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# Maximizing genetic gain over multiple generations with quantitative trait locus selection and control of inbreeding<sup>1</sup>

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**ABSTRACT:** Stochastic computer simulation was used to investigate the potential extra genetic gains obtained from gene-assisted selection (GAS) by combining 1) optimization of genetic contributions for maximizing gain, while restricting the rate of inbreeding with 2) optimization of the relative emphasis given to the QTL over generations. The genetic model assumed implied a mixed inheritance model in which a single quantitative trait locus (i.e., QTL) is segregating together with polygenes. When compared with standard GAS (i.e., fixed contributions and equal emphasis on the QTL and polygenic EBV), combined optimization of contributions of selection candidates and weights on

the QTL across generations allowed substantial increases in gain at a fixed rate of inbreeding and avoided the conflict between short- and long-term responses in GAS schemes. Most of the increase of gain was produced by optimization of selection candidates' contributions. Optimization of the relative emphasis given to the QTL over generations had, however, a greater effect on avoiding the long-term loss usually observed in GAS schemes. Optimized contribution schemes led to lower gametic phase disequilibrium between the QTL and polygenes and to higher selection intensities both on the QTL and polygenes than with standard truncation selection with fixed contributions of selection candidates.

Key Words: Gene-Assisted Selection, Genetic Gain, Optimization, Optimized Contributions Selection, Restricted Inbreeding

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## Introduction

Following the rapid development of DNA technologies, many studies have been published in recent years

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on the value of gene- and marker-assisted selection (GAS and MAS, respectively) in practical breeding programs. In particular, substantial efforts have been devoted to predicting the potential extra rates of genetic gain from GAS or MAS in mixed inheritance models in which a particular QTL is segregating together with polygenes. Most studies evaluating GAS or MAS have assumed standard truncation selection (where all selected parents contribute equally to the next generation) and equal emphasis on EBV for the QTL and polygenes (Gibson, 1994; Larzul et al., 1997; Pong-Wong and Woolliams, 1998). The general finding has been that extra gains are expected from GAS and MAS (relative to standard selection on EBV without genotype information) in the early generations of selection, but these extra gains are not maintained in the long-term.

Villanueva et al. (1999) used BLUP evaluation and optimized (rather than fixed) contributions of selection candidates to maximize gains with restrictions on inbreeding. The emphasis given to the QTL EBV relative to the polygenic EBV was, however, fixed (equal emphasis), and therefore not optimal. In contrast, Dekkers and Van Arendonk (1998) and Manfredi et al. (1998) optimized weights on the QTL to maximize response

over multiple generations but assumed fixed contributions of candidates and infinite population sizes with no accumulation of inbreeding.

The methods used by Dekkers and van Arendonk (1998) and Villanueva et al. (1999) could be combined to further increase the benefits from GAS in finite population sizes. The objective of this study was to evaluate, through stochastic simulation, the gains obtained by optimizing both the contributions of selection candidates and the emphasis given to the QTL in the selection criterion across generations.

## Experimental Procedures

### Genetic and Population Models

The trait under selection was genetically controlled by an infinite number of additive loci, each with infinitesimal effect (polygenes), plus a single biallelic (alleles B and b) QTL. The total genetic value of the  $i$ th individual was  $G_i = q_i + u_i$ , where  $q_i$  is the genotypic value due to the QTL and  $u_i$  is the polygenic effect. The QTL had an additive effect ( $a$ ), defined as half the difference between the two homozygotes, and a dominance effect ( $d$ ) defined as the difference between the heterozygote and the average of the two homozygotes. Thus, genotypic values due to the QTL were  $a$ ,  $d$ , and  $-a$  for individuals with genotypes BB, Bb, and bb, respectively (Falconer and Mackay, 1996). The additive genetic variance explained by the QTL in the base population was  $\sigma_q^2 = 2p(1-p)\alpha^2$ , where  $p$  is the initial frequency of the favorable allele (B) and  $\alpha$  is the average effect of gene substitution, equal to  $a + (1-2p)d$  (Falconer and Mackay, 1996).

The base population ( $t = 0$ ) was composed of  $N$  unrelated individuals ( $N/2$  males and  $N/2$  females). Generation 1 ( $t = 1$ ) was obtained from mating of individuals selected at  $t = 0$ . The number of selection candidates ( $N$ ) was constant across generations. At  $t = 0$ , the polygenic effect for each individual was obtained from a normal distribution with mean zero and variance  $\sigma_u^2$ . Alleles at the QTL were chosen at random with appropriate probabilities (i.e., those given by the initial allele frequencies). The QTL and polygenes were in linkage phase equilibrium. The phenotypic value for an individual  $i$  ( $P_i$ ) was obtained by adding to the total genetic value ( $G_i$ ) a normally distributed environmental component with mean zero and variance  $\sigma_e^2$ .

In subsequent generations, the polygenic effect of the offspring was generated as the average of the polygenic effects of their parents plus a random Mendelian deviation. The latter was sampled from a normal distribution with mean zero and variance  $(\sigma_u^2/2)[1 - (F_s + F_d)/2]$ , where  $F_s$  and  $F_d$  are the inbreeding coefficients of the sire and dam, respectively. The QTL alleles were transmitted from parents to offspring in classical Mendelian fashion. A total of 1,000 replicates were performed for each simulation.

### Estimation of Breeding Values

All candidates were phenotyped and genotyped for the QTL prior to selection. The effect of the QTL was assumed known without error. Three types of schemes for estimation of breeding values were compared and they are described below: conventional phenotypic selection (i.e., selection ignoring QTL information; **PHE**), standard GAS (GAS), and optimal GAS (**GAO**). In most simulations, EBV for these three breeding value estimation schemes were obtained from BLUP (i.e., using phenotypes of the candidates and all their relatives). However, in some scenarios, only phenotypic values for the candidates were used (i.e., phenotypic information on their relatives was ignored), and here these schemes are referred to as "mass selection" schemes. Thus, in total, there were six different breeding value estimation schemes: mass selection-PHE, mass selection-GAS, mass selection-GAO, BLUP-PHE, BLUP-GAS, and BLUP-GAO.

