# DETECTION AND EXPLOITATION OF MARKERS LINKED TO QUANTITATIVE TRAITS IN FARM ANIMALS

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## SUMMARY

Information on linkage between a marker and a locus affecting a quantitative trait has to be accumulated on a within-family basis. In the analysis of livestock linkage experiments it is important to account for variation due to genes not linked to the marker. New ways to tackle these complicated genetic models are described.

An animal model is described for BLUP of additive effects at the marked QTL and additive effects of polygenes. Influence of number and effects of alleles at the QTL on cumulative genetic gain using marker assisted selection are determined. The BLUP approach was found to be a robust method and it can account for differences in allelic effects at a QTL as a result of interactions with background genotypes or with environmental conditions. Close linkage between markers is expected to be advantageous but will not circumvent the need to use marker QTL associations within families.

## INTRODUCTION

The discovery of microsatellites and the use of polymerase chain reaction (Saiki *et al.*, 1988) make it possible to identify differences between animals at many genomic sites. These sites, which are referred to as marker loci, are not likely to be quantitative trait loci (QTL) themselves, but may be linked to QTL (Soller, 1978). In recent years, a large number of markers has been developed and mapped for the major livestock species (Georges *et al.*, 1991; Bumstead and Palyga, 1992; Anderson *et al.*, 1993; Hetzel, 1993).

In this paper, we describe methods to identify marker loci linked to quantitative trait loci in segregating livestock populations. Further, attention is paid to exploitation of information on marker loci linked to QTLs in a selection programme.

## DETECTION OF LINKAGE

*Experimental design:* Loci affecting quantitative traits can be detected through their linkage with markers. Detection of a QTL with the aid of markers requires linkage disequilibrium between the QTL and a marker locus. Linkage disequilibria between marker and QTL across the population are only expected in populations that were recently derived from a cross between two divergent populations ($F_2$ or backcross populations), particularly two inbred lines. The original linkage disequilibrium ($D$) at formation of the population depends upon genetic differences between the founding populations. This disequilibrium is gradually reduced to $D(1-r)^n$ by recombination ($r$) over $n$ generations. Anderson *et al.* (1994) recently used a cross between a European pig breed and Swedish Wild pigs for the detection of marker linked QTL. In the analysis both breeds where assumed to be homozygous at the QTL and consequently genes which explain the between breed difference were found. For most livestock species, such populations are not available and would be difficult to set up. In addition, interest for selection purposes is in detection of genes which explain within breed differences.

Most livestock populations are segregating populations, and linkage disequilibrium between marker and QTL across the population is unlikely. Even loose linkage between marker and QTL, however, will cause linkage disequilibria within families (Neimann-Sorensen and Robertson, 1961). The phase of linkage between the marker and QTL varies across families and, as a result,

information on linkage has to be accumulated on a within family basis (Soller, 1990).

To determine linkage between a genetic marker and a QTL, large experiments are needed in which genotypes for markers are determined and phenotypic performance is recorded. Weller *et al.* (1990) suggested a grandsire design for dairy cattle, in which marker genotypes are determined in sons of heterozygote grandsires and quantitative trait values recorded on daughters of these sons. In this design, scoring of individuals for markers, often the most costly part of the program, is minimized. The grandsire design might also be useful for other livestock species in which traits are routinely recorded on a large number of progeny. The power of an experiment to detect linkage between a marker and a QTL depends on the recombination rate between the marker and the QTL, number of individuals informative for the marker, heritability of the trait, and size of effect and frequency of alleles at the QTL. The number of uninformative families and offspring can be reduced by using flanking markers instead of single markers. Darvasi *et al.* (1993) showed that the power to detect a QTL using marker brackets was hardly affected by the distance between markers.

