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On the Causes of Selection for Recombination underlying the Red Queen Hypothesis

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Abstract

The vast majority of plant and animal species reproduce sexually despite the costs associated with sexual reproduction. Genetic recombination might outweigh these costs if it helps to escape parasite pressure by creating rare or novel genotypes, an idea known as the Red Queen Hypothesis. Selection for recombination can be driven by short-term and long-term effects, but the relative importance of these effects and their dependency on the parameters of an antagonistic species interaction remain unclear. We use computer simulations of a mathematical model of host-parasite coevolution to measure those effects under a wide range of parameters. We find that the real driving force underlying the Red Queen Hypothesis is neither the immediate, next generation short-term effect nor the long term effect, but in fact a delayed short-term effect. Our results highlight the importance to differentiate clearly between the immediate and the delayed short-term effect when attempting to elucidate the mechanism underlying selection for recombination in the Red Queen Hypothesis.

Keywords

recombination; evolution of sex; red queen hypothesis; fluctuating epistasis; short-term effect; long-term effect

Introduction

Why is it that in almost all animal and plant species, offspring individuals have different combinations of genes from their parents? While the proximate cause of this phenomenon, genetic recombination, has been worked out in great detail, its ultimate cause continues to remain enigmatic (see Otto 2008, this issue). Numerous hypotheses have been proposed to explain the evolutionary maintenance of recombination. Because the only direct effect of genetic recombination is the reduction of statistical associations among genes (i.e., linkage disequilibria, LD), any hypothesis that aims to explain the selective benefit of recombination must explain (i) why breaking up genetic associations is beneficial, and (ii) by which process such genetic associations are continually recreated.

One possible benefit of recombination is that breaking up genetic associations may result in an increase in genetic variance, which may in turn increase the response to selection. The problem with this argument is that recombination only increases genetic variance when genotypes with intermediate fitness are over-represented in a population (or, in mathematical

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terms, when $LD < 0$). If the genotypes with high or low fitness are over-represented (i.e., $LD > 0$), recombination will result in a decrease of genetic variance, which in turn hampers the response to selection.

Two processes have been identified as potential causes of negative LD: negative epistasis among deleterious alleles, and drift in conjunction with selection. Negative epistasis among deleterious alleles implies that alleles have a stronger fitness reducing effect in combination than expected based on their effect in isolation. Whenever combinations of deleterious alleles are more unfit than expected (negative epistasis), it is intuitive that these combinations become less frequent following selection than expected on the basis of the frequency of the individual alleles. Hence, negative epistasis acts as a force that generates negative LD. Drift refers to the change of allele frequencies in finite populations due to chance events, and while drift can cause both negative and positive LD, positive LD disappear faster by selection than negative LD. The net result of this process is a prevalence of negative LD, an effect commonly known as the Hill-Robertson effect (Hill & Robertson, 1966).

Speeding up selection by increasing variance is a process that takes some time: first, the associations must be broken down, releasing beneficial alleles from their deleterious backgrounds, and then those alleles must spread in the population, dragging alleles that increase rates of recombination with them. This effect, known as the *long-term effect*, however, is not the only effect of recombination (Barton 1995). By breaking down genetic associations, recombination also has an effect that is immediate: it creates new combinations of alleles that might be more or less fit than the combinations of alleles in the previous generation. This effect is known as the *short-term effect*, because it becomes manifest immediately in the next generation. The effect is generally thought to be detrimental in systems at selection-mutation (-drift) balance. The reason is that the combinations of alleles that are overrepresented in a population have been favoured by selection in the past, and thus breaking them down typically results in a population whose average fitness is lower.

The net selective effect on any gene that influences the rate of recombination is thus a result of two effects, the short-term and the long-term effect. In models that are based on simple fitness landscapes that are constant over time, it is well understood under which circumstances the two effects lead to a net benefit for recombination (for a review, see Otto & Lenormand 2002). In such models, the short-term effect generally tends to be negative, because recombination breaks down the overly fit and thus overly frequent allele combinations. Provided the population is sufficiently large such that epistasis is the dominating force generating LD, the long-term effect is beneficial only when epistasis (and thus LD) is negative. The long-term effect can outweigh the short-term effect if epistasis is negative, but sufficiently weak.

