 1$ imposes stronger selection on the parasite relative to the selection on the host). This generalized model reflects the biological characteristic that host and parasite fitness are inversely correlated. The model can be continually varied as function of the parameters s_1 , s_2 , and a , and contains the MA and AMA models as special cases (MA: $s_1 = 0$; AMA, $s_2 = 2s_1$, dashed line). Only fitness landscapes in which $s_1 \leq s_2$ are shown. The parameters s_1 and s_2 range from 0 to 0.25 with 0.0025 gradation, and each of the points on a graph shows the average result of 10 simulation runs with different random initial conditions. The values for a in (A), (B), (C) and (D) are 1, 2, 3 and 4, respectively. Generally there are two regions that indicate selection against sex/recombination. The first region, which surrounds the AMA (dashed line), is largely independent of a . The second region, on the bottom left of the panels, shrinks with increasing a . Note that selection on parasites in this region is only strong in relative but not in absolute terms.

and Otto 2007) (although such an approach would impose further simplifying assumptions and thus further reduce the realism of the model).

Strong selection against parasites that fail to infect is widespread in natural host–parasite systems, as most microparasites can only have direct reproduction within the host (Anderson and May 1991). Under the simple assumptions of the model presented here, the Red Queen generally selects for increased recombination unless the host-imposed selection on the parasite is weak (e.g., when the fitness costs of noninfecting parasites is low, and when parasites have similar generation times as their hosts). Although such parasitic species probably do exist, for example among macroparasites, they are likely to be the exception. Thus,

the Red Queen might not only explain the origin of sex (Hamilton et al. 1990; Otto and Nuismer 2004; Peters and Lively 2007), but also the evolution of substantial levels of recombination.

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Supplementary Material

The following supplementary material is available for this article:

Figure S1. Selection on a modifier increasing the recombination rate ($r_{mm} = 0.1$, $r_{mM} = 0.15$, $r_{MM} = 0.2$) for different selection pressures on hosts (s_H) and parasites (s_P) with $k = 3$ (A) and $k = 4$ (B).

Figure S2. Simulation of multiple parasite populations.

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