Effects of Partial Inbreeding on Fixation Rates and Variation of Mutant Genes

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ABSTRACT

Diffusion methods were used to investigate the fixation probability, average time until fixation and extinction, and cumulative heterozygosity and genetic variance for single mutant genes in finite populations with partial inbreeding. The critical parameters in the approximation are the coefficient of inbreeding due to nonrandom mating (F) and the effective population size (N_e), which also depends on F and the variance of family size. For large Ns, the fixation probability (u) is $u = 2(N_e/N)s(F + h - Fh)$, where N is the population census, s is the coefficient of selection of the mutant homozygote and h is the coefficient of dominance. For Poisson family size (independent Poisson distributions of selfed and nonselfed offspring with partial selfing, and independent Poisson distributions of male and female numbers with partial sib mating), $N_e = N/(1 + F)$, and the time until fixation is approximately equal to N_e/N times the time to fixation with random mating, but this relation does not hold, however, for other distributions of family size. The cumulative nonadditive variance until fixation or loss for dominant genes is reduced with increasing F while for recessive genes it is increased with intermediate values of F. The average time until extinction of deleterious mutations is reduced by increasing F. This reduction, when expressed as a proportion, is approximately independent of the initial gene frequency as well as the selective disadvantage if this is large.

ALTHOUGH most population genetics theory has been developed on the assumption of random mating, a substantial amount of nonrandom mating may be present in natural populations. Many plants engage in substantial self-fertilization [see *e.g.*, reviews by JAIN (1976) and SCHEMSKE and LANDE (1985)]. Predominant selfing and predominant outcrossing have been shown by theoretical analysis to be the two alternative stable states of the mating system in most plant populations (LANDE and SCHEMSKE 1985). This result is supported by empirical information (SCHEMSKE and LANDE 1985), though a great variation in the proportion of selfing may exist. In some animal species, mating between close relatives, especially full- and half-sibs, may also be common [see *e.g.*, FUTUYMA (1986, pp. 124–128) for references]. This raises the question of how partial inbreeding affects the fate and properties of non-neutral mutants arising in finite populations.

Recessive mutants with a large effect on quantitative traits occasionally appear in selection experiments (for example in that of CABALLERO, TORO and LOPEZ-FANJUL 1991). These recessives are, however, likely to be lost if the population size is large. CABALLERO, KEIGHTLEY and HILL (1991), referred to henceforth as CKH91, studied a variety of population structures and breeding systems in order to find an optimal design for maximizing fixation probabilities of recessives without impairing those for non-recessives or delaying times to fixation. The most successful scheme analyzed consisted of practicing individual selection and mating full-sibs whenever possible, otherwise at random. Accurate predictions of the fixation probability of mutant genes with this breeding system were made by means of diffusion approximations, the main parameters being the coefficient of inbreeding due to nonrandom mating and the effective population size. The lack of an equation for correctly estimating effective size, however, impeded a complete prediction, but subsequently an appropriate formula has been obtained (CABALLERO and HILL 1992). In this paper, fixation probabilities of single mutant genes in populations with partial inbreeding are further investigated with diffusion methods making use of this predictive equation.

POLLAK (1987, 1988) undertook a theoretical analysis of some consequences of such partial inbreeding in finite populations, including the probability of ultimate survival of mutant alleles initially present in single copy. His calculations were based on an approximation of the model by a branching process assuming, in the case of selfing, that each individual carrying the mutant gene gives rise to a line that develops independently of lines descended from other individuals of the same generation. His equation for the fixation probability contains a mistake and, after correction, gives a valid approximation [this paper and POLLAK and SABRAN (1992)]. For the case of partial full-sib

mating the same argument was applied but couples rather than individuals were considered as reproducing units for the branching process theory.

The probability of survival of a mutant gene is essential in studies of evolution for calculating the rate of substitution, and in artificial selection schemes it gives the asymptotic rate of response due to new mutations. Nevertheless, other parameters are also relevant both from an evolutionary and practical point of view. It is important to know how long it will take the mutant to be fixed and, in combination with its fixation rate, how much genetic variation will be contributed to the population during its lifetime. These relevant parameters are also investigated here by means of the same diffusion approach.

In plants, the major selective force maintaining outcrossing appears to be inbreeding depression in the fitness of inbred offspring due to the expression of deleterious mutations in homozygotes (see *e.g.*, CHARLESWORTH and CHARLESWORTH 1987). Thus, the genetic load present in normally outbred populations has been shown empirically to be due to moderately detrimental partial recessives (BARRET and CHARLESWORTH 1991). Inbreeding increases the rate of extinction of this type of mutant (SIRKKOMAA 1986; BERG and CHRISTENSEN 1990) and therefore it can purge the population of such mutant alleles. This has been shown as an increase in the relative survivorship of the products of selfing in outbreeding plants with each generation of selfing (LEVIN 1991). In this paper, the decrease in the time until extinction of deleterious mutations by inbreeding is quantified for varying proportions of inbred matings.

Stochastic simulation has been carried out both to check the diffusion approximations and the generality of their predictions.

DIFFUSION APPROXIMATIONS

The probability of fixation $u(q)$ of a gene with initial frequency q in a finite population can be calculated as

$$u(q) = \frac{\int_0^q G(x)\,dx}{\int_0^1 G(x)\,dx}, \tag{1}$$

where

$$G(x) = \exp\left(\int \frac{-2M_{\delta x}}{V_{\delta x}}\,dx\right) \tag{2}$$

and $M_{\delta x}$ and $V_{\delta x}$ are the mean and the variance of the change in gene frequency, x, per generation (KIMURA 1962).

The possibility of nonrandom mating in Equation 1 was accounted for by CKH91, but the derivation is summarized here to make this paper self-contained. Let us assume a locus has two alleles A and A', and that the relative fitnesses of the three genotypes AA, AA' and $A'A'$ are 1, $1 + sh$ and $1 + s$, respectively, s being the coefficient of selection and h that of dominance. When nonrandom mating is allowed in the population, the expected genotypic frequencies are $(1 - x)^2 + x(1 - x)F$, $2x(1 - x)(1 - F)$ and $x^2 + x(1 - x)F$, respectively, where x is the frequency of allele A' and F is the correlation between uniting gametes due to nonrandom mating, the F_{IS} defined by WRIGHT (1969, pp. 294–295). In infinite populations, it is the total asymptotic coefficient of inbreeding attained when the reduction in heterozygotes caused by the inbreeding is counteracted by their increase caused by the random mating. Both in finite and infinite populations, this asymptotic value is more quickly reached the smaller is the proportion of inbred matings (GHAI 1969; CROW and KIMURA 1970, pp. 92–94). Alternatively, it is a measure of the deviation from the Hardy-Weinberg proportions when correcting for the finite size by adding the deviation with random mating, this value being approximately $-1/(2N - 1)$ (KIMURA and CROW 1963; ROBERTSON 1965), where N is the population size.

Hence, the general formula for the mean change in gene frequency (correcting a typographical error in Equation 3 of CKH91) is

$$M_{\delta x} = x(1 - x)s[h + x(1 - 2h) + F(1 - x - h + 2xh)], \tag{3}$$

and if the sole factor causing random fluctuations in the mutant frequency is random sampling of gametes (which would be applicable when s is small as assumed in the diffusion approximation), the variance of this change is

$$V_{\delta x} = x(1 - x)/2N_e, \tag{4}$$

where N_e is the effective population size. Thus, by substituting (3) and (4) into (2) and integrating, $G(x)$ becomes

$$G(x) = \exp(-2N_e sx[2F + (1 - F) \cdot (x + 2h - 2xh)]) \tag{5}$$

(CKH91).

Nonrandom mating clearly affects the fixation probability both through the magnitude of F in Equation 3 and the effective size in Equation 4.

The value of F can be calculated for different systems of partial inbreeding and random mating provided we know the proportion (or average proportion) of inbred matings per generation (β). Thus, for partial selfing

$$F = \beta/(2 - \beta), \tag{6}$$

a result first obtained by HALDANE (1924). With partial full-sib mating

$$F = \beta/(4 - 3\beta) \tag{7}$$

(GHAI 1969; LI 1976, p. 245) and, with partial half-

sib mating where mothers of half-sibs are themselves half-sibs,

$$F = \beta/(8 - 7\beta) \tag{8}$$

(GHAI and KEMPTHORNE 1971; HEDRICK and COCKERHAM 1986). Values of F for other systems of partial inbreeding can also be calculated (HEDRICK and COCKERHAM 1986), but for more distant relatives the relevance of partial inbreeding is lessened. Equations 6, 7 and 8 are only valid asymptotically and, therefore, the population must have undergone partial inbreeding since the mutant gene first occurred in single copy. The asymptote is, nevertheless, quickly reached for small values of F, as pointed out above.

