BRIEF COMMUNICATIONS

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LETHALS IN FINITE POPULATIONS

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Abstract.—It has been assumed, based on theoretical studies, that lethals with the level of dominance estimated from experimental studies would have an allele frequency that is virtually independent of effective population size. However, here it is shown numerically that the expected frequency of lethals with low levels of dominance is also dependent on finite population size, although not as much as completely recessive lethals. This finding is significant in determining the standing level of inbreeding depression and the consequent potential for the evolution of self-fertilization. In addition, the architecture of genetic variation influencing inbreeding depression in populations with a history of small size may be of important consequence in endangered species. Finally, it is shown that the loss of lethal genetic variation often occurs much more quickly than the regeneration of lethal variation by mutation. This asymmetry may result in a lower standing genetic variation for inbreeding depression than expected from mutation rates and contemporary population size data.

Key words.—Conservation genetics, evolution of selfing, genetic drift, inbreeding depression, mutation.

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A major research area in evolutionary and conservation biology is the investigation of the extent and characteristics of the genetic variation influencing inbreeding depression. General estimates of the extent of genetic variation influencing inbreeding depression have been obtained by comparing the fitness of offspring from inbred and random matings. The extent of this variation for viability can be translated into the number of lethal equivalents for a given population, where a lethal equivalent is defined as a set of alleles that would result in mortality in a given individual (e.g., Hedrick and Kalinowski 2000). For example, Lynch and Walsh (1998) summarized data on lethal equivalents in a number of organisms, and Ralls et al. (1988) observed that the median number of lethal equivalents was 3.14 in a survey of captive populations of 40 species, although for a number of species the lethal equivalent estimate was not significantly greater than zero.

Only in *Drosophila* has there been experimental work carried out to separate the extent of this genetic variation that is actually generated by lethals and that caused by variation of genes with smaller detrimental effects. In several different species of *Drosophila* and a number of studies, about half of the variation is due to nearly recessive lethals and half due to genes of smaller detrimental effect and lower dominance (for reviews, see Simmons and Crow 1977; Charlesworth and Charlesworth 1987; Lynch and Walsh 1998). This partitioning has been used in theoretical work to understand the effects of various evolutionary factors on detrimental genetic variation (Hedrick 1994; Wang et al. 1999).

Background

Wright (1937) and Nei (1968, 1969) theoretically examined the expected distribution of lethals in finite populations. To summarize their results pertinent to the discussion below, let us assume that the relative fitnesses of genotypes A_1A_1, A_1A_2, and A_2A_2, are 1, $1 - hs$, and $1 - s$, where h measures the level of dominance and s is the selective disadvantage ($s = 1$ indicates a lethal). First, assume that the effective population size is N, the rate of mutation from A_1 to A_2 is u, and that the detrimental allele is completely recessive ($h = 0$). If $2Nu$ is larger than unity, then the mean frequency of A_2 at equilibrium is approximately

$$\bar{q}_\infty \approx \left(\frac{u}{s}\right)^{1/2}. \tag{1a}$$

If $2Nu$ is much smaller than unity for a population of size N, the frequency of A_2 at equilibrium is approximately

$$\bar{q}_N \approx u\left(\frac{2\pi N}{s}\right)^{1/2}. \tag{1b}$$

In other words, when the population size is small, the mean frequency of a recessive allele may be greatly reduced.

One way to see this effect is to look at the ratio of these two expressions,

$$\frac{q_N}{\bar{q}_\infty} \approx (2\pi Nu)^{1/2}. \tag{1c}$$

For example, if $Nu = 0.0001$ or 0.01, then this ratio is approximately 2.5% or 25%, respectively, illustrating that the frequency of a completely recessive lethal in a finite population may be only a small proportion of that in an infinite population.

