MULLER's Ratchet Under Epistatic Selection

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ABSTRACT

In a finite asexual population mean fitness may decrease by a process known as Muller's ratchet, which proceeds if all individuals with the minimum number of deleterious alleles are randomly lost. If these alleles have independent effects on fitness, previous analysis suggested that the rate of this decrease either remains constant or, if accumulation of mutations leads to the decline of the population size, grows. Here I show that this conclusion is quite sensitive to the assumption of independence. If deleterious alleles have synergistic fitness effects, then, as the ratchet advances, the frequency of the best available genotype will necessarily increase, making its loss less and less probable. As a result, sufficiently strong synergistic epistasis can effectively halt the action of Muller's ratchet. Instead of being driven extinct, a finite asexual population could then survive practically indefinitely, although with lower mean fitness than without random drift.

IN an asexual population random loss of all individuals free of deleterious mutations is irreversible (MULLER 1964), ignoring back mutations. Drift can lead to the successive extinction of all individuals carrying only one deleterious mutation, two mutations, and so on. This process, called MULLER's ratchet, can thus lead to unlimited accumulation of deleterious alleles. The rate with which the ratchet clicks (*i.e.*, the expected time between losses of all individuals with successive minimal numbers of mutations) depends chiefly on the expected absolute number of individuals with the minimal number m of mutations, $N_m = q_m N$, where q_m is their expected frequency and N is the effective population size. If $N_m \approx 1$ or less, the ratchet operates rapidly, if $N_m \approx 10$ it acts slowly, and if $N_m \approx 100$ or more, the time between clicks becomes very large (HAIGH 1978; STEPHAN *et al.* 1993).

With one exception, the ratchet has been studied only under non-epistatic selection where the fitness of individuals with i mutations is $w(i) = (1 - s)^i$ (or e^{-si} in a continuous approximation). Then, if initially the best genotype available carries $m \geq 0$ mutations, $q_m = e^{-U/s}$ regardless of m, where U is the genomic deleterious mutation rate (KIMURA and MARUYAMA 1966). Thus, the ratchet advances with a constant speed. This is caused by the fact that the rate of the relative decline of $w(i)$ is constant, because $w(i + 1)/w(i) = 1 - s$ with any i, and the distribution of the number of mutations in the genome, $p(i)$, in an infinite equilibrium population is Poisson with the parameter U/s, shifted to the right by m. Thus, $p(m) = q_m = e^{-U/s}$.

For $U \approx 1$ (MUKAI *et al.* 1972; HOULE *et al.* 1992) and $s = 0.1$, $q_m \approx 0.00005$, while if $s = 0.02$ (CROW 1979), $q_m \approx 10^{-22}$. Even in the first case mutations accumulate rapidly in obligately asexual populations with $N < 10^6$. If accumulation of mutations due to MULLER's ratchet leads to the decrease of N, the ratchet is facilitated further and the population can rapidly go extinct (mutational meltdown; LYNCH and GABRIEL 1990; GABRIEL *et al.* 1992).

Some data (MUKAI 1969; MALMBERG 1977) suggest that, rather than acting independently, deleterious alleles may act synergistically in the sense that each additional mutation causes a larger decline of relative fitness (see SHNOL and KONDRASHOV 1993). The only investigation of the ratchet under such selection was so far made by CHARLESWORTH *et al.* (1993, Table 6). Using computer simulations they observed that weak epistasis slows the ratchet down, but that the rate of decline of the mean fitness remains essentially the same, because under epistasis each successive click leads to a larger decline of fitness.

Obviously, stronger epistasis can lead to an even more pronounced effect. In the extreme case of truncation selection ($w(i) = 1$ for $i \leq T$, and $w(i) = 0$ for $i > T$) after selection all individuals in an equilibrium population have exactly T mutations, so that $m = T$ and $q_m = 1$. Thus, the ratchet does not operate, unless the population is very small, where one click leads to immediate extinction because every member of the next generation has acquired at least one new mutation.

In this report I will study MULLER's ratchet under more moderate, although still strong, synergistic epistasis. I will use deterministic iterations to find q_m, which should be sufficient to determine qualitatively the rate with which the ratchet operates in a population of a known size (see STEPHAN *et al.* 1993). A stochastic computer model will be used to check this.

