Opposites attract? Mate choice for parasite evasion and the evolutionary stability of sex

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Abstract

If sex is naturally selected as a way to combat parasites, then sexual selection for disease resistance might increase the overall strength of selection for outcrossing. In the present study, we compared how two forms of mate choice affect the evolutionary stability of outcrossing in simultaneous hermaphrodites. In the first form, individuals preferred to mate with uninfected individuals (condition-dependent choice). In the second form, individuals preferred to mate with individuals that shared the least number of alleles in common at disease-resistance loci. The comparisons were made using individual-based computer simulations in which we varied parasite virulence, parasite transmission rate, and the rate of deleterious mutation at 500 viability loci. We found that alleles controlling both forms of mate choice spread when rare, but their effects on the evolutionary stability of sex were markedly different. Surprisingly, condition-dependent choice for uninfected mates had little effect on the evolutionary stability of sexual reproduction. In contrast, active choice for mates having different alleles at disease-resistance loci had a pronounced positive effect, especially under low rates of deleterious mutation. Based on these results, we suggest that mate choice that increases the genetic diversity of offspring can spread when rare in a randomly mating population, and, as an indirect consequence, increase the range of conditions under which sexual reproduction is evolutionarily stable.

Introduction

One of the leading ideas for the evolutionary maintenance of cross-fertilization is that antagonistic coevolution can favour at least some outcrossing over complete parthenogenesis or obligate self-fertilization (Glesener & Tilman, 1978; Jaenike, 1978; Hamilton, 1980; Bell, 1982; Hamilton *et al.*, 1990; Agrawal & Lively, 2001). The basic idea [now known as the Red Queen hypothesis following Bell (1982)] is that biparental sex and recombination are favoured over uniparental forms of reproduction when virulent parasites can quickly evolve to disproportionately infect locally common host genotypes. Although the Red Queen Hypothesis is difficult to directly test, the basic tenets of the hypothesis are now supported by a number of different studies. Specifically, experimental and observation studies have shown that: (1) increasing genetic diversity reduces the risk of infection (Lively *et al.*, 1990; Baer & Schmid-Hempel, 1999); (2) there is parasite-mediated selection against common genotypes (Antonovics & Ellstrand, 1984; Schmitt & Antonovics, 1986; Kelley *et al.*, 1988; Dybdahl & Lively, 1998; Lively & Dybdahl, 2000); and that sexual reproduction in the wild is associated with the prevalence of infection (Lively, 1992; Schrag *et al.*, 1994; Lively & Jokela, 2002). The strict model, nonetheless, has one difficulty in that frequency-dependent selection, by itself, cannot eliminate asexual clones (Lively & Howard, 1994; Judson, 1997; Lythgoe, 2000). Thus, if there are repeated mutations to parthenogenetic reproduction, parasite-mediated selection can lead to the accumulation of sufficient clonal diversity to eliminate the advantage to outcrossing sexual individuals (Lively &

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Howard, 1994). It is for this reason that we have begun combining antagonistic coevolution with classical models, such as Muller's ratchet, as a way to generate selection against parthenogens. Our early studies showed that such a combination greatly expanded the conditions for which sexual reproduction was favoured over asexual reproduction in hosts (Howard & Lively, 1994, 1998). More recently, we found that the same combination of selective forces can also expand the conditions under which sex is favoured in parasites (Howard & Lively, 2002).

In the present study, we expand on this pluralistic theme (West *et al.*, 1999) to include sexual selection. If parasites do indeed favour outcrossing in hosts, then sexual selection for disease resistance might increase the conditions for which sexual reproduction is resistant to invasion by parthenogenetic mutants (Kodric-Brown & Brown, 1987; Ochoa & Jaffé, 1999). Toward this end, we considered the two models for mate choice that have received the most attention by behavioural ecologists. In the first model, which we call condition-dependent (CD) choice, females use indicator traits as a primary criterion for mate choice (Hamilton & Zuk, 1981; Kodric-Brown & Brown, 1987). As such traits may indicate general health, females may be indirectly choosing mates with genotypes that confer parasite resistance (Hamilton & Zuk, 1981; Von Schantz *et al.*, 1996; Siva-Jothy, 1999, 2000). These genotypes are likely to be rare, at least periodically, when parasites are driving genotypic oscillations in their host populations. We assume in the present model that an individual's condition is determined by its infection status; hence there is choice for uninfected individuals over infected individuals. In the other model, which we call the opposites attract (OA) model, females choose mates that differ from themselves at one or more loci that code for self–nonself recognition and parasite resistance (Penn & Potts, 1999); the effect of such choice would be to increase the within-brood genetic diversity. Our goal was to determine whether these two forms of mate choice would spread when rare in an outcrossing population practising random mating, and, if so, whether the presence of mate choice would affect the evolutionary stability of sex following the introduction of a parthenogenetic mutant.

