Host-Parasite Coevolution and Selection on Sex through the Effects of Segregation

Aneil F. Agrawal[1,*] **and Sarah P. Otto**[2,†]

1. Department of Ecology and Evolutionary Biology, University of Toronto, 25 Harbord Street, Toronto, Ontario M5S 3G5, Canada; 2. Department of Zoology, University of British Columbia, 6250 University Boulevard, Vancouver, British Columbia V6T 1Z4, Canada

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abstract: The advantage of producing novel variation to keep apace of coevolving species has been invoked as a major explanation for the evolution and maintenance of sex (the Red Queen hypothesis). Recent theoretical investigations of the Red Queen hypothesis have focused on the effects of recombination in haploid species, finding that species interactions rarely favor the evolution of sex unless selection is strong. Yet by focusing on haploids, these studies have ignored a potential advantage of sex in diploids: generating novel combinations of alleles at a particular locus through segregation. Here we investigate models of host-parasite coevolution in diploid species to determine whether the advantages of segregation might rescue the Red Queen hypothesis as a more general explanation for the evolution of sex. We find that the effects of segregation can favor the evolution of sex but only under some models of infection and some parameter combinations, almost always requiring inbreeding. In all other cases, the effects of segregation on selected loci favor reductions in the frequency of sex. In cases where segregation and recombination act in opposite directions, we found that the effects of segregation dominate as an evolutionary force acting on sex in diploids.

Keywords: Red Queen hypothesis, host-parasite coevolution, evolution of sex, segregation, modifier model.

The idea that coevolution with parasites might favor the evolution of sex has been popular for more than 2 decades (Jaenike 1978; Bremermann 1980; Hamilton 1980; Bell 1982) and is now commonly called the Red Queen hypothesis. This idea is based on the premise that parasites adapt to exploit host genotypes and that sex allows hosts to change genotypes rapidly so that they can remain a step ahead of their relentless enemies.

Most of the theoretical work on the subject has involved computer simulations in which an obligately sexual host species competes against obligately asexual mutants (e.g., Hamilton et al. 1990; Howard and Lively 1994; Galvani et al. 2003). Because these obligately asexual mutants are completely reproductively isolated from their sexual progenitors, such models investigate the "group selection" advantages of sex in that a sexual group competes against an asexual group. There are numerous examples where sexual species give rise to fully asexual mutants in which case such models are appropriate.

However, these models do not address more subtle changes in the mode of reproduction. For example, rather than the extremes of all or none, an organism may produce some fraction σ of its offspring sexually and the remainder, $1 - \sigma$, asexually, where σ can take any value from 0 to 1. In general, the results of group selectionist models provide a poor guide for what to expect when reproductive mode can evolve via small, gradual steps. This problem is best studied using "modifier" models (Feldman et al. 1997), in which one tracks the evolutionary fate of a gene that modifies reproductive mode (e.g., a gene that alters σ).

Following this approach, previous authors have investigated theoretically whether parasites favor the spread of a gene that increases the amount of sex and/or recombination in haploid species (Parker 1994; Peters and Lively 1999; Otto and Nuismer 2004). This work has demonstrated that coevolution with parasites can select for increased levels of sex or recombination but only under specific conditions (e.g., particular genetic architectures of infection and high virulence). In fact, the most general modifier analysis of the Red Queen suggests that parasites typically generate selection against sex and recombination (Otto and Nuismer 2004).

In these haploid models, any advantage of sex must arise from the beneficial consequences of recombination. How-

* Corresponding author; e-mail: afagrawal@zoo.utoronto.ca.

† E-mail: otto@zoology.ubc.ca.

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Table 1: Matching alleles model

Host genotype	Parasite genotype		
	AA	*Aa*	*Aa*
AA	$w_{HAAPAA} = 1 - v$	$w_{HAAPAa} = 1$	$w_{HAAPaa} = 1$
	$w_{PAAHAA} = 1$	$w_{PAaHAA} = 1 - u$	$w_{PaaHAA} = 1 - u$
Aa	$w_{HAaPAA} = 1 - v$	$w_{HAaPAa} = 1 - v$	$w_{HAaPaa} = 1 - v$
	$w_{PAAHAa} = 1$	$w_{PAaHAa} = 1$	$w_{PaaHAa} = 1$
aa	$w_{HaaPAA} = 1$	$w_{HaaPAa} = 1$	$w_{HaaPaa} = 1 - v$
	$w_{PAAHaa} = 1 - u$	$w_{PAaHaa} = 1 - u$	$w_{PaaHaa} = 1$

Note: Fitness of host genotype *ij* when exposed to parasite genotype *mn* (w_{HijPmn}) and fitness of parasite genotype *mn* when exposed to host genotype *ij* (w_{PmnHij}).

ever, sexual reproduction in diploids involves two processes: recombination and segregation. To appreciate fully how the Red Queen might shape reproductive mode, we must also understand whether segregation is advantageous in the presence of parasites. In diploids, segregation breaks down associations at a locus between the alleles on homologous chromosomes (measured by a positive or negative inbreeding coefficient). Because such associations do not exist in haploids, the potential advantages of segregation were absent in these previous theoretical studies of the Red Queen hypothesis. While the studies above have provided an understanding of how the Red Queen acts on recombination, they have said nothing of segregation. Because sex and recombination are not functionally equivalent in diploids, haploid Red Queen models provide a qualitatively incomplete picture of how parasites affect the evolution of sex in diploid hosts.

Here we use a modifier approach to identify the conditions under which parasites generate selection for increased sex in diploid hosts. We study a model in which only a single locus directly affects fitness (with selection mediated by parasites) so that any observed advantage to sex must arise through the effects of segregation at a locus rather than recombination among loci. As we shall see, coevolution with parasites can favor the spread of modifier alleles that increase the frequency of sex in the host, but it more often favors modifier alleles that decrease the frequency of sex.

Why do host-parasite interactions select against sex in this model of segregation? Hosts that have survived selection have genotypes at the selected locus that tend to resist parasites more often than expected at Hardy-Weinberg equilibrium; these favorable associations are broken down by segregation. That is, segregation (like recombination) breaks apart beneficial combinations of alleles that have been built up by past generations of selection.

When can host-parasite interactions favor sex? Higher rates of sex tend to evolve when hosts inbreed and when host-parasite interactions cause heterozygotes to be fitter on average than homozygotes. Under these conditions, genetic associations at a locus have been built up by past generations of inbreeding (not selection), and these genetic associations reduce fitness. Consequently, segregation can be advantageous because it brings descendants closer to Hardy-Weinberg equilibrium, favoring the evolution of sex.

Our results allow us to compare the conditions under which parasites select for recombination versus segregation and the relative strength of these two effects (see "Discussion"). Overall, our results indicate that parasites typically select against sex in populations of randomly mating diploid hosts but can select for sex when inbreeding is present and heterozygotes have higher than average fitness in host-parasite interactions.

Model and Results

We model a single host species interacting with a single parasite species, where the **A** locus mediates the interactions and affects fitness, whereas the **M** (modifier) locus affects the mode of reproduction. Our model is completely deterministic, so there is no benefit to sex from segregation recreating genotypes that are lost stochastically in finite populations (Galvani et al. 2003; see also Antezana and Hudson 1997).

