

EFFECT OF THE ACCURACY OF AN ESTIMATED QTL EFFECT ON RESPONSE TO MARKER-ASSISTED SELECTION

N. Moghaddar^{1,2} and J.H.J van der Werf²

¹Ferdowsi University of Mashhad, Iran. ²University of New England, Armidale, NSW, Australia

SUMMARY

The effect of the accuracy of estimated QTL effects on relative efficiency of marker-assisted selection (MAS) to non-MAS was investigated in a simulation study in a single trait selection scheme under variable heritability, different QTL effect and different initial QTL allele frequencies. The results showed that the probability of realized MAS response being less than expected response increased with higher standard error associated with an estimated QTL effect. This probability was significantly higher when a high standard error was associated with large QTL effects in lower QTL allele frequencies and/or lower heritability. The MAS responses could be equal or even less than non-MAS when the QTL variance from an inaccurate QTL effect constitutes a considerable proportion of overall genetic variance. This study showed that incorporating prior information about the QTL in a Bayesian approach can effectively remedy the problem of over prediction of MAS response.

INTRODUCTION

Information about quantitative trait loci (QTL) in economically important traits in livestock species, can be utilized to improve the rate of genetic gain via marker assisted selection. To achieve a high accuracy in estimation of QTL effects, the QTL mapping experiment needs to have a large number of progeny. However, because of the cost of experiments, QTL detection studies generally have a limited size, which restricts the accuracy of parameter estimation (Alison *et al.* 2002). Moreover, QTL detection experiments have considered a continuous distribution, normal distribution or no distribution for QTL effects (Hayes and Goddard 2001). The limited sample size along with ignoring the distribution of QTL effects result in upward biased estimation of QTL effects in QTL mapping experiments. The objectives of this study were to determine how the accuracy of estimated QTL parameters influence the realized response in MAS and how we can incorporate prior information about the QTL in prediction of realized MAS response.

MATERIALS AND METHODS

A stochastic simulation method was used to produce a base population of 500 unrelated, non inbred and unselected individuals with phenotypic variance equal to unity. The phenotypic values (y_p) consisted of polygenic effect (*poly*), a QTL genotype effect (*g*) and residual effect (*e*): $y_p = poly + (g - \mu) + e$. One QTL was assumed with two alleles with the difference between the two homozygotes being $2a$, and assuming no dominance effect at the QTL. The QTL variance was therefore $V_g = 2pq(a)^2$, where, p and q represent initial QTL allele frequencies and a is the QTL allele substitution effect (Falconer and Mackay, 1996). The heritability of the QTL and the proportion (in percent) of the QTL in overall additive genetic variance were calculated respectively as: $h^2_{(g)} = V_{(g)} / (V_{(poly)} + V_{(g)} + V_{(E)})$, $\%V_{(g)} = V_{(g)} / (V_{(poly)} + V_{(g)}) * 100$. We assumed to genotype directly for the QTL but we will use the term marker assisted selection (MAS) throughout this paper.

We considered variable heritability (0.1, 0.3 and 0.5), different standard errors, (SE: 0.0, 0.05, 0.1 and 0.15) associated with the estimated QTL effects and different initial allele frequency. Given an estimate of QTL effect and its standard error, we sampled a true QTL effect according to an appropriate posterior distribution and assigned a genotype and genotypic effect to each animal

according to the allele frequency. A polygenic and a residual effect was allocated randomly to each animal from a normally distributed polygenic effect with mean and variance equal to 0.0 and σ^2_A and from a normal distribution of residual effects, with mean and variance equal to 0.0 and residual variance σ^2_E respectively.

For each true QTL effect a MAS and non-MAS selection index were calculated using the selection index theory (Lande and Thompson 1990) and the top twenty percent of animals were selected. To find realized MAS response a gamma distribution was considered as a prior for the true underlying QTL effects (Hayes and Goddard 2001) and based on the Bayes theorem a posterior QTL distribution of the true QTL effect was derived given the prior distribution and the likelihood associated with the estimated QTL effect with its SE. The posterior probability of true QTL effect according to the Bayes theorem can be shown by this equation: $P(x_i|y_i) = P(y_i|x_i).P(x_i)/P(y_i)$ where x_i and y_i are the i^{th} true and estimated QTL effect respectively, $P(x_i|y_i)$ is the posterior probability of true QTL effect given the estimated QTL effect, $P(y_i | x_i)$ is the probability density function of the estimated QTL given the true value, which is the same as the likelihood function of the QTL effect, $P(x_i)$ and $P(y_i)$ are the prior probability of the true and estimated QTL effect respectively. The relative response of MAS over non-MAS for each estimated QTL value and associated SE was calculated based on deterministically sampling true QTL effects with 0.02 increments from the posterior distribution of QTL effects. For each value of possible QTL effect we assigned a polygenic value, residual value and genotypic value to animals stochastically according to polygenic variance, residual variance and genotypic value and response was calculated based on average of 500 iterations.

