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QUANTITATIVE VARIATION IN FINITE PARTHENOGENETIC POPULATIONS: WHAT STOPS MULLER'S RATCHET IN THE ABSENCE OF RECOMBINATION?

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Abstract.—Finite parthenogenetic populations with high genomic mutation rates accumulate deleterious mutations if back mutations are rare. This mechanism, known as Muller's ratchet, can explain the rarity of parthenogenetic species among so called higher organisms. However, estimates of genomic mutation rates for deleterious alleles and their average effect in the diploid condition in *Drosophila* suggest that Muller's ratchet should eliminate parthenogenetic insect populations within several hundred generations, provided all mutations are unconditionally deleterious. This fact is inconsistent with the existence of obligatory parthenogenetic insect species. In this paper an analysis of the extent to which compensatory mutations can counter Muller's ratchet is presented. Compensatory mutations are defined as all mutations that compensate for the phenotypic effects of a deleterious mutation. In the case of quantitative traits under stabilizing selection, the rate of compensatory mutations is easily predicted. It is shown that there is a strong analogy between the Muller's ratchet model of Felsenstein (1974) and the quantitative genetic model considered here, except for the frequency of compensatory mutations. If the intensity of stabilizing selection is too small or the mutation rate too high, the optimal genotype becomes extinct and the population mean drifts from the optimum but still reaches a stationary distribution. This distance is essentially the same as predicted for sexually reproducing populations under the same circumstances. Hence, at least in the short run, compensatory mutations for quantitative characters are as effective as recombination in halting the decline of mean fitness otherwise caused by Muller's ratchet. However, it is questionable whether compensatory mutations can prevent Muller's ratchet in the long run because there might be a limit to the capacity of the genome to provide compensatory mutations without eliminating deleterious mutations at least during occasional episodes of sex.

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In small populations, slightly deleterious mutations have a reasonable chance of becoming fixed due to random drift (Crow and Kimura, 1970). Hence, small populations are likely to accumulate deleterious mutations leading to a deterioration of the genetic material if this process is not balanced by some kind of compensatory process.

Sexually and asexually reproducing populations differ considerably in their ability to limit the accumulation of deleterious mutations (Muller, 1964; Felsenstein, 1974; Maynard Smith, 1978; Kondrashov, 1982, 1984; Pamilo et al., 1987; Bell, 1988). If back mutations are rare and selection coefficients small, parthenogenetic populations are committed to an irreversible decay of the genetic material, a mechanism known as Muller's ratchet (Haigh, 1978). In sexually reproducing populations, recombination reduces genetic load at a rate sufficient to halt Muller's ratchet (Bell, 1988; Keightley and Hill, 1987). Obligatory parthenogenetic populations can persist only if population size is large and genomic mutation rate is low, whereas sexual populations can be stable even if population size is small and genomic mutation rate is high.

Muller's ratchet may explain the prevalence of sexual reproduction in multicellular organisms, especially in those populations with low inherent growth rate and small effective population size (Maynard Smith, 1978; Bell, 1988). But, even in sexually reproducing populations, Muller's ratchet can be active in parts of the genome in which for some reason the recombination rate is low. Muller's ratchet may thus explain the genetic inactivation of Y chromosomes by heterochromatization (Charlesworth, 1978). As shown in the "neo-Y chromosome" of *Drosophila miranda*, heterochromatization of Y chromosomes can be caused by the accumulation of repetitive DNA (Steinemann, 1982).

The rate of accumulation of deleterious mutations depends on the ratio θ of the genomic mutation rate U to the average se-

lection coefficient of the mutants (Haigh, 1978). A parthenogenetic population can resist the action of Muller's ratchet if the equilibrium frequency of the currently best genotype

$$\hat{p}_0 N = N \exp - \theta$$

is much higher than 1. Otherwise Muller's ratchet works, provided that back mutations are rare. Based on the most conservative estimate of the genomic mutation rate and the average selection coefficient of viability mutations in *Drosophila* (Mukai et al., 1972), it can be predicted that a parthenogenetic *Drosophila* species needs a population size of much larger than 10^9 to withstand genetic deterioration (see Appendix A). Other estimates based on Mukai's data lead to required population sizes of 1.3×10^{32} and 2.1×10^{77}, which is much larger than the most optimistic estimates of *Drosophila* population sizes (Ayala, 1972). A population would become extinct within a few hundred generations if all these mutations were unconditionally deleterious. Nevertheless, there is at least one obligatory parthenogenetic *Drosophila* species, *Drosophila mangabeiri* (Carson, 1967), and at least 52 other Dipteran species that show some kind of parthenogenesis, as for instance *Smittia* (Adelbauer, 1986). In addition about 10% (38 species) of European Psocopterans and 3.5% (44 species) of European Curculionid beetles are obligatory parthenogenetic (Adelbauer, 1986). Muller's ratchet would eliminate these species within a few hundred generations provided that the estimates from *Drosophila* are representative for insects and if back mutations play no part.

In all models of Muller's ratchet analyzed so far, back mutations have been neglected. This assumption is motivated by the low chance of restoring exactly the same nucleotide sequence by mutation. However, natural selection often does not act on the primary structure of nuclear DNA directly. Instead the fitness of organisms usually depends on a number of highly complex and polygenic traits, such as body size and fertility. What matters are not differences in DNA structure directly but their effects on these organismic properties.

The effects of gene mutations can roughly be classified in two categories: unconditional and conditional. Unconditional effects are most closely in accordance with the assumptions of Muller's ratchet model. These are mutations that have deleterious effects regardless of the genetic background in which they occur. Examples may be mutations that lead to biochemical defects that cannot be compensated by mutations at other loci. For these mutations, back mutations have to occur at the very locus at which the deleterious mutation occurred. The probability of such back mutations is very low. Conditional effects, however, depend on the genetic background in which they occur. They might be indirect effects of mutations on complex phenotypic characters, such as those responsible for the additive genetic variation of quantitative traits. To avoid confusion we denote those "back mutations" that restore the original phenotype by means other than restoring the original polynucleotide sequence as "compensatory mutations." Compensatory mutations can occur at as many places throughout the genome as there are genes that influence the same traits. The genetic literature shows that conditional genetic effects are very frequent. Many phenotypes, such as the bithorax phenotype of *Drosophila* (Waddington, 1956), Warfarin resistance in rats (Ford, 1975), and industrial melanism in the moth *Gonodontis bidentata* (see also Ford, 1975), can be produced by major mutations as well as by polygenic variation at other loci. This indicates that almost any phenotypic effect of one gene can be modified by variation at other gene loci (Lande, 1983).

True back mutations seem to be rare but compensatory mutations for conditional genetic effects seem to be more probable. Exactly how frequent they are depends on the particular trait that is affected by the conditional mutation. At a formal level, compensatory mutations have the same potential to halt Muller's ratchet as recombination, since natural selection acts on total fitness regardless of whether it is restored by recombination or compensatory mutations. Recombination may restore the original genotype, and compensatory mutations restore the original genotypic effect.

For the plausibility of Muller's ratchet, it

is essential to know how many of the deleterious mutations have unconditional effects, which lead unquestionably to Muller's ratchet, and how many have conditional effects. In addition it is necessary to know how large the probability of compensatory mutations is to determine whether they can halt the deteriorating effect of Muller's ratchet. It is difficult to obtain reasonable estimates of both values. The proportion of conditional versus unconditional mutations is perhaps hardest to estimate, and it is even difficult to see how this value can be determined empirically. However, the effects on quantitative characters under stabilizing selection are straightforward to predict, at least theoretically. If the mean genotypic value of the population is close to the optimum, almost every mutation affecting quantitative traits is deleterious (Fisher, 1958; Haldane, 1966). Their effects, however, can be compensated by mutations at other loci if these mutations have allele effects with a sign opposite to that of the first mutation.

