THE MAINTENANCE OF SEX BY PARASITISM AND MUTATION ACCUMULATION UNDER EPISTATIC FITNESS FUNCTIONS

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Abstract -- The mutation accumulation hypothesis predicts that sex functions to reduce the population mutational load, while the Red Queen hypothesis holds that sex is adaptive as a defense against coevolving pathogens. We used computer simulations to examine the combined and separate effects of mutation accumulation and host-parasite coevolution on the spread of a clone in an outcrossing sexual population. The results suggest that the two processes operating simultaneously may select for sex independent of the exact shape of the function that maps mutation number onto host fitness.

Keywords.--Host-parasite coevolution, Muller's ratchet, mutational deterministic hypothesis, Red Queen hypothesis, sexual reproduction, synergistic epistasis.

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Of the many hypotheses suggested for the evolutionary maintenance of sex (reviews in Bell 1982, Kondrashov 1993), two seem to dominate the present literature: the mutational accumulation hypothesis, and the Red Queen hypothesis. Under the mutational accumulation model, sexual populations gain an advantage over asexual populations due to the efficiency of recombination in reducing the population mutation load. Muller (1964) was the first to suggest that asexual populations might be undermined by mutation accumulation, reasoning that stochastic processes would lead to an inexorable decline in the fitness of clones. This version of the mutation accumulation hypothesis is widely known as "Muller's ratchet." More recent studies have extended Muller's basic idea to include cases in which mutation accumulation is decoupled from stochastic processes, such that an advantage to sex can accrue even in infinite populations. This extension represents the deterministic model of mutation accumulation put forward by Kondrashov (Kondrashov 1982, 1988). For both versions of the mutation accumulation hypothesis, any advantage to sex depends strongly on the genomic mutation rate and the relationship between mutation number and individual fitness (the "fitness function"). Unfortunately, estimates of mutation rate vary widely (review in Peck and Eyre-Walker 1997), and little is known about the general shape of the fitness function in natural populations.

Under the Red Queen hypothesis, cross fertilization is advantageous because it allows for the production of genetically variable progeny, some of which escape infection by parasites that are "tracking" common host genotypes (Jaenike 1978; Glesener and Tilman 1978; Bremermann 1980; Hamilton 1980). The theory has gained empirical support from a wide variety of approaches (e.g., Schmitt and Antonovics 1986; Burt and Bell 1987; Lively 1987, 1992; Schrag et al. 1994; Jokela and Lively 1996; Gemmill et al. 1997), but seems to require that parasites have very severe effects on host fitness, which could restrict its generality (May and Anderson 1983). In addition, parasites may select for clonal diversity instead of sex per se, which could lead to replacement of the ancestral sexual population by a set of genetically diverse clones (Lively and Howard 1994). Both of these difficulties can

be overcome, however, by either (1) rank-order truncation selection against the most infected individuals (Hamilton et al. 1990), or (2) by stochastic accumulation of mutations in clones that are driven though periodic bottlenecks by parasites (Howard and Lively 1994; Lively and Howard 1994).

The basic idea behind the second model is that there is an interaction between Muller's ratchet and Red Queen dynamics. If parasites prevent the fixation of clones in the short term, they will drive the clone through cycles (Red Queen dynamics), which accelerates the rate of mutation accumulation and reduces the time to extinction. In the original model, we found that moderate effects of parasites combined with mutation rates of 0.5 to 1.0 per genome per generation led to the evolutionary stability of sex (Howard and Lively 1984). We assumed, however, that mutations act independently (multiplicative selection). Here we relax this assumption and examine the interaction between mutation accumulation and antagonistic coevolution under the synergistic fitness functions required by the mutational deterministic hypothesis. This is an important step since synergism among mutations is expected to reduce the effectiveness of the ratchet (Charlesworth et al. 1993, Kondrashov 1994; but see Butcher 1995). We also employ a more conservative assumption regarding the mutational load of invading asexual mutants. The results suggest that mutation accumulation and antagonistic coevolution can combine to favor the maintenance of sexual reproduction, and that the outcome is robust to the exact shape of the fitness function.