The Red Queen hypothesis

The assumption that fitness landscapes are constant over time is overly simplistic for many biological scenarios. Thus an alternative hypothesis to explain the ubiquity of genetic recombination is that it may continually create novel genotypes that are at a selective advantage in an ever-changing environment. The idea that recombination might be beneficial in changing environments can already be found in the writings of Wright, Muller and others (Wright 1932; Muller 1932; Sturtevant & Mather 1938; Haldane 1949). Initially, there was some doubt as to whether environments change fast enough to cause selection for recombination (Charlesworth 1976; Bell 1982), but many theoretical studies have shown in the meanwhile that host-parasite coevolution, a process that likely affects almost all species, provides the necessary conditions for such a mechanism to work (for a review, see Salathé et al. 2008a). As parasites adapt quickly to become better at infecting the most frequent host genotype, recombination in the host might be beneficial because it creates rare or novel genotypes that

are at a selective advantage. This idea is nowadays known as the Red Queen hypothesis (RQH) (Bell 1982).

It is worth revisiting the conditions under which the RQH works. First, the outcome of an interaction between a host and a parasite needs to be at least in part genetically determined, an assumption that is likely to be met frequently. Second, selection needs to be strong on at least one of the coevolving species (Salathé et al. 2008b). There has been considerable debate about whether parasites are generally virulent enough to cause enough selection on hosts for recombination to be beneficial (Peters & Lively 1999; Schmid-Hempel & Jokela 2002; Otto & Nusimer 2004). However, it is plausible to assume that parasites often do experience substantial selection from the host, because many parasites cannot reproduce at all if they fail to infect a host (or reproduce at much slower rates outside of a host than within a host). Moreover, even if selection on the parasite was relatively weak, the fact that most parasites have much shorter generation times than their hosts implies that they can adapt much faster than their hosts, effectively increasing the selective pressure on hosts (Salathé et al. 2008b). Third, the interactions between host loci mediating parasite resistance need to be epistatic (Kouyos et al. 2007) or display dominance (Agrawal & Otto 2006). In the absence of epistatic interactions among loci, strong LD of constant sign build up quickly which cause strong selection against recombination (Kouyos et al. 2008). Data from plant and animal studies suggest that epistatic interactions among disease resistance loci are indeed prevalent (Kover & Caicedo 2001).

Thus, while theoretical studies have clarified the role of both the strength of selection and of the genetic interaction system necessary for the RQH to work, the exact causes of selection for recombination remain to be fully investigated. Three recent studies have shed some light on this issue. Peters & Lively (2007) investigated the spread of a gene for recombination in an initially non-recombining population and found that recombination provides an “immediate (next-generation) fitness benefit and a delayed (two or more generations) increase in the rate of response to directional selection”. Gandon & Otto (2007) analyzed a model where allele frequencies remain fixed over time (the so-called Nee model (Nee 1989)), which has the benefit that directional selection is absent, and a long-term effect based on increased genetic variance can thus be excluded. Their analysis focused on the time lag between epistasis and LD fluctuations, arguing that this lag yields a short-term benefit for recombination in generations where LD and epistasis have opposite sign. Finally, we argued (Salathé et al. 2008a) that the short-term effect should be subdivided into an immediate effect and a delayed effect. Using the Nee model, we demonstrated that the immediate short-term effect is often detrimental while the delayed short term-effect is generally beneficial for recombination. In particular, we argued that the immediate short-term effect, approximated by the product of epistasis and LD, has almost no predictive power on the evolution of recombination.

Disentangling the various effects affecting the selection pressure on a recombination modifier is important both theoretically and empirically. For example, if the immediate short-term effect in the next generation does not have any predictive power on the direction of selection for recombination, then measuring this effect will not be useful to demonstrate the role of the RQH in natural populations. Our previous analysis (Salathé 2008a) offered only limited insight into the mechanism underlying the selection for recombination in the RQH as it was based on the somewhat unrealistic Nee model, and was restricted to a small parameter space. In this study, we will extend our previous work by extending the parameter space and by presenting an approach that allows disentangling the short-term effect (both immediate and delayed) from the long-term effect in a model where both the short-term and the long-term effect are present. We find that neither the long-term effect nor the immediate short-term effect have much power in predicting whether recombination is favoured or disfavoured in Red Queen models. In fact, for most of the parameter space investigated, both effects are either irrelevant (i.e. of negligible

magnitude) or quite often misleading (i.e. pointing in the opposite direction) if looked at in isolation. We identify the delayed short-term effect as the best predictor for the evolution of recombination in the RQH.

Material & Methods

We use a frequency-based deterministic model that has been described elsewhere to simulate host-parasite coevolution (Kouyos et al. 2007). Briefly, hosts and parasites are haploid and have two loci with two possible alleles (0 and 1) that determine the outcome of an interaction between host and parasite, depending on the interaction model used (see below). Hosts possess an additional modifier locus with two possible alleles, m (wildtype) and M (mutant) that define the rate at which hosts recombine. The modifier locus is positioned at one end of the genome. Thus, there are 8 possible host haplotypes ($00m$, $00M$, $01m$, $01M$, $10m$, $10M$, $11m$ and $11M$) and 4 possible parasite haplotypes (00 , 01 , 10 and 11).