In this paper the effectiveness of compensatory mutations in halting Muller's ratchet is explored. In particular we analyze the evolution of a number of quantitative polygenic characters in an obligatory parthenogenetic population under stabilizing selection and high mutation rate. To explore the possibility of Muller's ratchet in this model, we ask whether there is a formal analogy between the model of Muller's ratchet proposed by Felsenstein (1974), which was analyzed by Haigh (1978), and the quantitative genetic model analyzed here. In addition, the effectiveness of compensatory mutations in stopping Muller's ratchet is studied. A preliminary report on simulation results has been published elsewhere (Gabriel and Wagner, 1988).

The Model

We consider a finite population of an obligatory parthenogenetic organism with effective population size N_e. We assume that the maternal genotype is transmitted intact with the exception of mutations. This is the case for apomixis as well as for many forms of meiotic parthenogenesis (White, 1973). The phenotype is described as an N-dimensional vector $\mathbf{z} = (z_1, \ldots, z_N)$, in Euclidian space. The components of $\mathbf{z}$, z_i, represent the phenotypic values of characters or traits. The value of each character is the result of genetic and environmental effects

$$z_i = x_i + e_i$$

with no genotype–environment interaction. Because of the absence of recombination, the genotype of each individual is fully determined by the vector $\mathbf{x} = (x_1, \ldots, x_N)$ of the genotypic values of all characters. Gene number, ploidy level, and allelic effects at individual loci are irrelevant in the present context.

For simplicity we assume that phenotypic differences influence viability $W(\mathbf{z})$ but not fertility. Each individual has the same number of offspring N_b. The life cycle consists of three stages: (1) selection by viability differences, (2) random sampling of N_p parental animals from the surviving progeny, and (3) reproduction and mutation. Since we sample from a finite pool of eggs without replacement, the effective population size is slightly larger than N_p (Crow and Kimura, 1970).

The genomic mutation rate is denoted by u. The transition density $u(\mathbf{x}', \mathbf{x})$ from genotype $\mathbf{x}$ to genotype $\mathbf{x}'$ by mutation is assumed to be a multivariate Gaussian distribution with mean vector $\mathbf{x}$ and variance m^2

$$\begin{aligned} \mathbf{x} \to \mathbf{x}' &= \mathbf{x} + \mathbf{dx} \\ u(\mathbf{x}', \mathbf{x}) &= (2\pi m^2)^{-N/2} \\ &\quad \exp\{-[\mathbf{x}' - \mathbf{x}]^2/2m^2\} \end{aligned} \tag{2.1}$$

where $[\mathbf{y}]$ denotes the Euclidian norm of a vector $\mathbf{y}$

$$[\mathbf{y}] = \left(\sum_{i=1}^{N} y_i^2\right)^{1/2}$$

The norm $[\mathbf{y}]$ is the (Euclidian) distance between the base and the "tip" of the vector $\mathbf{y}$. Equation (2.1) is equivalent to the assumption that the probability of reaching a genotype $\mathbf{x}'$ from a genotype $\mathbf{x}$ by mutation depends only on the distance $[\mathbf{dx}] = [\mathbf{x}' - \mathbf{x}]$ between $\mathbf{x}'$ and $\mathbf{x}$ in the space of genotypic values. As a consequence of (2.1) mutations stochastically affect each character independent of other characters.

The viability function $W(\mathbf{z})$ determines the probability that an individual with phenotype $\mathbf{z}$ survives to maturity. We assume

$W(\mathbf{z})$ to be a multivariate Gaussian fitness function

$$W(\mathbf{z}) = K \exp\{-[\mathbf{z} - \mathbf{z}_{opt}]^2/2w^2\} \quad (2.2)$$

where K is a positive constant less than or equal to 1 which determines the viability of the optimal phenotype $\mathbf{z}_{opt}$. Without loss of generality, the origin of phenotypic space is assumed to be identical with $\mathbf{z}_{opt}$. Equation (2.2) is a fitness function that leads to optimizing or stabilizing selection. The intensity of stabilizing selection is determined by the width of the fitness function, w. As w decreases, the intensity of the stabilizing selection increases. The environmental effects are also assumed to be multivariate Gaussian with mean zero and variance V_E. Finally, it is assumed that generations are nonoverlapping. The fitness of a given genotype is obtained from (2.2) by averaging over the environmental effects. This also yields a Gaussian function

$$W(\mathbf{x}) = W_0 \exp\{-[\mathbf{x}]^2/2V_s\} \quad (2.3)$$

with

$$W_0 = K(w^2/V_s)^{N/2}$$

$$V_s = w^2 + V_E$$

The Analogy to the Models of Felsenstein and Maynard Smith

Muller (1964) developed the ratchet mechanism by verbal arguments. The first detailed evaluation of Muller's ratchet was given by Felsenstein (1974), who performed stochastic computer simulations. In his model the genotype is characterized by an integer k, the number of deleterious mutations it is carrying. The fitness of individuals carrying k mutations was assumed to be

$$W(k) = (1 - s)^k \quad (3.1)$$

$(0 < s < 1)$, i.e., each additional mutation lowers fitness by a constant factor $(1 - s)$.

$$W(k + 1) = W(k)(1 - s) \quad (3.2)$$

Back mutations were ignored. Felsenstein was able to demonstrate a ratchet effect if $0.3 < N_e s < 30$ and $N_e\mu > 5$. Under these conditions the rate of accumulation of deleterious mutations is higher in parthenogenetic populations than in sexual populations.

This model was further analyzed by Haigh (1978) and Maynard Smith (1978) and will be called the Felsenstein–Maynard Smith model (F-MS model). Haigh gave an approximate expression for the deterministic equilibrium distribution of genotypes

$$\hat{n}_k = N_e(\theta^k/k!)\exp\{-\theta\} \quad (3.3)$$

with $\theta = \mu/s$ and n_k is the number of genotypes with exactly k mutations (Haigh, 1978). $\hat{n}_k$ is the number of genotypes with the k mutations in mutation selection equilibrium. The ratchet starts operating as $\hat{n}_0$

$$\hat{n}_0 = N_e\exp\{-\theta\} \quad (3.4)$$

becomes small enough so that extinction of the best genotype by random drift becomes inevitable within a few generations. Bell (1988) showed that the mean number of generations to extinction of the optimal genotype was roughly $10\hat{n}_0$. After extinction of the optimal genotype, the genotype with only one mutation, $k = 1$, becomes the genotype with the highest fitness and will have an equilibrium frequency given by (3.4). In turn the best current genotype will also go extinct within about $10\hat{n}_0$ generations. In this case the evolution of the population follows the direction of mutation pressure.

It will be shown that the F-MS model can be used to predict the levels of mutation rate and selection intensity where Muller's ratchet starts to work in our quantitative genetic model, provided the number of stochastically independent characters contributing to fitness is not too small.

Conditions for the Applicability of the F-MS Model to Quantitative Variation

The F-MS model contains two important assumptions: each mutation lowers the fitness of the genotype by a constant factor $(1 - s)$, and back mutations are rare. In this section it is shown that the quantitative genetic model is equivalent to the F-MS model provided the mean genotypic effect is close to the optimum.

The Change of Fitness Caused by Mutation.—Let us consider the effect of a mutation

$$\mathbf{x} \rightarrow \mathbf{x}' = \mathbf{x} + \mathbf{dx}$$

on the fitness of the genotype

$$W(\mathbf{x}') = W_0\exp\{-[\mathbf{x} + \mathbf{dx}]^2/2V_s\} \quad (3.5)$$

The distribution of mutational effects depends only on **dx** and is given by

$$u(\mathbf{dx}) = (2\pi m^2)^{-N/2}\exp\{-[\mathbf{dx}]^2/2m^2\} \quad (3.6)$$

Because the fitness of the genotype $\mathbf{x}'$ depends only on the distance of $\mathbf{x}'$ from the optimum, one has to calculate the norm of $[\mathbf{x}']$,

$$[\mathbf{x}']^2 = [\mathbf{x}]^2 + [\mathbf{dx}]^2 + 2(\mathbf{x}, \mathbf{dx}) \quad (3.7)$$

where $(\mathbf{x}, \mathbf{dx})$ is the inner product of the vectors **x** and **dx**. The term $[\mathbf{dx}]$ is the norm of **dx** and therefore always positive, whereas $(\mathbf{x}, \mathbf{dx})$ may be positive or negative. Whether the mutation is deleterious or favorable depends on the sign of

$$\begin{aligned} D &= [\mathbf{x}']^2 - [\mathbf{x}]^2 \\ &= [\mathbf{dx}]^2 + 2(\mathbf{x}, \mathbf{dx}) \end{aligned} \quad (3.8)$$

If D is greater than zero, $\mathbf{x}'$ will have a greater distance from the optimum and therefore lower fitness (deleterious mutation). If D is less than zero, $\mathbf{x}'$ will be closer to the optimum than **x** and $W(\mathbf{x}')$ will be greater than $W(\mathbf{x})$, i.e., $\mathbf{x}'$ is a favorable or a "compensatory mutation."

