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FIXATION OF NEW ALLELES AND THE EXTINCTION OF SMALL POPULATIONS: DRIFT LOAD, BENEFICIAL ALLELES, AND SEXUAL SELECTION

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Abstract.—With a small effective population size, random genetic drift is more important than selection in determining the fate of new alleles. Small populations therefore accumulate deleterious mutations. Left unchecked, the effect of these fixed alleles is to reduce the reproductive capacity of a species, eventually to the point of extinction. New beneficial mutations, if fixed by selection, can restore some of this lost fitness. This paper derives the overall change in fitness due to fixation of new deleterious and beneficial alleles, as a function of the distribution of effects of new mutations and the effective population size. There is a critical effective size below which a population will on average decline in fitness, but above which beneficial mutations allow the population to persist. With reasonable estimates of the relevant parameters, this critical effective size is likely to be a few hundred. Furthermore, sexual selection can act to reduce the fixation probability of deleterious new mutations and increase the probability of fixing new beneficial mutations. Sexual selection can therefore reduce the risk of extinction of small populations.

Key words.—Beneficial mutations, compensatory mutations, conservation genetics, drift load, genetic drift, mutation meltdown, sexual selection.

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Mutation is the ultimate source of all genetic variation, and without mutation evolution would quickly cease. Yet many mutations are deleterious, resulting in a reduction of the fitness of the individuals and species that harbor them (Lynch et al. 1999). Because all populations are finite in number, there is some chance that these deleterious alleles can fix and reduce the fitness of all individuals in the population (Fig. 1). If this process continues unabated, the fitness of populations would continue to decline and eventually the population would go extinct under this genetic load (Charlesworth et al. 1993; Lande 1994, 1995, 1998; Lynch et al. 1995a,b).

This scenario, however, makes many assumptions. In particular, in its simplest telling this story only allows for deleterious mutations and therefore only a net decline in fitness is possible. This is reasonable as a short-term first approximation, because the vast majority of mutations with effects on fitness are deleterious (Crow and Simmons 1983; Lynch et al. 1999). But mutation, and therefore evolution, is not one-sided. Beneficial mutations do arise, albeit at a low rate, and a proper theory of the persistence of populations should allow for the positive effects of mutations. There have been several approaches to this problem. Lande (1998) has shown that reverse mutations, those that return deleterious mutant alleles to the fit original form, can substantially slow the loss of fitness but not stop it completely. Schultz and Lynch's (1997) numerical results suggest that effective population sizes must be greater than several hundred to support indefinite persistence of a population with beneficial mutations. Their analysis assumed an exponential distribution of mutational effects. Finally, experimental work by Elena et al. (1998) and Burch and Chao (1999) has shown that beneficial mutations can allow even small populations to persist and increase in fitness, even if fixed for deleterious alleles. These experimental results are fascinating because they point strongly to a possibility ignored by theory—that the rate of beneficial mutations may *increase* as mean fitness drops. In a population declining in fitness, the potential for beneficial mutations will likely be much higher than in the fit populations commonly studied.

Another critical assumption made by models of drift load is that the strength of selection for or against alleles allows one to predict the effects of those alleles on the overall reproductive capacity of a population. In fact, many alleles can affect the fitness of an individual relative to the rest of the population, but not affect the total reproductive success of that population. In particular, alleles that affect male mating success may substantially change the relative fitness of an individual, but need not affect the mean fitness, or productivity, of the population. This is because females may be choosy yet still mate. Given that new mutations that affect survivorship and fecundity also affect male mating success in the same direction (Hughes 1995; Whitlock and Bourguet 2000; see Andersson 1994), segregating deleterious alleles may be selected against more strongly than would be reflected in their effects on the load of the population and therefore less likely to fix for a given size of effect. Similarly, beneficial alleles may be more likely to fix than would be expected by their effects on mean fitness alone.

In this paper, I derive the net change in fitness of populations experiencing both beneficial and deleterious mutations. I allow for correlations between productivity and mating success. A critical effective population size is found, above which a population may persist indefinitely without extinction due to genetic load.

