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DIFFERENCES BETWEEN SELECTION ON SEX VERSUS RECOMBINATION IN RED QUEEN MODELS WITH DIPLOID HOSTS

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The Red Queen hypothesis argues that parasites generate selection for genetic mixing (sex and recombination) in their hosts. A number of recent papers have examined this hypothesis using models with haploid hosts. In these haploid models, sex and recombination are selectively equivalent. However, sex and recombination are not equivalent in diploids because selection on sex depends on the consequences of segregation as well as recombination. Here I compare how parasites select on modifiers of sexual reproduction and modifiers of recombination rate. Across a wide set of parameters, parasites tend to select against both sex and recombination, though recombination is favored more often than is sex. There is little correspondence between the conditions favoring sex and those favoring recombination, indicating that the direction of selection on sex is often determined by the effects of segregation, not recombination. Moreover, when sex was favored it is usually due to a long-term advantage whereas short-term effects are often responsible for selection favoring recombination. These results strongly indicate that Red Queen models focusing exclusively on the effects of recombination cannot be used to infer the type of selection on sex that is generated by parasites on diploid hosts.

KEY WORDS: **Host–parasite coevolution, modifier model, recombination, Red Queen, segregation, sex.**

Selection is expected to eliminate unfit allele combinations and create an excess of good genotypes. If there is an excess of beneficial allele combinations following selection, why should organisms shuffle their genotypes through sex and recombination? Shuffling will tend to result in the conversion of good allele combinations into bad ones. This is one of the key problems in understanding the evolution of sex (Otto and Lenormand 2002; Agrawal 2006a). The logic that leads to this conundrum assumes that selection remains constant. If selection is constantly changing such that the combinations that were beneficial in the recent past are unfit in the near future, then it is much easier to understand the advantages of genetic mixing (Maynard Smith 1971; Charlesworth 1976). However, it is difficult to envisage why selection should be continuously changing in this peculiar manner.

A popular idea among evolutionary ecologists is that parasites might generate this type of fluctuating selection. Sex would be favored because it allows hosts to better evade their coevolving parasites, (Jaenike 1978; Bremermann 1980; Hamilton 1980). This idea is known as the Red Queen Hypothesis (Bell 1982). Group-selection effects drove many of the early Red Queen models, showing an advantage to sex when an obligately sexual group competed against an obligately asexual group (Hamilton 1980; May and Anderson 1983). Later models employed a modifier model approach (Nei 1967), which tracked the fate of alternative alleles at a gene that modified investment into sexual versus asexual reproduction in an organism capable of both modes of reproduction (Hutson and Law 1981; Bell and Maynard Smith 1987; Parker 1994; Peters and Lively 1999, 2007; Otto and Nuismer 2004; Gandon and Otto 2007; Salathé et al. 2008b).

These modifier models are the focus of the work described here. Red Queen modifier models have shown that parasites often select against sex (even in the absence of intrinsic costs of sex), although this is not always the case. Under some conditions, parasites do favor sex. This tends to occur with particular models of infection (matching alleles models rather than gene-for-gene models) involving high virulence. Although the authors of these previous papers have recognized that parasites favor sex under some conditions and select against it under other conditions, there is some disagreement over which conditions are most likely to prevail in nature (Salathé et al. 2008a).

Somewhat lost in this discussion is the important issue of ploidy. Most of the Red Queen modifier models have involved haploid hosts (Hutson and Law 1981; Bell and Maynard Smith 1987; Parker 1994; Peters and Lively 1999; Otto and Nuismer 2004; Gandon and Otto 2007; Peters and Lively 2007; Salathé et al. 2008b). For haploid hosts, sex and recombination are equivalent under typical selection scenarios (Otto and Nuismer 2004 but see Agrawal 2006b). This is not true for diploids. In diploids, the distribution of offspring genotypes produced through sex is affected by segregation as well as recombination. Recombination breaks down associations between genes on the same chromosome whereas segregation destroys associations between genes on homologous chromosomes.

Because sex in diploids involves segregation in addition to recombination, the conditions favoring sex need not be the same as those favoring recombination (Agrawal, in press). A previous paper showed that parasites often select against the effects of segregation in diploids (Agrawal and Otto 2006). That paper also reported one example in which the negative fitness effects of segregation overwhelmed benefits from recombination such that sex was disfavored. That example was biased in several respects toward segregation effects being stronger than recombination effects.

The primary purpose of the present work is to provide a much more thorough comparison of selection on sex and selection on recombination in diploids. The results indicate that the evolution of sex is often driven by the effects of segregation rather than recombination. Because the effects of segregation are often deleterious, parasites select against sex even under conditions in which parasites favor recombination. At the very least, these results imply that it can be extremely misleading to extrapolate the results of previous haploid models to predict the evolution of sex in diploid hosts.

The Model

The model is based on a diploid host interacting with a haploid parasite. As described below, whether a host can be infected depends on the alleles the host carries at its **A** and **B** loci relative to the alleles carried by the parasite at its corresponding loci. In hosts, there is a third locus, **M**. This modifier locus either affects the amount of sex or the amount of recombination. The modifier has no intrinsic fitness effects, that is there is no inherent cost to sex or reproduction. The loci are ordered on the chromosome as **MAB**.

LIFE CYCLE

The simulation model is based on the following life cycle: Hosts encounter parasites at random. Based on these interactions, there is selection on both hosts and parasites. Hosts and parasites reproduce.