A correction for the finite size is formally necessary when applying these equations for β is the proportional excess of inbred matings over that expected with random mating, namely one with selfing and full-sib mating and three with half-sib mating where mothers of half-sibs are themselves half-sibs. This correction is, however, small, when the population census is large.

From Equations 6, 7 and 8, it can be seen that the increase in F is not proportional to the increase in the proportion of inbred matings, as already noted by GHAI (1969) for the partial full-sib mating case. This effect is more marked with less intense inbreeding and so, for example, 18% selfing, 31% full-sib mating or 47% half-sib mating is needed to achieve $F = 0.1$.

Nonrandom mating causes a reduction in N_e because there is a correlation between the genes of related parents and between genes within inbred individuals which will increase the genetic drift. In a population of constant size where inbreeding is due to selfing, N_e is defined by

$$N_e = \frac{4N}{2(1 - F) + S_g^2\,(1 + F)}, \tag{9}$$

where S_g^2 is the variance of the number of successful gametes (KIMURA and CROW 1963; CABALLERO and HILL 1992). Analogously, in a population with equal number of sexes where inbreeding is due to mating of relatives without selfing, N_e is defined by

$$N_e = \frac{4N}{2(1 - F) + S_k^2(1 + 3F)} \tag{10}$$

(CABALLERO and HILL 1992), where S_k^2 is the variance of family size. For Poisson distribution of successful gametes (independent distribution of selfed and non-selfed offspring, *i.e.*, $S_g^2 = 2 + 2\beta$, where β is the proportion of selfing) in the first case, and uncorrelated Poisson distributions of male and female numbers ($S_k^2 = 2$) in the second case, both equations reduce to $N_e = N/(1 + F)$.

Substitution of Equations 9 or 10 into (5) and numerical integration of Equation 1 allows, therefore, computation of the fixation probability for a gene with initial frequency q and selective advantage s for a population with size N, variance of family size S_k^2 and inbreeding F. Some results can, however, be directly obtained from Equation 5. A general approximation for the fixation probability with large $N(Ns > 1)$ can be deduced from this equation. After rearrangement, if follows that $G(x) = \exp(-2N_e sx[x + 2h^*(1 - x)])$, *i.e.*, the same as with random mating but with $h^* = (F + h - Fh)$ instead of h. Thus, the probability of fixation can be approximated by

$$u = 2(N_e/N)sh^* = 2(N_e/N)s(F + h - Fh). \tag{11}$$

Hence, for Poisson number of successful gametes or progeny where $N_e = N/(1 + F)$, if $h = 0.5$ it follows that $u = s$ irrespective of F, because the mean and variance of the change in gene frequency both change in proportion to $(1 + F)$. For $h = 0$, $h^* = F$ and, therefore, the fixation probability for a completely recessive gene when there is inbreeding to the extent F is the same as for a gene with the same selective advantage in the homozygote but degree of dominance $F/(1 + F)$ and random mating. When $F = 1$, $u = s$ for any gene action.

Other relevant calculations can also be made using diffusion theory where account is taken of the nonrandom mating. The cumulative expected value, $C[f(x)]$, of any arbitrary function, $f(x)$, during the lifetime of a gene with initial frequency q is given by

$$C[f(x)] = [1 - u(q)] \int_0^q \psi(x)u(x)\,dx + u(q) \int_q^1 \psi(x)[1 - u(x)]\,dx, \tag{12}$$

(KIMURA 1969), where

$$\psi(x) = \frac{4N_e f(x) \int_0^1 G(z)\,dz}{x(1 - x)G(x)}, \tag{13}$$

and $u(x)$ and $G(x)$ are defined by (1) and (5), respectively. The average number of generations until fixation ($t_1[q]$) of a gene with initial frequency q is given by

$$t_1(q) = C[u(x)]/u(q) \tag{14}$$

(KIMURA and OHTA 1969a) and, analogously, the average number of generations until extinction of such a gene ($t_0[q]$) is

$$t_0(q) = C[1 - u(x)]/[1 - u(q)] \tag{15}$$

(KIMURA and OHTA 1969b).

By means of (12) we can also evaluate other parameters which determine the contribution of a mutant gene in a population, for example, the cumulative heterozygosity rendered by the mutant during its

lifetime is obtained by setting $f(x) = 2x(1 - x)(1 - F)$.

Likewise, the total genetic variance contributed by the mutant can also be calculated. Let us assume that the genotypes AA, AA' and $A'A'$ have genotypic values for a metric trait $-a$, d, and a, respectively. The genotypic mean equals $a(2x - 1) + 2dx(1 - x)(1 - F)$ and the genotypic values deviate from it by $-2ax - 2dx(1 - x)(1 - F)$, $-a(2x - 1) + d[1 - 2x(1 - x)(1 - F)]$ and $2a(1 - x) - 2dx(1 - x)(1 - F)$, respectively. From these values the genotypic variance (V_G) is

$$V_G = 2\alpha^2x(1 - x)(1 + F) + \{4d^2x(1 - x)F + [2dx(1 - x)(1 - F)]^2\}(1 - F)/(1 + F), \quad (16)$$

where α is the average effect of a gene substitution making allowances for the nonrandom mating and is expressed by $\alpha = a + d(1 - 2x)(1 - F)/(1 + F)$ (see, *e.g.*, FALCONER 1985). Equation 16 equals Equation 19 of GHAI (1969) with a different scale for the genotypic values. Its first term denotes the additive variance while the remaining includes the dominance variance plus covariances between additive and nonadditive values due to nonrandom mating. Using Equation 16 or its terms separately as $f(x)$ in Equation 13, the genetic variance (or its components) accumulated during the lifetime of the mutant can be computed.

Numerical integration of Equations 1 and 12 was undertaken by Simpson's rule with 1,000 or 10,000 intervals depending on the values for the different parameters.

SIMULATION PROCEDURE

Simulation was carried out both to check the diffusion results and to show their validity for different systems of partial inbreeding and distribution of progeny number. Furthermore, some results for which diffusion theory is not very accurate were obtained in this way.

Partial selfing with Poisson family size: A monoecious diploid model with a mix of selfing and random mating was chosen to check the diffusion results for different values of F as the proportion of selfing could be varied from 0 to 1 maintaining a constant selection pressure.

In this model, a mutant allele A' was randomly assigned to one individual of a population with size N completely homozygous for the other allele, A. Selection was performed by assigning probabilities of producing offspring with relative values 1, $1 + sh$ and $1 + s$ for the AA, AA' and $A'A'$ genotypes, respectively. In order to evaluate the genotypic variance accumulated over generations, genotypic values of 1, $1 + 2ah$ and $1 + 2a$ were assigned to the three genotypes, respectively. Individuals were selfed or randomly mated with a fixed probability (β) and, in particular, random mating, $\beta = 0.67$ or $\beta = 1$ were carried out to achieve the three values of F analyzed (0, 0.5, and approaching 1; see Equation 6). The distributions of selfed and nonselfed offspring were independent Poissons and thus the variance of successful gametes was approximately $S_g^2 = 2 + 2\beta$.

Simulation was continued until the mutant was fixed or lost and this was typically replicated 10,000 times though, for the smallest selective advantage, 50,000 replicates were performed to obtain adequate precision.

Other types of partial inbreeding and distribution of offspring number: The model of partial self-fertilization permitted a complete range of inbreeding values with a fixed selection intensity but only Poisson family size could be simulated properly. In order to generalize, a model with two sexes and truncation selection was also simulated. A mutant allele with effect $2a$ standard deviations as the difference between homozygotes was randomly assigned to one individual of the total 200 (100 of each sex) scored every generation, so the initial frequency was 1/400. Standardized random normal deviates were assigned to each genotypic value to compute the phenotypes. Truncation selection of the best 50% was performed and the 100 selected individuals were mated in couples to generate again 200 offspring. This model was compared to a diffusion approximation by using the corresponding selective advantage of the mutant $s = 2ai/\sigma$ (FALCONER 1989, p. 202), where i, the selection intensity (standardized selection differential) is approximately 0.798 and σ, the phenotypic standard deviation is 1. This approximation, however, holds only for values of s smaller than about 0.5 (LATTER 1965).

