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Selection by Parasites for Clonal Diversity and Mixed Mating [and Discussion]

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Selection by parasites for clonal diversity and mixed mating

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SUMMARY

On theoretical grounds, coevolutionary interactions with parasites can select for cross-fertilization, even when there is a twofold advantage gained by reproducing through uniparental means. The suspected advantage of cross-fertilization stems from the production of genetically rare offspring, which are expected to be more likely to escape infection by coevolving enemies. In the present study, we consider the effects that parasites have on parthenogenetic mutants in obligately sexual, dioecious populations. Computer simulations show that repeated mutation to parthenogenesis can lead to the accumulation of clones with different resistance genotypes, and that a moderately diverse set of clones could competitively exclude the ancestral sexual subpopulation. The simulations also show that, when there are reasonable rates of deleterious mutation, Muller's ratchet combined with coevolutionary interactions with parasites can lead to the evolutionary stability of cross-fertilization. In addition, we consider the effects that parasites can have on the evolution of uniparental reproduction in cosexual populations. Strategy models show that parasites and inbreeding depression could interact to select for evolutionarily stable reproductive strategies that involve mixtures of selfed and outcrossed progeny.

1. INTRODUCTION

Consider two obligately asexual clones, A and B, which are alike in all ways, except that clone A produces twice the number of daughters. If these two clones were to be placed in direct competition, clone A would eliminate clone B in very few generations. Now consider a similar competition between clone A and a sexual group. Both groups produce the same number of offspring, but only half of the offspring produced by the sexual individuals are daughters. Hence the production of daughters by the sexual group is the same as that for clone B above, and clone A is again expected to win. Why then is there sex (Maynard Smith 1971)? Any sexual population that generates a rare asexual mutant should be rapidly replaced by the descendants of that mutant, unless the clone actually produces fewer daughters.

The reasoning makes sense, but the predominance of sexual reproduction in eukaryotes suggests that there is more to the outcome than simple daughter production. The 'alike-in-all-ways' assumption made above is apparently false. One way in which the assumption is false is that clonal populations cannot reduce their mutational load by concentrating mutations in a few low-fitness offspring (Muller 1964). Because of the probabilistic nature of mutation, Muller viewed an asexual population as a monophyletic series of subclones, each having a different number of deleterious mutations. He reasoned that, by chance alone, all the members of the subclone with the lightest mutational load could fail to reproduce. Alternatively, by chance, all the offspring from the members of the least loaded clone could acquire an additional mutation. Using this kind of reasoning, Muller foresaw an 'irreversible ratchet mechanism' leading to an ever-increasing number of deleterious mutations in clonal lineages, especially in small clonal populations (Muller 1964). Some striking examples for the operation of Muller's ratchet are given by Leslie & Vrijenhoek (1980), Chao (1990), Bell (1988) and Rice (1994).

Another way in which the 'alike-in-all-ways' assumption is false is that clonal populations lack the genetic variability of sexual populations, and they therefore lack the same potential to respond to selection (Weismann 1989). Here we are mainly concerned with the second alternative, that sexual populations have an advantage that depends on their ability to produce variable progeny. Specifically, we are concerned with the recent idea that the production of variable progeny is advantageous as a defence against parasites (Levin 1975; Jaenike 1978; Glesener & Tilman 1978; Hamilton 1980, 1982; Bremermann 1980; Lloyd 1980). In its simplest form, the idea is very straightforward. Any clone will have an advantage when rare, because of its enhanced

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daughter production. However, as that clone becomes common, there is an increasing selection on its parasites to be able to infect it. This kind of frequency-dependent selection against the clone (and common genotypes in general) could prevent the clone from replacing its sexual ancestor.

The idea, now known as the Red Queen hypothesis (after Bell 1982), has appeal for two reasons. One is that parasites seem ubiquitous; there are even parasites of parasites. The other reason is that the ecological correlates of biparental reproduction are consistent with the Red Queen hypothesis. Sexual species tend to inhabit undisturbed, biologically complex habitats where parasitism is expected to be common (Levin 1975; Glesener & Tilman 1978; Bell 1982). In addition, recent studies have shown that cross-fertilization predominates within populations of the same species where parasites are common, and that uniparental modes of reproduction predominate in populations where parasites are rare (Lively 1987, 1992; Schrag *et al.* 1994*a*). Explaining the ecological distribution of cross-fertilization is a necessary requirement for any general theory of sex.

The most critical assumption of the parasite (or Red Queen) theory of sex is that there is increasing selection against host genotypes as they become common, independent of whether they are sexually or asexually produced. This selection imposed by parasites sets up the expected time-lagged oscillations in host and parasite gene frequencies from which the Red Queen hypothesis gets its name (Hutson & Law 1981; Bell 1982; Bell & Maynard Smith 1987; Nee 1989). In what follows, we present the results of computer simulations of host–parasite coevolution which suggest that time-lagged frequency-dependent selection may select for clonal diversity, and that sexual reproduction can be replaced by a moderately diverse set of clones. We also present strategy models for the evolution of selfing in cosexual populations. The results of these models suggest that parasites can select for mixtures of selfed and outcrossed progeny within a single brood.

2. PARASITES AND CLONAL DIVERSITY

Consider the spread of an initially rare apomictic clone in a dioecious sexual population. As indicated above, the clone should spread when rare, owing to its enhanced daughter production. Then, as the clone becomes common, it is expected to be 'tracked' by parasites, and driven down in frequency if the effects of parasites on host fitness are sufficiently severe. However, unless the clone is driven extinct, it should recover its original rare advantage and begin increasing again. Under these conditions, the outcome of repeated mutation to clonal reproduction could lead to the accumulation of clonal diversity, which would diminish the advantage of cross-fertilization. If, however, clones accumulate deleterious mutations, then the twofold advantage of parthenogenetic reproduction will be eroded during the initial spread of the clonal mutant, and each time the clone is driven down in frequency by the parasite (Howard & Lively 1994). Here we evaluate the effects of parasites on accumulation of clonal diversity under two conditions: (i) without recurrent deleterious mutations; and (ii) with an average of one deleterious mutation per genome per generation.