Selective genotyping and the use of DNA pools have been suggested as tools to increase the power of QTL detection experiments (Darvasi and Soller, 1992; Arnheim *et al.*, 1985). Selective genotyping must be applied within family and is restricted to single-trait evaluation. Selective genotyping, combined with the use of pooled DNA samples, is potentially useful to detect linkage or to confirm linkage found in other experiments. However, it does not allow for the estimation of recombination rate and size of effects at the QTL. Van der Beek *et al.* (1994) have shown that power of designs can be increased by using full-sib instead of half-sib families. In full-sib families, the number of informative meiosis is doubled and this contributes to an increased power. In a half sib-design, power to detect a QTL with allelic effect of $0.2\sigma_p$, i.e. half the difference between 2 homozygotes, was .85 if markers were assayed on 200 sons of 5 sires with 100 granddaughters per son for a trait with $h^2$ of .2 and type 1 error of .01 (Weller *et al.*, 1990). Using a full sib design in which markers were assayed on 200 offspring from 5 sire-dam combinations with 100 half-sib grandoffspring per offspring power increased to 0.99 (Van der Beek *et al.*, 1994).

*Analysis:* Methods of analysis for livestock linkage experiments that have been used include fixed regression (Weller *et al.*, 1990; Hoeschele and Meinert, 1990), iteratively reweighted regression (Dentine and Cowan, 1990), maximum likelihood (Weller, 1990; Bovenhuis and Weller, 1994) and Bayesian analysis (Hoeschele and VanRaden, 1993). Regression analysis estimates marker allele substitution effects, which are a function of recombination rate and effects of allele substitution at the QTL. To estimate QTL map location, however, maximum likelihood or Bayesian methods are required. These methods simultaneously estimate effects of allele substitution at the QTL, allele frequencies, and recombination rate between marker and QTL. Variation between families can be due to genetic effects unlinked to the marker or to environmental effects. Methods to analyze linkage experiments mentioned so far do not account for genetic variation due to QTLs not linked to the marker or due to common environmental effects and have been used to estimate effects of only a single QTL. Knapp (1991), Jansen (1992) and Martinez and Curnow (1992) studied the impact of multiple QTLs for populations derived from the cross of two inbred lines. They showed that estimates of size and position of a QTL from individual locus models are biased by QTLs lying outside of the studied region and recommended a multivariate search. For the population they studied, regression models that use information obtained from linked markers were useful to separate effects of QTLs in neighbouring regions. Knott and Haley (1992) presented a maximum likelihood method for mapping quantitative trait loci using full-sib families that incorporated a random component for common family effects due to additional segregating QTL or environmental effects. The exact form of the likelihood involves integration over all possible values and a summation over all possible

combinations of QTL genotypes and marker phases in the parents and offspring, and quickly becomes infeasible to compute as the number of full sibs increases. They replaced the integration with a weighted summation which results in a close approximation of the exact likelihood (Knott *et al.*, 1992). In testing for a linked QTL the test must be made against a model that allows for variation between families, i.e. that includes an unlinked QTL or a between-family variance component, otherwise the test statistic may be grossly inflated. Using the full model, mean parameter estimates were found to be unbiased. If the common family component was omitted, the effects of the QTL were overestimated for the data in which additional polygenic variation was simulated and when compared with an unlinked QTL model the power was reduced. Knott and Haley (1992) indicated that the analyses were very computationally intensive, which limits the size of data sets in which the method can be applied, and stressed the need for approximations.

Van Arendonk *et al.* (1993) developed a derivative free Restricted Maximum Likelihood (REML) method for simultaneous estimation of the variance due to a QTL linked to a marker ($\sigma^2_v$), recombination rate between QTL and marker ($r$) and polygenic variation due to additional unlinked QTLs ($\sigma^2_u$). Such an analysis was suggested by Fernando and Grossman (1989) and Goldgar (1990). Van Arendonk *et al.* (1993) used marker genotypes in building the gametic relationship matrix for the marked QTL. The method was used to analyze simulated data from a grandsire design in which grandsires were unrelated. Marker genotypes were available on grandsires and sires, whereas phenotypic information on the trait of interest was recorded only on granddaughters. Covariances between polygenic effects in granddaughters due to common sires or grandsires were taken into account. In a single marker analysis, the within-marker genetic variance, $(1-2r)^2\sigma^2_v$, was estimated without bias, but it was impossible to estimate $r$ and $\sigma^2_v$ separately. Separation of $r$ and $\sigma^2_v$ might be possible when using information from a marker bracket rather than from a single marker or by using a design with more generations. For the grandsire pedigree structure, likelihood evaluations could be done efficiently, which enabled the analysis of a data set containing 200,000 daughter records on a personal computer.