More specifically, the model worked as follows. The fitness of host genotype i is given by

$$w_{Hi} = \sum_j P_j W_{Hij}, \tag{1a}$$

where P_j is the frequency of parasite genotype j and W_{Hij} is the fitness of host i when interacting with parasite j. Similarly, the fitness of parasite genotype j is given by

$$w_{Pj} = \sum_i H_i W_{Pij}, \tag{1b}$$

where W_{Pij} is the fitness of parasite j when interacting with host i and H_i is the frequency of host genotype i at the beginning of the generation. The values for W_{Hij} and W_{Pij} terms depend on the model of infection and are described in detail below. Using the fitness given above, host and parasite genotype frequencies following selection are calculated in the usual manner, that is the frequency of host genotype i after selection is $H_i' = H_i w_{Hi}/\bar{w}_H$.

Reproduction in hosts, which can be sexual or asexual, occurs following selection. Hosts invest a minimum fraction σ of their resources into sexual reproduction and the remainder into asexual reproduction. When the modifier locus **M** affects sex, then individuals increase their investment into sexual reproduction by an amount $^1/_2\ \delta_\sigma$ for every copy of the M allele that they carry, that is investments into sex are σ, $\sigma + {}^1/_2\ \delta_\sigma$, and $\sigma + \delta_\sigma$, for genotypes *m/m*, *M/m*, and *M/M*, respectively. I assume that the M allele causes more sex ($\delta_\sigma > 0$).

Sexual reproduction is modeled as the random union of gametes. Host gametes are produced following the standard rules of segregation and recombination during meiosis. The recombination rates in the **M**-**A** interval and **A**-**B** interval are r_{MA}, r_{AB}, respectively. When the modifier locus **M** affects recombination, then the recombination rate in the **A**-**B** interval increases by an amount $^1/_2\ \delta_r$ for every copy of the M allele that an individual carries, that is recombination rates are r_{AB}, $r_{\mathrm{AB}} + {}^1/_2\ \delta_r$, and $r_{\mathrm{AB}} + \delta_r$, for genotypes *m/m*, *M/m*, and *M/M*, respectively. I assume that the M allele causes more recombination than m ($\delta_r > 0$). Using the recombination rates above and assuming no interference, the distribution of haplotypes among the gametes of any

genotype can be calculated using the standard rules of meiosis. The frequency of haplotype h among the gametes produced by an individual of genotype i is denoted by $\gamma_{h,i}$ (where $\Sigma_h \gamma_{h,i} = 1$).

Considering both sexual and asexual reproduction, the distribution of host offspring genotypes can be calculated as follows. Let $Z = \Sigma_i H_i' z_i$ be the frequency of offspring that are produced through sexual reproduction where z_i is the fraction of resources invested into sexual reproduction by an individual of genotype i. The frequency of haplotype h in the entire gamete pool is $g_h = \Sigma_i H_i' \gamma_{h,i} z_i/Z$. Let $K_{h1,h2,i}$ be an indicator variable that denotes whether the combination of gametic haplotypes $h1$ and $h2$ forms the diploid zygote of genotype i. The frequency of genotype i among the host offspring is

$$H_i'' = H_i'(1 - z_i) + Z \sum_{h1} \sum_{h2} g_{h1} g_{h2} K_{h1,h2,i}. \qquad (2)$$

For the haploid parasites, the genotype frequencies after selection are given by

$$\begin{aligned} P''_{\mathrm{AB}} &= q'_{\mathrm{A}} q'_{\mathrm{B}} - R_{\mathrm{AB}} D' \\ P''_{\mathrm{Ab}} &= q'_{\mathrm{A}} q'_{\mathrm{b}} + R_{\mathrm{AB}} D' \\ P''_{\mathrm{aB}} &= q'_{\mathrm{a}} q'_{\mathrm{B}} + R_{\mathrm{AB}} D' \\ P''_{\mathrm{ab}} &= q'_{\mathrm{a}} q'_{\mathrm{b}} - R_{\mathrm{AB}} D', \end{aligned} \qquad (3)$$

where q'_x is the frequency of allele x in parasites after selection and $D' = P'_{\mathrm{AB}} P'_{\mathrm{ab}} - P'_{\mathrm{Ab}} P'_{\mathrm{aB}}$ is the linkage disequilibrium in parasites after selection. The parameter R_{AB} is the effective recombination rate in parasites. (If parasites reproduce sexually at rate f and the actual recombination rate is ρ, then the effective rate of recombination is $R_{\mathrm{AB}} = f\rho$.)

In many real systems, parasites have faster generation times than their hosts. This can be modeled in a variety of ways. The approach used here is to scale time with respect to parasite generations and assume that the frequency of host genotype i after one complete parasite generation is

$$H_i[t+1] = \left(1 - \frac{1}{n}\right) H_i[t] + \frac{1}{n} H_i''[t], \qquad (4)$$

where n is the number of parasite generations per host generation. Functionally, this approach is equivalent to assuming that a fraction $(1 - 1/n)$ of hosts is in some form of stasis (e.g., seed bank) and the remainder proceeds through the life cycle at the same rate as the parasites. Although this may not be the most realistic way to model differences in generation times it should capture the essence of the problem. Moreover, this approach allows the interpretation of parasite virulence to remain reasonably consistent when comparing across different n values.

MODELS OF INFECTION GENETICS

Three types of models of infection genetics have been used extensively in Red Queen models: gene-for-gene (GFG), matching alleles (MA), and inverse matching alleles (IMA); see Parker (1996), Frank (1996), and Agrawal and Lively (2002) for discussion of GFG versus matching models. As in other Red Queen models, the different models of infection genetics are treated here as mutually exclusive alternatives although this need not be the case (Agrawal and Lively 2002, 2003).

Table 1. Probability that a haploid parasite matches its host at the A locus in the MA or IMA models. See text for description of parameters.