NOTATION AND ASSUMPTIONS

Assume a population has a constant population size and has been at that size long enough to reach an equilibrium between the number of new alleles arising by mutation and the loss of alleles due to fixation. Table 1 lists the terms of the model.

The probability of fixation of a new allele, $u[s]$, has been given by Crow and Kimura (1970):

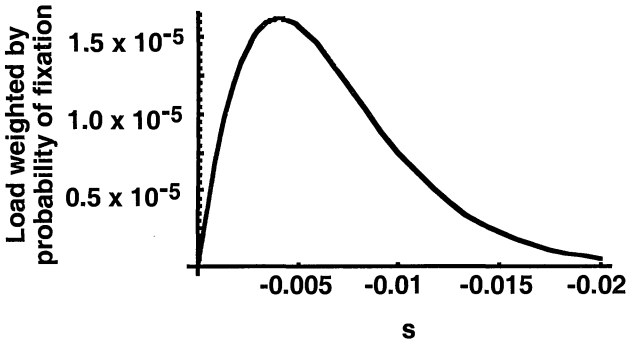

FIG. 1. The total drift load attributable to an average new mutation is the product of the effect of that mutation when homozygous and its probability of fixation. This load is maximized near a value of $s = -0.4/N_e$ (Lande 1994). In this graph, the effective size is set at 100.

$$u[s] = \frac{1 - \exp[-2s(N_e/N)]}{1 - \exp[-4N_e s]} \cong \frac{2s(N_e/N)}{1 - \exp[-4N_e s]}, \quad (1)$$

where the approximation holds for $|\, 2s\,(N_e / N)\,| << 1$. The probability of fixation is different in a population of changing size (Otto and Whitlock 1997) or in a subdivided population (M. C. Whitlock, in press), but for simplicity we will consider an undivided population of fixed size.

Assume that the fixation of alleles at different loci is independent. This implies that the loci interact multiplicatively to determine fitness and that the dynamics of fixation are not affected by alleles segregating at other loci. The first assumption may reasonably be true, but the second will not be with realistic values of the mutation rate. Due to background selection and the Hill-Robertson effect (Hill and Robertson 1966), segregating alleles that affect fitness at other loci will affect the fixation probability of the focal allele. Below, I assume that this effect can be summarized by use of an appropriate N_e (cf. Robertson 1961; Santiago and Caballero 1995) and that the existing measures of N_e / N (e.g., Frankham 1995) include this effect.

The Rate of Change of Mean Fitness Due to New Alleles

The mean fitness of a population will change as a result of the fixation of new beneficial and deleterious alleles. The rate of this decline depends on the number of new mutations appearing per generation, their probability of fixing, and their fitness effects when fixed. The number of new mutations of a particular type that appear per generation is a function of the number of individuals in a population, the mutation rate, and the distribution of mutant effects. The probability of fixation of a new mutation is a function of its effect and the effective population size. The effect on fitness of a fixed allele is $2s$. Putting these together, we can write the total change in fitness due to deleterious mutations as

$$\Delta W_D = U_D N \int_{-\infty}^{0} 2su[s]\Psi_D[s]\, ds. \quad (2)$$

If we assume that the distribution of the absolute values of the effects of new deleterious mutations is a gamma distribution with mean $|\lambda_D|$ and coefficient of variation C_D, we find

$$\Delta W_D = -\frac{\left(1 + \frac{1}{C_D^2}\right) U_D \zeta\left[2 + \frac{1}{C_D^2},\ 1 + \frac{1}{4C_D^2 N_e |\lambda_D|}\right]}{(4C_D^2 N_e)^{1+1/C_D^2} |\lambda_D|^{1/C_D^2}}, \quad (3)$$

where $\zeta[x, a] = \Sigma_{i=0}^{\infty} (i + a)^{-x}$ is the generalized Riemann zeta function, as found by Lande (1994). The first derivative of equation (3) shows that the rate of fitness loss due to drift load on new mutations is a decreasing function of the effective population size.