The fitness of $\mathbf{x}'$ can be written as

$$\begin{aligned} W(\mathbf{x}') = W(\mathbf{x})&\exp\{-[\mathbf{dx}]^2/2V_s\} \\ &\exp\{-2(\mathbf{x}, \mathbf{dx})/2V_s\} \end{aligned} \quad (3.9)$$

The mean fitness of all mutants of **x** is obtained from

$$W(\mathbf{x}'|\mathbf{x}) = \int \ldots \int W(\mathbf{x} + \mathbf{dx})u(\mathbf{dx})\, d(\mathbf{dx})$$

by direct integration.

$$\begin{aligned} W(\mathbf{x}'|\mathbf{x}) &= W(\mathbf{x})[V_s/(V_s + m^2)]^{N/2} \\ &\exp\{m^2[\mathbf{x}]^2/2V_s(V_s + m^2)\} \end{aligned} \quad (3.10)$$

As long as $[\mathbf{x}]$ is not too large, i.e., if

$$[\mathbf{x}]^2 \ll 2V_s(V_s + m^2)/m^2 \quad (3.11)$$

the last term in (3.10) can be ignored. Condition (3.11) is easily fulfilled as long as selection intensity is low and the average effect of the mutations is small ($V_s \gg m^2$). Consequently, the mean fitness of genotypes that carry only one more mutation than **x** (so called first-order mutants of **x**) is lower than $W(\mathbf{x})$ by a factor independent of $[\mathbf{x}]$

$$W(\mathbf{x}'|\mathbf{x}) \cong W(\mathbf{x})[V_s/(V_s + m^2)]^{N/2} \quad (3.12)$$

This is in concordance with the assumption of the F-MS model where this factor is $(1 - s)$. For $N \gg 1$ the factor in (3.12) can be expressed as a function of the average squared mutation step length $E([\mathbf{dx}]^2) = Nm^2$

$$(1 - s) \cong \exp[-E([\mathbf{dx}]^2)/2V_s] \quad (3.13)$$

The Probability of Compensatory Mutations.—Because fitness depends only on the distance of the genotypic values from the optimum $[\mathbf{x}]$, we are mainly interested in the influence of mutations on $[\mathbf{x}]$. This is a stochastic process on the positive real numbers, called the Bessel process (see Karlin and Taylor, 1975). However, direct calculation of the probability of compensatory mutations from the transition density of the Bessel process (see formula 6.2 on p. 368 in Karlin and Taylor, 1975) is tedious and does not lead to a formula for all N. Therefore, we give a formula for large N, which is easily proven.

As shown above [see Eq. (3.8)], a mutation is compensatory if

$$D = [\mathbf{dx}]^2 + 2(\mathbf{x}, \mathbf{dx})$$

is less than zero. The quantity $[\mathbf{dx}]^2$ is distributed according to a Pearson type III distribution (Wilks, 1962 p. 172) with expected value

$$E([\mathbf{dx}]^2) = Nm^2 \quad (3.14)$$

and variance

$$\mathrm{Var}([\mathbf{dx}]^2) = 2Nm^4 \quad (3.15)$$

Without loss of generality we may assume that $\mathbf{x} = ([\mathbf{x}], 0, \ldots, 0)$. Then the inner product in (3.8) becomes

$$(\mathbf{x}, \mathbf{dx}) = [\mathbf{x}]\, dx_1 \quad (3.16)$$

and dx_1 is normally distributed with $E(dx_1) = 0$ and

$$\mathrm{Var}(dx_1) = m^2 \quad (3.17)$$

From (3.8) and (3.14)–(3.17) it is easily deduced that D is distributed with the parameters

$$\begin{aligned} E(D) &= Nm^2 \\ \mathrm{Var}(D) &= 2Nm^4 + 4[\mathbf{x}]^2m^2 \end{aligned} \quad (3.18)$$

This follows from $\mathrm{Var}(D) = E(D^2) - E(D)^2$ with

$$E(D^2) = E\{([\mathbf{dx}]^2)^2 + 4(\mathbf{x}, \mathbf{dx})[\mathbf{dx}]^2 + 4(\mathbf{x}, \mathbf{dx})^2\}$$

For large N and $Nm^2 \ll 2[\mathbf{x}]^2$, the Pearson type III distribution is approximately Gaussian and the probability of compensatory mutations can be expressed as

$$P(D < 0) = \Phi(-Nm^2/\mathrm{Var}(D)^{1/2}) \quad (3.19)$$

with

$$\Phi(-t) = (2\pi)^{-1/2} \int_{-\infty}^{-t} \exp(-y^2/2)\, dy \quad (3.20)$$

From the properties of the cumulative Gaussian distribution function it is clear that $P(D < 0)$ is small if the absolute value of the argument in (3.19) is large. This is equivalent to the condition

$$[\mathbf{x}]^2 \ll (m^2/4)(N^2 - 2N) \quad (3.21)$$

i.e., compensatory mutations are rare as long as the vector of genotypic effects is close to the optimum, the mutation variance is large, and the number of characters high.

The Equilibrium Frequency of the Fittest Genotype.—The critical condition for the action of Muller's ratchet is the equilibrium frequency $\hat{n}_0$ of the fittest genotype $\mathbf{x}_0$ [see formula (3.4)]. As soon as $\hat{n}_0$ approaches zero the fittest genotype cannot be maintained in the population by selection. We will use the analogies between the F-MS model and the quantitative genetic model to predict the mutation rates and selection intensities under which $\hat{n}_0$ approaches zero.

By using the analogies demonstrated above the critical parameter of the F-MS model, $\theta = \mu/s$, can be calculated as

$$\theta = \mu[1 - \exp(-N\, m^2/2V_s)]^{-1} \quad (3.22)$$

The expected equilibrium frequency then is

$$\hat{n}_0 = N_e \exp\{-[\mu[1 - \exp(-Nm^2/2V_s)]^{-1}]\} \quad (3.23)$$

According to Maynard Smith (1978) we would expect Muller's ratchet to work in almost any population if $\theta > 20$.

The analogy of our model to the F-MS model has been derived under the condition that [x] is small. As Muller's ratchet starts to work one has to expect two effects: (1) a rapid turnover of genotypes, i.e., there will be no stable genotype distribution, and new mutations will rapidly replace the present nucleotide sequences, and (2) a correlated decrease in fitness. However, as fitness decreases, the average distance of the genotypic values to the optimum will increase, and the conditions for the analogy with the F-MS model are violated. Since the phenomenon of Muller's ratchet has two aspects, namely turnover of genotypes and decrease of fitness, there are three conceivable consequences: (1) Muller's ratchet goes on with genotype turnover and decrease in fitness, (2) Muller's ratchet stops completely, or (3) the decrease of fitness ceases but the turnover of genotypes goes on. The fourth conceivable alternative, a cessation of genotype turnover while the decrease of fitness continues, is biologically impossible. Simulation results indicate that the third alternative is the case, i.e., the decrease of fitness ceases, while the turnover of mutations continues (see Gabriel and Wagner, 1988; and below).