Several different alternatives were tested:

Partial full-sib mating: In a model with equal number of sexes in the breeding population (50 males and 50 females), full-sibs were mated whenever available, otherwise mating was at random. For instance, if two males and one female were selected from a family, one of the males was chosen at random to be mated to his sister while the other was outbred at random. With this scheme, three kinds of distributions of progeny number were analyzed: 1) multinomial distribution ($S_k^2 \approx 2$), when each couple randomly contributed offspring to the scored population; 2) multihypergeometric distribution ($S_k^2 \approx 1$), when each couple contributed exactly two offspring of each sex to the scored population; and 3) a distribution with $S_k^2 \approx 4$, which was performed by assigning additional differences in fertility, allocated randomly to each couple every generation. In the first two cases, the observed number of full-sib matings can be predicted very accurately by noting that selection increases this number very little with respect to the case with no selection (CKH91). For a population with $N/2$ families with the number of offspring of each sex (i,j) independently distributed

with probabilities $p(i)$ and $p(j)$, the maximum number of full-sib matings is

$$\sum_{i=0}^{N/2}\sum_{j=0}^{N/2} p(i)p(j)\min(i,j), \qquad (17)$$

where $p(i)$, $p(j)$ are Binomial index $N/2$, probability $2/N$ ($S_k^2 = 2$) or hypergeometric with sampling i, j from T with k per family ($S_k^2 = 1$).

Partial half-sib mating: A model was set up where there was a biased sex ratio so that matings between half-sibs could also be performed. Each generation, 20 males and 80 females were selected from the 200 scored individuals, giving $N_e = 64$ with random mating. Each male was mated to 4 females such that matings were between half-sibs whose mothers were again half-sibs whenever this was possible, otherwise at random. The distribution of progeny offspring from each couple approximated a Poisson.

For all these truncation selection runs, simulation and calculations were made as described above for the selfing case, but only one gene effect with a relatively large value was used, a difference between homozygotes 0.063 of phenotypic standard deviations, corresponding to $s = 0.05$, approximately.

For completeness, the values of F and N_e were also evaluated by simulation for these cases of partial sib mating. WRIGHT's (1969, pp. 294–295) F statistics were calculated every generation in 300 runs carried out with no selection. F was evaluated as the asymptotic value of F_{IS} calculated as $F_{IS} = 1 - [(1 - F_{IT})/(1 - F_{ST})]$ (WRIGHT 1969, p. 295), and N_e from the asymptotic rate of change in F_{ST} (ΔF_{ST}) as $N_e = (1/2\Delta F_{ST}) - (1/2)$ (FALCONER 1989, p. 71).

RESULTS

Poisson distribution of family size: Figure 1a shows the fixation probability (u) based on numerical integration of Equation 1 for a mutant initially present in single copy in a population with size N, Poisson distribution of family size (as defined above), three different degrees of inbreeding and a varying selective coefficient (expressed as Ns) with recessive ($h = 0$), additive ($h = 0.5$) or dominant ($h = 1$) gene action. The fixation probability is scaled by N so that the results apply approximately for any value of N and a constant Ns, provided this is not too large. This fact, already deduced intuitively by HILL and RASBASH (1986), can be shown from Equation 5 by noting that when the initial frequency of the mutant is small such that square terms can be neglected, the numerator in Equation 1 multiplied by N is approximately the same for all N if Ns is constant and small, while the denominator is always constant for a fixed Ns. This was checked (data not shown) to be valid for $N \geq 100$ for the largest Ns investigated in this paper.

Three interesting points in this graph, already deduced from Equation 11, are as follows: firstly, the fixation probability for an additive gene is independent of the value of F. Secondly, for a recessive gene it increases with increasing F up to the value for additivity which is reached when $F = 1$. And thirdly, for a dominant gene, it decreases to the same extent.

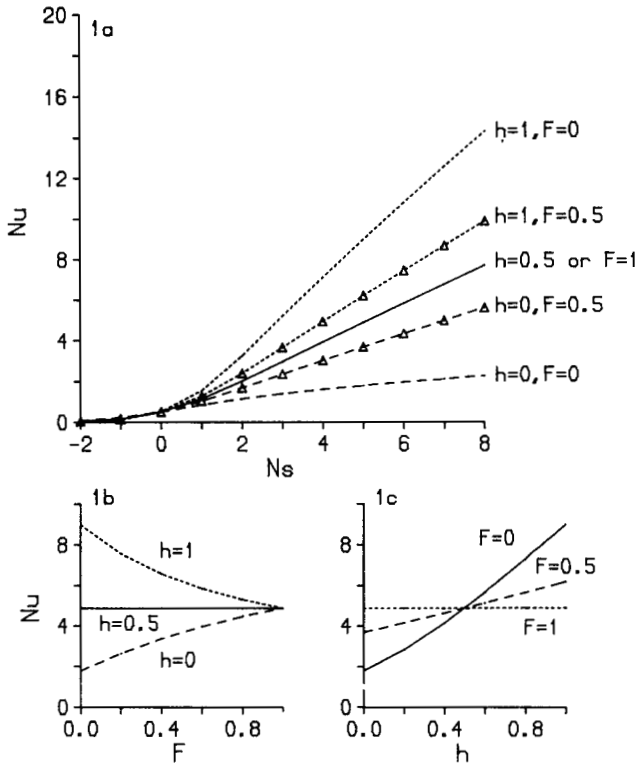

FIGURE 1.—Diffusion approximations for the fixation probability (u) of a single mutant arising in a population with size N, Poisson distribution of family size, varying degree of inbreeding (F), varying selective advantage (s) expressed as Ns and coefficient of dominance (h) for the mutant gene. In b and c, $Ns = 5$.

In Figure 1, b and c, fixation probabilities for the particular case of $Ns = 5$ are represented for varying values of F and h, respectively. Figure 1b shows that the fixation probability for non-additive genes is not exactly linear in F, changing faster for smaller values of F.

In Figure 2 is shown the effect on the fixation probability of increasing N while maintaining s constant (0.05, in particular). For all but only small values of N, the same fixation probabilities are obtained for all types of gene action and value of F, except for complete recessives and random mating where the fixation probability is reduced by increasing N.

Figure 3 shows the average number of generations until fixation (t_1, scaled by $4N$ in order to apply for any value of N) of a single mutant computed by numerical integration of Equation 14 for the same situations as those represented in Figure 1. With random mating ($F = 0$) and a mutant gene with positive selection coefficient, the time to fixation increases with the magnitude of the coefficient of dominance

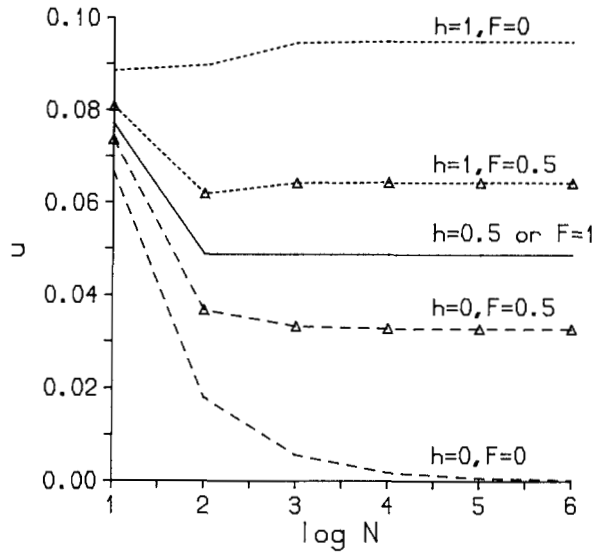

FIGURE 2.—As in Figure 1 for a range of population sizes (N) and $s = 0.05$.