If $C_D = 1$, then Ψ_D is an exponential distribution. For values of $N_e\,|\lambda_D| > \sim 1.5$, the ζ function is within 20% of unity. Thus, for reasonable values of λ_D ($\gtrsim -0.02$), with $N_e > 75$, we can get a good approximation of ΔW_D:

$$\Delta W_D \cong \frac{U_D}{8N_e^2 \lambda_D}. \quad (4)$$

The rate of change in fitness due to the fixation flux of beneficial alleles is

$$\Delta W_B = U_B N \int_0^{\infty} 2su[s]\Psi_B[s]\, ds = \frac{\left(1 + \frac{1}{C_B^2}\right) U_B \zeta\left[2 + \frac{1}{C_B^2},\ \frac{1}{4C_B^2 N_e \lambda_B}\right]}{\lambda_B^{1/C_B^2} (4C_B^2 N_e)^{1+1/C_B^2}} \quad (5)$$

For values of $4C_B^2 N_e \lambda_B > 1$,

$$\zeta\left[2 + \frac{1}{C_B^2}, \frac{1}{4C_B^2 N_e \lambda_B}\right]$$

is approximately $(4C_B^2 N_e \lambda_B)^{2+(1/C_B^2)}$. Thus, we get

TABLE 1. Terms used in the model.*

Variable	Description
N	the census population size
N_e	the effective population size
s	the selection coefficient, such that the fitnesses of the three biallelic genotypes are 1, $1 + s$, $1 + 2s$
U_D (U_B)	the total number of new deleterious (beneficial) mutations per diploid zygote
$u[s]$	the probability of fixation of a new allele with selection coefficient s
λ_D (λ_B)	the mean effect on fitness of all new deleterious (beneficial) mutations: $\lambda_D < 0$, $\lambda_B > 0$
$\Psi_D[s]$ ($\Psi_B[s]$	the distribution of deleterious (beneficial) mutation effects
C_D (C_B)	the coefficient of variation of the effect of new deleterious (beneficial) mutations (standard deviation of effect/$|\lambda|$)
ΔW_D (ΔW_B)	the change in fitness per generation due to fixation of deleterious (beneficial) mutations
s_A	the effect of an allele on mean fitness
M	the fraction by which the relative fitness of a segregating allele affects the mean fitness of a population; $M = s_A/s$.

* The terms "deleterious" and "beneficial" are meant to imply only that $s < 0$ or $s > 0$, respectively.

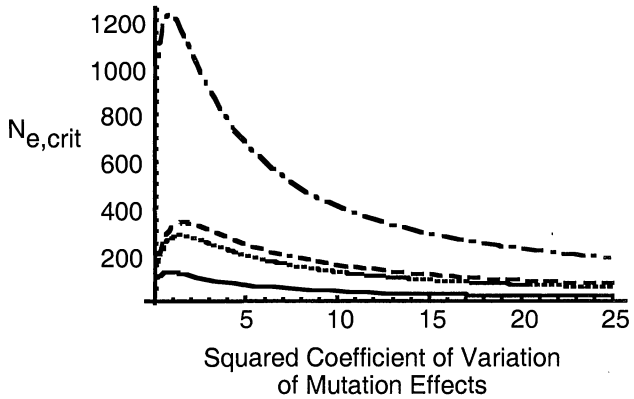

FIG. 2. The critical effective population size depends strongly on the coefficient of variation of the distribution of mutational effects. Four cases are plotted: (1) solid line, $U_D/U_B = 1000$ and $\lambda_B = -\lambda_D = 0.02$; (2) dotted line, same as case 1 except $U_D/U_B = 10{,}000$; (3) dashed line, same as case 1 except $\lambda_B = 0.005$; and (4) dot-dashed line, same as case 1 except $\lambda_B = -\lambda_D = 0.002$. The critical N_e at which fixation of beneficial alleles counters the loss of fitness due to deleterious mutations is highest for values of the coefficient of variation near unity, that is, when mutational effects are exponentially distributed. Reducing the mean effect of either beneficial or deleterious alleles increases the importance of genetic drift and therefore increases $N_{e,crit}$.