The first stage in the life cycle is selection via infection by parasites. We assume each diploid host encounters a single diploid parasite at random. Whether this encounter results in infection depends on the host's genotype at the **A** locus and the genotype of the parasite at its corresponding **A** locus. If an infection occurs, the host's fitness is reduced by v. The fitness of parasites that are resisted by hosts is reduced by u. Tables 1–3 show the fitness of each host genotype when interacting with each parasite genotype. We consider three different classes of host-parasite interaction models commonly used in Red Queen models (Otto and Michalakis 1998): a matching alleles (MA) model, an inverse matching alleles (IMA) model, and a gene-for-gene (GFG) model. In the MA model, the host can detect and then eliminate parasites carrying alleles that

Table 2: Inverse matching alleles model

Host genotype	Parasite genotype		
	AA	*Aa*	*aa*
AA	$w_{HAAPAA} = 1$	$w_{HAAPAa} = 1$	$w_{HAAPaa} = 1 - v$
	$w_{PAAHAA} = 1 - u$	$w_{PAaHAA} = 1 - u$	$w_{PaaHAA} = 1$
Aa	$w_{HAaPAA} = 1$	$w_{HAaPAa} = 1$	$w_{HAaPaa} = 1$
	$w_{PAAHAa} = 1 - u$	$w_{PAaHAa} = 1 - u$	$w_{PaaHAa} = 1 - u$
aa	$w_{HaaPAA} = 1 - v$	$w_{HaaPAa} = 1$	$w_{HaaPaa} = 1$
	$w_{PAAHaa} = 1$	$w_{PAaHaa} = 1 - u$	$w_{PaaHaa} = 1 - u$

Note: Fitness of host genotype *ij* when exposed to parasite genotype *mn* (w_{HijPmn}) and fitness of parasite genotype *mn* when exposed to host genotype *ij* (w_{PmnHij}).

Table 3: Gene-for-gene model

Host genotype	Parasite genotype		
	AA	*Aa*	*aa*
AA	$w_{HAAPAA} = 1 - c$	$w_{HAAPAa} = 1 - c$	$w_{HAAPaa} = (1 - c)(1 - v)$
	$w_{PAAHAA} = 1 - u$	$w_{PAaHAA} = 1 - u$	$w_{PaaHAA} = 1 - k$
Aa	$w_{HAaPAA} = 1 - c$	$w_{HAaPAa} = 1 - c$	$w_{HAaPaa} = (1 - c)(1 - v)$
	$w_{PAAHAa} = 1 - u$	$w_{PAaHAa} = 1 - u$	$w_{PaaHAa} = 1 - k$
aa	$w_{HaaPAA} = 1 - v$	$w_{HaaPAa} = 1 - v$	$w_{HaaPaa} = 1 - v$
	$w_{PAAHaa} = 1$	$w_{PAaHaa} = 1$	$w_{PaaHaa} = 1 - k$

Note: Fitness of host genotype *ij* when exposed to parasite genotype *mn* (w_{HijPmn}) and fitness of parasite genotype *mn* when exposed to host genotype *ij* (w_{PmnHij}).

differ from its own; this model is applicable to species with an immune system capable of recognizing and clearing nonself antigens. In the IMA model, each allele in the host confers the ability to recognize a particular allele in the parasite; infection occurs only if none of the host alleles are able to recognize any of the alleles carried by the parasite. In the GFG model, a host can resist a parasite only if the host expresses a resistance allele, *A*, and the parasite expresses a noninfectious (avirulent) allele, *A*; this genetic model is thought to underlie many plant-fungal interactions (Flor 1956; Crute et al. 1997).

To model host-parasite interactions in diploids, we must specify the susceptibility of heterozygous hosts and the infectiousness of heterozygous parasites (see Nuismer and Otto 2005). For the sake of brevity, we discuss only the simplest reasonable set of assumptions about the gene expression and fitness patterns in heterozygotes; more general results are presented in the appendix in the online edition of the *American Naturalist*. In the simplest version of the MA model, heterozygous hosts express both alleles and so are unable to identify any parasite as being nonself; consequently, the fitness of heterozygous hosts is always lower than or equal to the fitness of homozygous hosts. Conversely, in the simplest version of the IMA model, expression of both alleles allows heterozygous hosts to recognize and eradicate any parasite; consequently, heterozygotes are at least as fit as the best homozygote. Dominance relationships in the GFG model are better informed by empirical data than the other models (Flor 1956; Crute et al. 1997). Resistance alleles are typically dominant to susceptibility alleles, and noninfectious alleles are typically dominant to infectious alleles. Thus, in the simplest GFG model, a heterozygous host has the same fitness as the resistant *AA* homozygote.

It is often thought that resistant alleles in the host (or infectious alleles in the parasite) might be more costly to express than alleles that do not induce a resistance response (or do not mount a strong attack on the host). Thus, we incorporate two additional parameters in the GFG model. There is a cost to hosts of carrying and expressing the resistance allele, *A*, such that in the absence of parasites, the fitnesses of the *AA*, *Aa*, and *aa* genotypes are $1 - c$, $1 - c$, and 1, respectively. Similarly, there is a cost to parasites of carrying the infectious allele, *a*, such that the fitnesses of *AA*, *Aa*, and *aa* genotypes when on susceptible hosts are 1, 1, and $1 - k$, respectively.

What we refer to as the "infectious allele," *a*, is often referred to in the literature as the "virulent" or "virulence" allele. We prefer the term "infectious allele" because this allele allows its carrier to infect a broader array of host genotypes than does the alternative allele. The term "virulence" is used in this article to describe the reduction in host fitness caused by infection.

In the host, there are four types of chromosomes at the modifier and selected loci: *MA*, *Ma*, *mA*, and *ma*, which we refer to by the indices 1–4, respectively. Let H_{ij} be the frequency at the beginning of a generation of hosts carrying chromosomes i and j, where $i, j \in \{1, 2, 3, 4\}$. We distinguish between genotype *ij* and *ji* in our notation even though the frequencies of the two genotypes are equal ($H_{ij} = H_{ji}$) under the mating and selection regimes that we consider. The frequency of genotype *ij* after selection is $H_{ij}^{(s)} = H_{ij}w_{Hij}/w_H$, where w_{Hij} is the average fitness of hosts with genotype *ij* and w_H is the average fitness of all hosts. We calculate the average fitness of a host with genotype *ij* as $w_{Hij} = \sum_{kl} P_{kl}w_{HijPkl}$, where P_{kl} is the frequency of diploid parasites carrying chromosomes k and l and w_{HijPkl} is the fitness of a host with genotype *ij* when exposed to a parasite with genotype *kl*. To simplify the presentation, we focus on the evolution of sex in hosts and assume that the *M* allele is fixed at the modifier locus in parasites (analogous results for the evolution of sex in parasites are presented for comparison below). Consequently, we need to keep track of only chromosomes 1 and 2 (carrying alleles *A* and *a*) in parasites. The frequency of parasite genotypes after selection is given by $P_{kl}^{(s)} = P_{kl}w_{Pkl}/w_P$, where w_{Pkl} is the average fitness of parasites with genotype *kl* and w_P is the average fitness over all parasites. Specifically, $w_{Pkl} = \sum_{kl} H_{ij}w_{PklHij}$, where w_{PklHij} is the fitness of a parasite with genotype *kl* when exposed to a host with

Table 4: Selection coefficients for different models of infection to leading order in the virulence, v, and cost of resistance, c

