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Evolution, Vol. 51, No. 5. (Oct., 1997), pp. 1363-1371.

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MUTATION AND EXTINCTION: THE ROLE OF VARIABLE MUTATIONAL EFFECTS, SYNERGISTIC EPISTASIS, BENEFICIAL MUTATIONS, AND DEGREE OF OUTCROSSING

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Abstract.—Recent theoretical studies have illustrated the potential role of spontaneous deleterious mutation as a cause of extinction in small populations. However, these studies have not addressed several genetic issues, which can in principle have a substantial influence on the risk of extinction. These include the presence of synergistic epistasis, which can reduce the rate of mutation accumulation by progressively magnifying the selective effects of mutations, and the occurrence of beneficial mutations, which can offset the effects of previous deleterious mutations. In stochastic simulations of small populations (effective sizes on the order of 100 or less), we show that both synergistic epistasis and the rate of beneficial mutation must be unrealistically high to substantially reduce the risk of extinction due to random fixation of deleterious mutations. However, in analytical calculations based on diffusion theory, we show that in large, outcrossing populations (effective sizes greater than a few hundred), very low levels of beneficial mutation are sufficient to prevent mutational decay. Further simulation results indicate that in populations small enough to be highly vulnerable to mutational decay, variance in deleterious mutational effects reduces the risk of extinction, assuming that the mean deleterious mutational effect is on the order of a few percent or less. We also examine the magnitude of outcrossing that is necessary to liberate a predominantly selfing population from the threat of long-term mutational deterioration. The critical amount of outcrossing appears to be greater than is common in near-obligately selfing plant species, supporting the contention that such species are generally doomed to extinction via random drift of new mutations. Our results support the hypothesis that a long-term effective population size in the neighborhood of a few hundred individuals defines an approximate threshold, below which outcrossing populations are vulnerable to extinction via fixation of deleterious mutations, and above which immunity is acquired.

Key words.—Effective population size, epistasis, extinction, genetic drift, mutation, outcrossing, selfing.

Received October 18, 1996. Accepted May 30, 1997.

The potential significance of the accumulation of spontaneous deleterious mutations as a cause of extinction is now well established. Indeed, there seems to be little doubt that deleterious mutation can be a general mechanism responsible for the short longevity of obligately asexual and obligately selfing lineages of multicellular eukaryotes (Lynch and Gabriel 1990; Gabriel et al. 1993; Lynch et al. 1993, 1995a; Butcher 1995). With these modes of propagation, progeny typically inherit the full load of deleterious mutations carried by their parents (with only a slight deviation from this for recently arisen mutations in selfers) as well as acquire new mutations, and this mutation pressure combined with random genetic drift leads to an expected progressive decline in fitness (Muller 1964; Felsenstein 1974; Haigh 1978; Pamilo et al. 1987; Charlesworth 1990; Charlesworth et al. 1993; Stephan et al. 1993; Higgs 1994).

In contrast, sexual reproduction reduces the rate of accumulation of deleterious mutations, as well as enhances the rate of fixation of beneficial mutations, by allowing parents to contribute the best portions of their genomes to their progeny (Fisher 1930; Muller 1964). However, recent theoretical work has shown that small sexual populations can also be vulnerable to extinction via the accumulation of deleterious mutation (Lande 1994; Lynch et al. 1995a,b). This can occur for the simple reason that mutations with deleterious effects (s) on the order of the reciprocal of the effective population size ($1/N_e$) or smaller have a high probability of fixation, despite their negative effects on individual fitness (Kimura et al. 1963; Kondrashov 1995). Whenever these conditions

are met, either because N_e is small and/or because mutations with very small s are common, the effectiveness of recombination and segregation in eradicating mutations will be compromised.

That small sexual populations are vulnerable to the accumulation of deleterious mutation is supported by results from mutation-accumulation experiments with several organisms, which indicate that most spontaneous mutations have very small fitness effects. The average mutation generally reduces total fitness by no more than 5% in the homozygous state (see review in Lynch and Walsh, in press), and the distribution of mutational effects is likely to be L-shaped, with the maximum density well below the mean (Keightley 1994). Thus, populations of endangered species, which typically have dwindled to effective sizes on the order of 10 to 100 by the time they are afforded legal protection (Wilcove et al. 1993; Frankham 1995; Lynch 1996), are certainly potential victims of the accumulation of deleterious mutation. It is also possible that the accumulation of deleterious mutation has played a role in the extinction of some fossil lineages, which for ecological reasons were historically forced into demographic situations that reduced the efficiency of natural selection.

Previous studies of the influence of deleterious mutation on the extinction of sexual populations have relied upon a number of genetical simplifications to facilitate analytical and numerical tractability (as listed in Lande 1994). The sensitivity of estimates of extinction risk to these simplifications is the focus of this paper, and we address four issues.

First, we consider the role that the form of the distribution of mutational effects has on the vulnerability of a population to deleterious mutation accumulation. Most previous studies of this vulnerability treated all mutations as having identical selection coefficients (e.g., Lynch et al. 1995a,b). Lande (1994) considered the consequences of a gamma distribution of mutational effects, which is consistent with data on *Drosophila* (Keightley 1994), and he assumed that mutations have additive effects. In contrast, we assume that mutations are partially recessive, as indicated by many empirical studies (Crow and Simmons 1983; Lynch and Walsh, in press). Previous work has shown that recessivity of deleterious mutations increases their contribution to the risk of extinction because of their higher probability of fixation (Lynch et al. 1995a).