*Conventional Phenotypic Selection.* In PHE schemes, information on the QTL was ignored when obtaining EBV. With mass selection (i.e., ignoring phenotypic information on relatives), PHE involved selection on phenotypic values of the candidates without correction for QTL genotype. With BLUP selection, the total EBV ( $EBV_t$ ) was obtained from standard BLUP, using the total initial genetic additive variance ( $\sigma_q^2 + \sigma_u^2$ ) and phenotypic values uncorrected for the QTL effect (i.e.,  $P_i$ ).

*Standard Gene-Assisted Selection.* In GAS schemes,  $EBV_t$  was  $EBV_u + BV_q$ , where  $EBV_u$  is the estimate of the polygenic breeding value and  $BV_q$  is the (assumed known) breeding value due to the QTL. With mass selection,  $EBV_u$  for individual  $i$  was  $h_u^2(P_i - q_i)$ , where  $h_u^2$  is the polygenic heritability and  $q_i$  is the genotypic value for the QTL. With BLUP selection,  $EBV_u$  was obtained from standard BLUP using the polygenic variance ( $\sigma_u^2$ ) and phenotypic values corrected for the QTL effect ( $P_i - q_i$ ). The breeding value for the QTL ( $BV_q$ ) was  $2(1-p)\alpha$ ,  $(1-2p)\alpha$  and  $-2p\alpha$  for individuals with genotype BB, Bb, and bb, respectively (Falconer and Mackay, 1996). Frequency  $p$  was updated each generation to obtain  $BV_q$ .

*Optimal Gene-Assisted Selection.* In GAO schemes, the selection criterion was  $EBV_u + \lambda BV_q$ , where  $EBV_u$  and  $BV_q$  are obtained as in GAS and  $\lambda$  is the optimal weight given to  $BV_q$  for maximizing the sum of genetic means over the planning horizon (i.e., the objective function maximized was  $\Sigma = \sum_{t=1}^T$ , where  $G_t$  is the mean

total genetic value at Generation  $t$  and  $T$  is the number of generations of selection). This is equivalent to maximizing cumulative discounted gain with a discount rate of zero, following Dekkers and Chakraborty (2001). Weights  $\lambda$  were obtained for each sex, genotype, and generation using optimal control theory, following the deterministic model described in Dekkers and Chakraborty (2001) and Chakraborty et al. (2002). A short description of the optimization of weights given to the



QTL is in Appendix 1. Four QTL genotypes (BB, Bb, bB, and bb, where the first letter indicates the allele received from the father) and two sexes were distinguished, resulting in eight index weights to be optimized for each generation.

### Selection Procedures

For the three types of breeding value estimation schemes described above (PHE, GAS, and GAO), two types of selection strategies were considered: 1) standard truncation selection (i.e., selection on a linear index), where the number of parents ( $N_s$  sires and  $N_d$  dams) and family sizes were fixed across generations, and 2) selection on a quadratic index that optimizes the numbers of parents and their contributions each generation to maximize genetic gain, while restricting the rate of inbreeding (Meuwissen, 1997; Grundy et al., 1998; Villanueva et al., 1999). Selection on the linear and quadratic index will be referred to as **L** and **Q**, respectively. The rate of inbreeding in **Q** selection was restricted to the lowest value obtained with the corresponding **L** selection strategy across the three breeding value estimation schemes. The  $EBV_t$  used in the quadratic index differed for the three types of schemes (PHE, GAS, and GAO) and they were obtained as described previously. Weights on the QTL for **Q**-GAO could not be derived directly because the optimal control procedure that was used to optimize weights assumes truncation selection (Chakraborty et al., 2002). Instead, approximate optimal weights were derived assuming truncation selection of the number of parents that was selected with the quadratic index under GAS. Thus, selection decisions for GAO schemes were optimized in two steps. First, the **Q**-GAS scheme was run and the optimized number of males and females selected and the accuracies of EBV for both sexes obtained from this scheme were used as inputs for the optimal control model for obtaining the optimal weights to give to the QTL over generations. Secondly, contributions of candidates were optimized for GAO.

### Gametic Phase Disequilibrium Between the QTL and Polygenes

Selection introduces gametic phase disequilibrium between the QTL and polygenes. With random mating of selected parents, this disequilibrium can be accounted for by modeling mean polygenic values by type of gamete (Dekkers and Van Arendonk, 1998; Chakraborty et al., 2002). The amount of disequilibrium between the polygenes and the QTL at generation  $t$  was computed as the correlation between the QTL value and the polygenic breeding value. Details of this calculation are in Appendix 2.

### Achieved Selection Intensities on Polygenes and the QTL

Index weights  $\lambda$  express the emphasis given to the breeding values for the QTL relative to the polygenes

EBV when the selection criterion is computed. However, they do not give the amount of selection intensity applied on the QTL relative to the polygenes, which depends also on the amount of variation present in the population (Dekkers and Van Arendonk, 1998).

Selection intensity applied to polygenes at Generation  $t$  was computed as  $(\bar{u}_{t+1} - \bar{u}_t)/\sigma_t$ , where  $\bar{u}_t$  is the average true polygenic value at Generation  $t$  and  $\sigma_t$  is the standard deviation of estimated polygenic breeding values. For PHE schemes, estimates of polygenic breeding values were not available, and  $\sigma_t$  was approximated as  $h_u\sigma_u$ . Selection intensity applied to the QTL was computed as  $2(p_{t+1} - p_t)/[2(1 - p_t)]^{0.5}$  (Dekkers and Van Arendonk, 1998).

