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Host–parasite coevolution induces selection for condition-dependent sex

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Abstract

Sex and recombination remain one of the biggest riddles of evolutionary biology. One of the most prominent hypotheses, the Red Queen Hypothesis, claims that sex has evolved as a means to efficiently create genotypes that are resistant against coevolving parasites. However, previous models of the Red Queen have assumed that all individuals are equally likely to engage in sexual reproduction, regardless of their infection status, an assumption that may not be true in reality. Here, we consider a population genetic model of a host population coevolving with a parasite population, where the parasites are haploid and the hosts either haploid or diploid. We assume that the probability to engage in sex may be different in infected and uninfected hosts and ascertain the success of different reproductive strategies with a modifier-gene approach. Our model shows that in the large majority of the parameter space, infection-dependent sex is more successful than infection-independent sex. We identify at least two reasons for this: (i) an immediate short-term advantage of breaking-down gene combinations of unfit individuals and (ii) a selfish spread of the condition-dependent modifiers, in analogy to the 'abandon-ship' effect in single species. In diploids, these effects are often powerful enough to overcome the detrimental effects of segregation. These results raise the intriguing question of why infection-induced sex is not more commonly observed in nature.

Introduction

From an evolutionary point of view, the pervasiveness of sex and recombination is difficult to understand. Why pay a substantial fitness cost for a means of reproduction which may break down the fittest gene combinations? For a long time, the answer has been that genetic shuffling increases genetic variance in the population, thereby accelerating the population's response to selection. However, increased variance need not increase the population's fitness, a phenomenon known as the 'recombination load' (Otto & Lenormand, 2002; Otto, 2009). One scenario in which this effect might become overridden is when the environment changes rapidly with time because then the advantageous genotypes can quickly become detrimental and higher recombination rates can be favoured (Maynard Smith, 1971; Charlesworth, 1976). Parasites, being under continuous selective pressure to infect their hosts, have been recognized as a potential realization of such an environment (Levin, 1975). It has been suggested therefore that sexual reproduction in the hosts may be beneficial in the arms race with parasites as it helps creating novel genotypes that are at a selective advantage. This idea has become known as the Red Queen Hypothesis (RQH) for the evolution of sex (Jaenike, 1978; Hamilton, 1980; Bell, 1982).

In spite of recent advances in our theoretical understanding of the RQH (reviewed by Salathé *et al.*, 2008a; Lively, 2010a) and the accumulation of empirical support for it (Fischer & Schmid-Hempel, 2005; Decaestecker *et al.*, 2007; Jokela *et al.*, 2009; King *et al.*, 2009;

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Koskella & Lively, 2009; Wolinska & Spaak, 2009; Morran *et al.*, 2011), the hypothesis still suffers from a few weaknesses. One of those weaknesses is that strong selection on the parasites needs to be assumed for recombination in the hosts to be favoured (Salathé *et al.*, 2008b). This assumption, although reasonable for many obligate parasites, may not be justified in case of facultative parasites as well as those with a large host range. Furthermore, the RQH has been shown to work better when the recombination modifier and various interaction loci are all tightly linked (Peters & Lively, 2007). By contrast, QTL studies have demonstrated that host loci involved in interactions with parasites are often in different linkage groups (Wilfert & Schmid-Hempel, 2008). Finally, and perhaps most importantly, the RQH has struggled to explain the evolution of sex in diploid organisms (Agrawal & Otto, 2006; Agrawal, 2009a, b), which constitute the majority of eukaryotes (Bell, 1982). Given the ubiquity of sexual reproduction (Vrijenhoek, 1998), these as well as other restrictions are problematic for a general theory to explain the maintenance of sex.

At the same time, models of the RQH have generally assumed that individuals are either completely sexual or asexual and that recombination rates are equal among all sexual individuals in the population. However, rates of sex and recombination can vary between individuals. In particular, stressful conditions have been shown to affect the frequency of sexual reproduction in many organisms, including complete shifts from asexual to sexual reproduction (Kleiven *et al.*, 1992; Mai & Breeden, 2000; Rautiainen *et al.*, 2004; Foster, 2005), and elevated levels of recombination (Plough, 1917; Belyaev & Borodin, 1982; Kupiec, 2000; Abdullah & Borts, 2001; see Hadany & Otto, 2009, and Hadany, 2009, for a more comprehensive list of studies). Mathematical and computer simulation models of single-species systems have shown that even in the presence of substantial fitness costs, condition-dependent sex typically evolves much easier than condition-independent sex (Redfield, 1988; Gessler & Xu, 2000; Hadany & Beker, 2003; Hadany & Otto, 2009), and this is true in both haploid and diploid species (Hadany & Otto, 2007). Furthermore, environment-dependent recombination modifiers have been shown to be favoured in populations evolving in cyclically varying environments (Zhuchenko *et al.*, 1985). Two main reasons for a greater evolutionary success of conditional-sex strategy have been identified. First, populations undergoing conditional sex carry a smaller recombination load than populations that always recombine (recombination tends to destroy less optimal gene combinations). Second, modifiers inducing condition-dependent sex tend to become associated with fitter (nonstressed) genotypes just because the individuals undergoing stress recombine at a higher rate, which leads to a selfish gene effect called the 'abandon-ship' mechanism.

In the context of antagonistically interacting species, few studies have associated low performance with increased level of sexual reproduction. Larvae of parasitic nematodes from hosts that have developed immunity against them were shown to be more likely to develop into sexual adults (Gemmill *et al.*, 1997; but see also West *et al.*, 2001). In plants, changes in somatic and meiotic recombination frequencies due to infection by pathogens (but not only) is a widely known phenomenon (reviewed by Boyko & Kovalchuk, 2011). Furthermore, infection-induced upregulation of recombination may also be caused by genomic parasites (B-chromosomes; Camacho *et al.*, 2002). Finally, in plants, recombination rates that depend on parasite infection have been documented (Kathiria *et al.*, 2010; Boyko & Kovalchuk, 2011). It remains unclear whether the paucity of empirical support for stress-induced sex and recombination in antagonistic interactions is due to the inherent difficulty of the underlying experimental work or whether coevolutionary dynamics would commonly select against this form of plasticity.

In this study, we bring insight into the evolution of condition-dependent sex in the context of the RQH by constructing a mathematical model of host–parasite coevolution. In a world where the idea of a good and bad gene combination varies with time, the benefit of stress-induced recombination would likely depend on how fast these changes occur. Indeed, we find that condition-dependent sex evolves more easily than condition-independent sex, even under weak selection, loose genetic linkage between the interaction loci, and host diploidy. We identify two fundamentally different effects that might lead to this behaviour: (i) an immediate benefit of conditional sex in the presence of negative frequency-dependent selection and (ii) a coevolutionary version of the 'abandon-ship' phenomenon. Finally, we discuss what these results mean for the RQH as a theory, and whether they can help elucidate the reasons for the near universality of obligate and facultative sexual reproduction in eukaryotes.

The model

In order to investigate the evolution of conditional sex in hosts that coevolve with parasites, we consider a deterministic population genetic model of host–parasite coevolution (Nee, 1989; Otto & Nuismer, 2004) in which the reproductive strategy may depend on the infection status. The study is subdivided into two parts: in the first part, we assume that both species are haploid, and in the second part, we examine the situation where hosts are diploid and parasites are haploid.

Haploid hosts

The interaction between haploid hosts and their parasites is mediated by two biallelic loci **A** and **B** in the

host and four genotypes in the parasites (also denoted as *ab*, *aB*. *Ab*, and *AB*). Additionally, hosts carry a sex modifier locus **M** with two alternative alleles *m* and *M* which determine the reproductive strategy of the individual carrying a specific allele at this locus and which do not affect the individual's reproductive performance; the genome architecture is **MAB**. The life cycle comprises selection and reproduction in both species. Reproduction is fully asexual in the parasites, whereas each host may undergo sexual reproduction with a certain probability (see below). In both species, reproduction may also involve mutation.