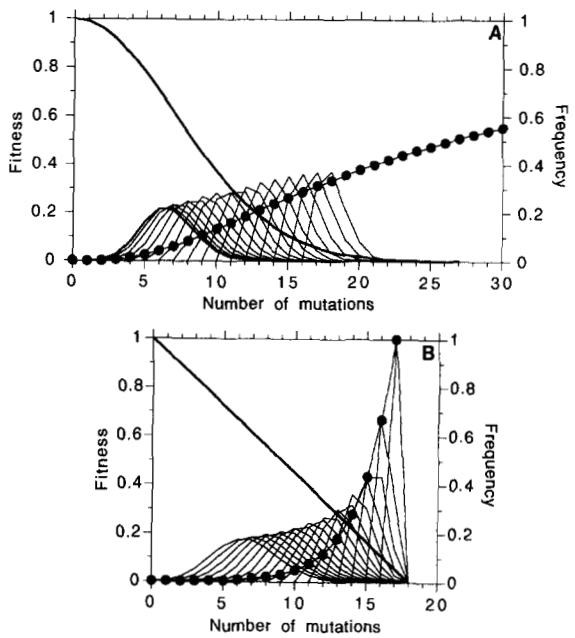

FIGURE 1.—Selection (thick line) and equilibrium distributions $\hat{p}_m(i)$ and q_m (circles) for $m = 0, 1, \ldots$ under $U = 0.5$ and $w(i) = \exp(-0.01i^2)$ (A) or $w(i) = 1 - 0.056i$ (B).

MODEL

Consider an infinitely large asexual population with discrete generations and the following life cycle: mutation and reproduction, followed by selection. All mutations are equally deleterious, so that the population is described by $p(i)$. An offspring receives k new mutations with probability $\mu(k) = e^{-U}U^k/k!$. Relative fitness $w(i)$ is non-increasing and $w(0) = 1$.

Mutation and selection cause the following changes in $p(i)$:

$$p'(i) = \sum_{j=0}^{i} \mu(i-j)p(j)$$

$$P(i) = p'(i)w(i)/W$$

where $P(i)$ denotes the distribution in the next generation and W is the population mean fitness (KIMURA and MARUYAMA 1966; Equation 3.1). This allows us to find the equilibrium distribution $\hat{p}(i)$ numerically. An analytical approach based on the assumption that $\hat{p}(i)$ is Gaussian (CHARLESWORTH 1990) will not be used here, because it significantly overestimates $\hat{p}$ (0) when its mean M_p is large.

RESULTS

Populations with different initial values of the minimal number of mutations m reach different equilibria $\hat{p}_m(i)$. Since an offspring never has fewer mutations than its parent, $\hat{p}_m(i) = 0$ for all $i < m$. On the other hand, if $w(m + 1) < w(m)$, $q_m = \hat{p}_m(m) > 0$. Figure 1 shows the families of $\hat{p}_m$(i) for $m = 0, 1, \ldots$ under Gaussian selection $w(i) = \exp(-\alpha i - (\beta/2)i^2)$ and linear selection $w(i) = \max(1 - ai, 0)$.

The equilibrium mean fitness $\hat{W}_m$ of a population with the distribution $\hat{p}_m(i)$ equals $w(m)e^{-U}$ (KIMURA and MARUYAMA 1966). Figure 2 presents the ratio $\hat{W}_m/\hat{W}_0 = w(m)$ and q_m under various m, $w(i)$, and U.

COMPUTER SIMULATIONS

A stochastic computer model of an asexual population of N individuals with discrete generations was studied to check the conclusions of the deterministic analysis. After reproduction, each organism produces many offspring, each of which carried all the mutations of its parent and k new ones with probability $\mu(k)$ (see above). During selection an offspring carrying i mutations survives with probability $w(i)$. Then exactly N survivors were chosen randomly to start a new generation. The program, written in MacFORTRAN, is available on request.

Each run was started from mutation-free individuals. If at some moment during the first 100 generations all mutation-free individuals were extinct, the number of mutations in the genome of one randomly chosen individual was artificially set to zero. Thus, the ratchet did not operate during this initial period, which allowed the population to equilibrate. After this the actual experiment was started.

