Mutation and Conservation

RUSSELL LANDE

Department of Biology, University of Oregon, Eugene, OR 97403, U.S.A., email russ@aylmer.uoregon.edu

Abstract: *Mutation can critically affect the viability of small populations by causing inbreeding depression, by maintaining potentially adaptive genetic variation in quantitative characters, and through the erosion of fitness by accumulation of mildly detrimental mutations. I review and integrate recent empirical and theoretical work on spontaneous mutation and its role in population viability and conservation planning. I analyze both the maintenance of potentially adaptive genetic variation in quantitative characters and the role of detrimental mutations in increasing the extinction risk of small populations. Recent experiments indicate that the rate of production of quasineutral, potentially adaptive genetic variance in quantitative characters is an order of magnitude smaller than the total mutational variance because mutations with large phenotypic effects tend to be strongly detrimental. This implies that, to maintain normal adaptive potential in quantitative characters under a balance between mutation and random genetic drift (or among mutation, drift, and stabilizing natural selection), the effective population size should be about 5000 rather than 500 (the Franklin-Soulé number). Recent theoretical results suggest that the risk of extinction due to the fixation of mildly detrimental mutations may be comparable in importance to environmental stochasticity and could substantially decrease the long-term viability of populations with effective sizes as large as a few thousand. These findings suggest that current recovery goals for many threatened and endangered species are inadequate to ensure long-term population viability.*

Mutación y conservación

Resumen: *La mutación puede afectar criticamente la viabilidad de poblaciones pequeñas al causar la depresión de endocría, mantener la variación genética potencialmente adaptativa en caracteres cuantitativos, y por medio de la erosión de la condiciòn por acumulación de mutaciones levemente perjudiciales. En el presente estudio revisé e integré trabajos empíricos y teóricos recientes sobre mutaciones espontáneas y su papel en la viabilidad de las poblaciones y la planificación para la conservación. Se analizó tanto el mantenimiento de la variabilidad genética potencialmente adaptativa en los caracteres cuantitativos como el papel de las mutaciones perjudiciales en el incremento de riesgo de extinción de las poblaciones pequeñas. Experimentos recientes indican que la tasa de producción de varianza genética cuasineutral y potencialmente adaptativa en los caracteres cuantitativos es de un orden de magnitud menor que la varianza mutacional total debido a que las mutaciones con efectos fenotípicos pronunciados tienden a ser fuertemente perjudiciales. Esto implica que a efecto de mantener el potencial adaptativo normal en los caracteres cuantitativos bajo un balance entre mutación y deriva génica al azar (o entre mutación, deriva génica y selección natural estabilizadora), el tamaño poblacional efectivo debe ser de aproximadamente 5000 y no 500 (numero de Franklin-Soulé). Resultados teóricos recientes sugieren que el riesgo de extinción debido a la fijación de mutaciones levemente perjudiciales podría ser comparable en importancia a la estocasticidad ambiental y podría reducir substancialmente la viabilidad a largo plazo de las poblaciones con un tamaño poblacional efectivo de solo unos pocos miles. Estos descubrimientos sugieren que las metas de recuperación para muchas especies en peligro y amenazadas son inadecuadas para asegurar la viabilidad poblacional a largo plazo.*

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Introduction

Mutation is the ultimate source of all genetic variation (Dobzhansky 1970). Different kinds of genetic variation can critically affect population viability, especially in small populations. Deleterious (partially) recessive mutations, such as recessive lethal alleles, contribute to inbreeding depression in fitness, which increases the risk of extinction. Mildly detrimental mutations accumulate and can become fixed by random genetic drift, gradually eroding fitness and increasing extinction risk. Quasineutral, potentially adaptive genetic variance in quantitative characters maintained by mutation becomes diminished by inbreeding and random genetic drift, reducing the ability of a population to adapt and persist in a changing environment.

Measurements of the rates at which different types of mutations arise spontaneously have been used in conjunction with population genetic theories to suggest minimum population sizes for different goals in species conservation, such as avoiding inbreeding depression, maintaining potential for adaptive evolution, and avoiding genetic erosion of fitness from the accumulation of detrimental mutations (Franklin 1980; Soulé 1980; Lynch & Gabriel 1990; Lynch et al. 1993). I review and integrate recent experimental and theoretical work on spontaneous mutation and discuss how this affects our understanding of conservation goals for threatened and endangered species. Following a brief review of the genetic basis of inbreeding depression, I summarize information on spontaneous mutations affecting fitness and quantitative (polygenic) characters. Drawing from recent experimental and theoretical results, I then reconsider the role of mutation in the maintenance of potentially adaptive genetic variance in quantitative characters and the risk of population extinction from fixation of new detrimental mutations.

Inbreeding Depression

Decrease in the mean value of a character upon inbreeding is known as inbreeding depression, which results from the segregation of partially recessive mutations within populations. In historically large outbreeding populations, rapid inbreeding decreases the mean of characters—such as body size—and of major fitness components—such as seed yield in corn or litter size in mice and pigs—by a few percentage points to 10% or more for every 10% increase in the inbreeding coefficient (Falconer 1989; Ralls & Ballou 1983). In most naturally outbreeding species, close inbreeding—as by brother-sister mating—results in rapid extinction of a high percentage of lines (Soulé 1980).

A typical human or *Drosophila* fly carries one or two nearly recessive lethal or sublethal mutations in heterozygous form, while in some species of coniferous trees individuals may be heterozygous for five to ten recessive lethal equivalents (Sorenson 1969; Dobzhansky 1970). Habitual inbreeding decreases this hidden (recessive) genetic load by eliminating recessive lethal and sublethal mutations from the population when they are expressed in homozygous form. Predominantly self-fertilizing plant species therefore manifest reduced levels of inbreeding depression for fitness (Lande & Schemske 1985; Charlesworth & Charlesworth 1987).

