

# Response to selection from new mutation and effective size of partially inbred populations. I. Theoretical results

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## Summary

The effects of partial inbreeding on effective population size and rates of fixation of mutant genes are investigated in selected populations. Truncation selection and an infinitesimal model of gene effects for the selected trait are assumed. Predictions of effective size under this model are given for partial selfing and partial full-sib mating and an extension to a more general model is outlined. The joint effect of selection and partial inbreeding causes a large reduction in the effective size relative to the case of random mating. This effect is especially remarkable for small amounts of selected genetic variation. For example, for initial heritability 0.1 and proportion selected 1/6, the ratio of effective size to population size is 0.10 in populations with about 90% selfing while it is 0.85 in random mating populations. The consequence is a reduction in the fixation probability of favourable genes and, therefore, a reduction in the final response to selection. Stochastic simulations are used to investigate the effects of partial inbreeding and selection on fixation and extinction rates of genes of large effect and of recessive lethals with effects on the selected trait. For genes of very large effect, the effective size is not a critical factor and it is expected that partial inbreeding will be efficient in increasing fixation rates of recessive mutants. Lethal recessives are eliminated more frequently and their equilibrium frequency is lower under partial inbreeding, but only when their effects on the heterozygote are not very large.

## 1. Introduction

Many plants, including most major crops, and some animal species exhibit substantial non-random mating such as selfing or full-sib mating (see e.g. Jain [1976]; Schemske & Lande [1985] or Futuyma [1986, pp. 124–128]). Also, deliberate inbreeding may be useful as a way of using non-additive genetic variance in breeding schemes (see e.g. Dickerson & Lindhé, 1977; Sirkkoma, 1986; Berg & Christensen, 1990; Caballero & Hill, 1992*c*; Toro, 1993*a, b*). Partial full-sib mating has been proposed as a means to increase fixation probabilities of recessive mutations in selection programmes (Caballero, Keightley & Hill, 1991) and as a way of detecting recessive visible alleles (Karlin & Tavaré, 1982; Caballero, Etheridge & Hill,

1992). Thus, it is justified to investigate the consequences of partial inbreeding both from a practical and evolutionary point of view.

The effects of partial inbreeding on fixation and variation of mutant genes have been investigated by a number of authors (Pollak, 1987, 1988; Caballero & Hill, 1992*b*; Charlesworth, 1992; Pollak & Sabran, 1992). The rate of substitution of alleles and the asymptotic rate of response from artificial selection both depend on the fixation probability, thus becoming an essential parameter in population and quantitative genetics. Results from previous analyses show that for populations where the number of offspring per family is multinomially distributed, partial inbreeding increases the fixation probability of recessive mutants, decreases that of dominants and does not change that of additives. These theoretical results were developed on the assumption that the only variation present in the population was that due to the selected mutation. In these circumstances, diffusion approximations using the effective population size predicted under random selection, but

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accounting for partial inbreeding (Caballero & Hill, 1992a), were shown to be very reliable estimators of results obtained by stochastic simulation (Caballero & Hill, 1992b). This situation, however, is not a realistic one, because it is expected that some additional genetic variation subject to selection will always be present in the population. Even in the extreme case of an isogenic or highly inbred population there will be some variation arising each generation by mutation.

The effective population size is reduced under selection and this reduction will be larger with intense selection and high heritability of the selected trait (Robertson, 1961). It is therefore expected that, if some variation for a selected trait is present in the population other than that contributed by the mutant gene, the effective size will be reduced and, accordingly, the fixation probability of advantageous mutations will also be reduced. The magnitude of this reduction in the effective size with selection critically depends on the recombination rate and system of mating. Charlesworth, Morgan & Charlesworth (1993) investigated the effect of background selection due to recurrent deleterious mutations on nucleotide diversity. They observed by simulation that, for a given set of mutation parameters, the genetic diversity for rates of selfing larger than about 0.5 was markedly reduced relative to the predictions of classical neutral theory, implying that even with loose linkage high rates of selfing can greatly reduce the effective population size when there is background selection. In the context of artificial selection on quantitative traits, Santiago & Caballero (1995) have also shown that the reduction in effective size under selection is much larger when partial full-sib mating is carried out among selected parents than when matings are panmictic.

In this paper, we quantify the effect of partial inbreeding on the effective population size and the rates of fixation and average times until fixation or extinction of a mutant gene appearing in a population with a genetic background. The model refers to truncation selection on a quantitative trait, with background genetic variation determined by an infinitesimal additive model of gene effects (Bulmer, 1980). No linkage is assumed between the mutant gene and the selected background. Expressions for approximate equilibrium parameters under this model are derived for partial selfing and partial full-sib mating, which allow predictions of the effective size in these two situations. It will be shown that, under truncation selection, a very small amount of variation in the selected trait is enough to reduce drastically the effective size of highly inbred populations. In a companion paper (Merchante, Caballero & López-Fanjul, 1995), an experimental check of this effect is presented using an artificially selected isogenic population in which there is a small amount of genetic variation in the selected trait due to a short period of exposure to new mutations.

**2. Prediction of rates and times to fixation and extinction**

Assume a locus with three genotypes *AA*, *Aa* and *aa*, genotypic frequencies  $(1-x)^2 + x(1-x)F_{IS}$ ,  $2x(1-x)(1-F_{IS})$ , and  $x^2 + x(1-x)F_{IS}$ , and relative fitnesses 1,  $1+sh$  and  $1+s$ , where *s* is the selective advantage of allele *a*, *h* is its coefficient of dominance and  $F_{IS}$  is the departure from Hardy–Weinberg proportions (Wright, 1969, pp. 294–295). The fixation probability of a gene with initial frequency *q* in a finite population can be calculated by means of diffusion approximations as

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

(Kimura, 1962), where

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

(Caballero *et al.* 1991), and  $N_e$  is the effective population size.

Additionally, the average number of generations until fixation ( $t_1[q]$ ) and extinction ( $t_0[q]$ ) of such a gene are given by

$$t_1(q) = \int_q^1 \psi(x) u(x) [1-u(x)] dx + \frac{1-u(q)}{u(q)} \int_0^q \psi(x) u^2(x) dx \tag{3}$$

(Kimura & Ohta, 1969a) and

$$t_0(q) = \frac{u(q)}{1-u(q)} \int_q^1 \psi(x) [1-u(x)]^2 dx + \int_0^q \psi(x) [1-u(x)] u(x) dx \tag{4}$$

(Kimura & Ohta, 1969b), where

$$\psi(x) = \frac{4N_e \int_0^1 G(z) dz}{x(1-x)G(x)}. \tag{5}$$

The fixation probability of a mutant gene with initial frequency  $q = 1/2N$ , where *N* is the population size, and large selection coefficient ( $Ns > 1$ ), can be approximated from equations (1) and (2) by

$$u(1/2N) = 2s(N_e/N)(F_{IS} + h - F_{IS}h) \tag{6}$$

(Caballero & Hill, 1992b; Pollak & Sabran, 1992). An approximation for smaller values of *Ns* is given by Charlesworth (1992). From (6) we observe that the fixation probability is directly proportional to the effective size of the population. Until recently, however, there were no equations available to predict  $N_e$  under selection and non-random mating. Santiago

& Caballero (1995) obtained a general expression to approximate the effective size of selected populations under partial full-sib mating and selection. In the next section, this predictive equation is explained and extended to the case of partial selfing.