(*a*) *Methods*

To address this question, we employed an individual-based computer simulation of host–parasite interactions. Hosts and parasites were treated as haploid individuals whose interactions were mediated by two unlinked diallelic loci. All hosts contained an additional 500 unlinked loci at which harmful mutations could accumulate with a probability of $U/500$ per generation, where U is the Poisson-distributed mean mutation rate per genome per generation. The host population ($N = 1000$) also received a sexual migrant on average once every two generations. These migrants were randomly assigned one of the four possible parasite-compatibility genotypes, and were initialized with a Poisson-distributed mean of U/s deleterious mutations, where s is the selection against deleterious mutations (Maynard Smith 1978).

Parasites were obligately sexual and reproduced twice for each bout of host reproduction. To maintain genetic variation in the parasite population, alleles at the interaction loci mutated to the alternative state with a mean probability of 0.03. At the beginning of each parasite generation, individual hosts were drawn sequentially from an array and matched against a randomly drawn parasite with probability (T). A parasite was successful at infecting a host if, and only if, an exact genetic match occurred at both interaction loci. Parasites that were successful at infecting hosts were placed in an array, and allowed to participate in a reproductive lottery at the end of each parasite generation; unsuccessful parasites died. Hosts were marked as either parasitized or unparasitized and returned to the source array; each host could be infected by a maximum of one parasite.

At the end of each host generation, individuals were selected randomly for reproduction. If the chosen host individual was sexual, a second host was selected at random to serve as a mate. Sexual pairs mated and gave rise to haploid embryos through a process analogous to zygotic meiosis; asexual females reproduced mitotically. The number of offspring produced by hosts was discounted according to the effects of parasitism (E) and selection against deleterious recurrent mutations. Viability of offspring in the presence of deleterious mutations was calculated as $(1 - s)^k$, where s is the selection coefficient and k is the number of mutations (after Maynard Smith 1978); here we set $s = 0.025$. Host reproduction was allowed to continue until the total number of broods produced equalled the number of adults in the population. Surviving embryos were then selected at random without replacement to become the next generation of adults. To simulate repeated mutation to parthenogenesis, a clonal mutant with a twofold reproductive advantage was randomly selected from the sexual

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population on average once every 60 host generations. Clones derived in this fashion were identical to their sexual parent with respect to the genetic configuration at their parasite interaction loci and the number of harmful mutations in their genomes. (Copies of the computer code are available on request.)

We conducted the initial runs of the model in a large region of parameter space in which we previously observed coexistence between a sexual population and a single clonal mutant (Howard & Lively 1994). Specifically, we initialized the parameters at $T = 0.90$ (90% risk of contact with a randomly drawn parasite), $E = 0.70$ (70% reduction in the fitness of infected hosts), and $U = 0$ (i.e. no deleterious mutation). The purpose here was to determine the number of clones needed to displace the sexual population in the absence of deleterious mutation. We then added deleterious mutations to the model at the rate of one per genome per generation. This rate of mutation has empirical support from studies on *Drosophila* (Mukai *et al.* 1972; Houle *et al.* 1992). Finally, we added a third diallelic locus to the model for both the host and the parasite.

(*b*) *Results*

In the absence of deleterious mutation ($U = 0$), a sexual population with four different resistance genotypes (two diallelic loci) was eliminated soon after invasion by only the second clonal host genotype. The mean time to elimination of sex was 27 generations ($N = 200$) after entry into the population by the second clone. A representative run is given in figure 1*a*. In this run, a randomly sampled clone was 'spun off' at generation zero, and it quickly began to oscillate with the sexual population. Then at generation 19, a second clone was randomly sampled from the sexual population, and it increased rapidly. By generation 80, the sexual population had been driven extinct, and the two clones continued in a stable oscillation with each other. The same basic result was observed in the three-locus model. In 200 runs of the simulation, the sexual population was driven extinct an average of 36 generations after the second clone entered the populations (a representative run is given in figure 1*b*). Hence, it seems that parasites by themselves are insufficient to provide protection for sex in the face of repeated mutations to parthenogenetic reproduction. The results also suggest that the diversity of resistance genotypes in a clonal population need not equal the diversity of the sexual population in order for clones to drive sexual populations to extinction.

A different result was gained when individuals gained an average of one deleterious mutation per generation ($U = 1$). In both the two-locus and the three-locus models, the sexual population persisted until the run was terminated at 5000 generations, even though a randomly sampled clonal mutant entered the sexual population every 60 generations, on average. Particularly interesting parts of these runs are presented in figure 2, which shows the successive invasion and extinction of clones having different

