

The state of affairs in the kingdom of the Red Queen

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One of the most prominent hypotheses to explain the ubiquity of sex and recombination is based on host–parasite interactions. Under the name of the Red Queen hypothesis (RQH), it has had theoretical and empirical support since its conception, but recent theoretical work has shown that the circumstances under which the RQH works remain unclear. Here we review the current status of the theory of the RQH. We argue that recent theoretical work calls for new experimental data and an increased theoretical effort to reveal the driving force of the RQH.

Parasites: an environment just right for sex?

One of the oldest arguments why genetic recombination might be beneficial is that the combinations of alleles which are favored by selection change with time [1–4]. The argument states that in an ever-changing environment, creating variable offspring can be beneficial because new genotypes might be better adapted to the future environment. However, theoretical studies have shown that for such a mechanism to work, the environment must fulfill very specific conditions: neither changeability nor unpredictability are sufficient conditions to create a selective advantage for recombination [5,6]. Rather, linkage disequilibrium (LD), which measures the statistical associations between alleles at different loci, must change rapidly in sign, on the order of a few generations [5,7]. These conditions seemed so stringent that Bell noted in 1982 that ‘although [such] environments may exist, it seems absurd to suggest that they are sufficiently common to explain the ubiquity of sexual reproduction’ [6].

At about the same time, however, it became clear that species interactions could in principle provide the necessary conditions for sex to be advantageous. Antagonistic coevolution between species that results in genotype frequency-dependent selection will under the right circumstances generate the LD oscillations that render recombination beneficial [8]. Hosts and their parasites represent a ubiquitous system of such antagonistic coevolution that is at least in part genetically determined. Sex might allow hosts to escape parasite pressure by creating rare offspring genotypes, which are at a selective advantage. This hypothesis, known as the Red Queen hypothesis (RQH) [6], has been studied extensively in theory and in practice. Today it is one of the most prominent theories to explain the maintenance of sex and recombination in plants and animals.

Since its conception in the latter half of the 1970s, the RQH has gained support through theoretical investigations and empirical evidence. However, the hypothesis also faces serious challenges. On the one hand, direct empirical evidence of Red Queen dynamics is rare, largely owing to the difficulty of tracking genotype and LD oscillations over a long time. On the other hand, several authors have challenged the RQH on theoretical grounds, arguing that specific assumptions must be met for the RQH to work which seem too stringent to make the hypothesis biologically widely applicable [9–11]. In this review, we will address these theoretical criticisms and suggest directions for both empirical and theoretical research to assess the validity of the RQH.

Selection, interactions and mechanisms

There are two problems associated with sex and recombination, and failure to separate the two is a potential cause of confusion. The first problem is to identify the benefit of a nonzero recombination rate in competition against any other recombination rate (including zero). Such a benefit is required because in a constant and uniform environment, recombination is likely to break up well-adapted genotypes [12]. The

Glossary

Directional selection: a type of selection that favors a single fittest genotype and thus causes change of allele frequencies in one direction.

Drift: the change in allele frequencies in a population from one generation to the next due to chance events, rather than to selection. Drift gets stronger as populations get smaller.

Epistasis: quantifies the fitness interaction between alleles at different loci. In a haploid two-locus/two-allele model with haplotypes ab , Ab , aB , AB and fitnesses w_{ab} , w_{Ab} , w_{aB} , w_{AB} , epistasis is defined as $e = w_{ab} w_{AB} - w_{Ab} w_{aB}$. Constant epistasis refers to epistasis that remains constant over time. Fluctuating epistasis refers to epistasis that changes sign over time (such that the combinations of alleles favored by selection change over time).

Linkage disequilibrium (LD): quantifies the statistical association between alleles at different loci. It measures the deviation of the actual frequency of a genotype from its expectation on the basis of the frequency of the individual alleles. Mathematically, the LD between alleles at two loci is defined as $D = f_{ab} - f_a f_b$, where f_a is the frequency of individuals having allele a at locus 1, f_b is the frequency of individuals having allele b at locus 2, and f_{ab} is the frequency of individuals having allele a at locus 1 and allele b at locus 2. A positive (negative) LD implies that the combination of both alleles is more (less) frequent than expected by the frequencies of the individual alleles.

Negative frequency-dependent selection: a type of selection in which the fitness of an allele or genotype decreases as its frequency increases.