**3. Effective population size under selection**

Throughout this paper we will consider the simplest case where numbers of breeding males and females are equal ( $N/2$  each) and constant over generations. A general approximation for the effective population size with continuous mass selection and the possibility of partial full-sib mating of selected parents is

$$N_e = \frac{4N}{2(1 - F_{IS}) + (S_k^2 + 4Q^2C^2)(1 + 3F_{IS})} \tag{7}$$

(Santiago & Caballero, 1995), where  $S_k^2$  is the variance of the number of selected offspring per family after random selection ( $\sigma_k^2$ ) with the Gaussian correction ( $S_k^2 = \sigma_k^2 N/[N - 1]$ ), and the term  $4Q^2C^2$  accounts for selection.  $C^2$  is the variance of relative fitnesses of families; equivalently,  $4C^2$  is the variance of the expected number of offspring per family based on its genotypic value for the selected trait.  $Q^2$  is the term accounting for the cumulative effect of selection, i.e. the fact that selective advantages of families are inherited (Robertson, 1961; Wray & Thompson, 1990) and can generally be obtained as

$$Q = \frac{2}{2 - G(1 + \beta)} \tag{8}$$

(Santiago & Caballero, 1995), where  $G$  is the proportion of the genetic variance remaining after selection has been practised, and  $\beta$  is the proportion of full-sib matings carried out among selected parents, the remainder,  $1 - \beta$ , being random. It is assumed that the full-sib mating habit is not inherited. Under a constant proportion of full-sib matings per generation,  $F_{IS}$  reaches an approximate asymptotic value of  $F_{IS} = \beta/(4 - 3\beta)$  (Ghai, 1969). Under random mating, the value of  $F_{IS}$  is of order  $1/N$  (Kimura & Crow, 1963), and we will assume that is equal to zero.

Equation (7) assumes no linkage between the neutral genes and the selected genes and it is an approximation because second-order terms in  $N$  are neglected. Santiago & Caballero (1995) also gave an approximate expression which extends (7) to the general case where there is a different number of parents of each sex. Similar equations for predicting  $N_e$  in selected population with random mating are given by Woolliams, Wray & Thompson (1993).

In the particular case of a multinomial distribution of the number of offspring per family available for selection ( $S_k^2 = 2$ ), equation (7) reduces to

$$N_e = \frac{N}{(1 + F_{IS}) + Q^2C^2(1 + 3F_{IS})} \tag{9}$$

The argument given by Santiago & Caballero (1995) can also be applied to the case of partial selfing, and equation (7) holds except that the term  $(1 + 3F_{IS})$  must be replaced by  $(1 + F_{IS})$  (see Caballero & Hill, 1992a) and  $\beta$  refers to the proportion of individual offspring that results from selfing. Thus, for partial selfing

$$N_e = \frac{4N}{2(1 - F_{IS}) + (S_k^2 + 4Q^2C^2)(1 + F_{IS})}, \tag{10}$$

where now  $S_k^2$  is the variance of the number of successful gametes produced per parent after random selection (again with the Gaussian correction), and  $F_{IS} = \beta/(2 - \beta)$  (Haldane, 1924).

Under independent multinomial distributions of selfed and non-selfed offspring per individual available for selection,  $S_k^2 = 2 + 2\beta$  (see Caballero & Hill, 1992a), and equation (10) reduces to

$$N_e = \frac{N}{(1 + F_{IS})(1 + Q^2C^2)}. \tag{11}$$

Equations (7) and (10) are general but the values of  $G$  and  $C^2$  depend on the selective system and genetic model. In later sections, expressions for these parameters will be given for the infinitesimal model of gene effects and truncation selection on the phenotype, and predictions for particular examples will be compared with simulation results.

**4. Predictions under truncation selection and the infinitesimal model**

For practical considerations in breeding schemes, and for convenience in the analyses and simulations, the model assumed in this paper for the genetic background variation will be that of a quantitative trait controlled by an infinitesimal additive model of unlinked gene effects (Bulmer, 1980) with heritability  $h^2$ . Selection is performed by truncation on the phenotype, the offspring with the highest phenotype being chosen as parents. (An outline of a more general model will be given in the discussion section.) Under the infinitesimal model,  $G = 1 - kh^2$  (Bulmer, 1980), where  $k = i(i - x)$ ,  $i$  is the selection intensity and  $x$  is the truncation point in the normal curve. Under random mating,  $C^2 \approx i^2\rho$  (Robertson, 1961; Milkman, 1978), where  $\rho$  is the intraclass correlation of family members. We will consider a practical situation in which the selection process starts with an unselected random mating population with initial genetic variance  $V_{A_0}$  and initial heritability  $h_0^2 = V_{A_0}/(V_{A_0} + V_E)$ , where  $V_E$  is the environmental variance, which is assumed to be constant over generations. The population is then subject to truncation selection for a number of generations, and we are interested in the asymptotic effective size, i.e. the value when the rate of inbreeding is approximately constant over generations. The initial genetic variance will be reduced by selection and inbreeding, especially at the beginning,

but in most cases this change will become negligible after a few generations and the rate of increase in inbreeding will become relatively stable. Therefore, the first step in the prediction of this asymptotic effective size is the prediction of the asymptotic values of  $h^2$  and  $\rho$  when their change due to selection is negligible. Approximate equations to predict these parameters under random mating are given by Gómez-Raya & Burnside (1990) and Santiago & Caballero (1995). In what follows we derive equivalent expressions for the general cases under partial selfing and partial full-sib mating.

(i) *Partial selfing*

Assume a hermaphroditic population where each parent may have selfed and/or crossbred offspring. Thus, parents have selfed offspring with probability  $\beta$  and crossbred offspring (produced by random union of gametes) with probability  $1 - \beta$ , the selfing habit not being inherited. Let  $V_A$  be the asymptotic variance before selection, and  $V_A(1 - kh^2) = V_A G$  the variance after truncation selection has been practised. The genetic variance between selfed progenies is  $V_A G$  and that between crossbred progenies is  $V_A G/2$ , so the average variance between matings is  $\beta V_A G + (1 - \beta) V_A G/2 = V_A G(1 + \beta)/2$ . The expected genetic variance of offspring within matings is

$$V_w = V_A(1 - F_{IS})/2, \tag{12}$$

where we will assume that  $F_{IS}$  is the equilibrium inbreeding coefficient for an infinite population, i.e.  $F_{IS} = \beta/(2 - \beta)$ . The total asymptotic genetic variance is, therefore,  $V_A = V_A G(1 + \beta)/2 + V_w$ . Substituting  $G$  and  $V_w$  from above and rearranging we obtain a second-degree equation

$$V_A^2[1 + k - \beta(1 - k)] + V_A[V_E(1 - \beta) - 2V_w] - 2V_E V_w = 0, \tag{13}$$

from where the asymptotic genetic variance and asymptotic heritability,  $h^2 = V_A/(V_A + V_E)$ , can be calculated.