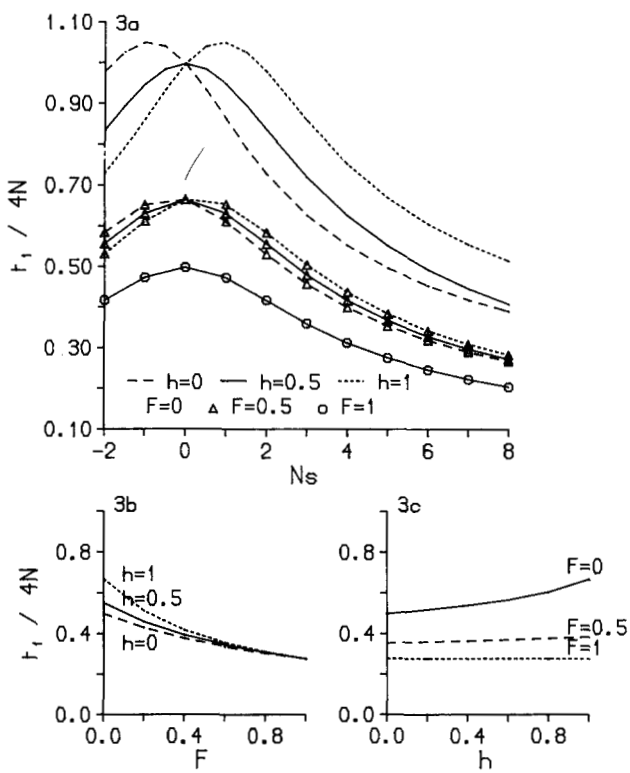

FIGURE 3.—As in Figure 1 for the average time to fixation (t_1) scaled by $4N$.

because the larger the effect of the heterozygote, the longer it takes to lose the unfavorable allele. The opposite happens with negative s though the chance of survival is then very small (see Figure 1a). The effect of an increasing F is both to reduce the time to fixation and the differences among different gene actions until they completely disappear when $F = 1$. The reduction caused by an enlarged F can be illustrated when $s = 0$. In that case, Equation 14 reduces to approximately $4N_e = 4N/(1 + F)$ and so the time

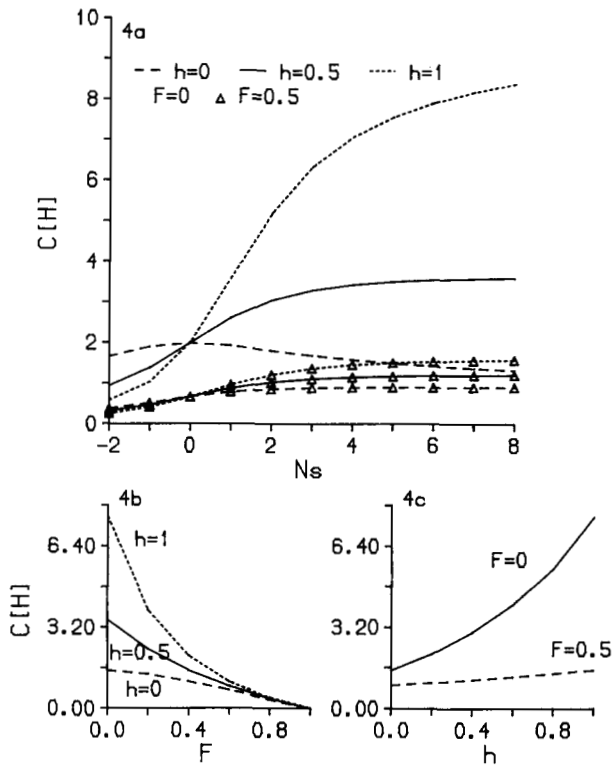

FIGURE 4.—As in Figure 1 for the expected heterozygosity accumulated during the mutant gene's lifetime ($C[H]$).

to fixation is halved when F approaches one. It is worth pointing out that for additivity, the time to fixation scaled by $4N_e$ is the same for all values of F, *i.e.*, the slope of the continuous curve in Figure 3b corresponds to the reduction in N_e with increasing F. For non-additive gene action this holds only approximately, however. In other words, for neutrality or additivity and, approximately for nonadditivity,

$$t_1 = (N_e/N)t_{1R}, \tag{18}$$

where t_{1R} is the time until fixation with random mating.

Figure 4 shows the heterozygosity accumulated during the mutant's lifetime evaluated by numerical integration of Equation 12 with the expected heterozygosity ($2x[1 - x][1 - F]$) as $f(x)$ in the term (13). As in Figures 1 and 3, the results apply for any value of N not too small (this was checked but the data are not shown). With random mating, the expected cumulative heterozygosity is approximately 2 for neutral or nearly neutral genes (KIMURA 1969). For genes acting additively it approximates 4 for large Ns (KIMURA 1969; HILL and KEIGHTLEY 1988), the asymptotic values for recessive and dominant genes being much lower and much higher, respectively. The effect of an increasing F is, of course, a quick reduction in heterozygotes with a corresponding reduction in the differences for different gene actions.

Figures 5 and 6 show the cumulative genotypic variance and its components evaluated by numerical

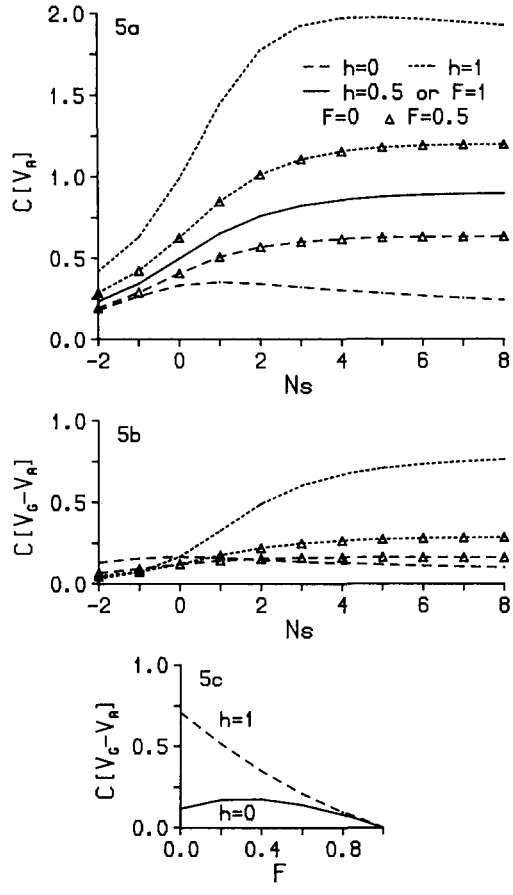

FIGURE 5.—As in Figure 1 for the expected additive ($C[V_A]$) and nonadditive ($C[V_G - V_A]$) genetic variances accumulated during the mutant gene's lifetime ($2a = 1$).

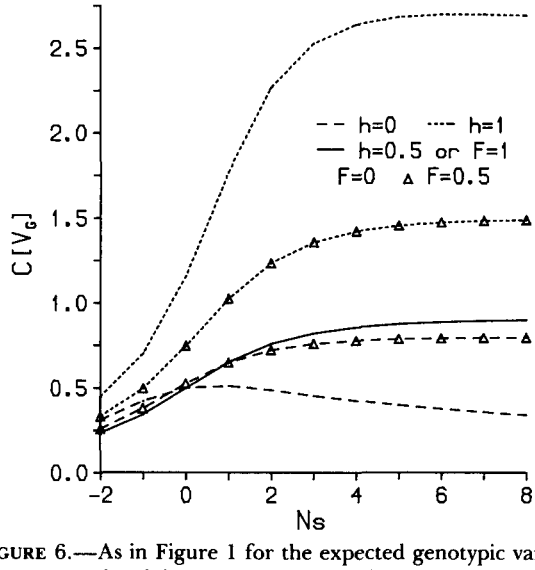

FIGURE 6.—As in Figure 1 for the expected genotypic variance ($C[V_G]$) accumulated during the mutant's lifetime ($2a = 1$).

integration of Equation 12 by including Expression 16 or its components as $f(x)$ in the term (13). For simplicity values are given for genes with effects $2a = 1$. As above, the results apply for all values of N. The graph for $C[V_A]$ (Figure 5a) would also give the expected final response to selection scaled by the intensity of selection, this being equal to s as the phenotypic standard deviation and the difference between homozygotes were one. This graph has, of course, the same relative pattern as Figure 1a, for the expected final response would also equal the probability of fixation.

The result shown in Figure 5a of the variance accumulated during the lifetime of an additive gene being independent of the level of inbreeding appears surprising, as it was for the fixation probability, when we bear in mind the well known increase in the genetic variance due to inbreeding with additive gene action and illustrated by

$$V_G = 2a^2x(1 - x)(1 + F). \qquad (19)$$

Thus, inbreeding increases the genetic variance by increasing the between-family variance but, at the same time, it reduces the frequency of heterozygotes. When accumulated over generations these two effects offset each other for Poisson family size and the genetic variance remains the same for all F. This can be seen as follows. If we calculate the cumulative value of $2x(1 - x)$ (the expected heterozygosity with random mating) by including it in (13) and solving (12), we obtain that for additive genes, $C[2x(1 - x)] \approx 4[u(q) - q]/[s(1 + F)]$, which for large Ns reduces to $C[2x(1 - x)] \approx 4/(1 + F)$. Thus, substituting this into (19), the cumulative genetic variance is $C[V_G] \approx 4a^2$ and, therefore, independent of F. Likewise, for neutral or quasi-neutral mutants, $C[2x(1 - x)] \approx 2/(1 + F)$, and $C[V_G] \approx 2a^2$.