## Results

### Mass Selection on Linear Index—Deterministic vs. Stochastic Predictions

Dekkers and Van Arendonk (1998) gave predictions of genetic gain for schemes PHE, GAS, and GAO under truncation mass selection. Table 1 shows a comparison of such deterministic predictions with simulation results. The first set of parameters simulated ( $p = 0.05$ ,  $\alpha = 0.25$ ,  $d = 0$ ,  $\sigma_u^2 = 0.3$ ,  $\sigma_e^2 = 0.7$ ,  $N = 160$  and  $N_s = N_d = 16$ ) were those used by Dekkers and Van Arendonk (1998), but for maximization of response in the final generation. For the three types of breeding value estimation schemes (PHE, GAS, and GAO), gains from the simulation were approximately 20% lower than those predicted with the Dekkers-Van Arendonk model because the latter assumes constant polygenic variance over generations. As expected, for this set of parameters, optimization of the weight given to the QTL (GAO) prevented the long-term loss in response at  $t = 15$  that was observed with standard QTL selection (GAS). The highest sum of genetic means over generations ( $\Sigma$ ) was achieved with GAO in both deterministic and stochastic predictions, although the extra gain from GAO over PHE was somewhat lower under the stochastic model. At  $t = 15$ , the QTL was still segregating ( $p = 0.75$ ) in PHE schemes but was fixed in schemes under QTL selection.

When the initial frequency and the QTL effect were increased to 0.15 and 1.0, respectively, the favorable allele was practically fixed ( $P \geq 0.99$ ) in all three schemes by  $t = 6$ . As before, with both deterministic and simulation predictions, the long-term loss in gain (relative to PHE schemes) was avoided with schemes GAO (but not with GAS). Also, GAO gave the highest value for  $\Sigma$ . The rate of inbreeding was very similar for the three schemes (around 2%) and for both sets of parameters.

### Selection on Quadratic Index vs. Selection on Linear Index—Additive QTL

Table 2 shows the gain obtained across generations with schemes PHE, GAS, and GAO under BLUP selection

**Table 1.** Deterministic and stochastic predicted genetic means over generations (*t*) from truncation mass selection for schemes PHE (phenotypic selection), GAS (standard gene-assisted selection), and GAO (optimal gene-assisted selection) for an additive QTL with effect *a* and initial frequency of the favorable allele *p*

<i>t</i>	Deterministic			Stochastic		
	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>
<i>p</i> = 0.05, <i>a</i> = 0.25						
1	0.431	+0.008	+0.008	0.421	+0.006	+0.002
2	0.861	+0.015	+0.013	0.791	+0.016	+0.001
3	1.293	+0.023	+0.020	1.150	+0.032	+0.005
4	1.727	+0.035	+0.029	1.499	+0.053	+0.016
5	2.163	+0.047	+0.041	1.847	+0.068	+0.028
6	2.601	+0.053	+0.052	2.190	+0.071	+0.037
8	3.485	+0.039	+0.071	2.864	+0.045	+0.053
10	4.377	-0.001	+0.071	3.520	-0.001	+0.052
15	6.601	-0.108	+0.004	5.055	-0.110	+0.000
Σ	52.485	-0.048	+0.613	42.268	+0.031	+0.393
<i>p</i> = 0.15, <i>a</i> = 1.00						
1	0.773	+0.192	+0.047	0.734	+0.194	+0.039
2	1.620	+0.404	+0.004	1.517	+0.423	+0.008
3	2.432	+0.073	-0.042	2.234	+0.090	-0.024
4	3.095	-0.118	-0.026	2.758	-0.087	-0.009
5	3.640	-0.190	+0.008	3.152	-0.146	+0.020
6	4.135	-0.213	+0.033	3.492	-0.160	+0.019
8	5.088	-0.221	+0.053	4.132	-0.163	+0.033
10	6.034	-0.222	+0.057	4.741	-0.157	+0.047
15	8.396	-0.222	+0.057	6.179	-0.140	+0.066
Σ <sup>b</sup>	74.248	-1.849	+0.520	59.088	-1.070	+0.498

<sup>a</sup>GAS and GAO values are those deviated from PHE.

<sup>b</sup>The last row shows the sum of genetic means over generations.

tion on a linear or a quadratic index for an additive QTL with *a* = 0.5 and *d* = 0. Additional simulation parameters were *N* = 160, *N<sub>s</sub>* = *N<sub>d</sub>* = 40,  $\sigma_u^2 = 0.2$ ,  $\sigma_e^2 = 0.8$ , and *p* = 0.15. Thus, at *t* = 0, the additive variance explained by the QTL and the total heritability were  $\sigma_q^2 = 0.064$  and  $h_t^2 = 0.25$ , respectively. Selection on the quadratic index restricted the rate of inbreeding to 1% per generation, which was the rate of inbreeding ob-

tained in the GAS and GAO schemes with truncation selection (the rate obtained in the PHE truncation selection scheme was about 0.9%). This combination of parameters avoided the loss of the favorable allele in all replicates, both in methods using and ignoring QTL information and with L and Q selection.

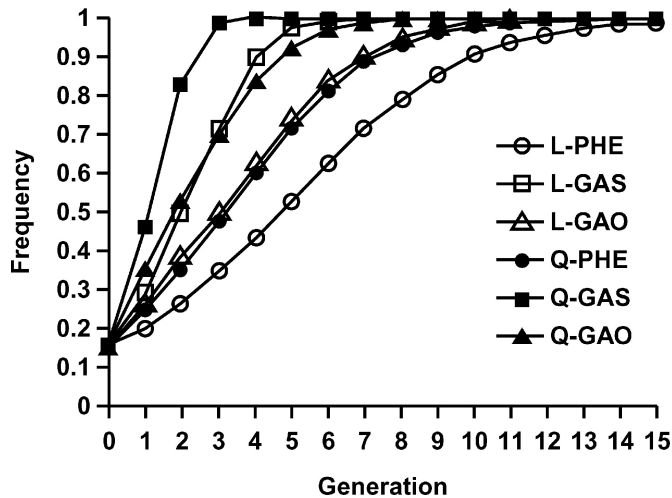
Optimization of contributions clearly improved rates of gain for all three schemes (Table 2). At any genera-

**Table 2.** Genetic means over generations (*t*) from BLUP selection on a linear or a quadratic index for three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO) for an additive QTL (*a* = 0.5, *d* = 0)

<i>t</i>	Linear index			Quadratic index		
	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>
1	0.202	+0.048	+0.041	0.329	+0.110	+0.074
2	0.433	+0.112	+0.076	0.660	+0.259	+0.125
3	0.663	+0.189	+0.111	0.986	+0.284	+0.167
4	0.897	+0.236	+0.140	1.315	+0.190	+0.179
5	1.136	+0.215	+0.155	1.633	+0.091	+0.155
6	1.368	+0.160	+0.157	1.925	+0.015	+0.114
7	1.595	+0.099	+0.146	2.198	-0.044	+0.073
8	1.816	+0.041	+0.122	2.451	-0.085	+0.036
9	2.022	-0.005	+0.094	2.685	-0.109	+0.014
10	2.216	-0.038	+0.070	2.909	-0.125	-0.001
15	3.058	-0.100	+0.011	3.948	-0.139	-0.014
Σ <sup>b</sup>	26.023	+0.619	+1.230	34.793	-0.112	+0.868

<sup>a</sup>GAS and GAO values are those deviated from PHE.