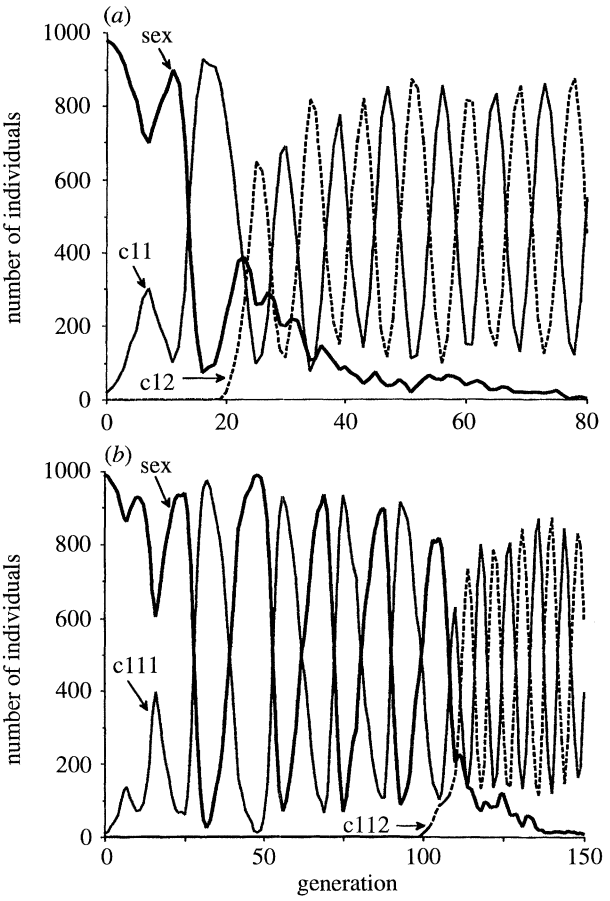

Figure 1. Selection for clonal diversity and the elimination of sex under parasitism in the absence of mutation accumulation. The heavy line represents the population trajectory of a freely recombining sexual population in competition with one, and then two, asexual genotypes. In (*a*), the two-locus model, each asexual lineage was initialized with one of the four possible parasite-compatibility genotypes extant in the sexual population (labelled c11, c12, c21, c22); in (*b*), the three-locus model, each asexual lineage was initialized with one of eight possible parasite-compatibility genotypes extant in the sexual population (labelled c111, c112...c222). Parameters for these runs of the simulation included a probability of parasite transmission (T) = 0.9 and an effect of parasites on host fitness (E) = 0.7 (i.e. an average of 70% reduction in host fecundity as a result of parasitism).

genotypes for parasite resistance. In all four cases, the clones oscillate several times before undergoing a mutational meltdown (in the sense of Lynch & Gabriel 1990). The meltdown is due to the accumulation of mutation through Muller's ratchet, which is aided by the parasite-driven oscillations in populations size of the clonal lineages (see Howard & Lively 1994).

We then reduced the effects of parasites from $E = 0.70$ to $E = 0.50$ and held all other parameters constant. The simulated sexual population again persisted until the run was terminated at 5000 generations in the two-locus model. Because of the reduced effect of infection, the clones persisted for a longer time; this persistence increased the likelihood that they would overlap in time. Figure 3*a* shows a part of the run in which three separate clones with different parasite-resistance genotypes coexisted for

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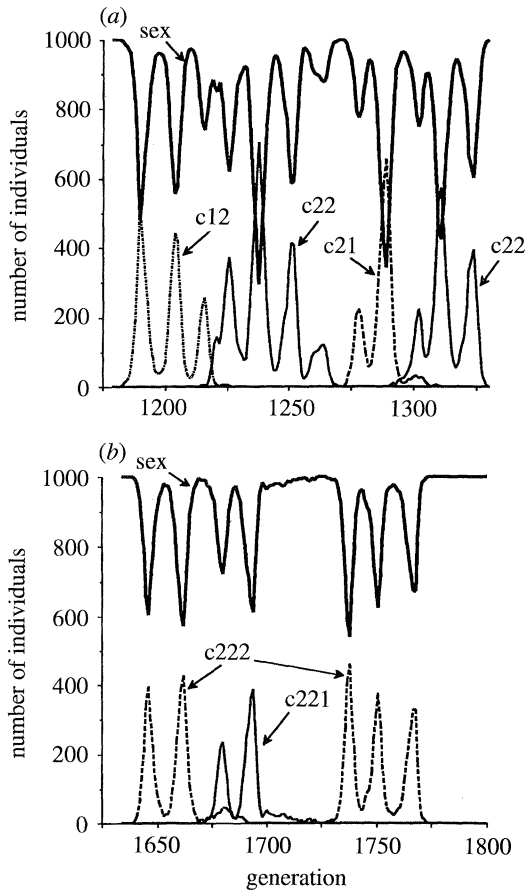

Figure 2. Elimination of asexual genotypes by the combined effects of parasitism and mutation accumulation. The heavy line labelled 'sex' represents the population trajectory of a freely recombining sexual population undergoing repeated mutation to parthenogenesis; asexuals were derived from the sexual population at an average rate of once every 60 generations. In (*a*), the two-locus model, the asexual lineages represented random samples of genetic variation in the sexual population with respect to both numbers of deleterious mutations and parasite compatibility genotypes (c11, c12, c21, c22). In (*b*), the three-locus model, the conditions were the same except that there were eight possible parasite compatibility genotypes (c111, c112 ... c222) that caused infection when they matched a similar eight possible host genotypes. Parameters for this run of the simulation included a per genome mutation rate (U) of 1.0, an effect of mutation (s) = 0.025, a probability of parasite transmission (T) = 0.9, and an effect of parasites on host fitness (E) = 0.7 (i.e. an average of 70% reduction in host fecundity as a result of parasitism).

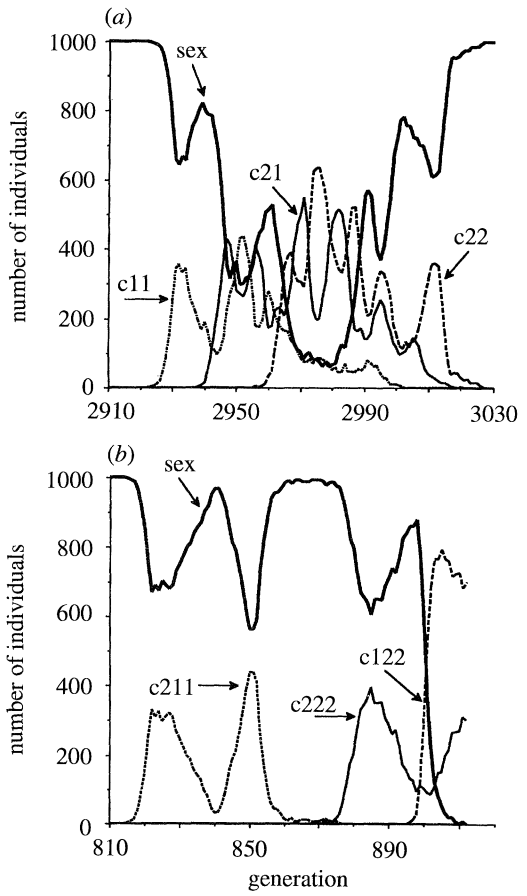

Figure 3. Competition between sexual and clonal populations facing the combined effects of parasitism and mutation accumulation. The parameter values are the same as in figure 2, except that the effects of parasites (E) = 0.5. (*a*) Two-locus model; (*b*) three-locus model, as described in figure 2. Note that the sexual population is driven extinct in the three-locus model.

over 40 generations. All three clones eventually went extinct, owing to the combined effects of parasites and mutation accumulation. However, in the three-locus model, the sexual population was eliminated by a pair of clones at generation 910.