$$\Delta W_B \cong 4(1 + C_B^2)U_B N_e \lambda_B^2, \tag{6}$$

which increases with the effective size and the mean effect of beneficial alleles. For the gamma distribution, the rate of change in fitness due to beneficial alleles also increases as the coefficient of variation of mutational effects increases. If Ψ_B is exponential and $\lambda_B > 1/4N_e$, equation (5) becomes approximately

$$\Delta W_B \cong 8U_B N_e \lambda_B^2. \tag{7}$$

The change in fitness due to new mutations depends strongly on the mean and shape of the distribution of allelic effects. If the distribution of the effects of deleterious alleles includes many very weakly selected alleles ($|s| < 1/4N_e$), then selection will be ineffective in preventing fixation of such alleles. The maximum load per mutation is contributed by alleles with effects around $s = -0.4/N_e$ (Lande 1994). With a gamma distribution of deleterious mutational effects, the frequency of such alleles increases as λ_D gets close to this value. Similarly, if C_D is large, the frequency of such alleles will increase. Estimates of C for viability and growth rates are quite large, between two and 20 (Keightley 1994; Elena et al. 1998), although the same data has been used to estimate $C \leq 1$ (García-Dorado 1997).

If the distribution of beneficial and deleterious allelic effects have the same shape, then the exponential distribution ($C_B = C_D = 1$) is close to the worst-case scenario for the parameters investigated (Fig. 2). With the exponential distribution, there are many deleterious alleles of moderate effect, but few beneficial alleles of large enough effect to regain fitness. Because the nature of these distributions is uncertain and because we seek to make relatively conservative conservation biological predictions, the remainder of this paper will focus on the exponential distribution.

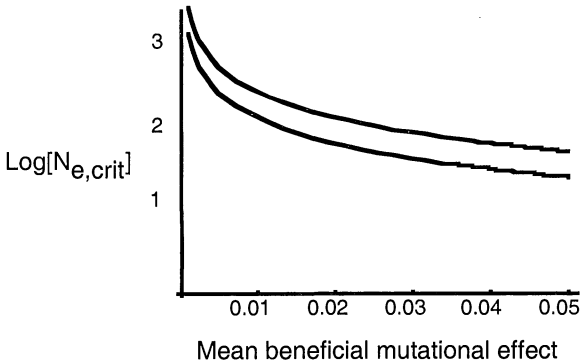

FIG. 3. The critical N_e depends on the mean effect of new mutations. As the absolute value of the mean effect of new alleles decreases, genetic drift becomes more important and the critical effective population size becomes very large. Two cases are presented, both with $U_D/U_B = 1000$ and an exponential distribution of mutational effects ($C = 1$): The bottom line corresponds to the case where $\lambda_D = -\lambda_B$, and the top line plots the case where $\lambda_D = -10\lambda_B$. Note the $\log_{10}$ scale on the y-axis.

THE CRITICAL EFFECTIVE SIZE

We can now derive a critical effective size, below which the effects of drift cause fixed deleterious alleles to overwhelm beneficial fixations and lead toward the extinction of the population. The overall rate of change in fitness of the population per generation is $\Delta W = \Delta W_B + \Delta W_D$, which can be solved numerically to find the critical value of N_e that allows a population to persist at a balance between the fixation of new beneficial and deleterious alleles (see Fig. 2).

With an exponential distribution of mutational effects, we can find a reasonable approximation of this critical size from equations (4) and (7). The total change in fitness is equal to

$$\Delta W = \Delta W_D + \Delta W_B \cong \frac{-U_D}{8N_e^2|\lambda_D|} + 8U_B N_e \lambda_B^2. \tag{8}$$

Setting this difference to zero, we can find the critical value of the effective size, $N_{e,crit}$:

$$N_{e,crit} \cong \sqrt[3]{\frac{U_D}{64\lambda_B^2|\lambda_D|U_B}}. \tag{9}$$

Given a reasonable value of λ_D of about -0.02 (Lynch and Walsh 1998; but see Keightley 1994; García-Dorado 1997) and guesses of the values of λ_B and U_D/U_B of 0.02 and 1000, respectively, the critical value of the effective size would be about 125. If the values of λ_D and λ_B were an order of magnitude smaller, then the critical size would be an order of magnitude larger. See Figure 3 for other examples. This population size that allows persistence can be much lower than that predicted by considering deleterious mutations alone.

