COMPARISON OF MARKER ASSISTED SELECTION USING MIXED MODEL (BLUP) AND MIXED MODEL WITH A TEST FOR THE QTL

J.M. Henshall and M.E. Goddard

Animal Genetics and Breeding Unit, NSW Agriculture and University of New England, Armidale, NSW, 2350

SUMMARY
Using simulation, the genetic gains achieved from mixed model marker assisted selection were compared to those achieved through mixed model selection where a test for the QTL was available. A production system was modelled over ten years, with overlapping generations. Three selection methods were tested, mixed model marker assisted selection, mixed model selection without markers (BLUP), and BLUP, when QTL genotypes and effects were known. The BLUP and BLUP with known QTL effects represent the minimum and maximum possible improvement in genetic gain achievable through marker assisted selection. The genetic gains observed for mixed model marker assisted selection methods were better than those obtained through conventional BLUP, but were not as great as those possible when a test for the QTL was available. Even after mixed model marker assisted selection had fixed the desirable QTL allele in the population, the overall response was still less than that achieved through having a test for the QTL.

Keywords: Marker assisted selection, mixed model, simulation

INTRODUCTION
Experiments to estimate the effects and locations of Quantitative Trait Loci (QTL) using genetic markers are being conducted on a variety of livestock animal species. It is expected that markers for QTL will be available to animal breeders in the near future. A number of methods of incorporating the marker/QTL information into breeding programs have been considered. Fernando and Grossman (1989) proposed a mixed model, with QTL effects treated as random. Alternatively, if tests for the QTL itself can be developed, then the QTL genotype for each animal in the pedigree can be determined, and the effect of the genotype can be included in a mixed model.

The aim of this work was to compare these methods over a number of generations on complex pedigree structures through simulating an animal breeding enterprise.

SIMULATION
A computer simulation of a breeding herd of animals under various selection strategies was conducted.
The QTL and Markers. It was assumed that a QTL had been found in an experiment on a similar population to the breeding herd. The QTL was assumed to have two alleles, with equal allele frequencies. Estimates of the effect of the QTL were assumed also to be available. Two markers, bracketing the QTL, were available. In the results presented here, the map distance between the markers was 0.1 Morgans, and the recombination rate between the QTL and the first marker was effectively zero. Under these circumstances, the second marker is not used in estimating QTL effects, but still has a role in estimating marker transmission at the first marker locus. In the base population, five marker alleles with equal allele frequencies occurred at each marker locus. The base population was in linkage equilibrium. In the marker data made available for selection, as in real marker data, the origin (paternal or maternal) of the marker alleles was not identified. The simulated parameters for QTL allele frequency, location and effect were the same as those assumed in the analyses. The sensitivity of the analyses to inaccurate estimates was not tested.

Traits simulated. A single trait was simulated, with phenotype measurable only on animals after slaughter, as for a carcase trait. Various heritabilities and proportions of QTL magnitude and polygenic variance were tested.

Breeding program. Ten years of selection and breeding took place, with all live, entire animals aged between two and eight years available for selection. Dams had one offspring per year. Each year five sires and fifty dams were selected. Animals not selected were treated as slaughtered, and their phenotypic information was made available. There was no attempt to monitor or control inbreeding, and inbreeding and marriage loops were common in the resulting pedigrees. The base population in year zero comprised a founder population, and two years' offspring from the founder population. Markers data was available from these animals, as was phenotypic data for those of the base population not selected in the breeding program. Of the male animals born each year, only five were left entire, with the rest slaughtered when two years of age. Each year, dams were selected first, so that phenotypic data on those not selected, and on two year old culled males, would be available in selecting sires.

SELECTION METHODS
Mixed model. A reference herd was simulated where conventional mixed model (BLUP) selection was applied. No use was made of the marker data. The model

\[ y_i = x_i \beta + a_i + e_i \]  

was used, where \( y_i \) is the phenotypic observation for animal \( i \), \( \beta \) is a vector of fixed effects for sex and year, \( x_i \) is a vector relating animal \( i \) to \( \beta \), \( a_i \) is the additive genetic effect for animal \( i \) and \( e_i \) is error.

