

# The Ratchet and the Red Queen: the maintenance of sex in parasites

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## Keywords:

mutation accumulation;  
parthenogenesis;  
Red Queen hypothesis;  
sexual reproduction.

## Abstract

The adaptive significance of sexual reproduction remains as an unsolved problem in evolutionary biology. One promising hypothesis is that frequency-dependent selection by parasites selects for sexual reproduction in hosts, but it is unclear whether such selection on hosts would feed back to select for sexual reproduction in parasites. Here we used individual-based computer simulations to explore this possibility. Specifically, we tracked the dynamics of asexual parasites following their introduction into sexual parasite populations for different combinations of parasite virulence and transmission. Our results suggest that coevolutionary interactions with hosts would generally lead to a stable coexistence between sexual parasites and a single parasite clone. However, if multiple mutations to asexual reproduction were allowed, we found that the interaction led to the accumulation of clonal diversity in the asexual parasite population, which led to the eventual extinction of the sexual parasites. Thus, coevolution with sexual hosts may not be generally sufficient to select for sex in parasites. We then allowed for the stochastic accumulation of mutations in the finite parasite populations (Muller's Ratchet). We found that, for higher levels of parasite virulence and transmission, the population bottlenecks resulting from host-parasite coevolution led to the rapid accumulation of mutations in the clonal parasites and their elimination from the population. This result may explain the observation that sexual reproduction is more common in parasitic animals than in their free-living relatives.

## Introduction

The evolutionary stability of sexual reproduction requires advantages sufficient to overcome the substantial costs of cross-fertilization (Williams, 1975; Maynard Smith, 1978; Bell, 1982; Lively & Lloyd, 1990). Such advantages have been sought primarily among those known to be associated with the production of variable offspring (but see Bernstein *et al.*, 1985). Of those considered, two advantages appear to remain as viable alternatives after three decades of empirical and theoretical research: mutation clearance and partial escape from coevolving parasites (West *et al.*, 1999).

Theories regarding mutation clearance fall into two general categories: stochastic and deterministic. Under the deterministic model, asexual populations have a lower mean fitness at mutation-selection balance than sexual populations (Kimura & Maruyama, 1966; Crow, 1970). The difference can be enough to maintain sex if there are strongly synergistic effects among deleterious mutations and the rate of mutation is greater than 1–2 per genome per generation (Kondrashov, 1982, 1988; Charlesworth, 1990; Howard, 1994). Recent studies have suggested that neither of these two conditions are generally met (Willis, 1993; De Visser *et al.*, 1997; Elena & Lenski, 1997; Keightley & Eyre-Walker, 2000; Peters & Keightley, 2000). More recent theory has suggested that synergistic effects among mutations are not required to give a deterministic advantage to sex, because sexual populations are more efficient at clearing partially recessive deleterious mutations (Chasnov, 2000; Agrawal &

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Chasnov, 2001); but this mechanism also depends on genomic mutation rates greater than unity for the evolutionary stability of sex. Present data suggest that mutation rates increase monotonically with generation time, with organisms having generation times of less than 1 year also having genomic mutation rates of less than unity (Keightley & Eyre-Walker, 2000). Taken together, these studies seem to suggest that a deterministic advantage resulting from mutation clearance alone is unlikely to fully account for the maintenance of sex.

Alternatively, under the stochastic model, mutations accumulate in finite asexual populations by chance (Muller, 1964). Stochastic factors may operate to increase the mutational load of asexual lineages in one of two ways. One way is through the chance loss of all individuals bearing the fewest mutations in a monophyletic clonal lineage. Another way is through the production of offspring with one or more mutations by all members of this same class of individuals. These mechanisms may operate simultaneously in the same lineage, and barring back mutation lead to an inexorable decline in population mean fitness of clones. The idea, known as Muller's Ratchet (Felsenstein & Yokoyama, 1976; Haigh, 1978), has abundant empirical support (Leslie & Vrijenhoek, 1980; Bell, 1988; Chao, 1990; Rice, 1994; Moran, 1996), but the mechanism would seem to operate too slowly to prevent the fixation of clones prior to their elimination of coexisting sexual populations (Bulmer, 1994; Howard & Lively, 1994, 1998), and it does not seem to explain the ecological correlates of sex (Bell, 1982, 1988).

