

# The interaction of selection intensity, inbreeding depression, and random genetic drift on short- and long-term response to selection: Results using finite locus and finite population size models incorporating directional dominance

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## Abstract

The impact of method of calculating breeding values (best linear unbiased prediction, BLUP, vs individual performance, MASS), selection intensity, and population size on short- (Generation 5) and long-term (Generation 20) response to selection with dominant (heterotic) and additive (nonheterotic) gene action traits was examined using a gene-level simulation program that assumed a finite number of loci and a finite population size with either a completely additive or dominant type of gene action. Results showed that for additive gene action there was a short-term advantage but a long-term disadvantage of increasing selection intensity. In the short term, maximum response for both methods was achieved with a proportion selected of 5%, and selections based on BLUP were always superior to those based on MASS. In the long term, BLUP selections remained superior to MASS, but maximum response for both methods was achieved with a proportion selected of 10%. In contrast, with dominant allele effects, MASS was superior to BLUP in the short term for proportions selected of less than 10% and in the long term for proportions selected of less than 20%. With intense selection the increased accuracy of selection based on BLUP breeding values could not offset negative impacts of associated increased inbreeding. With less intense selection, the increased accuracy of BLUP selection could offset negative impacts of associated increased inbreeding. However, the differences between selection based on BLUP and on MASS breeding values were not as important as optimizing the proportion selected. With dominant gene action in the long term, with a proportion selected of 20%, the superiority of BLUP over MASS was less than 2%, both of which were at least 100% greater than that achieved with a higher selection intensity corresponding to a proportion selected of 5%. This result was due to cumulative inbreeding depression associated with the smaller effective population size with intense selection. In general, the breeding program with the greatest rate of response per unit of inbreeding will give the greatest response in the long term. Breeders should be more concerned with increasing effective population size than with the method of computing expected breeding values.

*Key Words: Selection Methods, Best Linear Unbiased Prediction, Genetic Models, Inbreeding, Inbreeding Depression*

## Introduction

The primary factors affecting response to genetic selection are accuracy of selection, selection intensity, and effective population size. Current breeding theory indicates that optimum response to selection can be achieved by maximizing these factors (Robertson, 1960). Unfortunately, with limited resources, not all factors can be maximized simultaneously. For example, increasing selection intensity decreases effective population size and results in a decreased response to selection (Robertson, 1960). Similarly, increasing accuracy of selection by use of family selection indices or BLUP breeding values also reduces the effective population size and results in a more rapid increase in the rate of inbreeding (Robertson, 1961; Quinton et al., 1992; Quinton and Smith, 1995).

A second factor to consider is the time scale. Breeders are not only concerned with selection limits, but they must also stay in business long enough to achieve those limits. Thus, optimizing short-term response to selection is also economically crucial. The objective of this article is to examine the relationship between accuracy of selection and selection intensity on selection response in the short and long term

for traits with additive and heterotic inheritance using a model that incorporates linkage, finite population size, finite number of loci, and directional dominance effects.

## Background

Although the classic paper of Robertson (1960) thoroughly examined the relationship between effective population size and selection intensity, the results were limited to the case of additive gene action. Most traits of economic importance in poultry and livestock express effects of heterosis and inbreeding depression, indicating that dominant gene action and/or dominant  $\times$  dominant epistasis are important for those traits (Fairfull et al., 1985, 1987; Fairfull and Gowe, 1986; Fairfull, 1990; Lynch and Walsh, 1998).

Quinton et al. (1992) suggested that comparisons between selection programs based on BLUP (Henderson, 1984) and other methods of estimating breeding values should be based at the same level of inbreeding to adjust for the consequences of inbreeding. In this way, selection intensity could be allowed to vary with selection accuracy, making the comparison more balanced as long as the rate of inbreeding remained the same. Quinton et al. (1992) showed that pheno-

typic selection can yield higher response to selection than BLUP at the same level of inbreeding. They concluded that the extra response of BLUP is at the expense of extra inbreeding. Later, Quinton and Smith (1995), using an additive infinitesimal model, compared methods to reduce rates of inbreeding with BLUP such as restricting matings, use of inflated estimates of heritability, and assortative mating. They concluded that none of the methods was optimal under all conditions.

However, results of Quinton et al. (1992) and Quinton and Smith (1995) were based on an additive infinitesimal model. Use of this model presents at least two problems. First, gene frequencies are not allowed to vary; second, dominance effects are not included. The primary impacts of inbreeding are 1) loss of alleles due to random genetic drift, which is directly proportional to inbreeding level (Muir, 1991) and 2) inbreeding depression, which is due to directional dominance or higher-order epistasis (Falconer, 1981; Lynch and Walsh, 1998). Thus, the primary impacts of inbreeding are ignored with use of such a model. Although some of their conclusions may remain valid, the impact of inbreeding could be much more serious than that predicted by their model.

### Methods

In order to examine the relationships among selection intensity, population size, and gene action, a gene-level simulation program was developed. This program allows for any genetic architecture including effect of linkage and up to three traits. Variables include genome size, number and size of chromosomes, number of loci, number of alleles per locus, gene action, distribution of initial gene frequencies, distribution of gene effects, distribution of environmental effects, population structure and size, and mutation rate. Recombination is based on map distance using the Haldane (1919) map function. Environmental effects can be correlated and can interact with genotypes. In terms of selection, the program allows for calculation of EBV based on BLUP (single trait) or individual merit (MASS selection), for either sex-limited or non-sex-limited traits and index selection, independent culling levels, or tandem selection.

For these simulations, the genetic architecture was defined as the cumulative action of 500 loci, each with two alleles, positioned randomly over a genome size of 8,000 cM, distributed over 10 chromosomes. The chromosomes were set to random lengths based on a uniform distribution with the restriction that the total length be 8,000 cM. Mutations were not allowed. Effects of alleles were assigned randomly based on the unit normal distribution with a mean of zero. Effects at each locus were based on type of gene action. Two types of gene action were considered: 1) completely additive and 2) highly heterotic with 100% of the loci showing directional dominance. For additive effects, the contribution of a locus was the sum of the pair of allelic effects. For dominance effects, directional dominance was assumed, with the favorable allele having complete dominance and the contri-

bution of a locus having either one or two copies of the favorable allele being twice the effect of the favorable.