	Parasite genotype	
Host Genotype	*A*	*a*
A/A	1	0
A/a	$d_1+(1-d_1)$ d_2	$d_1+(1-d_1)$ $(1-d_2)$
a/a	0	1

MA models are based on the idea that hosts have a self/nonself recognition system that allows their immune system to detect parasites. Although this idea is easily translated into a model for infection for haploid hosts, it is less obvious how to apply this logic in diploids because of heterozygotes. The following approach was used. Let $E_{\mathrm{L},i,j}$ be the probability that parasite j matches host i with respect to locus **L**. Infection occurs if the parasite evades detection by matching the host at both the **A** and **B** loci. Thus, the probability of infection in an encounter between parasite j and host i is $E_{\mathrm{A},i,j} E_{\mathrm{B},i,j}$.

The values for $E_{\mathrm{A},i,j}$ are given in Table 1 (values for $E_{\mathrm{B},i,j}$ are calculated in the same way). With respect to the **A** locus, *A* parasites are able to match *A/A* hosts but not *a/a* hosts; the reverse is true for *a* parasites. A parasite of either genotype is automatically able to match an *A/a* heterozygote with probability d_1; d_1 is the probability that heterozygous hosts can be universally matched. With probability $(1 - d_1)$, there is no universal match, and the probability of match then depends on the parasite's allele in relation to the dominance of the *A* allele as specified by d_2 (i.e., d_2 gives the probability that an *A/a* heterozygote behaves like an *A/A* homozygote rather than *a/a* homozygote). When $d_1 = 1$, there is under-dominance in the sense that *A/a* heterozgyotes are completely unable to detect either *A* or *a* parasites as being different from self. When $d_1 = 0$, heterozygotes have no intrinsic disadvantage. In this case, heterozygotes are exactly intermediate to the two homozygotes with respect to susceptibility if $d_2 = 0.5$. If $d_2 > 0.5$ ($d_2 < 0.5$), then heterozygotes function more like *A/A* (*a/a*) homozygotes. For example, with $d_1 = 0$ and $d_2 = 1$, heterozygotes behave exactly as *A/A* homozygotes. Although there are numerous other ways to model infection patterns in diploids (Nuismer and Otto 2005; Agrawal and Otto 2006), the approach used here allows for a variety of possibilities (by choice of d_1 and d_2 values) that are consistent with the idea of

Table 2. Fitness of host genotype *i* in an interaction with parasite genotype *j* in the GFG model. The table gives the values for $W_{H,i,j}$. See text for description of parameters.

Host genotype	Parasite genotype			
	AB	*Ab*	*aB*	*ab*
AB/AB	$(1-c)^2$	$(1-c)^2$	$(1-c)^2$	$(1-c)^2(1-v)$
AB/Ab	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c) \times (1-v)$
AB/aB	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c)$	$(1-c)(1-d_1c) \times (1-v)$
AB/ab or *Ab/aB*	$(1-d_1c)^2$	$(1-d_1c)^2$	$(1-d_1c)^2$	$(1-d_1c)^2(1-v)$
Ab/Ab	$1-c$	$1-c$	$(1-c)(1-v)$	$(1-c)(1-v)$
Ab/ab	$1-d_1c$	$1-d_1c$	$(1-d_1c)(1-v)$	$(1-d_1c)(1-v)$
aB/aB	$1-c$	$(1-c)(1-v)$	$1-c$	$(1-c)(1-v)$
aB/ab	$1-d_1c$	$(1-d_1c)(1-v)$	$1-d_1c$	$(1-d_1c)(1-v)$
ab/ab	$1-v$	$1-v$	$1-v$	$1-v$

a self/nonself recognition system upon which MA models are based.

The fitness of both host and parasite depend on whether an infection occurs. When host i encounters a parasite of genotype j, the fitness of the host is given by $W_{H,i,j} = 1 - E_{A,i,j}E_{B,i,j}\ v$, where v represents the virulence of infection. The fitness of the parasite in this interaction is $W_{P,i,j} = 1 - (1 - E_{A,i,j}E_{B,i,j})t$, where t represents the strength of selection against the parasites who are unable to cause a successful infection.

An alternative to the MA model is the IMA model (Otto and Michalakis 1998). Opposite to the MA model, the host must match the parasite to successfully eradicate it in the IMA. Using the same rules for determining whether a match occurs as described for the MA model (Table 1), the fitness interactions in the IMA model are given by: $W_{H,i,j} = 1 - (1 - E_{A,i,j}E_{B,i,j})v$ and $W_{P,i,j} = 1 - E_{A,i,j}E_{B,i,j}\ t$. Because matching benefits parasites in the MA model but benefits hosts in the IMA model, the universal match parameter d_1 causes very different effects in the two models. A value of $d_1 > 0$ decreases the fitness of heterozygotes in the MA model but increases it in the IMA model.

It is much clearer how to build the GFG model because this model is based on empirical data in plants (Flor 1956; Parker 1996). In the GFG model, each host locus has a resistant allele (A, B) and a susceptible allele (a, b). Resistance alleles are dominant to susceptible alleles with respect to susceptibility to parasites. In parasites, there is a noninfectious (A, B) and an infectious (a, b) allele at each locus. An infection occurs unless the parasite caries a noninfectious allele at one or more loci for which the host carries the corresponding resistance allele. To maintain polymorphism, resistant alleles in hosts are believed to bear pleiotropic fitness costs (Tian et al. 2003). The pleiotropic fitness cost is c in homozygotes and d_1c in heterozygotes (note that the dominance parameter d_1 has a different biological interpretation in GFG than in the matching models). Similarly, infectious alleles are also thought to be costly. The pleiotropic fitness cost of an infectious allele is k. The fitness of host and parasites in the GFG model are given in Tables 2 and 3. The parameters v and

Table 3. Fitness of parasite genotype *j* in an interaction with host genotype *i* in the GFG model. The table gives the values for $W_{P,i,j}$. See text for description of parameters.