METHODS

We used individual-based computer simulation models to study host-parasite coevolution and mutation accumulation under four different fitness functions: multiplicative, exponential quadratic, linear, and threshold (Fig. 1). The host-parasite interaction was mediated by two unlinked, diallelic loci. Parasites were obligately sexual and underwent two generations for each host generation. In addition, all hosts possessed 500 unlinked loci at which harmful mutations accumulated randomly with a Poisson mean of U per genome per

generation. Finally, in order to maintain variation in the parasite alleles involved in the host-parasite interaction (especially under high parasite virulence), mutation between allelic forms in the parasite population occurred with a probability of 0.03. This high rate of "mutation" is more meant to mimic the effects of migration among structured deems rather than mutation per se.

At the beginning of each simulation, we initialized a freely recombining sexual population at mutation-selection balance for a given mutation rate and fitness function. A single asexual host genotype was then introduced into the population. Following Charlesworth (1990), the number of mutations in this asexual individual was calculated as $i = \bar{n} - 2\sqrt{\bar{n}}$, where $\bar{n}$ is equal to the equilibrium mean number of mutations in the sexual population. Since the variance is approximately equal to the mean, the variable *i* represents 2 standard deviations less than the mean for the sexual population, which is the minimum probable number of mutations (Charlesworth 1990). In our previous study, founders for asexual lineages were randomly sampled from the sexual population; thus, the present assumption makes the persistence of sexuals more difficult and provides a more conservative test.

For each parasite generation, hosts were drawn individually and exposed to a randomly selected parasite with probability *T*. If the parasite matched the host exactly at both loci, the host was marked as infected and the parasite entered into the pool of reproductives; parasites that failed to match hosts exactly at both loci died. Host reproduction was simulated by drawing individuals at random with replacement. If the selected individual was sexual, another individual was randomly selected for cross-fertilization. If uninfected, each individual produced a lifetime average of ten embryos and achieved a total of ten cross-fertilizations through male function. If infected, average fecundity was reduced by a factor of 1-*E*, where *E* is the loss of reproductive potential that results from infection. If the selected individual was asexual, 20 embryos were produced by uninfected females, and, on average, 20(1-*E*) embryos by infected parents. In the absence of

parasitism and selection against deleterious mutations, this scheme embodies the full two-fold cost of sexual reproduction (Maynard Smith 1978). Embryos were then subjected to selection against deleterious mutations according to the relationship between the fitness function and the number of mutations in their genomes. Under the multiplicative fitness function, for example, the probability of survival is evaluated as $(1-s)^n$, where s is the effect of a single deleterious mutation, and n is the number of such mutations in the genome.

For each of the four fitness functions investigated (Fig. 1), we conducted five replicate runs of the simulation for each of one hundred possible combinations of parasite effect (*E*) and probability of parasite transmission (*T*). At the end of each host generation, the number of sexual and asexual hosts was counted and population mutation loads were computed. These data were stored in a computer file for subsequent analysis. Individual runs were allowed to continue until either the sexual or asexual population went extinct, or until both coexisted for at least 300 generations. Runs in which asexual lineages failed to persist for at least 5 generations were not included.

RESULTS

The general pattern that emerged from the simulations is that the evolutionary stability of sexual reproduction is strongly dependent on both mutation rate and intensity of parasitism, but seems relatively unaffected by the shape of the fitness function (Fig. 2). For the case of multiplicative selection, a genomic mutation rate (*U*) of 0.5 resulted in protection for sex over 30% of the total parameter space (Table 1). Here, parasite effects (E) of 0.6 generated an advantage to sex when the probability of parasite transmission (*T*) was at least 0.7. For the case of extreme virulence ($E = 1.0$), sex was protected for values of T larger than 0.3. Increasing the mutation rate, *U*, to 1.0 generated an advantage to sex in 36% of the grids, and for parasite effects as low as 0.5, provided the probability of transmission was at least 0.8. For highly virulent parasites ($E = 1.0$), an advantage to sex was generated when *T* was greater than 0.2. A further increase in the mutation rate to 1.5 resulted in protection for sex over 40% of the parameter space. Here, transmission probabilities of 0.7 generated an

advantage to sex for virulence levels as low as $E = 0.5$. Finally, support for sex under extreme virulence ($E = 1.0$) was achieved for transmission probabilities greater than 0.2.

