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Patterns of the purging of deleterious genes with synergistic interactions in different breeding schemes

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Abstract The purging of deleterious genes for increasing progeny fitness and/or avoiding extinction in breeding programs, particularly with endangered species, has become of increased interest in recent years. Some studies have shown that purging can be effective only for deleterious genes of multiplicative, large effects, such as lethal or sublethal genes. In the present study, we examine the effectiveness of purging viability genes of synergistic, small effect with continuous selfing, full-sib mating, or half-sib mating, by computer simulation. A diploid breeding population with a constant progeny size of 10, 50 or 200 is simulated, one of the three breeding schemes referred to above is practiced over ten generations, and the patterns of purging, progeny survival and population extinction are examined. The rate and amount of purging generally increase with high dominance, strong synergism, high genetic load and low inbreeding. Progeny survival can increase only for a progeny size larger than 50 using schemes of mild inbreeding when there is a high level of dominance and strong synergism. The probability of extinction could greatly increase up to 100% for a progeny size of 10, but mostly is less than 10% for a progeny size larger than 50 in terms of the genetic load examined. The implications of these simulated results for purging deleterious genes of small effect in small breeding populations are discussed.

Key words Inbreeding depression · Deleterious genes · Synergism · Breeding schemes · Computer simulation

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Introduction

Knowledge of the behavior of purging deleterious genes in a population, especially one of small size, is important not only for understanding many issues in evolutionary and conservation biology (Hedrick and Miller 1992; Lynch et al. 1995) but also for the development of effective breeding schemes in breeding programs, particularly with endangered species (Templeton and Reed 1984; Ballou et al. 1995). In the breeding programs of endangered animal species, inbreeding is unavoidable as the breeding populations are usually small and, consequently, it may reduce individual survival (i.e., inbreeding depression) and affect population viability. For the general breeding programs aimed at increasing genetic gains, such as those in crops or forest trees, mating is usually constrained within a small group of selected individuals (the so-called subline) over generations. Such a practice generally results in the accumulation of inbreeding and the expression of deleterious genes, which in turn may affect the fitness of each subline. Thus, it is always desirable for breeders to take into account the behavior of deleterious genes in breeding populations in designs of effective breeding schemes. However, these designs are difficult to construct, largely because the conditions under which purging by inbreeding is effective in eliminating deleterious genes for increasing progeny fitness and/or avoiding population extinction are still poorly understood.

The effectiveness of purging can be affected by many factors such as the genetic basis of inbreeding depression, the proportion of deleterious genes segregating in breeding populations, the size and breeding history of the populations and the operational level of inbreeding. To examine the effectiveness of purging, Hedrick (1994) conducted a computer simulation of a breeding population of constant progeny size 10 with continuous full-sib mating, based on a multiplicative-fitness model of inbreeding depression, and found that inbreeding depression due to deleterious genes of large effect (such as lethals or sublethals) can be purged, but not that due to detrimental genes of small effect. This finding is supported in a study of comparing the relative effectiveness of purging among several breeding schemes (Fu et al. 1998). Less clear, however, is whether genes of small detrimental effect can be effectively purged when there is some synergistic interaction among loci. Some empirical data have suggested that such a synergism, although likely weak, exists in natural populations (see the review below). Recent theoretical studies (e.g., Charlesworth et al. 1991) have shown that a synergistic interaction can lower the number of deleterious alleles per individual and increase the mean fitness in a population. When these genes interact synergistically, their harmful effects on individual fitness increase in a synergistic manner, i.e., more harmful than that under multiplicativity, and thus the individuals carrying these synergistic viability genes could be more easily eliminated than under multiplicativity.

It is accepted that deleterious genes can interact in many ways and various forms of interaction may have different impacts on fitness. If the deleterious alleles act independently at different loci, the fitness effects of these loci multiply. For example, for an individual carrying n homozygous viability loci, each having equal deleterious effect $1 - s$, the probability of survival for the individual would be $(1 - s)^n$. Under this multiplicative fitness model, there is a linear relationship between the log of individual fitness and the number of mutations in the genome. When deleterious alleles interact synergistically between loci, the log of fitness declines at a greater than linear rate with the number of deleterious loci. In other words, the harmful effects of these deleterious loci on individual fitness increase in a synergistic manner, i.e., more harmful than that under multiplicativity. Such a synergism can lower the number of deleterious alleles per individuals and increase the mean fitness in large populations. This has been clearly shown, for example, by Charlesworth et al. (1991) in their theoretical investigation on the effects of synergism on the evolution of self-fertilization. In the literature, there are several proposed forms of synergism and they differ mainly in the weighting of heterozygous mutations by the dominance coefficient, but largely share the common property mentioned above (see Kimura and Maruyama 1966; Crow 1970; Kondrashov 1988; Sved and Wilton 1989; Charlesworth 1990). However, which form(s) of synergism occurs in nature remains unknown (Crow 1993).

There are some empirical data that indicate the existence of synergistic interactions among deleterious genes in natural populations. In his classic mutation-accumulation studies on *Drosophila*, Mukai (1969) found that synergistic interaction influencing viability occurred, but that the synergism was fairly weak. Such slight synergism was also detected in other *Drosophila* studies involving an examination of the interactions between the major chromosomes sampled from the wild with balancer chromosome techniques (see Simmons and Crow 1977 for a review). Some studies on RNA viruses (Chao 1988) and inbreeding depression in conifers (Griffin and Lindgren 1985; Woods and Heaman 1989) appeared to suggest that synergism occurred between harmful mutations. Willis (1993) conducted an experiment to examine the effects of different levels of inbreeding on fitness components in *Mimulus guttatus* and indicated that synergism existed among deleterious genes affecting pollen viability. Fu and Ritland (1996) applied a marker-based method to infer synergism for genes influencing inbreeding depression in *M. guttatus* and detected some synergistic interactions affecting viability, but not fecundity. These empirical results seem to provide evidence of a weak synergism, especially for viability, but how weak the synergistic interaction is in nature (i.e., the true distribution of the interaction magnitudes) remains to be experimentally determined (Fu and Ritland 1996).