Red Queen dynamics: oscillations of genotype frequencies that result from antagonistic coevolution between hosts and their parasites.

Red Queen hypothesis (RQH): the hypothesis that Red Queen dynamics cause selection for sex or recombination.

Truncation selection: a type of selection where individuals are assigned a fitness value of 0 or 1 depending on whether a specific trait value (e.g. parasite load) is below or above a certain threshold value.

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second problem is to identify the benefit of a nonzero recombination rate in competition with the absence of recombination when a nonzero recombination rate is associated with a potentially twofold cost [13]. The second problem is thus an extension of the first problem. The twofold cost stems from the fact that in species with two sexes and an equal sex ratio, a parthenogenetic female enjoys a twofold fitness advantage by not producing males. The first problem is often referred to as the problem of recombination, whereas the second is referred to as the problem of sex. Here we focus primarily on the first.

The strength of selection

Probably the most obvious assumption for the RQH is that parasites reduce the fitness of the hosts they infect. Such parasite-induced fitness reduction is generally referred to as virulence, although plant pathologists often use the term virulence to denote pathogen infectivity. In what follows, we will use the term in the first sense, that is, as selection acting on the host.

The first analytical model of antagonistic host–parasite coevolution, published in 1980, found that a sexual species has a geometric mean fitness greater than that of an asexual species by a factor of at least two, suggesting that frequency-dependent selection exerted by parasites might be responsible for the maintenance of sex [14]. Shortly thereafter, however, this conclusion was shown to be only tenable in the case of highly virulent pathogens, and that a twofold higher mean fitness in a sexual species cannot be obtained unless virulence (s_H) is close to unity ($s_H > 0.9$ in the case of a two-locus model) [9]. This criticism, based on group fitness arguments, was later confirmed using models based on individual fitness arguments [15]. The fact that the RQH cannot prevent invasion of parthenogenesis with a twofold fitness advantage unless parasites are highly virulent remains a major obstacle for the plausibility of the hypothesis as an explanation for the problem of sex [16].

The importance of the strength of selection has also been investigated with regard to the problem of recombination. One study demonstrated that an allele causing free recombination can initially spread when virulence is larger than $s_H = 0.4$ [17]. This result was later confirmed and extended in an analysis showing that a modifier allele causing a nonzero recombination rate can spread when virulence is as low as $s_H = 0.1$ [18]. The generality of these results has been questioned on the basis that previous studies had considered only a narrow region of parameter space [11]. Using an analytical approximation and extensive simulations, it was shown that Red Queen dynamics generally favor modifier alleles that reduce the rate of recombination unless selection is strong, thus seemingly contradicting previous results [11]. The discrepancy between the results of these studies, however, is to a large extent due to differing assumptions about the selection acting on the parasite (s_P) [19]: whereas the earlier studies assumed that parasites that failed to infect a host did not reproduce ($s_P = 1$) [17,18], Ref. [11] assumed $s_P \leq 0.5$. In general, as long as selection acting on the parasite is relatively high, modifier alleles that increase the rate of recombination in hosts are favored, an effect that is largely independent of

virulence [19]. Thus, the RQH requires strong fitness effects on at least one of the species involved to explain the maintenance of nonzero recombination rates. Although this requirement might be too stringent for species interactions in general, it is a plausible assumption in host–parasite systems because most parasites that fail to infect a host cannot reproduce at all, and parasites that have a high reproductive output independent of infection success are arguably the exception rather than the rule [20].

The strength of selection also plays an important role in determining the recombination rate attained in the long term. In particular, it has been shown that Red Queen dynamics favor low rates of recombination over no recombination under very broad conditions, but hardly ever favors maximal recombination [21,22]. The recombination rate that is expected to evolve in the long term typically increases with the strength of selection [21,22].

Interactions

A further key assumption of the RQH is that host susceptibility to parasite infection depends, at least in part, on the genotypes of host and parasite. Although there is ample empirical evidence for this assumption (see the last box on testing the RQ), the exact details of the genetic control are less clear. Several models have been proposed to capture the genetic mechanism underlying resistance and infection. These models are usually set up using a haploid two-locus/two-allele system, but other configurations are possible. Such a model consists of a 4×4 matrix where each dimension corresponds to the four possible genotypes (e.g. ab, aB, Ab and AB) of host and parasite, respectively. Each element of the matrix then corresponds to 1 of the 16 possible genotype interactions between host and parasite, and for each of these interactions, the fitness for both host and parasite are defined. Although conceptually straightforward, historical terminology issues are a potential cause of confusion (see Box 1).