The parasite-escape theory, on the other hand, suggests that the advantage to sex is generated through the production of rare offspring genotypes, which are more likely to escape infection by coevolving parasites (Jaenike, 1978; Bremermann, 1980; Hamilton, 1980, 1982; Lloyd, 1980). This idea, now known as the Red Queen hypothesis (following Bell, 1982), has empirical support from the distribution of sexual populations in nature (Glesener & Tilman, 1978; Bell, 1982; Lively, 1987, 1992; Schrag *et al.*, 1994) and from direct experimental evidence showing rare advantage in natural populations (Schmitt & Antonovics, 1986; Kelley *et al.*, 1988; Dybdahl & Lively, 1998; Lively & Dybdahl, 2000). Additional support for the basic idea comes from agricultural studies (Suneson, 1960; Barrett, 1981; Zhu *et al.*, 2000). The theory, nonetheless, has theoretical difficulties in that rare advantage, by itself, can lead to the accumulation of clonal diversity, which eventually leads to the elimination of sexual populations by a diverse assemblage of clones (Lively & Howard, 1994). Elsewhere, we have shown, however, that antagonistic coevolution combined with mutation accumulation can easily lead to the evolutionary stability of sexual host populations (Howard & Lively, 1994, 1998). Moreover, Hamilton *et al.* (1990) have shown that host-parasite coevolution combined with rank-order truncation selec-

tion against the most infected individuals can also lead to the evolutionary stability of sex.

Much of the work to date on the Red Queen theory of sex has focused on host reproductive strategies. In the present study, we turn our attention to the problem of maintaining sex in parasite populations. Previous theoretical studies have postulated an advantage to sex in parasites arising from (i) interactions with other parasites (Hamilton *et al.*, 1990) or through (ii) interactions with the vertebrate immune system (Lythgoe, 2000). Here, we consider a third possibility: that an advantage to sex in parasites may result from direct interactions with hosts. The work follows our earlier formulations of sex in host populations, where we examined the combined effects of antagonistic coevolution and mutation accumulation. This approach is attractive because it allows us to determine the independent effects of the two processes as well as any interactions between them. Results from the present study suggest that, acting in isolation, antagonistic interactions with hosts are not sufficient to maintain sex in parasites, but that such interactions in combination with stochastic mutation accumulation can easily lead to the evolutionary stability of sex. As such, the results may explain the observation that sexual reproduction is more common in long-lived parasitic species than in their free-living relatives (Bell, 1982).

## Methods

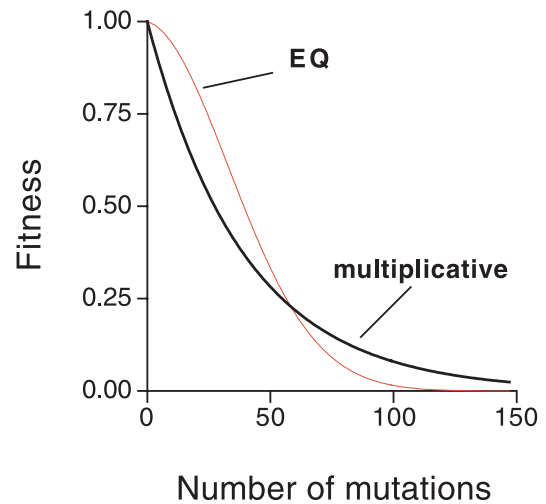
We used individual-based computer simulation to track the dynamics of rare parasite clones when introduced into sexual parasite populations. Parasites were either sexual hermaphrodites or asexual, and underwent two generations for each host generation; hosts were obligately sexual hermaphrodites. The life cycles of both hosts and parasites were modelled as discrete with nonoverlapping generations. The antagonistic interaction between parasites and hosts was mediated by matching alleles at either 2 or 3 diallelic loci (interaction loci). Only parasites that matched hosts exactly at all loci were able to establish infections. In addition to the interaction loci, parasites possessed 500 loci at which deleterious mutations could accumulate. In contrast to asexual parasites, which underwent no genetic recombination, sexual individuals (hosts and parasites) underwent free recombination across all loci in the genome.

At the beginning of each run, the interaction loci in the host and parasite populations were initialized so that the frequencies of alternative alleles (0 and 1) at each locus was 0.5. Loci encoding for deleterious mutations were initialized with the equilibrium mean and variance for mutation number for a given combination of mutation rate ( $U$ ) and fitness function (following Kimura & Maruyama, 1966; Charlesworth, 1990). Following initialization, the host and parasite populations were allowed to coevolve for 40 parasite generations, at which time a single haploid asexual parasite was introduced.