Figure 3 presents data on the amount of time preceding the mth click of the ratchet (*i.e.*, between random losses of the last individuals with $m - 1$ and m mutations) and on the mean fitness between mth and $(m + 1)$th clicks. We can see that the ratchet initially proceeds very fast, but later drastically slows down.

Comparison with Figure 1 shows that the expected absolute number of individuals with the minimal number of mutations $N_m = q_m N$ indeed allows one to predict the rate at which the ratchet advances. This process markedly slows down when, in the course of accumulation of mutations, N_m become larger than 30. After the minimal number of mutations becomes 19, 13 or 9 (Gaussian selection, $N = 100$, 300 or 1000, respectively) or 15, 14 or 11 (linear selection, $N = 100$, 300 or 1000, respectively), no further clicks of the ratchet occurred in the computer runs which lasted 5000 generations each. In all these cases N_m is of the order of 100, and the actual number of individuals with the minimal number of mutations is very close to N_m (data not presented).

DISCUSSION

The data from Figures 1 and 2 show that under strong synergistic epistasis q_m grows rapidly as m increases. The reason for this is the following. The processes in an asexual population with $m > 0$ which is under selection $w(i)$ are identical to those in a population with $m = 0$ under selection $w_m(i) = w(i + m)/w(m)$. The equilibrium distribution $\hat{p}_m(m)$ in the first case differs from that