Interest in the form of the distribution of effects of deleterious mutations is well motivated. Mutations with selective effects in the neighborhood of $1/(2N_e)$ pose the greatest threat to extinction because they have an appreciable rate of fixation as well as a relatively large effect on individual fitness (Lynch and Gabriel 1990; Gabriel et al. 1993; Lynch et al. 1993; Lande 1994). Mutations with effects less than $1/(4N_e)$ go to fixation at essentially the neutral rate, but this high rate of fixation is offset by their diminishing fitness effects. However, mutations with effects much greater than $1/N_e$ have negligible chances of accumulating via random genetic drift. Thus, the extent to which variance in mutational effects will increase the vulnerability of a population to extinction depends on the form of the distribution as well as on the effective size of the population. For example, even if the mean mutational effect is substantially greater than $1/(2N_e)$, deleterious mutations can still have significant cumulative effects on mean population fitness if a substantial fraction of the distribution of effects is near $1/(2N_e)$. However, if the mean mutational effect is near $1/(2N_e)$, increased variance in mutational effects can reduce the rate of fitness decline by placing a larger fraction of mutations in classes that have reduced cumulative effects on mean population fitness.

Second, we consider the extent to which synergistic epistasis between mutational effects can reduce the vulnerability of a population to the accumulation of deleterious mutations. The evidence for such epistasis is weak, relying almost entirely on a single data point generated by Mukai (1969), but interest in it is again well motivated on theoretical grounds (Crow and Kimura 1979; Kondrashov 1988, 1994; Charlesworth 1990). With synergistic epistasis, the selection coefficients of individual mutations are effectively magnified as deleterious mutations accumulate in a genome, and for mutations with equivalent effects, this has the effect of progressively reducing the probability of fixation, eventually to zero. This idea has led to the common belief that synergistic epistasis can only reduce the vulnerability of a population to deleterious mutation accumulation. However, Butcher (1995) provided a simple argument, closely related to the points made in the preceding paragraph, that calls into question the general validity of this conclusion. When mutations have a distribution of effects, those with initial effects that are below $1/(2N_e)$ will eventually move into the class that contributes most to fitness decline, while those with initial effects greater than $1/(2N_e)$ will progressively pose less of a threat. Thus,

whether epistasis will increase or decrease the vulnerability of a population to mutation accumulation again depends on the effective population size and on the form of the distribution of mutational effects.

Third, we consider the degree to which beneficial mutations can reduce the vulnerability of a population to deleterious mutation accumulation. Except for a brief consideration in Lande (1994), Lande (1994), and Lynch et al. (1995a,b) focus on the situation in which all new mutations are unconditionally deleterious, in which case a finite population can only decline in fitness in the long-term. Although beneficial mutations may be quite rare relative to deleterious mutations, they obviously occur, raising the question as to how often they must arise to offset the damage from much more frequent deleterious mutations. It is clear that when all mutations have absolute effects that are much less than $1/(2N_e)$, the cumulative beneficial and deleterious effects of mutations must be roughly equal to ensure long-term genetic viability, since the fixation probabilities of all mutations are essentially the same in this case. With larger population sizes, the frequency of beneficial mutations need not be so high, since the probability of fixation of a beneficial mutation will exceed that of a deleterious one with the same absolute magnitude of effect. Previous work has shown how the rate of mutation for a quantitative character can influence the vulnerability of a population to extinction in a changing environment (Lynch and Lande 1993; Bürger and Lynch 1995). Here, we consider a simpler situation—a constant environment in which mutations are either unconditionally beneficial or detrimental.

Finally, we noted above the central role that outcrossing plays in reducing the rate of accumulation of deleterious mutations. Nevertheless, self-fertilization has intrinsic genetic or energetic advantages that can lead to its rapid expansion in a population (see Fisher 1930), and as a consequence, many species, particularly plants, have evolved mechanisms that facilitate reproduction by partial self-fertilization (Schemske and Lande 1985; Barrett and Eckert 1990). If self-fertilization does not reduce the outcrossing success of male gametes (i.e., in the absence of “pollen discounting”), then an allele causing complete self-fertilization has a 50% fitness advantage in a completely outcrossing population (Fisher 1930). In the presence of pollen discounting, a selfing variant can theoretically gain a comparable advantage by simply not producing excess outcrossing pollen. A high rate of selfing can also be favored by ecological circumstances (e.g., rarity of mates or pollination vectors). Previous work has shown that obligate self-fertilization provides a reproductive setting that is genetically equivalent to that under obligate asexuality, except that under the former, segregation effectively reduces the genomic mutation rate by 50% while magnifying the mutational effect (as all polymorphic loci rapidly segregate out into one or the other homozygous class; Lynch et al. 1995a). Here we consider the magnitude of outcrossing that is necessary to substantially slow the accumulation of deleterious mutations in a partially selfing population.

METHODS

As in previous work, we assume that generations are discrete and that the sequence of events in the life cycle is

mating, mutation, then selection. The number of new mutations per zygote is assumed to be Poisson distributed with mean μ . In the absence of epistasis, the viability effect of mutation i is s_i when homozygous, and $h_i s_i$ when heterozygous, where h_i is the dominance coefficient of the mutation, which ranges from 0.5 for mutations with completely additive effects to 0.0 for completely recessive mutations. In all simulations, the initial population was assumed to be completely free of deleterious mutations.

In the absence of epistasis, the expected viability of a zygote, from birth to maturity, is calculated according to the multiplicative function

$$W = \prod_i^{n_1} (1 - s_i) \prod_i^{n_2} (1 - h_i s_i), \quad (1)$$

where n_1 and n_2 are respectively the numbers of mutations in the homozygous and heterozygous states. A zygote survives to adulthood if a uniform random number drawn from the interval (0,1) is less than its viability.

Density dependence is modeled simply by choosing the first K survivors from a maximum pool of RN offspring, where K is the expected number of adults in the next generation (defined by the carrying capacity of the environment), N is the number of adult females or hermaphrodites in the current generation, and R is the effective fecundity of a female or hermaphrodite individual. The effective fecundity is the number of offspring that do not suffer genotype-independent mortality prior to selection. With this form of density dependence, whereas mean viability declines as deleterious mutations accumulate in populations of small effective size, the population size need not decline until the mean number of surviving progeny is reduced to one per reproductive adult. Extinction occurs when none of the RN offspring survives to adulthood.