Finally, we reduced the effects of parasites to $E = 0.40$. In this simulation, a pair of clones drove the sexual population extinct in less than 2400 generations in both models (figure 4). Hence, under the conditions of our simulations, moderately severe effects of parasites ($E > 0.50$) were required to protect the sexual population from replacement by multiple clones. The minimum effects of parasites needed to stabilize sexual populations, however, may be reduced in populations larger than simulated here ($N = 1000$). This may be expected because, in larger populations, clonal lineages will have more time to accumulate deleterious mutations, which in combination with parasites helps to erode their fecundity advantage before they replace the sexual population.

3. PARASITES AND MIXED MATING

Nested within the question 'why cross-fertilize?' is a more subtle question: why partial cross-fertilization? Many organisms that produce cross-fertilized progeny also produce uniparental progeny in some form. Sponges, for example, produce outcrossed progeny, but they also produce gemmules, which are vegetatively produced, physiologically independent offspring. Bryozoans similarly produce mixtures of uniparental and biparental offspring, as do many other invertebrates and plants (reviews in Bell 1982; Bierzychudek 1987). Of particular interest is self-fertilization, which is a uniparental sexual process. The question is: why mix it up? And what is the optimal mixture of uniparental and biparental offspring? In what follows, we present models of

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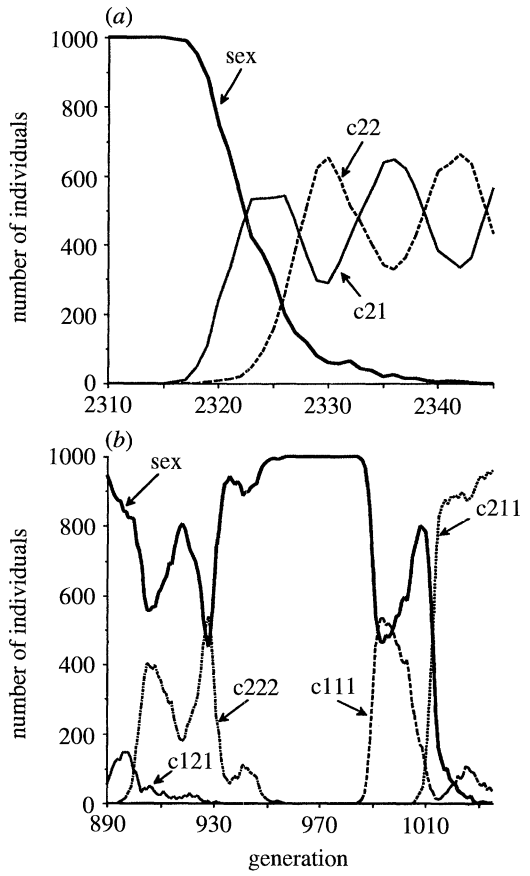

Figure 4. Selection for clonal diversity and the elimination of sex under parasitism in the presence of mutation accumulation. The parameter values are the same as in figures 2 and 3, except that the effects of parasites $(E) = 0.4$. (*a*) Two-locus model; (*b*) three-locus model, as described in figure 2. Note that the sexual population is driven extinct in both models. Compare with figure 1.

selection on mating systems when there are parasites and pathogens to contend with. The results suggest that mixed reproduction can be evolutionarily stable over a wide range of conditions, depending on how the risk of parasitism is associated with increasing levels of selfing in the population.

(*a*) *A strategy model*

Consider a simultaneous hermaphrodite in a large, randomly mating population. Assuming that reproduction through female function is resource limited, the expected fitness of this individual (W_i) can be approximated by summing up the fitness gains through male function (W_m), plus female function through outcrossing (W_f), plus female function through uniparental (parthenogenetic or self-fertilized) ova (W_p). Thus

$$W_i = W_m + W_f + W_p, \tag{1}$$

where:

$$W_m = a_i r_m V, \tag{2a}$$

$$W_f = (1 - a_i)(1 - p_i) r_f, \tag{2b}$$

$$W_p = (1 - a_i) p_i y. \tag{2c}$$

In this formulation, a_i is the individual's allocation to male function, and a is the population mean; p_i is the individual's allocation to uniparental ova, and p is the population mean; y is the fitness of uniparental ova, relative to fully outcrossed ova; r_f is the percentage of the genome passed onto amphimictic zygotes through female function, and r_m is the percentage of the genome passed onto amphimictic zygotes through male function $(r_f + r_m = 1)$. Finally, the reproductive value of male function, V, is equal to $(1 - a)(1 - p)/a$. This formulation for W_i assumes that the use of male gametes for the purpose of self-fertilization does not affect the total number of outcrossed progeny gained through male function (i.e. no 'pollen discounting' in the sense of Holsinger *et al.* 1984). It also assumes that all ova are fertilized, and that uniparental ova are not sequestered in cleistogamous flowers (see Lively & Lloyd 1990).

Consider the situation where the fitness of uniparental progeny, y, depends on three variables: (i) inbreeding depression (d), or, equivalently, the effects of developmental defects in parthenogenetic progeny; (ii) the effects of parasites (E); and (iii) the rate of parasite contact or transmission (T), as follows:

$$y = (1 - d)(1 - ET). \tag{3}$$

Here, we let the transmission rate, T, be a function of the average allocation to uniparental ova within the population (p). Specifically, we set the contact or transmission rate as

$$T = \left[\frac{(N - 1)p + p_i}{N}\right]^z, \tag{4}$$

where N is the number of individuals in the population. In effect, we assume that the probability of contact with parasites approaches unity as p and p_i approach one. The rationale for this assumption is that, as selfing or parthenogenesis increases in the population, genetic diversity decreases, thereby facilitating the spread of pathogens. The exponent (z) controls the shape of the transmission function, and is expected to depend on the type of uniparental progeny, the aggregation of siblings, the genetic basis for disease resistance, and the type of parasite or pathogen. The case $z > 1$ means an initially low but accumulating effect of increasing p on the probability of contact with parasites, whereas $z < 1$ means an initially high but decelerating effect (cf. 'peaky' and 'pitty' fitness profiles in Hamilton (1993)).

