Strategies for increasing fixation probabilities of recessive mutations

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Summary

Fixation probabilities and mean times to fixation of new mutant alleles in an isogenic population having an effect on a quantitative trait under truncation selection were computed using stochastic simulation. A variety of population structures and breeding systems were studied in order to find an optimal design for maximizing the fixation probability for recessive genes without impairing that for non-recessives or delaying times to fixation. Circular mating or cycles with repeated generations of close inbreeding alternating with combination of the families proved to be very inefficient. The most successful scheme found, considering fixation probabilities and times to fixation jointly, was to practise individual selection and mate full sibs whenever possible, otherwise mate at random. The benefit was directly proportional to the number of full-sib matings performed, which, in turn, almost exclusively depended on the number of selected individuals with very little effect of selection intensity or magnitude of gene effects. Fixation rates could be well approximated by diffusion methods. When selection was practised in only one sex and, therefore, the proportion of full-sib matings could be varied from zero to one, maximizing the amount of full-sib mating was found to maximize fixation probability, at least for single mutants.

1. Introduction

Previous analyses of the effect of new mutations on long-term response to artificial selection have shown that asymptotic responses from fixation of recessive genes are much lower than those from additive or dominant genes of the same effect in homozygotes, because the favourable recessive mutants are rarely fixed (Hill, 1982). Moreover, they are probably not a very common feature in traits of economic importance in animals, at least with respect to standing variation. Much less attention has therefore been paid to their contribution to selection response. However, some genes of large effect have been found to be recessive in several selection experiments (e.g. López-Fanjul & Caballero, 1990). As a first approach to the problem, fixation probabilities and times to fixation of single mutants in isolation are considered. It seems reasonable, therefore, to seek an appropriate method for increasing their fixation rate without reducing that for additive or dominant genes. This can be done by increasing the amount of local inbreeding, for example by subdividing the population or by mating close

relatives, which leads to a greater probability of producing the homozygous mutant genotype.

The effects of subdividing or structuring a population with a view to improving the response to selection have been investigated in several studies, though mostly for additive genes. Robertson (1960) showed that for unlinked additive genes subdivision and subsequent selection from the cross of all the sublines has the same limit as a single large population though it takes longer to attain. Maruyama (1970) generalized this result for additive genes, finding that any subdivision of a population into partially isolated colonies gives the same fixation probability, provided that selection and sampling occur separately in each colony and that no change in mean gene frequency in the whole population occurs when the subdivision is made. If intense selection between lines is practised, the latter condition is unfulfilled, however, and there is a reduction in the asymptotic response for additive genes compared to the single population, especially with low initial gene frequency (Madalena & Hill, 1972). This has been generally observed from experimental work (see López-Fanjul, 1989, for a review) and is in agreement with the observation that selection of whole families on family mean leads to lower fixation rates than other selection schemes (Hill, 1985).

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For recessive genes it is possible to obtain some first approximations. Assuming for simplicity that the effective population size equals the population census (*N*), the probability of fixation of a recessive mutant gene with selective advantage *s* is approximately $\sqrt{(2s/\pi N)}$ for large *Ns* (Crow & Kimura, 1970, p. 427). In a population subdivided into *n* such lines of size *N/n* with very low migration rates among lines, this probability can be approximated by $\sqrt{(2sn/\pi N)}$ again for large *Ns* (Gale, 1990, p. 180–181, following an equation obtained by Slatkin, 1981). Therefore the rate of fixation of a completely recessive favourable gene is increased with the subdivision by a factor of $\sqrt{n}$. Robertson (1952) demonstrated that for recessive genes at low initial frequency the genetic variance within lines may increase with initial inbreeding and, therefore, population subdivision can produce higher rates of response. With the same model, Madalena & Hill (1972) found that a higher limit can be reached from selection between sublines than with a single large population. However, any subdivision of the population will lead to an increase in the time to fixation, especially when the migration rate is small (Slatkin, 1981). It is therefore desirable to find a method which does not delay too much times to fixation at the expense of a reduced fixation probability. Schemes involving short periods of subdivision and reconstitution of the population or permanent subdivision with high migration seem, therefore, better than permanent subdivision with low migration. Between-line selection should be avoided due to its negative effect on fixation probability for additive genes referred to above, but it is far from obvious *a priori* which procedure would be most appropriate. An alternative to subdivision would be to maintain a large undivided population in which selection is practised but, instead of random mating, relatives are mated when available. This structure would be qualitatively different from the classical subdivision structure in which the sublines are maintained for periods with or without migration even if they do not carry the desirable recessive gene and its spread to the whole population may be slow depending on the rate of migration. In an undivided population with mating between relatives, however, inbreeding occurs every generation thereby increasing the probability of homozygosity of the recessive allele, but those individuals carrying it are more likely to leave progeny to the next generation, thereby accelerating the spread of the gene. A delay in the time to fixation would not, therefore, be expected, but it is not obvious how much fixation rates would be increased compared to population subdivision structures for genes of large effect. Pollak (1988) estimated fixation rates of slightly advantageous mutants.

