Parasitism, mutation accumulation and the maintenance of sex

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TWO classes of models attempt to explain why obligate parthenogenesis only rarely replaces sexual reproduction in natural populations, in spite of the apparent reproductive advantage that parthenogens gain by producing only female offspring[1]. The mutation-accumulation models suggest that sex is adaptive because it purges the genome of harmful recurrent mutations[2-3]. The ecological genetic models postulate that sex is adaptive in variable environments, particularly when the relevant variation is generated by coevolutionary interactions with parasites[4-7]. Both of these models have considerable merit, but would seem to have limitations. The mutation-accumulation models require high rates of mutation[3,8]. The coevolutionary models require that parasites have severe fitness effects on their hosts[9]. In addition, parasites could select for clonal diversity, and thereby erode any advantage that sex gains by producing variable progeny[10]. In the present study, we consider the interaction between mutation accumulation and host-parasite coevolution. The results suggest that even moderate effects by parasites combined with reasonable rates of mutation could render sex evolutionarily stable against repeated invasion by clones.

The crux of the Red Queen hypothesis is that there is time-lagged, frequency-dependent selection against common host genotypes[5-7]. Parasites are expected to rapidly evolve to disproportionately infect any genotype that becomes common, and thereby drive it down in frequency[11,12]. This sets up an oscillation where parasite gene frequencies track the gene frequencies of their host. This kind of antagonistic coevolution could theoretically prevent the local fixation of any host genotype; but, to prevent the fixation of a clone with a two-fold reproductive advantage, the direct effects of parasites would need to be severe[9], or there would have to be rank-order truncation selection against the most infected individuals[13].

Even with severe effects of parasites (e.g. parasitic castration), it would seem that clones would still have a reproductive advantage when rare. Such an advantage could easily explain the local coexistence of reproductively isolated sexual and parthenogenetic lines, but it leads to another potential problem. Repeated mutations to parthenogenetic reproduction would lead to the accumulation of clones; and assuming that these clones are random samples of the local genetic variation for parasite recognition, multiple clonal lineages with different recognition phenotypes are expected to result. Thus clones should accumulate, and the advantage of cross fertilization would be expected to diminish as the number of clones increases. If this reasoning is correct, then there must be some mechanism in addition to parasites that removes clones at least as fast as they are generated. One such mechanism could be mutation accumulation in the clonal lineages.

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Note: The figures in the original article were poorly reproduced (especially Figs. 1 & 2). In addition, Figs. 3a and 3b were reversed after the proofs were returned. All three figures were reproduced with better resolution and in the correct order in *Nature* 368: 358. Minor editorial differences were also generated during copy-editing of the published version.

We have evaluated the interacting effects of parasites and the accumulation of mutations through the ratchet-like process first noted by Muller[2], and later formalized by Felsenstein[14] and Haigh[15]. Muller's idea was that in finite populations there would be a good chance for the stochastic loss of the clonal class which is the least loaded with mutations. Computer simulations showed that, in the absence of mutation, parasites generated a decisive advantage to sex only when parasite transmission probabilities were high (> 70%) and the effects of parasites on host fitness were dire (> 80% loss of fitness), which accounts for only 4% of the possible parameter space (Fig. 1). This result is consistent with May and Anderson's[9] contention that antagonistic coevolution favours sex only when parasites have severe effects on host fitness. There was, however, a fairly large region of parameter space (25%) defined by more intermediate values under which sexual and parthenogenetic populations coexisted, but this coexistence would be expected to be temporary as selection for clonal diversity in this region would eventually erode the advantages that sex gains through the production of variable offspring.

The region of persistence by the sexual population increased dramatically by the addition of mutation to the model (Fig. 2). For example, for moderate mutation rates per genome (U = 0.5) and weak selection against mutation (s = 0.0125), sex was stable over 29% of the total parameter space. The region for coexistence of sexual and parthenogenetic populations for these values shrank to 9% of the total parameter space (Fig. 2A). Holding selection constant, but increasing the mutation rate to U = 1.0, sex was stable over 49% of the total parameter space, and the region of coexistence of sexual and asexual populations was completely eliminated (Fig. 2B). An almost identical result was gained by holding the per genome mutation rate at 0.5, but increasing the selection against mutations to s = 0.025; sex was stable over 48% of the parameter space, and there was no region of stable coexistence (Fig. 2C). Finally, for mutation rates of U = 1.0, and selection coefficients of s = 0.025, sex was stable over 71% of the total parameter space (Fig. 2D). Hence, host-parasite coevolution could interact with Muller's ratchet to confer evolutionary stability to sexual reproduction.