The effect of small changes in allocation to uniparental ova on individual fitness can be calculated by taking the first partial derivative of W_i with respect to p_i. At the evolutionarily stable strategy (ESS) (Maynard Smith 1982) or unbeatable strategy (Hamilton 1967), the population mean (p) is equal to the optimal allocation to uniparental progeny for the individual (p_i). Hence the derivative can be solved for $p_i = p$. Moreover, at the ESS, the derivative is equal to zero. Setting the derivative equal to zero and solving for the equilibrium value of $p(p^*)$ gives:

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$$p^* = \left[\frac{1 - d - r_f}{E(1-d)(1 + 1/N)}\right]^{1/z}. \quad (5)$$

Assuming that the number of individuals in the population (N) is large, and substituting one half for the relatedness to offspring through female function, r_f, into equation (5) gives:

$$p^* \approx \left[\frac{\frac{1}{2} - d}{E(1-d)}\right]^{1/z}. \quad (6)$$

The ESS is locally stable (i.e. the second partial derivative is less than one) when $2p(N+1)/p_i(x+1)$ is greater than one, which is whenever N is large.

(*b*) *Graphical results of the model*

A feel for the ESS given in equation (6) can be gained for the special case of selfing by examination of figure 5, where the equilibrium selfing rate (p^*) is plotted as a function of inbreeding depression (d) and the effects that parasites have on host fitness (E) for various exponents (z). For small exponents (e.g. $z = 0.1$), in which the transfer of infection increases very rapidly in mostly outcrossing population, there seems to be two alternative stable states, complete selfing and complete outcrossing, with a very sharp zone of transition between them (figure 5*a*). Complete selfing is favoured when inbreeding depression (d) and parasite effects (E) are both low (< 0.40). Complete outcrossing is favoured when the inbreeding depression is high (> 0.45) and when there are moderate to severe effects of parasites. Small exponents giving rise to rapid increases in the infection of selfed progeny in mostly outcrossed populations might be expected when there are aggregated sibships, especially when there are few loci involved in disease resistance. Aggregated sibships would allow for the direct transfer of disease among closely related individuals as suggested by Rice (1983), Augspurger (1983), Shykoff & Schmid-Hempel (1991) and Herre (1993). Larger exponents ($z = 0.5-2.0$), however, can easily give rise to mixed (selfed and outcrossed) mating systems for a large fraction of the parameter space. For the present model, mixed reproduction is an unbeatable strategy for moderate to severe effects of parasites, provided inbreeding depression is less than 0.5. For moderate inbreeding depression ($d = 0.4 - 0.5$), mixed mating is stable even when there are small ($E = 0.1 - 0.3$) effects of parasites (figure 5*b–d*).

Thus the results of this simple model of allocation-dependent fitnesses suggest that mixtures of selfed and outcrossed progeny can be evolutionarily stable over a wide range of conditions, and may be a partial explanation for mixed mating in natural populations. Although the general result may hold, it is none the less clear that detailed genetic models will be helpful to determine (i) the effects of different modes of inbreeding depression (see Jarne & Charlesworth (1993) for a thorough review) and (ii) the effect of repeated selfing on inbreeding depression (see Campbell 1986; Lande & Schemske 1985; Charlesworth *et al.* 1990). Such models would also aid in evaluating the oversimplification presented here that cross-fertilized plants are relatively uninfected, which depending on the level of selfing and the genetics of infection may not be met. This is especially true if the advantages to outcrossing decline with increases in the population-wide selfing rate. A glimpse of this effect, however, can be seen by letting

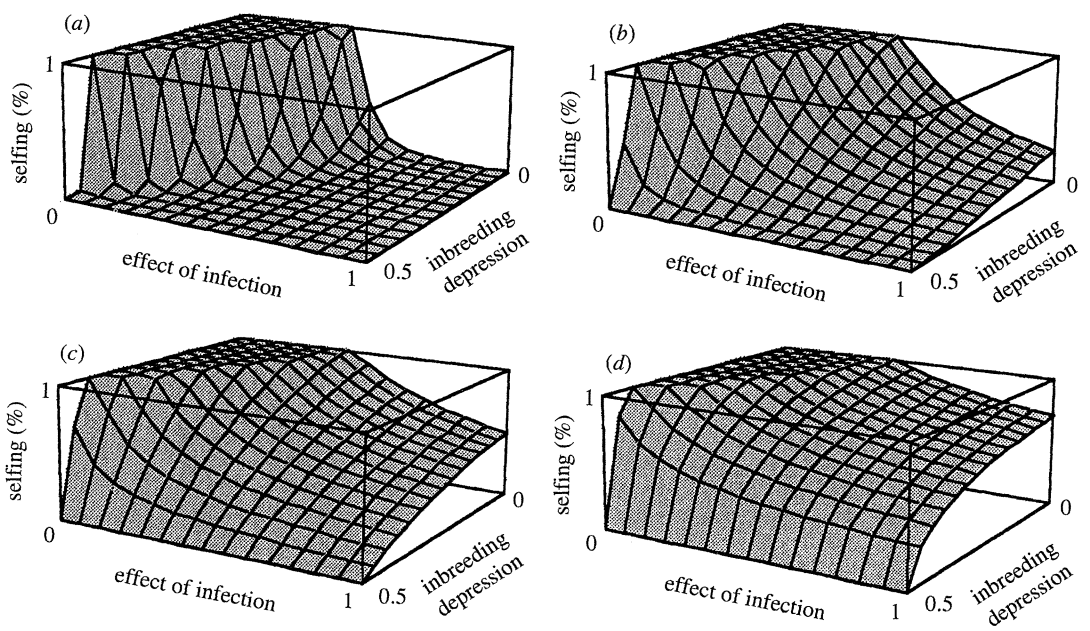

Figure 5. Graphical results for the evolutionarily stable percent of selfing (p^*) as a function of inbreeding depression (d) and the effects of parasites (E), as given in equation (6): (*a*) $z = 0.1$; (*b*) $z = 0.5$; (*c*) $z = 1.0$; (*d*) $z = 2.0$. Note that mixtures of selfed and outcrossed offspring are evolutionarily stable for large regions of the parameter space in (*b–d*).