The first model that was proposed for the genetics of host–parasite interactions, based on results of studies in a plant–pathogen system, was the gene-for-gene model (GFG) [23]. One particular feature of the GFG model is that it contains a parasite genotype – the so-called super-pathogen – against which no host is resistant. The lack of resistance to such a pathogen genotype results in the absence of negative frequency-dependent selection – because the super-pathogen will eventually spread to fixation – and thus prevents one of the necessary conditions for the RQH to work. Using the GFG model, Parker demonstrated that the Red Queen always selects against recombination unless fitness costs for the pathogen associated with higher infectivity are substantial [10]. Spatial structure and finite population sizes can promote genotype polymorphism in GFG systems [24,25], but whether this can cause selection for recombination remains to be investigated.

By contrast, most studies where the RQH was shown to work implemented a different interaction model, which has come to be known as the matching allele model (MA) [26]. The MA model is based on the widely observed principle of self- versus non-self-recognition [27]. Infection is not possible unless the parasite matches all alleles of the host

Box 1. Qualitative and quantitative interaction models

The exact nature of the fitness interaction between host and parasite genotypes has been shown to be of fundamental importance in the RQH. It was recognized quite early that qualitative differences in interaction models (i.e. differences between interaction models with only two possible states, infection or resistance) can lead to completely opposite results concerning the evolution of sex [10]. The two most prominent models of this class are the matching allele (MA) and the gene-for-gene models (GFG) (see Figure 1a). In the current terminology, the MA model assumes that a host is resistant unless the parasite matches all of its interaction alleles. The GFG model, by contrast, assumes that the host is resistant if it recognizes at least one protein of the parasite, that is, if it contains at least one resistance allele that matches a so-called avirulence allele in the parasite. The most important consequence of the GFG model is that it allows for a super-pathogen to which no host is resistant, thereby preventing genetic polymorphism. It is important to note that some early studies on the RQH used the term ‘gene-for-gene’ for interaction models that do not fall under the contemporary definition (e.g. [14,49]).

Quantitative interaction models, by contrast, assign a fitness value for host and parasite for each possible genotype combination. They thus implicitly define under which conditions a host is resistant but, contrary to qualitative models, partial resistance might be incorporated. Quantitative models allow exploration of a broad and continuous parameter range, and in doing so, they can interpolate between different qualitative models, often yielding unexpected results. For example, one study [32] showed that a small departure from a pure GFG model results in dynamics typical of the MA model. Another study [33] considered a generalized version of the MA model (see Figure 1a,b), allowing for partial resistance with continuous fitness changes. The study identified a hitherto unknown range of quantitative MA models that show strong selection for reduced recombination rates that is attributable to strong, nonfluctuating linkage disequilibria (black area in Figure 1c).

In general, such theoretical studies demonstrate the sensitivity of the RQH to the exact nature of the interaction models, and highlight the need for empirical studies to determine the fitness consequences of host–parasite genotype interactions.