Model	Parameter
Matching alleles	$s_{HAA}^{(MA)} \approx q_A^2 v$;
	$s_{HAa}^{(MA)} \approx v$;
	$s_{Haa}^{(MA)} \approx q_a^2 v$
	$\Phi_{MA} \approx -v(1 + 2q_A q_a)$
Inverse matching alleles	$s_{HAA}^{(IMA)} \approx q_a^2 v$;
	$s_{HAa}^{(IMA)} \approx 0$;
	$s_{Haa}^{(IMA)} \approx q_A^2 v$
	$\Phi_{IMA} \approx v(1 - 2q_A q_a)$
Gene-for-gene	$s_{HAA}^{(GFG)} \approx c + q_a^2 v$;
	$s_{HAa}^{(GFG)} \approx c + q_a^2 v$;
	$s_{Haa}^{(GFG)} \approx v$
	$\Phi_{GFG} \approx v(1 - q_a^2) - c$

genotype *ij*. Because the modifier locus has no direct effect on fitness, expressions for the w_{HijPkl} and w_{PklHij} terms depend only on the **A** locus. For example, w_{H11P11}, w_{H13P11}, and w_{H33P11} are all equivalent, because they refer to the fitness of an *AA* host interacting with an *AA* parasite; thus, we denote this fitness more clearly as w_{HAAPAA}. Fitnesses under the different host-parasite models are given in tables 1–3. Because we have limited ourselves to a single selected locus, **A**, selection on reproductive mode will reflect the advantages (or disadvantages) of segregation alone.

Following selection, reproduction occurs. The host can produce offspring both sexually and asexually. We denote the fraction of sexually produced offspring by genotype *ij* as σ_{ij}. This fraction is determined by the modifier locus, **M**. Individuals with genotype *MM* produce a fraction σ of their offspring sexually (i.e., $\sigma_{11} = \sigma_{12} = \sigma_{22} = \sigma$), while the fraction of sexually produced offspring in *Mm* and *mm* individuals is $\sigma + h_\sigma \delta\sigma$ and $\sigma + \delta\sigma$, respectively. For the sake of discussion, we will assume that the *m* allele increases the amount of sex in a directional fashion (i.e., $\delta\sigma > 0$ and $0 < h_\sigma < 1$), although the results apply generally to any type of modifier. Among offspring produced sexually, a fraction f are the result of gametophytic selfing (i.e., selfing among the genetically identical gametes produced by a haploid parent), and the remainder are produced by random union of gametes. We use gametophytic selfing as a proxy for the effects of inbreeding by any mechanism, including population subdivision, though we are aware that the effects are not exactly equivalent (see "Discussion").

Host genotype frequencies after reproduction are given by

$$H_{ii}^{(r)} = (1 - \sigma_{ii})H_{ii}^{(s)} + \bar{\sigma}[g_i^2(1 - f) + g_i f], \quad (1a)$$

$$H_{ij}^{(r)} = (1 - \sigma_{ij})H_{ij}^{(s)} + \bar{\sigma}[g_i g_j(1 - f)] \quad (1b)$$

for $i \neq j$, where $\bar{\sigma} = \sum_{ij} \sigma_{ij} H_{ij}^{(s)}$ is the proportion of all offspring that are produced sexually and g_i is the frequency of haplotype i in the gamete pool that forms the sexually produced offspring. The g_i are given by

$$g_1 = \frac{\sigma(H_{11}^{(s)} + H_{12}^{(s)}) + (\sigma + h_\sigma\delta\sigma)[H_{13}^{(s)} + H_{14}^{(s)}(1 - r) + H_{23}^{(s)} r]}{\bar{\sigma}}, \quad (2a)$$

$$g_2 = \frac{\sigma(H_{12}^{(s)} + H_{22}^{(s)}) + (\sigma + h_\sigma\delta\sigma)[H_{24}^{(s)} + H_{23}^{(s)}(1 - r) + H_{14}^{(s)} r]}{\bar{\sigma}}, \quad (2b)$$

$$g_3 = \frac{(\sigma + \delta\sigma)(H_{33}^{(s)} + H_{34}^{(s)}) + (\sigma + h_\sigma\delta\sigma)[H_{13}^{(s)} + H_{23}^{(s)}(1 - r) + H_{14}^{(s)} r]}{\bar{\sigma}}, \quad (2c)$$

$$g_4 = \frac{(\sigma + \delta\sigma)(H_{34}^{(s)} + H_{44}^{(s)}) + (\sigma + h_\sigma\delta\sigma)[H_{24}^{(s)} + H_{14}^{(s)}(1 - r) + H_{23}^{(s)} r]}{\bar{\sigma}}, \quad (2d)$$

where r is the recombination rate between the **M** and **A** loci.

The evolution of sex has attracted much attention because of the ubiquity of sex despite intrinsic costs (e.g., the cost of meiosis; Williams 1975; Charlesworth 1980). Before attempting to understand how the benefits of sex might overcome any intrinsic costs, we must first establish whether sex is advantageous in the absence of such costs. If modifiers increasing the frequency of sex are unable to spread in the absence of costs, they will be unable to spread with a cost. Having identified conditions where increased sex can evolve, we then add an intrinsic cost of sex to equations (1) to determine the extent to which the advantages of segregation outweigh these costs.

For simplicity, we assume that parasites reproduce sexually via random mating:

$$P_{11}^{(r)} = (P_{11}^{(s)} + P_{12}^{(s)})^2, \quad (3a)$$

$$P_{12}^{(r)} = (P_{11}^{(s)} + P_{12}^{(s)})(P_{12}^{(s)} + P_{22}^{(s)}), \quad (3b)$$

$$P_{22}^{(r)} = (P_{12}^{(s)} + P_{22}^{(s)})^2. \quad (3c)$$

We also examined models in which parasites could self or were haploid. The results (not shown) were qualitatively similar to our findings for diploid, randomly mating parasites.

As an alterative to describing the dynamics of genotype frequencies within the host population, we can describe the dynamics of the allele frequencies and the patterns of associations among these alleles. In doing so, we use the following variables: p_M, p_A, $C_{M,M}$, $C_{A,A}$, $C_{MA,\varnothing}$, $C_{M,A}$,

$C_{MA,M}$, $C_{MA,A}$, and $C_{MA,MA}$, where p_i is the frequency of allele i and $C_{S,T}$ is the association between the set of alleles in S on one chromosome with the set of alleles in T on the homologous chromosome. These associations are measured as central moments following Barton and Turelli (1991):

$$C_{S,T} = \sum_{ij}\left(H_{ij}\left\{\prod_{x\in S}[U_{ij}(x) - p_x]\right\}\left\{\prod_{x\in T}[V_{ij}(x) - p_x]\right\}\right),$$

where $U_{ij}(x)$ is an indicator variable that is unity if genotype ij carries allele x on the chromosome represented by i and is 0 otherwise. The function $V_{ij}(x)$ is defined analogously but for the homologous chromosome represented by j. These association measures also have straightforward interpretations. For example, $C_{A,A}$ is the covariance between alleles at the **A** locus within individuals and is 0 when the population is at Hardy-Weinberg equilibrium. The function $C_{MA,\varnothing}$ is the covariance between the M and A alleles on the same chromosome (i.e., the gametic disequilibrium). The function $C_{MA,A}$ is the three-way association between the M allele and homozygosity at the **A** locus, which is positive if the M allele tends to be found in homozygotes at the **A** locus more often than the m allele. As we will see, $C_{A,A}$ and $C_{MA,A}$ are of special importance in understanding the evolution of sex in this model. It is useful to describe the population in terms of allele frequencies and association measures, because the M allele evolves through its effects on the genetic associations. Analogously for parasites, we use q_A and $D_{A,A}$ to represent the frequency of the A allele and the covariance of A alleles within individuals.