However, Nei (1968, 1969), using an approximation of the general formula of Wright, showed that when $h > 0$, the equilibrium is approximately

$$\bar{q} \approx \frac{u}{hs}. \tag{2}$$

Unlike the expression for $h = 0$ above, this approximate expression is independent of the effective population size, a result that has been cited over the years (Crow and Kimura 1970; Lande and Barrowclough 1987; Bataillion and Kirkpatrick 2000).

The average estimate of h for lethals in *Drosophila* is be-

tween 0.01 and 0.03 (Simmons and Crow 1977), an estimate that is still generally accepted (Charlesworth and Charlesworth 1999). That is, the estimate of h for lethals appears to be greater than zero, suggesting that the equilibrium would be independent of the effective population size based on Nei's conclusion. However, it is not clear how quickly the strong dependence of the equilibrium on N when $h = 0$ is lost as the level of dominance increases.

The expected number of lethals equivalents in an individual from lethals is approximately

$$n_{le} \approx 2\bar{q}n, \tag{3}$$

where n is the number of loci in an organism that can carry a lethal allele (Hedrick et al. 1998). The expected number of lethal equivalents from lethals is therefore a direct function of the equilibrium allele frequency obtained from the equations above or the numerical calculations below.

Here this question is investigated using a numerical approach. More specifically, I examine the extent to which the genetic variation from lethals at equilibrium in a finite population will be reduced for lethals that are not completely recessive is examined. In addition, the rate at which lethals are reduced in frequency by genetic drift is examined and compared to the rate at which lethals are increased in frequency by mutation.

Method

To investigate the effects of finite population size on the expected frequency and distribution of lethals, a probability transition matrix approach was used (e.g., Hedrick 2000). Using this approach, the probability of i A_2 genes in generation $t + 1$ given j A_2 genes in generation t is

$$P_{ij} = C(1 - q')^{2N-i}(q')^i, \tag{4}$$

where C is the binomial coefficient. The frequency of A_2 is $q = j/2N$ and q' is the frequency of A_2 after mutation and selection. To find the equilibrium frequency, this matrix is multiplied by the allele-frequency vector containing all $2N + 1$ possible population states until there is less than 0.0001 change in average allele frequency per 100 generations. Equation (1b) of Wright (1937) was evaluated in this manner and found to be accurate to less than 0.1% when a full $(2N + 1) \times (2N + 1)$ was used. As a result, it is assumed that this equation is at least this accurate for larger population sizes below.

For the larger population sizes, the matrix becomes very large and the following procedure was used. First, only the portion of the matrix with the lowest q values was iterated (this was a 301×301 matrix when $2N > 300$). This approximation was compared to the theoretical predictions for $h = 0$ from expression (1b) for larger population sizes. For example, for $N = 500$ and 1000, iteration of this smaller matrix gave equilibrium values only 1.1% and 2.6% lower, respectively, than the theoretical prediction of expression (1b). This is the maximum difference that the iteration of the smaller matrix and equation (1b) is expected to have because the equilibrium allele frequencies are lower when $h > 0$. The values given below for $h > 0$ were corrected, based on the difference between the theoretical values for recessive lethals from expression (1b) and that observed from simulation, with the same N and approximate equilibrium. The maximum correction (increase in allele frequency) was 2.0% when $N = 1000$ and $h = 0.01$.