Under the exponential-quadratic fitness function, mutation rates of 0.5 generated an advantage to sex over 32% of the parameter space (Table 1). Parasite effects (E) of 0.5 led to protection for sex when the probability of parasite transmission (T) was greater than 0.9. For the case of extreme virulence ($E = 1.0$), sex won out for values of T larger than 0.2. An increase in the magnitude of U to 1.0 generated an advantage to sex 40% of the time. Sex won outright for parasite effects as low as 0.4 when probabilities of parasite transmission were greater than 0.9. For highly virulent parasites ($E = 1.0$), sex was protected for values of T greater than 0.2. Mutation rates of 1.5 led to protection for sex over 45% of the parameter space. Parasite transmission probabilities of 0.8 were sufficient to generate an advantage to sex for parasite effects as low as $E = 0.4$, and extreme virulence ($E = 1.0$) favored sex when transmission probabilities were greater than 0.2.

For the case of linear selection for $U = 0.5$, sex won outright over 25% of the total parameter space (Table 1). Parasite effects (E) as low as 0.6 generated an advantage to sex when coupled with transmission probabilities greater than 0.9. For the case of extreme virulence ($E = 1.0$), sex was protected for parasite transmission probabilities greater than 0.3. Increasing the mutation rate to 1.0 resulted in sex winning over 40% of the parameter space. As for exponential-quadratic selection, sex was favored for parasite effects of 0.4 when probabilities of parasite transmission were greater than 0.9. For high levels of parasite virulence ($E = 1.0$), an advantage to sex was generated provided parasite transmission probabilities exceeded 0.2. Increasing the mutation rate to 1.5 generated an advantage to sex over 49% of the parameter space. Parasite transmission probabilities of 0.7 resulted in protection for sex when parasite effects were as low as $E = 0.4$, and parasite effects of $E = 1.0$ favored sex when transmission probabilities were greater than 0.1.

Finally, for the case of threshold selection under mutation rates of 0.5, sex won outright 14% of the time (Table 1). Parasite effects (E) of 0.7 resulted in an advantage to

sex when transmission probabilities were greater than 0.8. For highly virulent parasites (E = 1.0), an advantage to sex was generated for parasite transmission probabilities greater than 0.3. Interestingly, long-term coexistence (>300 generations) occurred over a substantial (19%) region of parameter space. An increase in U to 1.0 led to protection for sex over 38% of the parameter space, and for parasite effects of 0.5 when probabilities of transmission exceeded 0.6. For extreme parasite virulence (E = 1.0), sex won outright provided parasite transmission probabilities exceeded values of 0.2. A region of coexistence remained under U = 1.0, covering 5% of the parameter space. A mutation rate of 1.5 generated a decisive advantage to sex over 47% of the parameter space, and the region of coexistence was eliminated. Protection for sex occurred for parasite transmission probabilities of 0.7 coupled with parasite effects of E = 0.4. Highly virulent parasites (E = 1.0) generated protection for sex when transmission probabilities were greater than 0.2.

In addition to testing for an advantage to sex under different combinations of parasite intensity and fitness functions, we examined the rate of fitness decline due to mutation accumulation in asexual lineages under threshold and exponential quadratic fitness functions (Fig. 3). In both cases, relaxing the assumption of infinite population size leads to an accelerated rate of fitness decline in parasite-free populations. Addition of parasites to the model resulted in an even faster rate of fitness decline. This apparently results from an increased efficiency of the ratchet as clonal host populations are driven through periodic bottlenecks. A major difference between the exponential-quadratic and threshold fitness models is that, under most of the parameter space investigated, threshold selection brings the ratchet to a halt as the population approaches K-1 mutations. In such situations, the terminal mutation load of asexual populations is equivalent to that of infinite populations, and the elimination of clones by Kondrashov's mechanism requires mutation rates of at least 1.0 per genome per generation.