<sup>b</sup>The last row shows the sum of genetic means over generations.



**Figure 1.** Frequency of the favorable allele for an additive QTL ( $a = 0.5$ ,  $d = 0.0$ ) over generations with BLUP selection on a linear (L) or a quadratic (Q) index for three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO).

tion, the lowest gain obtained with Q selection was higher than the highest gain from L selection. The benefit of the quadratic index over the linear index was greatest for Generation 1 (76% for GAS) and decreased over generations to 28% for GAO in Generation 15. Optimizing contributions increased the sum of genetic gains over generations ( $\Sigma$ ), which was the objective maximized to obtain the optimal QTL weights with GAO, by 33.7, 30.2, and 30.9% for PHE, GAS, and GAO, respectively.

The long-term loss in gain observed with standard GAS was not avoided when BLUP EBV were used together with optimized contributions. However, for both selection strategies (L and Q), optimization of the weight given to the QTL (GAO) prevented the long-term loss that was observed with standard QTL selection (GAS). With truncation selection, the favorable allele was fixed ( $P \geq 0.99$ ) by the end of the planning horizon ( $t = 15$ ) for all three schemes (Figure 1). At this point, cumulative gain from PHE was 3% higher than that from GAS, but 0.4% lower than that from GAO (Table 2). Optimization of contributions led to a faster increase in  $p$  than truncation selection (Figure 1). At  $t = 10$ , where the favorable allele was practically fixed for all three schemes, cumulative gain from GAO was practically the same as gain from PHE (Table 2). This represents a significant improvement over standard GAS, which produced 4% lower gain than PHE.

The highest value for  $\Sigma$  was obtained with GAO for both L and Q selection strategies, although differences were limited (Table 2); GAO resulted in 4.7 and 2.3% greater  $\Sigma$  than PHE and GAS, respectively, for L selection, and 2.5 and 2.8% greater  $\Sigma$  for Q selection.

### Selection on Quadratic Index vs. Selection on Linear Index—Dominant QTL

The advantage of GAO over both GAS and PHE was also observed when the favorable allele was completely dominant for both L and Q selection strategies (Table 3). Parameters simulated were the same as those for an additive gene (Table 2) except that  $d$  was equal to 0.5. The extra early gain from using the QTL information was lost in the long term with standard QTL selection (GAS) but maintained with optimal QTL selection (GAO). As with an additive QTL, the extra long-term response of GAO relative to PHE was higher with selection on the linear index than with selection on the quadratic index, although optimization of contributions always led to higher absolute gains than selection on the linear index.

As expected, the rate of fixation of the favorable allele was slower when the QTL showed dominance (Figure 2). At  $t = 15$ , the frequency of the favorable allele was 0.90, 0.98, and 0.94 for truncation PHE, GAS, and GAO, respectively. Corresponding values for optimized contributions selection were 0.92, 0.99 and 0.98. Average QTL frequencies greater than 0.95 were only achieved for L-GAS (at  $t = 9$ ), Q-GAS (at  $t = 5$ ), and Q-GAO (at  $t = 13$ ). Trends in average frequencies were very similar for PHE and GAO for both L and Q selection.

### Index Weights on the QTL

Figure 3 shows the index weights applied across generations for PHE, GAS, and GAO schemes under selection on the quadratic index. Corresponding weights applied under the linear index were very similar (results not shown). As mentioned above, for GAO, the weights used in Q selection were obtained from L selection and therefore no distinction is made between these two types of selection. Weights for GAS were constant (and equal to one), but weights for GAO changed over generations, as expected. For PHE, implicit weights on the QTL depend on the extent that phenotypes are regressed toward zero so the value given in Figure 3 (i.e., the heritability) represents a lower bound for the weight (i.e., for when own phenotype is all that is used). Weights for sires and dams were equal because equal numbers were selected ( $N_s = N_d = 40$  and approximately 32 for truncation and optimized contributions selection, respectively). This also meant that weights for the two types of heterozygotes (Bb and bB) were identical (i.e.,  $b_3 = b_2 = 0.0$ ) because polygenic means were identical.

Weights  $b_4$  were always greater than weights  $b_1$  (except at  $t = 14$  where  $b_1 = b_4$ ). Thus, more emphasis was given to selection against the undesired genotype (bb) than to selection in favor of the desired genotype (BB) (Dekkers and Van Arendonk, 1998). With  $d = 0.0$ , weights in the last generation were equal to those for GAS since the objective in that generation simply is to maximize response at  $t = 15$ . This is not the case for  $d = 0.5$ , because GAS uses the standard gene substitution

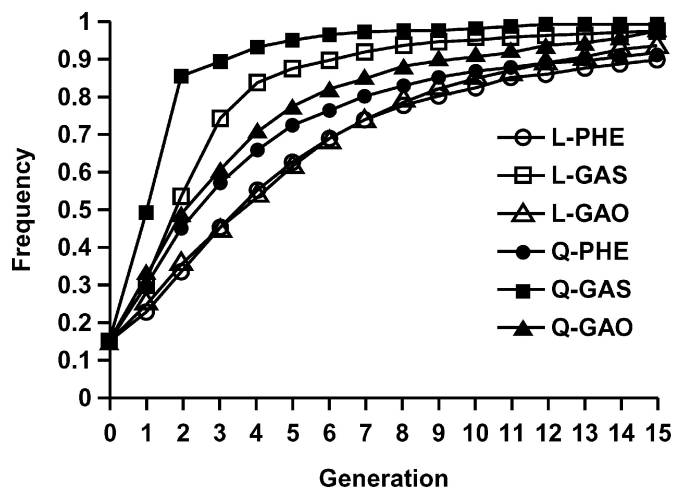
**Table 3.** Genetic means over generations ( $t$ ) from BLUP selection on a linear or a quadratic index for three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO) for a dominant QTL ( $a = d = 0.5$ )