The selection process in the parasite consists of a single step. The parasite frequency p_i' of genotype $i \in \{ab, aB, Ab, AB\}$ in the next generation given selection coefficient s_P and the frequency in the previous generation p_i is obtained via the recurrence equation

$$p_i' = w_i^p p_i, \tag{1}$$

where w_i^p is the frequency-dependent, relative fitness of parasite with genotype *i*. This fitness is given by

$$w_i^p = \frac{\sum_j w_{ij}^p h_j}{\sum_{i,j} w_{ij}^p p_i h_j}, \tag{2}$$

where h_j denotes the frequency of the host genotype $j \in \{mab, maB, mAb, mAB, Mab, MaB, MAb, MAB\}$. We assume a matching alleles model for the infection genetics, which means that $w_{ij}^p = 1$ when the host matches the corresponding parasite allele at both interaction loci, and $w_{ij}^p = 1 - s_P$ when the host fails to match the corresponding parasite allele at either interaction locus. For example, for the parasite genotype $i = aB$, the matching host genotypes are $j = maB, MaB$ and the nonmatching genotypes are $j = mab, mAb, mAB, Mab, MAb, MAB$.

The selection process in the host consists of two steps, namely infection and selection on the infected individuals. First, the number of infected and uninfected individuals is established by assuming genotype matching

$$h_i^+ = h_i p_i, \quad h_i^- = h_i(1 - p_i),$$

where the superscript '+' denotes infection (infecteds), and the superscript '−' denotes the lack of infection (uninfecteds). The infected individuals then undergo selection, and the host frequencies are updated according to

$$h_i'^- = \frac{h_i^-}{1 - s_H \sum_i h_i^+}, \tag{3}$$

where s_H is the selection coefficient for the infected individuals.

Each modifier allele, *m* and *M*, has its own assigned reproductive strategy that determines the likelihood of an individual carrying this allele to engage in sexual reproduction depending on whether it has been infected (+) or not (−). We thus define four probabilities that are defined by two strategy vectors: vector $\vec{\sigma}_m = (\sigma_{m-}, \sigma_{m+})$ defines a reproductive strategy for the *m* allele, and vector $\vec{\sigma}_M = (\sigma_{M-}, \sigma_{M+})$ defines a reproductive strategy for the *M* allele. Each σ value defines a probability of a given individual (or its gametes) to end up in a 'sex pool' (a gene pool where all individuals reproduce sexually); otherwise, the genotype goes to an 'asex pool' (a gene pool where all individuals reproduce asexually). Three default strategies are defined and referred to throughout the main text:

- the asexual strategy $\vec{\sigma}_{\text{asex}} = (0, 0)$ implies that each individual will always reproduce asexually, regardless of the infection status;
- the sexual strategy $\vec{\sigma}_{\text{sex}} = (1, 1)$ implies that each individual will always reproduce sexually, regardless of the infection status;
- the conditional strategy $\vec{\sigma}_{\text{cond}} = (0, 1)$ implies that each healthy individual will always reproduce asexually and each infected individual will always reproduce sexually.

We also define a general reproductive strategy $\vec{\sigma}_{\text{gen}} = (\sigma_-, \sigma_+)$, where a fraction σ_- of healthy individuals and a fraction σ_+ of infecteds will reproduce sexually, and all others will reproduce asexually. We compete different strategies by assigning one strategy to each modifier allele, *m* and *M*. For example, a modifier *m* coding for asexual strategy will be denoted as m_{asex} and a modifier *M* coding for conditional strategy will be denoted as M_{cond}.

The host frequencies in each of the pools are determined by the following equations

$$\begin{aligned} h_{m,k}^{\text{sex}} &= h_{m,k}^- \sigma_{m-} + h_{m,k}^+ \sigma_{m+}, \\ h_{M,k}^{\text{sex}} &= h_{M,k}^- \sigma_{M-} + h_{M,k}^+ \sigma_{M+}, \\ h_{m,k}^{\text{asex}} &= h_{m,k}^- (1 - \sigma_{m-}) + h_{m,k}^+ (1 - \sigma_{m+}), \\ h_{M,k}^{\text{asex}} &= h_{M,k}^- (1 - \sigma_{M-}) + h_{M,k}^+ (1 - \sigma_{M+}), \end{aligned} \tag{4}$$

where $k \in \{ab, aB, Ab, AB\}$. After that, all genotypes in the sex pool undergo sexual reproduction with random mating. We define two recombination rates, *R* and *r*, where *R* denotes the probability of cross-over between the **M** locus and the **A** locus, whereas *r* denotes the probability of cross-over between the **A** locus and the **B** locus; we assume that the latter is independent of the sex modifier, that is, $r = r_{MM} = r_{Mm} = r_{mm}$. The host frequencies after the recombination step are then given by the following equation

$$h_i' = \frac{1}{\theta_{\text{sex}}} \sum_{j,k} R_{i|j,k}^{\text{sex}} h_j^{\text{sex}} h_k^{\text{sex}} + h_i^{\text{asex}}, \tag{5}$$

where $\theta_{\text{sex}} = \sum_i h_i^{\text{sex}}$ and $R_{i|j,k}^{\text{sex}}$ denotes a probability of obtaining genotype *i* by recombination of genotypes *j* and *k* with recombination rates *R* and *r* (see appendix in Otto & Feldman, 1997, for the precise set of

equations that constitute the recombination step). We also assume no inherent cost of sex in our simulations (but see Discussion).

Finally, both species undergo mutation at their interaction loci. Backward and forward mutation rates in both species are the same and set to a default value of $\mu = 10^{-5}$ per locus per generation. Both species are initialized with random genotype frequencies during each simulation run, and in addition, the host population is initiated with the modifier M at frequency $f_M = 0$. After a burn-in phase of $N_0 = 1000$ generations, during which the system approaches its long-term dynamics, the modifier M is introduced at linkage equilibrium into the host population, with a frequency of $f_M = 50\%$. Following further $N = 1000$ generations of coevolution, the final modifier frequency f_M^{final} is recorded. Because the fate of the modifier in these models can depend on the initial conditions, particularly with weak selection (Agrawal & Otto, 2006; Kouyos *et al.*, 2007; Salathé *et al.*, 2008b), this entire procedure is repeated n times and the average of f_M^{final} is calculated. The effective selection coefficient of the modifier M during the N generations is then calculated using the formula

$$s_M = \left[f_M^{\text{final}}/(1 - f_M^{\text{final}})\right]^{1/N} - 1. \qquad (6)$$

Sex in diploids

In the diploid case, hosts carry two copies of the chromosome, and each copy has the same architecture as in the haploid case (**MAB**). Selection acts only in the diploid phase, and reproduction consists of meiosis, random mating of gametes and mutation. The coevolution of diploid hosts and haploid parasites is modelled in the same way as in the case of the haploid hosts with a few key differences, which are described below.

Like in the haploid model, selection acts on infected individuals, and infection occurs in host genotypes that are matched by the corresponding parasite genotype. A host genotype $i \in \{mab/mab, mab/maB, maB/mab, maB/maB, mab/mAb, \ldots, MAB/MAB\}$ can be matched by a parasite genotype $j \in \{ab, aB, Ab, AB\}$ with probability $\Pi_{ij} = A_{ij}B_{ij}$, where A_{ij} and B_{ij} denote the probability of matching at loci **A** and **B**, respectively. The values for A_{ij} and B_{ij} are given in Table 1. At homozygous loci, we assume full or zero matching, namely hosts a/a are always matched by parasites a but never by parasites A. At heterozygous loci, we assume probabilistic matching, namely hosts A/a are matched by parasites a with probability P and by parasites A with probability Q. (As they can be matched by neither or both parasite alleles, P and Q need not sum up to 1.) The probabilities for matching at the **B** locus are the same. $P = Q = 0$ corresponds to an extreme situation where parasites need to match all alleles at both loci in order to infect a host; because parasites are haploid, this means they can never infect hosts that are heterozygous at one or both loci. Conversely, $P = Q = 1$ means that the parasites need to match only one allele at each locus for successful infection; this implies that double heterozygotes can be infected by all parasites. Finally, intermediate values of P and Q could result from dosage dependence in the matching process between host and parasite gene products, or from random expression of only one allele and silencing of the other in heterozygote hosts.