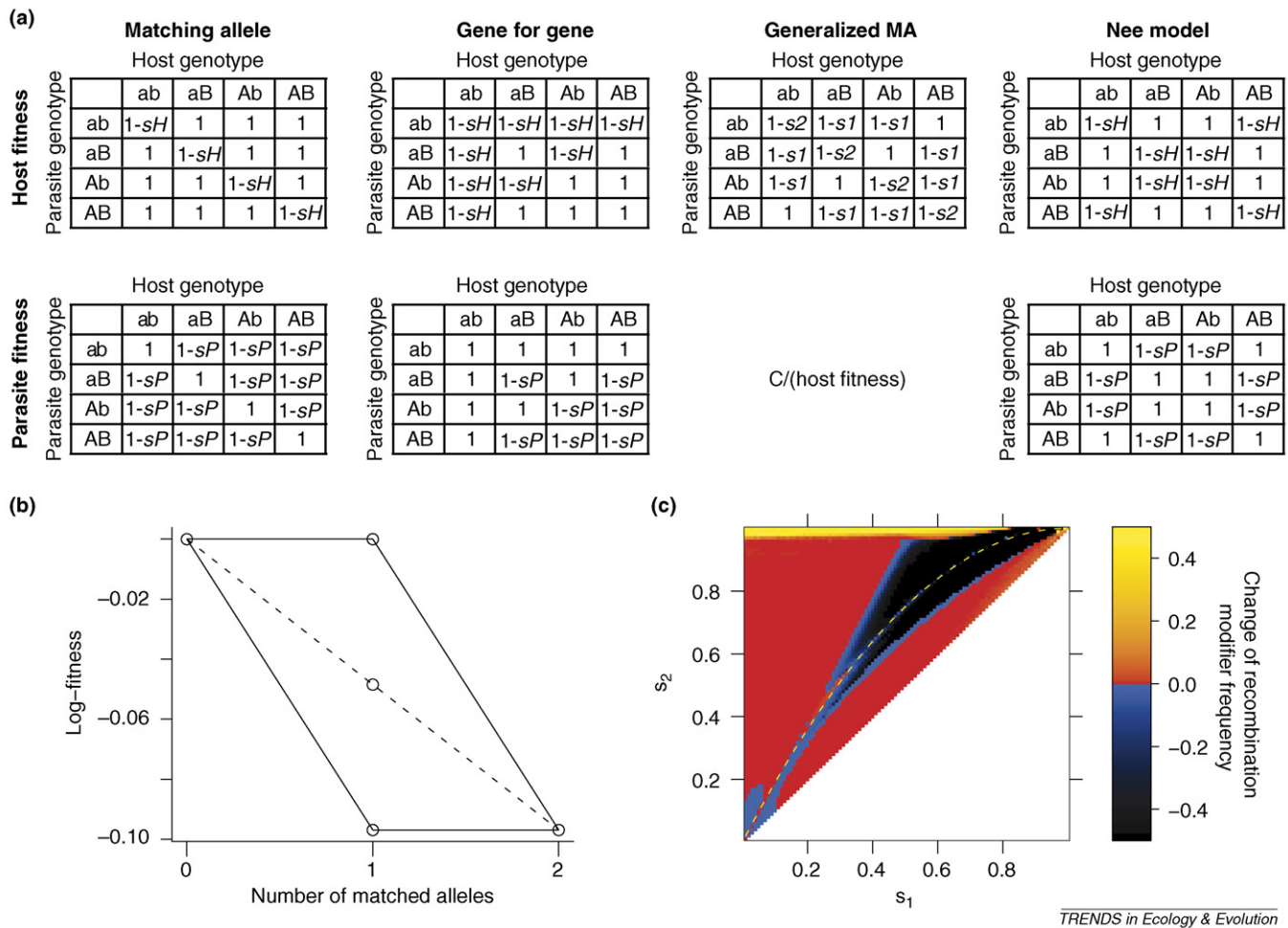


Figure 1. Interaction models. (a) The matrices display the fitness of host (upper row) and parasite (lower row) for different interaction models. The MA, GFG and Nee models distinguish only between genotype combinations in which the parasite can infect the host and between genotype combinations in which the host is fully resistant. Hence, these models are characterized by the cost of infection for the host, s_H , and the cost of not being able to infect for the parasite, s_P . By contrast, the generalized MA model allows for different fitness costs if the parasite matches one (s_1) or two (s_2) alleles. This interaction model assumes that host and parasite fitness are inversely proportional, where C is an arbitrary constant. (b) The graph displays host fitness as a function of the number of matched alleles for different versions of the generalized MA model. The upper solid line corresponds to the MA model, in which the host is fully resistant unless the parasite matches all loci. The lower solid line corresponds to the other extreme, in which the host is maximally susceptible already with one matched allele. The intermediate dashed line corresponds to the multiplicative matching allele (MMA) model, in which host fitness decreases multiplicatively with the number of matched alleles. (c) Selection on a modifier causing an increased recombination rate for the generalized MA model with varying coefficients s_1 and s_2 (see [a]). Notice that the modifier is selectively neutral (i.e. no cost of sex is included). The color of each of the points on the graph shows the frequency change of the recombination modifier during a simulation run (1000 host generations) averaged over ten simulation runs with different random initial conditions. The same model was used as in Ref. [33] (see Figure 6 therein). The following parameters were used: recombination rates: $r_{mm} = 0.1$, $r_{mM} = 0.15$, $r_{MM} = 0.2$, where the subscripts denote the combinations of modifier alleles m and M in the parents; mutation rate: 10^{-5} in both host and parasite; five parasite generations per host generation. (Note that s_H refers to the strength of selection per host generation independent of the number of parasite generations per host generation.)

it tries to infect, representing the sort of password mechanism Hamilton envisaged in his first analytical treatment of the problem [14]. Importantly, the MA model leads to negative frequency-dependent selection that results in continued genetic polymorphism. In several papers, Frank argued that the patterns of polymorphism observed in natural plant–pathogen systems can be explained by both the GFG and the MA model [26,28–31], and it was later shown that a small departure from the pure GFG model would result in the dynamical aspects normally exhibited by MA models [32].