In the present study, we have conducted a computer simulation to examine the effectiveness of purging viability genes of synergistic, detrimental effect by commonly used breeding schemes. Specifically, we consider deleterious genes that individually have relatively small effects but collectively have synergistic impacts on viability, simulate a breeding population of constant progeny sizes of 10, 50, and 200 practicing either continuous selfing, full-sib mating or half-sib mating, and examine the proportions of remaining lethal equivalents, progeny survival and population extinction over ten generations. This study should allow us a better understanding of the behavior of deleterious genes of small effect in breeding populations and provide information for the development of effective breeding schemes.

Simulation

Genetic model

We assume that each initial individual has n unlinked viability loci, each having two alleles A and a. At each locus, the three genotypes AA, Aa, and aa have relative viability values of 1, $1 - hs$ and $1 - s$, where s is the selective disadvantage of aa and h is the level of dominance. The viability of a progeny is determined by the synergistic fitness model:

$$w_i = \exp\left[-\left(\alpha n + \frac{\beta}{2} n^2 \right) \right], \qquad (1)$$

where $n = hz + y$ (the effective deleterious loci), z is the number of heterozygotes, y is the number of homozygotes, and two coefficients determine the strength of selection (α) and the degree of synergism (β/α), respectively. This model of synergism is used mainly because of its significance in the weighting of heterozygous mutations (see Charlesworth et al. 1991 for discussion); that is, mainly heterozygous mutations can be equivalent to one homozygous one. In this model, as discussed above, the effects of mutations are increasingly severe; when more of them are present in an individual, the effect of inbreeding on fitness is to cause a bigger decrease in fitness than with multiplicative fitness interactions. When $\beta = 0$, the model can approximate to a multiplicative fitness model (i.e., $\alpha \approx s$), especially when selection is weak; but with strong selection such an approximation can be severely biased. When $\beta \neq 0$, synergism exists among deleterious loci. If $\alpha = 0.01$ and $\beta = 0.02$, for example, the degree of synergism (β/α) is 2, which means that the synergistic interaction among effective deleterious loci (n) contributes to the reduction of fitness by a factor of

e^{-n^2}; the higher synergism the more it contributes to the reduction of fitness.

In this study we also assume that selection takes place at the diploid stage of the life cycle, that no mutation occurs during the period of inbreeding, that selection and dominance parameters are constant across all loci, and that no selection on other fitness components contributes to the viability of a progeny.

Breeding scheme

We examine three breeding schemes that are commonly practiced in breeding programs, i.e., continuous selfing, full-sib mating and half-sib mating. For the selfing scheme, we start with two parental individuals, at the initial generation G_0, that are mated to produce the progeny of the first generation (G_1), and one surviving progeny is then randomly chosen and self-fertilized to produce the G_2 progeny. Note that two individuals at G_0 are used for selfing simply for ease in the determination and calculation of lethal equivalents. For the full-sib mating, two individuals are selected and mated to produce the G_1 progeny. Two surviving progeny are randomly selected and mated to produce the G_2 progeny. For the half-sib mating, four individuals are selected and mated in pairs to produce two G_1 full-sib progeny. From each full-sib family, two surviving progeny are randomly chosen and mated once between two individuals (each from each full-sib family) to produce two full-sib progeny of the next generation. These breeding processes are repeated for ten generations.

Simulation procedure

For the selfing breeding scheme, simulation starts with two unrelated individuals for each replicate. For these two individuals, one of the four initial alleles at each locus is randomly designed to have a selective disadvantage as a homozygote; the other three alleles have no disadvantage and are selectively equivalent. From each mating, progeny of given size are generated. For each progeny, the genotype is determined, locus by locus, by randomly choosing (with equal probability) one of two gametes from each of two individuals to form a zygote. For each genotype, the numbers of homozygotes and heterozygotes of deleterious alleles are counted over loci, from which the number of deleterious alleles is calculated and the relative viability of a progeny is determined using Equation (1) in combination with various sets of genetic-parameter values.

If the relative viability of the progeny is unity, it survives to be a potential parent for next generation. If the relative viability is less than unity, a uniform random number is generated to determine if the progeny survives (i.e., it survives if the random number is between 0 and w_i). Thus, the number of the surviving progeny in one generation may be less than the given size. The relative survival of the progeny in one generation is defined as the actual proportion of the surviving progeny. The proportion of lethal equivalents remaining in the surviving progeny is calculated, following Hedrick (1994), as the average number of lethal equivalents divided by the initial number of lethal equivalents. The number of lethal equivalents in a progeny is equal to the sum of s, the selective disadvantage when homozygous, for all deleterious alleles (after Cavalli-Sforza and Bodmer 1971). If there are no surviving progeny for selfing in any generation (or less than two progeny for the other two schemes), the breeding population is considered as extinct.