The population architecture was determined by setting initial allele frequencies randomly for each locus based on the uniform distribution with a range of 0 to 1. Thus, the idealized infinite population based on this population architecture was in zygotic and gametic phase equilibrium. The initial population for each simulation was sampled from the same idealized infinite population and thus may have slightly different gene frequencies and disequilibrium due to random genetic drift resulting from initial subdivision of a population.

The genetic architecture was identical for all simulation with the exception of how the phenotype was determined for additive vs dominance allele effects. The phenotype was the sum of all locus effects plus an environmental effect, that is, there were no effects due to genotype  $\times$  environment interactions. The genetic variance was computed as the variance among genotypes. Given the genetic variance, environmental effects were generated from a normal distribution with a mean of zero and a variance set to give the desired specified heritability. The genetic parameters, calculated as above, were based on a large sample size ( $n = 5,000$ ) from the theoretical infinite population. These genetic parameters were then fixed for all simulations for each of the two genetic architectures regardless of the actual sample. Effects due to variation in initial gene frequencies as a result of sampling are expected to be averaged out over replicates.

The trait to be selected could be measured in both sexes with a narrow-sense heritability of 0.2. Expected breeding values were calculated based on either BLUP or individual performance. The mixed-model equations (MME) to obtain BLUP breeding values included only the additive random effect and one fixed effect for the overall mean. Genetic parameters used in the MME for additive and environmental variance were set to the values estimated for the theoretical infinite population for each architecture. The population size was set to 240 with 12, 16, 20, 24, 48, or 120 individuals saved for breeding in different sets of simulations, corresponding to approximately 5, 8, 10, 20, and 50% saved for breeding, respectively. An equal number of each sex were saved. Individuals were mated at random. Each female produced enough progeny to exactly reproduce the original population size. This selection procedure was repeated for 19 generations and constituted one replicate. One hundred replicates were completed for each combination of gene action, selection intensity, and selection method, with each replicate started with a new distribution of gene frequencies but with the same genetic architecture. Inbreeding coefficients were calculated for each individual from each pedigree using the method of Henderson (1976).

### Results

Figure 1 presents results of selection on BLUP breeding values with additive allele effects over generations. In general, with all selection proportions, except 50%, there was a short-term advantage and a long-term disadvantage of in-

creasing selection intensity. Figure 2 compares short-term (Generation 4) response to selection from using BLUP vs MASS breeding values as related to selection intensity. In the short term, as selection intensity increased (selection proportion decreased), response to selection increased with either method, and BLUP was always superior to MASS. Figure 3 compares long-term response (Generation 19) of BLUP to that of MASS selection as related to selection intensity. In the long term, BLUP selection remained superior to MASS, but the maximum response for both methods was achieved with a lower selection intensity, corresponding to a selection proportion of 10%.

Figure 4 presents results from BLUP selection with dominance effects over generations. Results are inversely related to those given in Figure 1 (i.e., except for the first generation, the greater the selection intensity the lower the long-term response to selection). Figure 5 compares short-term (Generation 4) response to selection from using BLUP vs MASS breeding values as related to selection intensity. In the short term, BLUP was superior to MASS only for proportions selected of 10% or greater. Optimal response to selection with both methods occurred with a selection proportion near 10%. Figure 6 compares long-term response (Generation 19) from BLUP to that from MASS selection as related to selection intensity. In the long term, MASS was superior to BLUP at selection proportions less than 20%, with an optimal selection proportion near 20% for both methods.

Inbreeding coefficients are given in Figure 7 for dominant gene action; these values were not greatly different from those for additive gene action (not shown). As expected, as selection intensity increased, the rate of inbreeding increased. Cumulative inbreeding coefficients at Generation 19 for BLUP and MASS selections are shown in Figure 8. Even though the inbreeding coefficient was always greater with BLUP than with MASS selection, the difference decreased with increasing proportions selected. Figures 9 and 10 show the regression of response to selection with additive and dominance gene action on inbreeding coefficients, respectively. These results show that response to selection per unit increase in inbreeding coefficient was linear for both types of gene action and increased with proportions selected.

### Discussion

A number of experiments failed to confirm the theoretical advantages of index selection (single trait, multiple sources of information) over mass selection (Kinney et al., 1970; Doolittle et al., 1972; Wilson, 1974; Campo and Tagarro, 1977; Garwood and Lowe, 1979; Garwood et al., 1980; Pérez-Enciso and Toro 1992). Wilson (1974) concluded that "there is no obvious explanation for the discrepancies that exist between these experimental results and the theoretical expectations." A possible explanation is inbreeding. The results presented here clearly show that inbreeding is a major factor limiting selection response and, with dominant gene action, can result in reversals from that predicted by additive theory, even in the short term.

Robertson (1961) warned that selection based on family indices would result in smaller effective population sizes because relatives tend to be selected. Quinton et al. (1992) concluded that comparisons between alternative breeding schemes should be made at the same level of inbreeding rather than at the same selection intensity due to adverse effects of inbreeding depression. However, conclusions of Quinton et al. (1992) and Quinton and Smith (1995) were based on an additive infinitesimal model in which gene frequencies were not allowed to vary and dominance effects were not included. Thus, the primary impacts of inbreeding would not have been included in such a model. Although their conclusions were supported for the case of additive gene action, they were not for the case of dominant gene action. This difference resulted because the rate of response for BLUP vs MASS selection per unit increase in inbreeding coefficient was essentially the same for additive, but not dominant, gene action (Figures 9 and 10). Therefore, for heterotic traits, comparisons between methods is not valid at the same level of inbreeding, as suggested by Quinton et al. (1992).

Jeyaruban et al. (1995) compared selection response for a sex-limited trait with BLUP to an optimum family selection index based on individual, full-, and half-sibs information, using an additive infinitesimal computer simulation of a breeding program for layer chickens. They also concluded that selection using BLUP always gave greater gains than a classic selection index, but at a cost in terms of increased level of inbreeding. They concluded that because commercial poultry production is based primarily on crossing programs, negative effects of inbreeding in the parental lines (loss of alleles and inbreeding depression) are eliminated in the cross. However, the additive infinitesimal model ignores loss of favorable genes due to drift, which is directly proportional to the rate of inbreeding (Muir, 1991). The probability that a favorable allele will be lost in both lines is also proportional to the level of inbreeding in each and becomes a permanent loss that cannot be overcome by crossing lines (Schamber and Muir, 2000).