Methods

Hosts were modelled as either sexual simultaneous hermaphrodites or parthenogenetic clones, whereas parasites were modelled as obligately sexual simultaneous hermaphrodites. Both parasite and host life cycles were discrete with non-overlapping generations, and parasites underwent two generations for each host generation. The antagonistic interaction was mediated by matching alleles at 2 or 3 diallelic loci (interaction loci) in the genomes of the both parasites and hosts. The genomes of hosts additionally contained 500 'mutation' loci at which deleterious mutations could accumulate. Free recombination occurred at all loci in sexual hosts and parasites, whereas the genomes of asexual hosts consisted of a single, non-recombining linkage group.

At the start of each run, the mutation loci in the sexual host population were initialized with the equilibrium variance and mean mutation number for a given combination of mutation rate (U) for a selection coefficient (s) = 0.0125; selection against mutation took the form of $(1 - s)^n$, where s is the effect of a single deleterious mutation and n is number of mutations in the genome. Similarly, the disease-resistance loci in the host and parasite populations were initialized so that the beginning frequencies of alternative alleles (0 and 1) at each locus was 0.5. The simulation was then started and allowed to run for 40 host generations, at which time a single asexual individual was introduced into the population. Following Charlesworth's approach, the founders of asexual lineages began with exactly $i = \bar{n} - 2\sqrt{\bar{n}}$ mutations, where $\bar{n}$ was the equilibrium mean number of mutations for the sexual population (Charlesworth, 1990). Genetic variation at the interaction loci in the sexual parasite population was maintained by setting the mutation rate between alternative alleles at 0.03 per generation. This very high value for mutation rate is meant to simulate the effects of both migration and mutation.

During each parasite generation, hosts were drawn sequentially and exposed to a randomly selected parasite with probability T. Parasites that matched hosts exactly at all loci were able to establish infections, otherwise they died (relaxing this assumption did not affect the dynamics in a similar model (Agrawal & Lively, 2002)). In cases where infections were established, the host was marked as infected, and the parasite was placed in an array of reproductive individuals.

Reproduction in hosts and parasites was simulated by drawing individuals at random with replacement from their respective populations. According to this scheme, the probability of an individual being drawn for reproduction during any generation followed a Poisson distribution with a mean of one. For the case of sexual reproduction, the first individual drawn was designated as 'female'. For the random mating case, this individual then accepted sperm from the next individual selected at random by the simulation. The mate choice runs were accomplished by allowing this 'female' to discriminate among 20 different individuals. For CD choice, 'females' mated with the first uninfected individual selected by the simulation. In the unlikely event that all 20 individuals were infected, 'she' returned to mate with the first encountered individual. In the OA model, 'females' mated with the individual that shared the least number of alleles in common at the disease-resistance loci. For example, in the three-locus model, a 'female' of genotype 0-0-1 would exhibit the strongest preference for individuals having genotype 1-1-0. The choice of mates in our models was not affected by mutational load, although

such choice has important effects if the load increases the variance in male success more than female success (Agrawal, 2001; Siller, 2001).

Following mating, the haploid genomes of the two parents were combined in a diploid zygote stage, where free recombination preceded the redistribution of genetic material to a brood of haploid progeny. All else being equal, sexual individuals (hosts and parasites) produced an expected lifetime average of 10 offspring through female function. Asexual hosts, on the other hand, gave rise to a lifetime average of 20 offspring through uniparental reproduction and thus gained the full two-fold numerical advantage in offspring number.