One surviving progeny is randomly selected as the parents for the next generation and is self-fertilized to produce the G_1 progeny. This process is followed for ten generations and 1000 replicates are run for each of 192 combinations of genetic-load parameters and progeny sizes. In this simulation, three progeny sizes (10, 50, 200) were considered and the following sets of genetic-load parameters were examined: selection coefficients ($\alpha = 0.01, 0.10$) and synergistic coefficients ($\beta = 0.02, 0.20$), dominance levels ($h = 0, 0.15, 0.30, 0.45$) and numbers of loci ($n = 5, 10, 20, 40$). It should be noted, however, that the true ranges of selection and synergistic coefficients in nature are still unknown (Fu and Ritland 1996) and the levels of selection and synergistic coefficients examined here are those of Charlesworth et al. (1991), which were approximately derived from limited data in *Drosophila* and seem to be reasonable.

For the other breeding schemes, the same procedures as in selfing are applied, but they differ in the use of initial parental individuals to form full-sib families and the selection of the surviving progeny as the parent of the next generation, as described in the preceding section. The simulation was done with a PC PASCAL program that was written specifically for this study and is available upon request.

Results

In order to comprehend the purging of synergistic, detrimental genes, as well as progeny survival and population extinction, we first examine the simulated results in a population of progeny size 200 with respect to the three genetic-load parameters, i.e., synergistic coefficient, dominance level and initial lethal equivalent. Then we summarize some general patterns of purging with respect to progeny size and the breeding scheme.

Different synergistic coefficients

Figure 1 gives the simulated results of purging lethal equivalents initially consisting of 20 deleterious genes with constant dominance ($h = 0.45$) and two different selection and synergistic coefficients ($\alpha = 0.01$ and 0.1; $\beta = 0.02$ and 0.2). It is clear that an increase in the selection coefficient from 0.01 to 0.1 results in a 5–10% increase in the purging of lethal equivalents, but an increase in the synergistic coefficient from 0.02 to 0.2 purges 35–40% more loci (see PS, PF and PH of Fig. 1). With high synergism ($\beta = 0.2$), the half-sib mating results in 70% of the load to be purged by the tenth generation, approximately 20% more than in the selfing scheme.

With weak synergistic interaction ($\beta = 0.02$), purging by the three breeding schemes does not result in any recovery of progeny survival after the reduction of survival in the first generation; even with high dominance ($h = 0.45$), progeny survival is basically maintained at the survival level of the first generation (see SS, SF, and SH of Fig. 1). When synergism is high ($\beta = 0.2$), a recovery of progeny survival after the reduction in the first generation is found, especially in combinations with high dominance. More recovery in progeny survival can be seen with mild inbreeding than with strong inbreeding; the survival rate from two- to ten generations increases from 13% to 70% in half-sib mating, 60% in full-sib mating, and 45% in selfing (see SS, SF, and SH of Fig. 1).

The probability of extinction with respect to these sets of selection and a synergistic coefficients is less than 10% for the three breeding schemes examined (data not shown).