Table 1 Matching probabilities A_{ij} at the **A** locus in the diploid model (same values at the **B** locus). We assume homozygotes can be either fully matched (1) or fully nonmatched (0). Matching of heterozygotes occurs with probabilities P and Q. Because we assume the matching alleles infection model, $P + Q > 1$ corresponds to the situation where heterozygotes are less resistant than expected from homozygotes, $P + Q < 1$ corresponds to the situation where heterozygotes are more resistant than expected from homozygotes, and $P + Q = 1$ corresponds to the situation where heterozygotes are as resistant as expected from homozygotes. When $P = Q$, heterozygotes match both parasite alleles equally well; otherwise, they become more specialized on one of the alleles ($P \neq Q$).

	Parasite	Genotype
Host genotype	*a*	*A*
a/a	1	0
A/a	*P*	*Q*
A/A	0	1

The frequencies of infected hosts are calculated according to the matching alleles model, and the overall infection probability is given as a product of infection probabilities at each locus:

$$h_i^+ = h_i \sum_{j=1}^{4} \Pi_{ij} p_j, \qquad h_i^- = h_i \sum_{j=1}^{4} (1 - \Pi_{ij}) p_j.$$

Selection is then performed according to eqn (3). As for the parasite, the selection step is performed by the use of eqns (1) and (2) with the fitness matrix $w_{ij}^p = 1 - (1 - \Pi_{ij})s_P$.

The host frequencies in the sexual and asexual pool are determined by the use of the following relations

$$\begin{aligned}
h_{m/m,k}^{\text{sex}} &= h_{m/m,k}^- \sigma_{mm-} + h_{m/m,k}^+ \sigma_{mm+},\\
h_{M/m,k}^{\text{sex}} &= h_{M/m,k}^- \sigma_{Mm-} + h_{M/m,k}^+ \sigma_{Mm+},\\
h_{M/M,k}^{\text{sex}} &= h_{M/M,k}^- \sigma_{MM-} + h_{M/M,k}^+ \sigma_{MM+},\\
h_{m/m,k}^{\text{asex}} &= h_{m/m,k}^- (1 - \sigma_{mm-}) + h_{m/m,k}^+ (1 - \sigma_{mm+}),\\
h_{M/m,k}^{\text{asex}} &= h_{M/m,k}^- (1 - \sigma_{Mm-}) + h_{M/m,k}^+ (1 - \sigma_{Mm+}),\\
h_{M/M,k}^{\text{asex}} &= h_{M/M,k}^- (1 - \sigma_{MM-}) + h_{M/M,k}^+ (1 - \sigma_{MM+}),
\end{aligned} \qquad (7)$$

where $k \in \{ab/ab, ab/aB, aB/ab, \ldots, AB/AB\}$ denote the 16 possible genotypes at the interaction loci. For the sake of simplicity, we assume additivity with respect to the propensity to engage in sex, namely that

$$\sigma_{mm\pm} = \sigma_{m\pm}, \quad \sigma_{Mm\pm} = \frac{1}{2}(\sigma_{m\pm} + \sigma_{M\pm}) \quad \sigma_{MM\pm} = \sigma_{M\pm}. \tag{8}$$

Individuals in the sex pool undergo meiosis and random mating of gametes. Combining both sexually and asexually produced offspring, the genotype frequencies in the next generation read

$$h_i' = \frac{1}{\theta_{\text{sex}}} \Lambda_i(h_1^{\text{sex}}, h_2^{\text{sex}}, \ldots, h_{64}^{\text{sex}}) + h_i^{\text{asex}}, \tag{9}$$

where again $\theta_{\text{sex}} = \sum_i h_i^{\text{sex}}$, and the function $\Lambda_i(x_1, \ldots, x_{64})$ returns the genotype frequency x_i after one round of sexual reproduction in a diploid population (see Data S1). Finally, both species undergo mutation with probability μ at each haploid locus.

Results

The aim of this study is to examine the evolution of condition-dependent sex in the host during its coevolution with the parasite. To this end, we use a mathematical model of host–parasite coevolution where infected and uninfected hosts can engage in sexual reproduction with different probabilities (see The Model). To disentangle the effects of recombination and segregation, we first analyse the population genetic forces that select for recombination in haploid populations. We then extend the analysis to sex in diploid hosts to account for the effects of segregation alone (single locus) and segregation with recombination (two loci).

Conditional sex in haploid hosts

We first consider three reproductive strategies: asexual (never reproduce sexually), sexual (always reproduce sexually) and conditional (when infected, always reproduce sexually; otherwise, asexually), and compete those three strategies in pairs in haploid hosts. Figure 1 shows the success of these strategies encoded by allele M (effective selection s_M) as a function of selection coefficients s_H, s_P. In particular, Fig. 1a,d show the standard RQH results, that is, the success of the sexual strategy when invading the asexual strategy. These results confirm the earlier findings that selection for the sexual strategy in haploid hosts is strongest when selection on the interaction loci is strong and recombination rates are low (Salathé *et al.*, 2008b). By contrast, Fig. 1b,c,e,f show that the success of the conditional strategy against purely sexual and asexual strategies is the highest when selection is weak or intermediate and recombination rates are high. Thus, we see that the condition-dependent sex

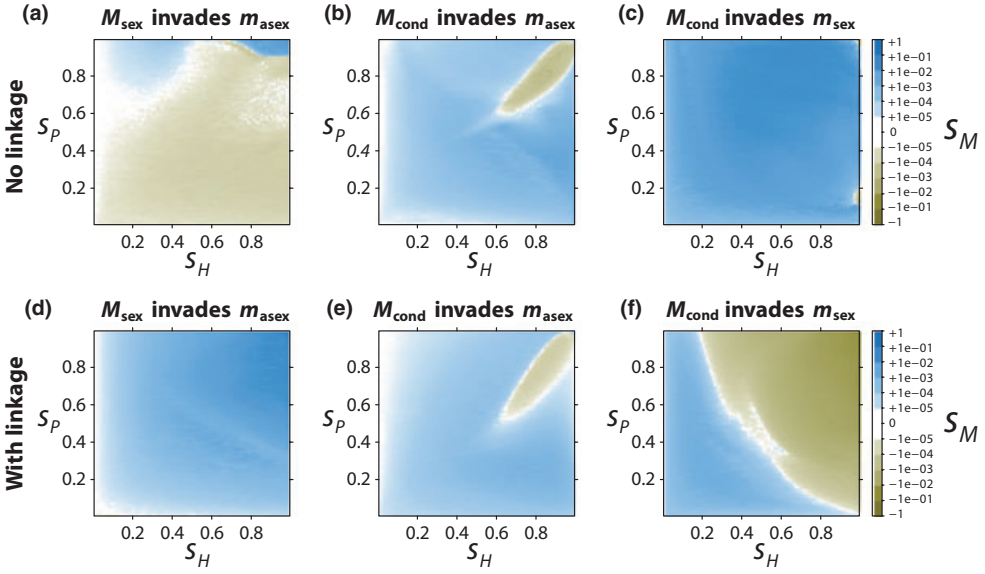

Fig. 1 Success of condition-dependent and condition-independent sex strategies. Three strategies are competed in pairs: the asexual strategy (asex; never engage in sexual reproduction), the sexual strategy (sex; always engage in sexual reproduction) and the conditional strategy (cond; always engage in sexual reproduction when infected; otherwise, never). The modifier m resides, the modifier M invades. The effective selective coefficient s_M acting on the invading strategy (encoded by modifier allele M) is plotted against the strength of selection acting on the host s_H and the parasite s_P. Blue areas denote positive selection (invasion), whereas olive-green areas denote negative selection (no invasion). We distinguish between no linkage between the host loci (a–c) and tight linkage between host loci (e–f). The following parameters were used: $N = N_0 = 1000$; (a–c) $r = R = 0.5$, and (d–f) $r = R = 0.05$. The reproductive strategies used: (a,d) $\vec{\sigma}_m = (0,0), \vec{\sigma}_M = (1,1)$; (b,e) $\vec{\sigma}_m = (0,0), \vec{\sigma}_M = (0,1)$; (c,f) $\vec{\sigma}_m = (1,1), \vec{\sigma}_M = (0,1)$. Plots were generated in a resolution of 99 × 99 and by averaging over $n = 100$ simulation runs for each combination of parameters.

strategy is selected for in regions of the parameter space where the condition-independent sex strategy is not. Furthermore, the magnitude of the effective selection pressure on the modifier suggests that invasion of the modifier may even be possible in the face of substantial costs of sex.