The expected number of offspring produced by hosts was discounted according to the detrimental effects of parasitism. The lifetime reproductive output of infected hosts was calculated as the proportion $(1 - E)$ of offspring produced by uninfected individuals, where E represents the effect of infection (virulence). For the case of deleterious mutations ($U > 0$), the viability of offspring was reduced according to the relationship between mutation number and fitness. An individual with $n = 55$ mutations, for example, would have a 50% chance of surviving to reproduce $[\bar{w} = (1 - s)^n = (1 - 0.0125)^{55} = 0.500]$. At the end of each generation, a maximum of 2000 parasite and 2000 host offspring were randomly selected to become the next generation of adults.

For each run of the simulation, the computer recorded the dynamics of the interacting populations for a maximum of 300 host generations following the introduction of the clone. We conducted 10 replicate runs of the simulation for each combination of mutation rate (U), number of interaction loci (2 or 3), and type of mate choice (OA and CD) under varying levels of parasite transmission (T) and virulence (E). We terminated runs for which asexual mutants failed to establish in six generations, and the results were omitted from the final

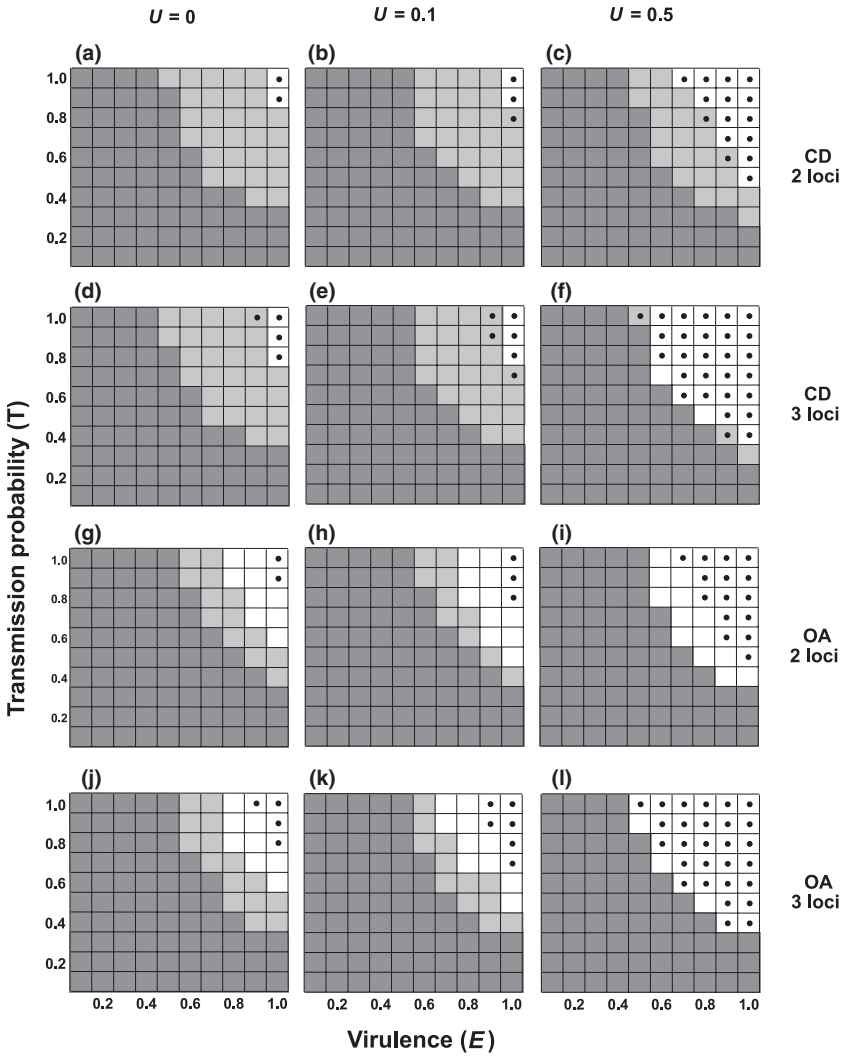

Fig. 1 Results from individual-based computer simulations in which sexual host populations competed against asexual lineages harbouring a two-fold numerical advantage in offspring production (Maynard Smith, 1978). Each block in the grids gives the majority outcome (sex wins: open, asex wins: light grey, or coexistence of asexual and sexual morphs: dark grey) from 10 replicate runs of the simulation. The 12 grids show the results for different values of the genomic mutation rate ($U = 0$; $U = 0.1$; $U = 0.5$), and for two types of mate choice [condition-dependent (CD) and opposites attracts (OA)], for both the two- and three-locus versions of the simulation. The effect of each mutation was assumed to be independent of the number of mutations and was set at 0.0125. The x-axis gives the effect of infection on host fitness (E), and the y-axis give the probability of exposure to infection (T). The cells marked with • in the middle give the conditions for which sex was favoured by selection in the absence of mate choice for the same set of parameters. So the effect of mate choice can be seen by comparing the open square to the squares having the. in the middle.

tally. Results of runs in which clones coexisted with sexual populations for 300 generations were recorded as 'coexistence', but previous studies have shown that such short-term coexistence leads to the accumulation of a genetically diverse group of clones, which eventually eliminates the sexual individuals in the population (Lively & Howard, 1994). We used log-linear models of multiway frequency analysis to test the hypothesis that rate of deleterious mutation, number of interaction loci, and type of mate choice influenced the evolutionary stability of sex in our simulations.

Results and discussion

Evolutionary stability of sex