The turnover of genotypes will stop only if a genotype occurs in considerably higher equilibrium frequency than the optimal genotype. Otherwise drift will wipe out the currently best genotypes as fast as the optimal one. The deterministic equilibrium frequency depends on the genomic mutation rate and the relative fitness of the mutants [see Eq. (3.3)]. Because we assume that all genotypes have equal genomic mutation rates, a higher equilibrium frequency can result only if the mutants of this genotype have a lower relative fitness than the mutants of the optimal genotype. In our model, however, the average fitness of mutants $W(\mathbf{x}'|\mathbf{x})$ becomes more similar to $W(\mathbf{x})$ as [x] increases [see Eq. (3.10)], and therefore such a genotype cannot exist. The equilibrium frequency of nonoptimal genotypes cannot be greater than the equilibrium frequency of the optimal genotype, even in the absence of the optimal genotype. As soon as Muller's ratchet starts to work the turnover of genotypes will never stop.

The Required Rate of Compensatory Mutations to Halt the Decrease in Fitness.—It has been shown above that as long as the population is close to the optimum, a strong analogy between the F-MS model and the quantitative model holds. However, as Muller's ratchet starts to work, the average distance of the genotypic values to the optimum might increase, and so will the rate

of compensatory mutations (see above; Fisher, 1958; Haldane, 1966). The question arises, at what distance from the optimum will the rate of compensatory mutations be large enough to halt the decrease of mean fitness?

This depends critically on the deterministic equilibrium frequency of the currently best genotype $\hat{p}_0$. If $\hat{p}_0$ can be realized in the population, i.e., if $\hat{n}_0 = N_e\hat{p}_0 > 1$, the answer can be given in a straightforward manner on the basis of the analogy to the F-MS model. If $\hat{n}_0 > 1$, the average waiting time until extinction of the currently best genotype is approximately $10\hat{n}_0$ (Bell, 1988). From this, Bell concluded that it is sufficient if about 0.1 unloaded genomes are generated by recombination per generation to halt Muller's ratchet. It is irrelevant in the present context whether "unloaded genomes" are produced by recombination or by compensatory mutations. It should be sufficient if about 0.1 compensatory mutations occur per generation in a parthenogenetic population. The number of compensatory mutations produced per generation is

$$n_c = (N_e - \hat{n}_0)\mu P(D < 0)$$

For instance if $\mu = 0.01$ and population size is of the order of 1,000, then the necessary rate of compensatory mutations would be $P(D < 0) = 0.01$. However, if $\hat{n}_0$ is less than 1, as is the case in most of our simulations, the required rate of compensatory mutation is much higher, because the time to extinction is much less than $10\hat{n}_0$. Exactly how large it is cannot be deduced from the analogy to the F-MS model because it depends on the distribution of genotypic values in the population. Therefore, we present a detailed analysis of this question below.

Simulation Results

Stochastic simulations were performed to examine three questions: (1) are the approximations given above [Eq. (3.23)] adequate to predict the mean equilibrium frequency of the optimal genotype, (2) does Muller's ratchet start to work if mutation rate is high and stabilizing selection weak [$\theta > 20$, see Eq. (3.22)], and (3) what happens if the conditions for the validity of the F-MS model are violated because the average [x] increases over time? The last question is examined in the following sections.

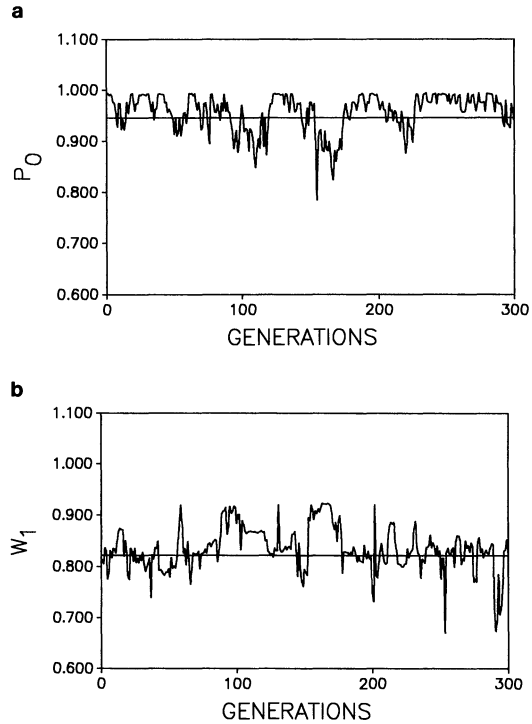

FIG. 1. Mutation–selection balance under strong selection ($w = 0.5$) and low genomic mutation rate ($\mu = 0.01$); (a) Fluctuations of the frequency of the optimal genotype p_0 around the deterministic prediction [see Eq. (3.23)] indicated by the horizontal line; (b) fluctuations of the average fitness of the first-order mutants of the optimal genotype ($N_p = 50$, $N = 10$, $N_b = 100$, $V_E = 0$, $m = 0.1$, $w = 0.5$).

In Figures 1a and 2a the fluctuations of p_0, the frequency of the optimal genotype, is shown over a period of 300 generations and compared with the prediction according to Eq. (3.23). There is good concordance between the average frequency and the predicted equilibrium frequency. To determine whether this concordance is due to chance or to a valid approximation, other predictions of the approximation were tested.

A reasonable test of the approximation is to check whether the results given above can predict the mean fitness of the first-order mutants of the optimal genotype. This is shown in Figures 1b and 2b. Only minor fluctuations in mean fitness of first-order mutants were found. The simulated values are similar to the predicted values but tend to be slightly higher than the prediction from

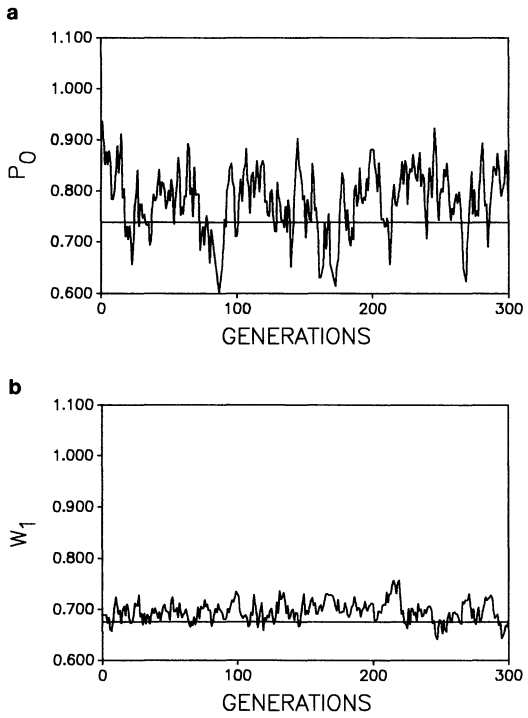

FIG. 2. As in Figure 1, the mutation–selection balance under strong selection ($w = 0.5$), but with higher mutation rate ($\mu = 0.1$) and larger number of characters; (a) fluctuations of the relative frequency p_0 of the optimal genotype; (b) fluctuations of the mean fitness of the first-order mutants of the optimal genotypes. Note that the fitness of the mutants is slightly higher than predicted, most probably because of selection processes among the mutants of the optimal genotype. ($N_p = 50$, $N = 20$, $N_b = 20$, $V_E = 0$, $m = 0.1$, $w = 0.5$).

Eq. (3.12). This discrepancy is probably due to the fact that in our model there is variance in fitness among the first-order mutants of the optimal genotype. Consequently the mean fitness of the first-order mutants will increase due to selection.

According to the F-MS model, the critical parameter, which determines whether Muller's ratchet works, is $\theta = \mu/s$, the ratio of the genomic mutation rate and the selection coefficient. In the quantitative genetic model considered here this parameter is given by Eq. (3.22). If θ is small, $\hat{n}_0$ should be high and Muller's ratchet should not work. If θ is large (>20), $N_e\hat{p}_0$ approaches zero in virtually all finite populations and if θ is of the order of 1, Muller's ratchet will work only in small populations. These predictions are confirmed by the simulation results. As long as $\theta < 0.2$ no extinction of the optimal genotype is recorded ($N = 9$). For $\theta = 0.5$ in about 40% of the simulations the optimal genotype is lost within the first 300 generations. If θ was greater than 2, Muller's ratchet worked in all runs examined.

Figure 3 shows the frequency distribution of mutants of different orders for five different time instances. It can be seen that the frequency of the fittest genotype becomes zero after 35 generations. By generation 47 even the first-order mutants become extinct and the process continues. Muller's ratchet apparently works as expected.