A simulation runs for t time steps, which corresponds to t host or parasite generations. Hosts and parasites are assumed to have the same generation time. All results presented below are from simulations that ran for 2,000 host generations. At each time step, the following processes occur: host reproduction, host selection, host mutation, parasite reproduction, parasite selection, and parasite mutation. The recursion equations for hosts and parasite genotype frequencies, f^H and f^P , are as follows:

$$f_{t+1}^P = RSM^P(f_t^H, f_t^P) \quad (1)$$

$$f_{t+1}^H = RSM^H(f_t^H, f_t^P) \quad (2)$$

where the superscripts H and P denote the host and parasite populations, respectively, and the function RSM denotes the successive action of reproduction, selection and mutation. We now describe these three processes in detail.

We assume that parasites reproduce clonally while hosts reproduce by recombining their genotypes. Recombination occurs at a rate that depends on the alleles present at the modifier locus of two recombining genotypes. The recombination rate between the interaction loci is $r_{baseline}$ if both recombining genomes carry allele m . It is increased by a small amount Δr or $2\Delta r$, respectively, if one or both genomes carry allele M . The recombination rate between the modifier and the interaction loci is $r_{modifier}$ (only one recombination rate has to be defined in this case, because a recombination event between the modifier locus and the interaction loci only has an effect if the modifier alleles of the two recombining genomes are different). Because we are interested in the fate of the allele M increasing the recombination rate, $\Delta r > 0$ in all simulations.

Selection is determined by a fitness matrix as defined by the interaction model chosen (see below, and Salathé et al. 2008a, Box 1) and by the genotype frequencies of the coevolving species. More explicitly, the fitness matrices $W^H := (w_{ij}^H)_{4 \times 4}$ and $W^P := (w_{ij}^P)_{4 \times 4}$ define the fitness of each possible interaction of host genotype i and parasite genotype j in a two-locus/two-allele system. Assuming that the probability of interaction between host genotype i and parasite genotype j is the product of their respective frequencies, f_i^H and f_j^P , the frequency of host genotype i after selection, f_i^H , is

$$f_i^H = f_i^H \frac{w_i^H}{\sum_k w_k^H f_k^H} \quad (3)$$

where w_i^H is the fitness of host genotype i , given by

$$w_i^H = \sum_j w_{ij}^H f_j^P \quad (4)$$

The parasite frequencies after selection, f^P , are calculated analogously.

Finally, mutations at the interaction loci occur at a rate of 10^{-5} per locus per generation, both in hosts and parasites. If a mutation occurs, allele 0 becomes allele 1 and vice versa. There is no mutation at the modifier locus.

Interaction model

We use two different interaction models: the so-called Nee model, and the matching allele model (MA model). The MA model is widely used in the context of the RQH, and in the two-locus/two-allele setup used here, the MA model assumes that a host genotype is susceptible to a given parasite genotype if and only if the alleles at both interaction loci match. In that case, the fitness of the host genotype is $1-s_H$, and the fitness of the parasite genotype is 1. In all other cases (i.e. where the host and parasite genotype do not fully match), the host is assumed to be fully resistant, and thus the fitness of the host genotype is 1, and the fitness of the parasite genotype is $1-s_P$.

The Nee model assumes that the host genotype is resistant to a given parasite genotype if and only if the alleles at exactly one interaction locus match; for example, the host genotype 01 is resistant to parasite genotypes 11 and 00, but not to 01 and 10. In the case of resistance, the fitness of the host genotype is 1, and the fitness of the parasite genotype is $1-s_P$. In all other cases, the fitness of the host genotype is $1-s_H$, and the fitness of the parasite genotype is 1. The Nee model lacks biological realism, but has the useful property that the allele frequencies converge to 0.5. Constant allele frequencies imply that directional selection is absent, and therefore, after a transient burn-in phase, directional selection can be neglected, and thus there is no long-term effect selecting for recombination in this model.

Simulations

Both host and parasite populations are assumed to be infinite in size, and they are initiated with random genotype frequencies, except at the modifier locus where only allele m is initially present (i.e. recombination occurs initially at a rate $r_{baseline}$). In order to investigate the fate of the modifier allele (M) increasing recombination, we introduce the M allele in 0.01% of the population after a burn-in phase of 1,000 host generations. We then let the simulation run for another 1,000 host generations, during which we measure a variety of quantities such as epistasis, linkage disequilibrium, and the frequency of the modifier allele M .

The effect of altering linkage disequilibrium on the mean fitness of offspring depends on epistasis measured on an additive scale. Epistasis in the host population is thus measured as

$$\varepsilon^H = \frac{w_{00}^H + w_{11}^H - w_{01}^H - w_{10}^H}{\bar{w}^H} \quad (5)$$

where w_i^H is the fitness of host genotype i as defined in eq. 4.