CHANGE IN MEAN FITNESS ABOVE AND BELOW THE CRITICAL EFFECTIVE SIZE

The total change in fitness per generation due to the fixation of new alleles, $\Delta W = \Delta W_B + \Delta W_D$, depends strongly on the effective population size (see Fig. 4), but this relationship is nonlinear. For values of N_e below $N_{e,crit}$, loss of fitness becomes rapid as N_e gets small; but for $N_e > N_{e,crit}$, the gain

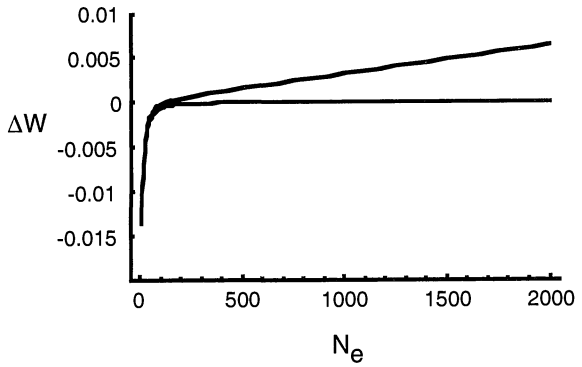

FIG. 4. Total change in fitness is a function of the effective population size. This figure plots two cases with exponentially distributed mutational effects. The top curve plots the rate of change in fitness per generation when $U_D = 1$, $U_B = 0.001$, and $\lambda_B = -\lambda_D = 0.02$; the bottom curve has the same parameters except $\lambda_B = 0.002$. On this scale, the two are indistinguishable from each other for negative ΔW-values. For positive ΔW-values, the bottom curve is very near zero. Note that the rate of loss of fitness below $N_{e,crit}$ is much greater than the gain in fitness for population sizes above $N_{e,crit}$.

in fitness changes quite slowly as a function of N_e. This has the unfortunate implication that short periods at a small size will require that the population spend many times longer at a large size to compensate for the fitness loss. This, in addition to uncertainties about parameter values, argues strongly for population sizes being kept at a level well above the predicted critical effective size.

The increase in fitness per generation for populations far above the critical population size is likely to reach a limit, due to several factors. First, the population may near an optimum such that the distribution of beneficial mutations will change so that ΔW_B is low. Second, as the population size increases, the assumption that mutations arise rarely is false, and the rate of fixation of new beneficial alleles will be reduced as a function of interference among mutations.

Sexual Selection, Frequency Dependence, and the Difference between Relative and Absolute Fitness

Sometimes, the effects of an allele on the relative fitness of its carrier are different from its absolute fitness effects when fixed. For example, if an allele affects male mating success in a negative way, then it will have a reduced relative fitness and be selected against. This same allele may not affect the absolute fitness of a population in which it is fixed, however; if all males carry this allele, then there is no basis for females to discriminate among them and all may mate equally. If the contribution of an allele to loss of mean absolute fitness is s_A, then the selection against this allele is $s = s_A/M$, where M is defined by the ratio of the effect on absolute fitness of a fixed allele relative to the effect of a segregating allele on relative fitness. With a positive correlation between the effects of novel alleles on male mating success and productivity measures such as survivorship or female fecundity, $0 < M < 1$.

For a given effect on mean fitness, an allele with $0 < M < 1$ will have a lower probability of fixing if deleterious and a higher probability of fixing if beneficial, relative to an allele with $M = 1$. The equations for the change per generation of mean fitness due to deleterious and beneficial alleles become

$$\Delta W_D = U_D N \int_{-\infty}^{0} 2s_A u[s_A/M]\Psi_D[s_A]\, ds_A \quad \text{and} \tag{10a}$$

$$\Delta W_B = U_B N \int_{0}^{\infty} 2s_A u[s_A/M]\Psi_B[s_A]\, ds_A. \tag{10b}$$

Most experiments investigating the effects of new mutations express the change in mean fitness of a population purely in terms of viability or female fecundity, not counting male mating success. Thus, the standard estimates of the effects of mutation on fitness are measures of the distribution of s_A.