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the fitness gains through outcrossed progeny (W_m and W_f) vary with the mean selfing rate (p). This is easily accomplished by multiplying equations 2*a* and 2*b* by $(1 - ehp^x)$, where h is the frequency of outcrossed progeny that are infected relative to uniparental progeny. Under these conditions, the equilibrium selfing rate in a large population becomes:

$$p^* \approx \left[\frac{1 - 2d}{E(2 - 2d - h)}\right]^{1/z}. \qquad (7)$$

The results are shown graphically in figure 6 for h equal to one half (i.e. outcrossed progeny are half as infected as uniparental progeny). As expected, the region of parameter space increases for which complete selfing is evolutionarily stable, but mixed reproduction is none the less similarly stable over a significant portion of the same parameter space.

4. DISCUSSION

Parasites represent a potentially powerful source of selection on host reproductive strategies, especially if they can evolve rapidly enough to track the spread of common host genotypes. However, the parasite (or Red Queen) hypothesis for the maintenance of sex suffers from two general criticisms. One is that, to overcome the twofold advantage that clones may enjoy, the effects of parasites would seem to need to be severe if they are to keep the clone from fixing (May & Anderson 1983). One possible solution to this problem has been suggested by Hamilton *et al.* (1990). They argue convincingly that the effects of parasites can be exacerbated by intraspecific competition for resources. For example, infected plants in a greenhouse may show marginal reductions in fitness-related traits when compared with control plants. However, when these same plants are grown under intense competition with uninfected plants, the effect of infection may be greatly increased owing to a synergism between competition and infection. In fact it seems reasonable to suspect that disease could be indirectly responsible for the failure of the most infected plants to reproduce under high levels of competition. Hamilton *et al.* (1990) show that this kind of synergism between competition and infection dampens the host–parasite gene-frequency oscillations, and gives sex an advantage over parthenogenesis. They refer to the synergism as rank-order truncation selection (see also the MIS model in Hamilton (1993)).

As an alternative, the accumulation of mutations through Muller's ratchet can also greatly reduce the severity of parasites needed to prevent the fixation of clones (Howard & Lively 1994). The basic idea rests on the assumption that clones start as rare mutants in large sexual populations; as such, they are initially very sensitive to mutation accumulation via Muller's ratchet. For mutation rates of one per genome per generation or greater, it is unlikely that a newly formed clone will survive for more than a few generations before its mutational load is significantly increased. The combination of mutation accumulation and moderate effects of debilitating parasites could prevent the fixation of clonal mutants in the short term. Oscillations in clonal frequency driven by parasites then lead to the further accumulation of mutations in clonal lineages and their eventual elimination.

It is worth noting that, under this kind of reasoning, any force that drives populations through periodic bottlenecks would have the same effect. Periodic

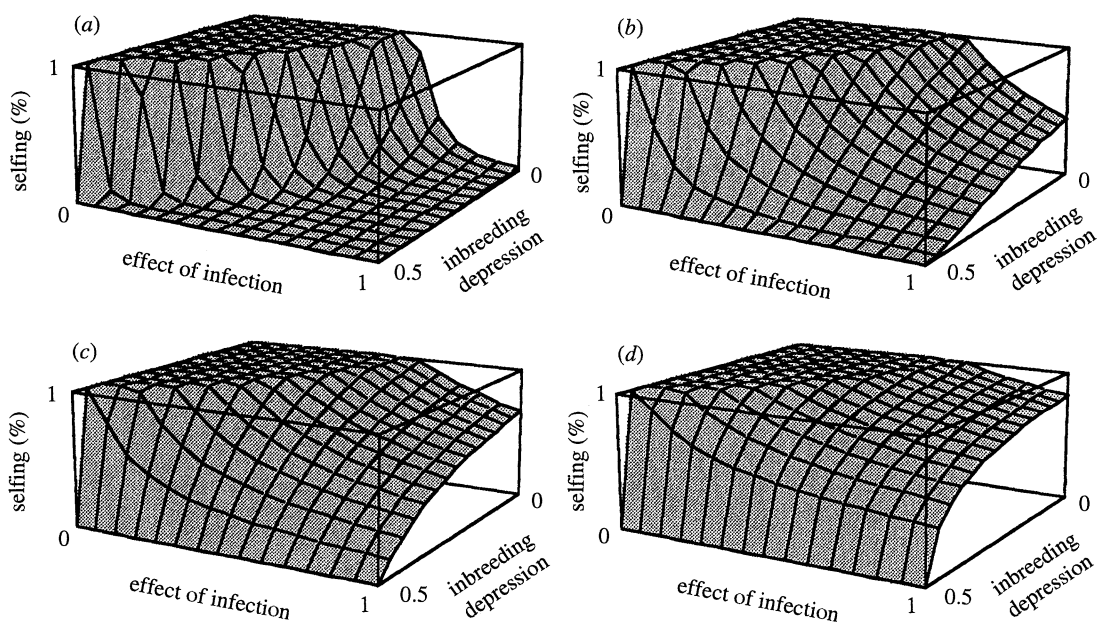

Figure 6. Graphical results for the evolutionarily stable percent of selfing (p^*) as a function of inbreeding depression (d) and the effects of parasites (E), as given in equation (7) for the relative frequency of infected sexual individuals (h) = 0.5: (*a*) $z = 0.1$; (*b*) $z = 0.5$; (*c*) $z = 1.0$; (*d*) $z = 2.0$. Compare with figure 5.

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epidemics, for example, could favour sex, even if the disease does not have the specific genetic basis required by frequency-dependent selection. In fact population cycles driven by any source (e.g. physical disturbance, predation, or resource competition) would also favour cross-fertilization by driving clonal populations through ratchet-cranking bottlenecks. A major advantage (in our view) of parasite-mediated frequency-dependent selection is that it should predictably drive cycling and thereby reliably favour sex over parthenogenesis. This is true even if there are some refugia from infection, provided such refuges contain a sufficiently small fraction of the population so that the ratchet will work.