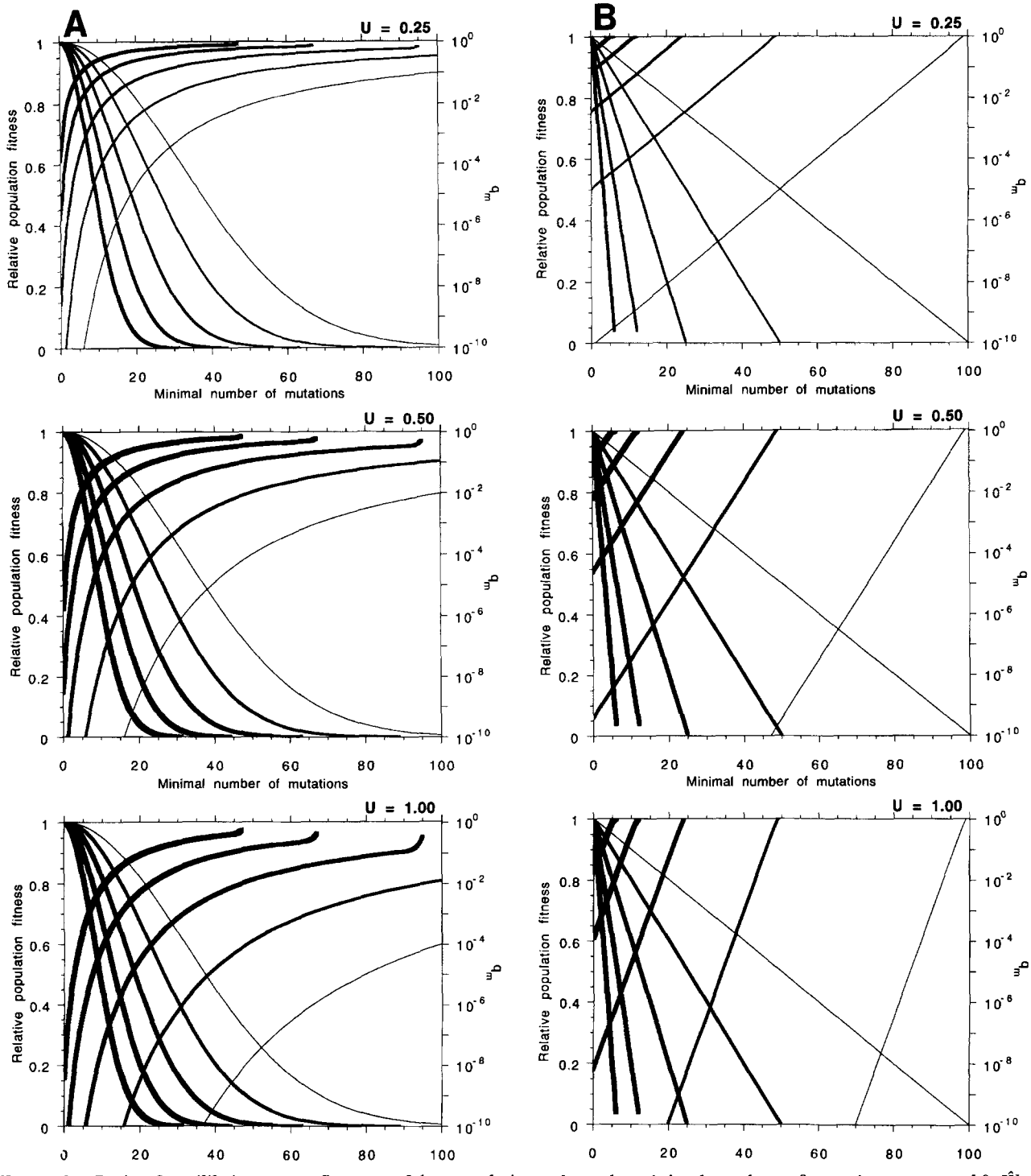

FIGURE 2.—Ratio of equilibrium mean fitnesses of the populations where the minimal numbers of mutations are m and 0, $\hat{W}_m/\hat{W}_0$ (decreasing lines) and q_m (increasing lines) for different m with Gaussian (A) ($\alpha = 0$; $\beta = 0.001$, 0.002, 0.004, 0.008 and 0.016, corresponding lines are of increased thickness) or linear (B) ($a = 0.01$, 0.02, 0.04, 0.08 and 0.16, corresponding lines are of increased thickness) selection under $U = 0.25$, 0.50 and 1.00.

in the second case only by the shift by m to the right. Under both Gaussian and linear selection, synergistic epistasis causes an accelerating decline of $w_m(i)$ when m increases. This leads to a smaller $M_p - m$ and higher q_m. In contrast, under multiplicative selection, $w_m(i) = (1 - s)^i$, $M_p - m = U/s$, and $q_m = e^{-U/s}$ under any m.

Under Gaussian selection with $\alpha = 0$, $w_m(i) = \exp(-m\beta i - (\beta/2)i^2)$. If $\alpha > 0$ a smaller m results in the same selection, so that $\hat{W}_m$ which corresponds to a particular q_m is higher (data not presented). Under linear selection $w_m(i) = 1 - (a/(1 - am))i$. With $m = 1/a$ this leads to strict truncation and to $q_m = 1$. Here q_m grows

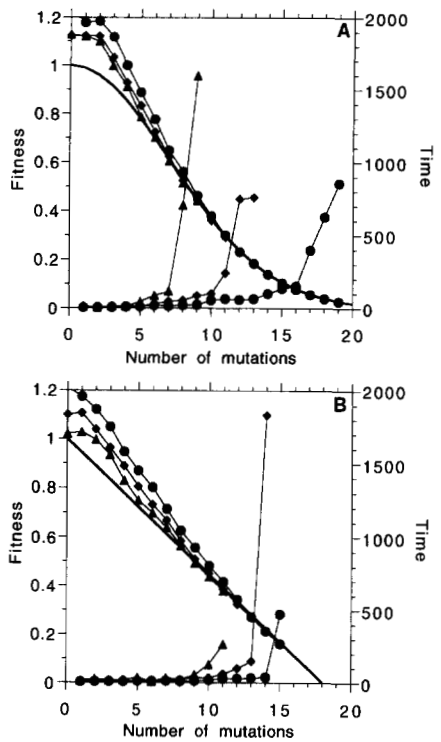

FIGURE 3.—Results of computer simulations. Mutation rate and selection in (A) and (B) are the same as in Figure 1, A and B, respectively. Population size N is 100 (circles), 300 (diamonds), and 1000 (triangles). The time between successive clicks of the ratchet (increasing curves) and the mean population fitness during this time (decreasing curves) are presented. Each point represents the average of five runs. Each run lasted 5000 generations, so that events which took longer were not observed.

exponentially with m (Figure 2B), although I do not have an analytical proof of this.

How this can be related to MULLER's ratchet, which operates only in finite populations? I assume that the distribution of the number of mutations in a finite population is close to that in an infinite population. Then, if initially $m = 0$, such a population reaches a quasi-equilibrium which is close to $\hat{p}_0(i)$. If in some generation individuals with 0 mutations are lost by chance and m becomes 1, the new quasi-equilibrium is close to $\hat{p}_1(i)$. This process goes on indefinitely, as long as N_m is not so large as to preclude the loss of the best genotypes by drift. As a rough guide such loss is unlikely if q_m becomes larger than $100/N$ under some m. Then the next click of the ratchet takes a very long time and in fact the population distribution remains close to $\hat{p}_m(i)$.