The assumption of an infinite number of loci for the infinitesimal model is necessary so that selection will not change gene frequencies (Bulmer, 1971). The assumption of additivity is also necessary to predict changes in variance structure with selection. With those assumptions, the changes in the additive variance due to gametic disequilibrium as a result of selection and inbreeding can be predicted (Bulmer, 1971; Sorensen and Kennedy, 1984). The validity of the infinitesimal model is clearly limited, but in the short term, if effective population size is large and a large number of additive loci influence the trait, predictions using the model may be adequate.

Quinton and Smith (1995) examined alternative methods to reduce the rate of inbreeding with selection on BLUP, including inflated heritabilities to reduce selection of families. They concluded that optimism about obtaining high response to selection at a low level of inbreeding by the inflation of heritability in the MME for BLUP solutions or by adjusting the EBV for relationships with individuals already

selected is not warranted. Quinton and Smith (1995) found that the same result could be achieved by simply increasing the number of sires selected.

The results found in this study support the conclusion that effective population size is critical for optimizing selection response. The differences in response between selection using BLUP and MASS breeding values were small compared with the increase in gains that could be achieved by optimizing the selection proportion. For example, with only additive gene action, after 19 generations with a selection proportion of 10%, superiority of selection using BLUP over MASS breeding values was 8%, whereas increasing the proportion selected (decreasing the selection intensity) from 5 to 10% increased response from selection using BLUP breeding values by 10% (calculated from the results given in Figure 3). With dominant gene action, the alternatives are even more dramatic. After 19 generations with a proportion selected of 20%, the superiority of selection based on BLUP rather than MASS breeding values was less than 2%, whereas increasing the proportion selected (decreasing the selection intensity) from 5 to 20% increased selection response by 135% (calculated from results given in Figure 6). Unfortunately, with dominance gene action determining the optimal selection proportion is not easy. Simulations such as this one can be used as guidelines, but the simulations must be as close to the actual population structure as possible.

Robertson (1960) showed that for a trait influenced by additive genetic effects, the maximum response to selection is achieved by using a selection proportion of 50% each generation and selecting an equal number of each sex. Results given in Figure 8 support his conclusion. The greater the selection proportion (lower selection intensity) up to 50%, the greater the regression of response on inbreeding coefficients. Figure 9 shows that result also holds with dominant gene action. By extension, in the limit, the breeding program with the greatest rate of response per unit of inbreeding will have the greatest overall response to selection. Because the regressions of response on inbreeding coefficient were linear, this result can be used to help determine the optimum breeding program from observed short-term responses.

Population sizes used in these simulations are small compared to those of some commercial operations. To examine the effect of increasing population size and number of generations, simulations were also completed using population sizes increased by an order of magnitude, but, because of computing limitations, only MASS selection was examined. Results are given in Figures 11 and 12 for additive and dominance gene action, respectively. With the same proportion selected, averaged inbreeding coefficients were approximately the same after 19 generations of selection with a population size of 240 and 199 generations with a population size of 2,400. However, many more generations of selection occurred with the large population before achieving that level of inbreeding. Nevertheless, with additive gene action a similar result occurred as with the smaller populations. In particular, the selection intensities that gave the highest early response produced the least long-term response. Although

selection response was not greatly different in the early generations with 5, 8, and 10% selected, the crossover between early and long-term benefits occurred between generations 42 (10% selection proportion superior to 5%) and 65 (20% selection proportion superior to 5%).

With dominant gene action, comparisons between selection programs with large and small populations are strikingly different and seem similar to those achieved with additive gene action, except the crossover of superiority of selection programs occurs earlier (25 generations for 10% selection superiority over 5%, and 42 generations for 20% selection superiority over 5%). These results can be explained in terms of the interaction of the effect of selection on gene frequency and inbreeding depression. Inbreeding depression has the greatest effect at intermediate gene frequencies, because the greatest proportion of heterozygotes also occurs at that frequency. As selection increases gene frequencies beyond 0.5, the impact of inbreeding depression, due to directional dominance, decreases. With small populations, the inbreeding coefficient rapidly increases before selection can appreciably increase the frequencies of favorable alleles. Although it seems possible to overcome impacts of inbreeding depression in this manner, this result is only true for the primary traits of selection. Inbreeding affects all loci in the genome simultaneously. For traits not under selection, results as shown in Figure 4 can still occur, although the time scale must be expanded in direct proportion to the effective population size used. Because fitness traits tend to be most affected by inbreeding depression, it may not be possible to maintain a selection differential even in large populations after a few to moderate number of generations if inbreeding is allowed to accumulate. Research is needed to examine multitrait impacts of the interaction of selection intensity and inbreeding depression, in particular when one of the traits is associated with reproduction and the other is associated with production.

Future research will examine the impact of including both additive and dominance random effects in the MME. Inclusion of dominance in the MME will increase accuracy of selection but will not alter the negative impacts of inbreeding depression. As seen above, the increased accuracy of BLUP selection was not adequate to offset the negative impacts of inbreeding depression with high selection intensities. It remains to be seen whether this is also true when both random effects are included in the model.

### Implications

The optimal selection strategy partially depends on the trait being selected and is not necessarily the strategy that either maximizes selection intensity or accuracy. Primary attention must be given to the rate of inbreeding, which is increased by increasing either accuracy of selection or selection intensity. Results based on the infinitesimal model should be avoided with small effective population sizes or for examination of limits to selection. In this situation, simulations such as the ones presented in this article are the only alternative. However, one generalization that can be inferred