Mixed model, marker assisted. If a QTL exists for a trait, the additive genetic effect for animal \( i \) in equation (1) can be decomposed into \( a_i = v_i^p + v_i^m + u_i \), where \( v_i^p \) and \( v_i^m \) are the effects of
the paternal and maternal QTL alleles, and $u_i$ is the additive effect not due to the QTL. This results in the model

$$y_i = x_i'\beta + v_i' + v_i'' + u_i + e_i$$

(Fernando and Grossman 1989). The variance of $e$ is $\sigma^2$, the covariance of the vector of additive effects is $A\sigma^2_a$, where $A$ is the numerator relationship matrix, and $\sigma^2_a$ is the genetic variance excluding the component due to the QTL. The covariance of the matrix of QTL effects is $G\sigma^2_G$, where $G$ is the gametic relationship matrix, and $\sigma^2_G$ is the QTL component of the genetic variance. To estimate $\beta$, $v_i'$, $v_i''$ and $u_i$ the system

$$\begin{bmatrix} X'X & X'Z_u & X'Z_v \\ Z_u'X & Z_u'Z_u + A^{-1}\lambda & Z_u'Z_v \\ Z_v'X & Z_v'Z_u & Z_v'Z_v + G^{-1}\gamma \end{bmatrix} \begin{bmatrix} \beta \\ \hat{u} \\ \hat{\nu} \end{bmatrix} = \begin{bmatrix} X'y \\ Z_u'y \\ Z_v'y \end{bmatrix}$$

is solved, where $\hat{\beta}$, $\hat{u}$ and $\hat{\nu}$ are estimates of vectors of fixed effects, additive genetic effects and QTL effects, $Z_u$ is a matrix relating animals to polygenic effects, and $Z_v$ is a matrix relating animals to QTL effects. $\lambda$ is $\frac{\sigma^2}{\sigma^2_a}$ and $\gamma$ is $\frac{\sigma^2_G}{\sigma^2_G}$ (Goddard, 1992). The method of Wang et al. (1991) was used to generate the inverse of the gametic relationship matrix, as it does not require that the origin of marker alleles be known.

**Mixed model, with estimates of QTL effects.** The same model (equation (2)) was assumed as for the mixed model approach, but instead of fitting the QTL effect as a random effect with covariance matrix $G$, the phenotypic data was pre-adjusted for QTL effects. While it may be some time before tests able to provide such QTL data become available, this does give an upper bound for the improvement possible with any marker assisted selection method.

**RESULTS AND DISCUSSION**

The results presented here are for a heritability of 50% with two levels of QTL variance as a percentage of additive genetic variance, 20% and 50%. Each of the three breeding value estimation methods was tested with the same base population. There were fifty repetitions for each heritability, QTL percentage and breeding value estimation method combination.

The graphs in figure 1 summarise the average trait value of animals born in each year of the simulated breeding experiment. The BLUP results are the improvement possible without including marker data in the analysis. The BLUP with QTL effects fitted results are the most improvement that could be achieved using marker assisted selection.
With the QTL variance 50% of the additive genetic variance, three years are required before the mixed model method is able to exploit the associations between markers and QTL to enable improvement in genetic gain. In contrast, if the QTL alleles are known without error, there is an immediate gain over the other two selection methods. Over the next five or six years, the marker assisted mixed model selection is better than conventional BLUP. However, even though the desirable QTL allele is almost fixed in the final years of the simulation, the marker assisted mixed model selection is unable to close the gap created by the initial rapid gains achieved through selection with a test for the QTL.

\[
V_q = 0.2 \, V_a
\]

\[
V_q = 0.5 \, V_a
\]

Figure 1. Average response (standard deviations of genetic variation) over time for selection using BLUP, marker assisted mixed model (MM), and BLUP with QTL effects fitted (BLUPQ). Heritability is 50%.

With the QTL accounting for 20% of the additive genetic variance, the situation is similar, but it takes many more years for the association between the markers and the QTL to be detected in the mixed model analysis. This would suggest that the smaller the effect of the QTL, the more accurate the test for the QTL needs to be, in order to achieve rapid advances in genetic merit.

These results are not directly comparable, but are consistent with those of Meuwissen and Goddard (1996). One of their discreet generations is roughly equivalent to four years in the results presented here, and the improvement in genetic gain over the first four years when a test is available for the QTL is of similar magnitude to the 64% reported for the first discrete generation.

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REFERENCES