DISCUSSION

Muller's Ratchet operates on asexual populations when the class of individuals containing the fewest mutations is lost by drift, which can happen in two ways. One is through chance loss of all individuals in the class having the fewest number of mutations. Since this class is unlikely to be recreated by back mutation, the "ratchet" clicks one notch. The rate of clicking depends on the number of individuals in the least-loaded class, which depends in part on population size. We refer to the chance loss of all individuals in the least-loaded class as "stochastic elimination." The second way the least-loaded class can be lost is through mutation pressure; if all progeny of the least-loaded individuals receive at least one additional mutation, the ratchet will click one notch. For example, if there are 6 offspring produced by the individuals in the least-loaded class, the probability that they all get at least a single mutation is $(1 - e^{-U})^6$, which is 0.064 for $U = 1$. We refer to this mechanism (which depends on mutation rate and population size) as "stochastic loading." Clicking of the ratchet will most often result from some combination of the two mechanisms. For example, the ratchet will click one notch when half the individuals in the least-loaded class fail to breed (stochastic elimination) and the other half produce progeny that gain at least one additional mutation (stochastic loading). Our results suggest that, independent of the shape of the fitness function, both aspects contribute to mutational gains in a clonal lineage during its early spread.

Kondrashov's (1982, 1988) mechanism can be envisioned as follows. When the function that maps mutation number onto fitness is strictly truncated, a large clonal population will come into mutation-selection balance at exactly K-1 mutations, where K is the threshold number of mutations. If the number of mutations is Poisson-distributed with a mean of one, then about two-thirds ($1 - e^{-U} = 0.632$) of the offspring will exceed the threshold and die. This is sufficient to give an advantage to sex, in spite of a two-fold cost of producing males for most values of K, because recombination maintains a lower mean number of mutations and a higher variance at mutation-selection balance (Kondrashov

1988). Muller's ratchet will not operate under Kondrashov's assumption of infinite population size, and it's efficiency will be severely retarded even in small populations when selection against deleterious mutations act synergistically. In particular, the action of the ratchet should cease once all members of a clonal population contain exactly *K*-1 mutations (Fig. 3). The reason is that the least-loaded class now consists of the entire set of clonal individuals; and, in all but the smallest populations, this class is unlikely to be lost by either stochastic loading or stochastic elimination. Hence, under threshold selection, large and small asexual populations should equilibrate at the same terminal mutation load.

The ratchet, however, will operate up until the finite clonal population reaches its terminal mutation load, and the time it takes to reach this point is therefore crucial. Consider a clone, founded from a single individual, which was randomly sampled from the sexual population. It is extremely unlikely that this clone will be at mutation-selection balance (*K*-1 mutations). For example, given a mutation rate of 1.0, 92% of the members of a sexual population will contain fewer than the threshold number of mutations. Hence, 92% of the time, a clone derived from this sexual population will initially have a relative fitness of one, and a full two-fold advantage of not producing males. If the clone fixes before it reaches mutation-selection balance, then there are no sexual individuals left to "save." Hence it is important to relax Kondrashov's (1982) original assumption that the asexual population begins in mutation-selection balance, and examine the fates of asexual lineages initialized with fewer than the equilibrium number of mutations (Kondrashov 1985, Charlesworth 1990).

Following Charlesworth (1990), we initiated clones at two standard deviations less than the mean number of mutations in the sexual population. We then followed the fate of these rare clones under different fitness functions where the effects of parasites and the probability of encounter with parasites were variables. We found that, when parasites had low rates of transmission or minor effects on fitness, the asexual population replaced a sexual population of 1000 individuals under all types of fitness functions, even for mutation

rates as high as 1.5 per-genome-per-generation (see Charlesworth 1990 for a similar result using the exponential quadratic function). As parasite virulence and transmission were increased, we found that sex became increasingly favored by selection.