From a genetic perspective, this study differs from previous work (Lynch et al. 1995a,b) by simultaneously incorporating synergistic epistasis, beneficial and deleterious mutations, variable effects of mutations on viability in both the homozygous and heterozygous states, and a finite number of loci. In addition, we explicitly incorporate a minimal level of demographic stochasticity by allowing the realized carrying capacity K to follow a Poisson distribution with mean \bar{K} among generations. Finally, we consider an array of sexual mating systems, including those common in many plant species: complete random mating, random mating with separate sexes, and obligate and partial self-fertilization.

We model synergistic epistasis by mapping the multiplicative viability W to the epistatic viability W^* , where

$$W^* = e^{a(1-1/W)}, \quad (2)$$

with a being an arbitrary positive constant. Other approaches have been used to model the general effects of epistasis. For example, Charlesworth (1990) defined fitness to be an exponential function of a quadratic expression of the number of mutations. However, that approach does not readily extend to treatments in which mutations are allowed to have variable effects, and it can in some cases yield fitnesses outside of the (0,1) range. In Peck et al. (in press), total fitness is a power function of the individual selection coefficients, but

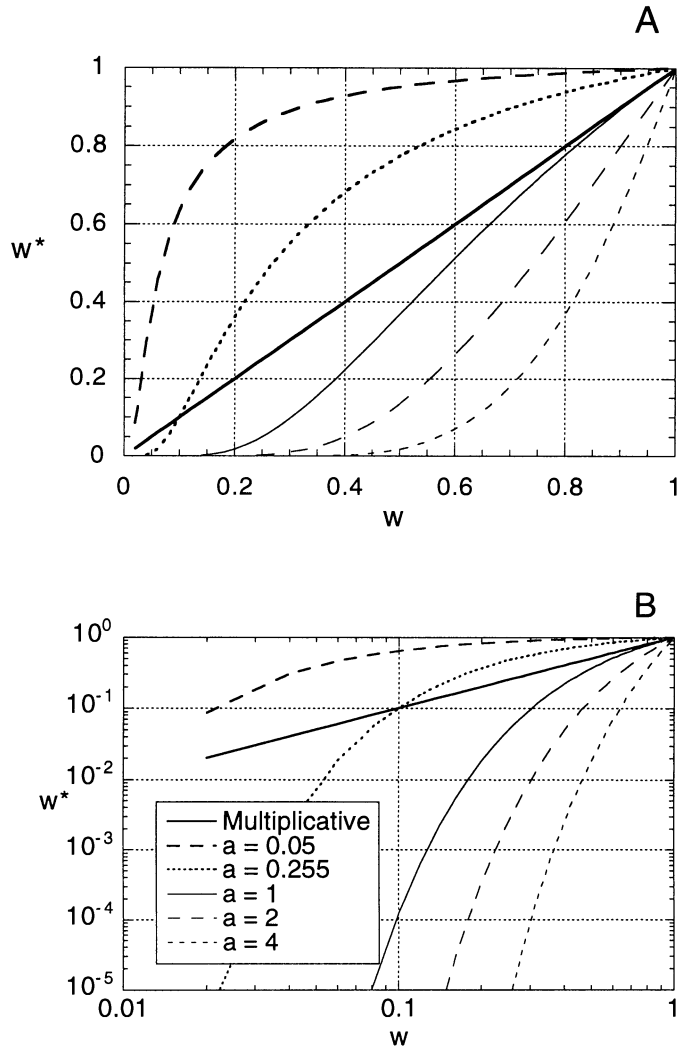


FIG. 1. Mappings of multiplicative to epistatic fitness functions for various values of the scaling parameter A , given on both the arithmetic and logarithmic scales.

that changes the selection effects of even single mutations. With our approach, as W declines from one to zero, W^* also declines from one to zero at a rate depending on A (Fig. 1), so fitness values outside of the realistic (0,1) range are not possible. Moreover, for values of A near one, $W^* \cong W$ when W is large, so that the effects of single mutations are essentially the same as those for the nonepistatic case.

The effects of beneficial and deleterious mutations are drawn from a gamma distribution, such that the probability that a mutational effect lies between s and $s + ds$ is

$$p(s)ds = \frac{\beta^\alpha s^{\alpha-1} \exp(-\beta s)}{\Gamma(\alpha)} ds, \quad (3)$$

where $\Gamma(\alpha)$ is the gamma function, which is equal to $(\alpha - 1)!$ when α is a positive integer. The mean and the variance of the distribution of mutational effects are respectively $\bar{s} = \alpha/\beta$ and $\sigma_s^2 = \alpha/\beta^2$. When $\alpha = 1$, equation (3) defines the exponential distribution, with probability density decaying exponentially from a maximum at $s = 0$ to zero at $s = \infty$

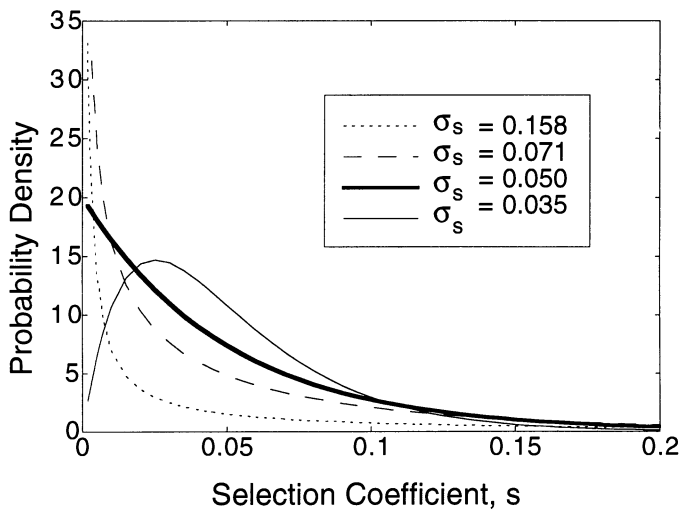


FIG. 2. Gamma distributions of mutational effects, with constant mean $\bar{s} = 0.05$.