What drives the spread of modifiers inducing condition-dependent sex in haploid populations? One possibility is that those modifiers benefit more from breaking down maladapted gene combinations in the infected subpopulation than in the uninfected subpopulation. If this were true, one would expect that the statistical associations between alleles in the infected and the uninfected host subpopulations differ and that these differences underlie varying selection pressures on modifiers inducing condition-dependent and condition-independent strategies. In order to test this hypothesis, we assess the linkage disequilibrium (association between alleles at two interaction loci) in all, infected and uninfected individuals, D, D^+ and D^-, respectively. These are given by the following equations:

$$\begin{aligned} D &= h_{ab}h_{AB} - h_{aB}h_{Ab} \\ D^+ &= \frac{1}{(\theta^+)^2}\left(h^+_{ab}h^+_{AB} - h^+_{aB}h^+_{Ab}\right), \\ D^- &= \frac{1}{(\theta^-)^2}\left(h^-_{ab}h^-_{AB} - h^-_{aB}h^-_{Ab}\right), \end{aligned} \tag{10}$$

where $\theta^+ = \sum_i h_i^+$ and $\theta^- = 1 - \theta^+$. We then calculate epistasis in the host population as

$$E = w^h_{ab}w^h_{AB} - w^h_{aB}w^h_{Ab}, \tag{11}$$

where w_i^h denotes host fitness (conditional on parasite frequencies) and is given analogously to eqn (2). Finally, we calculate the products $E \times D, E \times D^+$ and $E \times D^-$, which measure whether the disproportionally fit genotypes are also more common than expected in the entire host population, in the infected subpopulation and in the uninfected subpopulation, respectively. A negative sign of these products suggests that fit genotypes are also underrepresented, and the modifiers that induce genetic shuffling will have an immediate advantage over the nonrecombining ones. In contrast, if the product is of positive sign, recombination will be likely to break down well-adapted combinations of genotypes and will be selected against in the short term (Peters & Lively, 1999).

Figure 2 shows the mean values over time of $E \times D, E \times D^+$ and $E \times D^-$ as a function of selection coefficients s_H and s_P. When the population undergoes asexual reproduction (Fig. 2, panels a–c), we generally observe $E \times D^+$ and, except for high s_H, that $E \times D^- > 0$. This suggests that in those regions, conditional modifiers will have an immediate advantage over the asexual modifiers. Comparison of Fig. 2b,c with Fig. 1b,e suggests that this short-term effect can indeed explain the success of the conditional strategy in the majority of the parameter space. Example linkage disequilibrium against epistasis dynamics which select for conditional modifiers are shown in subplots of Fig. 2a–c. Furthermore, when the population undergoes sexual reproduction (Fig. 2d–f), we generally observe $E \times D^- \geq 0$. This result is qualitatively similar for lower recombination rates (data not shown). Comparison of Fig. 2f with Fig. 1c,f suggests that the short-term benefit could promote the spread of conditional modifiers in a large fraction of the parameter space. However, as such spread occurs mostly when selection is weak or intermediate, especially under tight linkage, the immediate short-term effect appears to be insufficient to promote conditional modifiers when selection is strong. This can be seen directly when quantifying the role of the immediate short-term effect in explaining the selection for the invading strategy s_M. We hypothesize that the sign of $E \times D^+$ in the asexual population (Fig. 2b) should be a good predictor of the success of the conditional strategy when invading the asexual population (Fig. 1b,e). We also hypothesize that the sign of $E \times D^-$ in the sexual population (Fig. 2f) should be a good predictor of the success of the conditional strategy when invading the sexual population (Fig. 1c,f). We find that over the entire selection space 0, the immediate short-term effect explains 23.6%, and 33.9% of the variance in s_M, respectively (Spearman's rank correlation, all p). However, in the weak selection space 0, the immediate short-term effect explains 96.2%, 77.6% of the variance in s_M, respectively (p; results qualitatively identical for tighter genetic linkage). Overall, we see that the immediate benefit of recombination in infected individuals can explain the advantage of the conditional strategy over both the exclusively sexual and exclusively asexual strategies, but that its importance will highly depend on the value of selection and genetic linkage and that other effects are also likely to play an important role.

We next examine the impact of genetic linkage on selection for the conditional strategy. Figure 3 shows the invasion success of the conditional strategy in sexual and asexual haploid populations for various recombination rates R and r. The results show that the conditional strategy is more successful when recombination rates are high, especially when selection pressure is intermediate, in accordance with Fig. 1. When selection is weak, condition-dependent sex modifiers are selected for in the presence of both the sexual and the asexual strategies, regardless of the recombination rates (Fig. 3a,d). As selection becomes stronger, the conditional strategy becomes less successful. However, whereas the invasion success of the conditional modifier in an asexual population depends solely on the strength of selection (Fig. 3a–c), the invasion success in a sexual population is largely determined by the recombination rates, r and R (Fig. 3d–f). Interestingly, when $r = 0$ (which is equivalent to the case of a single