The long-term evolutionary stability of sex in our simulations varied in response to parasite virulence and transmission probability (Fig. 1). The distribution of this advantage also varied significantly depending on the rate of deleterious mutations, the number of disease-resistance (interaction) loci, and the type of mate choice (Table 1). In addition to these main effects, the interaction between the deleterious mutation rate and the type of mate choice was also statistically significant (Table 1).

Consistent with results obtained from previous studies (Howard & Lively, 1994, 1998), protection for sex increased as a function of the deleterious mutation rate (Table 1). This result held for random mating, OA, and CD runs of the simulations for both the two and three-locus models.

Increasing the number of disease resistance loci from two to three also had a positive effect on the evolutionary stability of sex. This agrees with results obtained from previous studies of host-parasite coevolution, in which the effects of deleterious mutation and mate choice were not considered (Hamilton *et al.*, 1990).

The two types of mate choice had very different effects on the evolutionary stability of sex (Fig. 1). When compared with random mating, CD choice did not increase the virulence-by-transmission parameter space under which sex was favoured (partial $\chi^2 = 0.547$, n.s.). This surprising result held for both the two-locus and three-locus models across the whole range of deleterious mutation rates (Fig. 1a–f). In fact, for the lower rates of mutation, CD choice led to a slight reduction in the range of conditions under which sex was favoured over asexual reproduction. In contrast, OA mate choice increased (compared with random mating) the parameter space under which sex was evolutionarily stable (partial $\chi^2 = 28.687$, $P < 0.0001$) (Fig. 1g–l). This later result differs from that reported by Ochoa & Jaffé (1999), who found that asexuals outcompeted sexuals that were preferentially mating with opposite genotypes. Our approach differed from that of Ochoa & Jaffé (1999), however, in that we incorporated deleterious mutations into our model; the advantage to sex in our simulations was in large part because of an interaction between the type of mate choice and the deleterious mutation rate (Table 1).

Table 1 Multiway frequency analysis for the proportion of sex obtained from the simulations for various combinations of deleterious mutation rate ($U = 0$, 0.1 and 0.5), number of interaction loci (2 or 3), and type of mate choice [Random mating, condition-dependent (CD) and opposites attracts OA)].

Mate choice	*U*	Number of loci	% sex
Random mating	0.0	2	2
Random mating	0.0	3	4
Random mating	0.1	2	3
Random mating	0.1	3	6
Random mating	0.5	2	15
Random mating	0.5	3	28
CD	0.0	2	2
CD	0.0	3	3
CD	0.1	2	2
CD	0.1	3	3
CD	0.5	2	13
CD	0.5	3	28
OA	0.0	2	11
OA	0.0	3	12
OA	0.1	2	14
OA	0.1	3	16
OA	0.5	2	28
OA	0.5	3	31
Tests of partial associations			
Effect	d.f.	Partial χ^2	Probability
Mutation	2	108.855	<0.0001*
Loci	1	9.490	0.0021*
Mate choice	2	35.436	<0.0001*
Mutation × Loci	2	0.154	0.9259
Mutation × Mate choice	4	13.109	0.0108*
Loci × Mate choice	2	3.931	0.1401

*Indicates statistical significance.