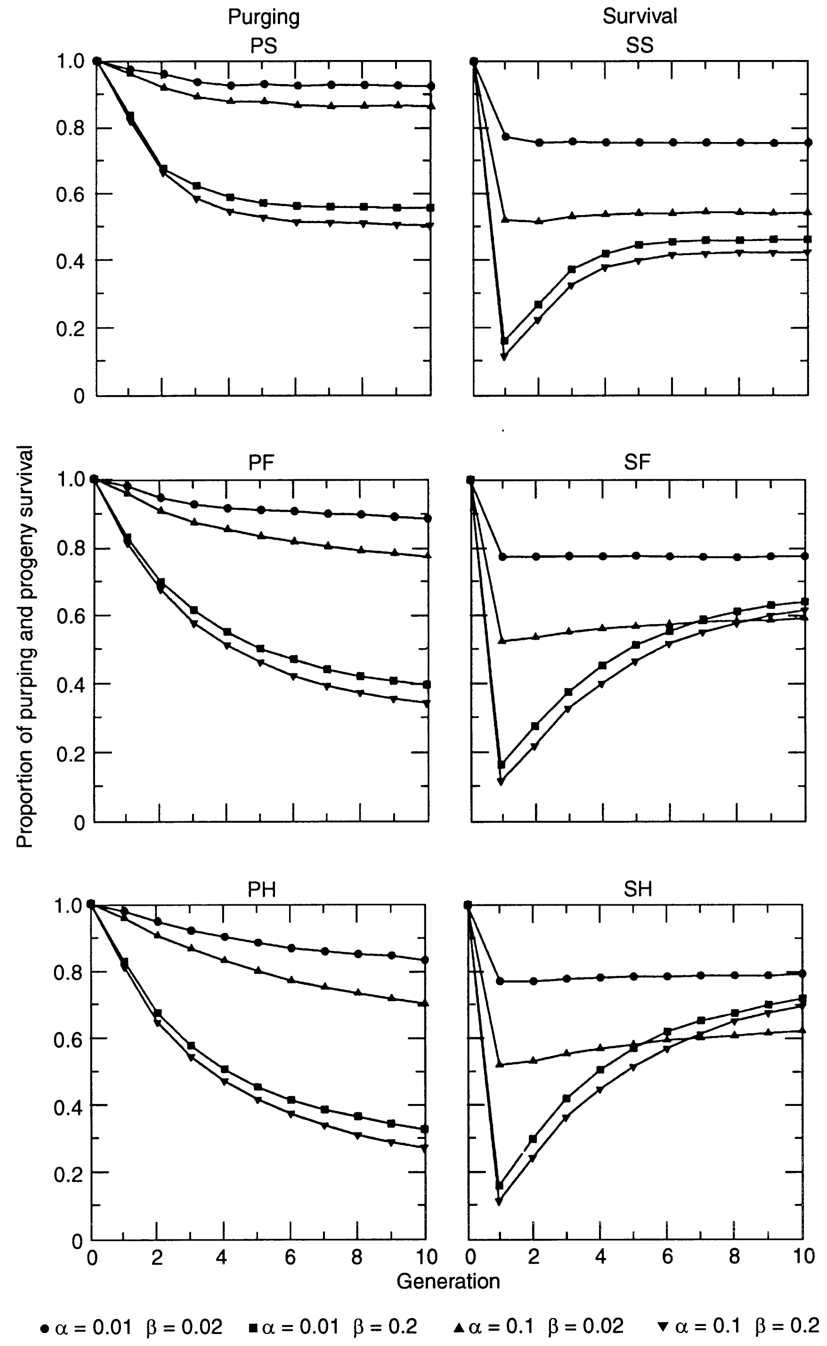


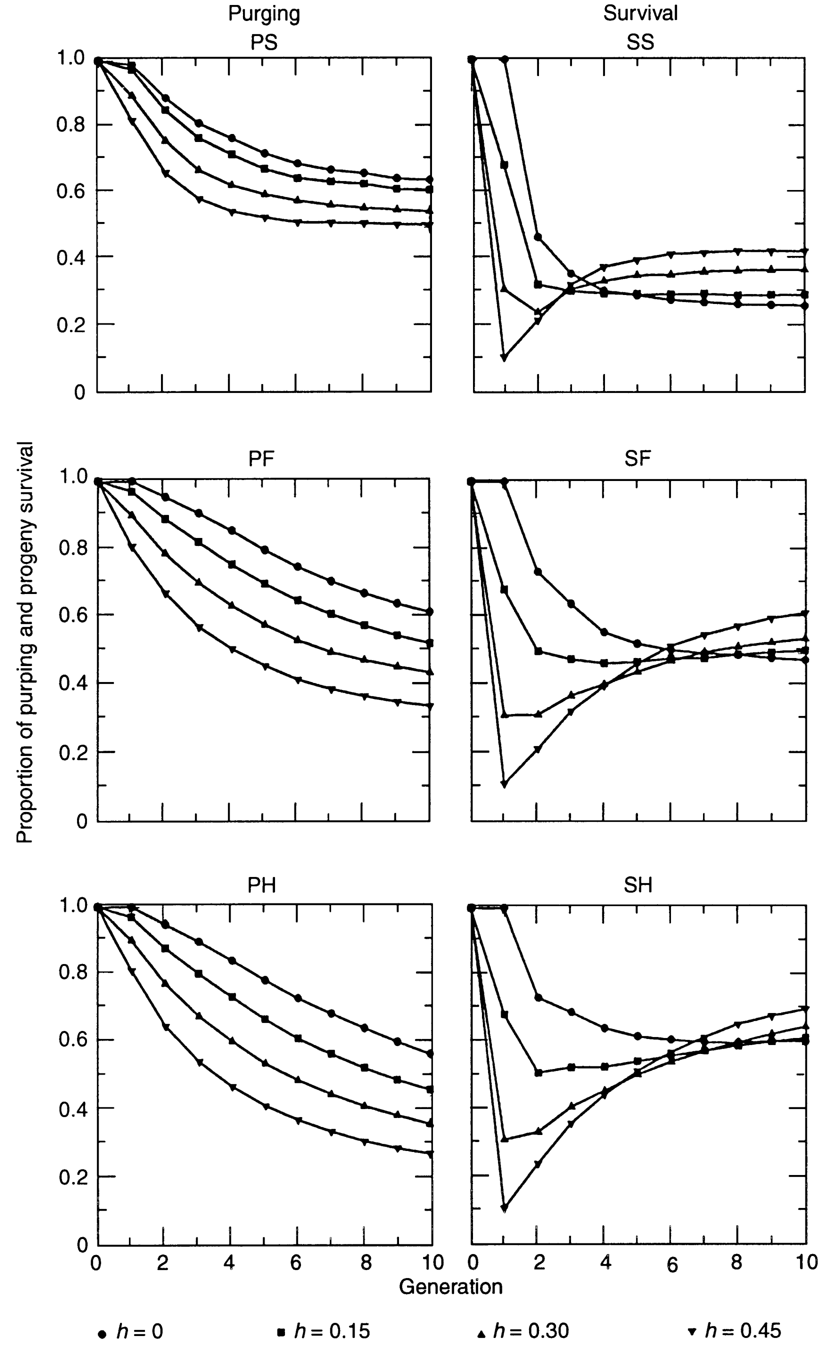
Fig. 1 The effect of the three breeding schemes on the purging of deleterious genes and on progeny survival in a breeding population of progeny size 200 over ten generations, given initial lethal equivalents consisting of 20 deleterious genes with a constant level of dominance ($h = 0.45$) and different selection and synergistic coefficients ($\alpha = 0.01$ and 0.1; $\beta = 0.02$ and 0.2). There are six graphs labeled with two capital letters, the first representing either the purging rate *P* or the survival rate *S* and the second standing for a breeding scheme of selfing *S*, full-sib mating *F*, or half-sib mating *H*. For example, the graph *SF* gives the patterns of progeny survival over ten generations under full-sib mating

Different dominance levels

Examination of the simulated results with respect to dominance level shows that dominance has a great impact on purging and progeny survival, especially with a strong synergistic interaction among loci. Figure 2 gives some representative results and shows such an impact under the three breeding schemes. For a population of progeny size 200 with initial lethal equivalents consisting of 20 deleterious genes with constant selection and a synergistic coefficients ($\alpha = 0.1$ and $\beta = 0.2$), an increase in dominance from 0 to 0.45 results in a 15% increase in purging by selfing by the tenth generation, 25% by full-sib mating, and 30% by half-sib mating. Clearly, such an impact is more apparent when less inbreeding (such as half-sib mating) was applied (Fig. 2).