Analytical Approximations

To make analytical progress, we assume selection is weak relative to the amount of genetic mixing (segregation and recombination). Doing so allows us to employ a separation of timescales known as the quasi-linkage equilibrium (QLE; Kimura 1965; Nagylaki 1993), in which the genetic associations reach their steady state faster than the alleles change in frequency. Though the assumptions underlying the QLE may seem counter to the idea of coevolution, this technique has been shown to work well (Otto and Nuismer 2004), provided that selection is weak per locus, as it will be when virulence is low, resistance is weakly genetically based, and/or many loci mediate host-parasite interactions. The steady state (or QLE) associations are denoted by $\hat{C}$ and are calculated using the recursions above under the assumption that v, u, c, k, f, and $\delta\sigma$ are weak, that is, of order ξ, where ξ is some small term.

Assuming weak selection, we can approximate the expected fitness of host genotypes AA, Aa, and aa as $w_{HAA} = 1 - s_{HAA}$, $w_{HAa} = 1 - s_{HAa}$, and $w_{Haa} = 1 - s_{Haa}$, where the selection coefficients, s_i, depend on the model of infection, are of order ξ, and are given in table 4. At QLE, $\hat{C}_{M,A}$ and $\hat{C}_{MA,\varnothing}$ are 0 to $O(\xi^2)$. The leading order terms in the remaining associations are

$$\hat{C}_{A,A} = p_A p_a\left(f - \frac{1-\sigma}{\sigma}p_A p_a\Phi\right) + O(\xi^2), \tag{4a}$$

$$\hat{C}_{M,M} = p_M p_m\left[f + \frac{\delta\sigma}{\sigma}p_M p_m(2h_\sigma - 1)\right] + O(\xi^2), \tag{4b}$$

$$\hat{C}_{MA,M} = \frac{1}{\sigma}p_M p_m p_A p_a(1-\sigma)(s_{HAa} - s_{HAA} + p_A\Phi)f + O(\xi^2), \tag{4c}$$

$$\hat{C}_{MA,A} = -\frac{\delta\sigma}{\sigma^2}p_M p_m p_A^2 p_a^2[h_\sigma p_M + (1-h_\sigma)p_m]\Phi + \frac{\delta\sigma}{\sigma}p_M p_m p_A p_a[h_\sigma p_m + (1-h_\sigma)p_M]f + O(\xi^3), \tag{4d}$$

$$\hat{C}_{MA,MA} = f p_M p_m p_A p_a + O(\xi^2), \tag{4e}$$

where Φ is a measure of dominance: $\Phi = 2w_{HAa} - (w_{HAA} + w_{Haa})$. For each of the models of infection genetics (MA, IMA, and GFG), Φ is given in table 4 and is of order ξ.

Using these QLE associations, we can calculate changes in allele frequencies at the **A** and **M** loci. The change in frequency of the A allele in the host over a generation is

$$\Delta p_A \approx p_A p_a[p_A(s_{HAa} - s_{HAA}) + p_a(s_{Haa} - s_{HAa})] + O(\xi^2). \tag{5}$$

As expected, the sign and magnitude of the change in the frequency of the A allele depends on the distribution of parasite genotypes and the selection that they induce on the host.

The change in frequency of the host modifier allele, m, over a generation is

$$\Delta p_m = \hat{C}_{MA,A}\Phi + O(\xi^4) \tag{6a}$$

$$= -\frac{\delta\sigma}{\sigma^2}p_M p_m p_A^2 p_a^2 J_1\Phi^2 + \frac{\delta\sigma}{\sigma}p_M p_m p_A p_a J_2 f\Phi + O(\xi^4), \tag{6b}$$

where $J_1 = h_\sigma p_M + (1-h_\sigma)p_m$ and $J_2 = (1-h_\sigma)p_M + h_\sigma p_m$. Equation (6a) indicates that the modifier evolves in response to the three-way association $C_{MA,A}$, which arises as the modifier alters the intralocus association, $C_{A,A}$ (the departure from Hardy-Weinberg at the selected locus **A**). The selective consequences of altering $C_{A,A}$ depend on whether heterozygotes are more fit ($\Phi > 0$) or less fit ($\Phi < 0$) than expected on the basis of the fitness of the homozygotes. The first term in equation (6b) is always negative, indicating selection against sex. The second term

can be positive (i.e., favor sex), but only if there is inbreeding ($f > 0$) and if heterozygotes are more fit than the average of the two homozygotes ($\Phi > 0$). As inbreeding increases, the second term dominates equation (6b); altering the QLE analysis to allow for high rates of inbreeding demonstrates that equation (6b) remains a reasonable approximation, provided that f is replaced by $f(1 - f)$. Equation (6b) assumes that f and Φ are not both very small (i.e., of order ξ^2); if they are, additional terms must be considered to predict the fate of a modifier (see the one-species analysis of Otto 2003).

To evaluate whether the Red Queen can select for sex, we must determine whether Φ is positive. For the MA model, we find that $\Phi_{\text{MA}} \approx -v(1 + 2q_A q_a)$, which is always negative; thus, sex is never favored in hosts. This result makes sense because heterozygotes can be infected by all parasites and are least fit, but segregation restores heterozygosity in an inbred host population. In the IMA model, $\Phi_{\text{IMA}} \approx v(1 - 2q_A q_a)$, which is always positive; thus, the Red Queen can favor more sex, provided there is sufficient inbreeding. This result again makes sense because segregation restores heterozygosity in inbred hosts, and heterozygotes can resist all parasites and are most fit. In the GFG model, $\Phi_{\text{GFG}} \approx v(1 - q_a^2) - c$. Because $v > c$ is required to maintain a polymorphism, the sign of Φ_{GFG} changes from negative to positive depending on the frequency of the infectious parasite allele *a*. Whether these cycles favor or disfavor sex overall is explored via simulation in the next section.

These results apply only to the simplest version of each model of infection (tables 1–3). More general results are presented in the appendix, where we show that the value of Φ depends on the assumptions made about the susceptibility of heterozygous hosts and the infectiousness of heterozygous parasites.

In the above, we have assumed no intrinsic costs of sex. We have shown above that, under the right circumstances, the modifier can increase in frequency, demonstrating that indirect selection can favor sex, but it remains unclear whether these indirect benefits are sufficient to overcome intrinsic costs. Costs of sex can be added to the model by reducing the number of sexually produced offspring by an amount b relative to the number of asexually produced offspring of the same genotype ($b = 1/2$ represents a twofold cost of sex). Mathematically, the cost of sex is incorporated by multiplying $\bar{\sigma}$ in equations (1) by $1 - b$ and renormalizing the set of equations (dividing by their sum so that they remain frequencies). This cost of sex reflects the reduced efficiency of sexual reproduction as a result of the costs of searching for and courting a mate, the risks associated with mating, the reduction in number of offspring produced by a sexual couple versus two asexual individuals, and so on.