To obtain the correlation between family members ( $\rho$ ; where a family is the total offspring, selfed or non-selfed, from a parent) let us call  $g$  the breeding value of the selected parent. The expected breeding value of its selfed offspring will also be  $g$ , while that of its crossbred offspring will be  $g/2$  if these are obtained by mating with other individuals taken at random from the population. Hence, the expected breeding value of all possible offspring of an individual is  $\beta g + (1 - \beta)g/2 = g(1 + \beta)/2$ , from which the variance of family means and intraclass correlation will be

$$V_b = V_A G(1 + \beta)^2/4 \tag{14}$$

and

$$\rho = V_b/(V_A + V_E), \tag{15}$$

respectively.

(ii) *Partial full-sib mating*

For this model we assume monogamous matings, with proportions  $\beta$  between full sibs and  $1 - \beta$  at random. Again, the full-sib mating habit is not inherited. The genetic variance within families is given by equation (12) where we assume again that  $F_{IS}$  is the equilibrium inbreeding in an infinite population,  $F_{IS} = \beta/(4 - 3\beta)$ . The variance between full-sib progeny equals  $V_b G + V_w G/2$ , and that between non-sib progeny is  $(V_b G + V_w G)/2$ , assuming that the reduction of variance by selection in the previous generation ( $1 - G$ ) affects equally both the variances between and within families in the current generation. Thus, the total variance between families is

$$V_b = \beta(V_b G + V_w G/2) + (1 - \beta)(V_b G + V_w G)/2 = [V_b(1 + \beta) + V_w]G/2. \tag{16}$$

Substituting  $h^2 = (V_b + V_w)/(V_b + V_w + V_E)$ ,  $G$  from above, and rearranging, we obtain the second-degree equation

$$V_b^2[1 + k - \beta(1 - k)] + V_b[V_E(1 - \beta) + V_w(k\beta - \beta + 2k)] - V_w[V_w(1 - k) + V_E] = 0, \tag{17}$$

from where an approximation for the asymptotic variance between families can be obtained, and

$$\rho = V_b/(V_b + V_w + V_E). \tag{18}$$

The above expressions give the values of  $\rho$  and  $h^2$  in the asymptotic state for a given initial genetic variance or heritability and environmental variance in this model. It is also worth expressing the equilibrium  $\rho$  in terms of the equilibrium heritability. For partial selfing, substituting equation (14) into (15),

$$\rho = \frac{h^2 G(1 + \beta)^2}{4}. \tag{19}$$

For partial full-sib mating, substituting (16) into (18),

$$\rho = \frac{(V_A + V_b \beta) G/2}{V_A + V_E} = \frac{(h^2 + \rho \beta) G}{2}$$

and, rearranging,

$$\rho = \frac{h^2 G}{2 - \beta G}. \tag{20}$$

Thus, under random mating  $\beta = 0$  and  $\rho = h^2 G/4$  in the monoecious polygamous case, and  $\rho = h^2 G/2$  in the dioecious monogamous case, as would be expected.

**5. Stochastic simulation procedure**

Stochastic simulation was used to investigate fixation or extinction rates of mutants of very large effect for which diffusion approximations break down, for example for lethal recessive mutants with effects on the heterozygote, or for mutations appearing in populations where such a lethal gene is segregating at

equilibrium frequencies. Some runs were also devoted to check the prediction equations for effective size and fixation parameters of mutant genes of small effect.

In the simulations to check out predictions of effective size, artificial selection was carried out on a trait controlled by an infinitesimal additive model of gene effects with initial heritability  $h_0^2$ . In generation 0, genotypic values were assumed to be normally distributed with mean zero and variance  $V_{A_0} = h_0^2$ . Phenotypes were obtained by adding to the genotypic value a random environmental deviation normally distributed with mean zero and variance  $V_E = 1 - h_0^2$ . Truncation selection on the phenotypes was carried out each generation. In the monoecious case, the best  $N = 100$  individuals out of  $T = 200, 300$  or  $600$  available for selection (i.e. proportions selected of  $1/2, 1/3$  and  $1/6$ ) were selected to be parents of the next generation. The number of selfed (with probability  $\beta$ ) and cross-bred (with probability  $1 - \beta$ ) offspring available for selection per parent were independently multinomially distributed with parameters  $T$  and  $1/N$ , such that  $S_k^2 = 2 + 2\beta$ . In the dioecious case, the best  $N/2 = 50$  individuals of each sex out of  $T/2 = 100, 150$  or  $300$  available for selection of each sex, were chosen as parents. The number of offspring available for selection per family was multinomially distributed with parameters  $T/2$  and  $2/N$ , such that  $S_k^2 = 2$ . In the monoecious case, mating of selected individuals was at random ( $\beta = 0, F_{IS} = 0$ ) or with a probability of selfing  $\beta = 1/3, 2/3$  or  $8/9$ , which correspond to values of  $F_{IS} = 0.2, 0.5$  and  $0.8$ , respectively. In the dioecious case, monogamous matings were made at random ( $\beta = 0, F_{IS} = 0$ ) or matings were made between full sibs whenever possible, at random otherwise, giving an average proportion of  $\beta = 0.48$  ( $F_{IS} = 0.19$ ). Discrete generations were assumed in all cases. Genotypic values of the offspring were obtained as the average of the genotypic values of their parents plus a random Mendelian deviation normally distributed with mean zero and variance  $(V_{A_0}/2)[1 - (F_m + F_f)/2]$ , where  $F_s$  is the inbreeding coefficient of the parent of sex  $s$  (or the donor of gamete sex  $s$  is monoecious populations), obtained from pedigrees. Each generation, Wright's (1922) numerator relationship matrix was constructed and the average coancestry between individuals ( $F_t$ ) in generation  $t$  was computed. Effective population size was obtained from the average rate of inbreeding  $\Delta F = [F_{t+1} - F_t]/[1 - F_t]$  between generations 10 and 20, as  $N_e = 1/2\Delta F$  in the monoecious case, and  $N_e = (1/2\Delta F) - (1/2)$  in the dioecious case. This latter correction is made for the sake of comparison between predictions and simulations of  $N_e$ , as equation (7) considers absence of self-fertilization (see e.g. Caballero, 1994). 500 replicates were run for each case and results were averaged among replicates.

In the simulations to check predictions of rates and times to fixation of mutant genes, the procedure for the dioecious population with random mating or

partial full-sib matings explained above, with proportion selected  $1/3$  and initial heritability  $h_0^2 = 0, 0.1$  or  $0.4$ , was used. In these runs, a mutant appeared in one of the individuals available for selection (initial frequency  $1/600$ ) in generation 4, in which the rate of inbreeding is already approximately constant in most cases. The effect of the mutant was to produce a difference between the mutant and wild-type homozygotes of  $2a = 0.046$  phenotypic standard deviations ( $\sigma$ ) of the selected trait. As the selection intensity is  $i \approx 1.085$ , this gives a coefficient of selection  $s \approx 2ai = 0.05$  (see e.g. Falconer [1989], p. 202). Additive or recessive gene action for the mutant was considered. 30000 replicates were run for each case simulated. Each replicate was stopped when the mutant was lost or fixed and fixation probabilities and average numbers of generations until fixation of the mutant gene were computed.