Host genotype	Parasite genotype			
	AB	*Ab*	*aB*	*ab*
AB/AB	$1-t$	$(1-k)(1-t)$	$(1-k)(1-t)$	$(1-k)^2$
AB/Ab	$1-t$	$(1-k)(1-t)$	$(1-k)(1-t)$	$(1-k)^2$
AB/aB	$1-t$	$(1-k)(1-t)$	$(1-k)(1-t)$	$(1-k)^2$
AB/ab or *Ab/aB*	$1-t$	$(1-k)(1-t)$	$(1-k)(1-t)$	$(1-k)^2$
Ab/Ab	$1-t$	$(1-k)(1-t)$	$1-k$	$(1-k)^2$
Ab/ab	$1-t$	$(1-k)(1-t)$	$1-k$	$(1-k)^2$
aB/aB	$1-t$	$1-k$	$(1-k)(1-t)$	$(1-k)^2$
aB/ab	$1-t$	$1-k$	$(1-k)(1-t)$	$(1-k)^2$
ab/ab	1	$1-k$	$1-k$	$(1-k)^2$

t in the GFG model have the same meaning as in the matching models.

Population genetics of selection on sex and recombination

The results presented here are based entirely on simulations of a diploid host interacting with a haploid parasite. However, several relevant analytical models (Barton 1995; Otto and Nuismer 2004; Agrawal and Otto 2006; Agrawal, in press) provide a useful frame of reference for interpreting the results presented here.

The modifier allele has no intrinsic fitness effects; it evolves because it becomes associated with genes that do directly affect fitness (i.e., **A** and **B**). The change in the frequency of the modifier allele due to selection can be decomposed into two parts:

$$\Delta p_M = \Delta p_{M,short} + \Delta p_{M,long.} \quad (5)$$

This decomposition was suggested by Barton (1995, eq. 10) in a general model of recombination and the details of the application to the present model are given in the Supporting Information.

The first part, $\Delta p_{M,short}$, consists of terms involving associations of the modifier with "combinations" of selected alleles (e.g., $C_{\mathrm{MAB}/\emptyset}$, $C_{\mathrm{MA/A}}$, $C_{\mathrm{MAB/AB}}$—see Supporting information for symbol definitions). Such associations arise directly from the modifier's effect on sex or recombination; the modifier allele breaks down associations by inducing more sex or recombination. For example, if there is linkage disequilibrium between the **A** and **B** loci prior to reproduction, then following reproduction the M allele will be associated with less disequilibrium than the m allele because the former causes more recombination than the latter. Because $\Delta p_{M,short}$ reflects the effects of changing allele combinations, it is driven by nonadditive selection (e.g., dominance and epistasis). This term can also be thought of as the "short-term" effect (Lenormand and Otto 2000; Gandon and Otto 2007) because the immediate effect of sex or recombination is to change allele combinations, not allele frequencies. (Note that this approach to measuring the short-term effect accurately captures the "delayed" effect discussed by Salathé et al. [2008a].)

The second part, $\Delta p_{M,long}$, consists of terms involving associations of the modifier with selected alleles (e.g., $C_{\mathrm{MA}/\emptyset}$, $C_{\mathrm{MB}/\emptyset}$,), rather than with combinations of selected alleles as in the first part. These associations develop because of subsequent selection on the associations underlying the short-term effect. By shuffling allele combinations through sex or recombination, the M allele changes the genetic backgrounds on which it is found relative to m. By doing so, the M allele may be found in genetic backgrounds that are more (or less) variable in fitness than the m allele. If it is in a more (less) variable background, the M allele will experience a greater (lesser) response to "directional selection" on fitness-affecting loci. As a consequence, the M allele forms associations with alleles directly under selection and can then hitchhike with them. This type of selection on the modifier is known as the "long-term" effect (Lenormand and Otto 2000; Gandon and Otto 2007) because it results from associations that are not an immediate byproduct of sex or recombination but rather develop from subsequent selection. See Agrawal (2006a) for further discussion of long- and short-term effects in modifier evolution.

Following Peters and Lively (1999, 2007), I examine the short- and long-term effects on the modifier generated through selection by parasites. Peters and Lively determined the sign of the short- and long-term effects essentially by calculating the effect of recombination on the mean and variance in fitness, respectively. Here I measure these effects directly from the two terms in equation (5). This approach allows short- and long-term effects to be compared quantitatively, rather than just qualitatively.

The total change due to short-term effects is

$$\Delta P_{short} = \sum_t \Delta p_{M,short}[t], \quad (6)$$

where the summation is over all the generations in the simulation in which the modifier is turned on (see below). The total change due to long-term effects, ΔP_{long}, is calculated in the same manner.

SIMULATIONS

Based on the model described above, a C++ program was created to perform simulations. Each simulation was initiated with $p_M = 0.5$, random allele frequencies at the **A** and **B** loci in both hosts and parasites, and complete linkage equilibrium in both species. Each simulation began with a 10,000 generation "burn-in" period during which the modifier had no effect on the amount of sex and recombination. Because it had no phenotypic effect during this time, the modifier did not form any associations or change in frequency. Following the burn-in period, the state of the population was saved into computer memory. The modifier was then "turned on" as a sex modifier with $\delta_\sigma = 0.05$ (and $\delta_r = 0$). The simulation then continued for 5000 generations or until the modifier reached near fixation ($p_M < 0.0001$ or $p_M > 0.9999$), whichever happened first. After the sex simulation was completed, the population was returned to the saved state after the burn-in. The modifier was then turned on as a recombination modifier with $\delta_r = 0.05\, r_{\mathrm{AB}}/\sigma$ (and $\delta_\sigma = 0$). This value of δ_r was chosen so that the recombination modifier would cause the same increase in the effective rate of recombination in the **A**-**B** interval as occurs with a sex modifier of $\delta_\sigma = 0.05$. The simulation with the recombination modifier was allowed to proceed in the same fashion as with the sex modifier. A new "burn-in" was done after a simulation had been completed with one sex modifier and one recombination modifier.