The cumulative value of $V_G - V_A$ (Figure 5, b and c), which includes the dominance variance plus covariances between additive and non-additive values due to the inbreeding, is always reduced with increased F for dominant gene action. For recessive genes, however, there is an increase with intermediate values of F, to finally diminish as F approaches unity, in agreement with ROBERTSON (1952). As a result of this, the genetic variance contributed by completely recessive mutants when F is intermediate is very close to that contributed by additive genes (see Figure 6).

LYNCH and HILL (1986) showed that the equilibrium variance maintained with random mating in the absence of selection is very little affected by dominance. Figure 6 is in accordance with this prediction for recessive gene action, but with complete dominance, however, there is a substantially higher variance than for the additive case.

The majority of the results shown so far relate to advantageous mutations and only slightly deleterious effects are considered in the figures above. For strongly deleterious mutations, fixation probabilities and variance contributed become negligible and the only critical parameter is the time until extinction of such mutants. In Figure 7a is shown the proportional reduction in time until extinction for varying values

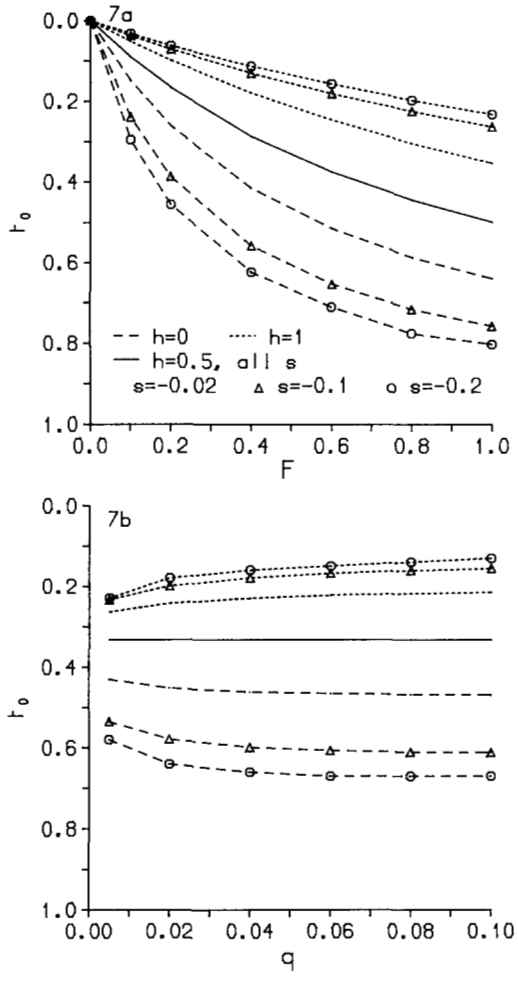

FIGURE 7.—a, Proportional reduction in the time until extinction (t_0) relative to that with random mating. b, Proportional reduction for $F = 0.5$ relative to $F = 0$.

of F relative to that for random mating, obtained by numerical integration of Equation 15. In this case, the fate of mutants segregating in the population at low frequency appears to be more interesting than single new mutations and hence, results refer to mutants with an initial frequency of 0.1.

Inbreeding reduces the time until extinction (t_0) to a greater extent for smaller values of h. For additive genes the reduction is the same for any selective disadvantage and it is verified that $t_0 = (N_e/N)t_{0R}$, where t_{0R} is the time until extinction with random mating. Therefore, the continuous curve in Figure 7a coincides with the proportional reduction in N_e with F. For dominant and recessive genes the proportional reduction decreases or increases, respectively, for increasing values of s and the above expression does not hold. However, this trend is progressively lessened such that for very detrimental genes the proportional reduction for non-additive genes is approximately constant. For example for a lethal gene ($s = -1$), the proportional reduction in time until extinction for $F = 0.5$ relative to $F = 0$ is 0.74 (value obtained by simulation), which is not very different from the corresponding value for $s = -0.2$ shown in the figure.

The reduction in time until extinction is rather drastic for recessive genes, especially for strong selection. So, for lethal genes, 35% of the reduction achieved with complete inbreeding ($F \approx 1$) is obtained with only 18% selfing ($F = 0.1$) and 60% of it with only 33% selfing ($F = 0.2$) (simulation data).

Another interesting result showed by the diffusion analysis is that the proportional reduction is essentially independent of the initial frequency, as can be seen in Figure 7b for $N = 100$ and a range of frequencies from $1/2N$ to 0.1. Thus, the effect of nonrandom mating on the rate of elimination of deleterious recessive genes is similar both for new mutants and for genes already established in the population.

Other distributions of family size: So far, all the discussion has focussed on a Poisson distribution of progeny number defined by independent Poisson distribution of the number of selfed and nonselfed offspring ($S_g^2 = 2 + 2\beta$) in the case of selfing, and independent Poisson distributions of male and female offspring per family ($S_k^2 = 2$) in the case of sib mating, for both of which $N_e = N/(1 + F)$. For other distributions the results can be very different, however, and are illustrated, in the sib mating case, for values of S_k^2 of 1 and 4, *i.e.*, both smaller and greater than 2. This would correspond in the selfing case to values of S_g^2 of $1 + \beta$ and $4 + 4\beta$, respectively, but, from now on, we only refer to S_k^2 for simplicity.

Fixation probabilities and times to fixation for these cases are plotted in Figures 8 and 9, respectively, in a similar manner to Figures 1 and 3, for comparison. For $S_k^2 = 1$, times to fixation are plotted only for values of Ns up to 6 because too much computing time is required to accurately integrate Equation 14 for greater values. It should be noted, firstly, that the fixation probability for additive genes is no longer independent of F. Increasing F yields an increase in the fixation probability for $S_k^2 = 1$ but a decrease for $S_k^2 = 4$. Secondly, the fixation rate for recessive genes is enormously increased, and that for dominant genes very little reduced, with increasing F for $S_k^2 = 1$ and, again, the opposite applies for $S_k^2 = 4$. Of course, the approximation (11) for large Ns still applies for S_k^2 other than 2, provided the appropriate value of N_e is utilized.

It is evident, therefore, that with respect to fixation probabilities and comparing the three cases analyzed ($S_k^2 = 1$, 2 and 4), the most beneficial effect of inbreeding for any gene effect comes with the smaller S_k^2 with which an increase in F produces an increase in fixation probability for additive genes, the highest increase for recessives and the smallest reduction for dominants.

It is clear, however, that the smaller S_k^2, the longer the mutant takes to be fixed and the smaller is the proportional reduction of this time with inbreeding.

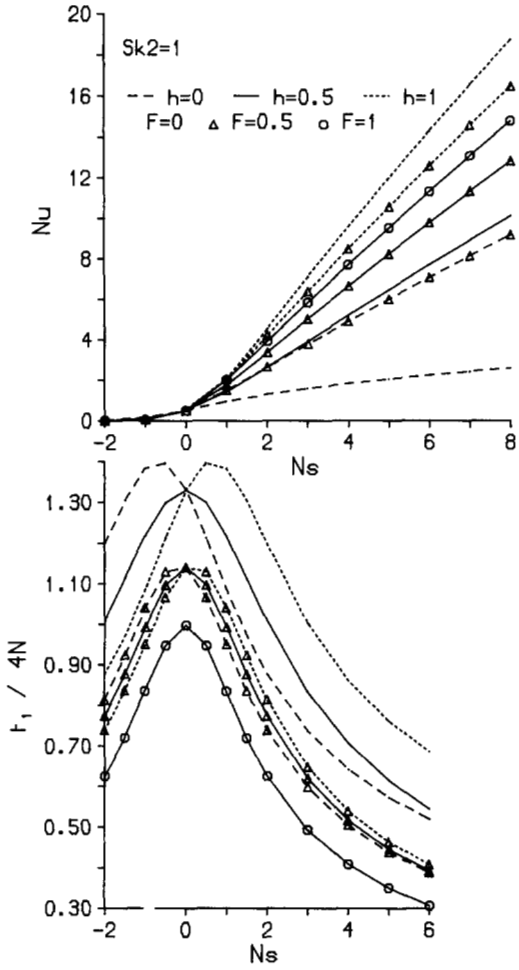

FIGURE 8.—As in Figures 1 and 3 for a distribution of family size with variance $S_k^2 = 1$.