The genetic basis of inbreeding depression for fitness has been studied more carefully in *Drosophila* than in other species. Using special genetic techniques available in *Drosophila*, chromosomes have been sampled intact, without recombination, from wild populations and tested in homozygous and in heterozygous form. The distribution of egg-to-adult viability in chromosomal heterozygotes is approximately normal, with a standard deviation of several percent of the mean. In chromosomal homozygotes, egg-to-adult viability has a strongly bimodal distribution, with a lethal and sublethal mode and a quasinormal mode that has a smaller mean and larger variance than that of chromosomal heterozygotes (Dobzhansky 1970). Genetic and statistical analysis shows that about half of the inbreeding depression in viability is caused by rare, nearly recessive lethal and sublethal point mutations, with the remainder attributable to numerous mildly detrimental mutations of small, more nearly additive effect (Simmons & Crow 1977). There is little evidence that overdominance (heterozygote advantage) contributes substantially to inbreeding depression (Charlesworth & Charlesworth 1987, 1990; Crow 1993).

The amount of inbreeding depression manifested by a population depends on the rate of inbreeding and the opportunity for selection to purge recessive lethal and semilethal mutations; this important point is neglected in some recent models that therefore overestimate the impact of inbreeding depression on population viability (Senner 1980; Halley & Manasse 1993; Mills & Smouse 1994). Gradual inbreeding by incremental reductions in population size over several or many generations allows selection to eliminate at least the lethal and sublethal mutations when they become homozygous (Falconer 1989). In contrast, the component of inbreeding depression from more nearly additive mutations of small effect may be difficult or impossible to purge by inbreeding, and even habitually self-fertilizing plants show considerable inbreeding depression manifested as heterosis (increased fitness) upon crossing different lines (Lande & Schemske 1985; Charlesworth & Charlesworth 1987; Charlesworth et al. 1990; Hedrick 1994).

Mutation Rates

In *Drosophila melanogaster* about 5000 lethal-producing loci mutate at an average rate of $\bar{\mu} = 2 \times 10^{-6}$ per allele per generation, giving a gametic mutation rate of

10^{-2} per generation. Lethal and sublethal mutations are not completely recessive, decreasing the fitness of heterozygotes by about 2% on average (Simmons & Crow 1977). In large populations, selection keeps such strongly deleterious mutations at low equilibrium frequencies ($\approx 4 \times 10^{-4}$). The expected frequency of slightly dominant lethal and sublethal mutations in a population of constant size is approximately independent of population size, provided that the effective population size, N_e, is large enough for selection to keep them at low frequency ($N_e >> 2$) (Crow & Kimura 1970:448–449). N_e refers to an ideal population of constant size, reproducing by random union of gametes, that gives the same rate of random genetic drift as an actual population of size N. Because of temporal fluctuations in population size, greater than Poisson variance in reproductive success, and unequal sex ratio, N_e is generally substantially less than N (Wright 1969; Crow & Kimura 1970; Lande & Barrowclough 1987).

Mildly detrimental mutations in *Drosophila melanogaster* have a heterozygote disadvantage of about one-third to one-half that of homozygotes (Mukai et al. 1972; Crow & Simmons 1983). Upper bounds for the average homozygous effect of mildly detrimental mutations are 4%–5% for viability (Simmons & Crow 1977; Crow & Simmons 1983) and about twice as large for fitness (Houle et al. 1992). These estimates are upper bounds because they neglect variation in selection coefficients among new mutations, which would decrease the estimated average effect by a factor of $1/(1 + c^2)$. c is the coefficient of variation (standard deviation/mean) of the effects of mildly detrimental mutations on fitness (Crow & Simmons 1983), which is likely to be substantial, perhaps of order 1 (Keightly 1994; Lande 1994). We therefore assume that mildly detrimental mutations have additive effects with an average heterozygous fitness loss of 2.5%. Such slightly deleterious mutations arise frequently, with total genomic mutation rates on the order of $U \approx 1$ per generation (Mukai et al. 1972; Mukai 1979), and they have a much higher probability of fixation than do mutations of large effect if N_e exceeds a few individuals.

The rate of phenotypic divergence by random genetic drift among replicated, highly inbred lines, and/or the rate of response in the mean phenotype to artificial selection on a highly inbred line, can be used to measure the genomic mutation rate and the production of genetic variance by spontaneous mutation in quantitative characters. For typical quantitative traits of plant and animal morphology, in excess of one in a hundred gametes contains a new mutation with a small effect on any character (Sprague et al. 1960; Russell et al. 1963; Hoi-Sen 1972). Thus, the (diploid) genomic mutation rate summed over all loci producing mutations that affect a particular character, $U = 2\Sigma\mu_i$, is typically about 0.02 per generation. For a variety of quantitative characters in plants and animals, the additive genetic variance created each generation by spontaneous mutation, V_m, is roughly 10^{-3} times the environmental (nongenetic) variance in the character that would be expressed in a vigorous inbred line, V_e (Lande 1975; Lynch 1988). Assuming that mutational changes are symmetric (equally often increasing and decreasing the character), the average squared mutational effect is then about $\alpha^2 = 0.05V_e$. Recent experiments with *Drosophila* indicate that nearly half of these mutations, especially those with large phenotypic effects, are highly detrimental (recessive lethal), and that the rate of production of quasineutral mutational variance per generation, denoted as $\tilde{V}_m$ (which is likely responsible for much of the standing variation in quantitative traits of natural populations), is roughly an order of magnitude lower, $\tilde{V}_m \cong 10^{-4}V_e$ (Mackay et al. 1992; López & López-Fanjul 1993*a*, 1993*b*). Thus, in comparison to the total set of mutations affecting a typical quantitative character, the genomic mutation rate is about half as large for quasineutral mutations, $U = 0.01$, and the mean squared mutational effect is about one-fifth as large, $\alpha^2 = 0.01V_e$.