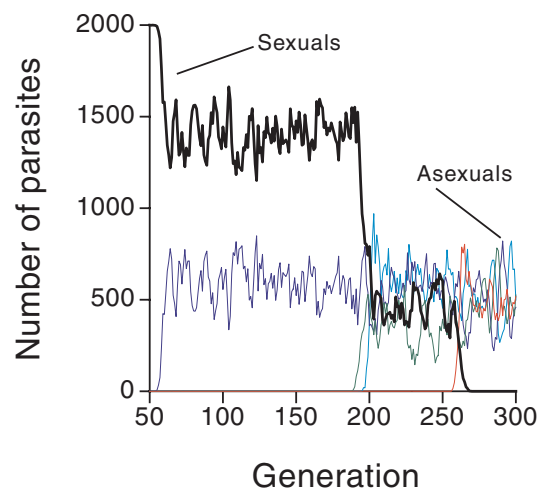
The founders of such lineages were initialized with  $i = \bar{n} - 2\sqrt{\bar{n}}$  mutations, where  $\bar{n}$  is the equilibrium mean number of mutations in a sexual population for a given combination of mutation rate ( $U$ ) and fitness function (Charlesworth, 1990). Under the assumptions that asexuals are derived from sexual parents, and that the mean equals the variance for mutation number in a freely recombining sexual population,  $i$  gives the minimum probable number of mutations expected in the founders of asexual lineages (Charlesworth, 1990). Finally, to maintain genetic variation in the sexual parasite population, the mutation rate between alleles at the interaction loci was set at 0.03 per generation. This simulates the movement of parasites between structured demes, and prevents the fixation of interaction alleles in situations where high risks of parasite exposure are coupled with high virulence.

During each parasite generation, hosts were drawn sequentially and exposed to a number of randomly selected parasites with the Poisson distributed mean of  $T$ . If a parasite matched a host exactly at all loci, the host was marked as infected and the parasite was placed in an array of reproductives. Once marked as infected, individual hosts were protected against infection by additional parasites. The effects of multiple infections will be considered in a future study.

Reproduction in both hosts and parasites was accomplished by drawing individuals from their respective populations at random with replacement. In the case of parasites (sexual and asexual), individuals emerged from hosts to mate during a simulated 'free-living' stage of the life cycle. Parasites were identified as either sexual or asexual according to their configuration at a single locus (0 sexual, 1 asexual). When a sexual individual (host or parasite) was drawn for reproduction, a second sexual individual was randomly selected for cross-fertilization. The genomes of the two haploid 'parents' were then brought together in a diploid zygote stage, where free recombination between all loci made possible the production of a genetically diverse brood of haploid progeny. All else equal, sexual individuals (hosts and parasites) gave rise to a lifetime average of 10 haploid offspring. Asexual parasites, on the other hand, gave rise to a lifetime average of 20 haploid progeny through uniparental reproduction and thus gained the full two-fold numerical advantage in offspring production (Maynard Smith, 1978). In the presence of mutation accumulation ( $U > 0$ ), reproduction in parasites was reduced according to the relationship between mutation number and offspring viability under multiplicative and exponential-quadratic fitness functions (Fig. 1). In the case of hosts, the number of offspring produced by each parent was reduced according to the status of parasitic infection. Here, the lifetime reproductive output of each parent was computed as  $10(1 - E)$ , where  $E$  is the effect of parasitism on host reproduction (virulence). Following reproduction, a maximum of 2000 parasite and 2000 host



**Fig. 1** Fitness as a function of number of mutations ( $n$ ) under the multiplicative [ $w(n) = (1 - s)^n$ , for  $s = 0.025$ ] and exponential-quadratic [ $w(n) = \exp[-(an + bn^2)]$ , for  $a = 0.002$ ,  $b = 0.0008$ ] models.



**Fig. 2** Elimination of a sexual population (black line) by a genetically diverse population of parasite clones (colored lines). The result was obtained in the 2-locus model in which the rate to deleterious mutation ( $U$ ) was set to zero. Parasite clones were spun off sporadically from individuals drawn at random from the sexual population; the probability that a sexual individual would produce a clonal offspring was set at 0.000001 per individual per generation. Each clone was derived from one of the four possible genotypes present in the parent sexual population. Parameters for this run included a parasite exposure level of  $T = 2.0$  and virulence of  $E = 0.8$ . Note that the sexual population went extinct within about 10 generations following the spread of the fourth clonal genotype in the population.

offspring were randomly selected to become the next generation of adults.