In the present study, some of these alternative schemes are compared by stochastic simulation with a non-structured population in order to ascertain how they influence fixation rates and times to fixation both

of recessive and of additive mutant genes, since it is to be hoped that schemes satisfactory for recessives are still so for additive genes.

2. Methods

(i) *Simulation procedure*

The following mating structures were investigated and, for reference, are listed in Table 1.

Undivided population with random mating. Each replicate consisted of a diploid population of *T*/2 individuals of each sex isogenic at a single locus. A mutant allele with effect *a*, measured as the difference between the homozygotes in environmental standard deviations, was randomly assigned to one individual. Phenotypic values were computed by adding a standardized random normal deviate with mean zero and unit variance to each genotypic value. Each generation, truncation selection with a range of selection intensities was carried out and the individuals of each sex with the best performance were mated in pairs at random to generate a new population of *T* individuals with family sizes either multinomially distributed (UMR) or constant (UCR). Schemes involving mass mating (i.e. when multiple mating between individuals was allowed) proved to be nearly identical to UMR both in fixation rates and times to fixation and, therefore, are not shown. Simulation was continued until the mutant allele was fixed or lost. Fixation probabilities and average times to fixation were computed by carrying out 10000 replicates for each genetic model analysed: additive or recessive gene action with effects $a = 0.25$ or 1 environmental standard deviations.

Undivided population with mating between relatives. (*a*) Selection was practised in the population as a whole, but mating between selected individuals was not at random. Instead, full sibs were mated whenever available, otherwise following the random mating programme. For example, if two males and one female were selected from a family, one of the males was chosen at random and mated to his sister and the other was outbred at random. These schemes are abbreviated UMFS and UCFS for cases of multinomial or constant size, respectively.

(*b*) A similar structure was investigated in which selection was practised in only one sex and, therefore, the number of full-sib matings performed could be varied. For a specified number of the selected individuals a full sib was sampled at random for mating, and for the rest an individual was sampled from a different, randomly chosen family. Rates and times to fixation of single mutants were obtained for cases involving none to all full-sib matings. Favourable dominant mutants were also analysed in this scheme for illustration.

Subdivided populations. (*a*) Cycles of selection within families and individual selection in the complete population: As the maximum subdivision of a

Table 1. *Brief description of the population structures*

Populations	(Selection always performed in the complete population)
Undivided	
UMR	Mating pairs at random; multinomial distribution of family size
UMFS	Mating pairs of full sibs when available, at random otherwise; multinomial distribution of family size
UCR (UCFS)	As UMR (UMFS) but with constant family size
Subdivided	
WFI2	Cycles of three generations with two of selection and mating within families and one of selection in the complete population, mating in pairs at random to reconstitute the families
WF2	Cycles of three generations of selection within families, first and second mating within families, third, mating in pairs at random of the selected individuals of all families
WFI5 (WF5)	As WFI2 (WF2) with cycles of six generations instead of three
WFVFS	Selection within families and mating full-sib pairs or at random with different proportions
CM	Selection within families and circular mating pairs of selected individuals of consecutive families

population comes from sublines of minimum size, the analysis degenerated into a subdivision of the population into families. Therefore the initial population was subdivided in $T/4$ families, each with two males and two females. Phenotypes were assigned as above and the best male and female were selected in each family and mated to generate four offspring again. This selection within families was conducted for two (WFI2) or five (WFI5) generations. To complete the cycle, one generation of individual selection of the best 50 % was performed from among the offspring of all the families. The best $T/4$ males were randomly and individually mated to the best $T/4$ females to generate again the $T/4$ families and begin a new cycle. The mutant was assigned initially to different generations of the first cycle with equal frequency and for each case an equal number of replicates was carried out.

(*b*) Cycles of within-family selection with full-sib and random mating: This scheme was similar to the previous but within-family selection was performed in all generations. In each cycle, two (WF2) or five (WF5) generations were carried out in which the two selected full sibs of each family were mated and in the final generation the selected individuals of all families were mated in pairs at random to set up a new cycle. The remainder of the procedure was identical to (*a*).