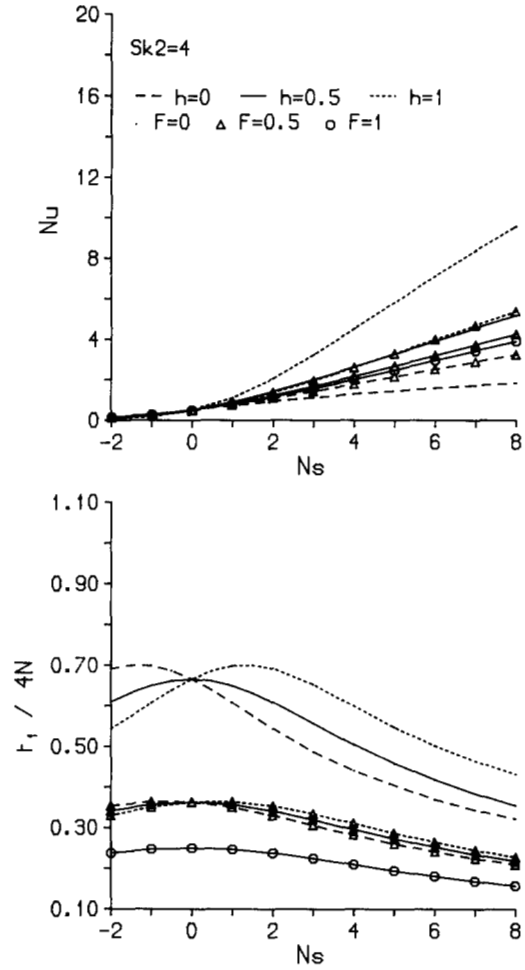

FIGURE 9.—As in Figures 1 and 3 for a distribution of family size with variance $S_k^2 = 4$.

Nevertheless, for relatively strong selection, the differences in this proportional reduction for the different S_k^2 are largely reduced and, therefore, the superiority of $S_k^2 = 1$ (among the three cases analyzed in this paper) remains when considering fixation rates and times to fixation jointly. To visualize this with a particular example, consider the case for $Ns = 5$. Then, the increment (or decrement, if negative) in the fixation probability with $F = 0.5$ with respect to $F = 0$ is for $S_k^2 = 1$, 2 and 4, respectively, 186%, 105% and 47% for recessive genes, 28%, 0% and −18% for additive genes, and −12%, −31% and −43% for dominant genes. The corresponding reduction in time to fixation is much more uniform, however, being 23%, 30% and 35% for recessive genes, 28%, 33% and 41% for additive genes, and 39%, 43% and 47% for dominant genes. These are relative values, but in absolute terms the result is not very different. For example, with $F = 0.5$ a recessive gene takes on average 176 generations to be fixed with $S_k^2 = 1$ (in the case $N = 100$, $s = 0.05$), 140 with $S_k^2 = 2$ and 104 with $S_k^2 = 4$. Nevertheless, the fixation rate is 1.6 times larger with $S_k^2 = 1$ than with $S_k^2 = 2$ and 2.8 times larger than with $S_k^2 = 4$. In general, Equation 18 does not apply for values of S_k^2 other than 2 (except in the neutral case) and, for $S_k^2 < 2$, $t_1 < (N_e/N_R)t_{1R}$, while for $S_k^2 > 2$, $t_1 > (N_e/N_R)t_{1R}$, where R denotes random mating.

Check on the diffusion approximation by simulation: *Partial selfing with Poisson family size*: Tables 1 and 2 show a comparison between simulation results (Sim), using a model of monoecious individuals and differences in fertility with varying proportions of selfing, and the diffusion approximation (Diff) for the fixation probability of mutant genes and other parameters analyzed, for the cases given in Figure 1. In Table 1 are also shown the approximations (Appr) for large Ns to the fixation probability by Equation 11. Simulation and diffusion results show a very good agreement even for values of s as large as 0.08 where the diffusion approach might be less accurate.

The average time until extinction of deleterious mutations was also checked by simulation and although diffusion values were slight overestimations (given the large values of s), the proportional reductions shown in Figure 7 were exceptionally accurate.

TABLE 1

Fixation probabilities (%) of a single mutant gene with selective advantage s and degree of dominance h in an isogenic population with size $N = 100$, Poisson distribution of successful gametes and coefficient of inbreeding F

	$h = 0$			$h = 0.5$			$h = 1$		
	$F = 0$	$F = 0.5$	$F \to 1$	$F = 0$	$F = 0.5$	$F \to 1$	$F = 0$	$F = 0.5$	$F \to 1$
$s = 0.005$									
Sim	0.67	0.71	0.81	0.80	0.71	0.80	0.93	0.81	0.78
Diff	0.67	0.75	0.79	0.79	0.79	0.79	0.92	0.83	0.79
Appr	0.00	0.33	0.50	0.50	0.50	0.50	1.00	0.67	0.50
$s = 0.02$									
Sim	1.10	1.50	1.90	2.07	2.02	1.80	3.17	2.41	1.97
Diff	1.13	1.68	2.02	2.02	2.02	2.02	3.25	2.39	2.02
Appr	0.00	1.33	2.00	2.00	2.00	2.00	4.00	2.67	2.00
$s = 0.08$									
Sim	2.25	5.10	6.87	8.01	7.14	7.41	13.94	9.65	7.91
Diff	2.26	5.61	7.69	7.69	7.69	7.69	14.29	9.87	7.69
Appr	0.00	5.34	8.00	8.00	8.00	8.00	16.00	10.67	8.00

Sim: Simulation data based on 10,000 replicates[a] for $s = 0.02$ and 0.08 and 50,000 for $s = 0.005$. Diff: Approximation by diffusion methods. Appr: Approximation for large Ns.

[a] Standard errors of fixation probability with 10,000 replicates:

u(%)	1	2	3	5	7	13
SE(%) $= \sqrt{u(1-u)/10{,}000}$	0.1	0.1	0.2	0.2	0.3	0.3

TABLE 2

Time to fixation (t_1, scaled by $4N$, SE up to 0.06), cumulative heterozygosity ($C[H]$, SE up to 0.23) and cumulative genetic variance (100 × $C[V_G]$, SE up to 0.09) of a single mutant gene with selective advantage s and degree of dominance h in an isogenic population with size $N = 100$ and coefficient of inbreeding F

		$h = 0$			$h = 0.5$			$h = 1$		
		$F = 0$	$F = 0.5$	$F \to 1$	$F = 0$	$F = 0.5$	$F \to 1$	$F = 0$	$F = 0.5$	$F \to 1$
$s = 0.005$										
$t_1/4N$	Sim	0.96	0.61	0.49	0.98	0.63	0.49	1.00	0.65	0.51
	Diff	0.93	0.64	0.49	0.98	0.66	0.49	1.02	0.67	0.49
$C[H]$	Sim	2.01	0.69	0.02	2.33	0.72	0.02	2.72	0.83	0.02
	Diff	1.97	0.73	0.00	2.31	0.77	0.00	2.72	0.81	0.00
$C[V_G]$	Sim	0.55	0.61	0.63	0.59	0.61	0.58	1.44	0.98	0.62
	Diff	0.51	0.59	0.59	0.58	0.58	0.58	1.46	0.89	0.58
$s = 0.08$										
$t_1/4N$	Sim	0.38	0.26	0.20	0.41	0.27	0.21	0.52	0.28	0.20
	Diff	0.39	0.27	0.20	0.41	0.27	0.20	0.51	0.28	0.20
$C[H]$	Sim	1.33	0.80	0.02	3.76	1.16	0.02	8.48	1.60	0.02
	Diff	1.32	0.89	0.00	3.59	1.20	0.00	8.38	1.57	0.00
$C[V_G]$	Sim	0.33	0.74	0.83	0.89	0.90	0.85	2.59	1.53	0.94
	Diff	0.34	0.79	0.90	0.90	0.90	0.90	2.69	1.48	0.90

Simulation data based on 10,000 replicates for $s = 0.08$ and 50,000 for $s = 0.005$.

For example, for the largest s (−0.2), diffusion results for the reduction in time until extinction with $F = 0.5$ relative to $F = 0$ were 0.67, 0.33 and 0.14 for $h = 0$, 0.5 and 1, respectively, while simulation results were 0.65, 0.31 and 0.11.