Consistent with previous studies (May & Anderson, 1983; Howard & Lively, 1994), the results of the present study showed that, in the absence of deleterious mutation accumulation, asexual clones typically replaced sexual populations, unless both parasite transmission and parasite virulence were very high (Fig. 1). The addition of deleterious mutation to the model greatly increased the range of conditions in the virulence-by-transmission parameter space where sexual reproduction was evolutionarily stable, and the effect increased in proportion to the mutation rate (Fig. 1). Mate choice also increased the range of conditions under which sexual reproduction was evolutionarily stable, but the increase was only observed in populations where individuals preferred to mate with individuals having a different genotype at disease-resistance loci (Fig. 1). CD choice had virtually no effect on the evolutionary stability of sex. Hence, sexual selection interacted with natural selection to expand the conditions under which cross-fertilization

was stable, but only when the choice of mates was for genetic opposites.

Population genetic consequences of mate choice

In order to understand these unexpected results, we examined the population genetic consequences of the two types of mate choice using additional runs of the simulation model. We introduced rare alleles for either CD or OA mate choice into the simulation at generation 500, and followed the fate of these alleles and their effects on the population (Fig. 2). Both types of mate choice increased when rare in the population, and CD choice quickly went to fixation. In addition, under the CD model, we found that the genotypic oscillations at the disease-resistance loci became more extreme as the choice allele increased in frequency (Fig. 2a) and that the linkage disequilibrium increased (Fig. 2c). This result stems from the fact that rare host genotypes, which were currently more resistant to parasites, were also most likely to be chosen as mates. The combination of positive sexual and natural selection increased the epistasis for fitness, leading to more extreme genotypic oscillations and higher values of linkage disequilibrium.

The allele for OA choice also spread when rare in a randomly mating sexual population, but the existence of OA choice had the opposite effect of CD choice. Specifically, the spread of the allele for OA choice was coupled with dramatic decreases in both the genotypic oscillations (Fig. 2b) and the linkage disequilibrium (Fig. 2d). This result stems from the fact that 'opposites attract', leading to a rare advantage under sexual selection. But, unlike the rare advantage under sexual selection generated by the CD model, the rare advantage under OA is not lagged in time, as it is independent of the genotypic cycles in the parasite population. As such, OA would indirectly reduce linkage disequilibria by reducing the overall epistasis for fitness. The increase in the parameter space under which outcrossing was evolutionarily stable under OA choice (Fig. 1) probably stems, at least in part, from the fact that OA choice works in concert with recombination to reduce the level of linkage disequilibrium in the sexual population.