(Fig. 2). For $\alpha < 1$, the distribution becomes more L-shaped, and for $\alpha > 1$, it becomes more bell-shaped. In our simulations, random gamma deviates were obtained by use of the algorithm in Law and Kelton (1982, p. 256). Because the gamma distribution places no upper bound on s , it can in principle generate rare deleterious mutations with effects in excess of one, which would cause viability to become negative. However, with the small mean values of s employed in this study, this never occurred.

Selection coefficients for deleterious and beneficial mutations were chosen from separate probability distributions that differ in both mean and total density. The respective mean selection coefficients \bar{s}_d and \bar{s}_b were assumed to be 0.05 and -0.01 . The value for \bar{s}_d approximates the upper statistical bound on this value observed for the only two organisms for which data are available, *D. melanogaster* and *E. coli* (Crow and Simmons 1983; Kibota and Lynch 1996; Lynch and Walsh, in press). We set \bar{s}_d to its current empirical upper bound to minimize the effective size above which populations are essentially immune to deleterious mutation accumulation. If the true value of \bar{s}_d is lower than 0.05, then our results are likely to apply to populations larger than those studied here.

No empirical estimates exist for \bar{s}_b , but we assume a lower average magnitude of effects for beneficial mutations because deleterious mutations can be reasonably assumed to disrupt or eliminate the functioning of an organism in a greater variety of ways than beneficial mutations can be expected to improve function. Due to the lack of data on the spectra of beneficial mutations, for simplicity, we assumed the effects of beneficial mutations to have an exponential distribution.

The dominance coefficient of a mutation with selection coefficient s_i when heterozygous with another allele of effect s_j is assumed to be

$$h_i = 0.02 + 0.48e^{-13|s_i - s_j|} \quad (4)$$

(in our simulations, s_j is almost always equal to zero, except when different mutations by chance occur at the same locus). This relationship is chosen to yield (s_i, h_i) pairs (when $s_j = 0$) of (1.0, 0.02), (0.0, 0.5), and (0.03, 0.35), in rough accord

with the existing information on the relationship between mean dominance and mean effect of alleles in the major classes of deleterious mutations in *D. melanogaster* (Crow and Simmons 1983; Caballero and Keightley 1994; Lynch and Walsh, in press). For the rare cases in which two different mutations at the same locus were combined into a single individual, the viability contribution of that locus was assumed to be $1 - s_j - h_i(s_i - s_j)$, where $s_j < s_i$. Under this treatment, heterozygous fitness is reduced below that of the better of the two homozygotes ($1 - s_j$) by a fraction (h_i) of the difference between homozygote fitnesses.

Unless noted otherwise, we assume throughout that the total genomic mutation rate for fitness is equal to one per zygote per generation, as this approximates the estimates that are available for most higher organisms (Lynch and Walsh, in press). The number of new beneficial mutations per zygote is assumed to be a Poisson deviate with mean μ_b such that $\mu_b + \mu_d = 1$, so that μ_b is also equivalent to the fraction of mutations for fitness that is beneficial. Viability resulting from a combination of deleterious and beneficial mutations is calculated according to the equations presented above, with negative s coefficients for beneficial mutations and positive coefficients for deleterious mutations, except that viability is never allowed to exceed one.

Previous studies of M. Lynch et al. (1995a,b) have usually employed an infinite-sites model in which all mutations arise at unique loci. In this study, the total genome is represented by 50,000 loci (although we found that a genome of only 1000 loci yields essentially the same results for random-mating populations). Mutations occur randomly at these loci, independently of the location of preexisting mutations in any individual, including the zygote undergoing new mutation. In the very rare event that the allele randomly chosen for mutation was already a mutation, the selection coefficient s_i of the twice-mutated allele was chosen so that its fitness in the homozygous state was $1 - s_i = (1 - s_{new})(1 - s_{old})$, where s_{new} is the selection coefficient that the new mutation would produce in the wild-type allele, and s_{old} is the previous selection coefficient of the allele. This adjustment allows the fitness effects of successive mutations in the same allele to increment from the previous fitness rather than from one.

For each set of mutation and mating parameters, we report the mean time to extinction based on 10 to 100 replicate runs.

RESULTS

The Effects of Mating System and Synergistic Epistasis.— In Figure 3, the average time to extinction versus carrying capacity is shown for various mating systems, for both multiplicative viability and synergistic epistasis. Here the mutational effects were assumed to be exponentially distributed with mean $\bar{s} = 0.05$, and the beneficial mutation rate was assumed to be zero. Several things can be noted from this figure. First, the longevity of populations is usually prolonged by synergistic epistasis. However, this effect is generally not great (increasing the mean time to extinction by less than an order of magnitude) even with very strong epistasis. Second, the longevity-enhancing effect of synergistic epistasis is diminished in partially or completely selfing populations, to the point of being almost negligible in the latter, and even