(*c*) Within-family selection with a varying proportion of full-sib matings (WFVFS): This breeding structure was used to investigate the effect of a varying proportion of full-sib matings every generation. In this case, within-family selection was performed in all generations but each selected male was mated to his sister with a certain probability, otherwise to a female

from another family. The procedure was done for a range of probabilities of full-sib mating.

(*d*) Circular mating (CM): Subdivision and selection within families were carried out as in the cyclical mating schemes but every generation the selected male of a family was mated to the selected female of the following one in order to generate a new family. This procedure would lead to maximum effective sizes in the long term (Kimura & Crow, 1963) but, at the same time, it could generate inbreeding in the early stages which could be useful for increasing the frequency of recessive genes.

(ii) *Predictions with the diffusion approximation*

The probability of fixation $u(1/2T)$ of a gene present in single copy can be calculated following diffusion methods as

$$u(1/2T) = \frac{\int_0^{1/2T} G(x)\,dx}{\int_0^1 G(x)\,dx},\qquad(1)$$

where

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

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 schemes involving undivided populations with either random or full-sib mating whenever possible and random mating otherwise can be equivalently

expressed in terms of populations in which the genotypic frequencies are in approximate Hardy–Weinberg proportions in the former scheme, or have a deviation from this by a quantity which depends on the number of excess full-sib matings, in the latter.

In the general case the relative fitnesses and frequencies with respect to the mutant gene A' are as follows

Genotype	Fitness	Frequency
AA	1	$(1-x)^2 + x(1-x)f$
AA'	$1+hs$	$2x(1-x)(1-f)$
$A'A'$	$1+s$	$x^2 + x(1-x)f$

where h denotes the coefficient of dominance and f the deviation from Hardy–Weinberg proportions as the correlation between uniting gametes due to non-random mating (the f_{IS} defined in Crow & Kimura, 1970, p. 105). For the random mating scheme this value would be, in fact, slightly negative due to the finite population size (Robertson, 1965; Crow & Kimura, 1970, p. 55).

The mean change in gene frequency can therefore be approximated by

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

and if s is small (as is assumed in the diffusion approximation) the variance of this change is obtained from the formula appropriate to neutral genes,

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

where N_e is the effective population size. Therefore, by substituting (3) and (4) into (2) and integrating, equation (1) can be evaluated with

$$G(x) = \exp(-2N_e sx[2h-2xh+x$$
$$+f(2-x-2h+2xh)]). \quad (5)$$

From (5) it can be seen that a deviation from the Hardy–Weinberg proportions in the recessive case is equivalent to partial recessivity. Thus $G(x)$ equals $-2N_e sx[x+f(2-x)]$ with complete recessivity, and $-2N_e sx[x+h(2-2x)]$ with $f = 0$, but degree of dominance h. So, for mutant genes with low initial frequency, the fixation probability for a recessive when there is inbreeding to the extent f must be approximately the same as for a gene with the same effect in the homozygote but degree of dominance h and random mating. The numerator and denominator in (1) were integrated numerically by Simpson's rule. The values of f were obtained by including in the simulation a gene with no effect on the trait and initial frequency 0·5 in Hardy–Weinberg proportions, and calculating in every replicate and generation in which the gene is segregating, the relative deviation of its observed frequency in homozygosis from its expectation with the Hardy–Weinberg assumption. These calculations were based on 5000 replicates where no mutant gene was included. The values obtained from all the replicates and generations (except the first three generations) were averaged. Estimates of the effective

population size were computed measuring the asymptotic rate of decline in heterozygosity of this neutral gene. The selective values were approximated by iu where i, the selection intensity (standardized selection differential), was calculated by means of Burrows' equation (1972) (although this relationship becomes invalid for values of s larger than about 0·5 (Latter, 1965)).

3. Results

(i) Comparison of schemes

Fixation probabilities and mean times to fixation computed by stochastic simulation for the alternative schemes are shown in Table 2 for two values of gene effect and population sizes but, for simplicity, only one proportion selected (50 %). The schemes of subdivided populations with cycles of two or five generations of selection within families and one generation of individual selection (WFI2 and WFI5, respectively) yielded similar fixation rates for additive genes to those from the undivided random mating population (UMR) in accordance with theory (Maruyama, 1970), but only for the smaller gene effect. For the larger effect there was a reduction which increased with the number of generations of full-sib mating in the cycle. This was shown to be a consequence of simulating two sexes, because similar simulations carried out with a haploid model or a diploid model with only one sex and selfing permitted (using differences in fertility instead of truncation selection) did not have such reductions (data not shown). The reason is that with only two individuals of each sex per family the intensity of selection applied by selecting the best of each sex is proportionately smaller than the intensity applied over the undivided population, so the more generations of selection within families, the greater the reduction. Likewise, subdivision of the population into larger lines yielded smaller reductions (data not shown). For the recessive case these schemes (WFI2 and, especially, WFI5) gave a considerable increase in the fixation probability but also, as in the additive case, the expected substantial increase in the mean time to fixation. Cycles with more than five generations of full-sib mating produced additional delays and insignificant increases in the fixation rate.