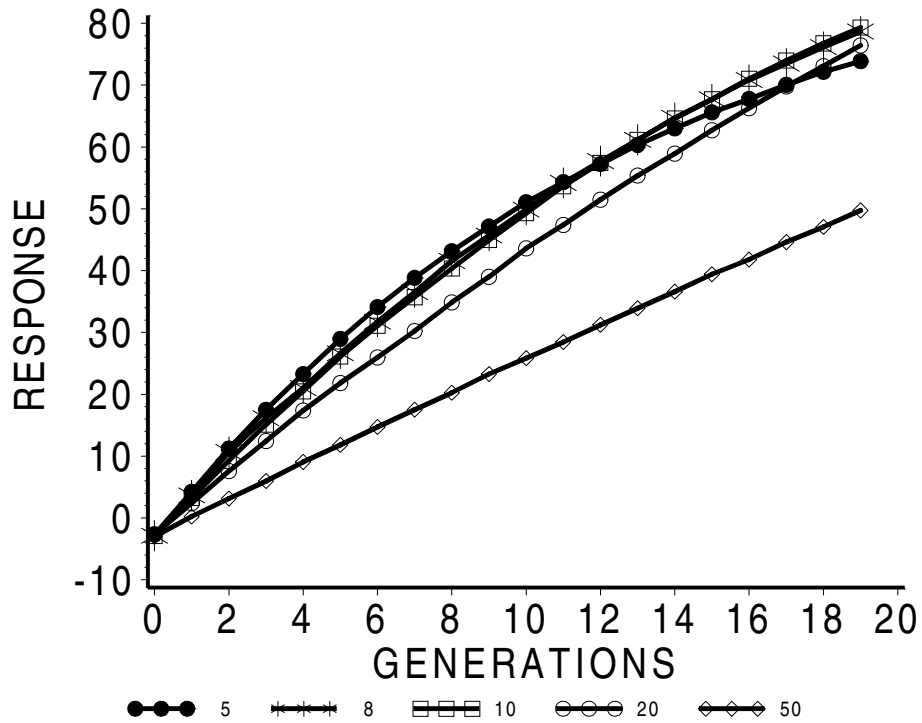
from these results is that for non-sex-limited traits, breeders should be more concerned with increasing effective population size than with the method of computing expected breeding values. In general, the program with the greatest rate of response per unit of inbreeding will give the greatest response in the long term.

### Literature Cited

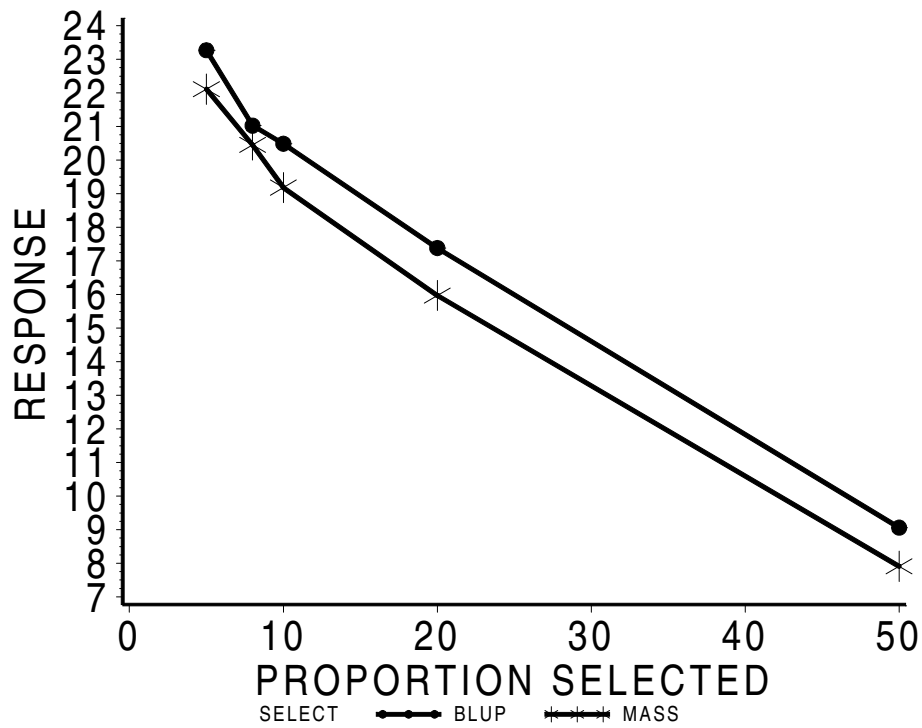
- Bulmer, M. 1971. Effect of selection on genetic variability. *Am. Nat.* 105:201-211.
- Campo, J. L., and P. Tagarro. 1977. Comparison of three selection methods for pupal weight in *Tribolium castaneum*. *Ann. Genet. Sel. Anim.* 9:259-268.
- Doolittle, D. P., S. P. Wilson, and L. Hulbert. 1972. A comparison of multiple trait selection methods in the mouse. *J. Hered.* 63:366-372.
- Fairfull, R. W. 1990. Heterosis. In: R. D. Crawford (ed.) *Poultry Breeding and Genetics*. chap. 37. pp 913-933. Elsevier Science Publishers, Amsterdam.
- Fairfull, R. W., and R. S. Gowe. 1986. Use of breed resources for poultry egg and meat production. In: 3rd World Congr. Genet. Appl. Livest. Prod. 10: 242-256.
- Fairfull, R. W., R. S. Gowe, and J. Nagai. 1985. Heterosis in White Leghorn strain crosses. In: Proc. British Poultry Breeders Roundtable, Edinburgh, Scotland.
- Fairfull, R. W., R. S. Gowe, and J. Nagai. 1987. Dominance and epistasis in heterosis of White Leghorn strain crosses. *Can. J. Anim. Sci.* 67:663-680.
- Falconer, D.S. 1981. *Introduction to Quantitative Genetics*. 2nd ed. p 227. Longerman, London.
- Garwood, V. A., and P. C. Lowe. 1979. Comparison of individual, sire family and index selection for short-term rate of egg production in chickens. *Poult. Sci.* 58:751-753.
- Garwood, V. A., P. C. Lowe, and B. B. Bohren. 1980. An experimental test of the efficiency of family selection in chickens. *Theor. Appl. Genet.* 56:5-9.
- Haldane, J. B. S. 1919. The combination of linkage values and the calculation of distances between the loci of linked factors. *J. Genet.* 8:299-309.
- Henderson, C. R. 1976. A simple method for the inverse of a numerator relationship matrix used in prediction of breeding values. *Biometrics* 32: 69-83.
- Henderson, C. R. 1984. Application of linear models in animal breeding. Univ. of Guelph, Guelph, ON, Canada.
- Jeyaruban, M. G., J. P. Gibson, and R. S. Gowe. 1995. Comparison of index selection and best linear unbiased prediction for simulated layer poultry data. *Poult. Sci.* 74:1566-1576.
- Kinney, T., Jr., B. B. Bohren, J. V. Craig, and P. C. Lowe. 1970. Responses to individual, family or index selection for short-term rate of egg production in chickens. *Poult. Sci.* 49:1052-1064.
- Lynch, M., and B. Walsh. 1998. *Genetics and Analysis of Quantitative Traits*. Sinauer Associates, Sunderland, MA.
- Muir, W. M. 1991. Estimation of response to selection in non-replicated populations. In: Proc. 41st National Breeders Roundtable, St. Louis, MO. pp 95-121.
- Pérez-Enciso, M., and M. Toro. 1992. Classical and mixed-model analysis of an index selection experiment for fecundity in *Drosophila melanogaster*. *J. Anim. Sci.* 70:2673-2681.
- Quinton, M., and C. Smith. 1995. Comparison of evaluation-selection systems for maximizing genetic response at the same level of inbreeding. *J. Anim. Sci.* 73:2208-2212.
- Quinton, M., C. Smith, and M. E. Goddard. 1992. Comparison of selection methods at the same level of inbreeding. *J. Anim. Sci.* 70:1060-1067.
- Robertson, A. 1960. A theory of limits in artificial selection. *Proc. R. Soc. Lond. B Biol. Sci.* 153:234-249.
- Robertson, A. 1961. Inbreeding in artificial selection programmes. *Genet. Res.* 2:189
- Schamber, E. M., and W. M. Muir. 2000. Utilization of Wright's shifting balance theory of evolution in artificial breeding programs: Empirical testing using the model organism *Tribolium castaneum*. *J. Anim. Breed. Genet.* (In press).
- Sorensen, D. A., and B. W. Kennedy. 1984. Estimation of response to selection using least-squares and mixed model methodology. *J. Anim. Sci.* 58:1097-1106.
- Wilson, S. 1974. An experimental comparison of individual, family and combination selection. *Genetics* 76:823-836.