$t$	Linear index			Quadratic index		
	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>	PHE	GAS <sup>a</sup>	GAO <sup>a</sup>
1	0.276	+0.056	+0.031	0.449	+0.102	+0.051
2	0.573	+0.087	+0.030	0.838	+0.076	+0.047
3	0.839	+0.078	+0.027	1.163	+0.013	+0.043
4	1.078	+0.038	+0.029	1.439	-0.039	+0.041
5	1.288	+0.006	+0.036	1.688	-0.066	+0.037
6	1.480	-0.021	+0.040	1.918	-0.081	+0.034
10	2.162	-0.057	+0.055	2.782	-0.095	+0.021
15	2.950	-0.064	+0.050	3.801	-0.087	+0.027
$\Sigma^b$	26.377	-0.259	+0.665	34.328	-0.814	+0.479

<sup>a</sup>GAS and GAO values are those deviated from PHE.

<sup>b</sup>The last row shows the sum of genetic means over generations.

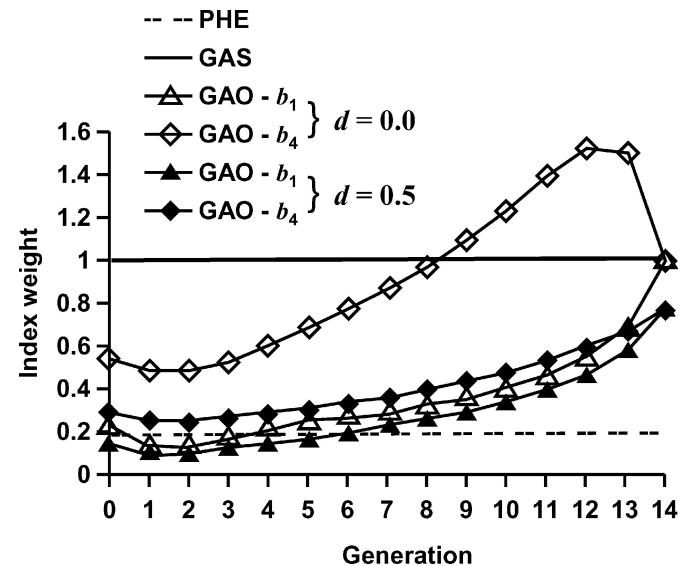
effect for the QTL ( $\alpha = a + [1 - 2p]d$ ), using frequencies among selection candidates, rather than frequencies among selected mates, and does, therefore, not maximize the mean of progeny (Dekkers, 1999). Index weights decreased slightly in the first generation and increased afterwards. For an additive QTL,  $b_4$  was intermediate to those for PHE and GAS in the earlier generations ( $t < 9$ ), but greater than that for GAS in later generations ( $t > 9$ ), when the QTL was close to fixation with GAO (see Figure 1). For a dominant QTL,  $b_4$  was intermediate to those for PHE and GAS across generations. Index weight  $b_1$  was initially lower for GAO than for PHE (when the frequency of the favorable allele was less than 0.6) and intermediate to those for PHE and GAS in later generations.



**Figure 2.** Frequency of the favorable allele for a dominant QTL ( $a = d = 0.5$ ) over generations with BLUP selection on a linear (L) or a quadratic (Q) index for three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO).

### Gametic Phase Disequilibrium between the QTL and the Polygenes

When the QTL was additive, the rate of fixation was high for schemes using the QTL, and gametic phase disequilibrium between the QTL and polygenes could only be computed in early generations (before fixation), particularly for schemes GAS. The amount of disequilibrium generated between the QTL and the polygenes is shown in Figure 4 for a dominant QTL. The disequilibrium generated was always lower for selection on the quadratic index than for selection on the linear index. With L selection, the amount of disequilibrium increased initially (i.e., at low frequencies of the favor-



**Figure 3.** Index weights applied to an additive ( $a = 0.5$ ,  $d = 0.0$ ) or a dominant ( $a = d = 0.5$ ) QTL with phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO) schemes under BLUP selection on a quadratic index.



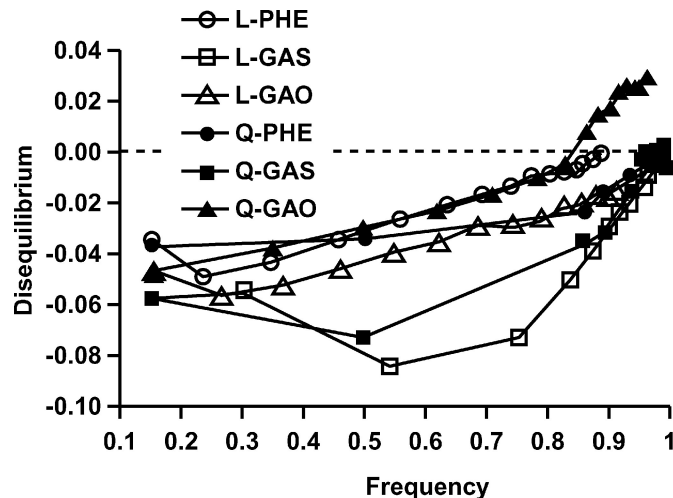
able allele) and decreased afterward. With Q selection, the initial increase only occurred with the GAS scheme. In general, with both L and Q selection, the highest amount of disequilibrium was observed with GAS. For  $p$  greater than 0.4, the lowest amount of disequilibrium was observed in the PHE scheme with L selection, and in the GAO scheme with Q selection. Surprisingly, for the latter scheme, disequilibrium became positive even when the frequency of the favorable allele was high ( $p > 0.80$ ).