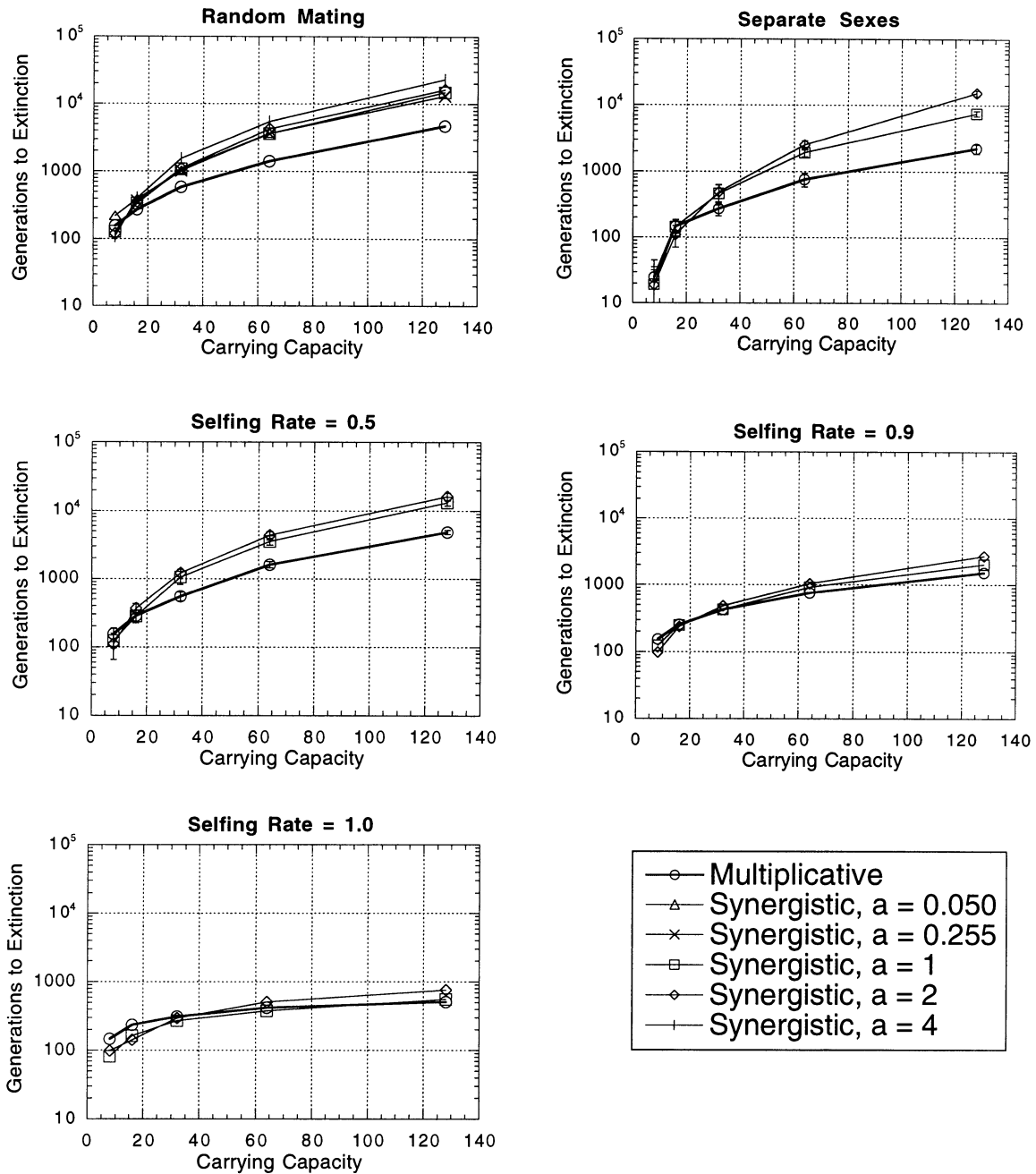


FIG. 3. Mean number of generations to extinction as a function of expected population carrying capacity (\bar{K}) and mating system, for cases in which mutations act independently and with synergistic epistasis. Maximum effective fecundity of females/hermaphrodites (R) was 10 in all runs.

reducing the time to extinction when such populations are small. Third, a substantial amount of outcrossing is needed to greatly elevate the longevity of a partially selfing population relative to that of an obligate selfer. For example, 10% outcrossing (which exceeds the outcrossing rate of many highly selfing plant species; see Schemske and Lande 1985; Barrett and Eckert 1990) increases the time to extinction by a factor of only three or so. On the other hand, a selfing rate of 50% gives essentially the same results as for random mating. Fourth, the demographic and genetic stochasticity induced in populations with separate sexes (relative to random-

mating hermaphrodites) reduces the time to extinction by several fold when $K \lesssim 50$.

Variation in Mutational Effects.—The pattern and magnitude of variation in deleterious mutational effects can have a dramatic effect on the mean time to extinction of randomly mating populations. However, the qualitative impact of a variable spectrum of mutational effects is highly dependent on population size. Results for the situation in which the beneficial mutation rate was set to zero are shown in Figure 4.

Large populations ($\bar{K} \gg 1/\bar{s}$) are much more vulnerable to deleterious mutation accumulation when effects are variable

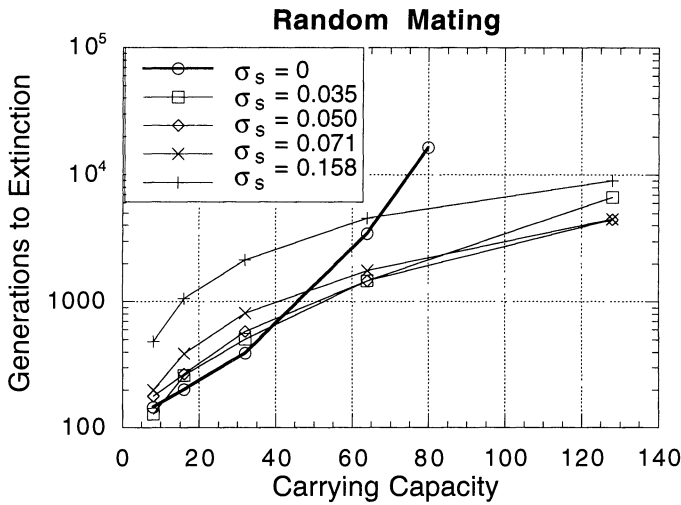


FIG. 4. Mean number of generations to extinction as a function of population carrying capacity and the variance of deleterious mutational effects. Mutations are assumed to have multiplicative effects on fitness, and the average selection coefficient is equal to 0.05 in all cases. All mutations are assumed to be deleterious and to be drawn from an underlying gamma distribution. Mating was random, and the maximum effective fecundity (R) was 10 in all runs. With constant mutational effects, the expected time to extinction with $K = 96$ is in excess of 10^6 generations, although we have not generated accurate estimates of this because of the extremely long simulation runs.