### Notes

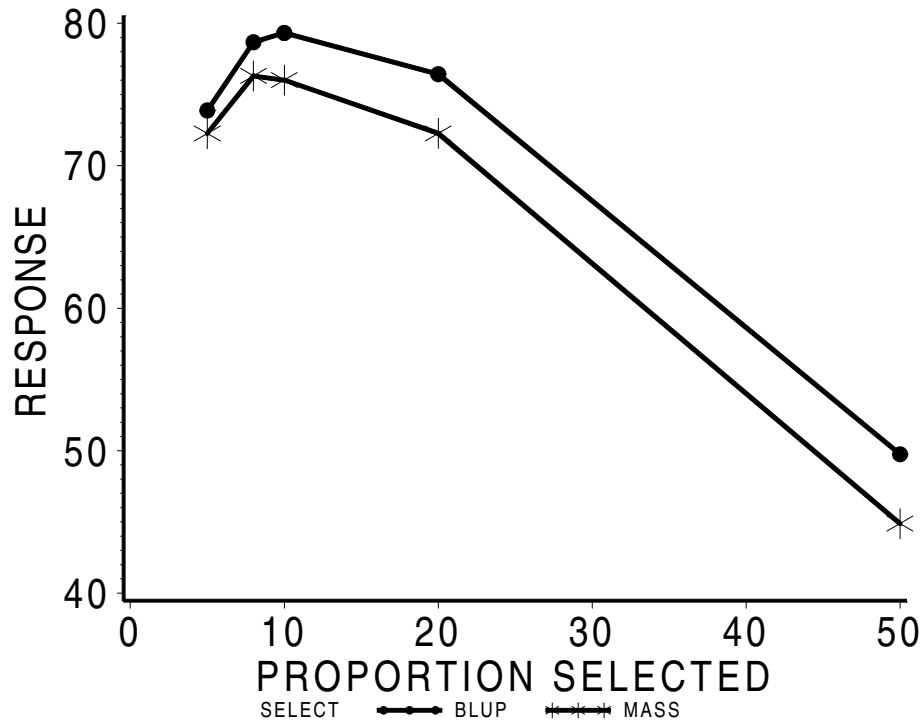
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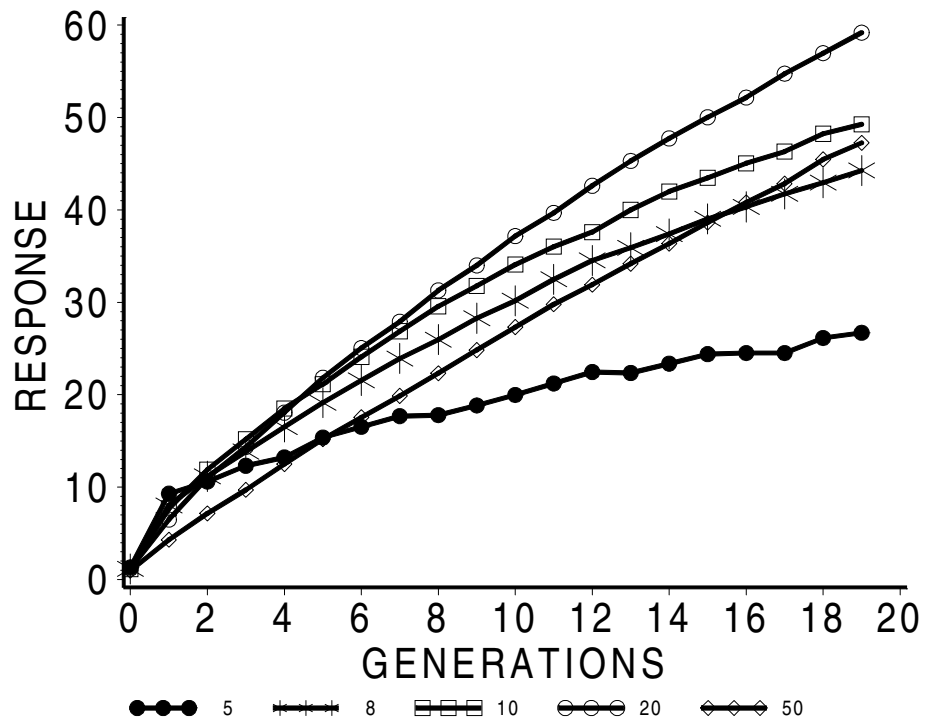
**Figure 1.** Genetic gain (Response) with additive gene effects using BLUP breeding values with 5, 8, 10, 20, or 50% selected.