Other types of partial inbreeding and distribution of family size: The diffusion approximation for any distribution of family size and type of partial inbreeding can be obtained by using the appropriate values of F and N_e. This was checked by simulation for the cases of partial full-sib mating and partial half-sib mating and distributions of offspring number larger and smaller than the Poisson expectation.

In Table 3 are presented cases where inbreeding was achieved by partial full-sib mating (FS) and partial half-sib mating where mothers of half-sibs were again half-sibs (HS), with distribution of family size with $S_k^2 = 1$, 2 or 4. In each case, full-sib or half-sib mating was practised between the selected individuals whenever they were available. The average number of full-sib matings performed every generation for $S_k^2 = 1$ and 2 was very close to its expectation without selection by Expression 17. With the proportion of inbred matings, the corresponding values of F were calculated using Equations 7 and 8. These expected values (in parentheses) were very similar to the observed

TABLE 3

Comparison between simulation results and expected values or diffusion approximations (in parentheses) for the case of partial full-sib mating (*FS*) and partial half-sib mating (*HS*) with $S_k^2 = 1$, 2 or 4

	FS	$S_k^2 = 2$		HS	$S_k^2 = 2$	
NIM	24.03	(24.03)		40.01		
F	0.177	(0.176)		0.093	(0.097)	
N_e	84.8	(85.0)		58.4	(58.3)	
	$h = 0$	$h = 0.5$	$h = 1$	$h = 0$	$h = 0.5$	$h = 1$
u(%)	1.25 (1.27)	2.20 (2.47)	3.94 (3.93)	0.65 (0.84)	1.56 (1.59)	2.90 (2.59)
$t_1/4N$	0.44 (0.44)	0.48 (0.47)	0.53 (0.53)	0.31 (0.36)	0.41 (0.41)	0.46 (0.47)
$C[H]$	0.68 (0.69)	1.14 (1.24)	2.20 (2.14)	0.41 (0.50)	0.92 (0.88)	1.68 (1.54)
$C[V_G]$	0.11 (0.11)	0.16 (0.17)	0.43 (0.42)	0.05 (0.07)	0.11 (0.10)	0.30 (0.28)
	FS	$S_k^2 = 1$		FS	$S_k^2 = 4$	
NIM	31.37	(31.38)		27.46		
S_k^2	1.01	(1.01)		4.05		
F	0.287	(0.279)		0.217	(0.219)	
N_e	120.1	(121.3)		48.42	(48.35)	
	$h = 0$	$h = 0.5$	$h = 1$	$h = 0$	$h = 0.5$	$h = 1$
u(%)	1.99 (2.11)	3.52 (3.80)	6.00 (5.70)	0.96 (0.92)	1.55 (1.47)	2.23 (2.15)
$t_1/4N$	0.47 (0.49)	0.49 (0.51)	0.56 (0.55)	0.32 (0.32)	0.35 (0.35)	0.42 (0.39)
$C[H]$	0.88 (0.95)	1.47 (1.60)	2.71 (2.56)	0.43 (0.41)	0.68 (0.62)	1.08 (0.95)
$C[V_G]$	0.19 (0.20)	0.26 (0.28)	0.63 (0.60)	0.07 (0.07)	0.09 (0.09)	0.24 (0.22)

Two hundred scored individuals, $N = 100$, $s = 0.05$, $2a = 0.063$. *NIM*: number of inbred matings. Other definitions as in tables 1 and 2. SE: *NIM* (0.05–0.09), S_k^2 (0.00–0.08), *F* (0.01), u(%) (0.08–0.36), $t_1/4N$ (0.01), $C[H]$ (0.03–0.12), $C[V_G] \times 100$ (0.01–0.02).

values obtained from the computation of *F* WRIGHT's statistics in 300 runs carried out with no selection. Substituting the predicted values of *F* and S_k^2 in Equation 10 [with the appropriate modifications from CROW and DENNISTON (1988) in the case of different number of males and females], the N_e estimated (in parentheses) was in very good agreement with its simulated value from these runs. Fixation probabilities, times to fixation and cumulative heterozygosity and genotypic variance obtained by simulation agreed very well with diffusion approximations incorporating the expected values of *F*, N_e and *s*.

Other approximations to the fixation probability: POLLAK (1987, 1988) obtained approximations for the probability of ultimate survival of mutant alleles in finite populations with partial inbreeding by means of branching process methods. His equation for the case of partial selfing was incorrect because it did not properly take into account the effective population size. After correction, however, it leads to Equation 11, *i.e.*, the correct approximation for large *Ns*. This mistake has also been noticed by POLLAK and SABRAN (1992).

POLLAK's equation for calculating the fixation probability with partial full-sib mating cannot be used in our case because it apparently relates to a different model to that dealt with in this paper. POLLAK considered couples rather than individuals as reproducing units and selection was applied as differential viability of such couples. In our model (exemplified by the simulation), selection operates on differential viability of individuals (by truncation selection) and those selected individuals are then mated. Thus, our model is compatible with that used for partial selfing (where selection is always made on individuals) and the mean change in gene frequency with selection (Equation 3) is the same in both cases. Therefore, in this paper, there is no distinction between models for selfing and full-sib mating or other types of inbred matings if expressed as a function of *F*, and both the diffusion results and Equation 11 are general. Hence, simulated values identical to those shown in Table 1 for partial selfing would also be obtained for the case of mixed full-sib and random mating with, in particular, random mating ($F = 0$), 80% of full-sib mating ($F = 0.5$) or 100% of full-sib mating ($F \approx 1$) (see Equation 7), provided S_k^2 is maintained equal to 2, so that N_e is the same in both models.

DISCUSSION

Fixation probabilities, average times to fixation and extinction and heterozygosity and genetic variance contributed by single mutant genes in finite populations where there is partial inbreeding have been investigated by means of diffusion methods.

The key parameters in the prediction are the equilibrium coefficient of inbreeding due to nonrandom mating, which can be derived from the proportion of inbred matings, and the effective population size which, in turn, depends on the former and the variance of family size. If considered separately, these two parameters have a similar effect on the fixation prob-

ability, *i.e.*, an increase in any of them causes an increase in the fixation probability. However, increasing F generally reduces N_e and, therefore, they counteract each other partially or even completely. When the variance of family size corresponds to a Poisson distribution the offset is complete for additive genes and their fixation probability is independent of F. This might tentatively be seen as an extension of MARUYAMA's (1970) result that subdivision of a population does not affect the fixation rate of an additive gene provided there is no change in mean gene frequency in the population, although there is no such subdivision in the situations discussed in this paper. Other distributions of family offspring change this result for additive genes, leading to an increase ($S_k^2 < 2$) or decrease ($S_k^2 > 2$) in their fixation probability with an increment in the degree of inbreeding. This is caused by a proportionally smaller reduction in N_e with inbreeding when S_k^2 is smaller (see Equation 11). For example, in the three cases analyzed in this paper, *i.e.*, $S_k^2 = 1$, 2 and 4, the reduction in N_e with $F = 0.5$ relative to $F = 0$ is 14%, 33% and 46%, respectively. This proportional reduction in N_e quickly approaches an asymptote of around 60% as S_k^2 further increases, such that for values of S_k^2 greater than 4, it is not very different from the case with $S_k^2 = 4$.

Inbreeding increases the fixation probability of recessive genes and decreases that for dominant genes. The effect of an increased F on increasing the change in mean gene frequency (see Equation 3) is now much more important than its corresponding effect on reducing N_e and the variance of that change (Equation 4) for recessive genes (as shown by CKH91), and the opposite happens with dominant genes. The highest increments for recessives are achieved with smaller S_k^2 and the highest decrements for dominants with larger S_k^2.

Increasing inbreeding for recessive genes not only implies an increase in additive variance (which would be caused by the increase in fixation probability), but also an increase in non-additive variance with intermediate degrees of inbreeding as shown by ROBERTSON (1952) for neutral recessives. As a consequence the cumulative genetic variance for completely recessive genes is very close to that for additive genes when F is intermediate. The genetic variance accumulated during the mutant's lifetime can alternatively be viewed as proportional to the equilibrium variance maintained due to a steady flux of mutations and, therefore, the results can be generalized to the variance maintained in the population when many genes are segregating simultaneously by multiplying the cumulative variance by the mutation rate and summing over loci.