Maintenance of Potentially Adaptive Genetic Variance

Franklin (1980) and Soulé (1980) proposed that N_e 500 is sufficient for long-term maintenance of genetic variability in quantitative characters, and this number was quickly adopted as the basis of management plans for captive as well as wild populations (Lande 1988). The Franklin-Soulé number was derived by assuming a balance between mutation and random genetic drift and by using experimental measurements of mutability of quantitative characters to determine an effective population size sufficient to maintain typical amounts of heritable variation and adaptive potential (Lande & Barrowclough 1987). Explicit connections between additive genetic variance, adaptation, and population persistence were later analyzed by Lynch and Lande (1993), Bürger and Lynch (1994) and Lande and Shannon (1995).

Mutation in a Finite Population

Quantitative characters of morphology, physiology, and behavior are of great importance in adaptation to natural environments. The rate of evolution of the mean phenotype in response to directional natural selection is proportional to the additive genetic variance (the heritable portion of the genetic variance responsible for the resemblance between relatives) when selection acts on a single character (Falconer 1989), or to the additive genetic variance-covariance matrix when selection acts on a set of correlated characters (Lande & Arnold 1983).

Let V_g be the (purely) additive genetic variance in a quantitative character. Assuming a wide range of possi-

ble allelic effects at each locus, with a constant rate and distribution of mutational changes to altered allelic effects on the character, the input of additive genetic variance from mutation each generation is a constant, V_m. In a diploid randomly mating population, the expected rate of loss of heterozygosity, or additive genetic variance in a quantitative trait, due to random genetic drift in the absence of selection is $1/(2N_e)$ per generation (Wright 1931; Lande & Barrowclough 1987). Measuring time, t in generations, the expected value of the additive genetic variance, $\overline{V_g}$, under random genetic drift and mutation obeys the dynamics

$$\frac{d\overline{V_g}}{dt} = -\frac{\overline{V_g}}{2N_e} + V_m . \quad (1)$$

At equilibrium between mutation and random genetic drift, the expected genetic variance is $\overline{V_g} = 2N_eV_m$. The heritability of a character is the proportion of the total phenotypic variance due to additive effects of genetic variation. For quantitative characters of morphology, physiology, and behavior, excluding major components of fitness such as viability and fecundity, heritabilities usually range between 0.2 and 0.8 (Mousseau & Roff 1987; Falconer 1989). Assuming a typical heritability of 0.5, so that $\overline{V_g} = V_e$, using $V_m = 10^{-3}V_e$ and solving for the effective population size gives $N_e = 500$.

If we incorporate the finding that only about 10% of the spontaneous mutational variance is quasineutral (López & López-Fanjul 1993*a*, 1993*b*), we should substitute $\tilde{V}_m \cong 10^{-4}V_e$ for V_m into the above formulas, and the Franklin-Soulé number would have to be increased by a factor of 10, to $N_e = 5000$.

Mutation and Stabilizing Selection in a Finite Population

Natural selection on quantitative characters (other than major components of fitness) generally favors an intermediate optimum phenotype that may fluctuate with time. Weak stabilizing selection on a quantitative character can be described by a bell-shaped (Gaussian) curve giving the fitness per generation as a function of the individual phenotype. The strength of stabilizing selection is measured by V_s, the "width" (or variance analog) of the fitness function. Stabilizing selection acting directly on a given character and indirectly on correlated characters (Lande & Arnold 1983) decreases the phenotypic variance of a typical trait within a generation by a few to several percent (Johnson 1976; Endler 1986). The total strength of (direct + indirect) stabilizing selection on a typical character is therefore about $V_s \cong 25V_e$.

The expected additive genetic variance maintained by mutation in a finite population for a quantitative character under stabilizing selection is accurately described by the formula

$$\overline{V_g} = \frac{2N_eV_mV_g(\infty)}{2N_eV_m + V_g(\infty)} . \quad (2)$$

$V_g(\infty)$ is the additive genetic variance that would be maintained at mutation-selection equilibrium in an infinitely large population (Bürger & Lande 1994). Two approximations for the amount of additive genetic variance maintained in an infinite population under the polygenic mutation model described above are known as the house-of-cards model and the Gaussian allelic model.

The house-of-cards model assumes a large number of loci, n, and low mutation rates per locus, μ, such that with a typical strength of stabilizing selection each locus has one common "wild-type" allele in high frequency and rare mutant alleles with relatively large effects. Under the house-of-cards approximation, $V_g(\infty) \cong 4n\mu V_s$ (Turelli 1984; Keightley & Hill 1988; Bürger et al. 1989; Houle 1989).

The Gaussian allelic model assumes a relatively small or moderate effective number of loci, N_E, with high per-locus mutation rates such that each locus has several or many segregating alleles per locus, with an approximately Gaussian distribution of small phenotypic effects. Under the Gaussian allelic approximation, $V_g(\infty) \cong \sqrt{(2n_EV_mV_s)}$, where n_E is typically around 5 or 10 (Kimura 1965; Lande 1975, 1981).

In the house-of-cards approximation, the additive genetic variance maintained in an infinite population with $V_s = 25V_e$ and $U = 2n\mu = 0.02$ is $V_g(\infty) = 1.0V_e$. In the Gaussian allelic approximation, with $V_s = 25V_e$, $V_m = 10^{-3}V_e$, and $n_E = 10$, a somewhat lower additive genetic variance is maintained in an infinite population, $V_g(\infty) = 0.71V_e$. These correspond, respectively, to heritabilities of 0.50 and 0.42, both of which are in the typical range for quantitative characters (0.2 to 0.8; Mousseau & Roff 1987; Falconer 1989).

If we exclude recessive lethal mutations and include only the quasineutral, potentially adaptive mutations, the additive genetic variance maintained in an infinite population under the house-of-cards approximation becomes $V_g(\infty) = 0.50V_e$ and under the Gaussian allelic approximation, assuming n_E remains at 10, the additive genetic variance becomes $V_g(\infty) = 0.225V_e$. These correspond, respectively, to the reduced heritabilities of 0.33 and 0.18. It should be noted, however, that mutation is only one of several factors contributing to the maintenance of potentially adaptive genetic variance, including gene flow among differentiated populations, and density- and frequency-dependent competition (Felsenstein 1977; Slatkin 1979). The segregation of rare excessive lethal mutations contributes only a small fraction of the additive genetic variance in most quantitative characters (Falconer 1989).