The circular mating scheme (CM) produced a reduction of the fixation probability in the additive case with respect to UMR and an increase in the recessive case only with large population size. In all cases, the mean time to fixation was notably longer. There are two reasons: firstly, the appearance of homozygotes is delayed. In fact, even with only two families, homozygotes could not be present until the third generation, while this is possible in the second generation with full-sib mating or random mating. For genes with relatively large effect the 'decisions' about their fate are essentially taken in the early

Table 2. *Fixation probabilities[a]* (%) *and mean number of generations to fixation* (*in parentheses*) *of a single mutant gene with effect a phenotypic standard deviations in an isogenic population with T scored and N selected individuals.* (*See Table* 1 *for a description of the different population structures.*)

	$T = 32, N = 16$				$T = 128, N = 64$			
	Additive		Recessive		Additive		Recessive	
				$a = 0.25$				
UMR	9·6	(45)	3·9	(39)	9·4	(75)	2·1	(79)
WFI2	8·8	(56)	4·4	(51)	8·7	(97)	3·2	(100)
WFI5	9·2	(76)	5·8	(71)	9·4	(129)	4·8	(129)
WF2	7·1	(121)	4·8	(115)	7·1	(244)	3·7	(247)
WF5	6·8	(164)	5·5	(160)	6·7	(345)	5·3	(348)
CM	7·0	(107)	4·0	(94)	7·1	(373)	4·2	(400)
UMFS	9·3	(40)	4·8	(35)	9·5	(65)	3·6	(64)
UCR	11·8	(49)	4·8	(45)	12·2	(80)	2·7	(89)
UCFS	12·8	(41)	6·8	(37)	13·2	(65)	6·2	(63)
				$a = 1$				
UMR	33·9	(19)	6·7	(20)	34·9	(26)	3·8	(38)
WFI2	32·3	(25)	9·4	(26)	32·9	(35)	6·9	(43)
WFI5	30·9	(34)	12·6	(34)	31·6	(47)	11·0	(51)
WF2	27·4	(75)	10·1	(79)	27·6	(88)	10·4	(99)
WF5	27·7	(77)	13·3	(81)	27·3	(123)	13·1	(135)
CM	27·4	(48)	7·9	(52)	27·3	(138)	8·2	(182)
UMFS	33·7	(18)	8·8	(17)	34·6	(23)	7·5	(25)
UCR	40·8	(20)	8·2	(22)	42·5	(27)	4·5	(43)
UCFS	41·2	(17)	13·2	(16)	42·5	(22)	12·4	(21)

[a] Standard errors of fixation probability with 10000 or 12000 (cycles) replicates:

u (%)	2	4	6	10	20	40
s.e. (%) = $\sqrt{(u(1-u)/\text{no. of replicates})}$	0·1	0·2	0·2	0·3	0·4	0·5

generations and so the delay is important. Secondly, the initial increase in inbreeding which could overcome the effects of the delay is only apparent when the population size is large. Actually, the coefficient of inbreeding generated by, say, five generations of CM is 0·121 for both population sizes studied while that generated by random mating would be approximately 0·143 and 0·075 for 16 and 64 selected individuals, respectively. It is clear that the CM might be better only with a large population size, but the huge number of generations required on average to reach fixation removes any possible utility of the scheme.

The cycles in which only within-family selection was involved with generations of full-sib mating and random mating (WF2 and WF5) gave substantially smaller fixation rates than UMR in the additive case, and though the benefit in the recessives was a little better than with WFI2 and WFI5, there was also an additional delay in times to fixation.

The scheme in which individual selection is practised in an undivided population with multinomial distribution of family size and crossing full sibs whenever possible (UMFS) was not worse for additive genes and clearly better for recessive genes than the random scheme (UMR), the benefit increasing with increase in gene effect and especially with increase in population

size. Moreover, the time to fixation was always reduced. With a constant distribution of family size, fixation probabilities were of course greater and the effects of full-sib crossing were even enhanced. In most cases UCFS gave higher fixation rates than UCR in the additive case and the benefits for the recessive case were proportionately larger than with the multinomial family size because the number of full-sib matings performed was larger. The time to fixation was generally the shortest achieved among all methods. Clearly, the schemes involving individual selection and full-sib mating when possible were the best with respect to both fixation rates and times to fixation, and this was especially so for the constant family size. So far, subdivided populations have been compared to an undivided population with random mating and multinomial distribution of family size (UMR) as this is more typical of a random mating population. The subdivided populations studied, however, involved in all cases constant family sizes and therefore their results should be better compared to UCR rather than UMR. In that case, the observed advantages of UCFS over the subdivided population schemes would be even greater.