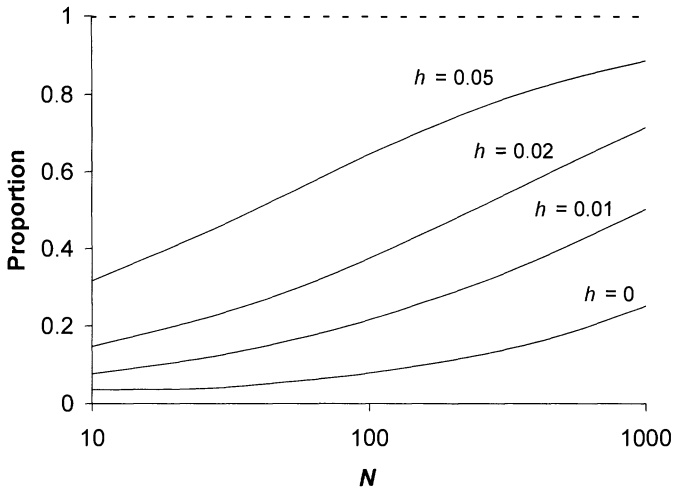

FIG. 1. The proportion of the equilibrium allele frequency for a given population size, N, to that expected for an infinite population, $\bar{q}_N/\bar{q}_\infty$, for four different levels of dominance, h. The broken line across the top indicates the expectation when the equilibrium is independent of population size.

I used a range of dominance, $h = 0$ to 0.05, that encompasses the estimated the average level of dominance and the average dominance, $h = 0.02$, suggested by Simmons and Crow (1977). For the mutation rate to lethals per locus, the level suggested by Crow (1993) of 3×10^{-6} was used. Using higher or lower mutation rates resulted in virtually identical results for the relative values reported below.

Results

For completely recessive lethals, the equilibrium allele frequency is very dependent on population size. In fact, for independence, the population must be very large, in the tens of thousands, to closely approach the infinite population equilibrium frequency (Wright 1937; Robertson 1962; Crow and Kimura 1970). As a comparison, the broken line across the top of Figure 1 gives the expectation when the equilibrium is independent of population size. The lowest line in Figure 1 gives the equilibrium for recessive lethals in populations of different size, as a proportion of the equilibrium in an infinite population, or $\bar{q}_N/\bar{q}_\infty$, when $u = 3 \times 10^{-6}$. For $N = 1000$, the equilibrium is only 25% of the infinite population allele frequency.

As the level of dominance increases, the proportion of the equilibrium for a given population size increases, compared to that for an infinite population ($\bar{q}_\infty \approx u/hs$). Although the equilibrium is less dependent on population size than for $h = 0$, it is obviously not independent of it. For example, for $N = 100$ and for $h = 0.01$ and 0.02, the equilibria are 22% and 38%, respectively, of that expected in an infinite population. Even for a population size of 1000 and $h = 0.01$, the equilibrium is only 50% that in an infinite population. As the level of h increases further, the equilibrium becomes in-

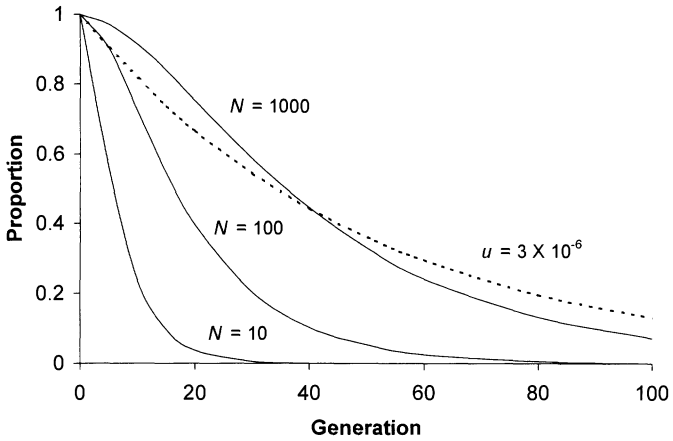

FIG. 2. The solid lines illustrate the rate in loss of lethal allele frequency ($h = 0.02$) from a population of infinite size to one of size N. This is given as the proportion of the difference in equilibrium allele frequency in an infinite population to that for a given population size N in generation t, or $(\bar{q}_t - \bar{q}_N)/(\bar{q}_\infty - \bar{q}_N)$. The broken line illustrates the recovery of lethal allele frequency ($h = 0.02$) from mutation by examining the change in a finite population to an infinite one. This is given as the complement of the difference in equilibrium allele frequency in an infinite population to that for a given population size N in generation t, or $1 - (\bar{q}_t - \bar{q}_N)/(\bar{q}_\infty - \bar{q}_N)$.

dependent of N (values not shown but indicated by the broken line), consistent with the prediction of Nei (1968).