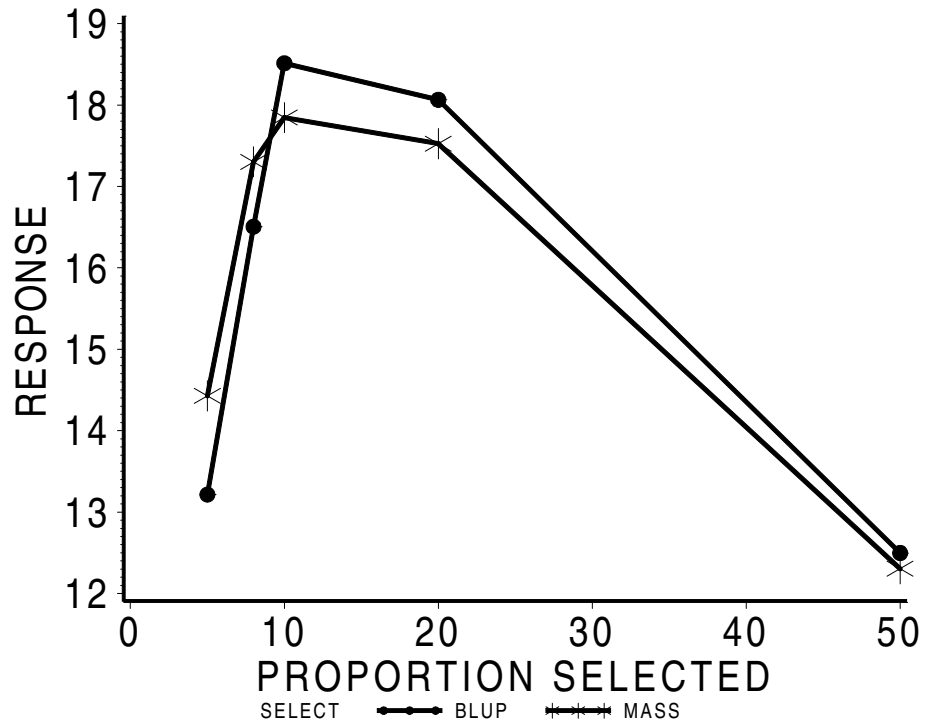
**Figure 2.** Comparison of genetic gain (Response) at Generation 4 with additive gene effects using either BLUP or MASS breeding values for selection.



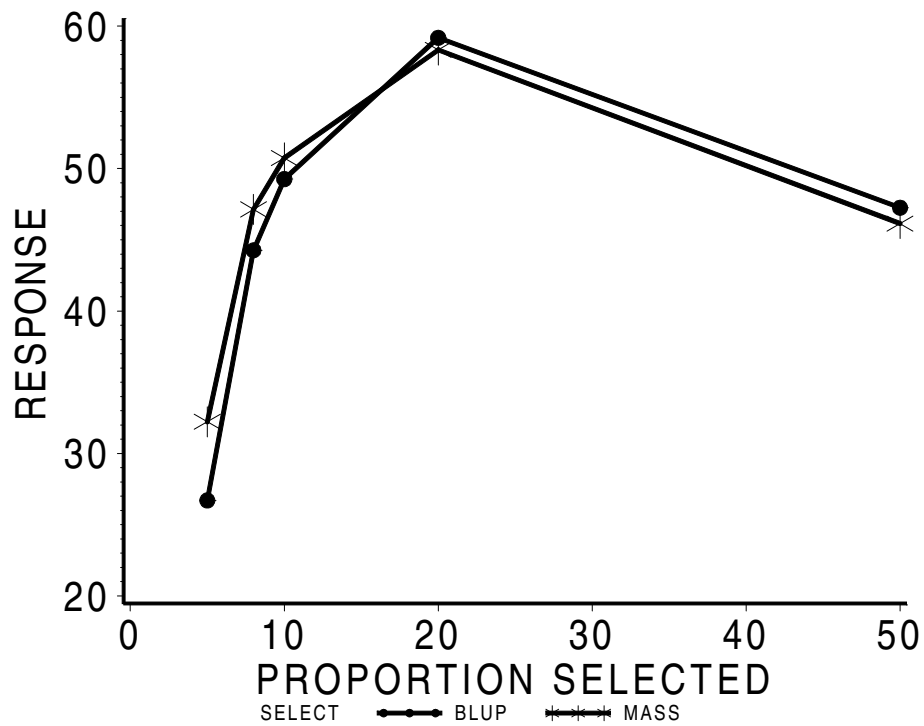
**Figure 3.** Comparison of genetic gain (Response) at Generation 19 with additive gene effects using either BLUP or MASS breeding values for selection.



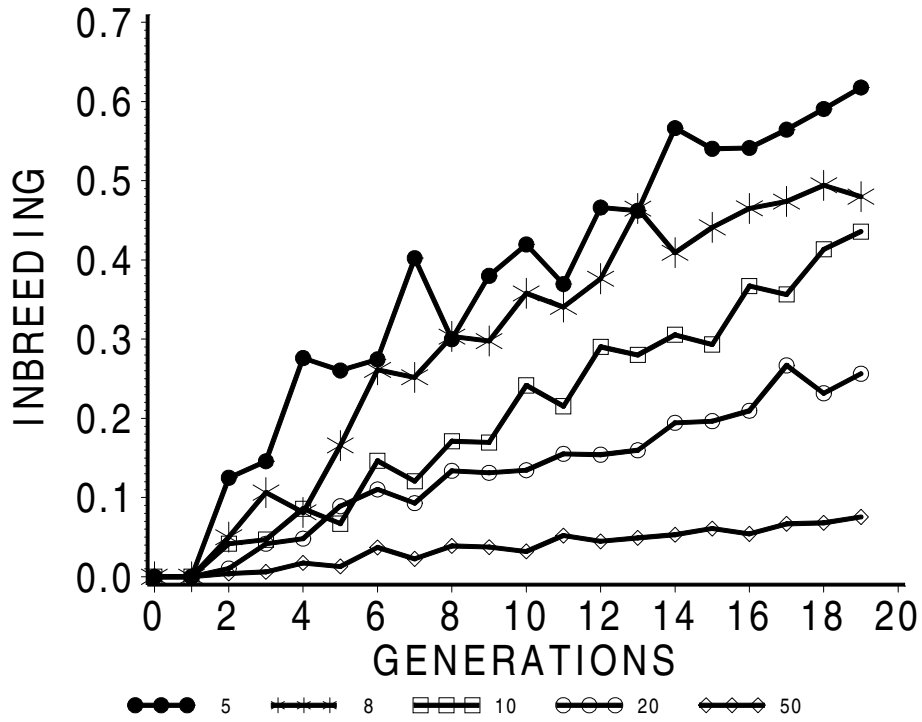
**Figure 4.** Genetic gain (Response) with dominant gene effects using BLUP breeding values with 5, 8, 10, 20, or 50% selected.