A second weakness of the parasite theory for sex is that parasites do not select for sex *per se*, but for rarity, however generated (figure 1). Hence, any theory of sex must be able to cope with the possibility of repeated mutations to parthenogenetic reproduction. We have found that the interaction between parasites and mutation accumulation can operate to render sex stable to invasion by multiple, independently derived clones (figures 2 and 3). The idea here is that, if the clone fails to fix, it begins to oscillate with the sexual population. However, during these oscillations, each time the clone is depressed to a low frequency by the parasite, it is subjected to the accumulation of further mutations through the action of the ratchet. This leads to the rapid extinction of clones (Howard & Lively 1994) and the stability of sexual reproduction when there is repeated mutation to parthenogenesis (figures 2 and 3).

As an aside, it is worth pointing out that rank-order truncation selection and parasite-aided mutation accumulation are not mutually exclusive alternatives. In fact, it would seem that both should operate in the wild. Moreover, it seems reasonable to think that they would interact in a synergistic way if competition for resources exacerbates the effects of infection, thereby slowing the growth rate of any clonal mutant and thus allowing for a greater rate of mutation accumulation. Another kind of synergism that merits future consideration is that between parasite load and mutational load. If, for example, individuals with high mutational loads were sicker when infected, then mutational load and parasites would have a synergistic, negative effect on host fitness.

It now seems that parasites should be at least part of the reason why dioecious outcrossing populations are stable to invasion by obligately parthenogenetic mutants. But what about hermaphroditic populations: can parasites prevent the fixation of alleles for self-fertilization? This is an important question for at least two reasons. One is that the 'cost of sex' is different. In a competition between obligately parthenogenetic and obligately sexual females, the cost of sex is proportional to the investment that sexual females put into sons (Maynard Smith 1971, 1978); relatedness is not relevant, except in how it might affect son production. However, for the self-fertilization of potentially outcrossing (non-cleistogamous) eggs, the cost of sex is due to the reduction in relatedness between the parent and its outcrossed offspring (Williams 1975; Charlesworth 1980; Lloyd 1980; Lively & Lloyd 1990). The second, and more important, reason is that the evolution of self-fertilization in cosexual populations represents the indisputable evolution of uniparental reproduction at the individual level. Whereas obligate parthenogens and their sexual ancestors are reproductively isolated groups (Williams 1992), partly selfing individuals are not reproductively isolated from other partly selfing individuals. Any general theory of sex should be able to explain not only why sexual females are not replaced by obligately parthenogenetic females, but why cross-fertilization is not replaced by self-fertilization. In fact, the latter explanation would seem to be a more difficult challenge for the parasite theory of sex, because there is no single clone for the parasites to track in evolutionary time.

It may, of course, be that parasites are not needed (unless they are responsible for genetic load). Inbreeding depression seems to be universally associated with self-fertilization of individuals from outcrossing populations; if inbreeding depression reduces the fitness of selfed progeny by more than 50%, then inbreeding depression alone is sufficient for the maintenance of sex (Lloyd 1979). If, however, inbreeding depression reduces the fitness of selfed offspring by less than 50%, then selfing should have an advantage (Fisher 1941; Lloyd 1979). Hence, in the absence of additional factors, there are two alternative stable states that depend on inbreeding depression: complete selfing is stable if inbreeding depression is low, and complete outcrossing is stable if inbreeding depression is high. However, because mutation loads and inbreeding depression vary among individuals, complete selfing may be a stronger attractor (Lande & Schemske 1985).

The models presented here add parasites to inbreeding depression as a factor contributing to the 'cost' of selfing. They make the simplest possible assumption that the spread of parasites is related to the degree of self-fertilization in a population, which could result from either the reduction in heterozygosity or genetic diversity (or both) caused by selfing. The results depend on how the selfing rate maps onto the transfer of parasites. If small increases in selfing from an outcrossing ancestral state lead to dramatic increases in the transfer of disease (small values of z in equation (6)), then selfing and crossing seem to be alternative stable states as suggested by Lloyd (1979) and Lande & Schemske (1985). The main difference is that, with the addition of parasites, crossing is stable for values of inbreeding depression less than 50% (figure 5*a*). If, however, small increases in selfing lead to significant, but less dramatic, increases in the likelihood of infection, then mixtures of selfing and outcrossing are expected at the ESS for a large range of parameter values (figure 5*b–d*). This explanation is fundamentally different from the argument for time-lagged selection against common clones discussed above. Parasites might none the less explain mixed mating systems in plants and animals where inbreeding depression is less than 50%.

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Finally, it seems reasonable to suggest that parasites could select for temporal mixtures of uniparental and biparental offspring, as observed in many facultatively parthenogenetic and selfing animals. Such selection would require that there are reliable cues indicative of the risk of parasite attack, such as high population density. In cyclically parthenogenetic zooplankton, for example, high population density is known to induce the production of males and sexual females (review in Bell 1982). Before such induction, genetic diversity in the population could be eroded by interclonal competition at the same time that population size is increasing. This is precisely the kind of situation that should favour the spread of disease and a facultative switch to cross-fertilization. Similarly, warmer water temperatures have been shown to induce a cross-fertilizing morph of an otherwise selfing hermaphroditic snail (Schrag & Read 1992; Schrag *et al.* 1994*b*). Such temperatures are indicative in some populations of an enhanced risk of attack by digenetic trematodes that castrate infected individuals (Schrag *et al.* 1994*a*).

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Discussion

J. Godfrey (*41 Lawford Road, London, U.K.*). Dr Lively's argument that the mutation rate has a crucial influence on the relative advantage of sexual and asexual reproduction needs to take account of the probable effect of latitude on mutation. In the laboratory mutation goes up with an increase in temperature, exhibiting a Q_{10} like other chemical processes. So natural populations near to the equator could be expected to have a higher mutation rate than related populations nearer to a pole. This effect has not been investigated as far as I know. If natural selection adjusts the mutation rate towards an optimum, the effect would be less than a doubling of the mutation rate for each 10°C increase in temperature. To test whether this is so would require stoic study of the mutation rate of natural populations of species with wide distribution. If there is a latitudinal effect, could it explain the fact that a majority of carbon has been accumulated by asexual plants in parts of the world far from the tropics? May the Red Queen not race in a circle, but rather in a spiral, trending towards the equator?