RESULTS

Tables 1 and 2 show, and Figure 1 plots the ratio of expected and realized MAS to non-MAS response for different combinations of QTL size, QTL allele frequency, standard error of the estimated effect for heritability values 0.1 and 0.3. The results show that in all cases the realized response of an estimated QTL associated with some degree of error was less than expected response. The difference was highly dependent on the accuracy of estimated effect. At each SE the difference between expected and realized response was bigger when the QTL variance was higher (bigger QTL effect, higher favourable allele frequency and lower heritable trait). As expected the probability of MAS response to be more than non-MAS response (P1) and probability of true QTL being smaller than estimated effect (P2) increased with higher QTL variance.

Table 1. Ratio of realized MAS over non-MAS response, probability of MAS response to be more than non-MAS response (P1) and probability of true QTL to be less than estimated effect (P2) for estimated QTL effect at different accuracy, (heritability = 0.1)

α^1	$p^{(2)}$	$V_{QTL}^{(3)}$	SE =0.0	SE=0.05			SE=0.1			SE=0.15		
			Resp ⁽⁴⁾	Resp	P1	P2	Resp	P1	P2	Resp	P1	P2
0.1	0.1	1.8	1.091	1.065	0.804	0.699	1.059	0.605	0.656	1.051	0.511	0.625
0.3	0.1	16.2	1.762	1.663	0.994	0.748	1.358	0.751	0.841	1.125	0.523	0.891
0.5	0.1	45.0	2.683	2.572	0.993	0.753	2.241	0.991	0.854	1.725	0.826	0.930
0.7	0.1	88.2	3.350	3.232	0.993	0.657	2.967	0.998	0.869	2.480	0.984	0.951
0.1	0.3	4.20	1.174	1.131	0.804	0.699	1.128	0.725	0.655	1.117	0.592	0.625
0.3	0.3	37.8	2.094	1.970	0.992	0.748	1.626	0.870	0.843	1.370	0.670	0.896
0.1	0.5	5.0	1.188	1.139	0.804	0.699	1.119	0.725	0.655	1.082	0.72	0.625
0.3	0.5	45.0	2.270	2.122	0.992	0.748	1.682	0.869	0.847	1.321	0.667	0.902

(1) = Estimated QTL Effect, (2) = QTL favourable allele frequency, (3) = Variance of QTL (as percent of heritability), (4) = Ratio of realized MAS to non-MAS response, SE = Standard Error of estimated QTL effect.

Table 2. Ratio of realized MAS over non-MAS response, probability of MAS response to be more than non-MAS response (P1) and probability of true QTL to be less than estimated effect (P2) for estimated QTL effect at different accuracy, (*heritability* = 0.3)

α^1	$p^{(2)}$	$V_{QTL}^{(3)}$	SE=0.0	SE=0.05			SE=0.1			SE=0.15		
			Resp ⁽⁴⁾	Resp	P1	P2	Resp	P1	P2	Resp	P1	P2
0.1	0.1	0.60	1.007	1.003	0.643	0.699	1.007	0.585	0.655	1.010	0.591	0.624
0.3	0.1	5.40	1.058	1.044	0.912	0.748	1.006	0.597	0.843	0.978	0.385	0.891
0.5	0.1	15.0	1.170	1.151	0.998	0.753	1.078	0.776	0.854	0.969	0.411	0.928
0.7	0.1	29.4	1.356	1.318	0.999	0.809	1.229	0.959	0.859	1.062	0.655	0.934
0.1	0.3	1.40	1.013	1.010	0.643	0.699	1.007	0.585	0.655	1.009	0.591	0.625
0.3	0.3	12.6	1.119	1.092	0.960	0.748	1.018	0.598	0.841	0.961	0.385	0.891
0.5	0.3	35.0	1.319	1.282	0.999	0.753	1.171	0.877	0.854	0.998	0.522	0.928
0.1	0.5	1.66	1.016	1.008	0.641	0.699	1.008	0.586	0.655	1.010	0.591	0.624
0.3	0.5	15.0	1.125	1.094	0.960	0.604	1.019	0.597	0.841	0.960	0.385	0.891
0.5	0.5	41.6	1.357	1.309	0.998	0.753	1.168	0.832	0.854	0.958	0.410	0.958

(1) = Estimated QTL Effect, (2) = QTL favourable allele frequency, (3) = Variance of QTL (as percent of heritability), (4) = Ratio of realized MAS to non-MAS response, SE = Standard Error of estimated QTL effect.

Figure 2 shows the effect of heritability on realized response of inaccurate QTL effect. In some cases when a considerable QTL variance was due to a QTL with high SE the realized response was even less than non-MAS response.