Simulations were also made in order to investigate fixation rates and times to fixation of mutants of very large effect, elimination of lethals with effects on the heterozygote, and fixation rates of genes in populations where a lethal is segregating. In these simulations the procedure was as in the dioecious model explained above, except that the number of breeding individuals was 20 of each sex, and five individuals of each sex were available for selection per family. This design is identical to the experimental one followed by Merchante *et al.* (1995) in order to allow comparisons between simulation results and experimental observations. The mutation investigated had an initial frequency of  $1/400$  ( $1/300$  for X-linked, where the mutation appeared with probability twice as high in females than in males) and caused a difference between homozygotes with a range between  $0.25$  and  $4\sigma$  (hemizygous effect for X-linked), being additive or recessive. Background variation with  $h_0^2 = 0, 0.1$  and  $0.4$  was considered. In other runs, the mutation was a lethal recessive with an effect on the heterozygote within a range of  $0.125$  to  $1\sigma$  and background variation with  $h_0^2 = 0.1$ . Finally, in some runs the fixation probability of a neutral mutation appearing in a random mating population where a lethal with effect on the trait is segregating at its equilibrium frequency was investigated. 5000 replicates were run for each of these simulations.

## 6. Results

### (i) Effective population size

Tables 1 and 2 show simulated and predicted (in parentheses) values of the effective size for a range of initial heritabilities ( $h_0^2$ ), proportions selected ( $P$ ) and asymptotic values of  $F_{IS}$ , for monoecious and dioecious populations, respectively. Predictions are generally quite close to simulations, at least giving the right order of magnitude. The largest absolute errors occur for large proportions of inbred matings ( $F_{IS} = 0.8$ , Table 1) and small heritabilities. This is pre-

Table 1. Simulated and predicted (in parentheses; using equations [8], [11], [13], [14] & [15]) values of effective population size in a monoecious population with  $N = 100$  breeding individuals, and 200, 300 or 600 individuals available for selection (proportion selected  $P$ ), with an initial background heritability  $h_0^2$

$h_0^2$	$P = 1/2$	$P = 1/3$	$P = 1/6$
$F_{IS} = 0$			
0.0	100.0 (100.0)	99.7 (100.0)	99.9 (100.0)
0.1	95.7 (95.2)	92.3 (91.6)	86.2 (85.6)
0.4	89.6 (89.6)	83.0 (83.1)	72.8 (74.4)
0.8	88.6 (89.6)	83.0 (84.1)	74.7 (78.2)
$F_{IS} = 0.2$			
0.0	83.4 (83.3)	83.8 (83.3)	83.3 (83.3)
0.1	70.3 (69.8)	59.5 (61.8)	47.0 (51.3)
0.4	61.0 (62.6)	50.9 (53.1)	37.1 (43.1)
0.8	62.6 (65.5)	54.5 (58.0)	44.7 (51.3)
$F_{IS} = 0.5$			
0.0	66.7 (66.7)	67.0 (66.7)	66.5 (66.7)
0.1	35.4 (35.3)	28.3 (26.0)	20.3 (18.2)
0.4	31.3 (33.6)	24.0 (25.1)	17.2 (18.5)
0.8	35.3 (40.7)	30.0 (33.3)	21.9 (27.6)
$F_{IS} = 0.8$			
0.0	55.8 (55.6)	56.1 (55.6)	55.7 (55.6)
0.1	15.5 (11.2)	12.5 (7.2)	10.7 (4.6)
0.4	14.4 (14.5)	11.8 (9.8)	8.9 (6.8)
0.8	17.5 (22.6)	14.9 (16.8)	10.2 (12.9)

The number of progeny available for selection per parent is multinomially distributed. Mating is at random ( $F_{IS} = 0$ ) or with a proportion  $\beta = 1/3, 2/3$  or  $8/9$  ( $F_{IS} = 0.2, 0.5$  and  $0.8$ , respectively) of selfing. Standard errors range from 0.2 to 1.2 (with an average of 0.4).

Table 2. Simulated and predicted (in parentheses; using equations [7], [8], [16], [17] & [18]) values of effective population size in a dioecious population with  $N = 100$  breeding individuals (half of each sex), with 100, 150 or 300 individuals of each sex available for selection (proportion selected  $P$ ), with an initial background heritability  $h_0^2$

$h_0^2$	$P = 1/2$	$P = 1/3$	$P = 1/6$
$F_{IS} = 0$			
0.0	100.0 (100.0)	100.0 (100.0)	99.9 (100.0)
0.1	91.7 (90.9)	85.8 (84.6)	75.3 (74.9)
0.4	81.1 (81.2)	71.5 (71.8)	57.2 (59.1)
0.8	80.1 (81.1)	70.6 (73.9)	58.4 (63.9)
$F_{IS} = 0.2$			
0.0	84.6 (84.2)	84.1 (84.2)	84.7 (84.2)
0.1	53.9 (54.7)	42.1 (43.3)	29.3 (31.2)
0.4	44.0 (47.3)	34.0 (37.4)	27.7 (27.2)
0.8	53.6 (54.6)	45.6 (47.5)	36.9 (39.0)

The number of progeny available for selection per family is multinomially distributed. Mating is at random ( $F_{IS} = 0$ ) or with a maximum possible number of full-sib matings among the selected individuals ( $F_{IS} = 0.2$ ). Standard errors range from 0.1 to 0.8 (with an average of 0.4).

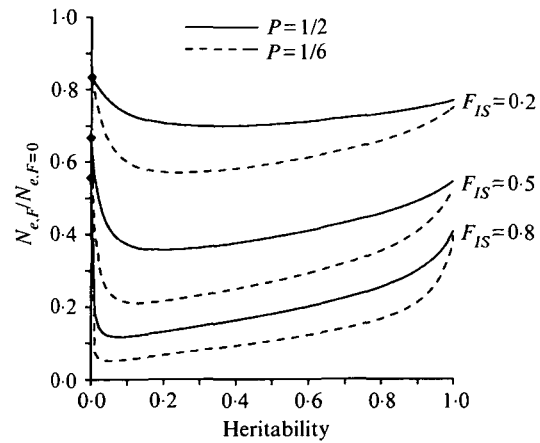


Fig. 1. Ratio of the effective size of a partially selfed selected population with coefficient of inbreeding  $F_{IS}$  ( $N_{e,F}$ ) to that of a random mating selected population ( $N_{e,F=0}$ ), plotted against the initial heritability for the selected trait.  $P$ : proportion selected.

sumably because for very large values of  $F_{IS}$  and small heritabilities the value of  $Q$  is extremely large and sensitive to errors in predictions.

An example of the prediction for selfing populations follows. Assume that a population has  $N = 100$  breeding individuals selected out of  $T = 300$  available for selection each generation, with initial genetic variance  $V_{A_0} = 0.4$  and environmental variance  $V_E = 0.6$  (thus, the initial heritability is  $h_0^2 = 0.4$ ). Offspring available for selection per parent are produced by selfing with probability  $\beta = 1/3$  or random mating otherwise, with independent multinomial distributions with parameters  $T$  and  $1/N$ . Thus,  $S_k^2 = 2 + 2\beta = 2.666$  and  $F_{IS} = \beta/(2 - \beta) = 0.2$ . From standard statistical tables,  $i = 1.088$ ,  $x = 0.452$  and  $k = i(i - x) = 0.692$ . First we approximate the equilibrium parameters. From (12),  $V_w = 0.160$ . The positive solution of (13) gives  $V_A = 0.323$ . Therefore,  $h^2 = V_A/(V_A + V_E) = 0.350$ , and from (14) and (15),  $V_b = 0.109$  and  $\rho = 0.118$ . Thus,  $C^2 = i^2\rho = 0.140$  and from (8),  $Q = 2.02$ . Substituting into (10) we obtain  $N_e = 53.1$ , while the simulated value is 50.9.