All combinations of the following parameter values were used: baseline rate of sex, $\sigma = \{0.1, 0.5, 0.9\}$; virulence, $v = \{0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, 0.99\}$; selection against unsuccessful parasites, $t = \{0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 0.95, 0.99\}$; probability of universal match for heterozgygotes for MA and IMA model or dominance of costs of resistance in GFG, $d_1 = \{0, 0.1, 0.3, 0.5, 0.7, 0.9, 1\}$; number of parasite generations per host generation, $n = \{1, 2, 5, 10\}$. In the MA and IMA models, the following values were used for the second dominance parameter: $d_2 = \{0.5, 0.7, 0.9, 1\}$. In the GFG model, the following four pairs of values were used for costs of resistance and infectiousness: $(c, k) = \{(0.05v, 0.05t), (0.05v, 0.3t), (0.3v, 0.05t), (0.3v, 0.3t)\}$. Other parameter values used were $r_{MA} = 0.2$, $r_{AB} = 0.3$, $R_{AB} = 0.1$. For parasites, bidirection mutation was included in the model with $\mu = 10^{-5}$. Considering all combinations of values, 56,784 unique parameter combinations were investigated for each of the three models of infection. Two replicate simulations were performed for each parameter combination. Thus, the results discussed here represent 340,704 simulations for sex modifiers and an equal number for recombination modifiers.

Results

With three different models of infection each involving six (MA, IMA) or seven (GFG) variable parameters, it is not practical to provide a detailed description of the conditions that favor sex and recombination, nor is that the goal. Rather, the results are summarized to provide an overall picture of how often parasites favor more genetic mixing and to contrast how parasites select for sex versus recombination.

In the GFG model, there were no simulations in which a modifier that increased sex or recombination increased in frequency. In the vast majority of cases (97%), the modifier declined in frequency. In the remaining cases, no change in the modifier was detected. (The frequency of the modifier had to change by more than10^{-9} to be considered a detectable change to avoid complications from round-off error.) The remaining results focus on the two matching models for which selection did favor increased genetic mixing under some circumstances.

In the MA model, recombination modifiers were favored in 53.1% of simulations whereas sex modifiers were favored in only 5.6% of simulations. In the IMA model, recombination modifiers were favored in 17.6% of simulations but sex modifiers were only favored in 7.2% of simulations. (The percentages reported above are based only on simulations in which a detectable change in the modifier occurred, either positive or negative.)

Although sex was favored less frequently than recombination, sex was not simply favored under a subset of the conditions favoring recombination. For example, in the MA model, 38% of the parameter combinations favoring sex selected against recombination. In the IMA model, 59% of the parameter combinations favoring sex selected against recombination. (These percentages are calculated using only those replicates in which a detectable change was observed for both sex and recombination modifiers.)

To provide a measure of the extent to which selection for sex was related to selection for recombination, the correlation between the fate of sex and recombination modifiers, $\rho_{sex,rec}$, was calculated as follows. For each replicate parameter combination, the fate of the sex modifier was scored as $X = -1$ if $\Delta p_{sex} < 0$, $X = 0$ if $\Delta p_{sex} \approx 0$ (no detectable change), or $X = 1$ if $\Delta p_{sex} > 0$. For the same replicate, the fate of the recombination modifier was scored as Y in the analogous manner with respect to Δp_{rec}. The correlation $\rho_{sex,rec}$, is the correlation of X and Y. For both the MA and IMA models, this correlation was low; MA: $\rho_{sex,rec} = 0.03$, IMA: $\rho_{sex,rec} = 0.11$.

To illustrate how the model parameters affect selection on genetic mixing, the frequency of simulations in which the modifier increased is plotted as a function of each parameter (Fig. 1). Some parameters have similar effects on sex and recombination. For example, in the MA model, higher levels of virulence select for more recombination and more sex, although the effect is greater on the former (Fig. 1A). Other parameters affect sex and recombination very differently. The universal match parameter, d_1, is negatively correlated to the fate of sex modifiers but positively correlated to the fate of recombination modifiers in the MA model (Fig. 1E). In the IMA model, sex modifiers are most likely to increase when the baseline level of sex, σ, is low whereas the opposite is true for recombination modifiers (Fig. 1L).

There are also differences between the infection models. Intermediate levels of virulence are most favorable to increased recombination in the IMA model rather than high levels of virulence as in the MA model (Fig. 1A, B). The strength of selection against parasites, t, is quite important in determining the fate of sex and recombination modifiers in the IMA model but not the MA model (Fig. 1C, D). The universal match parameter affects recombination modifiers in the MA and IMA models in opposite directions (Fig. 1E, F). In contrast, this parameter affects sex modifiers in the same way in both models.

The patterns of selection with respect to short- and long-term effects differ between recombination and sex modifiers and between models (Table 4). In the MA model, a fairly large fraction of parameter values resulted in positive selection on recombination modifiers through short- and long-term effects, (52% and 56%, respectively). In contrast, only a small fraction of parameter combinations caused positive selection on sex modifiers through short- or long-term effects, (5% and 21%, respectively).