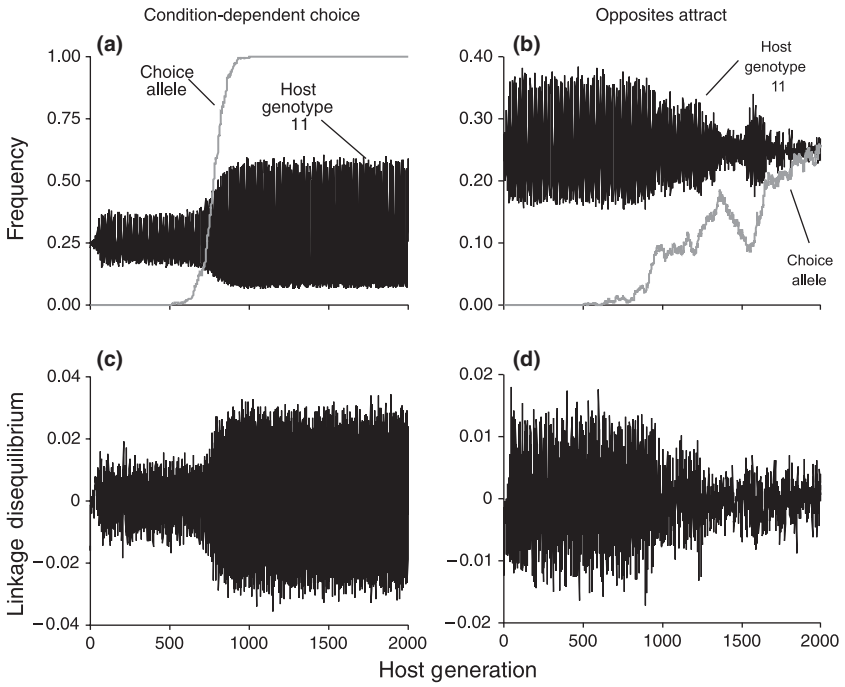

Fig. 2 Results from simulations where rare alleles for mate choice were introduced into random mating populations. At generation 500, the allele encoding either condition-dependent (CD) or opposites attracts (OA) mate choice was initialized at a frequency of 0.001. Parameters for this 2-locus simulation included parasite virulence (E) of 0.8, rate of parasite transmission (T) of 0.8, and population size (N) of 20 000 (the larger population size was used to minimize genetic drift). (a) The spread of an allele for CD mate choice through a random mating host population (thick grey line), and the resulting effect on the dynamics of host genotype 11 (thin black line; the dynamics for the other host genotypes are similar). (b) The spread of an allele for OA mate choice (thick grey line) in a random mating host population, and the effect on host genotype 11 (thin black line). (c) The change in linkage disequilibrium in the host population associated with the spread of the allele for CD mate choice. The coefficient of linkage disequilibrium was calculated each generation as $D = p_{00}p_{11} - p_{10}p_{01}$ where p_{ij} represents the frequency for each of the four possible host genotypes (Felsenstein, 1965). (d) The change in linkage disequilibrium in the host population associated with the spread of the allele encoding OA mate choice.

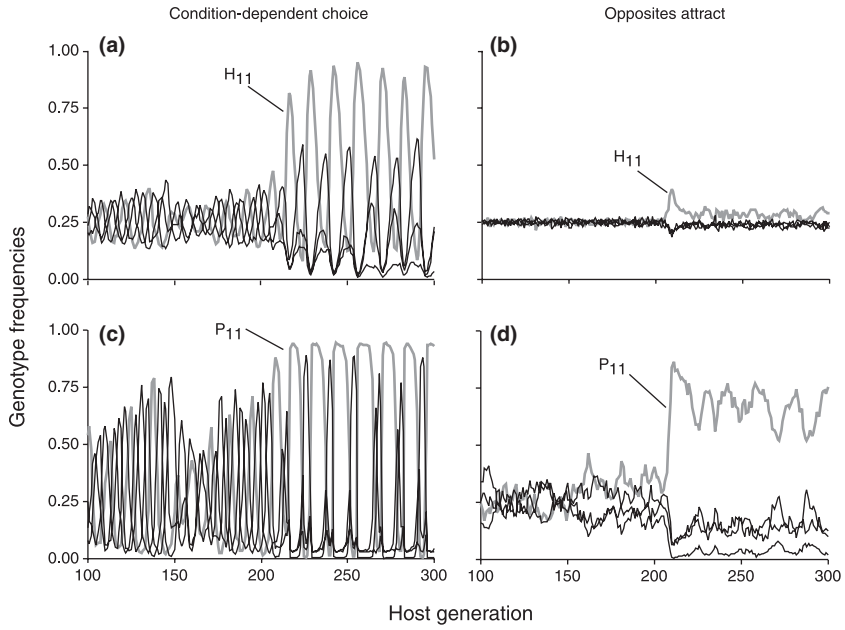

Fig. 3 Host and parasite genotype frequencies under condition-dependent (CD) and opposites attracts (OA) mate choice before and after the introduction of a host clone having genotype H_{11} (at generation 200) with a two-fold reproductive advantage. (a) Host genotype frequencies in CD population. (b) Host genotype frequencies in OA population. (c) Parasite genotype frequencies in CD population. (d) Parasite genotype frequencies in OA population. Parameters for this two-locus run included probability of parasite transmission (T) = 0.8, parasite virulence (E) = 0.8, deleterious mutation rate (U) = 0.0, and population size of 2000.