For the exponential distribution of mutational effects and $M > 0$, the changes in fitness per generation due to deleterious and beneficial alleles are therefore approximately given by

$$\Delta W_D \cong \frac{U_D M^2}{8N_e^2\lambda_D} \quad \text{and} \tag{11a}$$

$$\Delta W_B \cong \frac{8U_B N_e \lambda_B^2}{M}, \tag{11b}$$

where the λs refer to the mean of effects on absolute fitness. If M is even somewhat less than one, the rate of loss of fitness due to deleterious mutations can be significantly slowed and the rate of gain of fitness by beneficial mutations can be increased. This effect is particularly strong for mutations of large effect (see Fig. 5).

If we look at the effect of a relationship between mating success and productivity on the net change in fitness, we find

$$\Delta W = \Delta W_D + \Delta W_B \cong \frac{-U_D M^2}{8N_e^2|\lambda_D|} + \frac{8U_B N_e \lambda_B^2}{M}, \tag{12}$$

The critical effective size is then given by

$$N_{e,crit} \cong M \cdot \sqrt[3]{\frac{U_D}{64\lambda_B^2|\lambda_D|U_B}}, \tag{13}$$

changed by a factor M relative to the case where alleles affect mean fitness and relative fitness equally. Because it is likely that for *new* mutations $0 < M < 1$, sexual selection allows smaller populations to persist longer.

Whether $0 < M < 1$ is an empirical question that has been insufficiently answered. Sexual selection theory has accustomed us to thinking of alleles that have antagonistic effects on mating success and longevity, but theory has focussed on these types of alleles because it is trivial to predict the deterministic outcome of selection when sexual selection and survivorship selection coincide. Despite this emphasis of theory, it is likely that the vast majority of alleles with deleterious effects on productivity also decrease mating success. A change in a gene that reduces function is likely to make an organism less healthy however that it measured, which is consistent with known evidence about new mutations (see Discussion).

Discussion

Small populations are more prone to extinction for a wide variety of reasons, both ecological and genetic. Small pop-

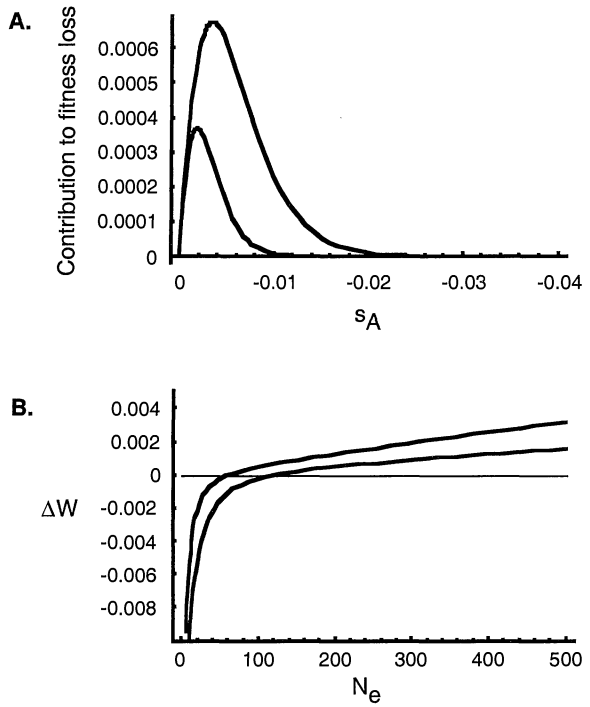

FIG. 5. Sexual selection can reduce drift load. (A) The contribution of a new deleterious allele to fitness loss as a function of the effects of that allele on the mean fitness of a population when fixed. The y-axis is a product of the probability of fixation of an allele and its effects on mean absolute fitness. The top line corresponds to $M = 1$, where there is no additional selection due to male mating success, and the lower line corresponds to the case of $M = 0.5$, where half of the selection against alleles is due to sexual selection. For alleles of large effect, sexual selection can effectively eliminate drift load, but it has negligible impact on alleles of small effect. $N_e = 100$. (B) The rate of change in fitness (including the effects of both beneficial and deleterious alleles). Here $U_D = 1$, $U_B = 0.001$, and $\lambda_B = -\lambda_D = 0.02$. The top curve corresponds to $M = 0.5$ and the lower curve to $M = 1$. Sexual selection can substantially slow the rate of loss of fitness in small populations and accelerate the recovery of fitness in larger populations.