The effect of the interaction between parasites and mutation can be seen in Fig. 3. At generation zero, a rare mutant that reproduces by parthenogenesis is introduced into a sexual population (N = 1000). The mutant rapidly spreads, but is knocked back at about generation twenty by time-lagged frequency-dependent selection from the parasite. As expected, the mutant clone then oscillates in density over time. However, each time the clone is depressed in number by the parasite, it becomes more susceptible to the accumulation of mutations by Muller's ratchet. (We use Muller's ratchet here to include both the gain of mutations through the stochastic loss of the least-loaded subclones, and the probabilistic gain of mutations due to mutation pressure.) Note that in Fig. 3, due to the accumulation of mutations, the trough of each oscillation by the clone gets lower with time. Eventually the clone cannot replace itself and "melts down"[16]. Hence, there is short-term coexistence of the sexual and parthenogenetic host populations due to the effects of the parasite, but mutation accumulation eventually eliminates the clone. Sex would be expected to be stable in the long term if clones are eliminated by this process at least as fast as they are generated by mutation.

In summary, moderate effects by parasites combined with reasonable rates of mutation could render sex evolutionarily stable against repeated invasion by clones. Parasites prevent the fixation of clones and the elimination of sex in the short term; and they increase the rate at which clones accumulate mutations through the action of Muller's ratchet, by periodically depressing the population size of the clone. Mutation accumulation eventually leads to the extinction of clones. These results suggest that, where sexual and asexual populations coexist, the individual clones are transitory.

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1. Maynard Smith, J. *The Evolution of Sex* (Cambridge University Press, 1978).
2. Muller, H.J. Mutat. Res. **1**:2-9 (1964).
3. Kondrashov, A.S. Nature **336**:435-440 (1988).
4. Levin, D. *Am*. *Nat*. **109,** 437-451 (1975).
5. Jaenike, J. *Evol. Theory* **3,** 191-194 (1978).
6. Hamilton, W. D. *Oikos* **35,** 282-290 (1980).
7. Bell, G. *The Masterpiece of Nature* (University of California Press, Berkeley, 1982).
8. Howard, R.S. *Theor. Popul. Biol*. (in the press)
9. May, R.M. & Anderson, R.M. *Proc*. *Roy*. *Soc., Lond*. *B* **219**:281-313 (1983)
10. Lively, C.M. *Evolution* **46**:907-913 (1992)
11. Clarke, B. in *Genetic Aspects of Host-Parasite Relationships* Vol. 14 (eds. Taylor, A. E. R. & Muller, R.) 87-103 (Blackwell Scientific, Oxford, 1976).
12. Hutson, V. & Law, R. *Proc*. *Roy*. *Soc., Lond*. *B* **213**, 345-359 (1981).
13. Hamilton, W.D., Axelrod, R. & Tanese, R. *Proc*. *Nat*. *Acad*. *Sci*., *USA*:**87**, 3566-3573 (1990)
14. Felsenstein, J. *Genetics* **78**:737-756 (1974)
15. Haigh, J. *Theor. Pop. Biol.* **14**:251-267 (1978)
16. Lynch, M. & Gabriel, W. *Evolution,* **44**, 1725-1737 (1990)