This difference between sex and recombination is not too surprising given the earlier observation that recombination modifiers are much more likely to be favored than sex modifiers. A

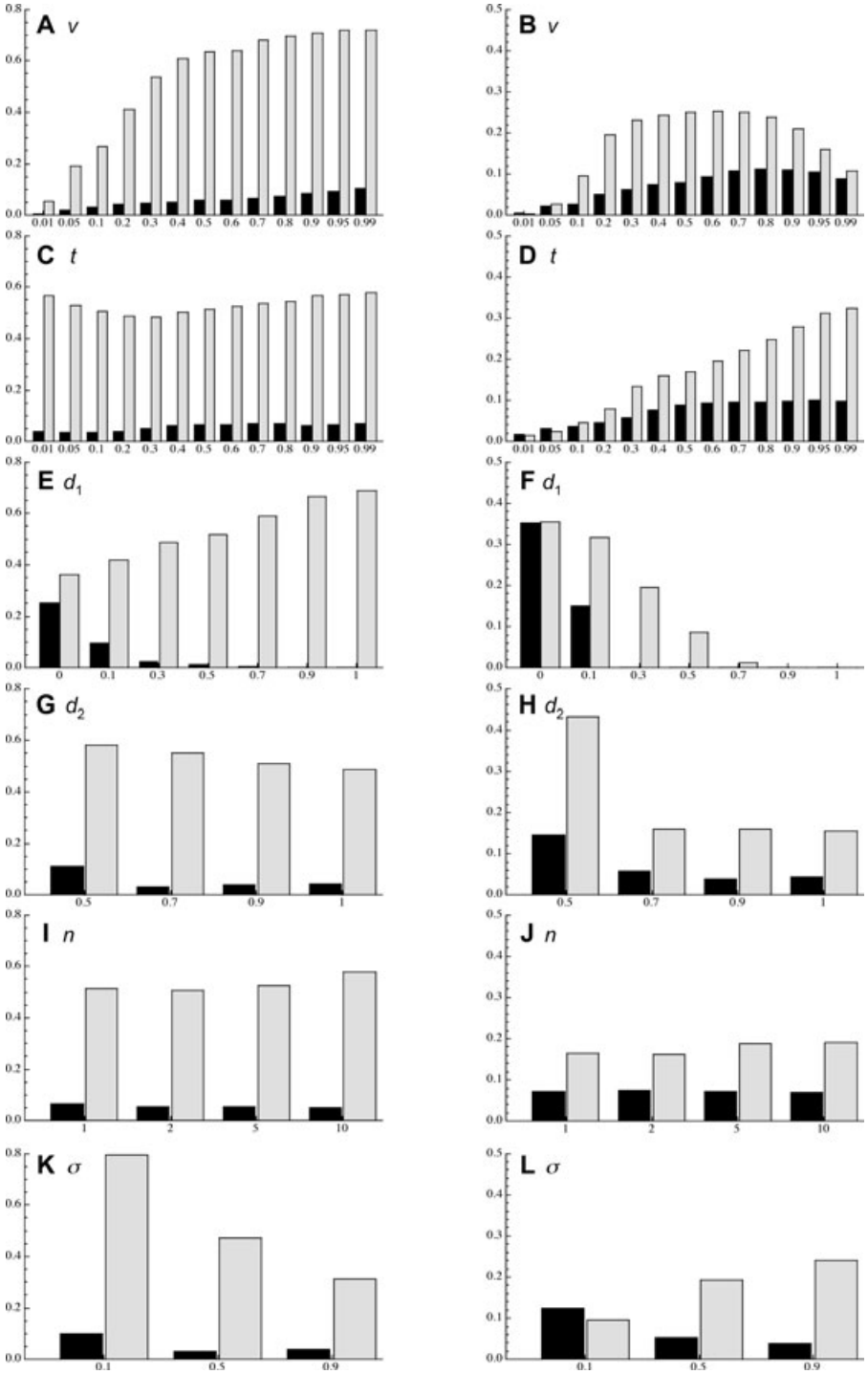

Figure 1. Effect of individual parameters on the evolution of sex and recombination. The frequency of simulations in which a sex (black bars) or recombination (gray bars) modifier increased in frequency is plotted as function of each of the six model parameters. Left column: MA model; right column: IMA model. (A, B) virulence, v; (C, D) strength of selection on parasites, t; (E, F) universal match parameter, d_1; (G, H) secondary dominance parameter, d_2; (I, J) number of parasite generations per host generation, n; (K, L) baseline level of sex, σ. For each focal parameter, results were calculated over simulations involving all combinations of nonfocal parameter values. For example, in (A) the value reported for each value of v is calculated from simulations involving all combinations of values for t, d_1, d_2, n, and σ. Simulations in which there was no detectable change in the frequency of the modifier were excluded.

Table 4. Evolution of sex modifiers through short- and long-term effects. The rows show (from top to bottom): (1) the frequency of cases in which short-term effects were positive; (2) the frequency of cases in which long-term effects were positive; (3) the frequency of cases in which short-term effects were larger in magnitude than long-term effects; (4) the frequency of cases in which short-term effects were in the opposite direction to long-term effects; and (5) the frequency of cases in which short-term effects were larger in magnitude among those cases in which short- and long-term effects were in opposing directions. Within each row, the upper number is with respect to all simulations and the number in parentheses is with respect to those simulations in which the modifier increased in frequency. The latter category is not applicable to the GFG model because the modifier never increased in frequency.