Both Tables 1 and 2 show that when there is a genetic background for the selected trait ( $h_0^2 > 0$ ), the effective size is much more reduced under partial inbreeding ( $F_{IS} > 0$ ) than under random mating ( $F_{IS} = 0$ ). A drastic reduction is observed with low heritability but this is not much further increased with increasing heritability for reasons which will be explained below. It is also observed that the effect is more marked with more intense selection. For the same value of  $F_{IS}$  (compare  $F_{IS} = 0.2$  in Tables 1 and 2, which correspond to about 33% selfing and 50% full-sib mating), the reduction in  $N_e$  is larger with partial full-sib mating. For the same proportion of inbred matings, however, partial selfing reduces  $N_e$  more (data not shown), as would be expected.

The combined effect of selection and partial inbreeding is better visualized in Fig. 1, where we

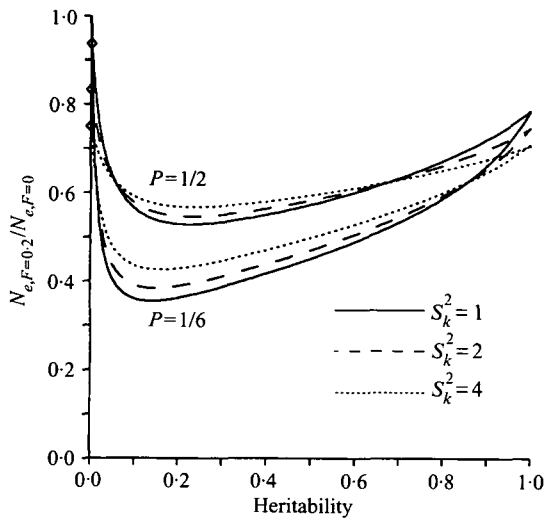


Fig. 2. Ratio of the effective size of a partial full-sib mating selected population with coefficient of inbreeding  $F_{IS} = 0.2$  ( $N_{e, F=0.2}$ ) to that of a random mating selected population ( $N_{e, F=0}$ ), plotted against the initial heritability for the selected trait.  $P$ : proportion selected.  $S_k^2$ : variance of family size after random selection.

represent the ratio between the predicted  $N_e$  with a given proportion of selfed matings ( $F_{IS} > 0$ ) and  $N_e$  under random mating ( $F_{IS} = 0$ ) for a given initial heritability and proportion selected ( $P$ ). Clearly, when there is genetic background variation for the selected trait, the effect of partial selfing is to decrease  $N_e$  by a large amount, and the minimum value of the ratio occurs for small heritabilities, say around 0.1 or 0.2.

The reduction in effective size by selection occurs because changes in gene frequency of a neutral gene are correlated over generations, due to associations between this gene and the selected system. Thus, the frequency of neutral genes associated to high fitness background genotypes will increase, while that of those associated to low fitness genotypes will decrease. The term  $Q$  gives the magnitude of these correlated changes or, in other words, the total influence over time of the original background genotypes. With partial inbreeding, the associations are removed at a slower rate than with random mating, even if free recombination is assumed, so  $Q$  can be much larger and  $N_e$  much smaller.

The intuitive explanation of the larger effect under small heritabilities than under larger ones can also be given in terms of  $Q$ . The fortuitous associations between a neutral allele and selected genes created each generation are partly removed by the reduction in genetic variance due to selection ( $1 - G$ ). When the heritability is small, this reduction is small ( $G$  is close to 1) and little association is lost, so that the associations and, therefore, the correlated changes in gene frequency last longer, particularly with partial inbreeding (see equation [8]).

Figure 2 represents similar ratios to those in Fig. 1 between  $N_e$  for dioecious populations with partial full-sib mating ( $\beta = 0.5, F_{IS} = 0.2$ ) and those with random

mating ( $F_{IS} = 0$ ) when the variance of family size after random selection is  $S_k^2 = 1, 2$  or 4. In our truncation selection model, this variance accounts for a different distribution of offspring available for selection. If the number of offspring per family available for selection is multinomially distributed,  $S_k^2 = 2$ , and if this distribution is less or more variable than the multinomial distribution,  $S_k^2 < 2$  or  $S_k^2 > 2$ , respectively. For example, in selection experiments it is a common practice to evaluate a constant number of offspring per family and  $S_k^2$  will be the variance of a multihypergeometric distribution.

We observe in Fig. 2 similar results, perhaps even more accentuated, than those in Fig. 1. The reduction of  $N_e$  with selection and partial inbreeding is more marked for smaller values of  $S_k^2$ . The reason is that with random mating, the effect of selection, i.e. that represented by the term  $4Q^2C^2$  in equation (7), is not very large so that the magnitude of  $S_k^2$  in the same equation has a large impact on the magnitude of  $N_e$ : the larger  $S_k^2$ , the smaller  $N_e$ . However, if  $F_{IS}$  is large, the effect of selection may become so large relative to  $S_k^2$  that there is not much difference between models with different  $S_k^2$ . Therefore, the proportional reduction of  $N_e$  with small variance of family size will be more marked than with large variance of family size.

(ii) Fixation rate of mutant genes

Table 3 shows simulated and predicted (in parentheses) values of fixation probability ( $u$ ) and times until fixation ( $t_1$ ) of an additive or recessive mutant appearing in a population with background variation with heritability  $h_0^2$ . Predictions are based on diffusion approximations using equations (1) and (3) and the predicted values of  $N_e$  from Table 2. Integrations were made numerically by Simpson's rule.

With no background variation ( $h_0^2 = 0$ ), it is predicted that the fixation probability of additive mutations is the same for both systems of mating. This can be seen by substituting  $h = 0.5$  (additive gene action) and equation (11) with  $Q^2C^2 = 0$  (random selection) into equation (6). When a background selected variation ( $h_0^2$ ) is considered, however, fixation rates are much smaller under partial inbreeding. Analogously, the benefit of partial inbreeding for recessive mutants with no background variation is lost when  $h_0^2 > 0$ . Times to fixation are also reduced with partial inbreeding.