The UCFS scheme was analysed in more detail and the results for recessive alleles and different combin-

Table 3. *Fixation probabilities (u, in %)[a] of a recessive mutant gene with effect of a phenotypic standard deviations in an isogenic population with individual selection (T scored and N selected) and constant family size*

		a = 0·25				a = 1				f	N_e
		u	NFS	% Δ	DA	u	NFS	% Δ	DA		
T = 16	R	6·6	1·0	—	6·3	10·6	1·0	—	10·7	−0·070	10·4
N = 8	FS	7·4	2·6	12	7·7	13·4	2·7	26	17·8	0·103	9·2
T = 64	R	2·1	1·0	—	2·0	3·1	1·1	—	3·2	−0·065	8·8
N = 8	FS	2·4	2·2	14	2·4	4·2	2·4	35	5·3	0·039	7·9
T = 32	R	4·8	1·0	—	4·5	8·2	1·0	—	8·2	−0·034	20·5
N = 16	FS	6·8	5·1	42	7·1	13·2	5·2	61	19·8	0·191	18·4
T = 128	R	1·5	1·0	—	1·4	2·4	1·1	—	2·5	−0·032	16·9
N = 16	FS	2·1	4·3	40	2·2	3·6	4·5	50	5·9	0·115	14·7
T = 128	R	1·9	1·0	—	1·9	3·7	1·0	—	3·5	−0·016	34·8
N = 32	FS	3·6	8·8	89	3·8	6·5	9·0	76	11·9	0·179	31·5
T = 128	R	2·7	1·0	—	2·4	4·5	1·0	—	4·6	−0·008	85·2
N = 64	FS	6·2	20·1	130	6·9	12·4	20·4	175	23·0	0·269	75·0

NFS = mean number of full-sib matings; % Δ = increase in the fixation probability from making full-sib matings (FS) compared to random mating (R); DA = diffusion approximation to fixation probability (%); f = measurement of the deviation from the Hardy–Weinberg proportions due to the inbreeding; N_e = effective population size computed in the simulation.
[a] Standard errors of fixation probability as in Table 2.

Table 4. *Fixation probabilities[a] ($\times 10^2$) and mean times to fixation (in parentheses) of a mutant gene with effect of a phenotypic standard deviations in an isogenic population with individual selection in one sex only*

NFS	a = 0·25				a = 1			
	Additive		Recessive		Additive		Recessive	
	T = 32; N = 16							
0	5·8	(72)	3·3	(60)	21·2	(35)	5·4	(36)
4	6·8	(55)	4·2	(49)	22·7	(27)	7·9	(25)
8	7·8	(23)	5·8	(24)	26·3	(13)	11·4	(12)
	T = 128; N = 64							
0	6·1	(131)	1·7	(127)	22·8	(49)	3·2	(64)
16	7·5	(95)	3·1	(89)	24·5	(36)	7·5	(38)
32	8·4	(39)	6·0	(38)	26·7	(16)	11·9	(16)

T = total population size; N = number of mated individuals); NFS = number of full-sib matings performed every generation.
[a] Standard errors of fixation probability as in Table 2.