because this produces classes of mutations that are highly vulnerable to fixation (with $s \leq 1/\bar{K}$) when otherwise all mutations would be eliminated by selection. Note, however, that for large K the mean time to extinction does not decrease monotonically with an increase in the variance of mutational effects. For gamma distributions of effects in which the standard deviation is on the order of the mean or smaller, the mean time to extinction is relatively insensitive to the variance of the distribution of effects. However, as the distribution of effects becomes extremely L-shaped, the mean time to extinction is elevated. This occurs because extremely leptokurtic distributions of effects decrease the frequency of mutations with effects in the class that is most damaging (i.e., $s \approx 1/N_e$).

For populations that are very small, the mean time to extinction is elevated by variation in mutational effects (relative to the case in which s is constant), with the range of population sizes over which this occurs increasing with increasing variance of mutational effects. This again can be understood in terms of the selective effects that are most damaging at the population level. Consider a population with $\bar{K} = 20$. With constant mutational effects equal to $s = 0.05$, as used in this study, such a population would be highly vulnerable to deleterious mutation accumulation because all mutant alleles would be subject to random genetic drift while also having substantial effects on individual fitness. An increase in the variance of mutational effects results in some mutations having high enough s to be eliminated by selection, but it also shifts the median of the distribution of effects to a lower value of s (Fig. 2), that is, to classes of mutations that are more vulnerable to drift but less damaging at the population level. The net effect is an increase in the mean time to ex-

inction (Fig. 4). Because a larger population (e.g., $\bar{K} = 64$) removes deleterious mutations more efficiently, the mutations that are subject to drift, and hence cause maximum damage, must have a smaller effect. In this case, increasing the variance of the distribution of effects a *small* amount moves the median of the distribution a small distance to the left, which increases the number of mutations that occur in the region of maximum damage. The net effect is to reduce the mean time to extinction (Fig. 4). Increasing the variance of the distribution further moves the median further to the left, where mutations are dominated by drift but are too neutral to cause much damage, and the time to extinction again increases (Fig. 4). Thus, higher values of \bar{K} require higher variance of mutational effects to produce this longevity-enhancing effect.

Beneficial Mutations.—A rough idea of the magnitude of the beneficial mutation rate necessary to halt the decline in fitness in a small population can be acquired by using the standard diffusion approximations for the fixation probabilities of deleterious and beneficial alleles (Crow and Kimura 1970). Letting u denote the probability of fixation, μ the genomic mutation rate, and s the selection coefficient for mutant homozygotes, then the long-term effects of beneficial and deleterious mutations will be balanced when $\mu_b u_b s_b = -\mu_d u_d s_d$ when mutations have constant effects. With exponentially distributed effects, $p(s_b)$ and $p(s_d)$ for beneficial and deleterious mutations, and assuming mutations with additive effects, the expected per-generation loss of fitness due to fixation of deleterious alleles is

$$\begin{aligned} & \mu_d \int u_d(s_d) p(s_d) s_d ds_d \\ &= \mu_d \sum_{i=1}^{\infty} \frac{2\bar{s}_d^2}{(2\bar{K}i\bar{s}_d + 1)(4\bar{K}^2i^2\bar{s}_d + 4\bar{K}i\bar{s}_d + 1)}, \end{aligned} \quad (5a)$$

whereas the expected gain due to fixation of beneficial alleles is

$$\begin{aligned} & -\mu_b \int u_b(s_b) p(s_b) s_b ds_b \\ &= \mu_b \left(2\bar{s}_b^2 + \int u_d(s_b) p(s_b) s_b ds_b \right). \end{aligned} \quad (5b)$$

For any given genomic deleterious mutation rate (μ_d), the critical beneficial mutation rate necessary to prevent a net decline in fitness can be computed by setting equations (5a,b) equal to each other, and solving for μ_b .

This analytical approach can only be expected to roughly approximate the critical beneficial mutation rate because it assumes mutations with additive effects and because it ignores the effects of gametic-phase disequilibrium and background variance on the probability of fixation. In general, equations (5a,b) can be expected to underestimate the true critical beneficial mutation rate, because with the single-locus diffusion approximation, the deleterious fixation rate is underestimated while the beneficial fixation rate is overestimated. Nevertheless, the solution of equations (5a,b) suggests that for random-mating populations with carrying capacities below 200 or so individuals, the beneficial mutation rate needs to be quite high to offset the cumulative damage caused

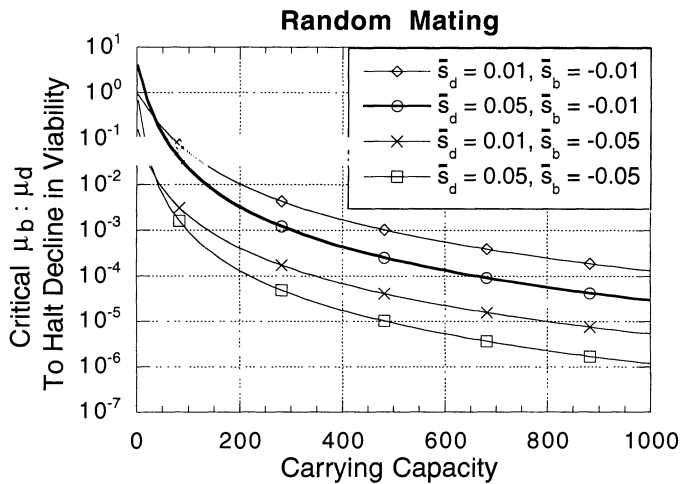


FIG. 5. The critical ratio of beneficial and deleterious mutation rates needed to stabilize mean population fitness as a function of population size (K) and beneficial and deleterious effects of mutations. The approximate results, obtained from the diffusion equations for fixation probabilities, apply to mutations with additive effects and exponential distributions.

by deleterious mutations (Fig. 5). The critical ratio of μ_b/μ_d increases as the effects of deleterious mutations decline, as this allows more such alleles to drift to fixation, and decreases as the effects of beneficial mutations increase. However, provided the beneficial mutations are not effectively neutral ($\bar{K}s_b > 0.25$), the critical ratio μ_b/μ_d is very small. On this basis, it seems plausible that outcrossing populations with effective sizes on the order of several hundreds of individuals are invulnerable to extinction via deleterious mutation accumulation.