ulations are likely to have less genetic variation and are therefore less able to respond via natural selection to changes in the environment than are larger populations. More generally, in small populations the importance of random genetic drift relative to selection is increased, such that beneficial alleles are more likely to be lost and deleterious alleles are more likely to reach high frequencies, compared to larger populations. This latter factor has been the source of significant concern in conservation biology, as it seems to imply that small populations are doomed to extinction due to a steady accumulation of deleterious alleles.

Population Size and the Time to Extinction

The results of this paper confirm that there are populations so small that they have a very high probability of extinction due to the accumulation of deleterious alleles. However, there is some good news. Populations above a critical threshold size can persist indefinitely as a result of the balancing effects of fixation of beneficial alleles. This threshold is at a smaller population size when: (1) the rate of beneficial mutation is large relative to that of deleterious mutation; (2) the mean effects of mutation are high; (3) the ratio of effective to census population size is high; (4) sexual selection acts to remove deleterious alleles; and (5) beneficial mutations are more likely or larger in effect when compensating for previous fitness decline. Unfortunately, we do not have empirical estimates of many of the important parameters (and the estimates we have are in much doubt; Keightley 1994; García-Dorado 1997; Lynch et al. 1999), but rough guesses of these parameters suggest that an effective population size in the hundreds is capable of persisting indefinitely without great risk of extinction due to genetic problems.

Therefore, for populations with thousands of individuals, the probability of extinction due to deleterious alleles being fixed faster than beneficial ones is low. The chance of a population going extinct from an environmental catastrophe or epidemic is much greater (see Lande 1998) and should be given more consideration in conservation. As effective population size drops below a few hundred, the rate of fitness loss becomes substantial and the risk of extinction due to the combined effects of deleterious alleles and stochastic environmental effects becomes quite substantial. We still do not know how much fitness a population can lose without risk of extinction; most species have reproductive excess that may buffer them from some load (Wallace 1991). Of course, the loss of fitness due to genetic processes can interact with environmental challenges to increase the rate of extinction; populations already weakened by fixing deleterious alleles are likely to be less able to weather periods of bad conditions.

Even when a population falls below the critical effective size, the fixation of beneficial alleles can still slow the rate of fitness loss, relative to the commonly considered case where all new mutations are deleterious. As N_e drops below $N_{e,crit}$, though, the effect of beneficial alleles becomes negligible (Fig. 4). Furthermore, the negative effects of periods of small population size on fitness are much greater than the positive effects of periods of large population size. Even if a population were to survive a prolonged bottleneck, the time it must spend at a larger population size to recover could be very long.

Changing Values of U and λ: Compensatory Mutations

The process of mutational meltdown is expected to have several phases. First a population is reduced in population size by external forces, such as human activity. Next the population reaches a new equilibrium mutation load that is not much different from the old load (Lynch et al. 1995b). Then the population begins to fix new deleterious mutations due to drift. In this phase, the population is expected to remain at a more or less constant population size, because the population is expected to have a reproductive excess, such that each surviving adult can create at least one offspring that survives to adulthood and reproduces (Lynch et al. 1995b). When this reproductive excess disappears and the mean absolute fitness of the population becomes less than one, the population is no longer able to completely replace itself and begins to decline in population size, ending in extinction.

If the reproductive excess is large, then many deleterious mutations can be fixed in a population before the decline in

population size begins. If the number of possible beneficial mutations increases with the number of fixed deleterious mutations, then the minimal criteria for preserving a population without decline in fitness to extinction is that the parameters for U and λ allow the current effective size to exceed the critical effective size of the population at the point where mean absolute fitness is just under one.