ations of selection intensity and population size are shown in Table 3. In the table are also shown the average number of full-sib matings achieved in each case, the observed deviation from the Hardy–Weinberg proportions, the benefit obtained by making full-sib matings compared to random mating, the estimated effective population size and the predicted fixation rate calculated from equations (1) and (5) by inserting the appropriate parameters. The benefit depends clearly on the number of full-sib matings performed which in turn is a function of the number of selected individuals. With random mating the number of full-sib crosses was in nearly all cases equal to its expectation without selection (i.e. one). For non-random mating, the larger the number of selected individuals, the larger the proportion of full-sib matings and thus the greater the increase in the fixation probability. For a given number of selected individuals, an increase in the number scored (i.e. an increase in selection intensity) produced a very small reduction in the number of full-sib matings and accordingly, a small reduction in the benefit (although this is not observed for the N = 8 case probably due to random sampling). This can be shown by calculating the expected number of full-sib matings without selection if they are made whenever possible. For example, for 8 scored and 4 selected this number is 1·54 and for 16 scored and 4 selected it is 1·51. Also an
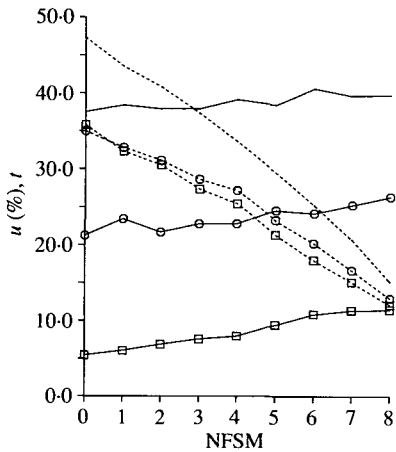
Fig. 1. Fixation probabilities (u, in %) and mean times to fixation (t, in generations) of a mutant gene with an effect in the homozygote of 1 phenotypic standard deviation in an isogenic population with individual selection in only one sex, 32 individuals scored, 16 selected, constant distribution of family size and a varying number of full-sib matings every generation (NFSM). ———, probability of fixation; -----, mean time to fixation. ·, dominance; ○, additivity; □, recessivity.
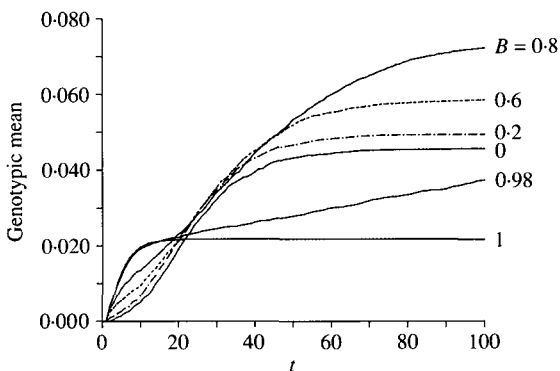

Fig. 2. Average genotypic means each generation for an initially isogenic population of 32 scored and 16 selected individuals in which a mutant gene with an effect in homozygote of one phenotypic standard deviation appears. The population is structured in 8 families of equal size and each generation within-family selection is practised and the selected male of each family is mated with his selected sister with probability B, otherwise he is crossed with a female selected in a different family.

increase in the gene effect produced only a very small increase in the number of full-sib matings. Indeed, the numbers achieved for the small gene effect ($a = 0.25$) and no selection ($a = 0$) were identical in all cases to the first decimal place.

The diffusion approximations were very accurate for small gene effect, with a slight underestimation in the random mating case and a slight overestimation for full-sib mating. For the large effect, the diffusion assumptions break down and the prediction was poorer.

(ii) *Variation in the number of full-sib matings*

The special case in which selection is practised in only one sex and, therefore, the number of full-sib matings

can be fixed each generation, is shown in Table 4 and Fig. 1 for some examples with constant family size. It is clear that the larger the number of full-sib matings, the greater the fixation rate and the shorter the time to fixation, not only for recessive but also for non-recessive genes. Table 4 also shows that the benefit increases with increasing gene effect and especially with increasing population size for recessives, but decreases with increasing gene effect for additives because the larger the effect in the heterozygote the relatively smaller would be the benefit of reaching homozygosity by inbreeding.

An alternative scheme (WFVFS) involves within-family selection in which the probability of full-sib mating, B, is varied. For an additive gene (data not shown) the rates of fixation were approximately the same for the whole range of B (except of course for $B = 1$ in which fixation occurs only in one family). For recessive genes the genotypic means plotted over generations are shown in Fig. 2. It is interesting to note that for intermediate values of B (say between 0.2 and 0.6) both limits and times to achieve them are very similar. Only when the number of full-sib matings approaches the maximum is there a large increase in the asymptotic response, though much more time is needed to reach it. Ironically, these cases are slightly better in the short term, the same or worse in the medium and much better in the long term. However, the scheme does not seem very useful from a practical point of view because large increases in fixation probabilities are only obtained at the expense of longer times to fixation.

4. Discussion

Alternative population structures and breeding schemes have been analysed with the aim of finding how to increase the fixation rate for recessive mutant genes without causing a reduction in that for additive genes or a delay in the time to fixation. The dominant case has not been dealt with because the general pattern is likely to be similar to that for additive genes and also because there are not expected to be benefits from inbreeding.