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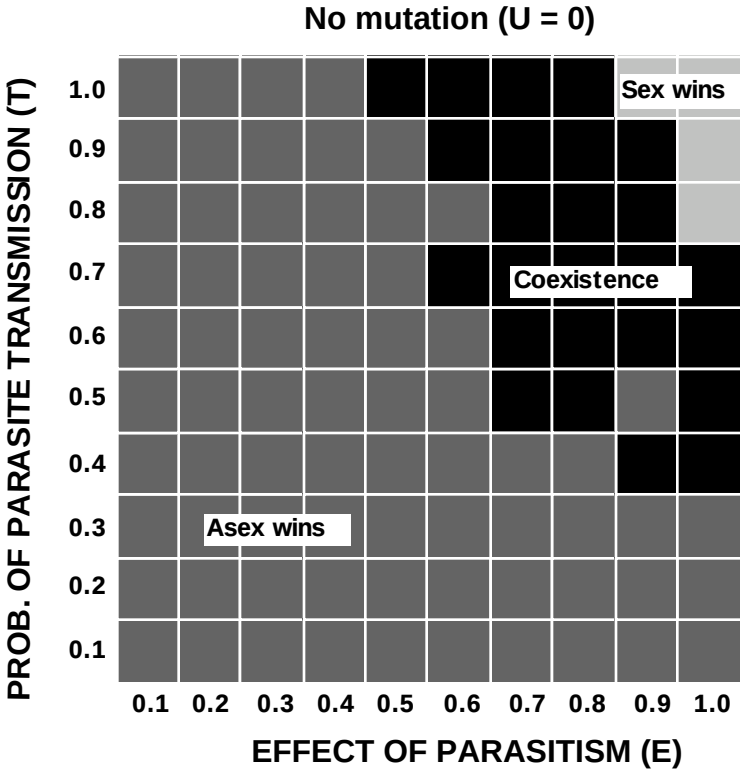

Fig 1. Results from computer simulations in which sexual populations were challenged by asexual lineages in the presence of coevolving parasites. Each block in the grid represents the majority outcome from 5 replicate runs of the simulation for a single combination of parasite transmission probability (T) and effect of parasitism (E). Coexistence was defined as the persistence of both types for more than 300 generations. At the beginning of each simulation, 500 unlinked loci in each of 1000 sexual individuals received a mutation with probability $U/s/500$ ($\underline{U}$ is the Poisson-distributed mutation rate per-haploid-genome-per-generation; s is the effect of a single mutation). The fitness of an individual with k mutations was calculated as $(1 - s)^k$. Thus, the sexual population was initialized with the equilibrium mean (U/s) and variance for mutation number. A clonal genotype of 20 individuals was similarly initialized with U/s mutations. Following initialization, both sexual and asexual hosts randomly accumulated mutations each generation with a Poisson mean of U.

There were two parasite generations for each host generation. The genetic interaction was simulated by considering two unlinked loci, each with two alleles, for both host and parasite. To maintain variation in the parasite population, mutation between allelic forms occurred with a probability of 0.03. For each parasite generation, hosts were individually drawn and exposed to a randomly selected parasite genotype with probability T. If exact matching occurred at both loci, the host was marked as infected, and the parasite entered into the pool of reproductives. If there was less than complete matching the parasite died. Allele frequencies for host and parasites were all initialized at 0.5.

Host reproduction was simulated by drawing individuals at random with replacement. If the selected individual was sexual, then a second individual was randomly selected for cross fertilization. Each individual then produced 5 embryos if they were uninfected, and an average of $5(1 - E)$ embryos if infected. The haploid embryos were then randomly assigned at each locus the allele from one of the two parents. If, instead, the selected individual was parthenogenetic, 20 embryos identical to uninfected parents were produced; and, on average, $20(1 - E)$ embryos identical to infected parents were produced. Reproduction was simulated in this way until the number of broods produced equaled the total number of adults in the population. A maximum of 1000 juveniles were then selected randomly to become the next generation of adults.