During each run of the simulations, the computer tracked the dynamics of the interacting populations for a

maximum of 300 parasite generations. We conducted 10 replicate runs of the simulation for each of the 60 possible combinations of virulence and risk of parasite exposure to hosts. We terminated runs for which asexual mutants failed to establish in six generations, and the results were omitted from the final tally. Results of runs in which clones coexisted with sexual populations for 300 generations were scored in favour of asexual, as coexistence leads to the accumulation of a genetically diverse group of clones, which eventually leads to the elimination of sexual individuals in the population (Fig. 2).

In some additional runs of the simulations, we tested the potential for multiple clonal genotypes to invade sexual populations when both parasitism and mutation accumulation were involved. This is an important question, as the long-term stability of sex in natural populations requires that clones be eliminated at least as fast as they are generated through spontaneous mutation. For these runs, sexual parents gave rise to an occasional asexual offspring with probability 0.000001 per generation. The transition from sexual to asexual type was accomplished by changing the value of a single locus that encoded for reproductive mode. Asexual 'mutants' derived in this fashion enjoyed the full two-fold advantage of uniparental reproduction. All other features of the sexual ancestor, including the genetic configuration at the mutation and interaction loci, were transmitted unchanged to the asexual 'mutant'.

## Results

### Without mutation accumulation

For the 2-locus model, we found that, in the absence of mutation accumulation ( $U = 0$ ), asexual parasites either coexisted with or displaced sexual parasites in a majority of runs over the entire parameter space (Fig. 3a). For all levels of parasite virulence, parasite exposure levels of  $T$  (the average number of parasites contacted by individual hosts during a generation) of 1.0 or greater gave rise to coevolutionary dynamics that generally favoured coexistence of sexual and asexual individuals (e.g. Figs 4 and 5). Parasite exposure values of 0.5 coupled with virulence levels of 0.5 or greater also tended to promote coexistence (Fig. 6b), but lower virulence levels ( $E < 0.5$ ) increased the likelihood of clones winning outright (Fig. 6a).

The results obtained from the 3-locus model were qualitatively similar to those for the 2-locus model, with asexual winning over most of the parameter space (Fig. 3b). As before, parasite exposure values of 1.0 or greater promoted coevolutionary dynamics that favoured long-term coexistence (Fig. 5). One rather surprising difference was that sex was favoured when low exposure values ( $T = 0.5$ ) were coupled with moderate-to-high levels of virulence (Fig. 3b). One possible explanation for

this difference from the 2-locus model is as follows. Increasing the number of interaction loci in the model from two to three results in more host genotypes distributed at lower average frequencies. A major consequence of this increase in genotypes is that low exposure values can preclude successful infection once a parasite clone has driven its corresponding host genotype to very low frequencies. A comparison of 2- and 3-locus runs under these conditions illustrates the effect (Fig. 6b,d). This result suggests that, in general, increasing the number of genotypes involved in the interaction may be generally favourable to sexual parasites, at least when exposure values are low.