Because the costs of sex are thought to be large, but we have assumed weak selection at locus **A**, it would be impossible for a single gene to pay for the entire costs of sex. Thus, to determine whether sex can evolve in the face of such costs, we must scale our results up to the total effect of selection across a genome. We now allow there to be n independently selected loci rather than just one. For example, this model could describe a host species under attack by n different parasite species in which resistance to each parasite is controlled by a single locus specific to that parasite. Alternatively, resistance to a single parasite could be under multilocus control, but the effect of each locus on the probability of infection is independent of the other loci. With these changes to the model, and assuming that n is $O(1/\xi)$, equations (6) become

$$\begin{aligned}\Delta p_m = &-\frac{\delta\sigma}{\sigma^2}\frac{1}{1-b}p_M p_m J_1\left[\sum_i^n p_i^2(1-p_i)^2\Phi_i^2\right]\\ &+\frac{\delta\sigma}{\sigma}\frac{1+b}{1-b}p_M p_m J_2 f\left[\sum_i^n p_i(1-p_i)\Phi_i\right]\\ &-\frac{b}{1-b\sigma}\delta\sigma p_M p_m J_1\left\{1+\frac{b}{1-b\sigma}\delta\sigma p_m[1+(2h_\sigma-1)p_M]\right\}\\ &+O(\xi^3),\end{aligned} \tag{7}$$

where p_i is the allele frequency at the ith locus and Φ_i is the dominance measure for fitness at that locus. The first two terms are similar to those in equation (6b). They reflect the indirect selection that arises because of the associations that the modifier develops with selected loci. As in equation (6b), the first term is always negative, but the second term can be positive. The last term shows the decrease in the modifier due to the intrinsic cost of sex, that is, direct selection against the modifier. If the intrinsic cost of sex is large, then this cost will overwhelm the indirect selection the modifier experiences through its association with any one selected locus. If there are a sufficient number of selected loci, and if inbreeding is present and heterozygotes are more fit on average than homozygotes, then the summed indirect benefits could offset the intrinsic cost of sex.

Although our focus is on hosts, we can also consider the evolution of sex in parasites by evaluating the analogous measure of dominance in parasites, ${}_{\text{P}}\Phi$. In short, parasitic sex is never favored in the MA or IMA models, because the dominance measure, ${}_{\text{P}}\Phi_{\text{MA}}$, ${}_{\text{P}}\Phi_{\text{IMA}} = -u(1 - H_{Aa})$, is always negative ($H_{Aa}$ is the frequency of *Aa* hosts). This reflects the fact that heterozygous parasites are poor mimics of homozygous hosts (MA model) and have twice as many antigens that the host might recognize (in the IMA model), causing heterozygotes to be less fit than the average fitness of homozygotes. Sex can be favored because

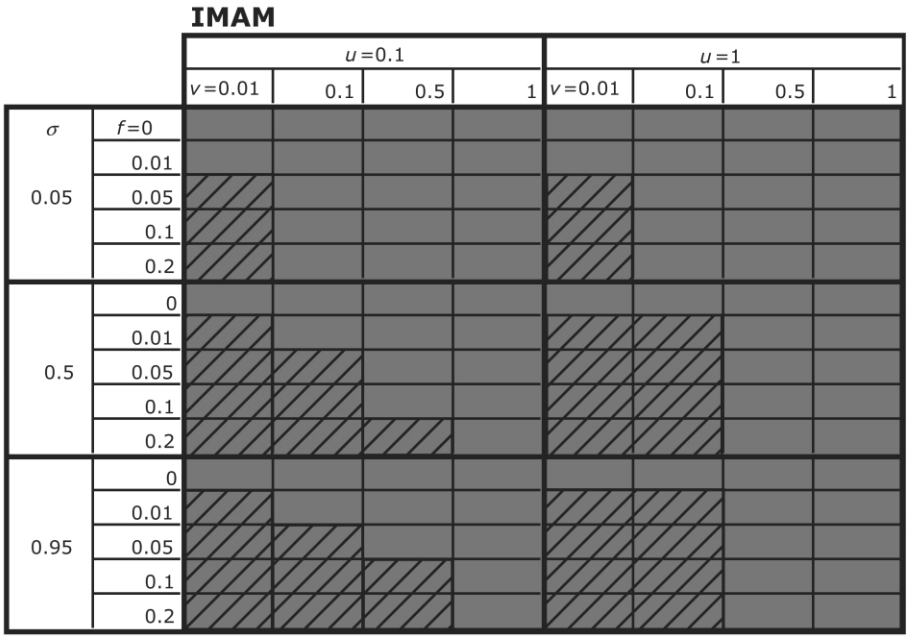

Figure 1: Simulation results for inverse matching alleles model. Dark shading indicates cases where heterozygotes were more fit, on average, than homozygotes ($\Phi > 0$). Striped cells indicate that selection favored the spread of a modifier increasing the frequency of sex. Selection for sex was observed only when there was some inbreeding and selection was not too strong.

of the advantages of segregation in the GFG model but only during those periods of time when *aa* hosts are sufficiently common, so that ${}_{\mathrm{p}}\Phi_{\mathrm{GFG}} = -u(1 - H_{aa}) + k$ becomes positive.

Computer Simulations

The analytical approximations presented above assume that selection is weak relative to the amount of genetic mixing. To examine the evolution of the modifier in hosts over a broader set of conditions, we performed computer simulations in which we iterated recursions (1)–(3). In the following, we again ignore the costs of sex and focus on a single selected locus ($b = 0$, $n = 1$). In the simulations, we allowed the **A** locus in both hosts and parasites to mutate at rate $\mu = 10^{-4}$ to prevent alleles from fixing during coevolutionary oscillations. For each run, the initial value for p_m was 50%, whereas values for p_A and q_A were chosen at random. Initial genotype frequencies were calculated from these allele frequencies assuming no initial genetic associations (i.e., loci were at Hardy-Weinberg with no linkage disequilibrium). We used a "burn-in" period of 15,000 generations to allow the system to approach its long-term dynamics; during this period, the modifier allele had no effect on reproductive mode. Starting in generation 15,001, the modifier increased the amount of sex as described above. The change in the frequency of the modifier during generations 15,001–20,000 was calculated. To survey parameter space, we simulated all combinations of the following parameter values: (i) baseline frequency of sex, $\sigma = 0.05$, 0.50, 0.95; (ii) dominance of the modifier, $h_\sigma = 0.5$; (iii) effect of the modifier, $\delta\sigma = 0.02$; (iv) inbreeding level, $f = 0$, 0.01, 0.10; (v) effect on host fitness of infection, $v = 0.01$, 0.1, 0.5, 1.0; (vi) effect on parasite fitness of failing to infect, $u = 0.1$, 1.0; and (vii) costs of resistance and virulence in the GFG model, $c = 0.1v$, $0.9v$; $k = 0.1u$, $0.9u$. For each unique set of parameter combinations, 10 replicate simulations were performed from different initial allele frequencies. Typically, results were very similar across replicate simulations.