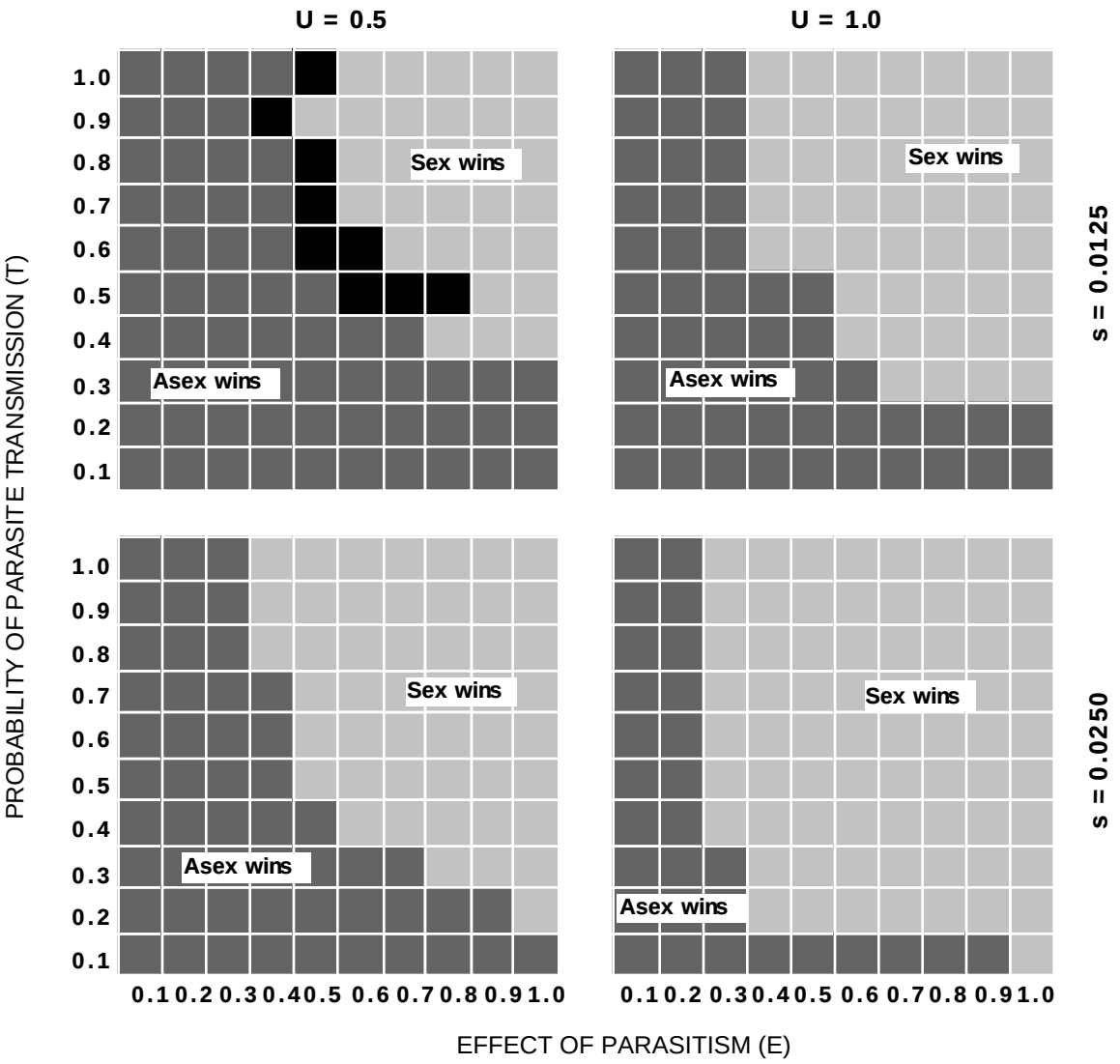

Fig 2. Results from computer simulations in which sexual populations were challenged by monotypic asexual lineages in the presence of coevolving parasites and selection harmful recurrent mutations. Each block in the grids represents the majority outcome from 5 replicate runs of the simulation for a single combination of probability of parasite transmission (*T*) and the effect of parasitism (*E*). The simulations were run for four combinations of mutation rate (*U*) and effect of mutation (s): (**A**) *U* = 0.5 and *s* = 0.0125; (**B**) *U* = 1.0 and *s* = 0.0125; (**C**) *U* = 0.5 and *s* = 0.025; (**D**) *U* = 1.0 and *s* = 0.025. Note that the range of parameter space for which sex is evolutionarily stable to invasion by parthenogenesis increases as the mutation rate increases, and as selection against mutations increases.