C. M. Lively. This is an extraordinary suggestion. If mutation rates truly are greater at lower latitudes, then this could help explain, under our model, why sex is more common in these regions. It would also greatly aid Kondrashov's models for the evolution of sex by giving some explanation for the ecological distribution of cross-fertilizing species. I wholly agree that investigation into the possibility of such an effect would be worthwhile.

P. Higgs (*University of Sheffield, U.K.*). Dr Lively discussed modelling of both Muller's ratchet, and host–parasite coevolution, and appeared to conclude that a combination of both processes was necessary to give sexual reproduction an advantage over parthenogenesis. Muller's ratchet on its own has sometimes been proposed as a reason for the advantage of sex and recombination. Are there any situations in his model where the ratchet alone is sufficient? In his simulations, increasing the mutation rate gave an advantage to sex. Is there a simple reason why this should be the case? Muller's ratchet and host–parasite coevolution both share the common feature that the population is always evolving, and gene frequencies never reach a mutation selection balance. This is in contrast to the theory that the reason for the advantage of sex is due to the higher equilibrium fitness of the sexual population in certain fitness landscapes with epistatic interactions once mutation-selection balance has been reached. It would seem to be an important feature of real evolutionary processes that gene frequencies never have chance to reach equilibrium.

C. M. Lively. There were no situations in our simulations where Muller's ratchet was sufficient by itself to confer evolutionary stability on a sexual population. For the mutation rates and selection coefficients we used (which seem reasonable given what is presently known), the ratchet simply worked too slowly to prevent a clone with a twofold reproductive advantage from replacing the descendants of its sexual ancestor. The explanation is that the ratchet-like mechanism described by Muller slows down after the clonal lineage passes through its initial phase of growth from a single individual to several hundred individuals. The reason that parasites are so effective in driving the ratchet is that they periodically and predictably depress the size of the clonal population, and this increase the rate at which the ratchet 'clicks'. Hence, each time the parasites drive the clone through a population-size bottleneck, it emerges with a greater load and an eroded ability to compete with the sexual population. Eventually the clone cannot replace itself, and it goes extinct.

It is certainly true, as suggested, that the ratchet allows a clonal population to accumulate more mutations than they would otherwise have at mutation selection balance, while the sexual population has much less difficulty in this regard. It is also true that host–parasite interactions lead to dynamic cycles rather than static equilibria, and that understanding these cycles is the key to understanding the Red Queen theory for sex.

J. Shykoff (*Swiss Federal Institute of Technology, Zurich, Switzerland*). Using the model for the effects of parasites on the evolution of partial selfing, can Dr Lively distinguish between an individual mixed ESS and a population mixed ESS?

Individual mixed ESS versus population mixed ESS will explain different kinds of breeding systems. Some plant breeding systems such as gynodioecy represent a population mixed strategy where each individual follows a pure strategy. Other breeding systems such as gynomonoecy in plants or aphally in snails represent individual mixed strategies. Which types of breeding system will this model help to explain?

C. M. Lively. That is an interesting question. Dr Shykoff is asking whether the population could be dimorphic, so that some individuals are selfing, whereas others are outcrossing; or, in more formal terms whether the population is at a true evolutionary stable strategy or at an evolutionarily stable

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state. In our models, we performed the standard second derivative test, which indicated that the mixture of selfed and outcrossed offspring would occur within individuals, meeting the condition for a true ESS.

J. D. GILLETT (*London School of Hygiene and Tropical Medicine, U.K.*). I would like to ask three questions. First. Why confine this discussion to the threat from small enemies only? Surely, large or small, both make a living by exploiting the tissues of the host, one way or another: *Panthera leo*, for example, exploiting mainly muscle, *Plasmodium falciparum*, haemoglobin. Sex provides the plasticity – the polymorphism – to cope with threats of all dimensions and kinds, large or small. The means may differ, but the result is the same: survival by at least some of those attacked. A greenfly puts up one kind of defence against a virus and another against a ladybird; each is suited to the kind of threat and each is inherited.

Second. If parasitic disease, including those of viral origin, were the main threat that sex guards against then why do so many hundreds of species of insects in the temperate regions cease sexual reproduction, replacing it with asexual reproduction or parthenogenesis, during the summer months just when these threats are surely at their highest?

Third. What about bacteria, subject to attack by very many different viruses; how do they get by without sexual reproduction? Their plasticity of response must be through other channels.

C. M. LIVELY. Regarding Dr Gillett's first question, I did not mean to imply that the size of the enemies matters. What seems most important is that the enemy attacks in a frequency-dependent matter, and that the attack is lagged in time. It is the time lags that set up the dynamic oscillations that are so important to the Red Queen theory. It would seem to me, however, that small enemies (pathogens and parasites) are more likely than predators to attack in this way. This does not mean that predation is not sometimes dependent on the frequencies of prey genotypes; it would just seem to be much less common, especially for a predator like *Panthera leo*.

Your second question is a very good one. One of the biggest challenges for any theory of sex is to explain cyclical parthenogenesis. Under the parasite theory of sex, one would expect that a switch to sex should occur when the risk of disease is greatest. In freshwater zooplankton, this switch often occurs when population densities become high and resources are limited. This result could be used to support models for genetic polymorphism and sex which are based on resource competition in heterogeneous environments. But it is also possible that the risk of disease increases with host density, and that host density is used as a cue for the future risk of parasitic attack. Hence, although there is much to learn about the kinds of parthenogenesis mentioned, it would seem premature at present to reject the parasite theory.

Regarding sex in bacteria, I don't think they should be able to get away without some kind of genetic exchange if they are threatened by persistent attack by viruses, unless, of course, their mutation rates to alternative defensive types are very common.

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