*Selection Intensities Applied on the QTL and the Polygenes*

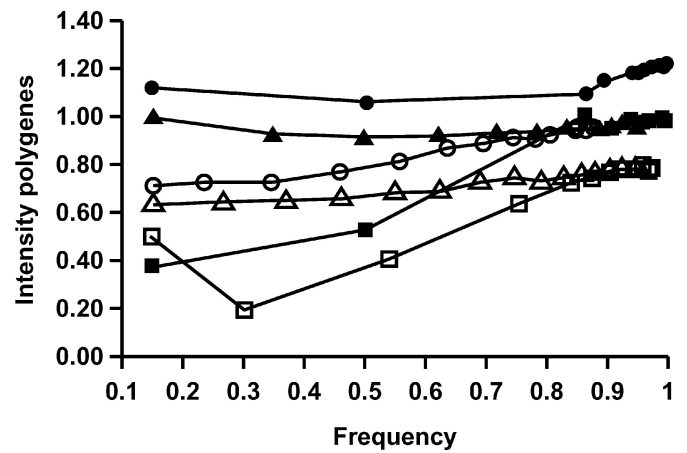
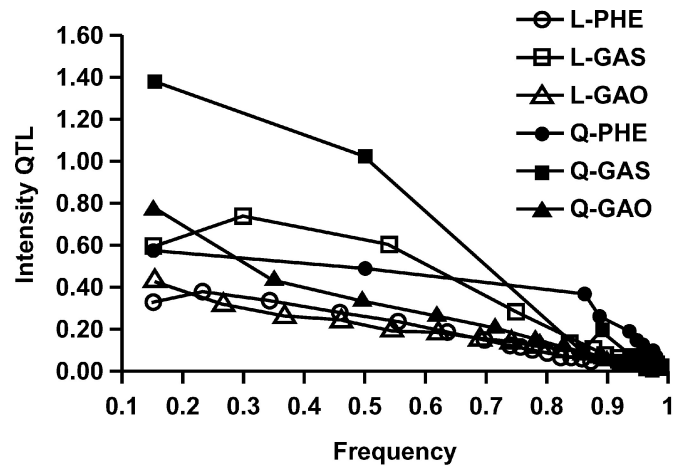
Selection intensities applied to the QTL and polygenes under the different schemes are shown in Figure 5. For all schemes (PHE, GAS, and GAO), higher intensities were applied to both the QTL and the polygenes when candidate contributions were optimized. In general, intensities applied to the QTL were highest for GAS and lowest for PHE (at low frequencies) or GAO (at higher frequencies). For polygenes, intensities were highest for PHE and lowest for GAS.

**Discussion**

This study has shown that substantial gains can be obtained by using information on an identified QTL when both the contributions of the selection candidates and the relative emphasis given to the QTL are optimized and also shows that these gains can be maintained in the long term. Importantly, extra genetic gains were not associated with an increase in inbreed-



**Figure 4.** Change in the amount of gametic phase disequilibrium generated between a dominant QTL ( $a = d = 0.5$ ) and polygenes in relation to the frequency of the favorable QTL allele for BLUP selection on a linear (L) or a quadratic (Q) index and three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO).



**Figure 5.** Change in achieved selection intensities on a dominant QTL ( $a = d = 0.5$ ) and on polygenes in relation to the frequency of the favorable QTL allele for BLUP selection on a linear (L) or a quadratic (Q) index and three types of schemes: phenotypic (PHE), standard (GAS), and optimal gene-assisted selection (GAO).

ing, as comparisons between L and Q schemes were made at the same inbreeding rate. Most of the increase in gain was produced by optimizing contributions of selection candidates. Optimization of the relative emphasis given to the QTL over generations had, however, a greater impact on avoiding the long-term loss usually observed in selection schemes using QTL information. Differences in long-term gains between GAO and PHE schemes were however very small.

The original method of Dekkers and Van Arendonk (1998) has been extended to include unequal selection in the two sexes, nonadditive QTL, multiple QTL, and discounted response (Dekkers and Chakraborty, 2001; Chakraborty et al., 2002; Dekkers et al., 2002) and has already proved to be efficient to avoid the long-term loss with fixed contributions (i.e., with linear index selection). However, an important assumption in their model was that polygenic genetic variance was constant across generations. When the reduction of polygenic variance as a result of selection was taken into account, gains (obtained from weights that were derived assum-

ing constant variance) were significantly lower, but the optimized weights still avoided the long-term conflict (Table 1).

There has been some controversy over whether there is always a loss in long-term gain by using information on the QTL or on (linked) markers, relative to selection schemes that ignore gene or marker information. The definition of “long-term” is somewhat arbitrary and this may have influenced this controversy. Here we define “long-term” as the generation where the favorable allele is fixed in all schemes compared. In general, the occurrence of the long-term loss depends on a number of parameters. Under mixed inheritance models where the QTL is segregating together with polygenes, and selection gives equal emphasis to EBV for the QTL and polygenes, selection intensity on the polygenes is reduced when high short-term selection pressure is imposed on the QTL. With truncation mass selection (i.e., EBV are estimated from phenotypes of candidates alone), the long-term loss from GAS is only avoided when the gene is completely recessive and has a large effect (e.g., 1.5 to 2 phenotypic standard deviations; Pong-Wong and Woolliams, 1998). This applies regardless of whether polygenic variance is modeled by an infinite or finite number of loci (e.g., Fournet et al., 1997). With finite locus models and infinite population size, the ultimate response will be the same for all selection strategies because all favorable alleles (QTL and polygenes) will eventually be moved to fixation, as shown by Dekkers and Settar (2003). The path to reaching that ultimate genetic level does, however, differ between GAS and phenotypic selection: GAS has greater short-term response than phenotypic selection, followed by lower response in the medium term. Unlike the infinitesimal model (where the loss in early polygenic response is not recovered), however, in finite locus models, the polygenic response that GAS loses in early generations is completely regained in the long term (because all favorable polygenic alleles eventually reach fixation). The lower medium-term response from GAS is, however, not very different when using an infinite vs. a finite locus model. An additional factor that plays a role in finite population sizes is the probability of losing favorable polygenes because of drift. This probability is slightly greater for GAS than for phenotypic selection (because GAS places less emphasis on polygenes). Although these differences are small, this does result in a slightly lower ultimate response for GAS than for phenotypic selection (Dekkers and Settar, 2003).