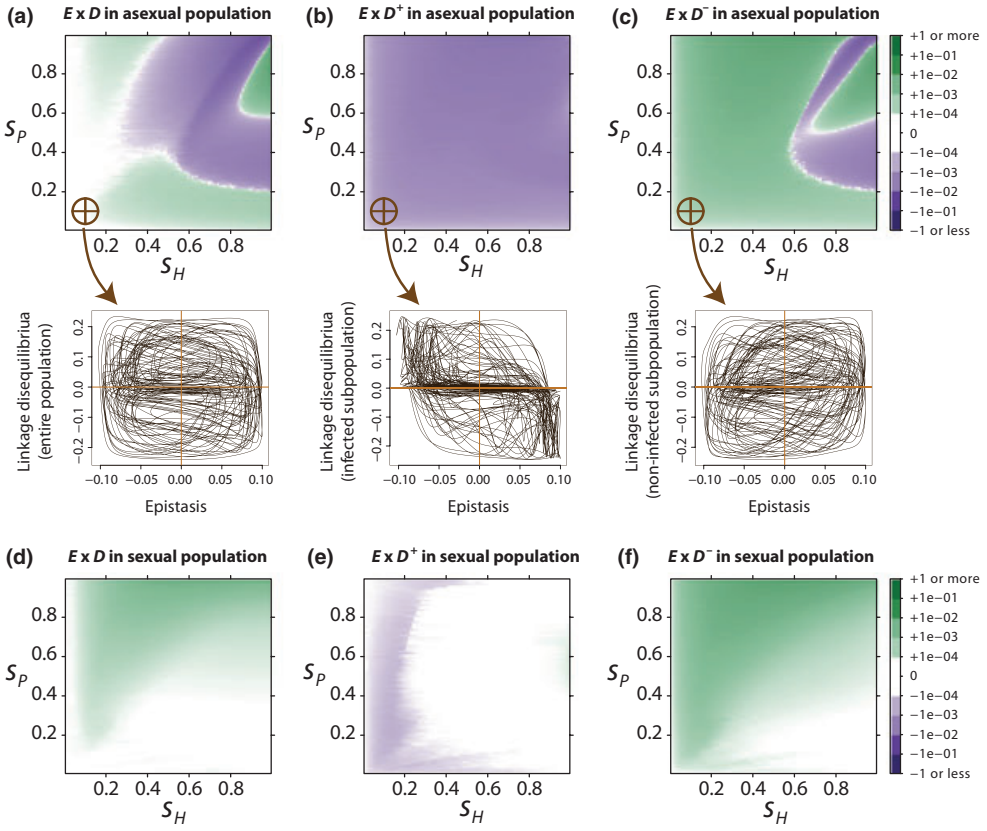

Fig. 2 Short-term benefit of condition-dependent sex. The mean product of epistasis (E) and linkage disequilibrium (D) is plotted against selection coefficients s_H and s_P. The product is shown in the entire population ($E \times D$; a, d), in the infected subpopulation ($E \times D^+$; b, e) and in the uninfected subpopulation ($E \times D^-$; c, f). Green colours denote a positive sign of the product (recombination has an immediate disadvantage), and purple colours denote a negative sign of the product (recombination has an immediate advantage). The product is plotted in an asexual population (a–c) and a sexual population (d–f). Example dynamics for each of the three cases in the asexual population are plotted in the subplots below the main panels (a–c), where linkage disequilibrium and epistasis from one simulation run were plotted against each other over the course of N generations for $s_H = s_P = 0.1$ after N_0 'burn-in' generations. The following parameters were used: $N_0 = 10\,000, N = 1000$, (a–c) $\vec{\sigma}_m = (0,0)$, (d–f) $\vec{\sigma}_m = (1,1), R = r = 0.5$. The frequency of modifier M was set to 0 at all times. Plots were generated in the resolution of 99 × 99; the mean of the product was taken over N generations, and averaged of $n = 50$ simulation runs; subplots in panels a–c were run for N generations.

interaction locus), the conditional strategy still spreads in the sexual population, and more so as R increases (see also Fig. S3). This spread cannot be caused by the generation of fit genotype combinations because there is no recombination that could affect the statistical distribution of the interaction loci in the population. Rather, it seems to be driven by a 'selfish gene effect' of the modifier allele. Because infected individuals are more likely to engage in sex than uninfected individuals, the modifier tends to associate itself more often with the uninfected individuals and thus with individuals of higher fitness. This effect is analogous to the so-called abandon-ship mechanism described in the context of single-species models (see Discussion). (Note that when the conditional strategy invades the asexual strategy (Fig. 3a–c), there is no sex between individuals carrying the two different modifier alleles and the selfish gene effect therefore does not play any role in the spread of the modifier.) Furthermore, when selection is strong, the conditional modifier can decrease in frequency for low recombination rates R (Fig. S3). This strongly suggests that for the 'abandon-ship' effect to occur in host–parasite systems, recombination needs to be high enough; otherwise, the modifier is too strongly linked to unfit alleles that will soon be rapidly selected against. However, the precise conditions for the increase/decrease in the conditional sex modifier in the strong selection regime remain to be analysed.

How successful are condition-dependent sex strategies in haploid hosts in a general sense? To answer this questions, we examine the evolutionary stability of all reproductive strategies $\vec{\sigma}_{\text{gen}} = (\sigma_-, \sigma_+)$, and we identify, for a given set of parameters, the evolutionarily stable

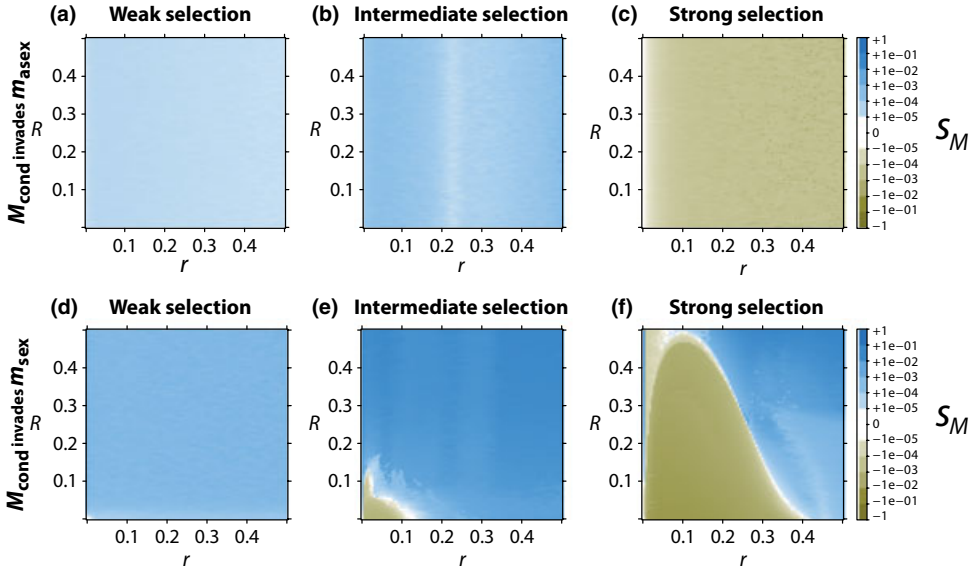

Fig. 3 The impact of genetic linkage on the spread of the conditional modifier. The plots show the effective selection s_M on the conditional modifier when introduced into a resident asexual population (a–c) or a sexual population (d–f), as a function of genetic linkage (recombination rates r and R). The colour scale is identical to the one in Fig. 1: blue areas denote success of the conditional strategy, and olive-green areas denote the failure of the conditional strategy. R is the recombination rate between the modifier and the first interaction locus, and r is the recombination rate between the two interaction loci. The following parameters were used: $N = N_0 = 1000$; (a, d) $s_H = s_P = 0.1$, (b, e) $s_H = s_P = 0.5$, (c, f) $s_H = s_P = 0.9$. The reproductive strategies used: $\vec{\sigma}_m = (0,0), \vec{\sigma}_M = (0,1)$ (a–c); $\vec{\sigma}_m = (1,1)$, $\vec{\sigma}_M = (0,1)$ (d–f). Plots were generated in the resolution of 101×101 and by averaging over $n = 100$ simulation runs.

strategy (ESS) $\vec{\sigma}_{\text{ESS}} = (\sigma^*_-, \sigma^*_+)$, that is, the strategy that cannot be invaded by any other strategy. In particular, the ESS strategy is obtained, for a given set of s_H, s_P, r and R, by estimating the effective selection on an invading strategy M given a resident strategy $m, s_M(\sigma_{m-}, \sigma_{m+}; \sigma_{M-}, \sigma_{M+})$, for all possible values of σ. We assume that the ESS strategy is characterized by

$$(\sigma^*_-, \sigma^*_+): \min_{\sigma_{m-}, \sigma_{m+}} \max_{\sigma_{M-}, \sigma_{M+}} s_M(\sigma_{m-}, \sigma_{m+}; \sigma_{M-}, \sigma_{M+}). \qquad (12)$$

The range of resident $\sigma_{m\pm}$ values where there is only weak (if any) selection for any mutant $\sigma_{M\pm}$ is obtained by the use of the following inequality