### With mutation accumulation

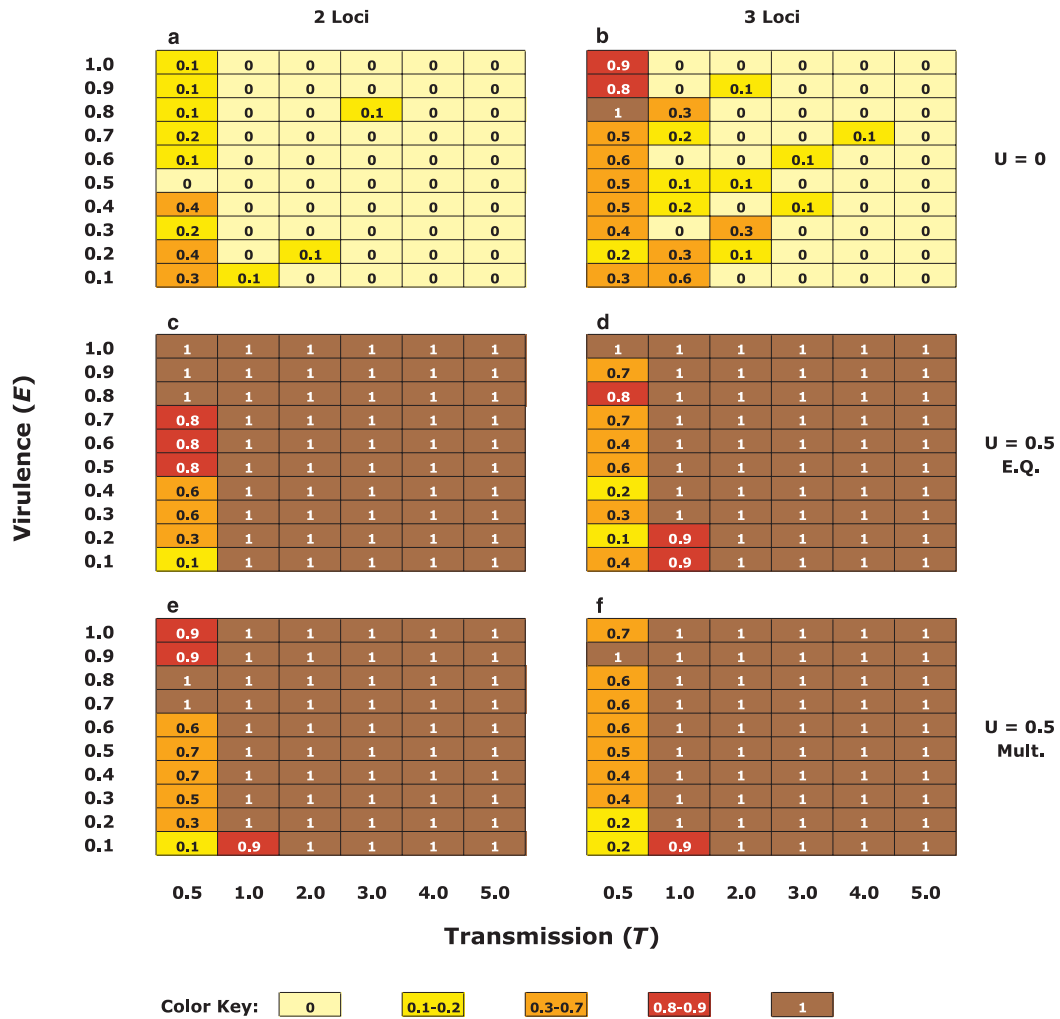
Adding mutation accumulation to the model resulted in dramatic increases in the range for which sex was evolutionarily stable (Fig. 3c-f). For both the 2-locus and 3-locus models, sexual parasites were always resistant to invasion by clonal parasites when exposure levels ( $T$ ) were 2.0 or greater. The result held for both the exponential quadratic and the multiplicative fitness functions (Fig. 3) for all levels of parasite virulence ( $E$ ). Reducing the level of exposure to 1.0 resulted in 100% protection for sex when parasite virulence was greater than 0.1.

Asexual reproduction was generally favoured for very low exposure values ( $T = 0.5$ ), coupled with moderate-to-low levels of virulence. Under these conditions, clones had a high probability of fixing before the mutation load reached the point where it offset the two-fold advantage of asexual reproduction.

## Discussion

Although much recent attention has been focused on the maintenance of sex by parasitism in host populations (Hamilton *et al.*, 1990; Howard & Lively, 1994, 1998), few studies have investigated the factors responsible for maintaining sex in parasites themselves (Lythgoe, 2000). This would seem an important problem, as most parasites retain sex at some stage in their life cycles (Hamilton *et al.*, 1990). Part of the explanation may result from the fact that almost all parasites serve as hosts to other parasites, in which case an advantage to sex is derived as in the traditional sense of the Red Queen hypothesis (Hamilton *et al.*, 1990). Another possibility is that sex could be advantageous in situations where parasites are confronted with acquired immunity in host populations (Lythgoe, 2000). In the present study, we used individual-based computer simulations to test a third possibility: sex in parasites is maintained as a direct result of antagonistic interactions with hosts.