Figure 1 shows the expected additive genetic variance maintained by mutation as a function of N_e for typical quantitative characters under the two approximations. The effective population size at which the expected additive genetic variance is equal to a proportion p of that

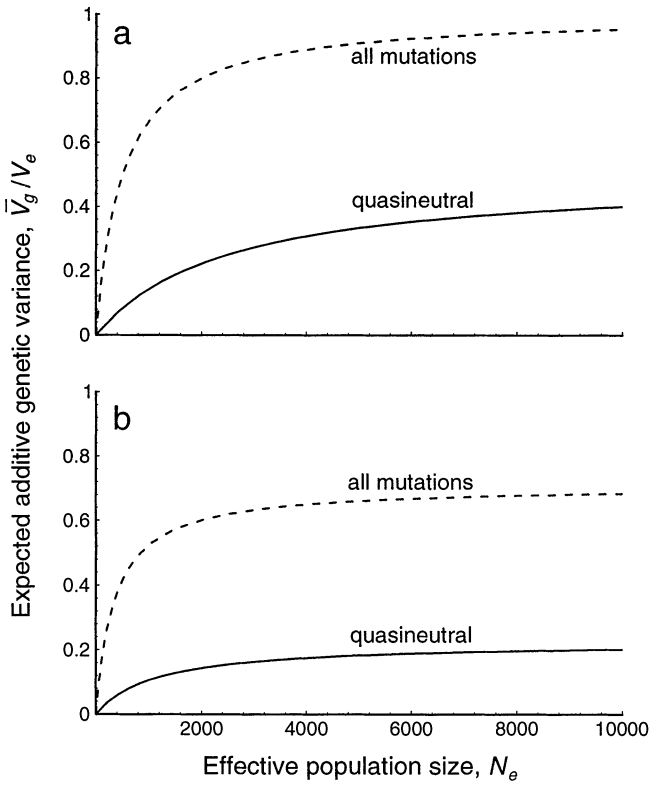

Figure 1. Expected additive genetic variance, $\overline{V_g}$, relative to environmental variance, V_e, maintained by mutation in a typical quantitative character under stabilizing selection in a finite population: house-of-cards approximation (a) and Gaussian allelic approximation (b). Dashed lines include all mutations; solid lines include only quasineutral mutations, excluding recessive lethals.

maintained in an infinitely large population is from equation 2, $N_e^* = [p/(1 - p)]V_g(\infty)/(2V_m)$. Table 1 gives numerical values of N_e^* corresponding to different values of p under both approximations. For example, under the house-of-cards approximation, including all mutations (ignoring recessive lethal effects), a population with $N_e = 1000$ is expected to maintain 67% of the additive genetic variance maintained in an infinite population; under the Gaussian allelic approximation, a population with $N_e = 707$ is expected to maintain 67% of the additive genetic variance maintained in an infinite population. Including only quasineutral mutations N_e would have to be five times larger (5000) in the house-of-cards approximation and 3.15 times larger in the Gaussian allelic approximation (2236) to maintain 67% of the additive genetic variance in an infinite population.

The house-of-cards approximation is most accurate for loci with relatively large effects and low mutation rates, and the Gaussian allelic approximation is most accurate for loci with relatively small effects and high mutation rates. Because both types of loci probably contribute to variance of quantitative characters, the actual amounts of additive genetic variance maintained by mutation are likely to be between these two approximations. Excluding recessive lethal mutations, and whether or not we include stabilizing selection, it therefore appears that the effective population size necessary to maintain a high proportion of the potentially adaptive, additive genetic variance that would occur in a large population requires effective population sizes an order of magnitude larger than the original Franklin-Soulé number, increasing the management goal from $N_e = 500$ to $N_e = 5000$.

Extinction from Fixation of New Mutations

Small populations risk extinction from a variety of genetic and demographic factors, including inbreeding depression as well as the fixation of new detrimental mutations. For large populations that have been reduced suddenly to a small size, inbreeding depression based on segregating detrimental mutations carried by the founders constitutes an important risk of rapid extinction (Soulé 1980). For populations that are reduced in size more gradually, the fixation of new detrimental mutations poses a more serious risk of eventual extinction. In this section I examine how the risk of extinction from fixation of new mutations scales with population size and how this compares with the risks from stochastic demographic factors.

Most mutations are either quasineutral or detrimental. In populations with effective sizes larger than a few individuals, fixations of new, mildly detrimental mutations are far more important in causing loss of fitness and eventual extinction than are new, lethal and semilethal mutations. This is because strongly detrimental mutations have an exceedingly low chance of fixation in comparison to selectively neutral mutations, which have a relatively high chance of fixation but do no damage to the population. Lande (1994) analyzed the fixation of new, mildly detrimental mutations in a randomly mating population of constant size. Mildly detrimental mutations were assumed to have additive effects on Malthu-

Table 1. Effective population sizes, N_e, required to maintain an expected additive genetic variance equal to a given fraction p of that in an infinite population including either all mutations or only quasineutral mutations (excluding recessive lethals).

		p			
Mutations	*Approximation*	*0.50*	*0.67*	*0.75*	*0.80*
All	house-of-cards	500	1000	1500	2000
	Gaussian allelic	354	707	1061	1414
Quasineutral	house-of-cards	2500	5000	7500	10,000
	Gaussian allelic	1118	2236	3354	4472

sian fitness (population growth rate), with a fitness decrement of s per heterozygote and $2s$ per mutant homozygote. He found that the magnitude of selection coefficient that minimizes the mean time to extinction is about $\hat{s} = 0.4/N_e$, which is close to the border between neutrality and selection defined by Wright (1931, 1969), $s \leq 1/(2N_e)$. For this reason, and because they arise at much higher spontaneous rates than do recessive lethal mutations, mildly detrimental mutations on the border of neutrality are the most damaging to population viability.