For example, under the multiplicative fitness function, sex is increasingly likely to be favored as parasite virulence and transmission rates increase and as the mutation rate increases (Fig. 2 and Table 1). Higher virulence by parasites drives clones through steeper cycles, which aids both aspects of the ratchet, while higher mutation rates fuel the stochastic-loading aspect of the ratchet. Nonetheless, the conditions for sex (in terms of parameter space) were reduced here under the more challenging assumption that clones are initialized at two standard deviations lower than the mean number of mutations for the sexual population (compare Fig. 2 herein to Fig. 2d in Howard and Lively 1994). The most surprising aspect of the present results is that they seem to be little affected by the shape of the fitness function. Increasing the level of synergism among mutations did not greatly alter the outcome of selection (Fig. 2), at least for mutation rates of 1.0 and greater. In general, higher parasite virulence and transmission rates led to selection for sex, and this effect was enhanced at higher mutation rates.

The result obtained for truncated fitness functions deserves closer scrutiny, however, because the ratchet is unlikely to work at mutation-selection balance under our assumption that all mutations have equal effects. But, as pointed out above, clones are unlikely to begin in mutation-selection balance. The present results suggest that parasites will exacerbate the effects of the ratchet as the clone spreads from its initially rare state until each individual in the clonal population contains exactly K - 1 mutations (Fig. 3). Once the clone acquires its terminal mutation load, it is driven extinct by Kondrashov's mechanism without further effects of parasites, provided mutation rates exceed 1.0 per genome per generation. An infrequent but interesting exception to this pattern occurs over a small region of parameter space in which sexual and asexual populations coexist for more than 300 generations (Fig. 3). Here, for a mutation rate of 1.0, the clone is able to persist with a terminal mutation load

that completely eliminates its twofold reproductive advantage. The advantage to a sex, however, is relatively small ($\overline{W}_{sex} / \overline{W}_{asex} = 2.5$), and can be offset as parasites evolve away from rare clones to attack common sexual genotypes. In such situations, parasites can act to prevent Kondrashov's mechanism from eliminating the clone by periodically depressing the fitness of the sexual population. In regions of the parameter space where sex wins outright, parasites prevent the fixation of clones in the short term, and then operate together with the ratchet to drive the clone to mutation-selection balance before it eliminates the parent sexual population. Hence, under these conditions, three separate mechanisms are acting to prevent the elimination of sexuals; the ratchet and the Red Queen drive the clone to mutation-selection balance at *K*-1 mutations, whereupon it is eliminated by the effects of mutation accumulation.

For mutation rates of less than 1, Kondrashov's mechanism is not sufficient to eliminate clones, but is aided by the addition of parasites to the model. In some situations, the coevolutionary dynamics that arise from parasitism can apparently restore the ability of Muller's ratchet to operate in populations at mutation selection balance under threshold selection. This occurs when highly transmissible, highly virulent parasites act to drive asexual populations through bottlenecks of extremely low populations size. Here, all members of the least loaded class contain *K*-1 mutations, and a single click of the ratchet dooms the asexual population to extinction. In cases where parasitism is less intense (lower E and T), the demographic cycles are less steep, and the action of the ratchet is severely restricted if not eliminated altogether. In this situation, Kondrashov's mechanism acting alone is incapable of eliminating the clone. Instead, parasites can select for clonal diversity, which should eventually lead to the elimination of the ancestral sexual population (Lively and Howard 1994). When the synergism between mutations is reduced, Kondrashov's mechanism becomes less important in actually eliminating clones, and Muller's ratchet becomes more important.

In summary, our results suggest that moderate to severe effects of parasites can act in combination with mutation accumulation to provide a short-term advantage to sex. This basic result is robust to the shape of the function that maps the number of mutations onto fitness. In all cases, parasites aid the accumulation of mutations during the early spread of the clone by driving common genotypes through bottlenecks. Under multiplicative, exponential quadratic, and linear fitness functions, the ratchet and the Red Queen will then also eliminate the clone in less than 300 generations. Under threshold selection, the clone is eliminated by Kondrashov's mechanism after it comes into mutation-selection balance, provided mutation rates are on the order on 1 per genome per generation. These results suggest that models of host-parasite coevolution and mutation accumulation are not mutually exclusive.

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TABLE 1: Advantage of sex under multiplicative, exponential-quadratic, linear, and threshold fitness functions. Variables include: U = mutation rate/genome/generation, n = approximate equilibrium number of mutations for a sexual population, i = minimum probable number of mutations in founders of asexual lineages, and % of parameter space occupied by sex, asex, and populations consisting of both types (coexistence).