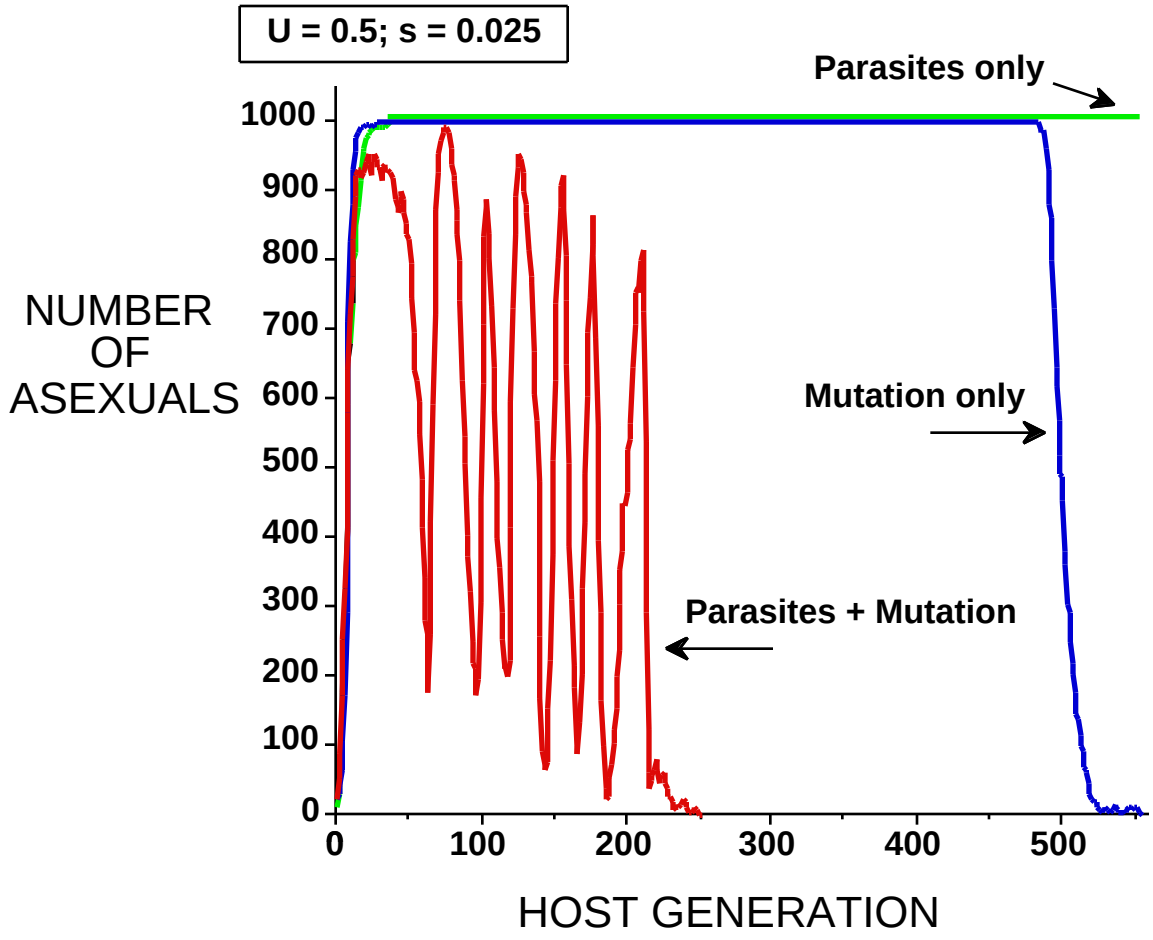

Fig 3*A*. Population dynamics for monotypic asexual lineages in competition with sexual populations in the presence of either parasites, mutation, or both. *a*, Parameters for theses runs included a mutation rate (*U*) of 0.5 per genome per generation, selection coefficient (*s*) = 0.025, probability of parasite transmission (*T*) = 0.5, and effect of parasites on host fitness (*E*) = 0.5. Note that, for mutation only, the clone fixes in a population of 1000 individuals in less that 50 generations; the clone then undergoes "mutational meltdown" (in the sense of Lynch and Gabriel[16]), beginning at about generation 480. In the presence of parasites, the clone also fixes in about 50 generations, but it does not later undergo the meltdown. Finally, for mutations combined with parasites, the clonal population does not replace the sexual population, but rather it oscillates. Each oscillation increase the mutational load through the action of Muller's ratchet, and there is a tendency for the lowest point of the oscillation to decline with time. Finally, the clone begins the "mutational melt-down" (see ref 16) at about generation 220, and it is quickly eliminated from the population.