	GFG		MA		IMA	
	sex	rec	sex	rec	sex	rec
Cases with short-term advantage,	0.00	0.00	0.05	0.52	0.03	0.20
$F[\Delta P_{short} > 0]$	(na)	(na)	(0.63)	(0.78)	(0.40)	(0.85)
Cases with long-term advantage,	0.56	0.56	0.21	0.56	0.58	0.29
$F[\Delta P_{long} > 0]$	(na)	(na)	(0.73)	(0.66)	(0.95)	(0.83)
Cases in which short-term effects outweigh long-term effects	0.97	0.91	0.67	0.57	0.94	0.48
$F[\lvert\Delta P_{short}\rvert > \lvert\Delta P_{long}\rvert]$	(na)	(na)	(0.49)	(0.62)	(0.25)	(0.50)
Cases in which short-term effects oppose long-term effects	0.56	0.56	0.21	0.65	0.54	0.33
$F[\Delta P_{short} \times \Delta P_{long} < 0]$	(na)	(na)	(0.43)	(0.56)	(0.46)	(0.31)
Cases in which short-term effects outweigh long-term effects when they oppose,	1.00	1.00	0.89	0.62	0.94	0.64
$F[\lvert\Delta P_{short}\rvert > \lvert\Delta P_{long}\rvert \mid \Delta P_{short} \times \Delta P_{long} < 0]$	(na)	(na)	(0.63)	(0.61)	(0.10)	(0.53)

more interesting comparison is between sex and recombination modifiers that are beneficial (i.e., cases in which the modifier increases in frequency). Do beneficial sex modifiers increase in frequency for the same reasons as beneficial recombination modifiers? Short-term effects outweighed long-term effects in 62% of simulations involving beneficial recombination modifiers but only 49% of beneficial sex modifiers. This indicates that sex modifiers are more likely, than recombination modifiers, to increase in frequency primarily through long-term effects.

In the IMA model, there is a larger difference between sex and recombination with respect to the relative importance of short- versus long-term effects. In only 25% of simulations involving beneficial sex modifiers are short-term effects larger than long-term effects whereas short-term effects are larger in 50% of cases involving beneficial recombination modifiers. In addition to differences in magnitude, short- and long-term effects differ in sign between beneficial sex and recombination modifiers. In the IMA model, short- and long-term effects are in opposite directions in 46% of the cases involving beneficial sex modifiers. In 90% of these cases, the sex modifier evolves because of a positive long-term effect despite a negative short-term effect. In contrast, when short- and long-term effects are in opposition with respect to beneficial recombination modifiers, the modifier is more often favored because a positive short-term effect overwhelms a negative long-term effect.

Although long-term effects can be important in understanding why beneficial modifiers are favored, short-term effects tend to be larger when considering all modifiers (beneficial and deleterious). This pattern is especially strong in the GFG model in which short-term effects outweigh long-term effects in the vast majority of cases for both sex and recombination modifiers. In the GFG model, short-term effects are never positive. Although long-term effects are beneficial in about half of the cases, positive long-term effects are never large enough to outweigh the negative short-term effects. Consequently, neither sex nor recombination is favored in this model.

Discussion

Most modifier models of the Red Queen hypothesis have focused on haploid hosts despite the vast interest in understanding the prevalence of sex in diploids. In haploids, sex and recombination are functionally equivalent under most selective scenarios (Otto and Nuismer 2004 but see Agrawal 2006b). In diploids, the consequences of segregation also affect selection on sex so it is not necessarily true that conditions favoring recombination will also favor sex.

The primary goal of the work presented here was to determine whether parasites select for or against sex and recombination in diploid versions of standard Red Queen models. Even though a number of previous authors have studied the evolution of recombination in Red Queen models, it was not obvious that the types of conditions favoring recombination in haploid models would have a similar effect on recombination in diploid models. However, at a heuristic level, the recombination results reported here are similar to those previously reported from haploid models. GFG models show selection against recombination whereas MA models are more favorable for recombination, especially when the baseline

level of genetic mixing is low (Parker 1994; Otto and Nuismer 2004). The IMA model, which had not previously been studied (but see Lythgoe 2000), was less favorable to recombination than the MA model but more so than the GFG model.

The most important results pertain to the evolution of sex modifiers. In the GFG model, which has considerable empirical support in plants (Parker 1996), parasites always select against sex under the parameters considered. Conditions favoring sex are present but rare in both of the two matching models. The difference between recombination and sex is particularly striking in the MA model in which parasites often favor recombination but almost always select against sex. In both the MA and IMA models, recombination is disfavored under many of the parameter values that favor sex and vice versa. The weak correlation between the fates of sex and recombination modifiers indicates that the evolution of sex is not a result of selection for recombination. This implies that the consequences of segregation (including interactions between segregation and recombination) are the primary source of selection on sex. Consequently, we can conclude that haploid Red Queen models can be very misleading with respect to the evolution of sex in diploids (although they have been very useful with respect to studying recombination and for providing a framework for examining Red Queen processes in general).

Although parasites selected against genetic mixing over many of the parameter combinations examined, it is worth noting the types of conditions that are most likely to select for sex. Echoing previous results (Peters and Lively 1999, 2007; Otto and Nuismer 2004; Salathé et al. 2008b), highly virulent parasites are more likely to select for increased recombination and sex than weakly virulent parasites (Fig. 1A, B). Strong selection on parasites also increases the likelihood of selection for genetic mixing in the IMA model (Fig. 1D). The most important parameter with respect to the evolution of sex was the universal match parameter, d_1 (Fig. 1E, F). Large values for d_1 tend to cause underdominance for fitness in the MA model but overdominance for fitness in the IMA model. The observation that large values of d_1 are associated with selection against sex in both models is consistent with the prediction that sex is disfavored with any strong form of dominance such as underdominance and overdominance (Otto 2003; Agrawal and Otto 2006).