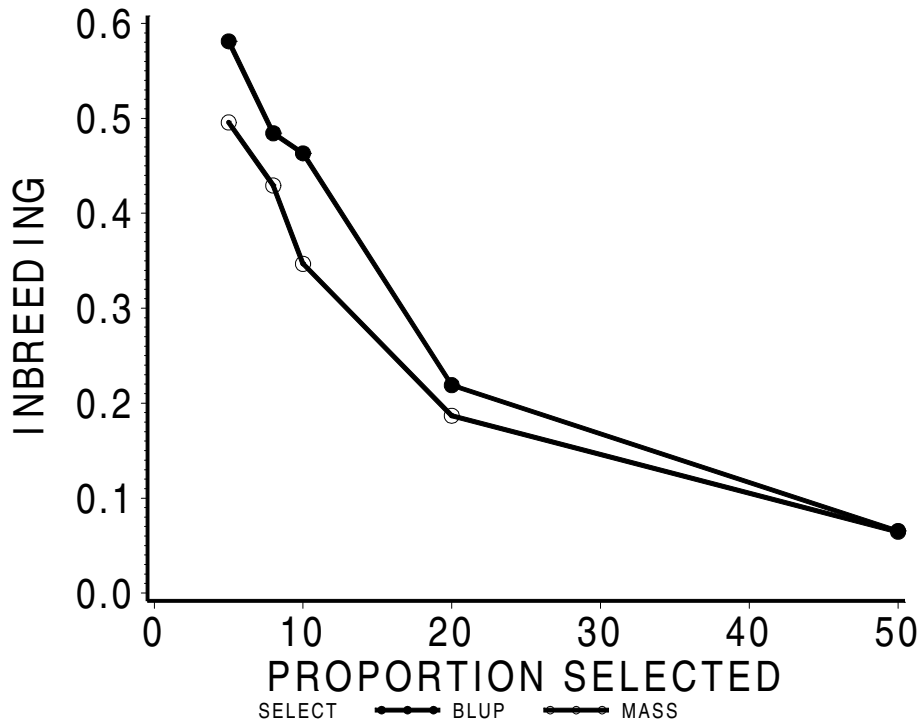
**Figure 5.** Comparison of genetic gain (Response) at Generation 4 with dominant gene effects using BLUP or MASS breeding values for selection.



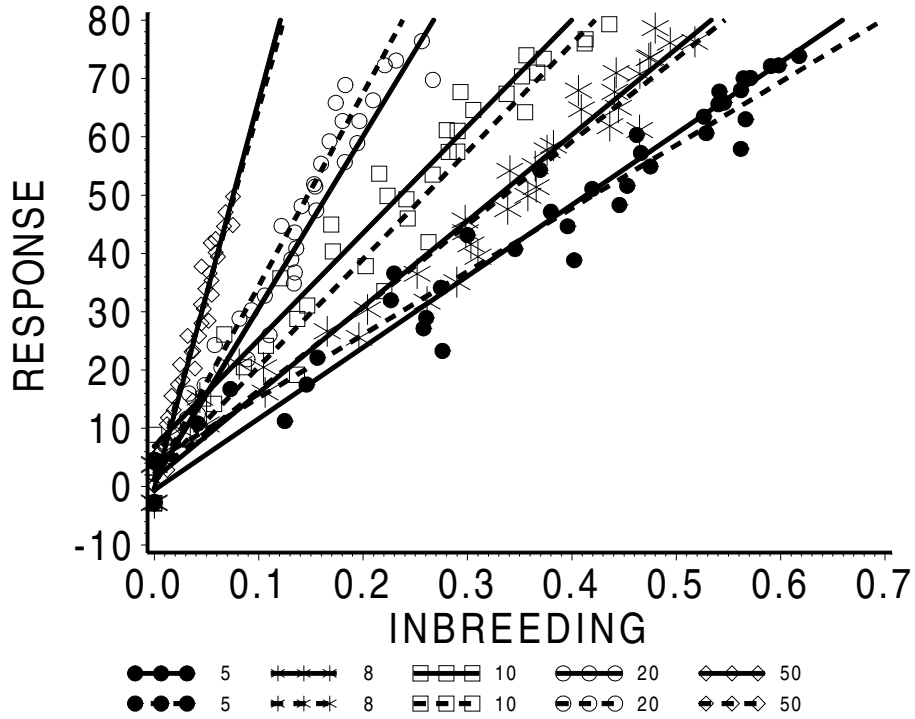
**Figure 6.** Comparison of genetic gain (Response) with dominant gene effects using BLUP or MASS breeding values at Generation 19.



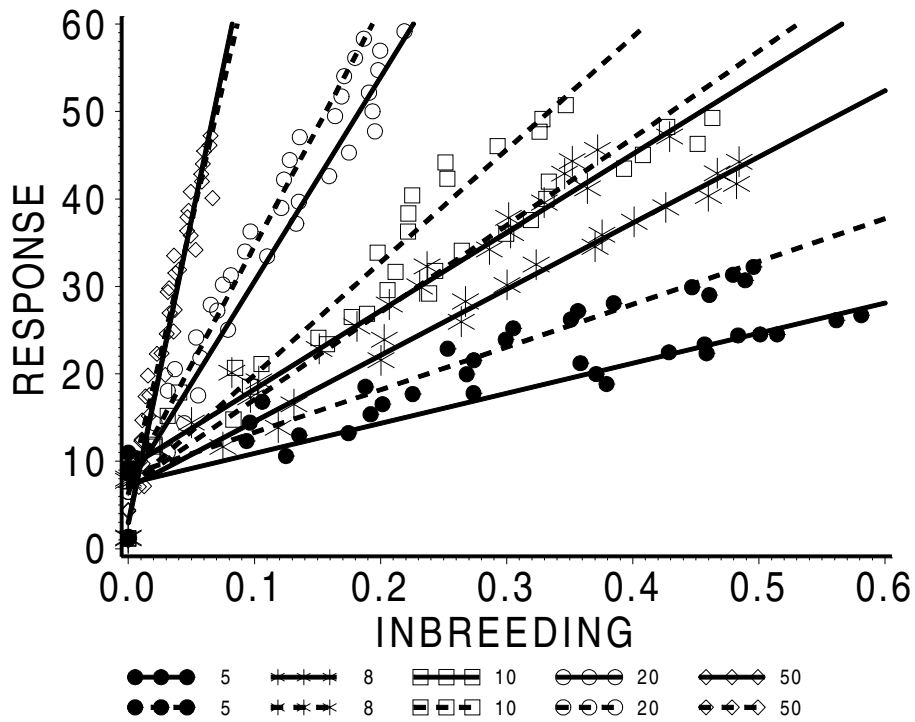
**Figure 7.** Rate of increase in the inbreeding coefficient using BLUP breeding values, and 5, 8, 10, 20, or 50% selected by generation.