Linkage disequilibrium in the host is measured as

$$LD^H = f_{00}^H f_{11}^H - f_{01}^H f_{10}^H \quad (6)$$

Measuring short-term and long-term effects

In order to disentangle the various effects of selection acting on a recombination modifier, we aim to quantify the short-term effect and the long-term effect on the recombination modifier allele M . The short-term effect acts in the generation immediately following a given recombination event (Figure 1, line A), but it is not limited only to that generation (Figure 1, line B). The long-term effect of a given recombination event only begins to act one generation after the event. In the generation immediately following the recombination event, genetic associations are broken down, but only in the subsequent generations does the increased (or decreased) variance have a selective effect on the modifier (Figure 1, line C).

In the Nee model, where directional selection is absent, we can directly measure the short-term effect acting immediately in the next generation (the so-called immediate short-term effect) and the short-term effect acting after one generation (the so-called delayed short-term effect). In essence, we measure the short-term effect by comparing populations that differ in their recombination rates only in a single generation. More precisely we implement the following procedure: After each generation of a simulation, we pause the simulation and create four test populations (two host populations $H1$ and $H2$, and two parasite populations $P1$ and $P2$), which we initiate with the current host and parasite frequencies of the main populations. We then let the test populations coevolve for 50 host generations ($H1$ with $P1$, and $H2$ with $P2$), with the only difference being that for the first generation in population $H2$, Δr is set to zero (i.e. the modifier has no effect on the recombination rate). After this first generation, Δr is set back to its original value. We then measure selection acting on the modifier n generations after the first generation (s_n) as the difference between the mean fitness of the genotypes carrying allele M in populations $H1$ and $H2$, divided by the total mean fitness, in the $(n+1)$ th generation after the initiation of the test populations:

$$s_n = \frac{\bar{w}_M^{H1}(n+1) - \bar{w}_M^{H2}(n+1)}{\bar{w}_M^{H1}(n+1)} \quad (7)$$

The value of s_0 corresponds to the immediate short-term effect, while the sum of all s_n values where $n > 0$ corresponds to the delayed short-term effect.

In the MA model, we use the same procedure to measure the immediate short-term effect, but because the delayed short-term effect and the long-term effect act at the same time, it is not possible to differentiate between these two effects with the method described above. Instead, we use a mathematical approximation to calculate the strength of selection acting on the modifier due to short-term and long-term effects. The short-term effect is due to differences in LD of the M -linked and m -linked genotypes, while the long-term effect is due to differences

in allele frequencies of the M -linked and m -linked genotypes. Mathematically, the strength of selection on the modifier can be expressed as

$$s_M = \frac{\bar{w}_M - \bar{w}_m}{\bar{w}} \quad (8)$$

where $\bar{w}_M$ and $\bar{w}_m$ denote the mean fitness of genotypes with modifier allele M and m , respectively. The mean fitness is a function of the allele frequencies and LD, i.e. $\bar{w} = \bar{w}(p_1, p_2, LD)$, where p_i denotes the allele frequency at interaction locus i . For a weak modifier, s_M can be approximated as

$$\begin{aligned} s_M &= \frac{(\bar{w}_M - \bar{w}_m)}{\bar{w}} \\ &= \frac{\bar{w}(p_1^M, p_2^M, LD^M) - \bar{w}(p_1^m, p_2^m, LD^m)}{\bar{w}(p_1, p_2, LD)} \\ &= \frac{(p_1^M - p_1^m) \partial_{p_1} \bar{w}(p_1^m, p_2^m, LD^m) + (p_2^M - p_2^m) \partial_{p_2} \bar{w}(p_1^m, p_2^m, LD^m) + (LD^M - LD^m) \partial_D \bar{w}(p_1^m, p_2^m, LD^m)}{\bar{w}(p_1, p_2, LD)} \end{aligned} \quad (9)$$

where p_i^M and D^M denote allele frequencies and LD of the subpopulation with allele M , and p_i^m and D^m denote allele frequencies and LD of the subpopulation with allele m . The first two terms correspond to the allele-frequency-dependent component of s_M , whereas the third term corresponds to the LD-dependent component of s_M . Hence

$$s_{Long} = \frac{(p_1^M - p_1^m) \partial_{p_1} \bar{w} + (p_2^M - p_2^m) \partial_{p_2} \bar{w}}{\bar{w}(p_1, p_2, LD)} \quad \text{and} \quad s_{Short} = \frac{(LD^M - LD^m) \partial_D \bar{w}}{\bar{w}(p_1, p_2, D)}. \quad (10)$$

(See appendix for explicit expressions of the short- and long-term effect).