With BLUP evaluation, there is also a decrease in the selection intensity applied to polygenes when QTL information is used. However, the long-term loss of using the genotype information with truncation selection on BLUP EBV can be decreased relative to mass selection and even avoided. There are several factors that contribute to this (Villanueva et al., 1999). The most important one is that there is an extra bias with BLUP when QTL information is ignored because with BLUP,

the EBV of an individual is regressed toward the performance of its parents, and this regression is not appropriate when a major gene is segregating. This leads to ranking errors within genotypes that do not occur with mass selection (Villanueva et al., 1999). Other factors are the greater accuracy of polygenic EBV with BLUP than with mass selection, which reduces the relative magnitude of QTL BV, the reduced bias in EBV as a consequence of selection-induced gametic phase disequilibrium between the QTL and polygenic effects, and the lack of bias in the heritability used in the evaluation when using the genotype information to correct the phenotypic records before BLUP evaluation (there is not an appropriate heritability to be used in standard BLUP evaluation when the phenotype includes major gene effects). In any case, whether or not long-term response with GAS-BLUP is lower than long-term response using BLUP without QTL information depends on selection intensity, gene effect, gene frequency, population size, and heritability.

The above comparisons are for one-generation optimization schemes (i.e., standard truncation selection and equal emphasis on the QTL and polygenic EBV in the selection criterion). The use of BLUP EBV and optimized contributions with a restriction on the rate of inbreeding per se did not avoid the long-term loss for a particular set of parameters for which the loss occurred under truncation selection (see GAS in Tables 2 and 3). Similar results were observed when selection was on markers rather than on the QTL itself (Villanueva et al., 2002). Thus, the only way to consistently eliminate the detrimental long-term effect with GAS and MAS is by optimizing weights on the QTL in the selection criterion.

The finding that using optimal contributions leads to a positive gametic phase disequilibrium between the QTL and polygenes during the fixation process (Figure 4) requires some explanation. It should be remembered that the quadratic index that defines the optimal contributions attempts to 1) make the contribution of a candidate to the next generation equal to its desired long-term contribution conditional on the observed information (Grundy et al., 1998) and 2) uses the estimated Mendelian sampling term as the selective advantage and not the breeding value (Avenidaño et al., 2003). Therefore, in each generation of selection, a considerable part of the selection pressure will be within families and between-family selection will be kept to the minimum (the degree of between-family selection depends inversely upon the accuracy of estimates of Mendelian sampling terms). In this context, families with a high frequency of the favored B allele will lose little or no selection intensity for the polygenic variation within families, whereas families with a lower frequency will lose selection intensity because the b allele is selected against within that family. Therefore, as selection toward fixation progresses, the optimal contributions method favors an emerging association of the B allele with greater polygenic merit. In contrast, truncation

selection increases the frequency of the B allele by placing a much stronger selection between families; families with high frequency of the B allele tend to be selected even if they have lower polygenic EBV, which creates the negative disequilibrium observed. Note that within families, a negative association between the Mendelian sampling term for the polygenic merit and the QTL will exist for both selection strategies.

Here, optimization of selection decisions in GAO was carried out in two steps. First, optimal weights on the QTL breeding value were obtained using the model of Dekkers and van Arendonk (1998), which assumes fixed contributions (i.e., truncation selection) and constant polygenic genetic variances. Secondly, contributions were optimized. Simultaneous optimization of both QTL weights and contributions is expected to lead to further benefits from GAS, both in the short and in the long term, but the optimization becomes very complex. Also, the objective function maximized to optimize QTL weights was the sum of the average total genetic value in each generation  $t$  of the planning horizon but the economic benefit of genotyping for the QTL depends on the relative costs of genotyping and the sale value of animals carrying one or two copies of the favorable allele (Amer and Villanueva, 2000). Including economic information would further complicate the optimization. Genetic algorithms could prove useful to solve this type of problem.

### Implications

This study demonstrates that the conflict between short- and long-term genetic gains usually observed when quantitative trait locus information is incorporated in the selection criterion (compared with gains obtained from selection that ignores quantitative trait locus information) can be consistently avoided when the weights given to the quantitative trait locus over generations are optimized. High benefits are achieved by combining optimization of genetic contributions with optimization of weights given to the quantitative trait locus. Importantly, there are no associated costs of further increases in inbreeding because the inbreeding rate is managed simultaneously. Therefore, commercial populations can only benefit from using these optimization tools when information on quantitative trait loci affecting traits of economic importance is available.

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### Appendix 1: Optimization of Weights Given to the QTL Relative to the Polygenes

The optimal weight to be given to the QTL relative to the polygenes was obtained by using the deterministic model described in Dekkers and Chakraborty (2001). Four QTL genotypes (BB, Bb, bB, and bb, where the first letter indicates the allele received from the father) and two sexes were distinguished. Genotypes BB, Bb, bB, and bb are denoted by  $m = 1, 2, 3,$  and  $4,$  respectively. Optimal control theory was used to obtain the weights given to the QTL breeding value for individuals of each sex and genotype. The optimal solutions were those that maximized the cumulated total genetic value over the planning horizon. The objective function maximized was  $\Sigma = \sum_{t=1}^T G_t$ , where  $G_t$  is the mean total genetic value at Generation  $t$  and  $T$  is the number of generations of selection.