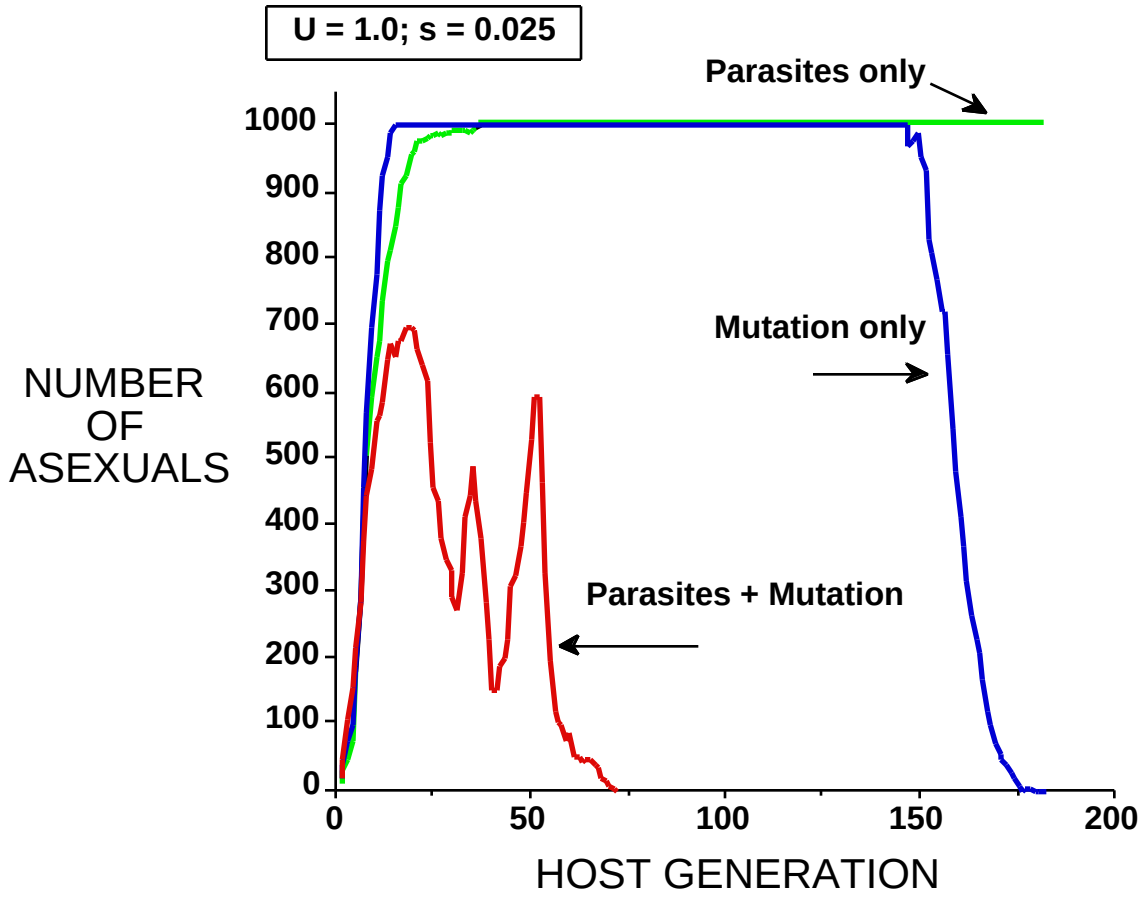

Fig. 3*B*. As for 3*A*, except that the mutation rate *U* has been increased from 0.5 to 1.0. Note the more rapid extinction of the asexual lineage as compared with *A.*