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OPTIMIZATION OF SELECTION FOR TWO IDENTIFIED QUANTITATIVE TRAIT LOCI

Y. Li, J.H.J. van der Werf and B.P. Kinghorn

Division of Animal Science, University of New England, Armidale, NSW 2351

SUMMARY

Selection to improve a single trait, where polygenic effects and two quantitative trait loci (QTL) both affected phenotype, was optimized by using a genetic algorithm for different values of additive effects, dominance effects and epistasis effects for the two QTL. The method accounted for gametic phase disequilibrium among polygenes and between QTL and polygenes. The extra cumulative discounted response (CDR) from optimal selection over genotypic selection depended on magnitude of additive and dominance effects of QTL. Maximum extra CDR from optimal selection with two QTL was 2.2% for additive QTL and 6.7% for dominant QTL while corresponding values from optimal selection with a single QTL were 2.1% and 5.3%. Benefit from optimal selection was decreased by additive-by-additive epistasis and increased by additive-by-dominance epistasis or dominance-by-dominance epistasis. It is most useful to optimize selection when QTL effects are dominant and when additive effects are between 0.25 and 2.0 times the genetic standard deviation.

Keywords: Optimisation, selection, QTL, cumulative discounted response.

INTRODUCTION

QTL mapping has been intensively studied and a number of QTL associated with economically important traits have been found in animal populations. Gibson (1994) reported that genotypic selection based on QTL led to short-term gain and long-term loss, compared to selection on phenotype, indicating that genotypic selection is not an optimum use of QTL information in selection schemes. Dekkers and Van Arendonk (1998) and Dekkers (1999) optimized weightings on QTL information over a number of generations, resulting in increased responses. Benefits from optimal selection over genotypic selection (optimised for the next generation alone) were 8% for additive QTL and 9% for fully dominant QTL when considering genetic mean at generation 10. Benefits increased with degree of dominance at QTL. The purpose of this paper is to investigate the benefits of optimization of selection with two identified QTL and the influences of additive, dominance and epistasis effects for these QTL.

METHODS

An unselected population of infinite size with discrete generations was assumed. Some males and females were selected and randomly mated. Selection was for a quantitative trait affected by polygenes and two identified QTL, A and B. Polygenic effects followed an infinitesimal model and a normal distribution. Phenotype was measured on all selection candidates prior to selection. QTL A and B were both bi-allelic. QTL A had three genotypes AA, Aa and aa with genotypic values g_{am}, where $g_{a1} = a$, $g_{a2} = a´ d_a$, $g_{a3} = -a$ and d_a is degree of dominance in QTL A. Similarly, QTL B had genotypic values g_{bk}, where $g_{b1} = b$, $g_{b2} = b´ d_b$, $g_{b3} = -b$ and d_b is degree of dominance in QTL B (Falconer and Mackay 1996).

Let Y_{imkt} be the phenotypic value for animal i with QTL A genotype m $(m = 1, 2 \text{ or } 3)$ and QTL B genotype k $(k = 1, 2 \text{ or } 3)$ in generation t. Let w_{at} (w_{bt}) be the index weight on QTL A (QTL B), at generation t. d_{amt} (d_{bkt}) indicates gametic phase disequilibrium between QTL A and polygenes (between QTL B and polygenes) at generation t as in Dekkers and van Arendonk (1998). h^2_{mkt} is the polygenic heritability within genotype group with QTL A genotype m and QTL B genotype k in generation t. A selection index was calculated using equation [1].

$$
\begin{aligned}
I_{imkt} = \; & w_{at}\,(g_{am} + \ddot{a}_{amt}) + w_{bt}\,(g_{bk} + \ddot{a}_{bkt}) \\
& + h^2_{mkt}[Y_{imkt} - (g_{am} + \ddot{a}_{amt}) - (g_{bk} + \ddot{a}_{bkt})]
\end{aligned}
\qquad [1]
$$

Polygenic means ($\hat{A}_{sz,t+1}$) and variances ($s^2_{A\,sz,t+1}$) of 16 possible genotypes (formed with four possible gametes) were calculated using equations [2] and [3], respectively.