Guo and Thompson (1992) introduced a Monte Carlo approach to combined segregation and linkage analysis for a quantitative trait observed in an extended human pedigree. The method is an application of a technique known as 'Gibbs sampling', in which random samples of each of the unknown parameters (here genotypes, polygenic effects, r, $\sigma^2_u$, QTL effects and gene frequency) are drawn from their conditional distributions, given the data and the current values of all other unknowns. The Gibbs sampling chain starts with an arbitrary set of realisations for all parameters. In subsequent cycles of the Gibbs chain, a new realisation is drawn for each parameter from its conditional distribution. Guo and Thompson (1992) used an EM algorithm to obtain parameter estimates from a series of realizations of the Gibbs chain. As an illustration, they applied the method to data on LDL cholesterol levels and LDL receptor genotypes in a 60-member, five generation pedigree. Wang *et al.* (1993) applied Gibbs sampling to estimate variance components in animal breeding data sets using a sire model. Janss *et al.* (1994[a]) have used Gibbs sampling technique to obtain estimates for a mixed inheritance model using all relationships between animals. The model included polygenic effects, a single gene and additional non-genetic effects. The single gene was modelled as an autosomal locus with two alleles. Non-genetic effects included fixed effects of sexes and herd and random effects of slaughter day. This approach has been used to identify a single gene affecting intramuscular fat in Meishan crossbreds (Janss *et al.*, 1994[b]). Guo and Thompson (1992) resampled additive genetic effects for each individual separately. In pedigrees with large progeny groups, this procedure resulted in virtual freezing of the chain and consequently a very large number of cycles are needed to obtain good estimates. The movement in the Gibbs markov chain was increased by resampling jointly effects of sires and their final progeny (Janss *et al.*, 1994[a]). The Gibbs sampling approach seems to offer great opportunities for combined segregation and linkage analysis in large livestock

populations. The greatest attraction of the approach is its ability to handle complex genetic models and data on large pedigrees (Guo and Thompson, 1992). It opens up new ways to tackle complicated genetic models for which analytical methods are often lacking.

In the future, data to (re-)estimate genetic parameters for most livestock species will originate from an on-going selection programme and consequently contain data on several generations. This is already the situation for estimation of heritabilities and genetic correlations between traits. This stresses the need for methods that can be applied to large populations with complicated pedigree structures.

## EXPLOITATION OF MARKER LINKED EFFECTS

Best linear unbiased prediction (BLUP) methods are currently used to predict breeding values of animals in a large number of countries and species. Selection in most cases is across generations and age classes. Consequently information on markers needs to be combined with BLUP breeding values into a single selection criterion (Hoeschele and Romano, 1993). The same data are used to predict polygenic and marker linked effects, which makes it necessary to predict both genetic effects simultaneously.