In Figure 4 the maximum, minimum, and average "mutation orders" of the genotypes in the population are plotted over time. The mutation order, k, of a genotype is the number of mutational events that led from the optimal genotype, which was the only genotype at the beginning, to the particular genotype with "mutation order" k. The average mutation order increases approximately linearly over time. This indicates that

TABLE 1. Average substitution rates of mutant genotypes for two population sizes and three selection intensities (mutation rate $\mu = 0.1$, number of characters $N = 10$, average mutational effect $m = 0.1$). The averages and the standard errors are estimated from eight simulations for each parameter combination. The substitution rates are calculated as the average number of mutations per genome accumulated over 600 generations divided by the number of generations. The substitution rate expected from the formula of Kimura (1962) for sexually reproducing populations is given in parentheses below the simulation result. Note that the substitution rate approaches the mutation rate if population size is small and/or selection is weak. In larger populations and under strong selection the substitution rates are higher than predicted by the formula of Kimura (1962).

	Intensity of stabilizing selection w		
N_p	3	5	10
50	0.084 ± 0.003 (0.075)	0.093 ± 0.003 (0.091)	0.099 ± 0.006 (0.098)
150	0.086 ± 0.003 (0.004)	0.095 ± 0.005 (0.073)	0.103 ± 0.003 (0.093)

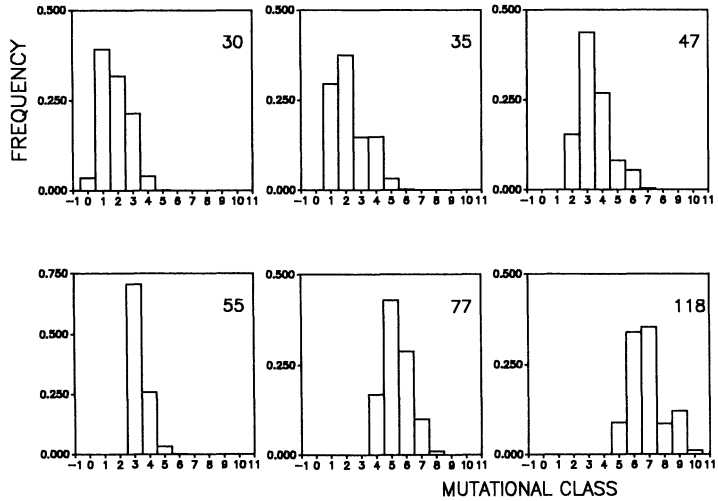

FIG. 3. The distribution of genotypes with 0, 1, . . . , 11 mutations at generation 30, 35, . . . , 118. The statistics are taken after selection and before randomly choosing the mothers of the next generation. The generation number is given on the right of each histogram ($N_p = 50$, $N = 40$, $N_b = 20$, $V_E = 0$, $m = 0.1$, $w = 3$, $\mu = 0.1$).

there is a continuous turnover of genotypes with a constant rate of genotype substitution. Table 1 gives the average substitution rates for various simulation runs. The observed substitution rates are larger than the substitution rates predicted for sexual populations (Kimura, 1962), if selection is relatively strong and population size is large. This result confirms the predictions of Felsenstein (1974) and is caused by the so called Hill-Robertson effect. The substitution rates approach the values predicted for sexual populations if selection is weak and population size small. The predictions of Bell (1988) are always smaller than the observed rates, most probably because the deterministic equilibrium frequency of the currently best genotype is always less than one, which is in contrast to Bell's assumptions.

In summary, the approximations derived in this section are adequate to predict the equilibrium frequency of the optimal genotype and to predict whether Muller's ratchet starts to work for given selection intensity, mutation rate, and average mutational effect.

THE EVOLUTION OF MEAN FITNESS AND PHENOTYPIC VARIATION

Muller's ratchet leads to a steady accumulation of mutations such that the average number of mutations per individual increases approximately linearly in time (Felsenstein, 1974; Maynard Smith, 1978). In the F-MS model the accumulation of mutations is associated with decreasing mean fitness, which ultimately may lead to genetic deterioration or extinction. Because in the F-MS model fitness decreases multiplicatively with the number of mutations, k, that a genotype carries, it is convenient to consider the logarithm of fitness (log-fitness)

$$\ln W(k) = k \ln(1 - s) \qquad (4.1)$$

instead of $W(k)$. Mean log-fitness is directly proportional to $\bar{k}$, the mean number of mu-

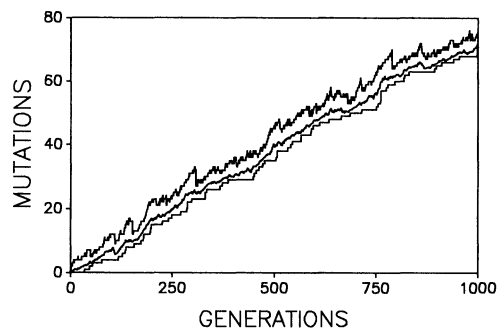

FIG. 4. Accumulation of mutations: the maximum, minimum, and average number of mutations per genotype are shown as a function of generation number. The parameters are the same as in Figure 3.

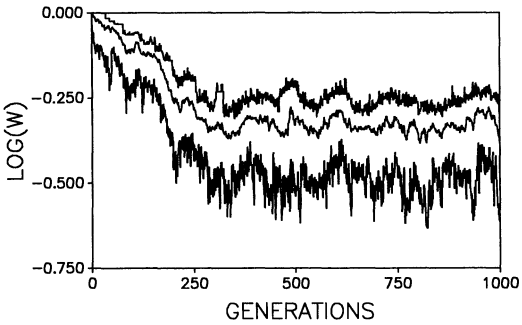

FIG. 5. Equilibration of fitness: the time courses of the maximum, minimum, and average log-fitness of genotypes are shown for the same simulations as in Figures 3 and 4.

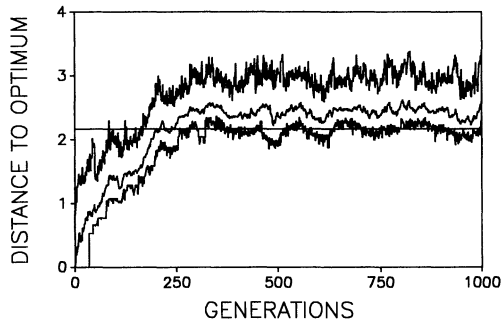

FIG. 6. Equilibration of the phenotypic distribution: the evolution of maximum, minimum, and average distance to the optimum is shown for the same simulations as in Figures 3, 4, and 5. The horizontal line gives the average distance to the optimum predicted for a biparental population under the same circumstances. Note that the equilibrium reached for a parthenogenetic population resembles that for a sexual population.

tations per genome,

$$\text{mean}(\ln W) = \bar{k} \ln(1 - s) \qquad (4.2)$$

Because $\ln(1 - s) < 0$, an increase in $\bar{k}$ will cause a corresponding decrease in mean fitness. Because genotype substitution rate is constant, mean log-fitness will decrease linearly with time T

$$\text{mean}(\ln W) = -\text{const. } T \qquad (4.3)$$

In our model random drift also leads to a steady accumulation of mutations (see above). In this section we examine whether prediction (4.3) also holds for our model or whether compensatory mutations are able to stop the decrease in fitness.

In Figure 5, prediction (4.3) is compared with the evolution of mean log-fitness during the simulation run shown in Figure 4. It can be seen that mean log-fitness decreases almost linearly during the first 300 generations but then levels off. After the first 300 generations, mean fitness remains constant in spite of the steady turnover of genotypes.