$$
\overline{A}_{sz,t+1} = \frac{\sum_{i=1,}^{16} \sum_{k=1}^{16} c_{is}\, c_{kz}\, f_{it}\, f_{kt}\, \frac{1}{2}(\tilde{A}_{it} + \tilde{A}_{kt})}{\sum_{i=1,}^{16} \sum_{k=1}^{16} c_{is}\, c_{kz}\, f_{it}\, f_{kt}} \qquad [2]
$$

$$
s^2_{A\,sz,t+1} = \frac{1}{2} \frac{\sum_{i=1,}^{16} \sum_{k=1}^{16} c_{is}\, c_{kz}\, f_{it}\, f_{kt}\, \frac{1}{2}(\tilde{v}_{it} + \tilde{v}_{kt})}{\sum_{i=1,}^{16} \sum_{k=1}^{16} c_{is}\, c_{kz}\, f_{it}\, f_{kt}} + \frac{1}{2} s^2_{A0} \qquad [3]
$$

where s and z take values of 1, 2, 3 or 4, corresponding to gamete AB, Ab, aB or ab, respectively, c_{is} (c_{kz}) is the probability for sire (dam) with genotype i (k) to produce gamete s (z), sz is the genotype produced from gametes s and z, $sz = (s - 1)$ ´ $4 + z$, (sz = 1, 2, ….., or 16), f_{it} (f_{kt}) is the frequency of genotype i (k) at generation t (i or k = 1, 2, ….., or 16), $\tilde{A}_{it}$ ($\tilde{A}_{kt}$) is the polygenic mean of sires (dams) with genotype i (k) in generation t, $\tilde{v}_{it}$ ($\tilde{v}_{kt}$) is the polygenic variance of sires (dams) with genotype i (k) in generation t, and s^2_{A0} is the polygenic variance at generation 0. Overall polygenic mean ($\hat{A}_{t+1}$) and variance ($s^2_{A\,t+1}$) for generation $t+1$ are the averages of the 16 genotypic groups.

Optimal selection index weights in each generation were found using a genetic algorithm. The criterion for optimisation was the cumulative discounted response (CDR) up to generation t, which was calculated with equation [4].

$$
CDR = \sum_{n=1}^{t} \frac{\sum_{i=1}^{16} g_i N_{in} \Big/ \sum_{i=1}^{16} N_{in} - \sum_{i=1}^{16} g_i N_{i0} \Big/ \sum_{i=1}^{16} N_{i0}}{(1+dr)^n} + \sum_{n=1}^{t} \frac{\overline{A}_n}{(1+dr)^n} \qquad [4]
$$

where dr is the discount rate, g_i is the genotypic value for QTL A and B combining genotype i, N_{in} (N_{i0}) is the number of animals with combining genotype i at generation n (generation 0). g_i is the sum of additive, dominance and epistasis effects of combining genotype *i*. Additive-by-additive (A×A) effects are E_{aa} for AABB and aabb genotypes, -E_{aa} for AAbb and aaBB genotypes and zero for the other genotypes. Additive-by-dominance (A×D) effects are E_{ad} for AABb and AabB genotypes, -E_{ad} for aaBb and aabB genotypes and zero for the other genotypes. Dominance-by-dominance (D×D) effects are E_{dd} for AaBb, AabB, aABb and aAbB genotypes and zero for the other genotypes.

Twenty-five percent of the males and fifty percent of the females were selected in each generation. A base population (at generation 0) was assumed to have phenotypic variance 1.0 and polygenic variance s_{A0} = 0.25. The favourable alleles at identified QTL A and QTL B had initial frequencies of 0.10 in generation 0. The additive effect of QTL A *(a)* had values of 0, 0.5, 1.0, …, or 2.0 times s_{A0}. The additive effect of QTL B (*b*) had values of 0.25, 0.5, …, or 2.0 times s_{A0}. Optimization was conducted when both QTL A and B were additive (d_a = 0 and d_b = 0), fully dominant (d_a = *1* and d_b = *1*) or when there was A×A, A×D or D×D epistasis between QTL, where E_{aa}, E_{ad} and E_{dd} were all equal to $1.5 s_{A0}$, which was 1.5 times of values of *a* and *b* used.