By describing the fitness effects of interactions between host and parasite genotypes, interaction models also define epistatic interactions between loci within a genotype. The strength of these epistatic interactions can have profound consequences on the evolution of recombination. In the pure MA model, for example, a host genotype is resistant unless the parasite alleles match the host alleles at all interaction loci. In the two-locus/two-allele case, this means that the fitness effect of an allele at one locus strongly depends on the allele at the other locus. At the other extreme of this scenario is the multiplicative MA model (MMA), where the number of matched alleles determines the fitness of host and parasite in a multiplicative way, and thus the fitness effect of an allele at one locus is completely independent of the allele at the other locus. In a previous study of a wide range of interaction models between those two extremes, selection for recombination was observed for most of the parameter range [33]. Interestingly, however, models that were quantitatively similar to the MMA model led to strong LD of constant sign in the host population, which, in line with the reduction principle [12], resulted in strong selection against recombination [12,33].

Mechanisms

How does the Red Queen cause selection for or against recombination? Ultimately, the only genetic effect of recombination is to break down LD, and like any other theory on the maintenance of recombination, the RQH must explain why breaking down LD is beneficial, and how LDs are maintained. Several studies on the RQH have included many factors simultaneously that could be responsible for selection on recombination either individually or in combination. An example is the well-known HAMAX model by Hamilton *et al.* where multiple parasites attack a finite population of iteroparous hosts, and truncation selection acts only against the most infected hosts [34]. A spatial extension of this model added an additional layer of complexity [35]. Although it is reasonable to ask whether the RQH can explain selection for recombination under such realistic assumptions, one would also like to identify the causes of selection for recombination. This requires studies that investigate the potential causes as isolated from each other as possible, even if such an isolation is not always empirically justified [21,36].

Assuming no spatial effects, several factors can be responsible for the generation of LD: constant epistasis (either at mutation selection balance [37] or under directional selection [7]), fluctuating epistasis [5,7] and drift [38]. In deterministic RQ models, where drift and constant

epistasis can be excluded, only fluctuating epistasis can generate LD. Under which circumstances will breaking down LD built up by fluctuating epistasis favor recombination? According to population genetic theory [7,39], the selection on a recombination modifier can be broken down into a short- and long-term effect. The long-term effect describes the effect of recombination on additive genetic variance for fitness and acts to improve the response to selection over time. It has been called a long-term effect because the beneficial effect of recombination does not arise immediately in the next generation, but only after a delay. The short-term effect considers whether breaking up current LD results in the generation of fit or unfit combinations of alleles. Whether breaking up LD results in selection for recombination does not only depend on the effect in the immediately following generation but also on the effect in subsequent generations. Hence, the short-term effect can also manifest itself with a delay.

The terminology of the short- and long-term effect can be misleading if the short-term effect is equated with the effect of recombination in only the next generation. To avoid this potential confusion, we here subdivide the short-term effect into immediate and delayed effects. The immediate effect occurs because recombination generates allele combinations that are disproportionately fit or unfit immediately after the action of recombination. The delayed effect (e.g. an effect delayed by $n > 0$ generations) occurs because the allele combinations produced by recombination become disproportionately fit or unfit after a delay (of $n > 0$ generations). For systems with constant epistasis, the distinction between immediate and delayed effects has no consequences for assessing the short-term effect: the allele combinations that are disproportionately fit or unfit immediately after a recombination event will also be disproportionately fit or unfit after a delay. This is, however, not the case for host–parasite systems with fluctuating epistasis, where the immediate effect might not be representative of the selection generated by the short-term effect, because immediate and delayed effects can cause selection in opposite directions (see Box 2).