This result is in contrast to the expectation gained from the F-MS model (4.3). In our model Muller's ratchet does not affect genetic deterioration and extinction most probably because of the frequency of compensatory mutations. In our model $\ln W$ is proportional to $[\mathbf{x}]^2$, i.e., to the squared distance of the genotypic values $\mathbf{x}$ to the optimum

$$\ln W = -[\mathbf{x}]^2/(2V_s) + C \qquad (4.4)$$

where C is a term independent of the genotype (see 2.3). Hence the mean log-fitness is proportional to mean($[\mathbf{x}]^2$), the mean squared distance to the optimum,

$$\text{mean}(\ln W) = -\text{mean}([\mathbf{x}]^2)/2V_s + C \qquad (4.5)$$

Mean fitness remains constant because the genotype distribution in the population remains within the vicinity of the optimum. This conclusion is confirmed by the analysis of the simulation run shown in Figure 5. In Figure 6 the mean($[\mathbf{x}]^2$) is plotted over time. It can be seen that the mean of $[\mathbf{x}]^2$ increases at the beginning and reaches a stationary level after about 300 generations. The stability of the stationary value has been tested by simulations in which the initial genotype had a greater distance to the optimum than the supposed equilibrium point from Figure 6. In Figure 7 it is shown that mean($[\mathbf{x}]^2$) approaches the stationary value of Figure 6. The population shows adaptation, i.e., the dispersion of genotypic values (the phenotypic effects of genotypes) approaches the optimum, even if no single "best genotype" can be selected under the influence of high mutation rates. This evolutionary stability of the phenotypic dispersion is never lost in our model, even at very high genomic mutation rates ($\mu = 1$, see Fig. 8). Moreover, the average genotypic value predicted for sexual populations is close to that observed in our simulations of parthenogenetic pop-

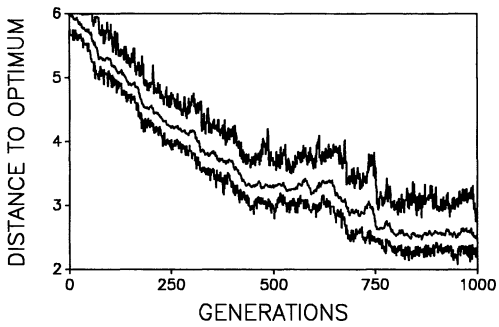

FIG. 7. Equilibration of the phenotypic distribution of a population as in Figure 6, but started far away from the optimum. Note that the population approaches the same stochastic equilibrium as in Figure 6. This indicates that the equilibrium seen in Figure 6 is most probably stable.

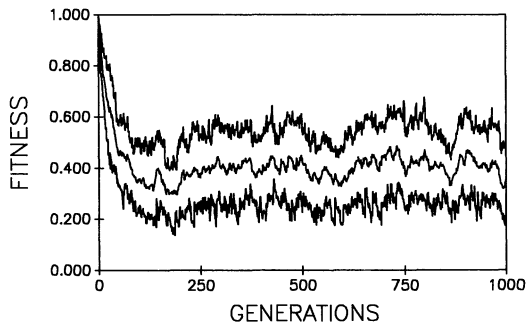

FIG. 8. Equilibration of fitness in spite of very high mutation rate ($\mu = 1$): the evolution of maximal, minimal, and average log-fitness is shown over 1,000 generations ($N_p = 50$, $N = 40$, $N_b = 20$, $V_E = 0$, $m = 0.1$, $w = 3$).

ulations (Lande, 1976*a*). Hence compensatory mutations affecting quantitative traits are as effective as recombination in balancing the loss of adapted genotypes due to random drift and mutations given the conditions of the model. The reasons for this stability are explored in the following section.

GENETIC VARIATION OF A QUANTITATIVE CHARACTER UNDER HIGH MUTATION RATE

On the basis of simulation results it has been shown that in spite of high mutation rate and weak stabilizing selection the population reaches a stable equilibrium distribution that is determined by the joint action of mutation, selection, and random drift. An approximate expression for the equilibrium distribution is derived in this section under the assumption of weak selection and high mutation rate ($\mu \cong 1$).

Because mean log-fitness is a function of mean($[\mathbf{x}]^2$), this value is the relevant parameter of the dispersion of genotypic values. Mean($[\mathbf{x}]^2$) can be expressed as a sum of three components:

$$\text{mean}([\mathbf{x}]^2) = [\bar{\mathbf{x}}]^2 + NV_G + NV_E \quad (5.1)$$

if we assume that all characters have approximately the same genetic variance V_G and environmental variance V_E. We use the mean genotypic effect $\bar{x}$ as synonymous with the mean phenotypic value because we assume no genotype–environment interaction.

Deterministic expectations for the evolution of the mean of the genotypic value are easily obtained if genetic variance is assumed to be approximately constant (Lynch and Gabriel, 1983). These equations are closely similar to those derived from quantitative genetic theory for sexually reproducing populations (Lande, 1976*a*). The equations for the evolution of the population mean $\bar{x}$ have been extended to include the effects of random drift (Lande, 1976*a*). The evolution of genetic variance is more complicated and no generally accepted theory is currently available (Turelli, 1984; Barton, 1986; Bürger, 1986, 1989; Barton and Turelli, 1987; Slatkin, 1987).

Based on deterministic models an expression of the genetic equilibrium variance was given by Kimura (1965) for a continuous time model and by Lynch and Gabriel (1983) for a model with nonoverlapping generations. The approach pioneered by Kimura was extended to sexually reproducing diploid populations by Lande (1976*b*). All these results are essentially second-order approximations of the exact models and they overestimate considerably the genetic variance if selection intensity is high or mutation rate low (Turelli, 1984; Bürger, 1986; Bürger et al., 1989). However, there is reasonable concordance between the values predicted by Kimura et al. on the one hand and the exact values if $\mu w > 0.01$ (Turelli, 1984; Bürger, 1986, 1989). The Gaussian approximation works because we investigate here only the case of high mutation rate and low

selection intensity ($\mu w \gg 0.01$), and we can confidently extend the approach of Lynch and Gabriel (1983) to include drift. More precisely we will restrict the genomic mutation rate to the limiting case $\mu = 1$, where the treatment by Lynch and Gabriel (1983) is exact.

Stochastic Difference Equations for Phenotypic Evolution

In our model the life cycle consists of three stages:

$$p(\mathbf{x}, t) \xrightarrow{\text{selection}} p_w(\mathbf{x}, t)$$

$$p_w(\mathbf{x}, t) \xrightarrow{\text{drift}} p_d(\mathbf{x}, t)$$

$$p_d(\mathbf{x}, t) \xrightarrow{\text{mutation}} p(\mathbf{x}, t + 1)$$

The mean and the variance are evaluated after mutation and before selection when the new eggs have been produced. After selection the frequency of genotypes with genotypic vector $\mathbf{x}$ is

$$p_w(\mathbf{x}, t) = w(\mathbf{x})p(\mathbf{x}, t)/\bar{w} \qquad (5.2)$$

Drift is assumed to be the consequence of sampling N_p individuals from an effectively infinite pool of genotypes. After random sampling the distribution of genotypic effects is $p_d(\mathbf{x}, t)$. The distribution of the next generation $p(\mathbf{x}, t + 1)$ is obtained by adding the random vector $\mathbf{dx}$ with density $u(\mathbf{dx})$ [formula (3.6)] to the distribution $p_d(\mathbf{x}, t)$. This convolution represents the effect of mutations in our model. Because we consider the case of high genomic mutation rates ($\mu = 1$), the dispersion of genotypic values remains Gaussian even after mutation. This is an important difference to the treatments of Kimura (1965), Lande (1976), and Lynch and Gabriel (1983), because the assumption that the genotypic values are Gaussian is violated for $\mu < 1$.

Chance effects due to random drift will cause deviations from the deterministic expectation in each generation. Therefore, it is not possible to predict exactly the evolution of a particular population. Instead one has to consider the ensemble of all possible populations and the evolution of the probability distribution $P[p(\mathbf{x}, t)]$ over all possible populations.

It will be essential to distinguish between two kinds of averages and variances. On the one hand we have averages over the distribution of genotypic values within a population $p(\mathbf{x}, t)$. These averages will be called population averages of x_i and are symbolized by a bar, e.g., $\bar{x}_i$ is the population average of the genotypic values of character i. Similarly, the variance of x_i within a particular population is the population variance that will be symbolized by V_{Gi}. On the other hand, we will consider averages over the ensemble of all populations; the ensemble average of a population mean will be written as $\langle \bar{x}_i \rangle$. The variance of the ensemble will be called ensemble variance and will be symbolized by S. For instance the ensemble variance of the population mean is $S(\bar{x}_i)$.