U	*n*	*i*	% sex	% asex	% coexistence
Multiplicative selection					
0.5	20	11	30%	70%	0%
1.0	40	27	36%	64%	0%
1.5	60	45	40%	60%	0%
Exponential-quadratic selection					
0.5	24	14	32%	68%	0%
1.0	35	23	40%	60%	0%
1.5	43	30	45%	55%	0%
Linear selection					
0.5	23	13	25%	75%	0%
1.0	30	19	40%	60%	0%
1.5	36	23	49%	51%	0%
Threshold selection					
0.5	48	34	14%	67%	19%
1.0	50	38	36%	57%	5%
1.5	51	39	37%	53%	0%

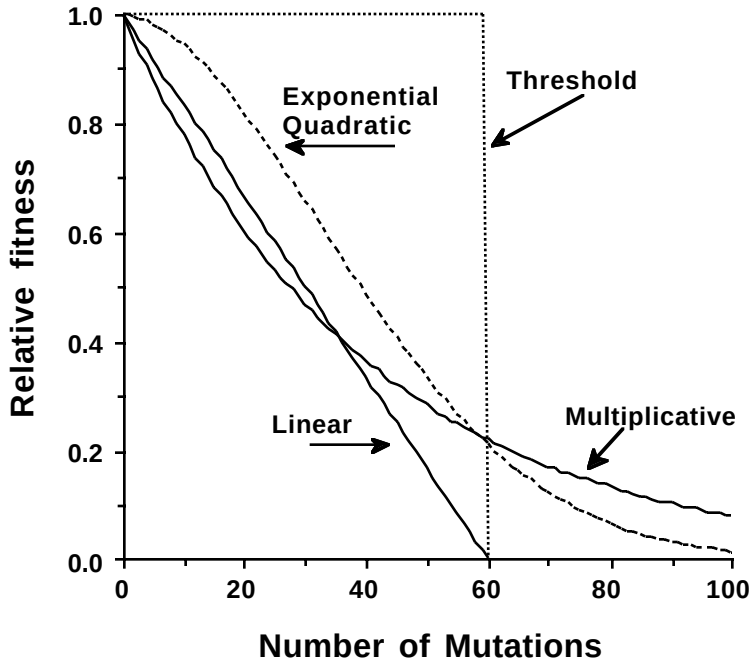

FIG. 1. Fitnesses of individuals with different numbers of mutations (n) under threshold [$w(n) = 1 - (n/k)^a$, for a = 1000], exponential quadratic [$w(n) = \exp-(\alpha n + 0.5\beta n^2)$, for α=0.002, β=0.0008], linear [$w(n) = 1 - (n/k)^a$, for $a = 1$], and multiplicative [$w(n) =(1 - s)^n$, for $s = 0.025$] fitness functions. For threshold and linear selection, individuals with more than $K = 60$ mutations are inviable. The values used for α and β in the exponential quadratic function are the same as those used by Charlesworth (1990).