Risks of Extinction from Genetic Stochasticity

To analyze the risk of population extinction from fixation of new mutations, and to compare this to extinction risks from demographic factors, Lande (1994) modeled a randomly mating population with no demographic or environmental stochasticity. Population size was assumed to remain constant as long as the mean Malthusian fitness, r (the intrinsic rate of increase of the population), is positive. This model accounts only for unconditionally detrimental mutations. Stochastic fixation of mildly detrimental mutations gradually erodes the mean Malthusian fitness until r becomes negative—the population then can no longer replace itself and declines relatively rapidly to extinction (Lynch et al. 1993). Lande (1994) derived analytical approximations for the mean time until the population becomes genetically inviable (or extinct) in the situation where all mildly detrimental mutations have the same selection coefficient, s against heterozygotes and $2s$ against homozygotes. Lynch et al. (1995*a*) analyze this situation in more detail and perform computer simulations to check the analytical results. Lande (1994) also analyzed the influence of variance in selection coefficients among new mutations. The results on the scaling of mean time to extinction with effective population size are as follows.

With a constant selection coefficient against new mutations, s, the mean time to extinction, $\bar{t}$, is a nearly exponential function of effective population size, N_e. Because the mean time to extinction is such a rapidly increasing function of N_e (see Fig. 2), with values of s around a few percent, this indicates that the fixation of new mutations poses little risk of extinction for populations with effective size about 100 individuals (Lande 1994). This conclusion is in agreement with extensive simulation results of Charlesworth et al. (1993). However, the inclusion of variance in selection coefficients in the model drastically decreases the mean time to extinction.

With variance in s, the mean time to extinction increases as a power of population size. If s is exponentially distributed, then $\bar{t}$ is asymptotically proportional to N_e^2. This more gradual increase in $\bar{t}$ with population size, shown in Figure 2, indicates a much greater risk of extinction than in the case of a constant selection coefficient. For reasonable variance in s (a coefficient of variation of about $c = 1$), it appears that fixation of new, slightly deleterious mutations poses a considerable risk of extinction for populations as large as a few thousand individuals. Numerical examples appear in Table 2. These results, in conjunction with data on the rate and magnitude of mildly detrimental mutations in *Drosophila melanogaster*, indicate that the long-term viability of even moderately large populations, with effective sizes of a few thousand (and actual sizes of several or many thousands), may be substantially reduced by the fixation of new mutations.

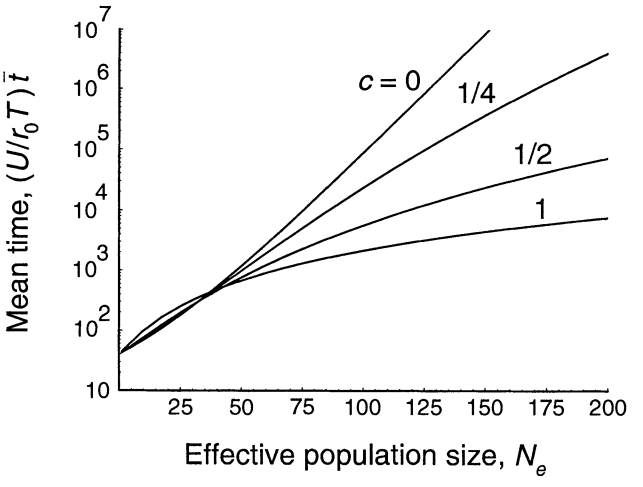

Figure 2. Mean time until extinction, in generations, as a function of effective population size, N_e, *due to fixation of new mutations.* U *is the genomic rate of mildly deleterious mutations,* r_0 *is the initial Malthusian fitness (intrinsic rate of increase), and* T *is the generation time. Selection coefficients against mildly deleterious mutations follows a gamma distribution with coefficient of variation* c. *For* c = *1, the selection coefficients are exponentially distributed. Mutations have additive effects on Malthusian fitness, with average selection coefficient* $\bar{s} = 0.025$ *against heterozygotes. (From Lande 1994.)*

RELATIVE RISKS FROM GENETIC AND DEMOGRAPHIC FACTORS

It is illuminating to compare the risks of population extinction from genetic stochasticity, due to fixation of new mutations, with the risks from demographic and environmental stochasticity. The relative risks of population extinction from different stochastic factors can be assessed by comparing asymptotic scaling relationships describing how the average time to extinction, $\bar{t}$, increases with equilibrium population size (or carrying capacity) under each stochastic factor alone. Although the actual extinction risk for a population of a given effec-

Table 2. Scaled mean times to extinction, $(U/r_0T)\bar{t}$, in generations (from Lande 1994).

	$(U/r_0T)\bar{t}$*	
Effective Population Size, N_e	*constant* s	*variable* s
2	44	49
5	52	65
10	69	99
20	128	193
50	1179	677
100	8.8×10^4	2149
200	9.7×10^8	7690
500	4.1×10^{21}	4.4×10^4
1000	1.1×10^{43}	1.7×10^5
2000	1.4×10^{86}	6.7×10^5

*U *is the genomic rate of mildly deleterious mutations,* r_0 *is the initial Malthusian fitness (intrinsic rate of increase), and* T *is the generation time. The selection coefficient,* s*, against mildly deleterious mutations either is constant or has an exponential distribution with* $\bar{s} = 0.025$*. For most species, the scale factor* r_0T/U *is likely to be in the range of about 1 to 10.*

Table 3. Asymptotic scaling laws for mean time to extinction, $\bar{t}$, as a function of the equilbrium population size, N, or effective population size, N_e, for demographic and genetic risk factors.