As predicted by our analytical results, the modifier declined in frequency for all parameters under the MA model (results not shown). Under the IMA model, the modifier increased in frequency, provided that there was sufficient inbreeding (fig. 1). The analytical approximation (eq. [6b]) accurately predicts the level of inbreeding required to favor sex when selection is weak, but the approximation worsens as selection becomes strong relative to the amount of sex (table 5). Interestingly, increasing the strength of selection in hosts made it harder, not easier, for sex to evolve, in contrast to results from haploid models that focus on the effects of recombination (Peters and Lively 1999; Otto and

Table 5: Comparison of analytical and simulation results for the inverse matching alleles model of infection

Virulence (v)	Baseline amount of sex (σ)		
	.05	.50	.95
.01	$f_A^* = .026$	$f_A^* = .003$	$f_A^* = .001$
	$.03 < f_S^* < .04$	$.003 < f_S^* < .004$	$.001 < f_S^* < .002$
.10	$f_A^* = .5$	$f_A^* = .026$	$f_A^* = .013$
	NP	$.03 < f_S^* < .04$	$.02 < f_S^* < .03$
.25	NP	$f_A^* = .067$	$f_A^* = .034$
	NP	$.15 < f_S^* < .16$	$.05 < f_S^* < .06$
.50	NP	$f_A^* = .146$	$f_A^* = .071$
	NP	NP	$.29 < f_S^* < .30$
1.00	NP	$f_A^* = .5$	$f_A^* = .156$
	NP	NP	NP

Note: Each cell gives the minimum level of inbreeding required to favor an increase in the amount of sex as predicted by the analytical approximation (f_A^*) and by computer simulations (f_S^*). NP indicates that it is not possible to favor sex under any level of inbreeding. In evaluating f_A^*, we used equation (6b) with f replaced by $f(1 - f)$, which provides a better approximation when f is large. We assume that $p_A = q_A = 0.5$ in evaluating f_A^* because allele frequencies oscillate around the midpoint in the simulations. We also assume $p_M = 0.5$ because simulations were initiated with this allele frequency. As expected, f_A^* is close to f_S^* under the assumptions of the analysis; that is, selection is weak relative to the amount of genetic mixing (top right of table).

Nuismer 2004). Simulation results from the GFG model are shown in figure 2. Selection favoring sex usually involved some inbreeding, positive Φ_{GFG} (i.e., higher average fitness of heterozygotes than homozygotes), low to intermediate levels of virulence, and relatively high costs of infectiousness. Increased sex was favored in some cases when Φ_{GFG} fluctuated in sign over time but never when Φ_{GFG} was consistently negative, as expected from equation (6b). Because $\Phi_{GFG} \approx v(1 - q_a^2) - c$, the sign of Φ_{GFG} depends on the frequency of the infectious allele, q_a, and hence on the coevolutionary dynamics of host and parasite. In particular, low costs of infectiousness, k, tend to elevate the frequency of the infectious allele, q_a, leading to a negative Φ_{GFG} and selection against sex for most parameter combinations. In contrast, the results appeared less sensitive to the cost of resistance, c.

Discussion

Sexual reproduction does not alter the frequency of alleles (assuming Mendelian inheritance), but it does change their patterns of association. In particular, recombination reduces the disequilibrium between alleles at different loci on a chromosome. Similarly, segregation reduces associations between alleles at the same locus on homologous chromosomes. From a population-genetics perspective, understanding the advantages of sex requires understanding how sexual processes (i.e., recombination and segregation) alter genetic associations among alleles and the selective consequences of doing so.

We built an explicitly coevolutionary model to examine whether a modifier that increased the amount of sex would be favored in the presence of parasites. The clearest result is that, in the absence of inbreeding, parasites typically select against hosts in the models we examined. This result was true both when selection was weak (analytical results) and when selection was strong (simulations). Consequently, parasites favor sex less often in our single-locus diploid models than in analogous two-locus haploid models when mating is random (Otto and Nuismer 2004). We discuss the effects of segregation on the evolution of sex and compare these effects to those of recombination.

In both the single-species model studied by Otto (2003) as well as the results presented here, the effects of segregation on the evolution of sex depend on whether the fitness of heterozygotes is greater or less than the average of the two homozygotes (i.e., the dominance factor, Φ). In Otto's model, the fitnesses of the three genotypes at locus **A** were constants rather than dynamical functions of parasite genotype frequencies. That these different models give analogous results is a reflection of the fact that, from the perspective of the modifier, only the pattern of selection in the focal species is important, not the agent of selection (parasites or otherwise). Nevertheless, parasites may be important agents of selection if immunity loci have particular dominance properties with respect to fitness.

It is therefore necessary to consider dominance in each of the models of infection investigated here. In the simplest version of the MA model, a heterozygous host is incapable of detecting and clearing any parasite because no parasite genotype carries an allele that does not match at least one of the heterozygous host's alleles. Heterozygous hosts can be infected by any parasite genotype, whereas each homozygous host is susceptible to only a single parasite genotype. Consequently, the heterozygous host can never be more fit than either homozygote, so Φ_{MA} is always negative. In the simplest version of the IMA model, a heterozygous host can recognize at least one allele carried by any of the parasite genotypes. Heterozygous hosts can thus resist all parasite genotypes, whereas each homozygous host is susceptible to a subset of parasite genotypes. As a result, the heterozygous host is never less fit than either homozygote, so Φ_{IMA} is always positive. In the simplest version of the GFG model, the A allele is assumed to be completely dominant so that the heterozygous host Aa has the same fitness as the AA host. As a result, the heterozygous genotype will be more fit than the average of the two homozygous genotypes ($\Phi_{GFG} > 0$) when the AA homozygote is more fit than the aa homozygote ($w_{AA} > w_{aa}$). Conversely, the heterozygote will be relatively unfit ($\Phi_{GFG} < 0$) when $w_{aa} >$