Selection was assumed to be by truncation on an index that combines the QTL and the polygenic breeding values. Let  $g_{mt}$  be the mean total breeding value of individuals of genotype  $m$  at Generation  $t$ , deviated from the mean total breeding value of individuals with genotype Bb ( $m = 2$ ). The selection index for individual  $i$  of sex  $j$  and genotype  $m$  at Generation  $t$  was

$$I_{ijmt} = b_{jmt}g_{mt} + (\hat{u}_{ijmt} - \bar{u}_{mt})$$

where  $b_{jmt}$  is the weight (optimized) given to the QTL breeding value for individuals of sex  $j$  and genotype  $m$  at Generation  $t$ ,  $\hat{u}_{ijmt}$  is the estimated polygenic breeding value for individual  $i$  and  $\bar{u}_{mt}$  is the average estimated polygenic breeding value of individuals with genotype  $m$ . The mean total breeding value of individuals of genotype  $m$ , expressed as a deviation from the average breeding value of individuals with genotype Bb was:

$$g_{mt} = n_m [\alpha + (1 - p_{st} - p_{dt}) d] \\ + (\bar{u}_{mt} - \bar{u}_{2t}) = n_m \alpha + (\bar{u}_{mt} - \bar{u}_{2t})$$

where  $n_m$  is an indicator variable equal to +1, 0, 0, and -1 for  $m$  equal to 1, 2, 3, and 4, respectively, and  $p_{st}$  and  $p_{dt}$  are the frequencies of the favorable allele (B) among paternal and maternal gametes that produce Generation  $t$ . Note that  $\alpha_t = \alpha + (1 - p_{st} - p_{dt})d$  (Dekkers and Chakraborty, 2001) and then  $g_{1t} = t + \hat{u}_{1t} - \hat{u}_{2t}$ ,  $g_{2t} = 0$ ,  $g_{3t} = \hat{u}_{3t} - \hat{u}_{2t}$ , and  $g_{4t} = -\alpha_t + \hat{u}_{4t} - \hat{u}_{2t}$ . This index reflects the fact that the difference in averages for the different QTL genotypes is a result not only of the difference due to the QTL but also a result of the linkage disequilibrium generated between QTL and the polygenes (Dekkers and Van Arendonk, 1998).

With mass selection the individual's polygenic breeding value estimate is  $\hat{u}_{ijmt} = h^2(P_{ijm} - q_m)$ , where  $h^2$  is the polygenic heritability,  $P_{ijm}$  is the phenotypic value of individual  $i$  of sex  $j$  and genotype  $m$  and  $q_m$  is the genetic value of the QTL genotype  $m$  (i.e.,  $q_1 = \alpha$ ,  $q_2 = q_3 = d$ , and  $q_4 = -\alpha$ ). With BLUP selection the individual's polygenic breeding value estimate ( $\hat{u}_{ijmt}$ ) is obtained from standard BLUP using the polygenic variance and the phenotypic values corrected for the major gene effect ( $P_{ijm} - q_m$ ).

Since  $b_{j2t}$  was set to zero, six variables (index weights for genotypes  $m = 1, 3$ , and 4 for both sexes) were optimized each generation.

Selection on index  $I_{ijmt}$  involves truncation selection across the four genotype classes (Dekkers and Chakraborty, 2001). Dekkers and Van Arendonk (1998) showed how the truncation points for each class can be transformed to index weights  $b_{jmt}$ :

$$b_{jmt} = \sigma_j (x_{jmt} - x_{j2t})/g_{mt}$$

where  $x_{jmt}$  is the truncation point corresponding to the fraction selected of individuals of sex  $j$  of genotype  $m$

in Generation  $t$  and  $\sigma_j$  is the standard deviation of polygenic EBV within genotype class. Optimal fractions selected that maximize the objective function were derived using optimal control procedures (Dekkers and Van Arendonk, 1998; Chakraborty et al., 2002).

### Appendix 2: Calculation of Gametic Phase Disequilibrium Between the QTL and Polygenes

The amount of disequilibrium between the polygenes and the QTL was computed for gametes as

$$Cov(X, u_g) / \sqrt{Var(X)Var(u_g)}$$

where  $X = 1$  if gamete carries allele B and  $X = 0$  if gamete carries allele b, and  $u_g$  is the polygenic value for the gamete.

Let  $f_{BB}$ ,  $f_{Bb}$ ,  $f_{bB}$ , and  $f_{bb}$  be the frequencies of selected parents with genotypes BB, Bb, bB and bb (i.e.,  $f_{BB} + f_{Bb} + f_{bB} + f_{bb} = 1$ ), respectively, and let  $\bar{u}_{BB}$ ,  $\bar{u}_{Bb}$ ,  $\bar{u}_{bB}$ , and  $\bar{u}_{bb}$  be the corresponding average polygenic values for the four genotypes. Parents BB produce 100% of gametes B with breeding value  $\bar{u}_{BB}/2$ , parents Bb produce 50% of gametes B with breeding value  $\bar{u}_{Bb}/2$ , parents bB produce 50% of gametes B with breeding value  $\bar{u}_{bB}/2$  and parents bb produce no B gametes with breeding value  $\bar{u}_{bb}/2$ .

The covariance between  $X$  and  $u_g$  is:

$$Cov(X, u_g) = E(X u_g) - E(X)E(u_g)$$

where

$$E(X) = f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}, \\ E(u_g) = (1/2)(f_{BB}\bar{u}_{BB} + f_{Bb}\bar{u}_{Bb} + f_{bB}\bar{u}_{bB} + f_{bb}\bar{u}_{bb}) \text{ and} \\ E(Xu_g) = Prob(X = 1)E(u_g|X = 1)$$

Now,

$$Prob(X = 1) = [f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}] / \\ (f_{BB} + f_{Bb} + f_{bB} + f_{bb}) \text{ and} \\ E(u_g|X = 1) = f_{BB} (\bar{u}_{BB}/2) / [f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}] \\ + (1/2)f_{Bb} (\bar{u}_{Bb}/2) / [f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}] + \\ (1/2)f_{bB} (\bar{u}_{bB}/2) / [f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}]$$

Thus,

$$Cov(X, u_g) = f_{BB} [(\bar{u}_{BB}/2) - E(u_g)] + (1/2)f_{Bb} [(\bar{u}_{Bb}/2) - E(u_g)] \\ + (1/2)f_{bB} [(\bar{u}_{bB}/2) - E(u_g)]$$

Now,  $Var(X) = E(X)$  because

$$Var(X) = p_B(1 - p_B), \text{ where } p_B = f_{BB} + (1/2)f_{Bb} + (1/2)f_{bB}$$

and  $Var(u_g) =$  variance of gametic polygenic effects among parents.



## References

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