Interestingly, dominance is the only parameter that can change the pattern of progeny survival over generations from a decrease to an increase. In the selfing scheme (see SS of Fig. 2), for example, progeny survival declines over ten generation when $h \leq 0.15$, but is

Fig. 2 The effect of the three breeding schemes on the purging of deleterious genes and on progeny survival in a breeding population of progeny size 200 over ten generations, given initial lethal equivalents consisting of 20 deleterious genes with constant selection and synergistic coefficients ($\alpha = 0.1$ and $\beta = 0.2$) and different levels of dominance ($h = 0.0$, 0.15, 0.30, and 0.45). See Fig. 1 for the labels of the six graphs



recovered after two generations when $h \geq 0.3$. Such an impact is more profound in half-sib mating than in selfing; progeny survival recovered up to 72% with half-sib mating by the tenth generation, 60% with full-sib mating, and 44% with selfing when $h = 0.45$ (see SS, SF and SH of Fig. 2). The same trend is observed for genes with a deleterious effect of 0.01, but not with weak synergism (i.e., $\beta = 0.02$; data not shown), suggesting that strong synergism ($\beta = 0.2$) also contributes to the observed recovery of progeny survival. Under this synergistic fitness model, which takes into account the joint effect of both heterozygotes and homozygotes (see Equation 1), the effect of the fixation of deleterious alleles as a homozygote due to genetic drift is expected to be less than the cost of maintaining a heterozygote for a relatively high level of dominance. In the schemes of less inbreeding, such as half-sib mating, the number of heterozygotes are expected to be higher so that deleterious genes can be more easily purged for an increased progeny survival, as seen in Fig. 2.

The impact of dominance on the probability of extinction for the population of progeny size 200 is small and there is less than a 10% probability of extinction for the three breeding schemes examined.