Results

Our first goal was to extend our previous analysis of the short-term effect in the Nee model where, due to the absence of directional selection, there is no long-term effect. We have previously argued that although the short-term effect is manifest *immediately* in the next generation, it is also manifest in subsequent generations (i.e., with a *delay*). Moreover, we showed that the immediate short-term effect can select against recombination, while the delayed short-term effect selects for recombination (Salathé et al. 2008a). In particular, the immediate short-term effect is usually much weaker than the delayed short-term effect and has thus almost no predictive power for the evolution of recombination. Figure 2 extends those results into the entire parameter space of possible selection strengths acting on both host (s_H , i.e. virulence) and parasite (s_P).

Figure 2a shows selection on a modifier causing increased recombination. Such a modifier is selected when at least one of the coevolving species experiences sufficient selection, confirming similar findings in the matching allele model (Salathé et al. 2008b). As expected, the product of LD and epistasis (fig. 2b) and the immediate short-term effect (fig. 2c) are qualitatively equivalent but opposite in sign: a negative product corresponds to a positive immediate short-term effect and vice versa. However, the immediate short-term effect (fig. 2c) is weak compared to the effective selection on the modifier (fig. 2a), in stark contrast to the delayed short-term effect which is much stronger (fig. 2d). It is the sum of the immediate and

the delayed short-term effect that is acting on the modifier, but as can be seen from figs. 2c and 2d, the immediate effect is largely irrelevant quantitatively, and can be misleading qualitatively.

Epistasis and LD for a certain time span of a typical simulation run are shown in Figure 3a. Figure 3b shows the short-term effect measured with a delay of 0 (solid line), 1 (dashed lines) and 2 (dotted line) generations. Thus, the solid line shows the immediate short-term effect ($n = 0$). Delayed short-term effects ($n > 0$) show positive selection more frequently than the immediate effect. The reason for this is that the immediate and the delayed short-term effect become negative at the same time, but the delayed short-term effect becomes positive earlier than the immediate short-term effect (around time step 8 and 24 in Figure 3b). Why is this so? The delayed effect depends on “future” epistasis in the sense that the combination of alleles created now will not only experience natural selection on the current fitness landscape, but also on the fitness landscape present in n generations. Thus, starting from a given value of LD at generation t , the immediate and delayed short-term effect can be qualitatively different only if the sign of epistasis at generation $t+n$ is different from the sign of epistasis at generation t . As can be seen in Figure 3a, epistasis changes its sign only after a period during which epistasis and LD were of the same sign (i.e. during which the immediate short-term effect selected against recombination). Consequently, the two effects can be qualitatively different only when the immediate short-term effect is negative (selecting against recombination), and the delayed short-term effect is positive.

We now turn our attention to the matching allele model. In contrast to the Nee model, the matching allele model exhibits directional selection and thus a potential for a long-term effect. We find that the immediate short-term effect (figs. 4c & 5c) is generally detrimental to recombination, in strong qualitative contrast to the observed selection on the modifier (figs. 4a & 5a). It is, however, quantitatively very weak and can thus be safely ignored. These observations are independent of how strongly the modifier is linked to the interaction loci. Interestingly, the only region where the immediate short-term effect is appreciably strong is when $s_P \approx 1$, which is consistent with previous findings (Peters & Lively, 2007).

In contrast, the delayed short-term effect (figs. 4f & 5f) is generally in good agreement with selection on the modifier. Again, this observation is largely independent of how strongly the modifier is linked to the interaction loci.

Finally, the long-term effect and the delayed short-term effect are of about the same magnitude, but the direction of the long-term effect depends strongly on the linkage between modifier and the interaction loci. When that linkage is very strong, the long-term effect is detrimental to recombination in areas of moderate selection and beneficial to recombination in areas of strong selection (fig. 4b). When the modifier is loosely linked, the opposite pattern is observed: the long-term effect is beneficial to recombination in areas of weak selection and detrimental to recombination in areas of strong selection (fig. 5b).

Taken together, these observations suggest that in general, the delayed short-term effect is the best qualitative predictor for selection of recombination. The long-term effect can support the delayed short-term effect, but even if it causes selection against recombination, it is hardly ever strong enough to override the effect of the delayed short-term effect. This is particularly apparent in the case of a completely unlinked modifier, where the long-term effect and the delayed short-term effect result in almost completely opposite selection pressures, with the long-term effect pointing in the wrong direction over almost the entire parameter space.

Discussion

Overall, our simulations suggest that the real driving force underlying the RQH is neither the immediate short-term effect nor the long-term effect, but in fact the delayed short-term effect. As always, things turn out to be more complicated when considering greater levels of detail, but in general, this statement holds, at least within the realm of the simulations presented here.