The mistake of equating the short-term effect with only the immediate effect has led to discrepant interpretations of the mechanisms underlying the RQH. Peters and Lively [22] quantified the relative importance of the short- and long-term effect in the Red Queen using the immediate effect as a proxy for the entire short-term effect. They argued that the short-term effect is typically detrimental (unless recombination is very rare) and thus concluded that the selection for higher recombination, when present, must be mediated by a long-term effect or, more precisely, through directional selection at individual loci. However, in models that exclude directional selection by design, such as the Nee model [21,36], it has been shown that recombination can be selected for even in the absence of directional selection. In our view, distinguishing between immediate and delayed effects will be necessary to elucidate the relative importance of the long- and short-term effect in the RQH (see Box 2).

Faster fluctuations of epistasis also favor the evolution of recombination [7], and strong selection on either host or parasite generates faster fluctuations [21]. Recent studies

Box 2. Delineation of immediate versus delayed effects of recombination in the Red Queen

To illustrate the relative importance of immediate versus delayed effects, we show here simulations that are based on the Nee model as implemented in Refs [21,36]. We chose the Nee model because it excludes directional selection by construction, and thus selection on recombination is entirely governed by the short-term effect.

Recombination between parents in a given generation t^* immediately affects offspring fitness in generation $t^* + 1$ and, accordingly, the recombination modifier frequency. The modifier frequency can also change at a later generation $t^* + 1 + n$ owing to a delayed effect of recombination in generation t^* . To determine the relative contribution of immediate and delayed effects, we set up two test populations in which recombination rate differs only at generation t^* . Comparing the fitness consequences of this single event in subsequent generations of the test populations yields the selection coefficients s_n , which correspond to the effect of recombination after a delay of n generations, with $n=0$ denoting the immediate effect (see figure legend). This approach is similar in spirit to the computation of the immediate effect in Ref. [22], but it extends the procedure to include delayed effects as

well. Figure 1a displays the selection coefficients s_n as a function of the delay n . In particular, it illustrates that the overall short-term effect, that is, the sum of the s_n , can be positive even though the immediate effect is negative ($s_0 < 0$). Figure 1b shows that the relative importance of the delayed effects (i.e. the difference between the total effect and the immediate effect) decreases as the linkage between the modifier and the selected loci becomes smaller, but even for minimal linkage (i.e. $r_{\text{modifier}} = 0.5$) the delayed effects clearly outweigh the immediate effect. Together, these figures illustrate that the benefit of recombination does not arise because recombination generates allele combinations that are disproportionately fit in the immediately following generation, but because the allele combinations will become fit after a certain delay.

The benefit of recombination in the RQH is widely attributed to the immediate fitness increase among the offspring. The simulations presented here, however, show that delayed effects play a central role for the RQH. Importantly, these delayed effects are not to be equated with the long-term effects that arise through directional selection, just as much as the short-term cannot be equated with the immediate effect.