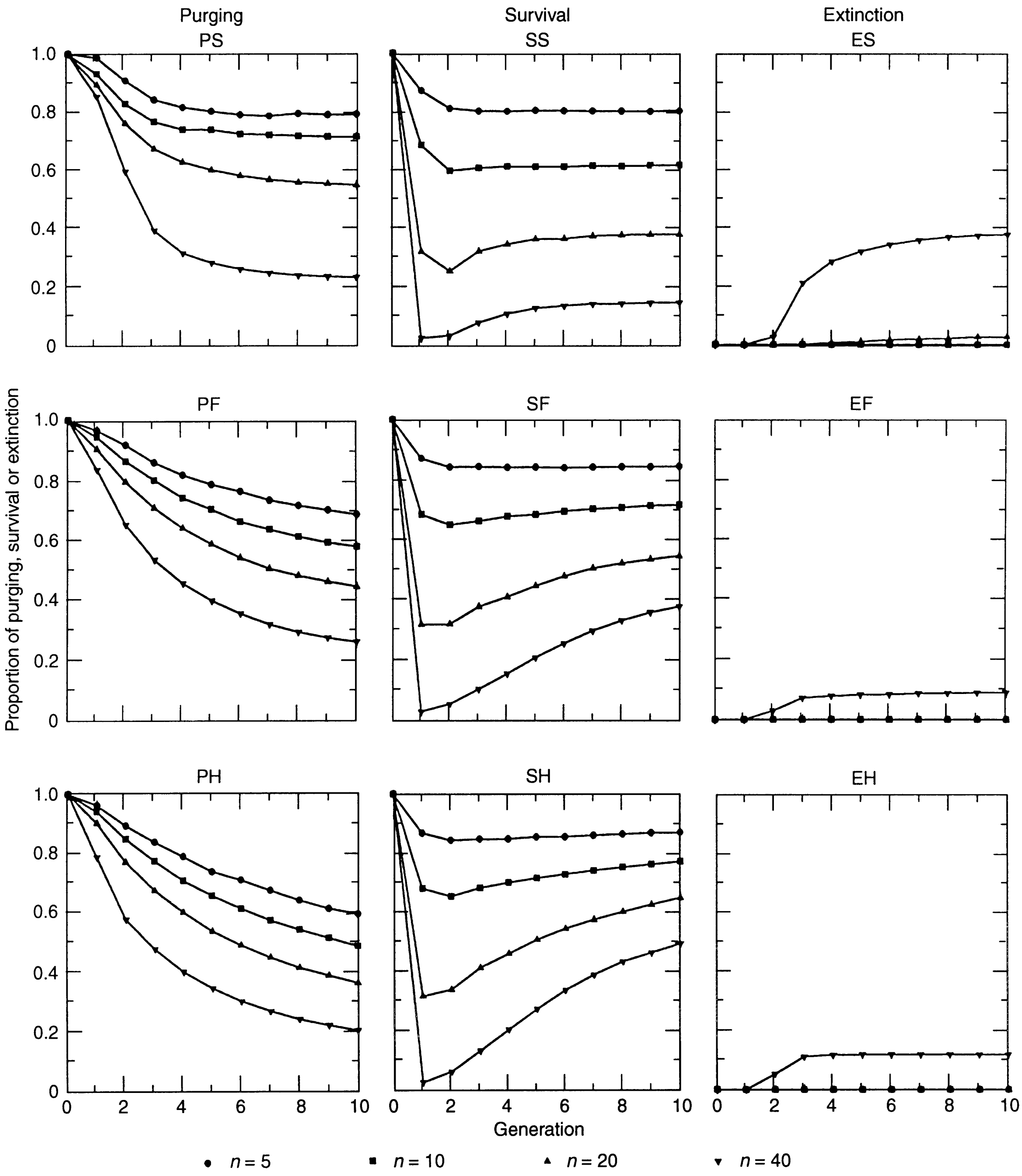


Fig. 3 The effect of the three breeding schemes on the purging of deleterious genes, progeny survival and the probability of extinction of a breeding population of progeny size 200 over ten generations, given different initial lethal equivalents consisting of 5, 10, 20, or 40 deleterious genes with constant selection, synergistic and dominance coefficients (i.e., $\alpha = 0.1$, $\beta = 0.2$ and $h = 0.30$, respectively). The labels of the nine graphs are the same as in Fig. 1, but the third column represents the probability of extinction with the first letter *E* followed by the letter for the breeding scheme (*S*, *F*, or *H*)

Different lethal equivalents

The lethal equivalents examined in this simulation range approximately from 0.025 to 2. Figure 3 gives a portion of the simulated results for initial lethal equivalents ranging from 0.25 to 2. Clearly, more purging can be seen with higher initial genetic loads; there are 0.05 lethal equivalents purged when the initial lethal equivalent is 0.25 (i.e., 20%) whereas approximately 1.6 lethal equivalents are purged with an initial load of two lethal equivalents (i.e., 78%) (see PS of Fig. 3). It is also clear that half-sib mating is more effective in purging than selfing, especially with a lower level of initial loads, although selfing usually results in more purging in the first several generations (see PS, PF, and PH of Fig. 3). When there are initial lethal equivalents of 0.5 or less, purging by various modes of inbreeding over generations does not result in any recovery of progeny survival after its reduction in the first generation. When the initial load increases to two lethal equivalents, progeny survival is reduced to 5% in the first generation, but is recovered over several generations, more so with less inbreeding. For example, progeny survival recovers up to 14% following selfing by the tenth generation, 38% following full-sib mating, and 52% following half-sib mating (see SS, SF and SH of Fig. 3 for $n = 40$). However, with 40 genes of detrimental effect $\alpha = 0.1$ initially segregating in the population, purging increases the probability of extinction, especially for selfing (see ES of Fig. 3).

Examination of all the simulated results in this study reveals several trends for increased initial genetic loads. First, there is more purging of deleterious genes, and this is achieved more quickly, with strong inbreeding. Second, the proportion of progeny survival is greatly reduced and could be recovered over generations if there are high levels of dominance and synergism, which is more likely with the schemes of less inbreeding. Third, the probability of extinction is generally higher for a larger initial genetic load, especially in populations of smaller progeny size.

Different progeny sizes

In this study we have examined three progeny sizes (10, 50, 200 of a breeding population and kept them constant over generations. As expected, progeny size has a great impact on the patterns of purging, progeny survival, and population extinction. Figure 4 shows a set of purging patterns corresponding to the three progeny sizes for the case of $n = 20$, $\alpha = 0.1$, $\beta = 0.2$, and $h = 0.45$. There is a marked difference in purging between the progeny sizes 10 and 50, but not between the progeny sizes 50 and 200, for any of the breeding schemes examined. For a progeny size of 10, 80–90% of lethal equivalents are purged in the only first two generations, but with progeny sizes of 50 and 200 the deleterious genes are removed gradually over generations. There is basically no recovery of progeny survival after its reduction in the first two generations for the progeny size of 10, but with the progeny sizes of 50 and 200 a dramatic recovery is observed, more so with less inbreeding over time. When the progeny size is 50 or larger, the recovery of progeny survival is from 12% to 68% for the half-sib mating, 12% to 56% for the full-sib mating, and 12% to 40% for the selfing scheme, by generation 10. The probability of extinction is much higher for the progeny size of 10 (i.e., 85–95%) than for the progeny sizes of 50 and 200 (i.e., 0–13%). Clearly, purging synergistic, detrimental genes for increasing progeny survival, or avoiding extinction, requires a relatively large progeny size (>50 as shown in this study).

For ease of comparison in purging with respect to progeny size and breeding scheme, in Table 1 we summarize the cases out of 64 combinations of four genetic-load parameters with recovered progeny survival after purging and the cases with an increased probability of extinction. This was obtained by examining all the simulated results and counting them according to the progeny sizes and breeding schemes. It is clear that the number of cases with recovered progeny survival after purging for the progeny size of 10 is approximately half that for the progeny size of 200, but the number of cases with an increased probability of extinction of more than 10% by the tenth generation is much larger for the progeny size of 10 (i.e., 23–26 cases) than for the progeny size of 200 (i.e., 3–8 cases). This result, along with those shown in Fig. 4, suggests that purging synergistic, detrimental genes in a population with a progeny size of 10 has a low chance of increasing progeny survival, but could face a high probability of population extinction. It should be noted, however, that such a comparison is only suggestive since the true nature of genetic loads is poorly known (Fu and Ritland 1994, 1996). It is also true that such probabilities are much smaller than those reported in empirical studies (see, e.g., Garcia et al. 1994). This is because we considered only deleterious genes of small effect, whereas, in reality, the nature of the genetic load may be more complex than we have examined. Also, we considered only the genetic causes, and not the demographic and environmental factors, that influence the extinction probability.