In the Nee model, where a long-term effect can be excluded, the delayed short-term effect is a perfect qualitative predictor for the evolution of recombination. In terms of quantitative prediction, the contribution of the delayed short-term effect is about an order of magnitude higher than the immediate short-term effect. As we have argued previously (Salathé et al. 2008a), equating the short-term effect with the immediate short-term effect only is therefore problematic. As can be seen clearly in Figure 2c, the immediate short-term effect would predict selection against higher levels of recombination in more than half of the parameter space, while higher recombination is in fact selected for in more than 90% of the parameter space.

Why is it that the immediate short-term effect is not a good predictor for selection of recombination? It is worth remembering that the short-term effect is the effect by which recombination creates new combinations of alleles that might be more or less fit than the combinations of alleles in the previous generation. While this effect becomes manifest immediately in the next generation, it is not confined to that generation only. A modifier associated with new allelic combinations created by recombination will also be subject to selection in future generations, i.e. with a delay. This delay is a fundamentally important idiosyncrasy of the RQH: because of fluctuating epistasis, the combinations of alleles that are unfit (or fit) in the current generation might be fit (or unfit) in future generations. Figure 3b shows that the effect in future generations is, on average, more positive (dashed and dotted line) than the effect in the first generation of recombinant offspring (solid line). Clearly, the delayed effects become less important as the linkage between the modifier and the interaction loci becomes weaker. We have shown previously, however, that even in the case of minimal linkage (i.e. full recombination between the modifier and the interaction loci), the delayed effects outweigh the immediate effect (see fig. 1b, Box 2, in Salathé 2008a).

The results of the matching allele model show that the discrepancy between immediate and delayed short-term effect is even more pronounced. Independent of the linkage between modifier and interaction loci, the immediate short-term effect causes selection against recombination across almost the entire parameter space (fig. 4c & 5c), while the delayed short-term effect causes selection for recombination. However, because the immediate short-term effect is one to two orders of magnitude weaker than the delayed short-term effect, it is also largely irrelevant in determining the fate of a recombination modifier. The delayed short-term effect appears to be a very good qualitative proxy for selection on the modifier.

The long-term effect is approximately of the same magnitude as the delayed short-term effect. However, the pattern of the long-term effect depends strongly on the linkage between modifier and interaction loci. When this linkage is strong (fig. 4), the long-term effect causes selection for recombination when at least one of the coevolving species experiences sufficient selection from their interaction (with the exception of very weak selection on both host and parasite). However, when linkage is loose (fig. 5), the opposite pattern emerges: the long-term effect then causes selection against recombination when at least one of the coevolving species experiences sufficient selection from their interaction (with the notable exception of very strong selection on both host and parasite). Thus, in the case of loose linkage between modifier and interaction loci, the long-term effect and the delayed short-term effect exhibit roughly opposite patterns, but because the delayed short-term effect is slightly stronger in this case, the

qualitative outcome on selection on the modifier is predicted better by the delayed short-term effect.

At first sight, it might seem that while the delayed short-term effect is a better proxy for the evolution of recombination than the long-term effect, its superiority is only marginal. However, this outcome strongly depends on which area in the parameter space one is looking at. Little is known about the effective fitness effects of parasites on hosts and vice versa, but while there are some parasites that have devastating effects on the fitness of their hosts (castrating parasites, for example), the majority of parasites probably exert much weaker selective pressure. If we zoom in on the area where $s_H \leq 0.2$, a clearer picture emerges: the long-term effect and the delayed short-term effect are almost in perfect disagreement about the direction of selection they cause on the modifier, independent of the linkage between modifier and interaction loci. The actual direction of selection on the modifier, however, is always in agreement with the delayed short-term effect: in no case is the long-term effect strong enough to reverse the selection caused by the delayed short-term effect.

Our results are limited in three important ways. First, the results obtained in this study are based on two specific interaction models (the Nee model and the matching allele model). To what extent these results hold in other models remains to be investigated. In the matching allele model, for example, the long-term effect is only of slightly weaker magnitude than the delayed short-term effect. Thus, it could very well be that a small departure from the strict matching allele model would affect the slightly skewed balance between the two effects and eventually reverse it. Second, we have focussed exclusively on the spread of a recombination modifier. Recent work (Peters & Lively 2007) has shown that the short- and long-term effects during the spread of a modifier can be very different from the effects at equilibrium. Finally, our results are based on relatively low recombination rates, an assumption that decreases the parameter regions where the conditions for quasi-linkage equilibrium (QLE) are met (i.e., weak selection relative to recombination). For example, Otto & Nuismer have shown (2004) that the long-term effect selects for recombination at QLE, indicating that the parameter region in figs. 4b and 5b (where the long-term effect selects for higher recombination near the origin) would expand.