Because we are mainly interested in the evolution of mean($[\mathbf{x}]^2$) it is sufficient to consider a simplified picture of the ensemble of populations. The ensemble average $\langle \text{mean}([\mathbf{x}]^2) \rangle$ is a function of ensemble averages of the squared norm of the mean genotypic values $\langle [\bar{\mathbf{x}}]^2 \rangle$ and the ensemble average of the genotypic variances $\langle V_{Gi} \rangle$

$$\langle R^2 \rangle = \langle [\bar{\mathbf{x}}]^2 \rangle + N(\langle V_G \rangle + V_E) \qquad (5.3)$$

Because the mutation variance of and the selection intensity at each character are assumed to be the same we can write V_G instead of V_{Gi} and

$$\langle [\bar{\mathbf{x}}]^2 \rangle = N\langle \bar{x}^2 \rangle \qquad (5.4)$$

where $\bar{x}$ is the mean genotypic value of a single character within a population. Hence it is sufficient to derive the stochastic difference equations for the mean genotypic value $\bar{x}$ and the genetic variance V_G for a single character.

If we trace the evolution of the population by changes in $\bar{x}$ and V_G, the life cycle reads

$$(\bar{x}, V_G) \xrightarrow{\text{selection}} (\bar{x}_w, V_{Gw})$$

$$(\bar{x}_w, V_{Gw}) \xrightarrow{\text{drift}} (\bar{x}_d, V_{Gd})$$

$$(\bar{x}_d, V_{Gd}) \xrightarrow{\text{mutation}} (\bar{x}', V_G')$$

Provided selection intensity is weak compared to mutational effects ($V_s \gg m^2$) the stochastic difference equations can be approximated as

$$\Delta\bar{x} = -\bar{x}V_G/(V_s + V_G) + d\bar{x} \quad (5.5)$$
$$\Delta V_G = -V_G^2/V_s + m^2 + dV_G \quad (5.6)$$

where $V_s = w^2 + V_E$ is the intensity of stabilizing selection on the genotypic values. The exact evaluation of the difference equations through the life cycles results approximately in Eqs. (5.5) and (5.6). However, these equations also follow intuitively from the results of Lynch and Gabriel (1983) by adding the terms for random drift (under the assumption $V_G \ll V_s$). The first term on the right-hand side of (5.5) represents the influence of selection on population mean. $d\bar{x}$ is the stochastic term due to random drift. The expected value of $d\bar{x}$ is zero and the variance is

$$\mathrm{Var}(d\bar{x}) = V_G/N_e \quad (5.7)$$

There is no mutation term in (5.5) because it is assumed that the mutational effects have an expected value of zero. Also in the stochastic difference equation for the evolution of V_G (5.6) the first term is a selection term, which is always negative. The second term is the input of genetic variance per generation by mutation, and dV_G is the stochastic term due to random drift. The stochastic term is a random variable that is distributed according to a Pearson type III function with

$$E(dV_G) = -V_G/N_e \quad (5.8)$$
$$\mathrm{Var}(dV_G) = 2V_G^2/N_e \quad (5.9)$$

Results

The stochastic difference equations (5.5) and (5.6) show an asymmetry in mutual dependence. The evolution of the population mean $\bar{x}$ depends on genetic variance but the evolution of genetic variance is independent of the mean genotypic value. We will use this property and consider first the evolution of variance alone and derive an expression for the stationary ensemble average of genetic variance $\langle V_G \rangle_{st} = \{V_G\}$. The stationary ensemble average is the average over the stationary ensemble distribution

$$P_{st}[p(x, t)] = \lim_{t\to\infty} P[p(x, t)]$$

From (5.6) the result

$$\{V_G\} = -a + [a^2 + m^2V_s/(1 - 1/N_e)]^{1/2} \quad (5.10)$$

with

$$a = 3V_s/4(N_e - 1)$$

is obtained (see Appendix B). To get an intuitive feeling for this result it is instructive to approximate the square root (see Appendix B). Then (5.10) reads

$$\{V_G\} = mV_s^{1/2} - 3V_s/4N_e \quad (5.11)$$

The first term on the right-hand side of (5.11) is the deterministic equilibrium variance given by Lynch and Gabriel (1983) in the case of weak selection and is independent of N_e. The second term is always negative and takes into account the loss of genetic variance due to random drift. As V_s becomes large, i.e., as the intensity of stabilizing selection becomes weak, the deterministic term increases proportionally to $V_s^{1/2}$, but the negative drift term decreases at a higher rate, proportionally to V_s.

To calculate the stationary ensemble average of $[\bar{\mathbf{x}}]^2$, we need to know the stationary average of $\bar{x}^2$. This can be obtained by assuming that the distribution of V_G already is close to the stationary distribution. Then we obtain

$$\{\bar{x}^2\} = (V_s + \{V_G\})/2N_e \quad (5.12)$$

By substituting (5.10) and (5.12) in (5.3) we get the stationary ensemble average of mean($[\mathbf{x}]^2$)

$$\{\mathrm{mean}([\mathbf{x}]^2)\} = N(mV_s^{1/2} - V_s/4N_e + V_E) \quad (5.13)$$

Note that this result has been derived for a very high genomic mutation rate and is therefore an upper limit of $\{\mathrm{mean}[\mathbf{x}]^2\}$ for a given intensity of stabilizing selection, mutational effects, and population size. Equation (5.13) allows prediction of a lower bound of mean log-fitness

$$\{\mathrm{mean}(\ln W)\} > -N(m/V_s^{1/2} - 1/4N_e + V_E/V_s)/2 \quad (5.14)$$

In summary it can be concluded that the reason why Muller's ratchet does not lead to genetic deterioration and extinction in our model is that drift eliminates the excess of genetic variation if stabilizing selection is weak, and that the mean phenotype remains within the vicinity of the optimum because stabilizing selection is acting on compensatory mutations.

Discussion

Mutations that restore the original phenotype are not necessarily mutations at the very nucleotide site where the deleterious mutation occurred. For instance restoration of function of a particular protein can be due to a nucleotide substitution at another site but within the same gene (Allen and Yanofsky, 1963) or by a mutation at another gene (Celis and Smith, 1979; Parkhurst and Corces, 1986). These mutations have been called suppressor mutations to distinguish them from true back mutations restoring the original DNA sequence of the gene. A special kind of "suppressor mutation" is a mutation with opposite effects on a quantitative polygenic character. They also compensate or "suppress" the effect of mutations at other loci if they have opposite effects on the genotypic value of that trait. The implication of this is that the probability of back mutations at a particular nucleotide site severely underestimates the probability that the phenotypic effect of a deleterious mutation can be reverted. Mutations that revert the phenotypic effect of other mutations collectively may be called *compensatory mutations,* including true back mutations, suppressor mutations, and additive genetic effects.

The plausibility of Muller's ratchet depends on the probability of compensatory mutations (Felsenstein, 1974; Maynard Smith, 1978; Haigh, 1978; Bell, 1988). Hence the question of whether the accumulation of deleterious mutations leads to an associated decrease in mean fitness depends in turn on the particular physiological system that is influenced by the deleterious mutation and the probability of obtaining compensatory mutations at other loci. In this paper it has been shown that at least for quantitative polygenic traits under stabilizing selection, the rate of compensatory mutation can be adequate to balance the action of Muller's ratchet if the mutational effects are Gaussian with a mean of zero. This is also true for multivariate phenotypes where the average fitness of mutations is always less than the fitness of the original phenotype. In addition it appears from our simulations that compensatory mutations in parthenogenetic populations are as effective as recombination in biparental populations in maintaining the level of adaptation of quantitative phenotypic characters. The mean genotypic value of the quantitative traits in a parthenogenetic population does not drift away from the optimum to a greater extent than expected for sexual populations under the same circumstances. Note that this result is relevant only for that fraction of the total mutational load that influences fitness by its effects on quantitative characters under stabilizing selection. This fraction of deleterious mutations does not lead to genetic deterioration because of the high probability of compensatory mutations.