These results suggest that clones entering sexual populations may experience different fates as an indirect consequence of how individuals in the sexual population are choosing mates. Clonal females entering a sexual host population practising OA choice will be entering a population wherein the disease resistance genotype frequencies are oscillating (Fig. 3b), but with a lower amplitude than in CD populations (Fig. 3a). As a consequence, the corresponding genotype frequencies in the parasite populations will also be oscillating less vigorously in populations tracking OA host populations (Fig. 3d) than in parasites tracking CD host populations (Fig. 3c). Thus, host clones may become exposed to selection sooner in OA populations, and would be subject to attack by parasites having a higher average level of allelic diversity.

In additional runs of the simulation, we monitored the frequency of infection in clonal lineages following their establishment in sexual populations practising either OA choice or CD choice. The results showed that clones invading OA populations suffered higher average rates of infection (with less variance) than clones invading CD populations (Fig. 4). When a host clone is introduced into a sexual population practising OA choice, the clone quickly becomes bearer of the most common resistance genotype in the population (Fig. 3b), and the parasite population quickly responds to infect this most common genotype (Fig. 3d). Even strong selection imposed by parasites, however, cannot reduce the overall frequency of the genotype of the clone below the relatively high level at which the same genotype is maintained by OA in the sexual population (Fig. 3b). Hence, the periodic advantage due to parasite-mediated frequency-dependent selection is lost, and the parasite attack against the clone is sustained over time. As a consequence, clones were held by parasites at a lower average population size in OA than CD populations, thereby increasing the rate of deleterious mutation accumulation under the action of Muller's ratchet (Fig. 5).

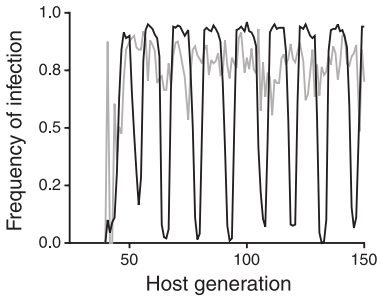

Fig. 4 The frequency of infection in clonal individuals over time in the condition-dependent (CD) population (thin black line) and in the opposites attracts (OA) population (thick grey line). Parameters for this two-locus run included probability of parasite transmission (T) = 0.8, parasite virulence (E) = 0.8, deleterious mutation rate (U) = 0.0, and population size of 2000.

Similarly we found that increasing the number of loci from two to three also damped the genotypic dynamics (results not shown) and increased the parameter space under which cross-fertilization was evolutionarily stable, even without mate choice (Fig. 1). Adding loci increases genetic diversity for disease resistance in the host population, and each genotype oscillates around a lower average frequency. In such situations, invading clonal lineages more