Our results suggest that, acting in isolation, coevolutionary interactions with hosts are unlikely to fully

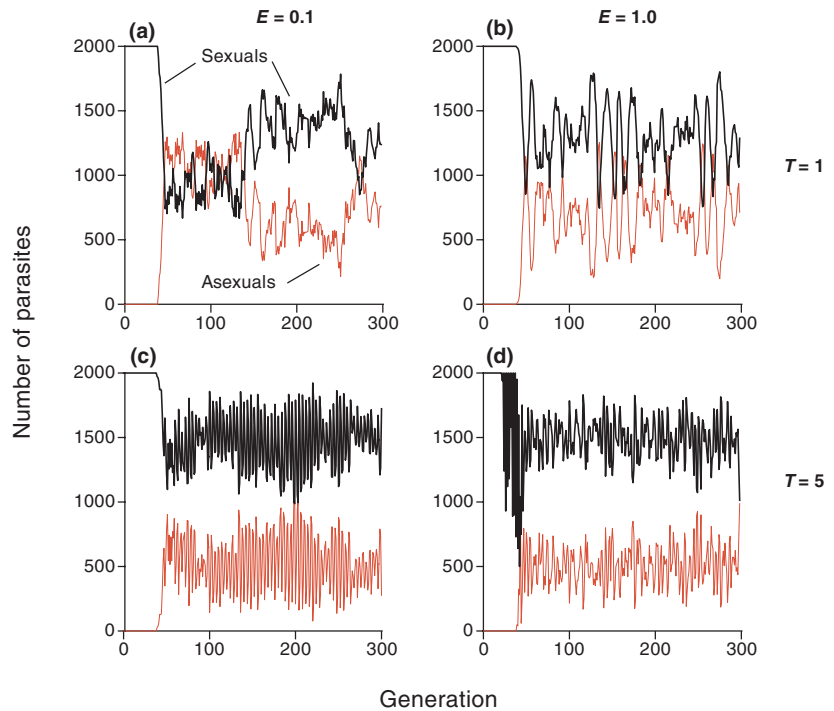


**Fig. 3** Outcome of competition between sexual and asexual parasite populations for multiple runs of the simulation model. Results reported in each of the six grids were obtained by running the simulation for 60 different combinations of parasite virulence ( $E$ ) and values of exposure to hosts ( $T$ ). Each data point represents the proportion of wins by a sexual population for 10 replicate runs of the simulation. Only runs in which asexual populations were completely eliminated were counted in favour of sex. The interaction between antagonistic coevolution and mutation accumulation was examined for the 2- and 3-locus versions of the model. Results from runs in which the rate to deleterious mutation ( $U$ ) was set to zero are reported in (a) 2-locus and (b) 3-locus. The case of exponential-quadratic selection for  $U = 0.5$  is reported in (c) 2-locus and (d) 3-locus. Finally, results from runs under multiplicative selection for  $U = 0.5$  are given in (e) 2-locus and (f) 3-locus.

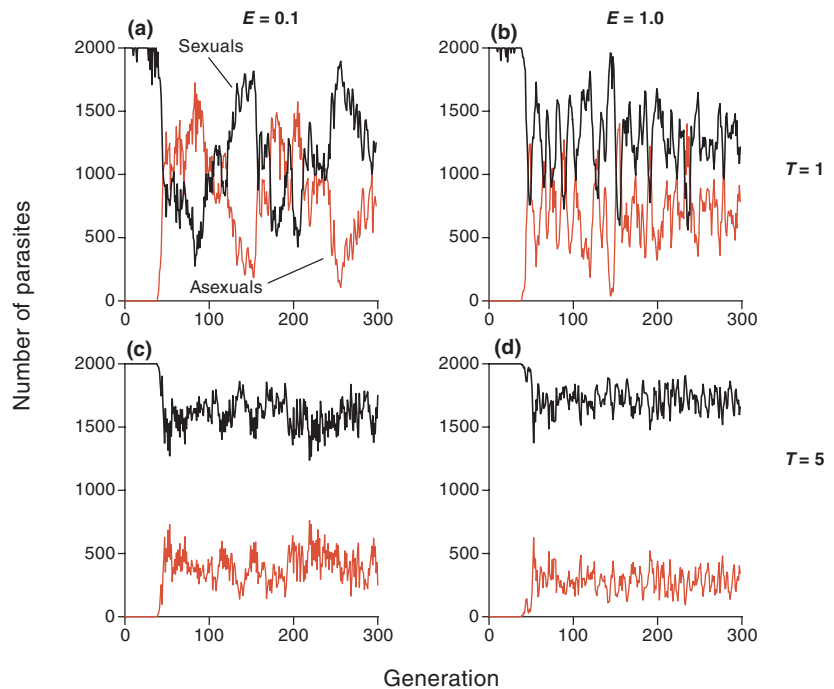
account for sex in parasites. In our simulations, asexual lineages with a two-fold advantage in reproduction were able to displace or coexist with sexual populations over a wide range of parameter space (Fig. 3). The pattern held for virtually all combinations of virulence and values of parasite exposure, and was similar for both the 2- and 3-locus models. For exposure values of 1.0 or greater, the majority of runs in both models resulted in long-term coexistence between sexual and asexual lines. Previous studies of the maintenance of sex in host populations have shown that long-term coexistence of sexuals and asexuals eventually leads to the accumulation of clonal