The prediction of an animal's breeding value using BLUP is based on phenotypes of the animal itself or those of its relatives. When only observations on the trait of interest are considered, the contribution of relatives to an animal's breeding value depends on the additive genetic relationship, i.e. the proportion of genes shared in common by descent, and the heritability of the trait. In building the numerator relationship matrix or its inverse no knowledge on the actual contribution of a parent to its offspring is used. Instead use is made of Wright's (1922) inbreeding coefficient and the coefficients of relationship between animals. Fernando and Grossman (1989) and Van Arendonk *et al.* (1994) have shown how information on a single marker could be used in a mixed model analysis by fitting additive effects for alleles at a QTL linked to the marker and additive polygenic effects for alleles at the remaining quantitative trait loci. The total additive genetic variance ($\sigma_a^2$) is equal to $\sigma_a^2 = \sigma_u^2 + 2\sigma_v^2$. Let $\alpha_u = \sigma_e^2/\sigma_u^2$ and $\alpha_v = \sigma_e^2/\sigma_v^2$, then the mixed model equations to predict genetic effects are:

$$\begin{bmatrix} X'X & X'Z & X'W \\ Z'X & Z'Z+A_u^{-1}\alpha_u & Z'W \\ W'X & W'Z & W'W+G_{v|r}^{-1}\alpha_v \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{u} \\ \hat{v} \end{bmatrix} = \begin{bmatrix} X'y \\ Z'y \\ W'y \end{bmatrix}$$

where:

- **y** is the vector of observations on the trait of interest,
- ß is the vector with fixed effects,
- **u** is the vector with random additive polygenic effects,
- **v** is the vector with random gametic effects at the marked QTL,
- **e** is the vector of random residual effects.

The matrices **X**, **Z** and **W** are incidence matrices relating observations to fixed effects, polygenic effects and gametic QTL effects, respectively. $\mathbf{A}_u$ is the numerator relationship matrix for polygenic effects and $\mathbf{G}_{v|r}$ is the gametic relationship matrix for the QTL linked to the marker. To build $\mathbf{G}_{v|r}$ information is used on marker allele transmission and the recombination rate ($r$) between marker and QTL. Efficient algorithms have been developed to obtain the inverse of $\mathbf{G}_{v|r}$. These algorithms differ in the way they treat inbreeding and whether they distinguish parental origin of gametic effects (see Bink and Van Arendonk, 1994 for review). In the mixed model information on several generations of relatives is used to predict effects at the QTL.

In most studies it has been assumed that all animals have genotypic information. In the most likely scenario for marker assisted selection, marker genotypes will be available only on a limited number of individuals. Many of the animals in a population may have unknown genotypes because several generations of ancestors are included in the animal model genetic evaluation and most of these ancestors will have unknown genotypes. Van Arendonk *et al.* (1994) and Wang *et al.* (1994) have presented procedures to incorporate information from animals whose genotypes are unknown. Information on several unlinked marker loci, each linked to a different QTL, can be used by including an effect for each MQTL. The number of equations per animal in this case is $2m+1$ where $m$ is the number of MQTL. The number of equations per animal can be reduced to 1 by combining information on all MQTL and polygenes and the use of a combined numerator relationship matrix (Van Arendonk *et al.*, 1994). The total number of equations can also be reduced by using a reduced animal model (Cantet and Smith, 1991; Goddard, 1992) or absorbing QTL equations for individuals whose marker genotypes are unknown (Hoeschele, 1993). Depending on the costs and benefits of marker genotyping, only elite animals of the current generation and their offspring will have known marker genotypes. In this case, marker information will only affect the structure of the inverse of the combined numerator relationship matrix for some animals, whereas for others (e.g. ancestors and offspring with unknown genotypes) the structure will be the same as without markers. This feature makes application of the combined model attractive in populations where marker genotypes are available on a limited number of animals. Research on the structure of the matrices might result in reductions of computational requirements.

## GENETIC MODEL

Genetic properties of the QTL in the animal model genetic evaluations differs from that used in most methods to detect linkage. In genetic evaluation, the allelic effects at the QTL are represented by a random effect with variance $\sigma^2_v$, i.e., a large number of alleles are assumed. In most methods to estimate marker QTL linkage, the underlying genetic model contains a QTL with two alleles. The real situation, however, is unknown. We have studied the consequence of using animal genetic evaluations for situations where the number of alleles at the QTL ranged from 2 up to 16. A population was generated in which selection was for a trait measured on both sexes and observations were available on all individuals after the age at which animals were selected as parents for the next generation. Cumulative genetic response to selection is given in Table 1. The cumulative genetic response after 2 generations of marker assisted selection was 12.4% to 19.1% higher than for selection without markers. The gain in cumulative response due to using markers decreased over time. The diminishing influence of markers assisted selection can be explained by the larger reduction in variance of allelic effects when markers were used. However, total response in the long run (10 generations) was not lower using MAS, as was found by Seafuddin and Gibson (1991).