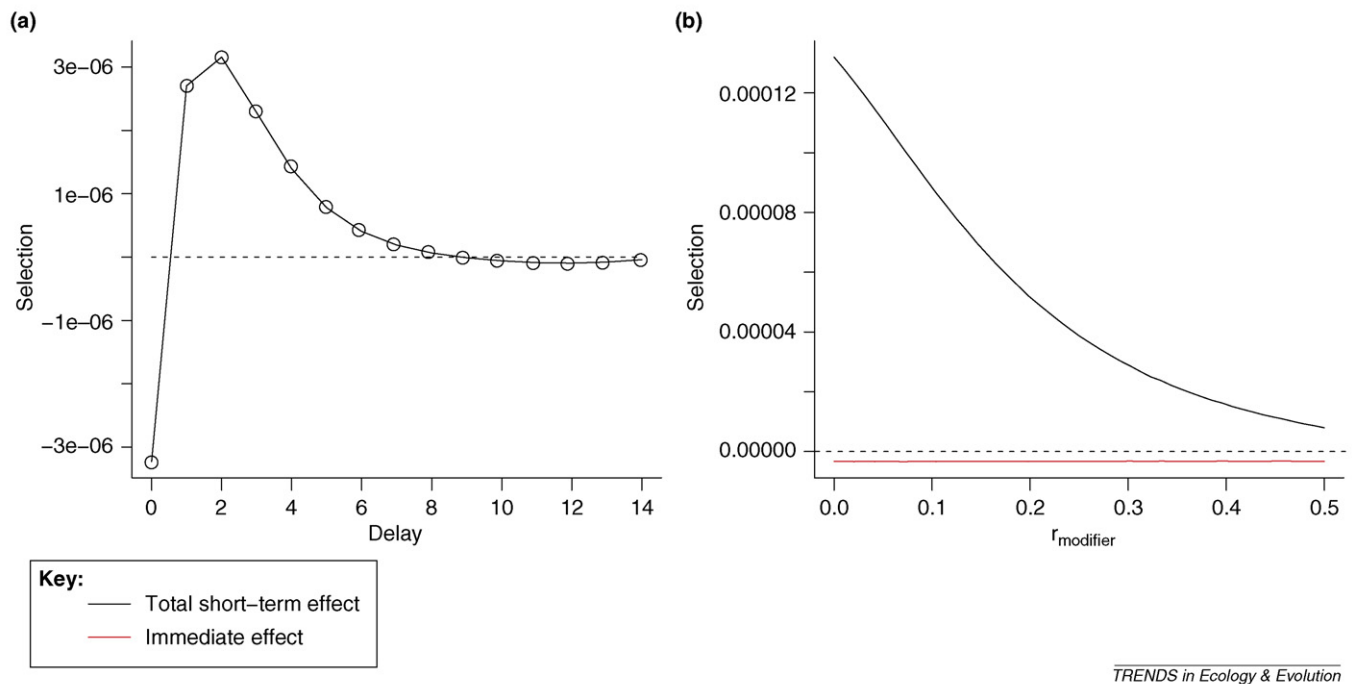


Figure 1. Immediate versus delayed effects. (a) Temporal average of the selection coefficients s_n as a function of the delay n (the first point corresponds to the immediate effect s_0). The horizontal dashed line marks no selection. (b) Immediate effect and total short-term effect as a function of the recombination rate between the modifier and the selected loci. The host genome consists of a recombination modifier locus (m/M) and two loci (a/A , b/B) that mediate the interaction with an asexual parasite (as implemented in Refs [21,36]). 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 $2\Delta r$ if one or both genomes carry allele M . The recombination rate between the modifier and the interaction loci, r_{modifier} , is constant and independent of the modifier allele. The selection coefficients for recombination, s_n , attributable to its effect after a delay of n generations, are measured as follows: a main population evolves according to the rules outlined above. The modifier allele M is rare in the main population, such that any genotype (carrying M or m) predominantly recombines with a genotype carrying m . For each time step of the main population, we generate two test populations, T_1 and T_2 , that are initiated with the genotype frequencies of the main population. We then let both test populations evolve for 50 generations, with the only difference being that for the first generation in population T_2 , Δr is temporarily set to zero. We measure s_n as the relative difference between the mean fitness of the genotypes carrying allele M in populations T_1 and T_2 in $(n+1)$ th generation after the initiation of the test populations. This measure is meaningful, because in the first generation of the test populations, the individuals carrying the M allele in T_1 recombine at the same rate as those carrying the allele M in the main population (i.e. $r_{\text{baseline}} + \Delta r$), whereas those carrying M in T_2 recombine at the same rate as those carrying m in the main population (i.e. r_{baseline}). (Parameters: $r_{\text{modifier}} = 0.5$ in (a), $r_{\text{baseline}} = 0.05$, $\Delta r = 10^{-3}$, Nee model with $s_H = 0.2$, $s_P = 1$, host and parasites have the same generation time.)

[17,21] suggest that selection for recombination can occur even when the sign of epistasis changes less frequently than every 2–5 generations (i.e. outside of the so-called Barton zone [7]), but it is important to note that Barton's conditions are only necessary for the evolution of high recombination rates. Lower rates of recombination can also evolve when fluctuations have much larger periods [21]. Finally, a multitude of factors might influence the

phase shift between epistasis and LD fluctuations – for example, the difference between host and parasite recombination rates has been shown to be a strong determinant [21].

Intriguingly, the effects of space and finite population sizes on the RQH are only marginally understood, although such effects are known to have a major effect on the dynamics of host–parasite interactions [40]. The few

Box 3. Testing the Red Queen hypothesis

To date, the great majority of studies have attempted to test the RQH indirectly, by determining whether key assumptions of the RQH are fulfilled or whether consequences that can be derived from these assumptions can be observed in nature. Examples for such indirect tests are studies that verified the genetic basis of host–parasite interactions (supported by a large body of medical literature; for natural populations, see Ref. [50]), the presence of negative frequency dependence (see, for example, Ref. [51]), the presence of oscillations in host and parasite genotype frequencies [51] and the presence of a correlation between frequency of sexual reproduction and infection [52–54]. Altogether these indirect tests thus broadly support the RQH.