Let us roughly estimate when this happens. For example, with $N = 10^6$, then q_m must be greater than 10^{-4} to arrest the ratchet. Under multiplicative selection, $q_0 = \exp(-U/(w(0) - w(1))$. With synergistic epistasis q_m is even larger than $\exp(-U/(w_m(0) - w_m(1))$ because $w_m(i)$ declines faster as i increases. Thus, for $U = 1$ the ratchet is arrested if m is so large that $(w(m) - w(m + 1))/w(m) > 0.1$. With Gaussian selection and $\alpha = 0$, this requires $m > 1/(10\beta)$ (a smaller m is sufficient if $\alpha > 0$), while with linear selection this requires $m > 1/a - 10$, so that the population is only 10 clicks from extinction (Figure 2).

Computer simulations confirm this analysis (Figure 3). Of course, further clicks of the ratchet would be detected in longer runs, but the time between them continues to grow rapidly and becomes unrealistic if $N_m > 1000$ (STEPHAN *et al.* 1993). This confirms that the deterministic estimates of q_m are sufficient to make qualitative predictions about operation of the ratchet in a finite population of a known size. During the first clicks of the ratchet the mean population fitness seen in the simulations was slightly higher than that predicted analytically, perhaps because the time between clicks was small, and the population did not have time to reach equilibrium.

Thus, in old asexual populations under epistatic selection, selection against each new deleterious mutation is strong due to their previous accumulation. The value of q_m under a given m decreases with U, which means that it takes a larger minimal number of mutations to have a given frequency of individuals carrying this number (Figure 2). However, in an asexual population where the mutation load is always $1 - e^{-U}$ (KIMURA and MARUYAMA 1966), U cannot be much higher than 1.

The relative mean population fitness $\hat{W}_m/\hat{W}_0$ corresponding to a particular q_m increases when epistasis is stronger (and equals 1 in the extreme case of truncation selection) or U is smaller. If $w(m + 1)/w(m) < 0.9$, $\hat{W}_m$ is no more than $\exp(-1/(200\beta))$ or $10a$ under Gaussian and linear selection, respectively. Thus, further clicks of the ratchet can be prevented without too large a decline of $\hat{W}_m$ if $\beta > 0.005$ or $a > 0.05$ (Figures 2 and 3).

The consequences of the decline in $\hat{W}_m$ caused by the increase of m depend on the population ecology (LYNCH *et al.* 1993). If N declines more slowly with growing m than q_m increases, $N_m = q_m N$ will become larger than 100 under some m, which may arrest the ratchet. Otherwise, it continues to act and the population goes extinct.

In a quasi-equilibrium population after m clicks of the ratchet we can define a genetic load (CROW 1970) caused by the action of the ratchet. This "ratchet load" is $L_r = (\hat{W}_0 - \hat{W}_m)/\hat{W}_0 = 1 - w(m)$. This may be compared with the increase of the load caused by stochastic processes in a sexual population (KIMURA *et al.* 1963). Thus, even if the ratchet is eventually arrested, it can maintain sexual reproduction if $L_r > 0.5$, which offsets the twofold cost of anisogamous sex. However, even a slow rate of recombination or outcrossing is enough to recreate mutation-free genotypes and reverse the ratchet, provided that normal alleles exist at all loci (CHARLESWORTH *et al.* 1993). Obviously, there is a negative trade-off between the applicability of mutational stochastic (based on MULLER's ratchet) and mutational deterministic (see KONDRASHOV 1993) hypotheses on the evolution of sex:

synergistic epistasis interferes with the first mechanism but is essential for the second one.

The ratchet can be dramatically slowed down in a population of size 1000 even under linear selection, which represents a rather moderate form of synergistic epistasis, and the ratchet load which is necessary for this may be only about 0.5 (Figure 3B). Asexual populations often have much larger sizes, and may have fecundities sufficient to tolerate much higher loads. Thus, the effect reported here may be biologically important.

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