diversity and extinction of the sexual population (Lively & Howard, 1994), and our present results suggest that this is also true for parasites (Fig. 2). Hence for parasite exposure values of 1.0 and greater, the persistence of sexual reproduction would seem to depend on some additional mechanism to eliminate clones.

For exposure values lower than 1.0, frequency-dependent selection is weak and the resulting coevolutionary dynamics are too diffuse to reliably promote coexistence. Under these conditions, clones displaced sexual populations outright in the majority of runs. Interestingly, the frequency of sex increased as a function



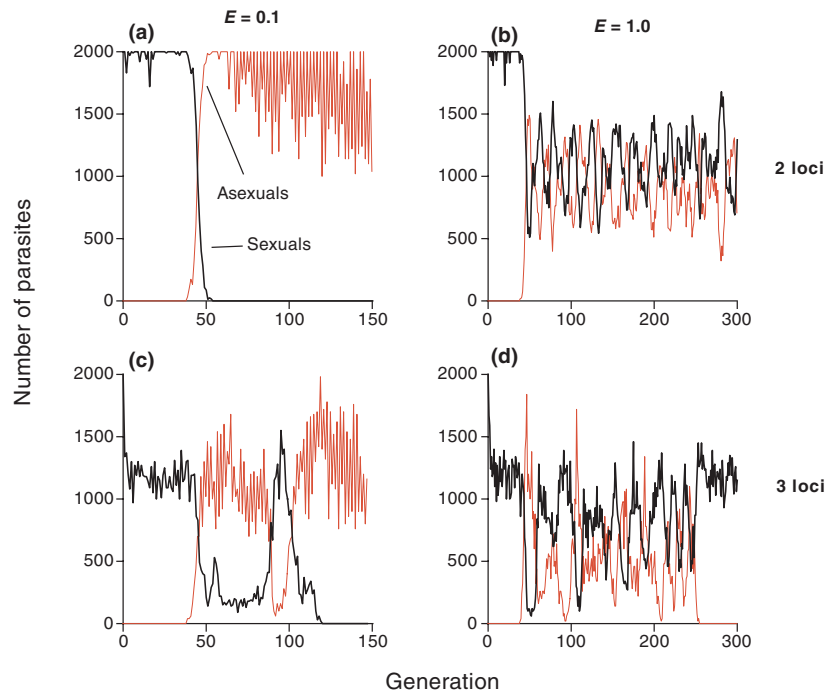
**Fig. 4** Population dynamics for sexual (black line) and asexual (colored line) populations obtained from the 2-locus model without mutation. (a) Low virulence ( $E = 0.1$ ) coupled with moderate exposure ( $T = 1.0$ ); (b) high virulence ( $E = 1.0$ ) coupled with moderate exposure; (c) high exposure ( $T = 5.0$ ) coupled with low virulence; and (d) high exposure ( $T = 5.0$ ) coupled with high virulence ( $E = 1.0$ ).



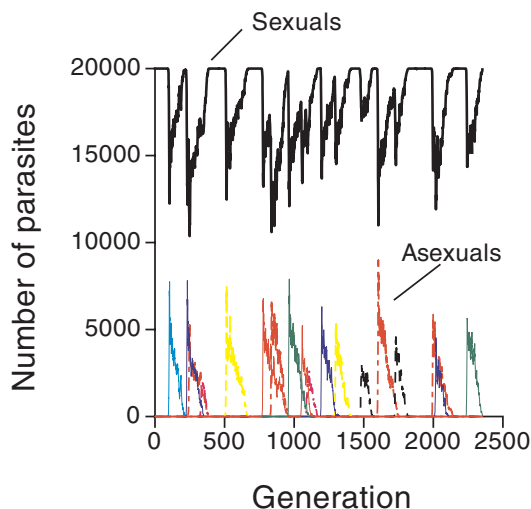
**Fig. 5** Population dynamics for sexual (black line) and asexual (colored line) populations obtained from the 3-locus model without mutation. (a) Low virulence ( $E = 0.1$ ) coupled with moderate exposure ( $T = 1.0$ ); (b) high virulence ( $E = 1.0$ ) coupled with moderate exposure; (c) high exposure ( $T = 5.0$ ) coupled with low virulence; and (d) high exposure ( $T = 5.0$ ) coupled with high virulence ( $E = 1.0$ ).