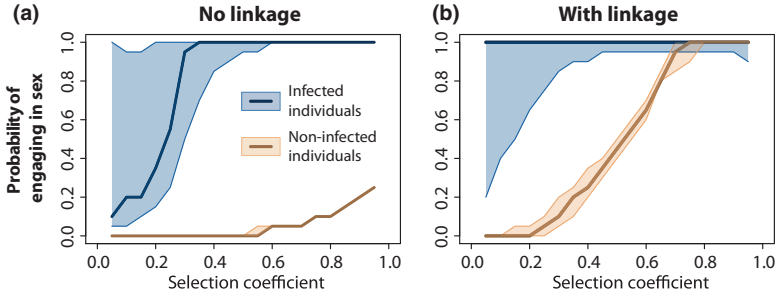

Fig. 4 Optimal reproductive strategy in haploid populations. The plots show an estimate of the evolutionarily stable reproductive strategy (ESS) in infected individuals (blue) and uninfected individuals (orange) as a function of selection coefficients s_H, s_P. For each parameter combination $(\sigma_{m-}, \sigma_{m+})$ of the resident population, an invader M, characterized by a combination $(\sigma_{M-}, \sigma_{M+})$, is introduced at 50% frequency after N_0 generations. The final frequency of the invading strategy M is recorded after N generations, and the result is averaged over n simulation runs. The parameter combination $\vec{\sigma}_{\text{ESS}} = (\sigma^*_-, \sigma^*_+)$ which cannot be invaded by any other strategy is considered an optimal reproductive (ESS) strategy (see main text). The bold lines correspond to the ESS estimates, $\min_{\sigma_m} \max_{\sigma_M}(s_M)$, and the colour areas correspond the range of strategies, $\max_{\sigma_M}(s_M) \leq \epsilon$. The values $\sigma_{m-}, \sigma_{m+}, \sigma_{M-}$, and σ_{M+} are varied between 0 and 1 with gradation of 0.05. The following parameters are used: $N = N_0 = 500, n = 100, \epsilon = 5 \times 10^{-3}, s_H = s_P$; (A) $r = R = 0.5$, (B) $r = R = 0.05$.

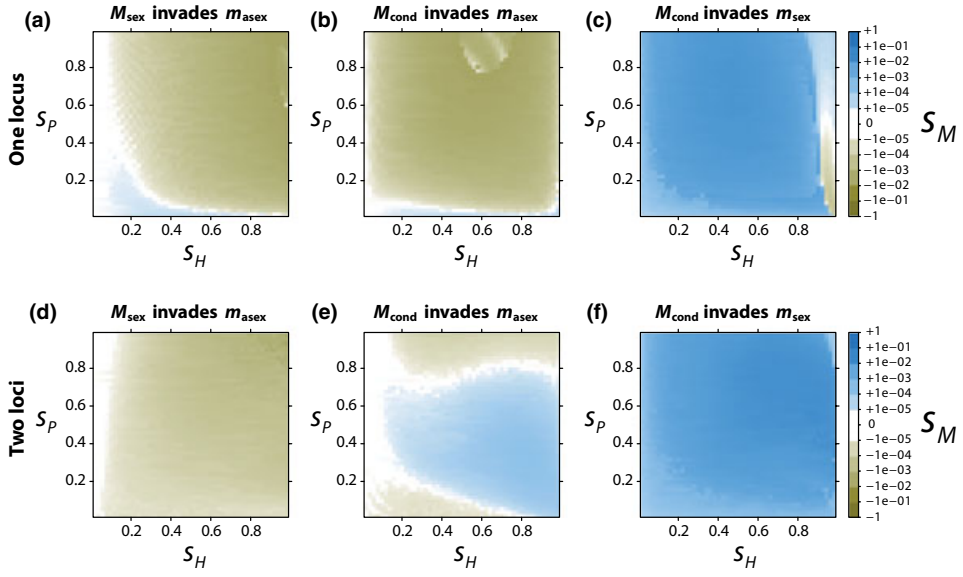

Fig. 5 The effect of segregation and recombination on the modifier frequency in diploid populations. The outcome of the competition between three default reproductive strategies (asexual, sexual and conditional) when host–parasite interactions are mediated via a single locus (a–c) and two loci (d–f). The modifier m resides, the modifier M invades. The three strategies are competed in pairs and effective selection s_M for the invading strategy M is plotted. As recombination does not have any effect in panels a–c, selection for sex is indicative of selection for segregation. The following parameters were used: $N = N_0 = 1000, r = R = 0.5, P = Q = 1/2$; (a–c) $B_{ij} = 1$. The reproductive strategies used: (a, d) $\vec{\sigma}_m = (0,0), \vec{\sigma}_M = (1,1)$; (b, e) $\vec{\sigma}_m = (0,0), \vec{\sigma}_M = (0,1)$; (c, f) $\vec{\sigma}_m = (1,1), \vec{\sigma}_M = (0,1)$. Plots were generated in a resolution of 49 × 49 and by averaging over $n = 200$ simulation runs for each combination of parameters. Colours used are the same as in Fig. 1.

$$\max_{\sigma_{M-},\sigma_{M+}} s_M(\sigma_{m-}, \sigma_{m+}; \sigma_{M-}, \sigma_{M+}) \leq \epsilon, \qquad (13)$$

where $\epsilon = 5 \times 10^{-3}$; if the maximum s_M for the ESS strategy is larger than ϵ, the strategy is not considered as ESS. The results are shown in Fig. 4. The figure shows that, in almost the entire parameter space, the ESS is characterized by $\sigma^*_+ > \sigma^*_-$, that is, infected individuals have a higher propensity to engage in sex than uninfected individuals. As linkage becomes tighter and selection stronger, the ESS converges towards $\vec{\sigma}_{\mathrm{ESS}} = (1,1)$ (obligate sex), in accordance with Fig. 1. Interestingly, as selection becomes weaker, the range of strategies in infected individuals which fulfil inequality (13) increases, in spite of the assumed infinite population size. This presumably happens because with weak selection, a modifier allele that changes σ_{M+} is more or less neutral. Moreover, the fact that we fail to observe this phenomenon for the optimal strategy in the uninfected individuals (σ^*_-) points again to different population genetic processes that underlie the evolution of sexual reproduction in infected and in uninfected individuals.

Conditional sex in diploid hosts

To understand how the results presented above are affected by diploidy of the hosts, we compete the three strategies considered in Fig. 1 (asexual, sexual and conditional; see also The Model) in a population of diploid hosts. Figure 5 shows the effective selection coefficient s_M of the modifier allele M as a function of selection coefficients s_H and s_P. Specifically, Fig. 5a–c shows the results when interactions are mediated via a single locus. In this case, sex does not entail recombination between two interaction loci, and the assessed effective selection coefficient s_M is therefore indicative of the strength of selection for or against segregation. As expected from previous studies (see for example Agrawal & Otto, 2006), we observe that segregation is typically detrimental for sex. Sex is selected against, particularly when selection is strong and both under obligate sexual reproduction (Fig. 5a) and conditional sexual reproduction (Fig. 5b). The detrimental effect of segregation is also evident when the conditional strategy invades the sexual strategy (Fig. 5c), indicating that suppressing segregation can be beneficial even if it occurs in uninfected individuals only.

Why is segregation typically detrimental for sex? This question has been extensively discussed in the past (Otto, 2003; Agrawal & Otto, 2006), and the argument goes as follows. Let F quantify the genetic associations between two alleles at a given locus, such that $F > 0$ denotes an overrepresentation of homozygotes and $F < 0$ denotes an overrepresentation of heterozygotes at

this locus; let also Φ measure the fitness interactions between two alleles at the same locus, such that $\Phi > 0$ denotes a fitness advantage of homozygotes with respect to heterozygotes and $\Phi < 0$ denotes a fitness advantage of heterozygotes with respect to homozygotes at this locus. F is known as the inbreeding coefficient and measures a deviation from Hardy–Weinberg equilibrium, and Φ is known as the dominance coefficient and measures one-locus fitness interactions on a multiplicative scale (see also Data S2 for the mathematical definitions of F and Φ). F and Φ are analogous to linkage disequilibrium (D) and epistasis (E), respectively: whereas D and E measure *between-locus* statistics, F and Φ measure *within-locus* statistics in diploids. We mentioned above that sex in haploids may become beneficial when $E \times D < 0$ because recombination then increases the proportion of genotypes that are currently fit. Likewise, for sex to become beneficial in diploids, one would expect that $F \times \Phi < 0$ because segregation then increases the proportion of genotypes that are currently fit. To see whether the sign of $F \times \Phi$ can explain (a) the prevalence of parameter regions where segregation is selected against (b) and differences between the invasion of the sexual and the conditional strategy, we have performed a similar analysis to the one in Fig. 2 and have analysed whether the sign of $F \times \Phi$ can explain the effective selection s_M. The results are presented in a Data S2. Overall, we see that a short-term benefit of segregation is indeed rare in our model, and the sign of $F \times \Phi$ can often explain both selection against the sexual strategy and the rare selection for the conditional strategy. However, in many cases, the immediate disadvantage of segregation is not the only force driving selection for or against sex. This suggests that, in analogy to the selection for recombination, nonimmediate benefits/detriments of segregation may play an important role in the evolution of sex in diploid hosts, regardless of the reproductive strategy employed.