The above results are generalized in Fig. 3. This shows fixation probabilities for mutants with selective coefficient  $Ns = 5$  and various coefficients of dominance ( $h$ ), such that  $h = 0$  is recessive,  $h = 0.5$  is additive, and  $h = 1$  is dominant. Lines without symbols refer to predictions under no background variation and are the same as in Caballero & Hill (1992*b*, fig. 1c) and similar to Charlesworth (1992, fig. 1). They show that, with increasing  $F_{IS}$ , fixation probabilities become more and more similar for any

Table 3. Simulated and predicted (in parentheses) values of the fixation probability ( $u$ , in %) and average number of generations until fixation ( $t_1$ ), of an additive or recessive mutant gene in a population with 50 breeding individuals of each sex, 150 individuals of each sex available for selection multinomially distributed and an initial background heritability  $h_0^2$

		Additive		Recessive	
		R	FS	R	FS
$h_0^2 = 0$	$u$	1.51 (1.65)	1.68 (1.65)	0.63 (0.59)	0.72 (0.87)
	$t_1$	218 (221)	188 (186)	202 (199)	178 (173)
$h_0^2 = 0.1$	$u$	1.36 (1.40)	0.81 (0.86)	0.53 (0.55)	0.57 (0.54)
	$t_1$	212 (206)	162 (133)	191 (183)	151 (121)
$h_0^2 = 0.4$	$u$	1.26 (1.19)	0.61 (0.75)	0.49 (0.50)	0.45 (0.49)
	$t_1$	202 (190)	132 (121)	172 (167)	122 (110)

Random mating (R) or maximum number of full-sib matings (FS) are carried out each generation. The mutant appears in the fourth generation of selection with initial frequency 1/600 and has a selective coefficient of  $s = 0.05$ . 30000 replicates were run for each simulated case. Standard errors of simulations range from 0.04 to 0.07 ( $u$ ) and 3 to 7 ( $t_1$ ).

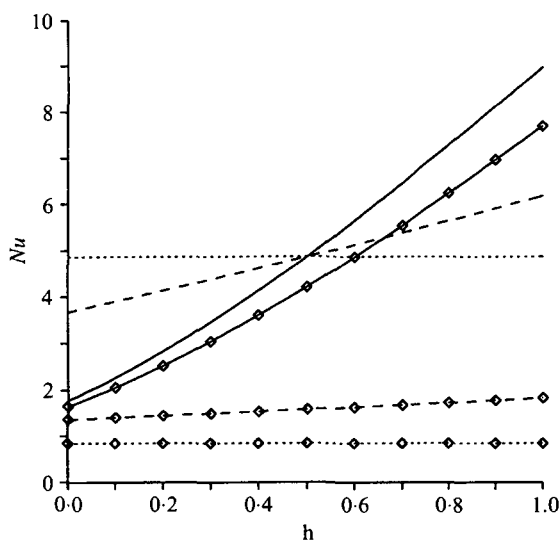


Fig. 3. Fixation probability ( $u$ ) scaled by population size ( $N$ ) of a mutant with coefficient of selection  $Ns = 5$  and coefficient of dominance  $h$ . Continuous lines: random mating of selected parents ( $F_{IS} = 0$ ). Broken lines: 2/3 of selfed offspring ( $F_{IS} = 0.5$ ). Dotted lines: 100% of selfed offspring ( $F_{IS} = 1$ ). Lines without symbols: no background variation for the selected trait. Lines with symbols: infinitesimal background variation with initial heritability 0.1 and proportion selected 1/6. Predictions used simulated values of  $N_e$ .

degree of dominance. Lines with symbols refer to the case of background selection with initial heritability 0.1 and proportion selected 1/6. The effect of selection and inbreeding is a general reduction in fixation probabilities, but especially so for large dominance values. This has the consequence that intermediate values of  $F_{IS}$  produce the same effect as  $F_{IS} = 1$  without background variation in making equal the fixation probability for any gene action.

Table 4. Predicted number of generations until extinction of a deleterious recessive allele with coefficient of selection  $s = -0.01$  and initial frequency 1/200, in a monoecious population with 100 breeding individuals, 200, 300 or 600 individuals available for selection multinomially distributed, a genetic background with initial heritability  $h_0^2$ , and random mating ( $F_{IS} = 0$ ) or a given proportion of selfed matings ( $F_{IS} > 0$ )

$F_{IS}$	$h_0^2 = 0$	$h_0^2 = 0.1$		
		$P = 1/2$	$P = 1/3$	$P = 1/6$
0	11.64	11.06	10.63	9.90
0.2	9.29	7.79	6.89	5.70
0.5	7.15	3.84	2.83	1.96
0.8	5.81	1.21	0.78	0.50

The effect of partial inbreeding and selection on  $N_e$  also produces an increase in the fixation probability of unfavourable mutants and a reduction in their time until extinction. To illustrate the latter, Table 4 shows the predicted average number of generations until extinction ( $t_0$ , obtained by means of equation [4]), for a deleterious recessive allele. With an intense selection and high proportion of selfed matings, the time until extinction is greatly reduced relative to the case with no genetic background ( $h_0^2 = 0$ ) and random mating ( $F_{IS} = 0$ ). Similar results were obtained (data not shown) for mutants with different gene action.

(iii) Mutants of large effect

In order to investigate fixation rates of mutants of large effect, for which diffusion approximations do



Table 5. Simulated fixation probability (in %) and average number of generations until fixation (in parentheses) of an additive or recessive autosomal (X-linked) mutant with a homozygous (hemizygous) effect of  $1/4$  to  $4\sigma$  in a population with 20 male and 20 female breeding individuals with five offspring of each sex available for selection per family

$2a$	$h_0^2$	Additive		Recessive	
		$R$	$FS$	$R$	$FS$
Autosomal					
$1/4$	0	8.4 (44.6)	8.0 (38.2)	1.6 (45.0)	2.7 (36.4)
	0.1	6.0 (45.2)	4.4 (37.6)	1.2 (43.2)	1.5 (34.3)
	0.4	4.9 (43.0)	2.8 (35.7)	1.1 (38.1)	1.0 (32.4)
$1/2$	0	14.7 (25.8)	15.0 (22.6)	2.0 (32.2)	4.2 (21.8)
	0.1	12.9 (26.6)	11.2 (24.8)	1.6 (31.3)	2.6 (22.3)
	0.4	10.2 (26.6)	7.0 (26.2)	1.3 (28.0)	1.9 (22.7)
1	0	27.8 (15.1)	27.8 (13.0)	2.7 (20.5)	5.8 (12.5)
	0.1	28.4 (15.6)	24.6 (14.7)	2.9 (21.1)	4.2 (14.1)
	0.4	23.1 (16.5)	17.9 (16.6)	2.0 (19.9)	2.9 (14.6)
2	0	53.3 (8.9)	53.8 (7.9)	3.1 (14.8)	6.2 (8.8)
	0.1	52.1 (9.2)	52.6 (8.6)	2.8 (14.3)	5.7 (8.6)
	0.4	48.7 (9.8)	49.0 (10.0)	2.7 (14.1)	4.8 (9.8)
X-linked					
$1/4$	0	9.9 (33.9)	10.1 (30.9)	6.0 (33.7)	6.1 (31.4)
	0.4	5.3 (37.6)	2.6 (36.4)	2.8 (38.1)	1.7 (31.0)
2	0	64.6 (7.1)	66.4 (6.8)	29.7 (8.9)	29.9 (7.8)
	0.4	62.1 (8.6)	61.4 (9.8)	18.3 (10.8)	16.7 (11.2)

The population has initial heritability  $h_0^2$ . 5000 replicates were run for each case. Standard errors of fixation probability range from 0.15 to 0.70. Those for time to fixation range from 0.02 to 1.80.