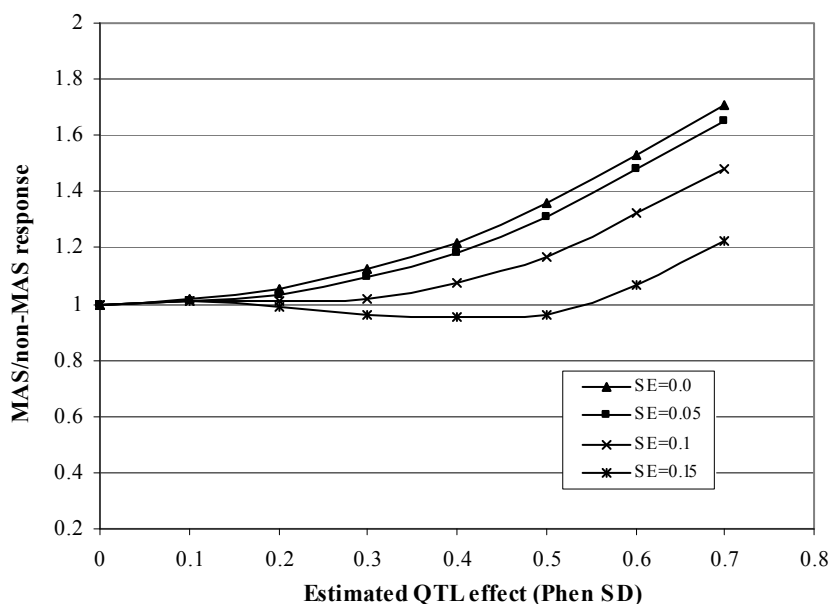


Figure 1. Ratio of MAS to non-MAS response for different SE associated with QTL effect, ($h^2=0.3$, QTL allele frequency=0.5)

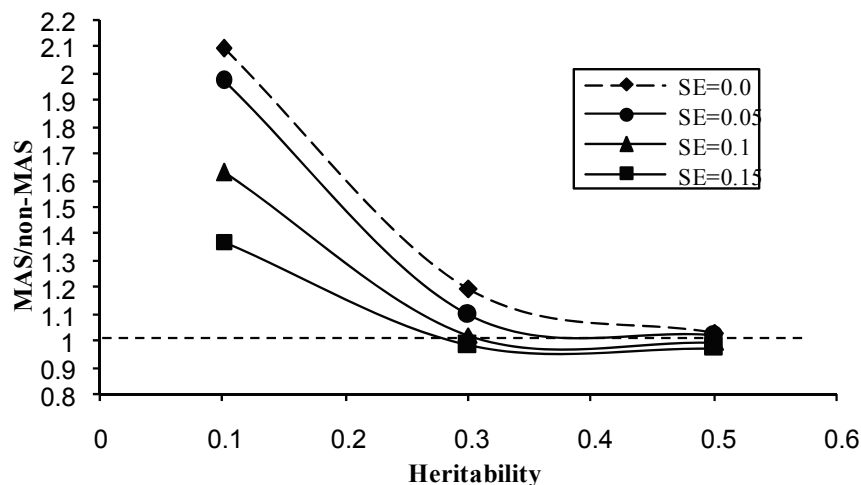


Figure 2. Effect of heritability on the relative efficiency of realized MAS GAS to non-MAS response (QTL effect=0.3 σ_P , Frequency=0.3)

DISCUSSION

This study showed that the realized MAS response from incorporation of information from an inaccurately estimated QTL is lower than the expected response and the deviation is bigger when the QTL constitutes a bigger part of the additive genetic variance. The simulation revealed that the difference between realized and expected MAS response is due to both incorrect prediction of QTL response and suboptimal prediction of response from polygenic effect.

This study also showed that using prior information about QTL effect distribution can give more accurate predictions of realized MAS response. In this study an average of derived parameters of QTL distribution in literature was used. However, using other parameters within a confidence interval had a small effect on our results except when QTL effects were large and had a high SE.

REFERENCES

- Alison, D.B., Fernandez, J.R. Moonseong, H. Zhu, A, Etzel, C. Beasley T. M. and Amos, C.I. (2002) *Am. J. Hum. Genet* **70**:575.
- Falconer, D. S. and Mackay, T.F.C (1996) "Introduction to Quantitative Genetics. 4th ed." Prentice Hall, Harlow, U.K.
- Hayes, B. J. and Goddard, M.E (2001) "The distribution of effects of gene affecting quantitative traits in livestock." *Genet. Sel. Evol.* **33**:209.
- Lande, R. and Thompson, T (1990) "Efficiency of Marker-Assisted Selection in the improvement of Quantitative Traits." *Genetics* **124**:743.