We next examine the net effect of segregation and recombination for the success of the conditional strategy. Figure 5d–f shows the results of the competition between the three reproductive strategies when interactions are mediated via two loci. Interestingly, whereas the sexual strategy is under negative selection in the asexual population for any combination of selection coefficients (Fig. 5d), the conditional strategy can invade the asexual strategy in the majority of the parameter space (Fig. 5e). We have found this result to hold for many combinations of heterozygote matching probabilities, P and Q, especially when heterozygotes are as resistant as expected from homozygotes, that is, when $P + Q = 1$ (see Table 1 and Fig. S2). This suggests that the benefit of conditional recombination described earlier (i.e. the benefit of conditional sex in haploid populations) can often outweigh the detrimental effects of segregation. However, the success of the conditional strategy depends strongly on the underlying infection genetics.

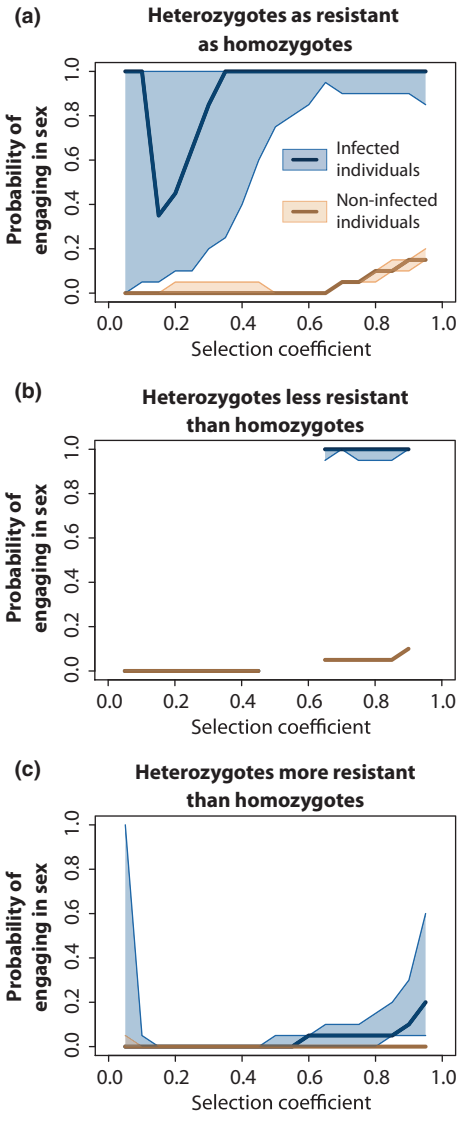

Fig. 6 Optimal reproductive strategy in diploid populations. The plots show an estimate of the evolutionarily stable reproductive strategy in infected individuals (blue) and uninfected individuals (orange) as a function of selection coefficients s_H, s_P. The ESS strategy was estimated in the same way as in Fig. 4. The plots show the results for different heterozygote matching probabilities P and Q, including the situation where heterozygotes are as resistant as expected from homozygotes (a), heterozygotes are less resistant than expected from homozygotes (b), heterozygotes are more resistant than expected from homozygotes (c). The parameters used are identical to those in Fig. 4; additionally, we used (a) $P = 0.2, Q = 0.8$, (b) $P = 0.5, Q = 0.8$, (c) $P = 0.2, Q = 0.5$.

To examine the success of conditional-sex strategies in a general sense in diploid hosts, we identify the ESS reproductive strategy $\vec{\sigma}_{\mathrm{ESS}} = (\sigma^*_-, \sigma^*_+)$ for a given set of

parameters (s_H, s_P, r, R, P, Q) in an analogous way to the one in Fig. 4. The results are shown in Fig. 6. As expected, we find that the evolutionary success of conditional sex depends on the genetics of infection as well as on the strength of selection. When heterozygotes are on average about as resistant as homozygotes ($P + Q \approx 1$), conditional sex is favoured regardless of the selection strength (Fig. 6a). As heterozygotes become more resistant ($P + Q < 1$) or less resistant ($P + Q > 1$) than homozygotes, the ESS propensity to engage in sex upon infection decreases. This can again be explained through the detrimental effect of segregation, because both situations usually lead to $F \times \Phi > 0$. With weak selection, unconditional asexual reproduction is evolutionarily stable in this scenario (Fig. 6b,c), but when $P + Q > 1$ and selection is stronger, conditional sex can also evolve. This latter effect may be at least partially attributed to the fact that with strong selection $F \times \Phi < 0$ is observed for $P + Q > 1$ but not $P + Q < 1$ (data not shown). Overall, we see that as in the haploid model, the ESS strategies are characterized by $\sigma^*_+ > \sigma^*_-$ in most of the parameter space. These results concerning the ESS reproductive strategy appear to be robust with respect to different recombination rates (not shown).

Discussion

In this article, we have studied the evolution of condition-dependent sex in the context of host–parasite interactions and the RQH. Our results indicate that a modifier allele inducing sex in infected individuals at a higher rate than in uninfected individuals will often spread to fixation. This holds in the majority of the parameter space and for both a haploid and a diploid host population. Although we have not explicitly implemented a fitness cost of sexual reproduction, strong positive selection acting on the modifier suggests that the spread of conditional reproductive strategies could occur even in the presence of substantial costs.

We first analysed the benefit of conditional sex in haploid hosts. Our results reveal at least two forces that produce selection for a condition-dependent sex modifier in haploid populations: (a) an immediate benefit of condition-dependent sex and (b) a selfish gene effect. The immediate benefit of condition-dependent sex stems from overrepresentation of deleterious gene combinations among the infected individuals (epistasis and LD of opposite sign). As in standard RQ models, breaking down those combinations results in an immediate benefit of recombination, which manifests itself already in the next generation and is typically referred to as the 'immediate short-term effect' (Peters & Lively, 2007). In uninfected individuals, however, beneficial gene combination is often overrepresented (epistasis and LD of same sign), so that recombination is selected against in these individuals. Unfortunately, this simple relationship between selection for the sex modifier and $E \times D$ does not hold in all regions of the parameter space, especially those where selection is strong. It therefore seems plausible that in those regions the benefit of conditional sex may not be immediate. In particular, it could manifest itself after two or more generations (the so-called delayed short-term effect) or after many generations by increasing the additive genetic variance for fitness in infected individuals and thereby increasing the efficacy of selection (the so-called long-term effect; see Salathé *et al.* (2009) for a detailed discussion of the role of these effects in the RQ models).

On the other hand, the induction of sexual reproduction in infected haploid individuals may often impart a selfish gene advantage to the modifier. This advantage is analogous to an effect described in single-species models with fitness-associated sex, called the 'abandonship' mechanism (Agrawal *et al.*, 2005). Here, modifiers inducing higher rates of sex and recombination in unfit individuals have been shown to spread to fixation by breaking away from their low-fitness haplotype background (Agrawal *et al.*, 2005; Hadany & Otto, 2007, 2009). In this way, modifiers spread by avoiding 'sinking ships'. In the context of antagonistic coevolution, condition-dependent sex also allows these modifiers to frequently become associated with fitter genotypes even though fitness changes with time. The main difference between this situation and the one described in single-species models is that at strong parasite-mediated selection, modifiers must recombine frequently enough to successfully spread in the population; otherwise, they will decrease in frequency (cf. Fig. S3). This is because unfit host genotypes will soon become fit genotypes during antagonistic coevolution. Metaphorically speaking, when sinking ships may soon change into lifeboats, one needs to jump fast enough between the ships to avoid drowning.