Risk Factor	*Proportional Scaling of* $\bar{t}$*
Demographic Stochasticity	$(1/N)e^{2Nr/V_1}$
Environmental Stochasticity	$N^{2r\bar{r}V_e-1}$
Fixation of New Mutations	
constant s	$(1/N_e)e^{4N_es}$
variance in s	N_e^{1+1/c^2}

*r *is the expected population growth rate (or mean Malthusian fitness);* V_1 *is the demographic variance in Malthusian fitness among individuals;* $\bar{r}$ *is the mean population growth rate;* V_e *is the (temporal) environmental variance in population growth rate;* $c = \sigma_s/\bar{s}$ *is the coefficient of variation of* s *among new mutations.*

tive size depends on details of life history, ecology, and genetics, the relative risks associated with different factors are, for sufficiently large populations, determined predominantly by the relative rates at which $\bar{t}$ increases with population size under each factor alone.

Under demographic stochasticity alone, due to chance events in individual birth and death, $\bar{t}$ increases nearly exponentially with population size. Under either environmental stochasticity or random catastrophes, which affect the birth and death rates of all individuals in a population in approximately the same way, $\bar{t}$ increases as a power of population size (Lande 1993). Thus, the risk of extinction from fixation of new mutations with a constant selection coefficient appears comparable to that of only the weakest demographic factor, demographic stochasticity. In contrast, with reasonable variance in selection coefficients, the fixation of new detrimental mutations poses an extinction risk potentially comparable to that of the strongest factor, environmental stochasticity (Table 3).

Nevertheless, Table 2 and Figure 2 show that in very small populations that have survived the inbreeding depression caused by founder effects and still retain a substantially positive r, environmental stochasticity is more likely than genetic stochasticity to cause extinction because the mean time to extinction due to fixation of new deleterious mutations is on the order of 100 generations or more. Of course, for populations on the brink of extinction, with r near zero, all risk factors and their interactions may be important.

LIMITATIONS OF THE MODELS

Several factors could modify the mean persistence times of populations in this simple model. The time required for mildly detrimental mutations to become fixed and the final decline of the population after r has become negative are both short in comparison to the mean time to reach genetic inviability, provided that the initial intrinsic rate of increase per generation (r_0T) is substantially positive and N_e is not very small (Lynch et al. 1995*b*). Partial recessivity of detrimental mutational effects would increase the probability of fixation and decrease the mean time to extinction. Synergistic epistatic interactions among mildly detrimental mutations, which has been documented for viability in *Drosophila melanogaster* (Mukai 1969), slows the loss of mean fitness if all mutations have the same selection coefficient (Charlesworth et al. 1993), but substantial variance in selection coefficients among new mutations is likely to minimize this effect (Lande 1994). Large populations may never become genetically inviable due to fixation of mildly detrimental mutations because selection against them is more efficient and the erosion of mean fitness may be counteracted by reverse and advantageous mutations. Finally, compensatory mutations at different loci are common, especially for quantitative characters under stabilizing selection (Fisher 1958:44–48), and even strongly deleterious mutations with major morphological effects can be gradually compensated for by the evolution of minor modifiers (Lewontin 1974:91).

Nevertheless, there may be a large class of mildly detrimental mutations that cannot be readily compensated, such as deletions of nonessential but fitness-enhancing loci that may compose the majority of single-copy genes (Cavallier-Smith 1985). The theory remains valid if the genomic mutation rate is multiplied by the proportion of mildly detrimental mutations that are unconditionally deleterious. If the fitness effects of a substantial fraction of all mildly detrimental mutations are unconditional, this would not change the result that with variance in selection coefficients the mean time to extinction is asymptotically proportional to a low power of N_e; one would still conclude that the risk of population extinction from fixation of new mutations is potentially of

comparable importance with that from environmental stochasticity.

Discussion

Mutation has been used in two different ways in the evaluation of population viability and the design of conservation plans. Quasineutral, potentially adaptive mutations have been used to establish minimum effective population sizes for the maintenance of typical levels of additive genetic variance in quantitative characters, which are known to be of great importance in adaptive evolution. Harmful mutations also have been used to set minimum effective population sizes for avoiding the immediate consequences of inbreeding depression and for preventing the erosion of fitness by accumulation of mildly detrimental mutations.

Recent experiments accumulating spontaneous mutations in *Drosophila melanogaster* indicate that the rate of production of quasineutral, genetic variance in quantitative characters is an order of magnitude smaller than the total mutational variance in the characters, because mutations with large effects tend to be strongly detrimental (recessive lethals). This suggests that the effective population size of about 5000, rather than the Franklin-Soulé number of 500, is necessary to maintain normal levels of potentially adaptive genetic variance in quantitative characters under a balance between mutation and random genetic drift. Including stabilizing selection toward an intermediate optimum phenotype does not much affect this conclusion. Of course, $N_e = 5000$ should not be regarded as a magic number sufficient to ensure the viability of all species, because of differences among characters and among species in genetic mutability and differences in environmental fluctuations and selective pressures to which populations are exposed. Maintenance of potentially adaptive genetic variation in single-locus traits (such as major disease resistance factors), which have mutation rates on the order of 10^{-6} per allele per generation, may require much larger effective population sizes, on the order of 10^4 or 10^5 (Lande & Barrowclough 1987; Lande 1988).

In stable populations, mildly detrimental mutations on the border of neutrality do the most damage to population viability because they arise far more frequently and have a much higher chance of fixation than strongly deleterious mutations. Accounting for the high variance in selection coefficients likely to exist among new mutations, the fixation of new, mildly detrimental mutations may be comparable in importance to environmental stochasticity and could substantially reduce the long-term viability of populations with effective sizes as large as a few thousand. In contrast to the rapid extinction caused by inbreeding depression in populations suddenly reduced to a few individuals (Soulé 1980), the fixation of mildly detrimental mutations in a stable population, even of very small size, produces only a gradual erosion of fitness that is likely to take many generations to cause extinction.