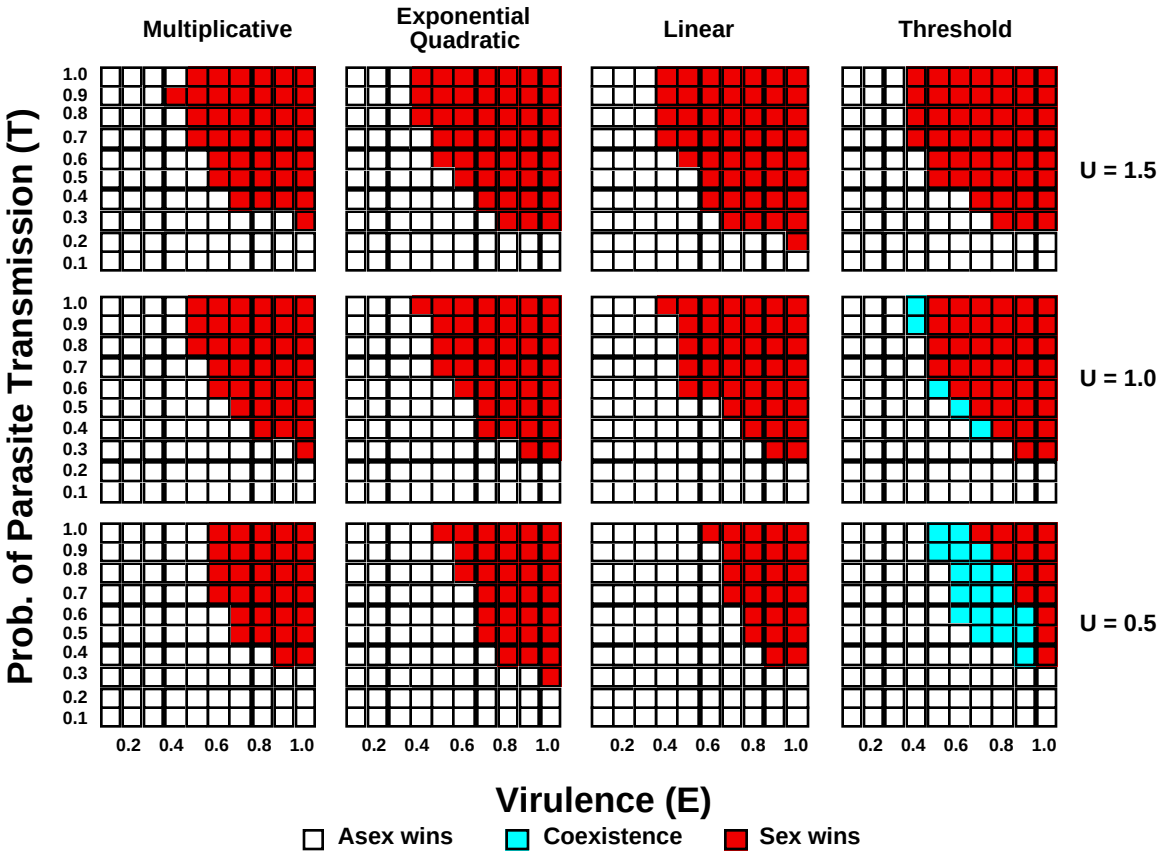

FIG. 2. Results from computer simulations in which sexual populations were challenged by asexual lineages in the presence of coevolving parasites and selection against harmful recurrent mutations. Each block in the grids represents the majority outcome from 5 replicate runs of the simulation for a single combination of parasite transmission probability (*T*) and effect of parasitism (*E*). The parameters for these runs included mutation rates of 0.5, 1.0 and 1.5 per genome per generation under threshold selection, linear, and exponential-quadratic fitness functions. The values used for these functions are the same as those given in Fig. 1.