Adaptation of quantitative traits in parthenogenetic populations is never lost, either under very high mutation rate or under very weak stabilizing selection or under both. The reason for this remarkable stability is that the average distance of the mean genotypic value from the optimum caused by random drift depends on the amount of genetic variance of the traits. The larger the genetic variance the larger the average distance of the mean genotypic value from the optimum. However, as previously shown, the genetic variance does not increase without limits even under very high mutation rate and weak selection because random drift tends to eliminate excess variance. Hence random drift not only leads to deviations from the adaptive optimum, but also limits the extent of this deviation from the optimum by limiting the amount of genetic variance maintained in a finite parthenogenetic population.

In summary, there is no reason to assume that the adaptation of quantitative traits in parthenogenetic populations may be affected by Muller's ratchet. Of course this does not exclude the possibility that Muller's ratchet can work on other fractions of genetic variation, especially on unconditional deleterious mutations.

The equilibrium reached by our model populations is a kind of mutation–selection balance. Nevertheless, this equilibrium differs in kind from the usual mutation–selection equilibria studied in classical population genetic theory. Usually, a mutation–

selection balance consists of a stable distribution of genotype frequencies with some fluctuations around this stable point due to random drift. However, in our model the stable genotype frequency distribution as predicted by the deterministic theory often cannot be realized because the absolute equilibrium frequency of the currently best genotype is less than one. A stable genotype frequency distribution simply does not exist. The equilibrium we see in the simulations is an equilibrium distribution of genotypic *values* and not of genotype frequencies. Such an equilibrium is possible because there are many genotypes that have similar fitnesses and the probability that compensatory mutations occur is high enough to halt Muller's ratchet.

The mechanism that accounts for the adaptive stability of quantitative traits in our model brings to mind the well known Red Queen hypothesis of ecological theory (Van Valen, 1973). The population relies on a steady supply of advantageous mutations to merely *keep* the level of adaptation already attained. One may speak of a *genetic analog of the Red Queen hypothesis.* In this case, however, the deterioration is not of the environment, as in the original "Red Queen" model, but of the genotype caused by the accumulation of mutations.

Even if compensatory mutations may be as effective as recombination in halting Muller's ratchet, the genetic consequences are quite different. Even low rates of recombination may be adequate to restore unloaded genomes at a rate that can balance the loss of unloaded genotypes (Bell, 1988). Although it might be impossible to restore the original genotypes of the parents if there is ample heterozygosity, recombination can still aid directly in purging deleterious alleles.

In the absence of recombination, the accumulation of deleterious mutations has to be balanced by an equivalent number of advantageous mutations, which leads to high degrees of linkage disequilibrium (Lynch and Gabriel, 1983). It is not yet clear whether there are limits to the ability of a genetic system to compensate for deleterious mutations with compensatory mutations. Nevertheless it seems plausible that in the long run, a genetic system may become exhausted with respect to opportunities to compensate for deleterious mutations (Lynch and Gabriel, 1983).

Even if in the short run compensatory mutations may be as effective as recombination in preventing Muller's ratchet, in the long run this option may lead to a "dead end." Periodic sex, where the hidden genetic variance becomes released, may be necessary to tolerate deleterious mutations over a longer period of time. After one generation of sexual reproduction, most of the hidden genetic variance becomes exposed to natural selection and the deleterious alleles can be eliminated. This may contribute to the long-term stability of cyclically parthenogenetic species, especially in many freshwater plankton organisms (Lynch and Gabriel, 1983).

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APPENDIX A

In Table 5 of Mukai et al. (1972) three estimates of viability mutation rate per chromosome II in *Drosophila melanogaster* are given: $\mu_{II,1} = 0.059$, $s_1 = 0.075$; $\mu_{II,2} = 0.172$, $s_2 = 0.023$; $\mu_{II,3} = 0.118$, $s_3 = 0.038$. To estimate the diploid genomic mutation rate, the chromosome II mutation rate is multiplied by the factor 5, assuming that the number of Balbiani rings is roughly proportional to the number of loci. Finally the average dominance factor of viability mutations is 0.21 (Mukai et al., 1972). These results lead to three estimates of θ: $\theta_1 = 18.7$, $\theta_2 = 178$, and $\theta_3 = 73.9$, which finally lead to predicted equilibrium frequencies of the optimal genotype of 7×10^{-9}, 4.7×10^{-78}, and 7.8×10^{-33}, respectively.

APPENDIX B

In this appendix the genetic variance $V_G(t)$ in generation t is denoted as V and in generation $t + 1$ as V'. From Eq. (5.6) we have

$$V' = V + \Delta V \text{ and } \Delta V = m^2 - V^2/V_s + dV$$

and with $\langle dV \mid V \rangle = -V/N_e$, therefore,

$$\langle V' \mid V \rangle = V + \langle \Delta V \mid V \rangle = V + m^2 - V^2/V_s - V/N_e$$

If we take the average over the stationary ensemble distribution and denote it by $\{\cdot\}$ instead of $\langle \cdot \rangle$, we get

$$\{V'\} = \{V\} + m^2 - \{V^2\}/V_s - \{V\}/N_e \qquad (1)$$

With $\{V'\} = \{V\}$ and $\{V^2\} = \{V\}^2 + S$ (S is the sta-

tionary ensemble variance of V) follows

$$\{V\} = -V_s/2N_e + (V_s^2/4N_e^2 + m^2V_s - S)^{1/2} \quad (2)$$

To calculate S we independently evaluate $\{V^2\}$ and $\{V\}^2$. From (1) we get

$$\{V'\}^2 = \{V^2\}^2/V_s^2 - 2\{V\}\{V^2\}(1 - 1/N_e)/V_s + \{V\}^2(1 - 1/N_e)^2 - 2\{V^2\}m^2/V_s + 2\{V\}(1 - 1/N_e)m^2 + m^4 \quad (3)$$

In an analogous way $\{V^2\}$ can be obtained from

$$V'^2 = (V + \Delta V)^2$$

and using $\{(dV)^2 | V\} = 2\{V^2\}/N_e$

$$\{V^2\} = \{V^4\}/V_s^2 - 2\{V^3\}(1 - 1/N_e)/V_s + \{V^2\}(1 - 2m^2/V_s) + 2\{V\}(1 - 1/N_e)m^2 + m^4 \quad (4)$$

Assuming the stationary ensemble distribution to be Gaussian leads to the following moment relations:

$$\{V^4\} - \{V^2\}^2 = 2S^2 + 4S\{V\}^2$$

and

$$\{V^3\} - \{V\}\{V^2\} = 2S\{V\}$$

Subtracting (3) from (4) and observing that in the stationary case $S' = S$ we get a quadratic equation for S:

$$2S^2/V_s^2 - 4S\{V\}(1 - 1/N_e - \{V\}/V_s)/V_s + \{V\}^2(2/N_e - 1/N_e^2) = 0$$

One has to choose the solution with the minus sign in front of the square root to allow S to approach 0 if N_e becomes large.

$$S = \{V\}V_s(1 - 1/N_e - \{V\}/V_s) - \{V\}V_s[(1 - 1/N_e - \{V\}/V_s)^2 - 1/N_e + \tfrac{1}{2}N_e^2]^{1/2} \quad (5)$$

For $N_e \to \infty$ we have $S = 0$ and with (2) we get $\{V\} = (m^2V_s)^{1/2}$ in accordance with the deterministic expectation. To solve Eq. (2) for finite N_e, we approximate the square root in (5) by dropping terms proportional to V_s^{-2} and N_e^{-2},

$$1 - \{V\}(1 - 1/N_e)/V_s - 3/2N_e$$

and obtain for S

$$S = \{V\}V_s/2N_e - \{V\}^2/N_e \quad (6)$$

Substituting (6) into (2) and solving for $\{V\}$ we obtain

$$\{V\} = -3V_s/4(N_e - 1) + \{[3V_s/4(N_e - 1)]^2 + m^2V_s/(1 - 1/N_e)\}^{1/2} \quad (7)$$

which is roughly

$$\{V\} \cong (m^2V_s)^{1/2} - 3V_s/4N_e$$

This gives an estimate of the stationary expectation of the genetic population variance.