Subdivision of the population with repeated generations of selection within families and mating of full sibs leads to the expected increase of the fixation probability for recessive genes compared to that from undivided random mating populations. This increase is smaller, however, than that predicted for a population subdivided into colonies with a very low migration rate among them and large Ns, i.e. by a factor of the square root of the number of colonies. Thus, with the largest population analysed (128 individuals scored and 64 selected), the largest gene effect ($a = 1$) and the maximum number of generations without genetic flow between sublines (WFI5 or WF5), the fixation probability for recessives is increased by a factor of 2.9 or 3.4, respectively (see

Table 2). These values are clearly smaller than the limiting expectation for 32 families of $\sqrt{32} = 5.7$, probably because our schemes are equivalent to groups of colonies with relatively large migration.

The amount of gene flow required among the inbred families to allow fixation to be reached rapidly in the whole population is less clear. Selection between families has been avoided because results of previous analyses indicated that it would not be advantageous (Madalena & Hill, 1971; Hill, 1985). Crossing the selected full sibs at random (WF2 and WF5) yields a reduction in the fixation rate for additive genes because only within-family selection is practised and therefore the selection intensity is reduced. One generation of individual selection over the complete population to close the cycles of repeated generations of inbreeding (WFI2 and WFI5) gives, however, much smaller reductions in the additive case. These reductions in the case of two sexes were unexpected from the theory developed for monoecious diploid individuals with random selfing (Maruyama, 1970; Madalena & Hill, 1972). Circular mating is not of practical use due to the delay in the appearance of homozygotes and the small amount of inbreeding generated with small population sizes. In all the above cases, the times to fixation are delayed compared to the undivided population as would be expected from previous theory (Slatkin, 1981).

The most successful scheme found consists of practising full-sib matings among the selected individuals whenever possible. This results in an increase of the fixation probability for recessives without impairing that for additives. Moreover, times to fixation are shortened, implying higher response in the short term, important in most breeding schemes. The highest fixation rates are obtained using a constant distribution of family size and increase with the number of full-sib matings performed. The larger the number of selected individuals and the gene effect, the greater the benefit in the recessive case. Change in the intensity of selection has less effect but especially for large population sizes the highest fixation probability is obtained with 50 % selection, in agreement with Robertson (1960).

The full-sib mating scheme causes a change in the fixation rate due to two opposite factors: firstly, the increase in the deviation from Hardy–Weinberg proportions produces an increase in the fixation rate [equation (3)]; and secondly, the decrease in N_e reduces the fixation rate [equation (4)]. The former is, however, much more important, as can clearly be seen in Table 3: the reduction in N_e in the full-sib mating programme with respect to the random programme is about 11 % for all population sizes while the increment in fixation rates increases in proportion with the increase in f. Moreover, if we use the N_e obtained in the random scheme for, say, the case $T = 128$, $N = 64$ with $a = 1$ ($N = 85.2$, see Table 3) but the f obtained in the full-sib scheme (0.269) to calculate the diffusion

approximation [equations (1) and (5)], a value of 25.6 % is obtained, a little greater than that obtained using the parameters corresponding to the full-sib programme alone (23.0 %). However, using the value of N_e from the full-sib mating programme but the f from the random scheme ($N_e = 75.0$ and $f = -0.008$), the calculated value (4.4 %) is far from the appropriate 23.0 %, demonstrating that the positive effect of f is more important than the negative effect of N_e.

A notable feature of this pragmatic scheme is that fixation rates can be accurately predicted (at least for small gene effects) by using diffusion methods. The only parameter needed to be estimated is the effective population size. The deviation from the Hardy–Weinberg proportions in the genotypic frequencies could be approximated in the following manner. For the random mating scheme, the expected departure due to the finite population size f_r equals $-(1/8M) - (1/8F)$, where M and F are the number of reproductive males and females, respectively (Robertson, 1965). For the full-sib mating scheme, the prediction is more difficult but, fortunately, the number of full-sib matings performed (NFS) is very little affected by selection and, therefore, it can be approximated by that corresponding to no selection calculated by standard probability theory. The average number of full-sib matings in the random scheme is very close to one, with selection, hence the excess of full-sib matings is approximately NFS-1. The offspring coming from these have a departure from the Hardy–Weinberg proportions of $[(NFS-1)/(4TNM-3NFS+3)]+f_r$ (Caballero & Hill, in preparation), where TNM is the total number of matings, and this would be an approximate measure of f for the entire population. For example, with 128 scored, 16 selected and $a = 0.25$, the values of f for the random and full-sib schemes would be -0.031 and 0.118, respectively, giving diffusion approximations to the fixation probability of 1.4 and 2.2 %, respectively.

Two cases in which the number of full-sib matings could be fixed were also analysed. In the situation in which a population is maintained in families and subject to within-family selection with a variable number of full-sib matings it is shown that intermediate levels of inbreeding do not give much benefit and only very high levels of inbreeding are advantageous at the expense of longer times to fixation. Over a reasonable time-scale this scheme would not therefore be of interest.