Partial inbreeding also causes a reduction in the time to fixation. This reduction is less marked for smaller values of S_k^2 though, for relatively large values of Ns, the differences among S_k^2 values are largely reduced. This has the implication that for strong selection, and considering fixation probabilities and time to fixation jointly, the case with $S_k^2 = 1$ is the most favorable among the three studied in the effect of inbreeding on the fixation of mutant genes.

Only three values of S_k^2 have been investigated in this paper, but they can be considered as suitable representatives of the whole range. The extreme case of $S_k^2 = 0$ was not analyzed because the model investigated assumes individual or mass selection. With only within-family selection (obligatory with $S_k^2 = 0$), the time to fixation would be increased with inbreeding. In a breeding system with individual selection and where the population is maintained with a fixed structure, the smallest variance of family size would be around one, achieved when couples contribute two offspring of each sex to the scored group. A greater or more variable contribution would yield higher values of S_k^2 and, therefore, the case of $S_k^2 = 1$ can be considered as a lower limit in the present study. Likewise, as pointed out above, higher variances than 4 would not cause important additional differences because the proportional reduction in N_e is, then, approximately constant.

Stochastic simulation has been useful in showing the high accuracy of the diffusion methods even for the cases with strong selection, as well as in illustrating its generality for different distributions of offspring number and systems of partial inbreeding. HILL (1985) already checked the validity of the diffusion approximations for the case of additive mutant genes with artificial selection and random mating and CKH91 did the same for some of the cases investigated in this paper, though simulated values of N_e were used instead of their predictions.

LANDE and SCHEMSKE (1985) showed that, in theory, predominant outcrossing ($F \approx 0$) and predominant selfing ($F \approx 1$) are the two stable states of the mating system in plants. This prediction was born out empirically and the distribution was found markedly bimodal with the classes $\beta \leq 0.20$ and $\beta \geq 0.80$ more frequent than expected, though a great variation could be observed in some taxa (SCHEMSKE and LANDE 1985). If this is true, it would mean that in completely selfed plants advantageous mutations would behave as additives irrespective of their gene action. Thus, if recessive mutations affecting a certain quantitative trait in a determined direction were more frequent than dominants, the average fixation rate and the average cumulative genetic variance would be higher in selfed than in random mating plants and vice versa. In any case, the time until fixation of all favorable mutations in a selfed plant would be approximately half of that in a random mating plant. For strongly

deleterious mutations, when fixation rates and cumulative variance are negligible, the time until their extinction in a selfed plant would be around 80% shorter than in a random mating plant, though a large part of this reduction could be achieved with a small proportion of selfing. Thus, the rate of evolution of selfing plants may exceed that of outcrossers.

Of course these predictions refer only to single mutants, the case dealt with in this paper. Other problems such as linkage have not been studied. Linkage disequilibrium among alleles at different loci is also common in populations of inbreeding plants (BROWN 1979) affecting the equilibrium genotypic frequencies [see WEIR and COCKERHAM (1973) and references therein], and this may deserve further investigation.

The Poisson distribution of family size, usually used as a simplifying model, needs careful definition with partial inbreeding, however. In this paper, in the case of selfing it has referred to independent distributions of selfed and nonselfed offspring and thus S_g^2 (the variance of successful gametes) is necessarily dependent on the proportion of selfing offspring (β) such that $S_g^2 = 2 + 2\beta$. For the cases of partial sib mating, however, it has referred to independent distributions of male and female offspring because selection preceded the formation of pair matings. Thus, S_k^2 has been maintained at 2 irrespective of β at the expense of the restriction of a maximum number of sib matings. In this situation, the results obtained for partial selfing and partial sib mating are the same because both the model of selection (on individual genotypes) and N_e are identical. There are, however, alternative models where S_k^2 is also a function of the proportion of sib matings. For example, if selection is applied after formation of pair mates, β can increase to 1 but S_k^2 cannot be maintained at 2 unless the number of males and females per family is subject to some restrictions and, in general, there will be a correlation between the proportion of sib matings and the variance of family size. Thus, if the number of male and female pairs of offspring that sib mate is Poisson with index β and the number of male and female offspring that do not is independently Poisson with index $1 - \beta$, $S_k^2 = 2 + 2\beta$ analogously to the partial selfing case. Hence, with $\beta = 1$ there are equal numbers of males and females per family and $S_k^2 = 4$ because there is a unit covariance of male and female numbers. In this situation, the results in this paper would be different because, for instance, with $\beta = 1$, N_e would be $N/4$ instead of $N/2$ as with $S_k^2 = 2$ and, therefore, the fixation probability with additivity would drop with $F = 1$ to half the value with $F = 0$, instead of remaining constant. Moreover, the selection model would also be different from that with selfing, and the models would not be comparable.

Among several alternative breeding schemes, CKH91 found that the most successful in increasing fixation probabilities for recessive genes without impairing that for nonadditive genes or delaying times to fixation would consist of practising individual selection and mating full-sibs whenever possible, otherwise at random. In particular, the best scheme was achieved with a multihypergeometric distribution of family offspring (constant number of scored individuals from each family), in accordance with the results of this paper. Both from that and the present study, it may be concluded that partial inbreeding is useful in increasing fixation rates of new advantageous mutations affecting a quantitative trait when the gene action is additive to complete recessive (in the case of $S_k^2 < 2$) or only recessive (partial or complete, in the case of $S_k^2 = 2$).

Information about the gene action of mutants affecting quantitative traits is scarce. Direct evidence comes from recent studies on spontaneous polygenic mutation in Drosophila. CABALLERO, TORO and LOPEZ-FANJUL (1991) artificially selected for abdominal bristle number starting from a completely homozygous population and analyzed a number of mutations arising during the course of the experiment. In only two cases the gene action could be ascertained, and additivity and complete recessivity were found. Moreover, the recessive mutant had the highest effect on the selected character. By maintaining 200 inbred lines without selection, starting from the same isogenic population, E. SANTIAGO, J. ALBORNOZ, A. DOMINGUEZ, M. A. TORO and C. LOPEZ-FANJUL (unpublished data) isolated a number of mutants affecting bristle number and wing length and width. Mutations showed a high level of pleiotropy among the three characters, ranging in their gene actions from additivity to complete recessivity. Only one mutant showed incomplete dominance for one trait but was additive for the two others. Mutations with recessive gene action were among those with the highest effect. *P* element inserts have also been shown to be partially recessive in their effects on bristle number (MACKAY, LYMAN and JACKSON 1992).

These observations would suggest a great advantage of inbreeding in fixing advantageous mutants quickly. However, there is an association between genes with large recessive effects and deleterious pleiotropic effects on fitness. CABALLERO, TORO and LOPEZ-FANJUL (1991) found that, although some mutations behaved as neutrals, most were lethal and the recessive with the highest score was semilethal. In the unselected inbred lines referred to above, the recessive mutations were deleterious while those additive were usually neutral. *P* element insertions causing extreme bristle effects in MACKAY, LYMAN and JACKSON (1992) were also greatly deleterious. But even in this situation

partial inbreeding may be useful. HILL (1982) suggested that strongly deleterious mutations, such as lethals in Drosophila, should be better eliminated from breeding programs. Partial inbreeding sharply decreases the time until extinction of strongly deleterious mutants, especially recessives, and therefore, it would also be useful in this aim. Thus, while increasing the probability of picking up possible neutral advantageous mutants, it also would serve to get rid of those with some effect on the trait but strongly detrimental in homozygosis.

The increase in the fixation probability caused by inbreeding indicates an increase in the additive variance and in the asymptotic response to selection. While this statement may be correct if isogenic populations and values of mutational variance usually obtained are considered (CKH91), something very different might happen in outbred populations where inbreeding has not been strong before. Inbreeding reduces the within-family variance and its use in practical terms has been questioned (DICKERSON and LINDHE 1977). These doubts come, however, from considerations relative to cyclical inbreeding in alternate generations, where specific problems such as a reduced intensity of selection are present. Inbreeding depression is expected to cause initial fitness problems, though after elimination of strongly deleterious mutations and, if the population survive such a process, response can be quicker than in a corresponding random mating population (MACNEIL *et al.* 1984). Increased inbreeding is also expected to cause an increase in variation of response which may be of importance in small populations. On the contrary, partial inbreeding decreases the time to fixation of new mutants and, therefore, increases short-term responses, which is more valuable in breeding schemes. On the whole, therefore, the possible usefulness of the schemes illustrated by CKH91 or in this paper in practical breeding management still remains an open question.

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