Different breeding schemes

A full examination of all the simulated results obtained in this study with respect to the three breeding schemes reveals several marked patterns of purging, progeny survival, and population extinction over ten generations (some of which are shown in Table 1). First, for the purging of detrimental genes, there is not much difference between the various breeding schemes examined when selection, dominance, synergism and initial genetic load are low or small. However, when these parameter values increase, especially for dominance and synergism, purging appears to be more effective, in terms of rate and amount, for less inbreeding; specifically the trend is half-sib mating > full-sib > selfing. Second, when there is no dominance, progeny survival generally declines over generations for the three breeding schemes, but is less with less inbreeding (i.e., half-sib mating < full-sib < selfing). If the dominance level is high, a dramatic change would occur in progeny survival for the schemes of less inbreeding (i.e., half-sib mating > full-sib > selfing), given that the other parameters are the same. This is

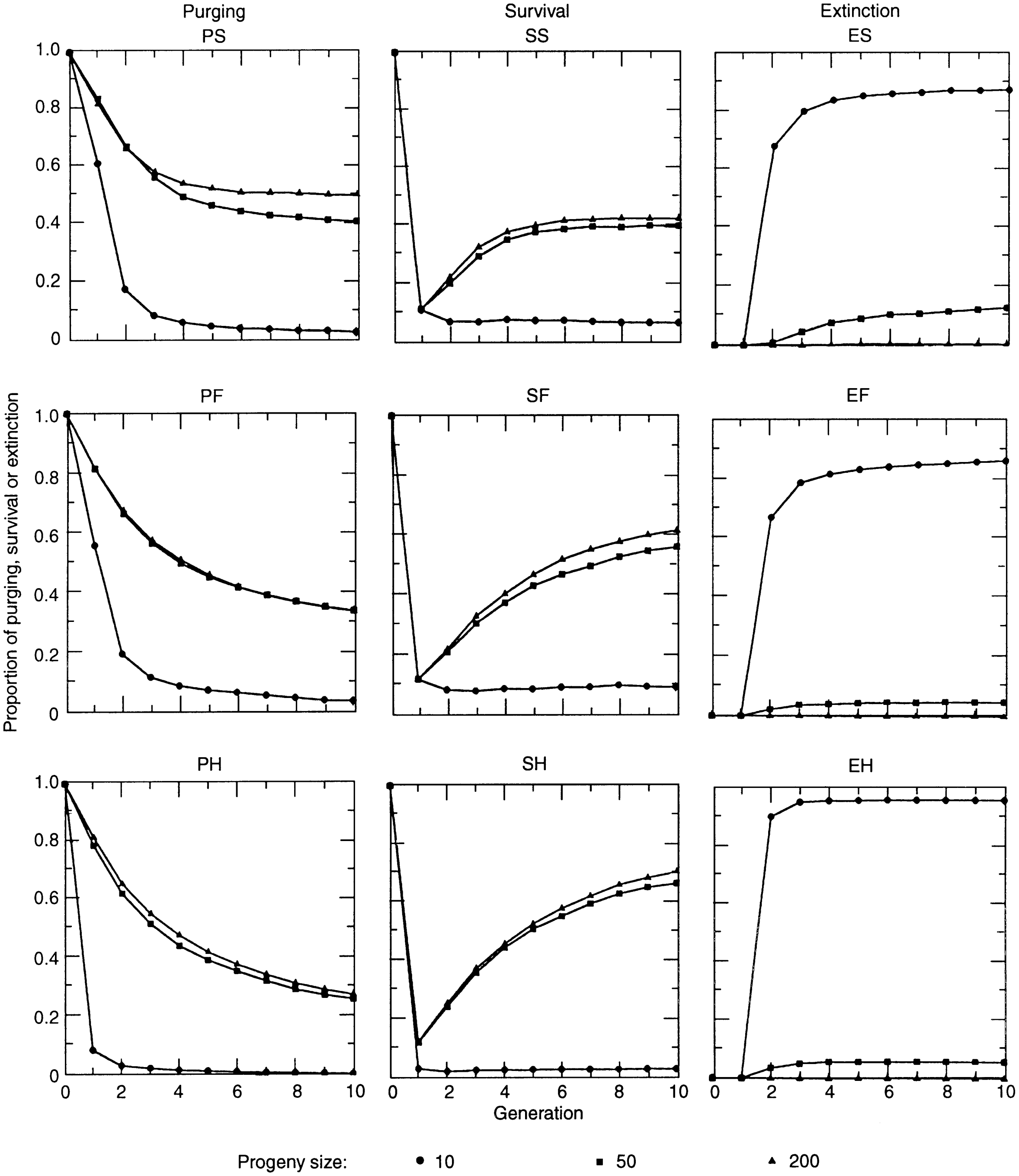


Fig. 4 The effect of progeny size and the three breeding schemes on the purging of deleterious genes, progeny survival and the probability of extinction over ten generations, given genetic-load parameter values of $n = 20$, $\alpha = 0.1$, $\beta = 0.2$ and $h = 0.45$. The labels of the nine graphs are as given in Figs. 1 and 3

much more apparent when selection, synergism and initial genetic load increase. Third, the probability of extinction, although largely depending on progeny size and initial genetic load, usually becomes smaller in the schemes of less inbreeding (i.e., half-sib mating < full-sib < selfing).