To evaluate the general validity of these results, we performed numerical analyses for a range of μ_b , assuming a fixed value for the total genomic mutation rate of one. By narrowing down the range of μ_b above which fitness asymptotically increases and below which fitness asymptotically declines, the critical rate was obtained by interpolation. With our simulations for random-mating populations, the relative rate of beneficial mutation necessary to halt the loss of viability is, as expected, somewhat higher than that predicted by equations (5a,b) (Fig. 6). However, the discrepancy is only on the order of a factor of two or three for the conditions that we evaluated. The simulations indicate that if the beneficial mutation rate is typically less than 1% of the deleterious rate, effective sizes of outcrossing populations need to be in excess of a few hundred individuals to prevent the gradual deterioration of fitness by deleterious mutation accumulation. The critical beneficial mutation rate is elevated substantially if the frequency of outcrossing is on the order of 10% or less. Thus, highly selfing populations need to be quite large to be stabilized by rare beneficial mutations. Under near-obligate selfing, extinction due to fixation of deleterious mutations may be inevitable in all but extremely large populations.

Effect of the Genomic Mutation Rate.—The long-term advantages of beneficial mutation are radically altered if the genomic deleterious mutation rate is elevated much above

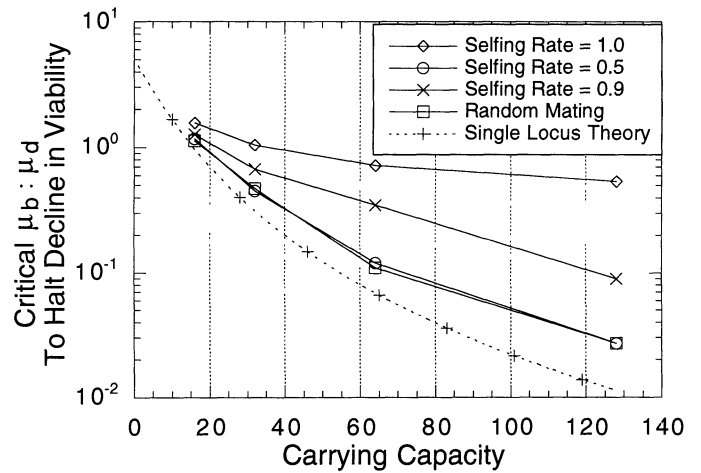


FIG. 6. The critical ratio of beneficial to deleterious mutations necessary to stabilize mean population fitness as a function of the carrying capacity, obtained by simulations. The expected rate of self-fertilization is equal to $1/K$ under random mating. Beneficial and deleterious mutations are drawn from two exponential distributions with respective means $\bar{s}_b = -0.01$ and $\bar{s}_d = 0.05$, with the total mutation rate being equal to one. The mutational effects on fitness combine multiplicatively. Each point is based on interpolation from at least 20 independent runs with different values of μ_b , the threshold μ_b for a given parameter set being that which gives no net decrease in mean viability from generations 1000 to 2000. The dashed line gives the predicted ratio from diffusion theory, equations (5a,b).

one per individual per generation (Fig. 7). If μ_d is on the order of three, the time to extinction is very brief and nearly independent of population size, and even a beneficial mutation rate as high as 0.3 has almost no effect on extinction.

DISCUSSION

The results from this study uphold previous contentions (Lande 1994; Lynch et al. 1995a,b) that sexual populations with long-term effective sizes less than a few hundred in-

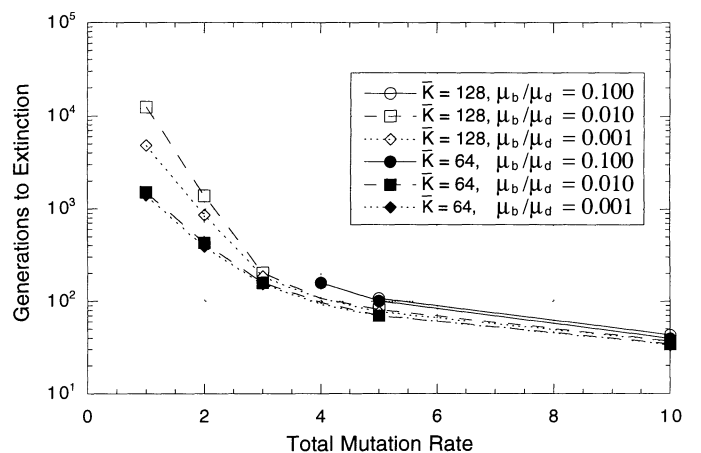


FIG. 7. Mean time to extinction (in generations) as a function of the total genomic mutation rate and the fraction of mutations that are beneficial versus detrimental. Both types of mutations were assumed to have exponential distributions, with mean selection coefficients of 0.05 for deleterious and 0.01 for beneficial mutations.

dividuals are vulnerable to extinction via deleterious mutation accumulation, especially when such populations are largely inbreeding. If general synergistic effects exist among deleterious mutations, this vulnerability is reduced in large, outcrossing populations, but the effect is not as pronounced as one might expect on the basis of simple models that assume constant mutational effects (Crow and Kimura 1979; Kondrashov 1988). Even extremely strong epistasis appears to increase the expected lifetime of a population by less than a factor of 10, and in small partially selfing populations, synergistic epistasis actually increases the vulnerability to extinction. As pointed out by Butcher (1995), with a continuous distribution of mutational effects, there are always likely to be some deleterious mutations with small enough effects to allow fixation. Once fixed, these mutations exert effects that can then become permanently magnified by synergistic epistasis as subsequent mutations accumulate. Thus, unless the synergistic interactions among all deleterious mutations are strong enough to prevent fixation, it does not appear that epistasis can prevent an ultimate decline in fitness in a small population. Although the mapping functions that we employed in our investigation of epistasis cover only a few of a large number of possible functions that could be used, these verbal arguments are general.