When listed, threatened and endangered species typically have actual population sizes on the order of 100 (plants) to 1000 (animals) (Wilcove et al. 1993), and population recovery goals frequently are not much larger than at the time of listing (Tear et al. 1993, 1995; Schemske et al. 1994). The above results cast doubt on whether populations of many threatened and endangered species will maintain adequate evolutionary potential and long-term genetic viability unless they recover to much large sizes. Effective population sizes generally are substantially lower than actual population sizes because of fluctuations in population size, high variance in reproductive success, and unequal sex ratios (Wright 1969; Crow & Kimura 1970; Lande & Barrowclough 1987); maintaining effective population sizes of several thousand in the wild therefore will usually require average actual population sizes on the order of 10^4 or more. Synergistic interactions among different genetic and demographic factors contributing to the risk of population extinction (Gilpin & Soulé 1986) are likely to cause the minimum population sizes for long-term viability of many wild species to be much larger than 10^4.

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Literature Cited

Bürger, R., and R. Lande. 1994. On the distribution of the mean and variance of a quantitative trait under mutation-selection-drift balance. Genetics **138**:901–912.

Bürger, R., and M. Lynch. 1995. Evolution and extinction in a changing environment: a quantitative genetic analysis. Evolution, in press.

Bürger, R., G. P. Wagner, and F. Stettinger. 1989. How much heritable variation can be maintained in a finite population by mutation selection balance? Evolution **43**:1748–1766.

Cavallier-Smith, T. 1985. Eukaryote gene numbers, non-coding DNA and genome size. Pages 69–103 in T. Cavallier-Smith, editor. The evolution of genome size. Wiley, New York.

Charlesworth, D., and B. Charlesworth. 1990. Inbreeding depression with heterozygote advantage and its effect on selection for modifiers changing the outcrossing rate. Evolution **44**:870–888.

Charlesworth, D., and B. Charlesworth. 1987. Inbreeding depression and its evolutionary consequences. Annual Review of Ecology and Systematics **118**:237–268.

Charlesworth, B., D. Charlesworth, and M. T. Morgan. 1990. Genetic loads and estimates of mutation rates in highly inbred plant populations. Nature **347**:380–382.

Charlesworth, D., M. T. Morgan, and B. Charlesworth. 1993. Mutation accumulation in finite outbreeding and inbreeding populations. Genetical Research **61**:39–56.

Crow, J. F. 1993. Mutation, mean fitness, and genetic load. Oxford Surveys in Evolutionary Biology **9**. Oxford University Press, Oxford, England.

Crow, J. F., and M. Kimura. 1970. An introduction to population genetics theory. Harper and Row, New York.

Crow, J. F., and M. J. Simmons. 1983. The mutation load in Drosophila. Pages 1–35 in M. Ashburner, H. L. Carson, and J. N. Thompson, Jr., editors. The genetics and biology of Drosophila, vol. 3c. Academic Press, New York.

Dobzhansky, Th. 1970. Genetics of the evolutionary process. Columbia University Press, New York.

Endler, J. 1986. Natural selection in the wild. Princeton University Press, Princeton, New Jersey.

Falconer, D. S. 1989. Introduction to quantitative genetics. 3rd edition. Longman, London.

Felsenstein, J. 1977. Multivariate normal genetic models with a finite number of loci. Pages 227–246 in E. Pollak, O. Kempthorne, and T.B. Bailey, Jr., editors. Proceedings of the International Conference on Quantitative Genetics. Iowa State University Press, Ames.

Fisher, R. A. 1958. The genetical theory of natural selection. 2nd edition. Dover, New York.

Franklin, I. R. 1980. Evolutionary changes in small populations. Pages 135–149 in M. E. Soulé and B. A. Wilcox, editors. Conservation biology: An evolutionary-ecological perspective. Sinauer Associates, Sunderland, Massachusetts.

Gilpin, M. E., and M. E. Soulé. 1986. Minimum viable populations: Processes of species extinction. Pages 19–34 in M. E. Soulé, editor. Conservation biology: The science of scarcity and diversity. Sinauer Associates, Sunderland, Massachusetts.

Halley, J. M., and R. S. Manasse. 1993. A population dynamics model subject to inbreeding depression. Evolutionary Ecology **7**:15–24.

Hedrick, P. W. 1994. Purging inbreeding depression and the probability of extinction: full-sib mating. Heredity **73**:363–372.

Hoi-Sen, Y. 1972. Is subline differentiation a continuing process in inbred stains of mice? Genetical Research **19**:53–59.

Houle, D. 1989. The maintenance of polygenic variation in finite populations. Evolution **43**:1767–1780.

Houle, D., D. K. Hoffmaster, S. Assimacopoulous, and B. Charlesworth. 1992. The genomic mutation rate for fitness. Nature **359**:58–60.

Johnson, C. 1976. Introduction to natural selection. University Park Press, Baltimore.

Keightley, P. D. 1994. The distribution of mutation effects on viability in *Drosophila melanogaster*. Genetics **138**:1315–1322.

Keightley, P. D., and W. G. Hill. 1989. Quantitative genetic variability maintained by mutation-stabilizing selection balance in finite populations. Genetical Research **52**:33–43.

Kimura, M. 1965. A stochastic model concerning the maintenance of genetic variability in quantitative characters. Proceedings of the National Academy of Sciences USA **54**:731–736.

Lande, R. 1975. The maintenance of genetic variability by mutation in a polygenic character with linked loci. Genetical Research **26**:221–235.

Lande R. 1981. The minimum number of genes contributing to quantitative variation between and within populations. Genetics **99**:541–553.

Lande, R. 1988. Genetics and demography in biological conservation. Science **241**:1455–1460.

Lande, R. 1993. Risks of population extinction from demographic and environmental stochasticity and random catastrophes. American Naturalist **142**:911–927.

Lande, R. 1994. Risk of population extinction from fixation of new deleterious mutations. Evolution **48**:1460–1469.