In small populations, the frequency of lethals can be reduced very quickly from that in an infinite population. The rate of reduction from the infinite population level varies with the population size (Fig. 2). Here the proportional difference between the equilibrium allele frequency in an infinite population and a finite population in generation t, $(\bar{q}_t - \bar{q}_N)/(\bar{q}_\infty - \bar{q}_N)$, is given. For example, after 20 generations the frequency of lethals are 4%, 40%, and 75% of that infinite population for population sizes of 10, 100, and 1000, respectively.

In contrast, the rate of regeneration of lethals by mutation is shown by the broken line in Figure 2. Here the mutation rate is 3×10^{-6} and the rate of regeneration is similar to the rate of loss when $N = 1000$. However, if the population size is smaller, say 100, the rate of loss is much faster than the rate of regeneration of variation when $u = 3 \times 10^{-6}$. For example, after 40 generations, a population of size 100 results in a reduction to 10% of the initial lethal frequency, whereas after 40 generations, only 56% of the lethal equilibrium frequency has been recovered by mutation.

DISCUSSION

The expected frequency of completely recessive lethals has long been known to be highly influenced by population size; when the level of dominance is higher, however, the equilibrium frequency is virtually independent of population size (Nei 1968, 1969). How sharp is the transition between these categories? This is particularly important because estimates of the level of dominance for lethals are in the range where this transition occurs.

From the results presented here, it is apparent that for the average level of dominance estimated for lethals ($h = 0.02$) that small population size may greatly decrease the equilibrium lethal allele frequency. Because the expected number of lethal equivalents from lethals is a direct function of the allele frequency (Hedrick et al. 1998), the expected impact on viability from inbreeding is a function of the past population size. For example, assume that the expected number of lethal equivalents from lethals in a finite population is 20% that in an infinite population. Therefore, if it is assumed that half of the genetic variation causing inbreeding depression is from lethals (and the detrimental half is unaffected by population size), then overall the number of lethal equivalents is about 60% that expected in an infinite population.

These general findings have important implications for several areas of evolutionary and conservation biology. First, an important aspect of the potential for the evolution of self-fertilization is the extent of inbreeding depression in the population (e.g., Charlesworth and Charlesworth 1987). It has long been recognized that small population size results in a low expected frequency of completely recessive lethals, and recently Bataillion and Kirkpatrick (2000) showed that a past history of small population size may reduce the expected level of inbreeding depression from detrimentals. Here it has been shown that lethals with the accepted estimated level of dominance also are greatly reduced in frequency by finite population size. In other words, overall it seems that small population size may greatly reduce the extent of genetic variation influencing inbreeding depression and therefore potentially facilitate the evolution of selfing.

Second, *Drosophila* have been used a model organism to examine inbreeding depression and related phenomena. However, the architecture of the variation influencing fitness may differ in an organism such as *Drosophila* with an estimated population size of 10^6 (e.g., Schug et al. 1997), essentially an infinite population from the theory and numerical results here. The accepted estimate of half the potential inbreeding depression from lethals and half from detrimentals obtained from *Drosophila* may be very different from that for species with smaller population sizes. In particular, species with chronically low population numbers would be expected to have less variation influencing inbreeding depression and the proportion of variation from lethals would be substantially less. For endangered species, this suggests that schemes to purge variation influencing inbreeding depression would be likely to have little positive impacts because most of the easily purged variation (lethals) would have been already removed.

Finally, the reduction in lethal frequency may occur very quickly, over the period of a few tens of generations. In contrast, recovery may occur much more slowly, particularly if the mutation rate to lethals is low. This asymmetry in effects may result in the observed frequency of lethals being lower than that expected from a balance from mutation and contemporary population size.

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