Discussion

This simulation has shown several marked patterns in the purging of viability genes of synergistic, detrimental effect. First, the rate and amount of purging generally increase with high dominance, strong synergism, high genetic load and low inbreeding. Second, the recovery of progeny survival, after its reduction in the early generations, depends largely on dominance, synergism, progeny size and inbreeding; a recovery of progeny survival was found with high dominance and synergism

Table 1 The number of cases with recovered progeny survival after purging and the number of cases with an increased probability of extinction, with respect to three progeny sizes and three breeding schemes[a]

Breeding scheme	Cases of survival[b]			Cases of extinction[c]		
	PS[d] = 10	50	200	PS = 10	50	200
Selfing	2	12	15	36	15	8
Full-sib	12	17	21	23	8	3
Half-sib	14	24	24	23	5	3

[a] In each cell, a total of 64 cases are examined (i.e., 64 combinations of four genetic load parameters)

[b] Recovered progeny survival means an increase in progeny survival after its initial reduction due to purging, though not necessarily up to the original level of 1

[c] The case where the probability of extinction is equal to or larger than 10% is observed by generation 10

[d] PS is progeny size

in the population of progeny size larger than 50 using schemes of mild inbreeding. Third, the probability of extinction due to purging can greatly increase up to 100% in the population of progeny size 10, especially when the initial genetic load is high and the inbreeding used is strong, but mostly it is less than 10% for a progeny size larger than 50.

This simulation has also shown that continuous half-sib mating is as effective in purging detrimental genes as continuous selfing, especially after a few generations, but usually with less risk of population extinction. This suggests that mild inbreeding schemes would be preferred, particularly in breeding populations of small progeny size, such as those of endangered animal species. This simulated result does not differ much from those obtained under multiplicativity (see Fu et al. 1998). It also accords well with the idea proposed in general breeding that the slower the rate of inbreeding, and the larger the effective population size immediately after a population crash, the greater the opportunity for selection to eliminate recessive deleterious mutations (Wright 1977; Falconer 1981; Latter et al. 1995). From this simulation, however, we do not know how mild (or low) an inbreeding is needed. Whether there is an optimum rate of increase in inbreeding over generations, i.e., a rate that both eliminates load and maintains fitness without causing an undue increase in extinction, deserves further study.

Another simulated result that is consistent with those under multiplicativity (Hedrick 1994; Fu et al. 1998) is that purging small detrimental genes is most effective only in the first several generations in most of the cases examined, which suggests that a long-term purging by inbreeding may not be a good strategy, particularly for the breeding programs of endangered species. After several generations of inbreeding, the proportion of load that can be further purged is small and most of the deleterious genes remaining in the populations have become fixed. Further inbreeding may not be able to increase progeny survival, but is more likely to increase the probability of extinction. Such a situation has been clearly shown in the study of self-fertilized lines of the normally outcrossing aquatic plant *Eichhornia paniculata* (Barrett and Charlesworth 1991). In their study, Barrett and Charlesworth (1991) found that inbreeding caused an immediate depression in fitness, but after two generations of selfing there was no further decline in fitness within the lines. Also, it is possible that purging over the long term may affect the genetic variation at other genes for future adaptation.

Our simulations here are based on several assumptions, some of which are obviously unrealistic. First we have assumed for simplicity that no mutation occurs during the period of purging. The presence of directional mutation over generations is expected to affect the rate of purging, and consequently the progeny survival, downward (Charlesworth et al. 1991). This is particularly true if mutations are detrimental rather lethal, and have a relatively high probability of fixation (Charlesworth 1992). Second, we have considered only the constant gene effects and gene frequencies in the initial population. Any variations in gene effect and gene frequency would affect the pattern of purging, at least quantitatively. Third, we have assumed that there is no linkage between any deleterious genes. As inbreeding increases, it is expected that linkage disequilibrium is also increased. Thus the effect of such a "hitchhiking" may be significant in preventing the purging of deleterious genes (Kojima and Lewinton 1970; Charlesworth et al. 1992). Fourth, we have examined only the deleterious viability genes of small effect. Fecundity genes of a similar nature can contribute to reductions in fitness and thus may affect the patterns of purging.

Considering these assumptions, some caution might be necessary in exploring these patterns for breeding programs, particularly with endangered species. These patterns would be more informative if we had a better understanding of the nature and magnitude of deleterious genes, or if real experiments could be performed. While some purging experiments can be found, such as those in *Drosophila* (e.g., see Garcia et al. 1994; Latter et al. 1995), it is difficult to determine the real contributions of various deleterious genes to the purging observed. However, the patterns presented here support the current view that purging may not be effective (e.g., see Hedrick 1994) and that inbreeding should always be minimized in breeding programs (e.g., see Fu et al. 1998). Moreover, our simulation results have some practical implications. While inbreeding depression has been observed for many plant and animal species, the proportion of deleterious genes with either large or small effects is rarely known. Thus, it is not realistic to design a specific breeding scheme to purge deleterious genes of small effect alone. More importantly, these genes are difficult to purge for an increasing progeny fitness in a small breeding population. As illustrated in the simulations, effective purging requires a high level of dominance and a strong synergism, but the empirical data obtained so far indicate the existence of a weak synergism among viability genes. Thus, such a level of synergism may not be strong enough to greatly enhance the effectiveness of purging in a small breeding population. When inbreeding becomes inevitable, an implementation of a mild inbreeding scheme would be preferred. Our simulation showed that continuous half-sib mating can be as effective as continuous selfing in purging detrimental genes for increasing progeny survival, but usually with less risk of population extinction.

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