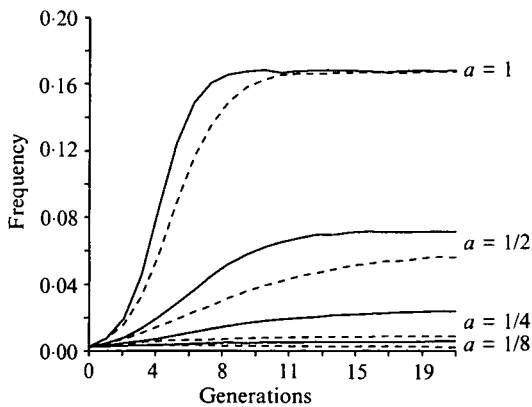


Fig. 4. Average frequency (5000 replicates) of a lethal recessive mutant with an effect of  $a$  phenotypic standard deviations in the heterozygote, appearing in a population with 40 selected parents (half of each sex) out of 200 scored. An infinitesimal background heritability of 0.1 is assumed in the initial generation. Continuous lines: random mating of selected parents. Broken lines: maximum possible number of matings between full sibs (about one half).

not hold, stochastic simulations were used. Table 5 shows fixation probabilities and times to fixation (in parentheses) for an autosomal or X-linked mutant. For small or intermediate effect ( $2a$ ), say up to 0.5 or

$1\sigma$ , fixation is a long-term process which requires a large number of generations (see average times to fixation in table) and is therefore dependent on the effective size of the population. The conclusions reached in previous sections can, therefore, be approximately applied for this type of mutant. When the mutant effects are very large, however, fixation gets faster and the dependence on the effective size is diminished. Thus, for genes of very large effect, say more than  $1\sigma$ , fixation rates are less dependent on the background heritability. For mutants with substantial effect on the heterozygote (additives or dominants), fixation rates are also independent of the system of mating while, of course, partial inbreeding increases the fixation rate of autosomal recessive mutants of very large effect but not that of X-linked mutants. Analogous conclusions can be reached for times to fixation. For autosomal recessive mutants of very large effect, times to fixation will be reduced by the inbred matings, but for autosomal additive or X-linked mutants the system of mating will have little or no effect.

The effect of partial inbreeding and selection was also studied for the case of lethal recessives with a heterozygous effect on the selected trait. Figure 4 shows the average frequency of such a mutant appearing in a population with background heri-

tability 0.1. The figure shows the average frequency each generation over 5000 replicates and, therefore, for a given generation includes replicates in which the lethal has been lost or it is still segregating. The average equilibrium frequency of the lethal in the replicates in which it is still segregating is the maximum possible value for a lethal (1/3) only when the effect is larger than about  $1\sigma$ . Equilibrium frequencies for effects of 1, 0.5, 0.25 and  $0.125\sigma$  were 0.31, 0.27, 0.19 and 0.12 with random mating, and 0.31, 0.26, 0.13 and 0.08 with partial full-sib mating, respectively. The figure shows that for lethals with effects of  $1\sigma$  or more there is no difference between random mating or partial full-sib mating in the final overall frequency of the lethal, although the final equilibrium value is reached sooner in the latter case. For smaller effects of the lethal, however, there is a higher chance of loss and lower final overall frequency of the lethal under partial inbreeding.

## 7. Discussion

### (i) Effective population size

Effective population size is reduced under selection due to correlated changes in allele frequency over generations caused by associations between the neutral genes under study and the selected genes (Robertson, 1961). These associations occur even in the absence of linkage but are larger if this is tight (N. H. Barton, unpublished results; E. Santiago, unpublished results). The association between neutral and selected genes is also increased by partial inbreeding, such as partial selfing (Charlesworth *et al.* 1993) or partial full-sib mating (Santiago & Caballero, 1995). In this paper we have quantified the effect of partial inbreeding on effective size under a model of truncation selection on a quantitative trait controlled by an infinitesimal model of gene effects. We have derived expressions for approximate asymptotic parameters under truncation selection with the infinitesimal model for the cases of partial selfing and partial full-sib mating, which allows us to make predictions of the effective size under these situations.

Predictions seem to be quite accurate for a wide spectrum of parameter values. However, underestimations occur when partial inbreeding is close to 100% and the heritabilities are small. This occurs because, in this situation, the value of  $Q$  becomes very large and sensitive to errors in the predictions. Moreover, a large  $Q$  means that many generations should pass before the associations between neutral and selected genes disappear, what can only be detected after many generations and with populations of very large size.

With the usual pressures of truncation selection carried out in breeding schemes, a clear reduction in effective size under partial inbreeding relative to the case of random mating is predicted. This reduction is

shown to be particularly high for small amounts of genetic variation. This occurs because, for low heritability of the selected trait, the amount of variation which is lost each generation by selection is small and, accordingly, the association between neutral and selected genes is maintained for a longer period of time.

An experimental evaluation of this effect was performed by selecting an initially isogenic line of *Drosophila melanogaster* for increased and decreased abdominal bristle number for 40 generations, using two systems of mating: random mating of selected parents or maximum possible number of full-sib matings (Merchante *et al.* 1995). The only selected genetic background variation present in the lines was that due to the appearance of spontaneous mutations. It was shown that a background heritability as small as 3% strongly reduces the effective size under partial full-sib mating relative to random mating, as predicted by theory.

Predictions of effective size of Santiago & Caballero (1995) and this paper refer to a model of truncation selection with infinitesimal gene effects. The values of  $C^2$  and  $G$  have been derived for this model. Now assume a general but simplistic model where the fitness of individual  $i$  is  $w_i = 1 + f_i + e_i$ , where  $f_i$  is the additive genetic value for fitness and  $e_i$  is an uncorrelated environmental deviation. Let  $m_i$  be the  $i$ th moment of the distribution of additive genetic values for fitness. Assume that before selection  $E[f_i] = m_1 = 0$ ,  $E[e_i] = 0$  and  $E[w_i] = 1$ , and that the equilibrium additive variance for fitness ( $E[f_i^2] = m_2$ ) is maintained constant over generations due to, for example, mutation–selection balance. (Note that  $m_2$  refers to fitness of individuals rather than families and, therefore,  $C^2 = m_2/2$ .) After selection the expected increase in fitness is  $E[w_i f_i] = E[(1 + f_i + e_i)f_i] = E[f_i + f_i^2 + f_i e_i] = m_2$ , in agreement with Fisher's Fundamental Theorem. The additive genetic variance after selection is  $E[w_i(f_i - m_2)^2] = E[(1 + f_i + e_i)(f_i^2 + m_2^2 - 2f_i m_2)] = m_2 - m_2^2 + m_3$ . Thus, the proportion of additive variance remaining after selection is the ratio of the variance after selection to that before selection  $G = (m_2 - m_2^2 + m_3)/m_2 = 1 - m_2 + m_3/m_2$ .

As an illustrative example, let us assume that the additive variance for fitness is  $m_2 = 0.1$  and there is normality of additive fitness values, so that  $G = 0.9$ . From (8),  $Q = 2/(2 - G) = 1.82$  for random mating and  $Q = 2/[2 - G(1 + \beta)] = 10$  for complete selfing ( $\beta = F = 1$ ). Replacing  $C^2$  by  $m_2/2$ , equation (11) gives  $N_e = N/[(1 + F_{IS})(1 + Q^2 m_2/2)]$ , and substituting,  $N_e = N/1.16$  for random mating and  $N_e = N/12$  for complete selfing, so the latter is about 10% of the former. This shows how severely complete selfing can reduce the effective size even with loose linkage.