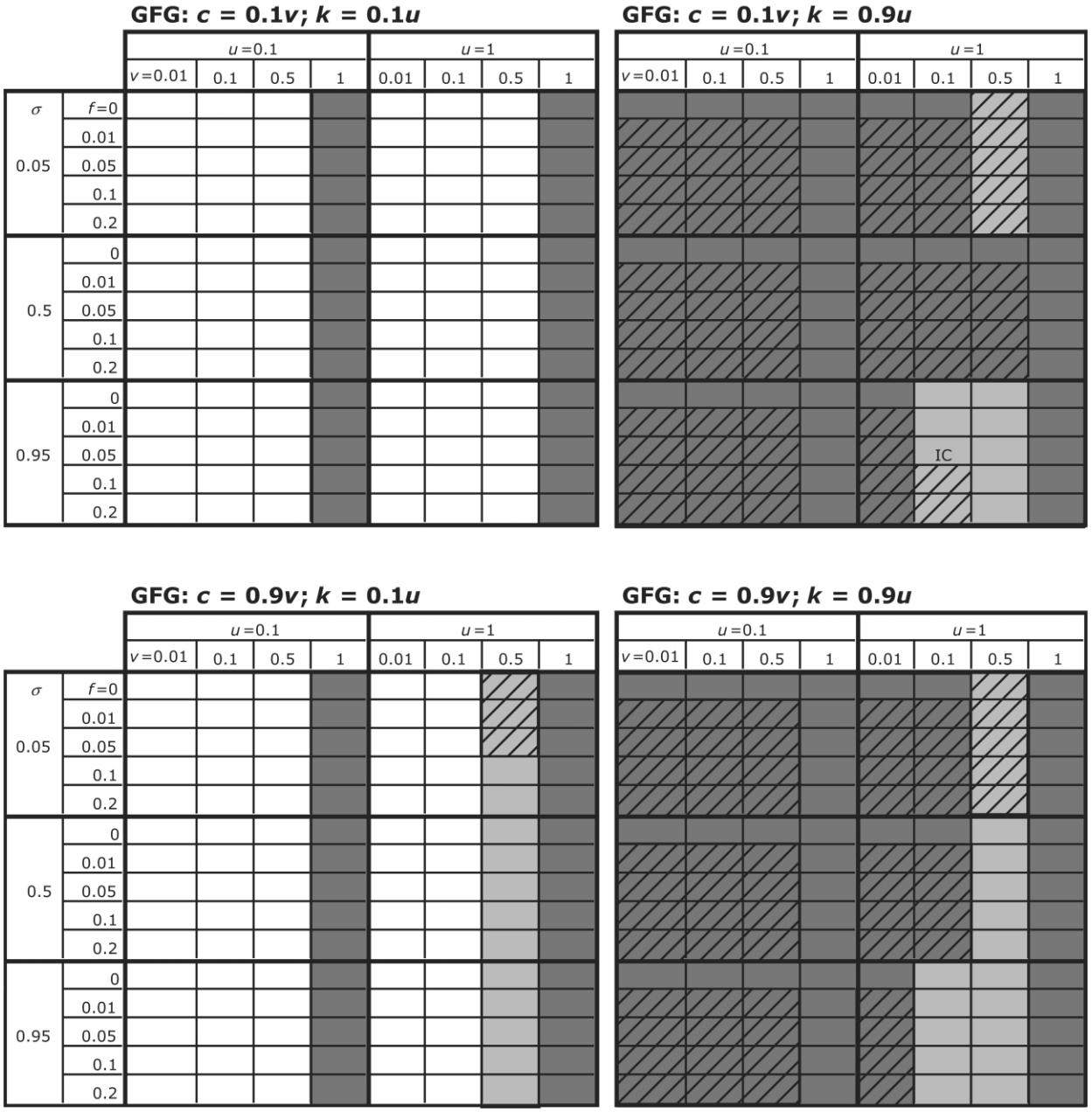

Figure 2: Simulation results for gene-for-gene model. Dark shading indicates cases where heterozygotes were always more fit, on average, than homozygotes ($\Phi > 0$); light shading indicates fluctuations in the sign of Φ. No shading indicates that Φ was always negative. Striped cells indicate that selection favored the spread of a modifier increasing the frequency of sex. The cell marked *IC* is the only part of parameter space in which the fate of the modifier appeared to depend on initial conditions. Selection for sex occurred only if (i) there was some inbreeding ($f > 0$) and heterozygotes were relatively fit ($\Phi > 0$) or (ii) heterozygotes fluctuated between being relatively fit and unfit. These conditions were necessary but not sufficient for sex to be favored.

w_{AA}. Our simulations indicate that Φ_{GFG} tends to be positive when the cost of infectiousness, k, is high (dark shading in fig. 2). Note that it is possible for Φ_{GFG} to fluctuate in sign, and such fluctuations are observed in some simulations (light shading in fig. 2).

Bearing these dominance attributes in mind, we first consider our results when mating is random. When selection is weak, our QLE approximation given by equations (6) (setting $f = 0$) shows that parasites always select against segregation (see also Otto 2003). In the absence

of other factors (e.g., inbreeding), the sign of the genetic association $C_{A,A}$ is determined only by selection. Sex is detrimental because it reduces the association created by selection. For example, if heterozygotes are relatively fit ($\Phi > 0$), selection by parasites causes an excess of heterozygotes ($C_{A,A} < 0$). Sex reduces this excess by producing homozygous offspring from these heterozygous parents ($Aa \times Aa \rightarrow AA$, Aa, aa), which reduces fitness because homozygotes are relatively unfit when $\Phi > 0$. If heterozygotes are relatively unfit ($\Phi < 0$), selection causes an excess of homozygotes ($C_{A,A} > 0$). Sex reduces this excess by producing heterozygous offspring from these homozygous parents ($AA \times aa \rightarrow Aa$), which again reduces fitness because heterozygotes are relatively unfit ($\Phi < 0$). Put simply, selection creates an excess of good allele combinations; sex destroys this excess.

The above logic and the QLE analysis on which it is based work well, provided that the sign of Φ remains constant. When parasites have low virulence, coevolutionary dynamics are slow, and we can think of selection as being approximately constant over short timescales. Although weak selection justifies the use of the QLE approximation, strong selection is also of interest. Parasites have been invoked in discussions of sex as a potentially important agent of selection because the pattern of selection they generate can change rapidly over time when virulence is strong. If parasites are virulent and coevolutionary dynamics are fast, the dominance parameter Φ could change signs over short timescales.

Imagine that heterozygotes are initially relatively fit ($\Phi > 0$) so that selection by parasites creates an excess of heterozygotes ($C_{A,A} < 0$). Sex reduces this excess by converting heterozygotes into homozygotes. As previously discussed, this conversion reduces fitness if the sign of Φ has not changed (i.e., if heterozygotes are relatively fit in the next generation). However, this conversion is beneficial if the sign of Φ has changed. This logic implies that selection for segregation may occur if Φ fluctuates sufficiently rapidly. However, we have little evidence for such fluctuations in the sign of Φ. The sign of Φ never changes in the simplest versions of MA and IMA models (Φ_{MA} is always negative, and Φ_{IMA} is always positive). The GFG model is capable of generating fluctuations in Φ, but this did not commonly occur in our simulations (fig. 2). In those cases where increased sex was favored in the absence of inbreeding (see fig. 2; $v = 0.5$, $k = 0.9u$, $\sigma = 0.05$), fluctuations in the sign of Φ were observed, suggesting that there can, under certain circumstances, be a short-term advantage to segregation.

As a historical aside, cycles favoring sex were observed by Hamilton (1980), who used a one-species diploid model to describe the case where heterozygotes were a unique genotype that could be attacked only by a specialized parasite. In Hamilton's model, the dominance measure, Φ, can switch signs over time when selection is strong. Examining his simulations in more detail, we confirmed that the advantage of sex that he observed was generated by rapid switches in the form of dominance, causing a modifier allele to become associated with departures from Hardy-Weinberg that were, on average, more fit in the next generation.

In summary, it is difficult to identify conditions under which parasites favor segregation in the absence of inbreeding; only in rare cases does Φ fluctuate sufficiently rapidly. Under most conditions, segregation is disfavored. This is because segregation reduces the genetic association $C_{A,A}$ that was built solely by selection. When inbreeding occurs, selection is no longer the only force affecting genetic associations. As noted by Bennett and Binet (1956), inbreeding creates not only an excess of homozygotes but also an excess of the four double homozygotes: *MMAA*, *MMaa*, *mmAA*, and *mmaa*. Because *mm* individuals are more likely to engage in sex than *MM* individuals, the cross *mmAA* × *mmaa* occurs more often than expected, given the genotype frequencies and the average frequency of sex. Conversely, *MMAA* and *MMaa* individuals are less likely to engage in sexual reproduction with one another. When heterozygotes are more fit ($\Phi > 0$), the cross *mmAA* × *mmaa* is beneficial to the *m* allele because it results in heterozygous offspring at the fitness locus (*mmAa*). This explains the second term in equation (6b), which favors the spread of the *m* allele as long as inbreeding is present and the form of host-parasite interactions causes the fitness of heterozygotes to be greater than the average fitness of homozygotes ($\Phi > 0$). If the extent of inbreeding, f, is too small relative to the degree of dominance, Φ, then the negative effect of random mating destroying the genetic associations built up by selection (i.e., first term of eq. [6b]) outweighs the advantage gained through generating *Aa* heterozygotes from the excess of double homozygotes (i.e., second term of eq. [6b]). Inbreeding has similar effects in a single-species model of segregation (Otto 2003). With respect to the models explored here, selection for sex does not occur in the MA model even with inbreeding because the fitness of heterozygotes is relatively low (Φ_{MA} is always negative). Sex can be favored when there is sufficient inbreeding in the IMA model because heterozygotes are relatively fit (Φ_{IMA} is always positive) and in the GFG model under conditions where Φ_{GFG} is predominantly positive. When parasites cause hosts to experience overdominance for fitness, as in the IMA model, our results are similar to results from a single-species model with overdominance (Dolgin and Otto 2003).