RESULTS AND DISCUSSION

Extra CDR from optimal selection over genotypic selection with two QTL is shown in Table 1 for additive effects and Table 2 for full dominance effects. It was found that magnitude of extra CDR in optimal selection depended on magnitude of additive and dominance effects of QTL. Selection with zero additive effect of QTL A could be considered as the selection with a single QTL B. In optimal selection with a single QTL for 10 generations, maximum extra CDR was 2.1% for additive QTL and 5.3% for fully dominant QTL, respectively. In the optimal selection with two QTL for 10 generations, maximum extra CDR was 2.2% for additive QTL and 6.7% for fully dominant QTL, respectively.

Table 1. Extra cumulative discounted response (%) from optimal selection over genotypic selection for varying additive effects of additive QTL A and B, optimizing for 10 generations

Additive effect	Additive effect of QTL B (σ_{A0})					
of QTL A (σ_{A0})	0.25	0.5	0.75	1	1.5	2
0	0.1	1.0	1.9	2.1	1.7	0.8
0.5	0.9	1.1	1.6	2.1	2.2	1.5
1	2.2	2.1	1.8	1.6	1.8	1.8
1.5	1.8	2.2	2.1	1.8	1.2	1.1
2	1.0	1.5	1.9	1.8	1.1	0.6

Results showed that A×A epistasis reduced benefit to 0.2% for additive QTL and 2.2% for fully dominant QTL because it changed genotypic values of double homozygous genotypes (e.g. AABB or aabb) and led to an easy fixation of the favourable alleles. Benefits from optimal selection were 5.9% under A×D epistasis for two additive QTL and benefit was 4.7% under D×D epistasis between two dominant QTL. The last two kinds of epistasis increased genotypic values of heterozygous (e.g.

AABb) and double heterozygous (e.g. AaBb) genotypes, leading to difficulty in fixation of the favourable alleles.

Table 2. Extra cumulative discounted response (%) from optimal selection over genotypic selection for varying additive effects of dominant QTL A and B, optimizing for 10 generations

Additive effect	Additive effect of QTL B (σ_{A0})					
of QTL A (σ_{A0})	0.25	0.5	0.75	1	1.5	2
0	2.2	5.2	5.3	4.3	2.1	1.1
0.5	6.0	6.6	6.7	6.6	5.0	3.5
1	5.5	6.6	5.0	3.4	3.7	3.3
1.5	3.3	5.0	4.9	3.7	1.3	2.1
2	2.0	3.5	3.7	3.3	2.1	0.5

The results of this study show that when considering CDR, benefit from two identified QTL is lower than those reported by Dekkers (1999) who optimized selection for a single QTL for the next generation alone. CDR takes into account short-term as well as long-term response, and short-term response is given larger emphasis, which makes differences between genotypic and optimal selection smaller. Dominance effects of QTL increased extra CDR from optimal selection with two identified QTL, a result similar to that of Dekkers (1999) for a single QTL. Table 2 shows that optimization of selection became more useful when the QTL expressed a dominance effect, especially when additive effects are small (*e.g.* $0.25\sigma_{A0}$). Dekkers *et al.* (1996) reported optimal weights on QTL changed over time. This study found the same results for two loci and, moreover, optimal weights are smaller for larger QTL effects and for fully dominant QTL. For example, where additive effects of QTL A and B are $0.5\sigma_{A0}$ and $1.0\sigma_{A0}$, optimal weights for QTL A will be larger than those for QTL B.

For additive QTL, optimization of more than one QTL did not necessarily increase extra CDR from optimal selection over genotypic selection. This makes sense when considering that inclusion of an increasing number of QTL approaches the polygenic state, for which genotypic selection aiming at the next generation alone is optimal. However, optimal selection could obtain significant additional CDR when two QTL had quite unequal effects (with the ratio of additive effects being about 2.5 to 5, Table 1). This is analogous to the increased value of family selection over mass selection with low heritability, when the benefit of separate treatment of different components of phenotype is large. Furthermore, the difference between genotypic and optimal selection is larger for dominant QTL, particularly when the size of one or both QTL are between $0.5\sigma_{A0}$ and $1.0\sigma_{A0}$ (Table 2).

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