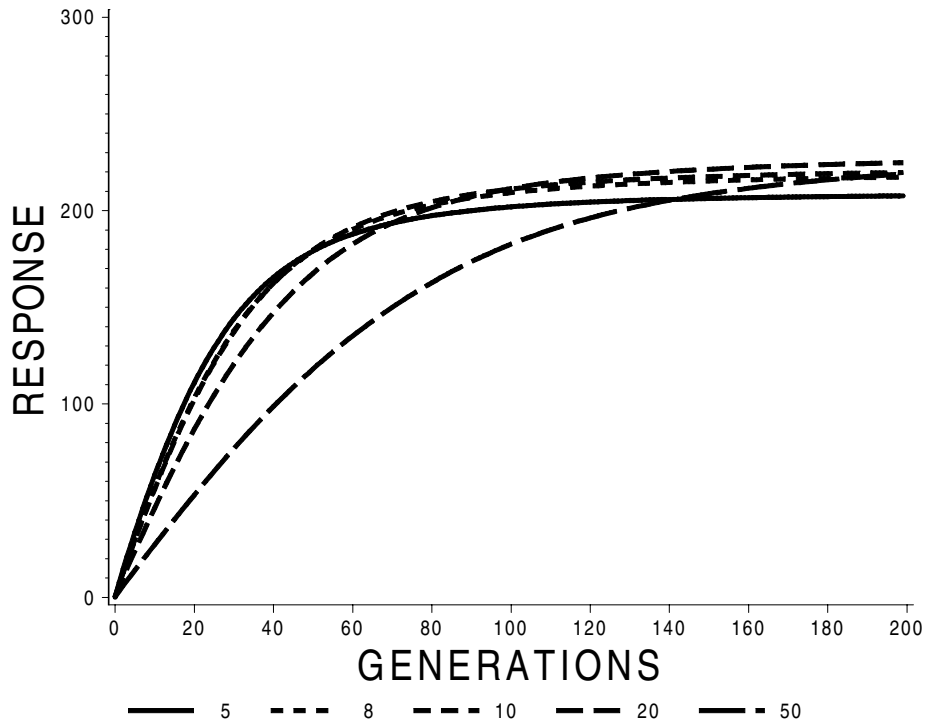
**Figure 8.** Comparison of inbreeding coefficients at generation 19 with BLUP or MASS breeding values used for selection.



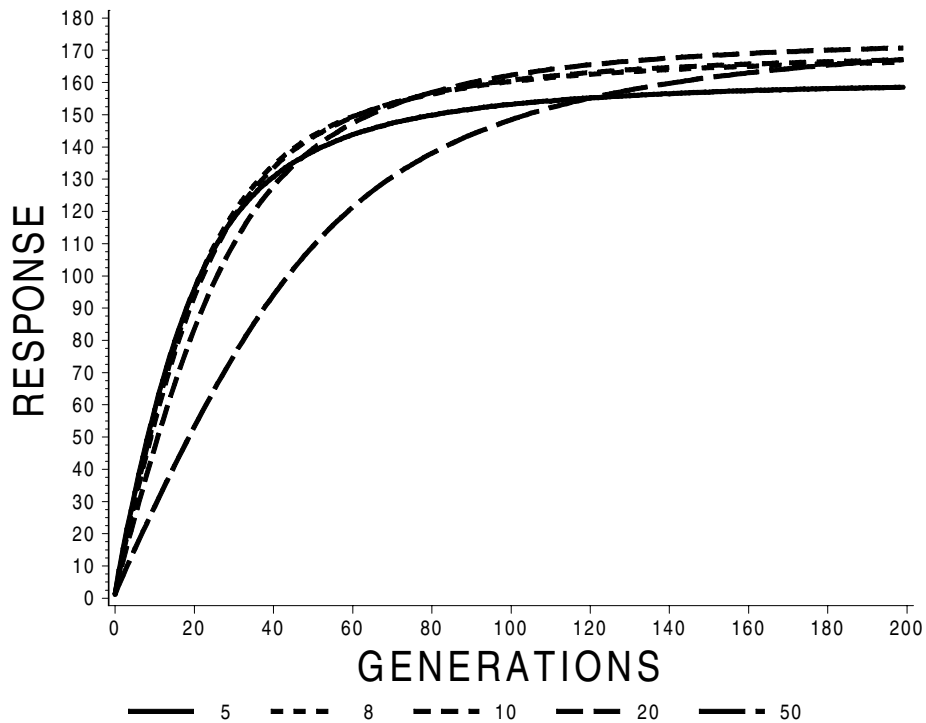
**Figure 9.** Regression of response to selection with additive gene effects on inbreeding coefficient by method of evaluation (BLUP solid line) and 5, 8, 10, 20, or 50% selected.



**Figure 10.** Regression of response to selection with dominant gene effects on inbreeding coefficient by method of evaluation (BLUP solid line) and with 5, 8, 10, 20, or 50% selected.



**Figure 11.** Genetic gain (Response) with additive gene effects using MASS breeding values and 5, 8, 10, 20, or 50% selected in large populations (n = 2,400).



**Figure 12.** Genetic gain (Response) with dominant gene effects using BLUP breeding values and 5, 8, 10, 20, or 50% selected in large populations (n = 2,400).