(ii) *Response to selection from new mutations*

The reduction in effective size brought about by partial inbreeding and selection is responsible for a reduction in the fixation probability and times until fixation of favourable mutations (Charlesworth, 1994; Peck, 1994; this paper; see also Barton, 1995). Thus, the benefits of partial inbreeding in increasing the fixation rate of recessive mutants predicted by previous papers (Caballero *et al.* 1991; Caballero & Hill, 1992*b*; Charlesworth, 1992; Pollak & Sabran, 1992) no longer hold, except for the case of mutants of very large effect on the selected trait, for which fixation is a short term issue with little dependence on  $N_e$  (see Table 5).

Charlesworth (1992) discussed the effects of partial inbreeding on the distribution of dominance coefficients of fixed mutations in natural populations. As with highly selfed populations ( $F_{IS} \approx 1$ ) the fixation probability of a mutation is the same for any coefficient of dominance, the spectrum of favourable mutations fixed by selection should be close to that for newly arising mutations, in contrast to what happens under random mating (see Fig. 3). The same conclusion can be reached when we consider background selection, but this is now extended to intermediate levels of selfing, because background selection reduces proportionally more the fixation rates of more dominant mutations.

Pollak & Sabran (1992) discussed the effects of partial selfing on the selection response to a quantitative trait for which there is additive gene action. They arrived at Wright's (1969, pp. 244–245) result that in a population with an equilibrium value of  $F_{IS}$  the response to one generation of selection is  $(1 + F_{IS})$  times that in a random mating population. They also showed that the selection plateau is  $2N_e$  times the response in the first generation, in agreement with the result obtained by Robertson (1960) for random mating populations. They were considering the effective size with random selection,  $N_e = N/(1 + F_{IS})$  in the particular case of multinomial distribution of offspring number and, therefore, they concluded that in this case the initial response in a partially selfed population is  $(1 + F_{IS})$  larger than in a random mating population but the final limit is the same. The results of the present paper imply that the second prediction is no longer valid as  $N_e$  will be generally smaller than  $N/(1 + F_{IS})$ , as shown by equation (11). For the range of parameters investigated in Table 1, we can observe that in no case is the product  $N_e(1 + F_{IS})$  larger under partial selfing ( $F_{IS} > 0$ ) than under random mating ( $F_{IS} = 0$ ) and, therefore, the limiting response under partial selfing for these parameter values will always be smaller than under random mating even though initial responses are larger. These conclusions only apply, of course, to an additive infinitesimal model. Results for models with dominance might be very different but predictions of covariances of relatives are

then much more complicated (Wright, 1988). Hayashi & Ukai (1994) give an expression to predict the mean genotypic value under truncation selection with the infinitesimal model in a completely selfed population but where dominance as well as additive models without epistasis can be fitted.

(iii) *Elimination of lethals and detrimental*

The reduction in effective size caused by the joint effects of inbreeding and selection drastically reduces the times until extinction of deleterious mutations, but slightly increases their fixation probability (Charlesworth *et al.* 1991; Table 4). Deliberate inbreeding has been suggested as a way of purging a population of deleterious genes (see e.g. Hedrick [1994] and references therein) because it is generally accepted that deleterious recessives and, particularly, lethal recessives, will be strongly selected against in partial inbreeding systems (Lande & Schemske, 1985). In *Drosophila*, for example, it seems that about half the genetic load is due to nearly recessive lethals and half is due to partially recessive detrimental genes of much smaller effects (Simmons & Crow, 1977). Under artificial selection, however, detrimental and lethal alleles might have a large effect on the selected trait (see e.g. Yoo, 1980; López & López-Fanjul, 1993; Merchante *et al.* 1995) and their elimination by inbreeding will depend on the magnitude of this effect. In the particular design investigated in Fig. 4 it is shown that even the maximum number of full-sib matings each generation (about half) is not efficient in eliminating lethals with effect above  $1\sigma$  or so. Only lethals with effects smaller than that will be more effectively removed or maintained at lower frequencies with inbreeding.

This selective elimination of lethals by inbreeding, however restricted, may have some advantages in selection schemes. Lethal recessives with effects on the selected trait, maintained in artificially selected populations at high frequency, not only have an impact on the fitness of their carriers but also have other consequences. On the one hand, selecting for lethal heterozygotes produces a reduction of the probability of losing lethal alleles at other loci that are in linkage disequilibrium with the first, irrespective of their effect on the selected trait (Madalena & Robertson, 1975; García-Dorado & López-Fanjul, 1983). On the other hand, by maintaining lethals at high frequency, the fixation rate of other mutations is decreased by reducing their effective selection intensity (Madalena & Robertson, 1975). This is illustrated in Table 6, which shows fixation probabilities for neutral mutations with an effect on the selected trait of  $1/8$ ,  $1/2$  or  $2\sigma$ , appearing in a selected population where a lethal gene with effect  $L\sigma$  is segregating at its equilibrium frequency. The example is the same as that for Table 5 and Fig. 4 and follows the experimental design of Merchante *et al.* (1995). The

Table 6. Fixation probability (in %) of a mutant with an effect of 1/8, 1/2 or 2 $\sigma$  and neutral for fitness, appearing in a population with 20 male and 20 female breeding individuals with five offspring of each sex available for selection per family, where a lethal recessive with effect  $L\sigma$  is segregating at equilibrium frequency (*freq*)

L	freq	Add			Rec			Dom		
		1/8	1/2	2	1/8	1/2	2	1/8	1/2	2
—	—	3.8	15	53	1.1	1.9	3.4	7.3	30	87
1/4	0.19	3.6	15	53	1.0	2.1	3.3	7.3	29	87
1/2	0.27	3.4	14	52	1.0	2.1	3.5	7.1	28	86
1	0.31	3.2	13	48	1.1	2.1	3.3	6.5	26	82
2	0.33	3.0	12	43	1.0	2.0	3.2	5.9	23	71
4	0.33	3.1	12	39	0.9	1.9	3.2	5.7	22	60

The population has initial heritability  $h_0^2 = 0$ . 20000 replicates were run with mutants of effect 1/8, 10000 replicates otherwise. Standard errors range from 0.1 to 0.3.

table shows that the fixation probability is reduced for dominant and additive mutants by up to 20–30% but very little for recessive mutations. The expected effect of a lethal of very large effect segregating at frequency 1/3 in the population would be to reduce the fixation rate of genes with effect on the heterozygote (additives or dominants) by 1/3, because non-carriers of the lethal will never be selected. Recessive mutants, however, behave like neutral mutants in the initial generation (when it is more likely that the mutant will be lost) and, therefore, its fixation rate is little or not affected by the presence of the lethal.

The joint effects of partial inbreeding and background selection investigated in this paper mostly refer to a model of artificial selection on quantitative traits. Obviously, there are similar consequences for different models such as those referring to populations under natural selection (Charlesworth *et al.* 1993). However, further research is necessary to investigate the effect for other models of selection such as, for example, stabilizing selection.

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