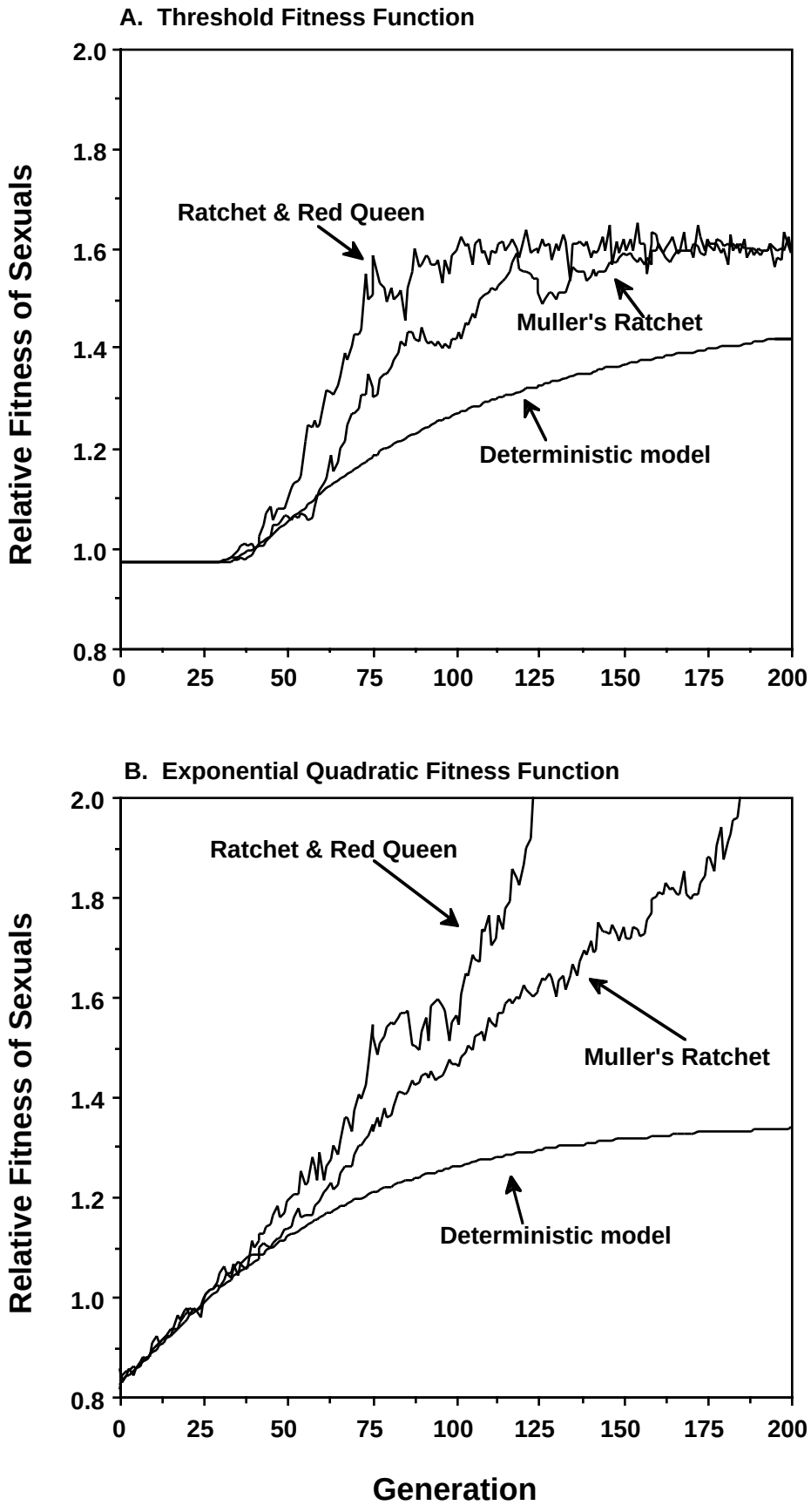
A. Threshold Fitness Function
Relative Fitness of Sexuals
2.0
1.8
1.6
1.4
1.2
1.0
0.8
Ratchet & Red Queen
Muller's Ratchet
Deterministic model
0
25
50
75
100
125
150
175
200
B. Exponential Quadratic Fitness Function
Relative Fitness of Sexuals
Ratchet & Red Queen
Muller's Ratchet
Deterministic model
Generation

FIG. 3. Erosion of the two-fold reproductive advantage of asexual lineages under mutational deterministic, Muller's ratchet, and the Ratchet-plus-Red-Queen models of mutation accumulation. Parameters for these runs included a genomic mutation rate (U) of 0.5 under threshold (3A) and exponential-quadratic (3B) fitness functions. For the coevolutionary model, the effect of parasitism (E) was set at 0.6, and probability of parasite transmission at 0.9. At the start of each generation, the mutation load (L) of the sexual and asexual populations was evaluated, and the ratio $(1-L_{sex})/(1-L_{asex})$ computed as a measure of the advantage to sexual reproduction. For exponential quadratic and threshold fitness functions, mutation accumulation acting alone is incapable of generating an advantage to sex under the deterministic model. The same result holds for the mutational stochastic model (Muller's ratchet), but the rate at which fitness declines in the asexual population is accelerated compared to the deterministic model; we attribute this to the combined effects of stochastic loading and stochastic elimination components of Muller's ratchet. The addition of parasites to the model results in protection for sex under the exponential quadratic fitness function, but not under threshold selection. Under threshold selection, Muller's ratchet is halted as the asexual population approaches the point where all individuals have exactly K-1 mutations, and the terminal mutation load equilibrates to that obtained under the deterministic model.