We next analysed the success of conditional sex in diploid hosts. Our results show that such a reproductive strategy is selected for in many regions of the parameter space (unlike obligate sex), however is much less successful than in haploid hosts. We have identified segregation as one of the key factors causing a disadvantage of conditional sex modifiers. Specifically, whether conditional sex is selected for depends mainly on how resistant heterozygotes are compared to homozygotes. If heterozygotes and homozygotes are comparably resistant on average ($P + Q \sim 1$), then dominance can fluctuate over time causing fit genotypes to be temporarily underrepresented ($F \times \Phi < 0$), thus providing an advantage for sex (Agrawal & Otto, 2006; Agrawal, 2009a). As heterozygotes become more or less resistant than homozygotes ($P + Q < 1$ or $P + Q > 1$), segregation tends to destroy favourable allele combinations within a locus (due to $F \times \Phi > 0$), which in turn leads to a disadvantage of sex. However, conditional sex can still evolve when $P + Q > 1$ provided that host and par-

asite suffer high fitness costs. Our analysis has also shown that in this case nonimmediate effects of segregation can play an important role in the evolution of conditional sex. Our findings thus suggest that the benefit of engaging in sex more frequently when infected can often override the detrimental effects of segregation, and that conditional sex is the optimal reproductive strategy in a large fraction of the parameter space.

In addition to segregation, other effects may be important determinants for selection on conditional sex modifiers in diploid compared to haploid hosts. First, the infection genetics in haploids and diploids are inevitably different. In haploid hosts, where a parasite must precisely match the host to infect it, every mutation in infected hosts will lead to resistance against this parasite, whereas in diploid hosts, it will often lead to only partial changes in resistance. Second, the diploid nature of the sex modifier locus may also be important. In our model, we assumed additivity with respect to the propensity to engage in sex. Dominance effects will add an additional layer of complexity and may in some cases be crucial for the evolutionary dynamics. As an extreme example, consider a strictly recessive modifier inducing sexual reproduction. If such a modifier arises in a completely asexual population, it will always remain in the heterozygous state and therefore be selectively neutral even when there is strong selection for sex. Finally, the selfish gene effect of conditional sex modifiers in diploids may differ from the one in haploids. The success of such modifiers has been previously shown to be largely independent of the ploidy of hosts in single-species models (Hadany & Otto, 2007); but note that this statement is not true for conditional *recombination* modifiers; see Agrawal *et al.* (2005) and below). It remains to be examined how the situation changes in the context of host–parasite interactions.

In order to obtain general insights into the problem of condition-dependent sex in a coevolutionary setting, we made a number of simplifying assumptions. In addition to ignoring the well-known twofold cost of sex, two of these assumptions in particular can be expected to make the invasion of a modifier that induces conditional sex more difficult than predicted by our model. First, if only a subset of the population undergo sexual reproduction, finding a mate may be difficult. This particular cost of sex will depend on how well the parasite population is adapted to the host population and will be most pronounced when only few parasites manage to infect hosts. Second, we assumed here that parasites are haploid; diploid parasites would result in additional areas of the parameter space in which the success of conditional sex remains to be examined. Third, the underlying interaction model assumes that parasites need to match the host at both loci to infect it (the matching alleles model); other models like the gene-for-gene model are known to be less favourable for selection on sex or recombination modifiers (Salathé *et al.*, 2008a). Finally, infection can induce instantaneous sexual reproduction in our model. By contrast, in both aphids and *Daphnia* (two of the best studied animal systems with facultative sex), environmental conditions induce asexual females to produce both males and females, and only these individuals then reproduce sexually. Thus, there is a time lag of one generation between induction of sex and the actual sexual reproduction. Although our preliminary simulations show that a simplified form of such a time lag is not expected to affect the results (not shown), this should be more thoroughly investigated in future by carefully implementing the details of the hosts' life cycle.

The population genetic approach taken here is likely to ignore the impact of epidemiological processes in host–parasite interactions, such as mating probability, density-dependent effects or time-lagged parasite-mediated selection. All of these processes have been shown to play an important role in coevolutionary models of hosts and parasites (May & Anderson, 1983), also in the context of the evolution of sex in antagonistic interactions (Galvani *et al.*, 2003; Lively, 2010b). For that reason, we suspect that epidemiological dynamics might also affect the results of models of conditional sex. Related to this point is a question about the dynamics of prevalence. Throughout this study, we have purposely assumed an infinite population size in host and parasite populations. This was done to dissect the 'Red Queen effect', which is independent of the population size, from the Hill–Robertson effect, which occurs at finite population sizes (reviewed in Otto, 2009). Nonetheless, it is important to understand the influence of genetic drift on the evolution of condition-dependent sex. This is because the Hill–Robertson effect could select for conditional sex in the parameter regimes where it does not occur in the deterministic limit, particularly in diploid hosts. It would also be interesting to see whether in such a setting condition-dependent sex is more likely to evolve with finite population sizes than obligate sex. Overall, we suspect that the incorporation of population dynamic effects might have important implications for the results presented here.

Another caveat is that the model designed here focuses on the evolution of conditional sex. An alternative approach would be to study the evolution of recombination. The difference between the two approaches is that conditional-sex models assume that the modifier affects an individual's tendency to engage in sexual reproduction, whereas conditional-recombination models assume that the modifier affects the recombination rate itself. It has been previously shown in models of diploids that conditional sex evolves more easily than conditional recombination. This is because in diploids there is not enough information for the modifier to 'know' whether it is associated with the fitter chromosome, but there is enough information for the modifier to know whether it is associated with a fit genome (Agrawal *et al.*, 2005; Hadany & Otto, 2007). Furthermore, obligate sex has

been shown to evolve more frequently than recombination in a diploid host–parasite model (Agrawal, 2009a). For these reasons, we expect that conditional sex modifiers will be more successful than conditional recombination modifiers. However, this hypothesis requires a more thorough investigation.

Our results support the RQH for the initial evolution of sexual reproduction. One problem with this hypothesis has been that a number of conditions must be met for the sexual modifier to spread to fixation, including tight genetic linkage, strong selection and host haploidy (Agrawal & Otto, 2006; Salathé *et al.*, 2008b). Our model shows that in its condition-dependent version, the RQH also works well with weak or intermediate selection, free recombination between all loci, and often host diploidy. The extension of the RQH to this type of nonuniform sexual reproduction makes the hypothesis consistent with findings, indicating that facultative sex was the first form of sexual reproduction to evolve (Dacks & Roger, 1999).

The flip side of this, however, is that the condition-dependent RQH struggles to explain the evolution and the evolutionary maintenance of obligate sex (as do single-species models of condition-dependent sex; see e.g. Hadany & Otto, 2007). Assuming weak selection or free recombination between all loci – the conditions that are favourable for the spread of a condition-dependent sex modifier in an asexual population – the same modifier can also spread in sexual populations (see Fig. 1c,f), and strategies that downregulate the rate of sex in uninfected individuals are usually favoured (see Figs 4 and 6). Condition-dependent sex thus seems to be superior to obligate sex, but at least in multicellular organisms, the latter is much more common. It has been previously suggested that strong sexual selection could explain the maintenance of obligate sex during invasion of facultative sex (Hadany & Beker, 2007) and asexuality (Roze & Otto, 2012). Given that female mate choice is often based on male infection status (e.g. Hamilton & Zuk, 1982; Milinski & Bakker, 1990; Houde & Torio, 1992), it would be interesting to explore the possibility that obligate sex is favoured over infection-dependent sex when sexual selection is taken into consideration.

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Supporting information

Additional Supporting Information may be found in the online version of this article:
Data S1 Recombination in diploid organisms.
Data S2 Short-term effect of segregation.
Figure S1 Short-term benefit of segregation.
Figure S2 Success of condition-dependent and condition-independent sex strategies in diploid hosts.
Figure S3 Quantification of the selfish effect of the conditional modifier.

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