Beneficial mutations obviously improve the situation (Lande 1994; Peck et al., in press). However, our results show that unless the beneficial mutation rate is on the order of 10% or more of the deleterious rate, then beneficial mutations can only slow (not prevent) the loss of fitness in small populations ($N_e < 100$). For larger N_e , the critical beneficial mutation rate declines dramatically, so that if a few percent of all mutations are beneficial, these populations maintain fitness even in the presence of moderate deleterious mutation. Nevertheless, for situations in which the genomic mutation rate is on the order of two or more, the beneficial mutation rate required to prevent mutational deterioration of a population appears to be implausibly high, even for fairly large populations. Thus, if the prevailing idea that $\mu_d \cong 1$ in a mutagenically benign environment is approximately correct, only moderate increases in the mutagenicity of the environment may be sufficient to send many populations rapidly to extinction. Even in the absence of fixation, high rates of deleterious mutation imperil populations through the sheer magnitude of the segregation load that they produce.

Using a different mutational model, Peck et al. (in press) found that mean fitness could be stabilized in populations with effective sizes as small as 100 individuals. However, as in many other theoretical investigations of mutation accumulation, to prevent extinction of simulated populations, Peck et al. (in press) assumed that fecundity is effectively infinite. Even then, to prevent mean viability from stabilizing at exceedingly low levels, it was necessary to invoke very strong synergistic epistasis. A major difference between Peck et al. (in press) and our approach to modeling the joint process of beneficial and deleterious mutation involves the way in which the mutational effects are defined. Peck et al. (in press) considered the case of selection operating on a single quantitative trait. With this type of model, the effects of mutations are conditional, increasing or decreasing fitness depending on whether the phenotype is moved away from or toward the

optimum. However, we have assumed that mutations have effects that are either unconditionally deleterious or unconditionally advantageous. The approach of Peck et al. (in press) is interesting in that many quantitative characters appear to be under stabilizing selection. However, we do not yet know whether observed selection functions are merely the "apparent" consequences of the pleiotropic effects of unconditionally deleterious alleles that yield phenotypes that deviate from the mean (Robertson 1956; Barton 1990; Keightley and Hill 1990; Kondrashov and Turelli 1992). While the approach that we have taken is the one that almost all studies of deleterious mutation have adhered to (that by Wagner and Gabriel [1990] being a notable exception), it is still an open question whether the approach of Peck et al. (in press) is closer to biological reality.

Our results on the influence of the form of the distribution of mutational effects are qualitatively consistent with previous arguments (Lynch and Gabriel 1990; Gabriel et al. 1993; Lynch et al. 1993; Lande 1994). A simple heuristic way to consider the problem is to note that deleterious mutations with selection coefficients in the neighborhood of $1/(2N_e)$ have the greatest impact on mean population fitness—mutations with larger effects are eliminated by selection, while mutations with effects close to zero have a high probability of fixation but little impact on fitness. Keeping the mean effect constant, whether an increase in the variance of mutational effects will increase or decrease the expected longevity of a population will depend on the position of the mean effect relative to $1/(2N_e)$ as well as on the form of the distribution. If the average selection coefficient is in the neighborhood of $1/(2N_e)$, increased variance of mutational effects will reduce the loss of fitness by deleterious mutations by moving a greater proportion of the mutations into classes that are less damaging at the population level.

Thus, in our analyses, where we focused on $\bar{s} = 0.05$ (which is roughly consistent with the few existing data), variation in mutational effects resulted in an enhanced longevity of populations with effective sizes on the order of 10 to 70 individuals. If the distribution of deleterious mutational effects is even more L-shaped than the ones that we employed, a possibility that is at least compatible with the existing data (Keightley 1994), variation in mutational effects is likely to be an indirect mechanism for reducing (not enhancing) the vulnerability of small populations to mutational decay. Although numerical results reported in Lande (1994) concentrate on the situation in which $\sigma_s/\bar{s} \leq 1$, the solution of his formulae for higher σ_s/\bar{s} yields results that are qualitatively very similar to those in Figure 4 (R. Lande, pers. comm.).

While variance in mutational effects can in principle increase the risk of extinction in large populations (on the order of $N_e = 10^3$; Lande 1994), the plausibility of this idea is diminished in the presence of beneficial mutation and synergistic epistasis, which in combination should render the likelihood of extinction small, or even negligible, in populations with effective size greater than a few hundred individuals. Thus, our results suggest that random drift of new mutations is less likely to pose a threat to outcrossing populations with N_e on the order of 10^3 than other sources of random variation, such as environmental stochasticity and random catastrophes (see also Lande 1988, 1993). However,

definitive answers in this area, as well as in most other areas of inquiry that involve deleterious-mutation load, await empirical data on the distribution of effects of beneficial and deleterious mutations.

ACKNOWLEDGMENTS

This work has been supported by a grant from the Oregon Department of Fish and Wildlife, by National Institutes of Health grant GM36827, and by National Science Foundation grant DEB-9629775. We thank K. Kostow for constant encouragement, and A. Kondrashov and R. Lande for helpful comments.

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Corresponding Editor: G. Wagner