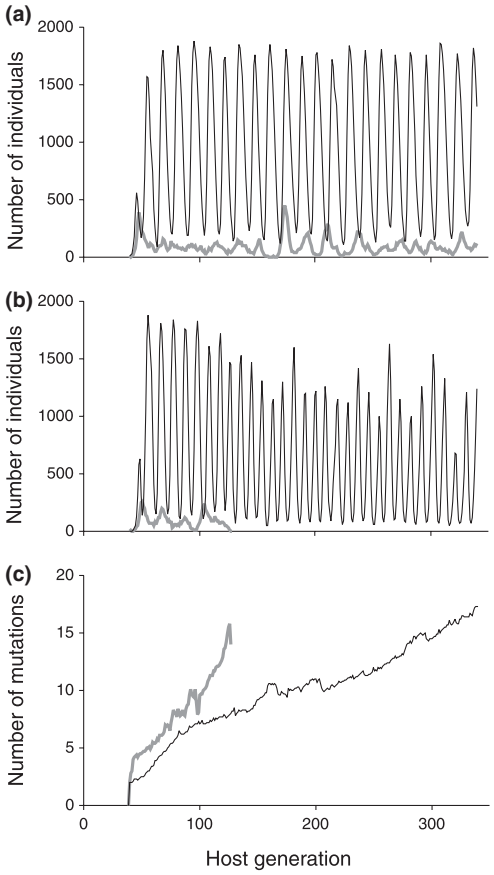

Fig. 5 Population dynamics and corresponding rates of mutation accumulation for invading clonal lineages under condition-dependent (CD) and opposites attracts (OA) mate choice. (a) The number of clonal individuals over time in the CD (thin black line) and OA populations (thick grey line) in the absence of deleterious mutation. (b) The number of clonal individuals over time in the CD (thin black line) and OA populations (thick grey line) in simulations for which the deleterious mutation rate had been set to $U = 0.1$. (c) The number of deleterious mutations in the clonal lineages over time in the CD (thin black line) and OA populations (thick grey line) depicted in b. Parameters for these 2-locus runs included parasite virulence (E) = 0.8, probability of parasite transmission (T) = 0.8. As in the main simulations, a single clonal genotype was introduced into a population of 2000 sexual individuals at generation 40.

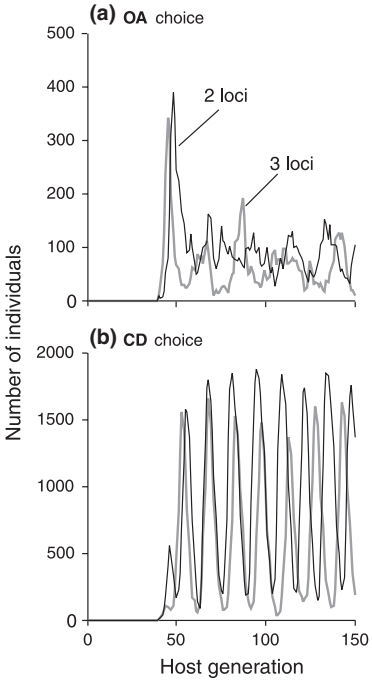

Fig. 6 Population dynamics of invading clonal lineages under (a) opposites attracts (OA) mate choice and (b) condition-dependent (CD) mate choice in two-locus runs of the simulations (thin black lines) and three-locus runs of the simulation (thick grey lines). Parameters for these runs included parasite virulence (E) = 0.8, probability of parasite transmission (T) = 0.8, and mutation rate (U) = 0. As in the main simulations, a single clonal genotype was introduced into a population of 2000 sexual individuals at generation 40.

quickly become the most common genotype in the host population, and are therefore subjected to earlier tracking by coevolving parasites. The efficiency of Muller's ratchet should also increase under these conditions, as clones will be held to lower average population sizes (Fig. 6). Hence, the maintenance of sex in host populations with high levels of genetic diversity for disease resistance may be achieved under lower rates of deleterious mutation (see also Hamilton *et al.*, 1990).

Summary and future directions

In summary, we suggest that OA choice is selected over random mating because it increases the genetic diversity of offspring (which is similar to sex and recombination), and that sexual reproduction is stable over a broader range of conditions as an indirect consequence of selection on mate choice. More generally, any form of mate choice (or gamete choice) that increases the within-brood genetic diversity for parasite resistance would be expected to have a similar effect, provided it does not lead to auto-immune responses or other correlated costs. For example, a recent study has shown that the competitive ability of sperm from male *Drosophila* is inversely related to the degree of relatedness among parents (Mack *et al.*, 2002). This difference in competitive ability may thus increase the genetic diversity of offspring and indirectly favour sexual reproduction. Mate choice and cryptic mate choice have been observed in a variety of different plants and animals (e.g. Marshall, 1988; Havens & Delph, 1996; Olsson *et al.*, 1996; Penn & Potts, 1999; Jennions & Petrie, 2000; Amos *et al.*, 2001; Reusch

et al., 2001; Blomqvist *et al.*, 2002), so the effect is at least potentially general.

Several important questions remain unanswered. One question is whether OA choice would be resistant to invasion and replacement by CD choice, and vice versa. Our preliminary results suggest that OA is, in fact, evolutionarily stable to CD choice, but that the converse in not true (Howard & Lively, unpublished data). Another question is whether CD choice would be more favourable to sex if overall condition were affected by mutational load as well as infection status (here we kept all else equal by allowing sexual selection to operate only on alleles that encode parasite resistance). Although the answers to these questions will be interesting, they should not affect our main conclusions that OA and CD mate choice can both spread when rare in random mating populations, and that OA choice can increase the range of conditions under which sex is stable to invasion by parthenogenetic mutants.

Acknowledgments

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