A continuing problem is that the terminology of short-term and long-term effects is potentially confusing, in particular in the context of the RQH. The short-term effect was named to reflect the fact that it already becomes manifest in the generation immediately following a recombination event. But since the short-term effect can also be felt many generations later (i.e. in the long-term), it can easily be confused with the long-term effect. At the same time, the short-term effect can also be confused with an effect restricted to the next generation only, which can be misleading too because, as we have shown here, the effect in the generation following a recombination event (the immediate short-term effect) can select against recombination while the effect in subsequent generations (the delayed short-term effect) can select for recombination. In practice, this also means that measuring the recombination load, given here by the immediate short term effect, will not be sufficient to assess the validity of the RQH. Because the delayed short-term effect turns out to be crucial for the evolution of recombination in the RQH - at least in the interaction models considered here - ignoring this effect can lead to the wrong conclusions. Our results therefore highlight the importance of differentiating clearly between the immediate and the delayed short-term effect when attempting to elucidate the mechanism underlying selection for recombination in the RQH.

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Appendix

The expressions for the short- and long-term effect (equation 10 in main text) can be reformulated as a function of LDs and allele frequencies. First, a short calculation shows that

$$\partial_{p_1} \bar{w} = (w_2 - w_4)(1 - p_2) + (w_1 - w_3)p_2 = s_1$$

$$\partial_{p_2} \bar{w} = (w_3 - w_4)(1 - p_1) + (w_1 - w_2)p_1 = s_2$$

and

$$\partial_D \bar{w} = (w_1 + w_4) - (w_2 + w_3) = \varepsilon_{ADD}$$

where the terms s_1 and s_2 correspond to the selection on the interaction loci 1 and 2, respectively. Furthermore, the conditional allele frequencies (p_i^m, p_i^M) and LDs (LD^m, LD^M) can be expressed in terms of allele frequencies (p_1, p_2, p_M), two-way LDs (D_{12}, D_{1M}, D_{2M}) and three-way LD (D_{12M}) (Barton 1995; Shpak & Gavrillets 2006). With these transformations, the long- and short-term effects read

$$s_{Long} = \frac{D_{1M}s_1 + D_{2M}s_2}{p_M(1 - p_M)\bar{w}} \quad (A1)$$

and

$$s_{Short} = \frac{D_{12M}p_M(1 - p_M) - D_{1M}D_{2M}(1 - 2p_M)}{(p_M(1 - p_M))^2\bar{w}} \varepsilon_{ADD} \quad (A2)$$

Following Barton (1995), an exact expression for the long and short-term effects can be derived as follows. The total selection acting on the modifier, s_M (see equation 8 in the main text) can be expressed in terms of allele-frequencies and LDs:

$$s_M = \frac{D_{1M}s_1 + D_{2M}s_2}{p_M(1 - p_M)\bar{w}} + \frac{D_{12M}\varepsilon_{ADD}}{p_M(1 - p_M)\bar{w}} \quad (A3)$$

Thus, s_M is the sum of the long-term effect which results from the association of the modifier with individual alleles (D_{1M} and D_{2M}) and the short-term effect which results from the association of the modifier with allele combinations (D_{12M}). Comparing this exact derivation of the long-term and short-term effects with the corresponding terms of the linear approximation (A1 and A2), we see that the exact calculation and the linear approximation of the long-term effect are identical, while the exact calculation and the linear approximation of the short-term effect differ by a term proportional to $D_{1M}D_{2M}$. Given the properties of the linear approximation, this term is negligible for weak modifiers (a result we confirmed by numerical simulation).