Lande, R., and S. J. Arnold. 1983. The measurement of selection on correlated characters. Evolution **37**:1210–1226.

Lande, R., and G. F. Barrowclough. 1987. Effective population size, genetic variation, and their use in population management. Pages 87–123 in M. E. Soulé, editor. Viable populations for conservation. Cambridge University Press, New York.

Lande, R., and D. W. Schemske. 1985. The evolution of self-fertilization and inbreeding depression in plants. I. Genetic models. Evolution **39**:24–40.

Lande, R. and S. Shannon. 1995. The role of genetic variation in adaptation and population persistence in a changing environment. Evolution, in press.

Lewontin, R. C. 1974. The genetic basis of evolutionary change. Columbia University Press, New York.

López, M. A., and C. López-Fanjul. 1993*a*. Spontaneous mutation for a quantitative trait in *Drosophila melanogaster*. I. Response to artificial selection. Genetical Research **61**:107–116.

López, M. A., and C. López-Fanjul. 1993*b*. Spontaneous mutation for a quantitative trait in *Drosophila melanogaster*. II. Distribution of mutant effects on the trait and fitness. Genetical Research **61**:117–126.

Lynch, M. 1988. The rate of polygenic mutation. Genetical Research **51**:137–148.

Lynch, M., and W. Gabriel. 1990. Mutation load and the survival of small populations. Evolution **44**:1725–1737.

Lynch, M., and R. Lande. 1993. Evolution and extinction in response to environmental change. Pages 234–250 in P. M. Kareiva, J. G. Kingsolver, and R. B. Huey, editors. Biotic interactions and global change. Sinauer Associates, Sunderland, Massachusetts.

Lynch, M., R. Bürger, D. Butcher, and W. Gabriel. 1993. The mutational meltdown in asexual populations. Journal of Heredity **84**: 339–344.

Lynch, M., J. Conery, and R. Bürger. 1995*a*. Mutational meltdowns in sexual populations. Evolution, in press.

Lynch, M., J. Conery, and R. Bürger. 1995*b*. Mutation accumulation and the extinction of small populations. American Naturalist, in press.

Mackay, T. F. C., R. F. Tyman, and M. S. Jackson. 1992. Effects of *P* element insertion on quantitative traits in *Drosophila melanogaster*. Genetics **130**:315–332.

Mills, L. S., and P. E. Smouse. 1994. Demographic consequences of inbreeding in remnant populations. American Naturalist **144**:412–431.

Mousseau, T. A., and D. A. Roff. 1987. Natural selection and the heritability of fitness components. Heredity **59**:181–198.

Mukai, T. 1979. Polygenic mutation. Pages 177–196 in J. N. Thompson, Jr., and J. M. Thoday, editors. Quantitative genetic variation. Academic Press, New York.

Mukai, T., S. I. Chigusa, L. E. Mettler, and J. F. Crow. 1972. Mutation rate and dominance of genes affecting viability in *Drosophila melanogaster*. Genetics **72**:335–355.

Ralls, K., and J. Ballou. 1983. Extinction: lessons from zoos. Pages 164–184 in C. M. Schonewald-Cox, S. M. Chambers, B. MacBryde, and L. Thomas, editors. Genetics and conservation: A reference for managing wild animal and plant populations. Benjamin-Cummings, New York.

Russell, W. A., G. F. Sprague, and L. H. Penny. 1963. Mutations affecting quantitative characters in long-time inbred lines of maize. Crop Science **3**:175–178.

Schemske, D. S., B. C. Husband, M. H. Ruckelshaus, C. Goodwillie, I. M. Parker, and J. G. Bishop. 1994. Evaluating approaches to the conservation of rare and endangered plants. Ecology **75**:584–606.

Senner, J. W. 1980. Inbreeding depression and the survival of zoo populations. Pages 209–224 in M. E. Soulé and B. A. Wilcox, editors. Conservation biology: An evolutionary-ecological perspective. Sinauer Associates, Sunderland, Massachusetts.

Simmons, M. J., and J. F. Crow. 1977. Mutations affecting fitness in *Drosophila* populations. Annual Reviews of Genetics **11**:49–78.

Slatkin, M. 1979. Frequency- and density-dependent selection on a quantitative character. Genetics **93**:755–771.

Sorensen, F. 1969. Embryonic genetic load in coastal Douglas fir, *Pseudotsuga menziesii* var. *menziesii*. American Naturalist **103**: 389–398.

Soulé, M. E. 1980. Thresholds for survival: maintaining fitness and evolutionary potential. Pages 151–170 in M. E. Soulé and B. A. Wilcox, editors. Conservation biology: An evolutionary-ecological perspective. Sinauer Associates, Sunderland, Massachusetts.

Sprague, G. F., W. A. Russell, and L. H. Penny. 1960. Mutations affecting quantitative traits in the selfed progeny of doubled monoploid maize stocks. Genetics **45**:855–866.

Tear, T. H., J. M. Scott, P. H. Hayward, and B. Griffith. 1993. Status and prospects for success of the Endangered Species Act: a look at recovery plans. Science **262**:976–977.

Tear, T. H., J. M. Scott, P. H. Hayward, and B. Griffith. 1995. Recovery plans and the Endangered Species Act: Are criticisms supported by data? Conservation Biology **9**:182–195.

Turelli, M. 1984. Heritable genetic variation via mutation-selection balance: Lerch's zeta meets the abdominal bristle. Theoretical Population Biology **25**:138–193.

Wilcove, D. S., M. McMillan, and K. C. Winston. 1993. What exactly is an endangered species? An analysis of the endangered species list, 1985–91. Conservation Biology **7**:87–93.

Wright, S. 1931. Evolution in Mendelian populations. Genetics **16**:97–139.

Wright, S. 1969. Genetics and the evolution of populations, vol. 2. The theory of gene frequencies. University of Chicago Press, Chicago.