Early theoretical studies have narrowed down the conditions under which the RQH is expected to work. In particular, they established a requirement for rapid fluctuations of LD and epistasis (2–5 generations; see Ref. [7]), for strong selection [9] and for particular kinds of interaction models (MA rather than GFG [10]). Recent theoretical investigations suggest that the first two conditions might have been too restrictive. One study [21] showed that selection for recombination is possible even if epistasis changes sign considerably less frequently than every 2–5 generations. It has also been shown that selection on the host population need not be strong provided it is strong on the parasite population [19]. Several papers [11,32,33] emphasize the importance of a precise quantification of the interaction model, as the RQH works only for particular interaction models. Moreover, epistatic interactions between parasite resistance loci have been shown to be a necessary requirement for the RQH to work [33]. These recent theoretical studies suggest new ways to test the RQH indirectly. In particular, they suggest a shift of focus away from testing for rapid LD fluctuations or for strong selection on the host to testing the strength of selection on the parasite and the presence of epistasis among disease resistance loci. It is worthwhile noting that meta-analyses of plant and animal data [55] indeed suggest that epistatic interactions are highly prevalent among disease resistance loci.

Direct evidence for the RQH is harder to obtain. To date, we are aware only of a single direct test of the RQH, which demonstrated that exposure of flour beetles to coevolving parasites led to an increase in recombination rate [56]. Further direct tests of the RQH are badly needed. Here, experimental microbial evolution might play an important role in the future, as it allows overcoming the problems of long generation times and small population sizes inherent to studies with large organisms.

simulation models on spatial effects on the evolution of recombination in the context of the RQH suggest that spatial structure disfavors sexual reproduction [35,41,42], but the results are highly sensitive to the strength of host and parasite migration. Although drift could be a potential confounding factor in these studies, recent deterministic work has confirmed that spatial structure can cause selection against recombination [21]. The effect of finite population sizes is even less understood: to our knowledge, there is only a single study that explicitly addresses the effect of drift on the evolution of recombination in the context of the RQH [33]. Drift was shown to have a beneficial effect for the evolution of recombination, and in some cases, it was even shown to be essential for the RQH because host–parasite interactions alone could not maintain LD oscillations in the long term [33].

The future of the Red Queen hypothesis

The plausibility of the idea that fluctuating selection, in particular in the context of host–parasite interactions, can select for sex and recombination, has itself fluctuated strongly since its conception. The RQH has received

increased attention in the past few years from both the theoretical and the experimental side, not least because other prominent theories such as the mutational deterministic hypothesis have lost ground in explaining the evolution of sex and recombination [43,44]. However, the recent theoretical advances reviewed above also show that we currently lack a full understanding of the circumstances under which the RQH works, and which of these circumstances are biologically justified. Although the latter question can ultimately only be settled by empirical evidence (see Box 3), substantial progress can be expected on the former question from theoretical studies. In comparison to mutational hypotheses on the evolution of recombination, the RQH has received comparatively little theoretical attention.

In recent years, the suggestion that the maintenance of sex – especially when associated with a substantial cost – might be explained by the combined effects of host–parasite interactions and mutation accumulation has become popular under the term ‘the pluralist theory of sex’ [16]. Although it is undoubtedly conceivable and even plausible that a twofold cost might only be paid by a simultaneous action of multiple factors, the potential danger of subscribing to the pluralist approach, in our view, is a lack of intellectual rigor at scrutinizing the current theories individually. We believe that it is too early to reject the hypothesis that host–parasite interactions alone can explain the continued presence of sexual reproduction, and that the maintenance of nonzero recombination rates is an important problem even in the absence of a cost of sex. Multiple parasites [24], sexual reproduction in parasites [21,45,46], nonrandom infection [47], segregation [48] and many other biologically important processes have all been demonstrated to affect the outcome of the RQH substantially, and the interactions between these processes wait to be investigated. Despite important advances, our understanding of the RQH remains incomplete, and clarifying under which ecologically realistic assumptions the RQH works is imperative. Thus, more research is needed to increase our understanding of the RQH, as anticipated by the Red Queen herself when she gave Alice the advice that ‘if you want to get somewhere else, you must run at least twice as fast as that!’

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