Both the analytical and simulation results indicate an important role for inbreeding. Although we have modeled

inbreeding as gametophytic selfing (i.e., syngamy of identical gametes), we suspect that these results will hold for some other types of inbreeding with only minor modifications. For example, we investigated sporophytic selfing (i.e., syngamy among independently produced gametes of a diploid parent) and found that the results are changed only by a factor of $1 - 2r(1 - r)$ in the second term of equation (6b). The results remain qualitatively the same if parasites also inbreed (results not shown). What we do not know, however, is how the model behaves if the inbreeding level of parasites and the inbreeding level of the hosts they attack are correlated. Such correlations could arise in spatially structured populations, especially when the dispersal distances of hosts and parasites are similar.

Our study of the Red Queen and segregation allows for a comparison with previous studies that have focused on recombination (table 6). We begin this comparison assuming random mating. Otto and Nuismer (2004) analyzed an explicitly coevolutionary haploid model to study the evolution of recombination under the Red Queen. Similar to our results with respect to segregation, they found that none of the models of infection (MA, IMA, or GFG) favored recombination under the assumptions of weak selection and random mating. In both our model and theirs, the sexual process of interest (segregation or recombination) reduces a genetic association (homozygosity or gametic disequilibrium, respectively) built by selection. Selection causes host genotypes that are better able to resist the current population of parasites to become more common; breaking apart these favorable host genotypes through sex produces offspring that are, on average, more susceptible to attack.

While the recombination and segregation results are very similar under weak selection and random mating, differences arise when selection is strong. The advantages of recombination can favor the evolution of sex when selection is strong in the MA and IMA models. In these models, host-parasite coevolution causes rapid fluctuations in the sign of the relevant nonlinear component of fitness (epistasis), resulting in a short-term benefit to recombination (Peters and Lively 1999). In our diploid MA and IMA models, the relevant nonlinear component of fitness (dominance, as represented by Φ) does not fluctuate in sign, so there is no comparable advantage to segregation. In the GFG model, the advantages of recombination can favor the evolution of sex when selection is sufficiently strong (Parker 1994; Otto and Nuismer 2004), but such cases are less common than in the MA and IMA models. Like epistasis, dominance can fluctuate rapidly in sign under some conditions in the GFG model, in which case segregation can also provide an advantage to sex. Overall, it appears that strong selection does not generate an advantage to segregation as often as it generates an advantage to recombination, because dominance (Φ) is less likely to vary in sign over time than epistasis.

In diploids, a modifier that increases the amount of sex simultaneously increases both segregation and recombination. Previous studies (Parker 1994; Peters and Lively 1999; Otto and Nuismer 2004) that have examined the Red Queen in haploid hosts have focused exclusively on the effects of recombination. Because segregation is almost always disadvantageous when mating is random, haploid models will tend to overestimate how often parasites select for sex in diploid hosts. For example, consider a diploid MA model involving two immunity loci. On the basis of the two-locus haploid model, we would predict that the advantages of recombination would favor sex in the presence of highly virulent parasites, but on the basis of the single-locus diploid model, we would predict that the disadvantages of segregation would select against sex for all levels of virulence. In simulations of a two-locus diploid MA model (not shown), we found that a modifier that

Table 6: Heuristic guide to the results of Red Queen models

Infection model	Advantages to sex through recombination	Advantages to sex through segregation
Weak selection:		
MA	No	No
IMA	No	Yes, but requires inbreeding
GFG	No	Yes, but requires inbreeding and high costs of infectiousness
Strong selection:		
MA	Yes	No
IMA	Yes	No
GFG	Possible, depends on strength of selection and costs of resistance and infectiousness	Yes, but usually less often than with weak selection

Note: MA = matching alleles, IMA = inverse matching alleles, GFG = gene-for-gene. Recombination results summarized from Parker (1994), Peters and Lively (1999), and Otto and Nuismer (2004), all of which assumed haploid hosts and parasites as well as random mating. Inbreeding may create benefits to recombination under some models of infection, but this has not been studied to date. Weak/strong selection is defined relative to the rates of sex and recombination within the population. Note that in a haploid two-locus, two-allele model, MA and IMA interactions generate equivalent results.

increased sex always declined in frequency even under high virulence. These results imply that the negative effects of segregation outweigh the positive effects of recombination.

Our comparison of segregation and recombination has so far assumed no inbreeding. We found that segregation can be advantageous in the presence of inbreeding in the IMA model and, under some conditions, in the GFG model, because segregation results in the production of heterozygotes, which are more fit, on average, than homozygotes under these models and yet are relatively infrequent because of inbreeding. To date, all of the Red Queen models investigating the effects of recombination between selected loci have assumed random mating (Parker 1994; Peters and Lively 1999; Otto and Nuismer 2004). A recent one-species model (Roze and Lenormand 2005) demonstrated that sporophytic selfing (and presumably population structure) can create an advantage to increased recombination if there is negative dominance × dominance ($d \times d$) epistasis. Host-parasite interactions might be a common source of such epistasis. Indeed, diploid versions of the MA, IMA, and GFG models with two immunity loci (**A** and **B**) generate negative $d \times d$ epistasis at QLE (A. F. Agrawal and S. P. Otto, unpublished data). This suggests that increased rates of recombination would be favored with any of the three infection models in diploid hosts undergoing sporophytic selfing. Recombination is favored because recombination makes it less likely that the selfed offspring of double heterozygotes are double homozygotes, whose average fitness is low under negative $d \times d$ epistasis. This advantage to recombination does not, however, imply that increased rates of sex would be favored, because the advantage to recombination arises from a difference in fitness between two types of sexually produced offspring (i.e., selfed recombinant offspring vs. selfed nonrecombinant offspring) rather than a difference between sexually versus asexually produced offspring. Simulations performed using a diploid model with two immunity loci and sporophytic selfing (not shown) did not differ qualitatively from the results described above with one immunity locus and gametophytic selfing. These results indicate that the effects of segregation rather than recombination determine the fate of a modifier of sex when there is inbreeding.

In summary, the Red Queen has weak theoretical support when we consider either recombination or segregation or both processes together. The most complete haploid modifier analysis (Otto and Nuismer 2004) concluded that parasites select against sex under most conditions. Supporters of the Red Queen are quick to point out that parasites select for sex under some scenarios (e.g., haploid MA model with high virulence). However, when hosts are diploid, parasites can select against segregation under these very same conditions. These negative effects of segregation often prevail, narrowing the conditions under which sex is favored in diploids relative to haploids. Only if there is significant inbreeding does segregation appear likely to increase the possibility for sex to evolve. Of course, it remains possible that the models ignore key aspects of the biology that are critical to understanding the Red Queen, such as finite population size (Martin et al. 2006) or nonrandom transmission (Agrawal 2006). If so, then the Red Queen may be more important than current models suggest, but the reasons will be more complicated than originally believed.

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