References

- Agrawal AF, Otto SP. Host-parasite coevolution and selection on sex through the effects of segregation. *Am. Nat* 2006;168:617–679. [PubMed: 17080361]
- Barton NH. A General-Model for the Evolution of Recombination. *Genet Res* 1995;65:123–144. [PubMed: 7605514]
- Bell, G. *The Masterpiece of Nature: The Evolution and Genetics of Sexuality*. University of California Press; 1982.
- Charlesworth B. Recombination Modification in a Fluctuating Environment. *Genetics* 1976;83:181–195. [PubMed: 1269919]
- Gandon S, Otto SP. The evolution of sex and recombination in response to abiotic or coevolutionary fluctuations in epistasis. *Genetics* 2007;175:1835–1853. [PubMed: 17277371]
- Haldane JBS. *Disease and Evolution*. *La Ricerca Scientifica* 1949;19:2–11.
- Hill WG, Robertson A. The effect of linkage on the limits to artificial selection. *Genetical Research, Cambridge* 1966;8:269–294.
- Kouyos RD, Salathé M, Bonhoeffer S. The Red Queen and the persistence of linkage-disequilibrium oscillations in finite and infinite populations. *BMC Evolutionary Biology* 2007;7:211. [PubMed: 17986336]
- Kouyos RD, Salathé M, Otto SP, Bonhoeffer S. The role of epistasis on the evolution of recombination in host-parasite coevolution. *Theoretical Population Biology*. 2008 (2008), doi:10.1016/j.tpb.2008.09.007.
- Kover PX, Caicedo AL. The genetic architecture of disease resistance in plants and the maintenance of recombination by parasites. *Mol. Ecol* 2001;10:1–16. [PubMed: 11251782]
- Muller HJ. Some genetic aspects of sex. *Am Nat* 1932;66:118–138.
- Nee S. Antagonistic Co-Evolution and the Evolution of Genotypic Randomization. *J Theor Biol* 1989;140:499–518. [PubMed: 2615403]
- Otto SP, Lenormand T. Resolving the paradox of sex and recombination. *Nature Reviews Genetics* 2002;3:252–261.
- Otto SP, Nuismer SL. Species interactions and the evolution of sex. *Science* 2004;304:1018–1020. [PubMed: 15143283]
- Peters AD, Lively CM. The red queen and fluctuating epistasis: A population genetic analysis of antagonistic coevolution. *Am Nat* 1999;154:393–405. [PubMed: 10523486]
- Peters AD, Lively CM. Short- and long-term benefits and detriments to recombination under antagonistic coevolution. *J Evolution Biol* 2007;20:1206–1217.
- Salathé M, Kouyos RD, Bonhoeffer S. The state of affairs in the kingdom of the Red Queen. *Trends in Ecology and Evolution* 2008a;23(8):439–445.
- Salathé M, Kouyos RD, Regoes RR, Bonhoeffer S. Rapid Parasite Adaptation drives Selection for High Recombination Rates. *Evolution* 2008b;62:295–300.
- Schmid-Hempel P, Jokela J. Socially structured populations and evolution of recombination under antagonistic coevolution. *Am Nat* 2002;160:403–408. [PubMed: 18707448]
- Shpak M, Gavrillets S. Population genetics: multilocus. *Nature Encyclopedia of Life Sciences*. 2006
- Sturtevant AH, Mather E. The interrelations of inversions, heterosis and recombination. *Am Nat* 1938;72:447–452.
- Wright, S. The roles of mutation, inbreeding, crossbreeding and selection in evolution. VI International Congress of Genetics; 1932. p. 356–366.

Figure 1.

Disentangling the effects of a recombination modifier. A recombination event is indicated by the thick dotted line. In the immediately following generation g_0 , only the immediate short-term effect (A) is causing selection for or against recombination. After that ($g_{n>0}$), two types of effects can be responsible for selection: the delayed short-term effect (B) which is a continuation of the short-term effect, and the long-term effect (C) based on directional selection. Because (B) and (C) occur at the same time, it is important to distinguish between them clearly. The total short-term effect is given by lines A + B.

Figure 2.

Results from the Nee model. The following colour-coding was used: red to yellow: selection for recombination; blue to black: selection against recombination. (A) Change of modifier frequency, (B) LD x epistasis, (C) immediate short-term effect, (D) delayed short-term effect. The short-term effects are measured as described in the main text (see “Material & Methods”). Parameters used: $r_{baseline} = 0.0025$; $\Delta r = 0.0005$; $r_{modifier} = 0.5$.

Figure 3.

Typical dynamics of the Nee model. (A) LD (solid line) and epistasis (dashed line) of host population. (B) immediate short-term effect (s_0) and the delayed short-term effect s_1 and s_2 . As an example of the immediate and delayed short-term effect pointing in different direction, consider time step 9 where the $s_0 < 0$ and $s_2 > 0$. The arrows point to the current and future epistasis experienced by the host population as present at time step 9 (see main text). Parameters used: $s_H = 0.2$, $s_P = 1$; $r_{baseline} = 0.0025$; $\Delta r = 0.0005$; $r_{modifier} = 0.5$.

Figure 4.

Results from the matching allele model. (A) Change of modifier frequency, (B) long-term effect, (C) immediate short-term effect (measured as in fig. 2C), (D) total short-term effect as calculated by equation 10, (E) sum of total short-term effect and long term effect as calculated by equation 10, (F) delayed short-term effect, given by (D) – (C). Parameters: $r_{baseline} = 0.0025$; $\Delta r = 0.0005$; $r_{modifier} = r_{baseline}$. Colour-coding as in Figure 2.

Figure 5. Same settings as in Figure 4, but with a completely unlinked modifier locus, i.e. $r_{modifier} = 0.5$. Colour-coding as in Figure 2.