As the mean fitness of a population declines and as more and more deleterious alleles become fixed in the population, the proportion and mean magnitude of beneficial mutations is expected to increase. This is because for most deleterious alleles, there exists not only a reverse mutation but also the potential for mutations at other loci to compensate for the loss in function. The experimental work of Lenski and his group (Lenski and Travisano 1994) and of Burch and Chao (1999) has clearly demonstrated that maladapted populations have higher beneficial mutation rates or higher mean effects of beneficial mutations than well-adapted populations do. Beneficial mutation rates measured in healthy populations with reproductive excess should be much lower than the rates after the population has accumulated a series of deleterious mutations. We have little data about the rates of beneficial mutations, but the work of Burch and Chao (1999) demonstrates that they can arise at sufficient rates to allow the recovery of mean fitness even in small populations (see Whitlock and Otto 1999). The critical effective size is determined not by the current rate and distribution of beneficial alleles, but by these parameters under conditions where the population can no longer replace itself. An application of Fisher's geometrical model to this problem finds similar results (Poon and Otto 2000).

Difficulties in Interpretation and Estimation

We should not have great confidence in the quantitative values of the predictions made in this paper. In addition to the usual concern that the theoretical model may not include enough relevant properties of the system (e.g., this model neglects dominance and interlocus interactions, the Hill-Robertson effect, the effects of changing environments), the empirical measurements of many of the most important genetic parameters range from merely controversial to nearly nonexistent.

The rate and distribution of effects of deleterious mutations is a subject of some controversy (see Keightley 1996; Lynch et al. 1999). In this paper, I have chosen to use similar values to that used in previous analyses, but the real mutation rate to deleterious alleles could be much lower (Keightley 1996). A lower rate of mutation would slow the process, but the critical N_e depends only on the ratio of the deleterious and beneficial mutation rates. The distribution of mutational effects is much more important. We have almost no information about this distribution, even for deleterious alleles. We know that the fitness effects of alleles have a broad range, with alleles of slight effect much more common than those of large effect, but the mean and shape of this distribution is unknown (Lynch et al. 1999).

The critical population size has been expressed in this paper in terms of the effective population size, but we normally have better information about the census population size. Thus, an important parameter in this model is the ratio N_e / N. We again have only limited and low-quality information about this ratio, but a recent review suggests that this ratio is on the order of 0.1, based on estimating changes in homozygosity over time (Frankham 1995). Thus, the census population size required to keep the effective population size above the critical levels is at least 10-fold higher. If a population requires N_e to be a few hundred to persist without genetic extinction, the total number of breeding-age individuals needs to be in the thousands.

We also have insufficient information about the relationship between the effects of alleles on relative fitness in segregating populations and their effects on absolute fitness when fixed. Whitlock and Bourguet (2000) have shown that for new mutations in *Drosophila melanogaster,* there is a positive correlation across alleles between the effects of alleles on productivity (a combined measure of the fecundity of adults and the survivorship of offspring) and male mating success. This productivity score should reflect effects of alleles on mean fitness, but the effects of male mating success are relative. Without choice, females will eventually mate with the males available, but given a choice the males with deleterious alleles have a low probability of mating. Other studies on the so-called good-genes hypothesis have confirmed that male mating success correlates with offspring fitness (e.g., Partridge 1980; Welch et al. 1998; see Andersson 1994).

This uncertainty in parameters, coupled with their obvious evolutionary and conservation importance, argues that we need much more empirical work to have any confidence in our predictions. More importantly, perhaps, we need experiments that test the overall process, because we will never have sufficiently reliable measures of the underlying parameters to know from purely theoretical arguments what the critical population sizes might be. This is hampered by the long time scale expected to extinction, making it difficult to do a large enough experiment for long enough. Some experiments have been done that do shed light on these problems, in particular those of Elena et al. (1998) and Burch and Chao (1999). In these experiments, we have seen that even small population sizes were sufficient to allow a population to recover from the fixation of a strongly deleterious allele. More experiments along these lines, especially in eukaryotes, would be well worth while.

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