The number of parasite generations per host generation, n, had little effect on the evolution of either sex or recombination modifiers (Fig. 1I, J). This observation contrasts sharply with the results reported by Salathé et al. (2008b), who found that reducing parasite generation time (increasing n) dramatically increased selection for genetic mixing. Although there are a number of differences between the model presented here and that of Salathé et al. (2008b), the discrepancy with respect to the effect of parasite generation time is likely due to differences in how the life cycle is modeled. In the model of Salathé et al. (2008b), when $n > 1$, parasites are able to adapt through repeated rounds of infection and reproduction without further reducing the fitness of the current generation of hosts. In that type of model, shorter generation times allow parasites to increase their level of adaptation without imposing more selection on the current generation of hosts but the parasites do cause selection on those host genotypes in the following host generation. This will tend to disconnect the fitness of host genotypes across generations, favoring genetic mixing. This does not happen in the model used here. Faster shorter generation times allow parasites to better adapt to hosts but the parasites impose more selection on the current hosts as they do so (i.e., infections caused by "second-generation" parasites cause a second round of selection on hosts).

Traditionally, the Red Queen hypothesis was thought to work because coevolving parasites were thought to constantly change the relative fitness of allele combinations (Jaenike 1978; Bell 1982; Bell and Maynard Smith 1987). If parasite-mediated selection on allele combinations is sufficiently temporally variable (i.e., rapid fluctuations in the sign of dominance and/or epistasis), there will be a short-term benefit to breaking-up existing gene combinations (Barton 1995; Peters and Lively 1999, 2007; Gandon and Otto 2007). However, parasites do not select exclusively on allele combinations but also generate net selection on individual genes (i.e., directional selection). Modifiers can hitchhike to higher frequency with alleles experiencing directional selection if the modifier is associated with more variance at the selected locus, that is a modifier experiences a long-term advantage if genetic mixing increases the variance. Peters and Lively (1999) pointed out that both short- and long-term effects occur in Red Queen models and one cannot simply assume that short-term effects dominate.

I quantified the total change in modifier frequency due to short- and long-term effects (Table 4). In the vast majority of cases, changes due to short-term effects were larger than changes due to long-term effects (i.e., $|\Delta P_{short}| > |\Delta P_{long}|$). With respect to sex modifiers, these short-term effects were usually negative. We can infer from these results that parasites typically do not generate rapid changes in the sign of nonadditive components of selection (dominance and epistasis). Genotypes that were good (i.e., resistant to infection) in the recent past are likely to be beneficial in the near future; sex is deleterious because it recreates susceptible genotypes from resistant ones. Even in those cases in which parasites selected for more sex, it was often due to a long-term advantage (especially in the IMA model), rather than a short-term advantage as is typically assumed. In comparison to sex modifiers, recombination modifiers were more likely to be favored because of short-term benefits, thus illustrating another dimension in which selection on sex and recombination can differ.

Given the results, is it fair to conclude that parasites are unlikely to be an important force in selecting for sex in diploids?

Although a diverse set of host–parasite interactions were examined here, this is not an exhaustive set of all possible interactions. The goal here was to examine reasonable diploid versions of oft-studied haploid models. For these diploid models, parasites usually select against sex and the effects of segregation overwhelm the effects of recombination. Insights from analytical theory could be used to generate models that would yield different results. For example, segregation should be favored by host–parasite interactions in which the parasites generate weak, negative dominance on hosts or in which dominance and/or components of epistasis involving dominance fluctuate rapidly (Otto 2003; Agrawal and Otto 2006). Analytical theory predicts that recombination should be more important than segregation in driving the evolution of sex in Red Queen models in which parasites generate additive-by-additive epistasis that is strong relative to dominance or components of epistasis involving dominance (Agrawal, in press).

Although selection for sex was observed under some conditions modeled here and analytical theory could be used to predict other suitable circumstances, the issue is whether real parasites are likely to conform to such a model. We have no reason to believe that host–parasite interactions typically fall into the narrow set of conditions that select for sex but we also do not know that they lie outside this range. All we can say with certainty is that many Red Queen models result in selection against sex.

As in most other Red Queen models, I assumed that hosts encounter parasites completely at random. A more realistic model would allow hosts to be biased toward encountering parasites transmitted by their mothers, which may commonly occur as a consequence of geography. Previous work has shown that even weak transmission biases greatly increase the potential for parasites to select for sex (Agrawal 2006b; see also Tooby 1982; Rice 1983). It is important to recognize that the population genetic mechanism by which sex is favored in this scenario is very different from the traditional Red Queen mechanism wherein sex is advantageous because parasites are constantly changing which allele combinations are most favorable. With transmission bias, sex is advantageous because parasites generate selection to be different from one's mother.

Sexual reproduction involves both segregation and recombination. For the most part, theoreticians have focused on the effects of recombination and largely ignored segregation (but see Kirkpatrick and Jenkins 1989; Agrawal and Chasnov 2001; Galvani et al. 2003; Otto 2003). The simulation results presented here show major differences between recombination and sex modifiers indicating that the effects of segregation rather than recombination are driving the evolution of sex in many of these Red Queen models. Segregation is also responsible for the advantages to sex observed in the Red Queen models with transmission bias (Agrawal 2006b). These examples demonstrate that the effects of segregation can overwhelm the effects of recombination and thus segregation should not be ignored in any comprehensive study of sex in diploids.

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Supporting Information

The following supporting information is available for this article:

Appendix S1. Measuring short- and long-term effects.

Supporting Information may be found in the online version of this article.
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