The alternative scheme in which individual selection is done in one sex allowing a variable number of full-sib matings shows that maximum fixation rates and shortest times to fixation are achieved where all the matings are between full sibs. However, this would only be so when a single mutant was fixed or reached a high frequency before another one appeared, for there would be no chance of both being fixed unless they were present in the same family. With a small population size or with a large gene effect and therefore

with few mutations very quickly fixed, this method would be optimal. However, with larger population sizes or smaller gene effects other schemes with an intermediate number of full-sib matings and therefore allowing some gene flow between families would be more appropriate. In any case, the scheme with all matings as full sibs is an extreme of this. We have seen that using a model of recurrent mutation with free recombination, our results with selection in both sexes and full-sib mating when possible are not affected when considering the value more commonly observed for the mutational heritability (about 10^{-3}; Lynch, 1988). This value, however, would refer to the mutational heritability corresponding to an additive gene, because it is calculated from the initial variance generated by the mutant, which is zero in the case of a recessive gene in single copy. For example, with ($T = 128$, $N = 64$), constant family size, $a = 0.25$ (equal for all mutants) and a recessive model, the average fixation rates and times to fixation (in parentheses) in the steady state are 2·2 % (86) and 6·0 % (70) for the random and full-sib schemes, respectively, compared to 2·7 % (89) and 6·2 % (63) for a single mutant.

Moreover, if the mutant gene arises in a segregating population instead of an isogenic population the results also hold. This was shown by creating an infinitesimal background (Bulmer, 1980) in which the single mutant appears. The matrix of Wright's numerator relationships (Wright, 1922) was set up every generation so that the coefficients of inbreeding of parents could be calculated and taken into account in the reduction of genetic variance in the infinitesimal background (see for example Wray & Thompson, 1990, for the details of the procedure). The mutant appeared in the fourth generation of selection to avoid the effects of the initial reduction in genetic variance due to selection (Bulmer, 1971). With, for instance, $T = 32$, $N = 16$, $a = 1$ and constant family size, fixation probabilities and mean times to fixation (in parentheses) of a recessive mutant appeared in a selected population with initial heritability 0·4 were 7·3 % (26) and 12·4 % (19) for the random and full-sib programmes, respectively, compared to 8·2 % (22) an 13·2 % (16) for the same situation in an isogenic background. The benefit from the full-sib scheme as a proportion of the random scheme is approximately the same in both cases though fixation rates are slightly smaller because of the reduction in effective population size due to selection (Robertson, 1961; Gallego & Caballero, 1990; Wray & Thompson, 1990).

Selective improvement in animal breeding generally depends on additive genetic variation, but many breeding strategies in plants attempt to maximize genetic gain from non-additive variation. Some schemes involving close inbreeding with selection among inbred lines followed by line-crossing (Simmonds, 1979) are similar to some of the schemes investigated here. In animals a large amount of

variation in quantitative traits can be generated by mobilization of transposable elements, but most of the new mutations are recessive (Mackay, 1990). Its efficient utilization would therefore depend on the use of a mating scheme involving some degree of inbreeding. This paper is a first approach to the problem by examining fixation probabilities and times to fixation for single mutations in an isogenic background. The results seem to hold for recurrent mutations in simplified conditions (no linkage and no epistasis) and for single mutants appeared in an infinitesimal background. There are, however, other many related problems to be considered, for example a possible decline in reproductive fitness, inbreeding depression and selection on an index of individual and relatives' performances. Dickerson & Lindhé (1977) have shown that cycles of temporary intense inbreeding followed by crossing among inbred families with index selection are expected to yield a greater gain than that from non-inbred populations. The lowered intensity of selection of parents used to produce inbred families in alternate generations and the limited increase in total genetic variance caused by using only selected parents to produce the inbred families offers little practical benefit from the scheme, however. A reduction in fitness due to a recessive deleterious gene can reduce the selection intensity. The inbreeding will, however, allow selective elimination of such genes though it will not eliminate all of them, especially if they are only mildly deleterious. López-Fanjul & Villaverde (1989) obtained 6·5 times more response to one generation of selection for egg-to-pupa viability in a *Drosophila melanogaster* outbred population with initial inbreeding ($F = 0.25$) than without inbreeding, but this benefit was small compared to the inbreeding depression experienced in the former. Of course this would be irrelevant in an isogenic population and if applied only to the nucleus, and not the commercial (offspring) population. More detailed analysis making allowances for these and other aspects is, however, required before specific population structures in practical breeding programmes could be recommended.

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