of virulence in the 3-locus runs (Fig. 3). The most plausible explanation is that extremely low values of parasite exposure can result in the stochastic extinction of clonal lineages if the compatible host genotype is

driven to very low frequencies. This effect should become more important as the number of interaction loci increases, because individual host genotypes become correspondingly rare.



**Fig. 6** Population dynamics obtained for low values of parasite exposure ( $T = 0.5$ ) and no mutation ( $U = 0$ ). (a) Two-locus model under low parasite virulence ( $E = 0.1$ ); (b) 2-locus model under high parasite virulence ( $E = 1.0$ ); (c) 3-locus model under low parasite virulence ( $E = 0.1$ ); and (d) 3-locus model under high parasite virulence ( $E = 1.0$ ).



**Fig. 7** Evolutionary stability of a sexual parasite population (black line) given repeated mutation to parthenogenesis in the 3-locus model. Sexual parasites gave rise to a single clonal lineage (colored lines) with a probability of 0.000001 per individual per generation. Each of the different peaks in the asexual population show a different origin of asexual reproduction, followed by mutational meltdown. Parameters for this run included a deleterious mutation rate ( $U$ ) of 0.5 under exponential-quadratic selection, a parasite exposure rate ( $T$ ) of 2.0, and parasite virulence of  $E = 0.8$ . Population size was set at 20 000.

The incorporation of mutation accumulation into the models generated a decisive advantage to sex for exposure values of 1.0 or greater. This result held for both the

2- and 3-locus models under multiplicative and exponential-quadratic selection. The advantage resulted from a combination of frequency-dependent selection and the accumulation of mutations through Muller's Ratchet. Frequency-dependent selection promoted coexistence (Figs 4 and 5) and kept asexual lineages from displacing sex in the short term, and mutation accumulation resulted in the eventual elimination of the clones.

Reducing the rate of parasite exposure to 0.5 reduced selection for sex in both the 2- and 3-locus models for both exponential-quadratic and multiplicative fitness functions (Fig. 3). The stability of sex increases as a function of parasite virulence, as frequency-dependent selection is strong enough to promote temporary coexistence (Fig. 6b,d), and mutation accumulation eventually results in the meltdown of asexual lineages. Low exposure values coupled with low virulence tend to dampen the coevolutionary dynamic (Fig. 6a,c), however, and clones are occasionally able to invade before the effects of mutation eliminate their two-fold advantage in reproduction.

We also ran simulations to examine the evolutionary stability of sexual populations subjected to repeated invasion by clones. Results from one such run show that the combination of antagonistic coevolution and mutation accumulation can impart an advantage to sex in populations as large as 20 000 individuals (Fig. 7). Sex may also gain an advantage in situations where deleterious mutation rates are lower than 0.5, provided antagonistic interactions hold clones at bay until the Ratchet takes them out. The long-term stability of sex under such conditions will require that clones be eliminated more

rapidly than they are generated from the parent sexual population.

Finally, we would like to point out that our assumption of free recombination between all loci in the sexual population prevents linkage between beneficial and deleterious mutations. In theory, such linkage could diminish the advantage to sex (Peck, 1994), but the extent to which this might happen in natural population is unknown.

In conclusion, our results show that host–parasite coevolution in combination with mutation accumulation through Muller's Ratchet can lead to the evolutionary stability of sexual reproduction in parasites. The results also hint that mutation accumulation may become less important as the number of loci increases, especially if exposure values are low, because the combination of these parameters increases the risk of clonal extinction.

## Acknowledgments

We thank James Dees and Andrew Heinsohn for helpful discussion, and Stu West, Phil Mathis and Jukka Jokela for comments on earlier versions of this paper. This work was supported by grants from the MTSU College of Graduate Studies and Office of Sponsored Programs to RSH, and by a US National Science Foundation grant to CML (DEB 9904840).

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*Received 12 December 2001; revised 20 January 2002; accepted 21 February 2002*