Cumulative response to selection increased with number of alleles at the QTL. Alternatives with a larger number of alleles also had alleles with a higher effect. In the long run, the best allele will be fixed and its allelic effect determines the total cumulative gain for the QTL. This is most clearly demonstrated by comparing the two alternatives with 4 alleles. In the situation where the best allele had a more extreme effect (ex), the cumulative response and gain were higher than in situation with uniform distribution of allelic effects (uni). For an accurate prediction of the gain of marker assisted selection, knowledge on frequency and effects of alleles segregating at the QTL is needed.

Table 1. Cumulative response after 2, 7 and 12 generations of marker assisted selection and gain in cumulative response due to using markers with different numbers of QTL alleles and distributions[b] of allelic effects at the QTL[a] (from: Kistemaker and Van Arendonk, 1994).

| | | Cumulative response ($\sigma_a$) | | | Gain (%) | | |
|---|---|---|---|---|---|---|---|
| Distribution | # alleles | 2 | 7 | 12 | 2 | 7 | 12 |
| uni | 2 | 0.62 | 2.22 | 3.60 | 13.4 | 6.2 | 1.4 |
| uni | 4 | 0.63 | 2.28 | 3.72 | 12.4 | 1.9 | -0.7 |
| uni | 16 | 0.68 | 2.41 | 3.89 | 13.8 | 4.3 | 1.7 |
| ex | 4 | 0.68 | 2.46 | 3.93 | 19.1 | 8.7 | 5.1 |

[a] Each generation had 640 animals that originated from 16 sires and 160 dams. Each dam had 2 male and 2 female offspring. Selection of full sib males was avoided whereas selection of females was within full sib family. Population parameters prior to selection: $\sigma^2_y = 5$, $\sigma^2_u = 30$, $\sigma^2_e = 60$ and $r = 0.1$. Marker had 20 equiprobable alleles and markers genotypes were determined for all animals before age of selection. Marker assisted selection started after 2 generations of mass selection. Results are averages of 100 replicates.

[b] Uni = uniform difference between successive alleles; Ex = uniform difference between lowest 3 alleles but 2 times higher difference between best and second best allele. Equal population frequency of all alleles in base population.

There is a risk of reduced genetic response from MAS compared to conventional selection if the marker information is inaccurate (Smith and Smith, 1993). We, therefore, looked at a situation where the QTL had no effect whereas a QTL that explained 25% of the genetic variance was assumed in genetic evaluation for the population in Table 1. The cumulative genetic gain after 12 generations of selection was $4.12\sigma_a$ with the use of markers and $4.13\sigma_a$ without. Similar absolute differences were found in earlier generations. It can be concluded that risk of reduced genetic progress due to inaccurate marker parameters is small. This can be explained as follows: information to distinguish between allelic effects in an animal has to come from the ancestors and progeny, hence no systematic differences linked to the marker are found and, consequently, no incorrect selection decisions are made.

Results in Table 1 show that BLUP is efficient in selecting on a QTL that has a small number of alleles. A model that would explicitly use knowledge on allelic effects and population frequencies might result in a larger initial response when correct values for these parameters are used and when the number of alleles is small. The method proposed by Kinghorn *et al.* (1993) might be adopted to predict polygenic values and assign genotypes to animals for that case. Obtaining unbiased estimates for allelic effects might be difficult and the method is expected to be more sensitive to errors in parameter estimates. It is well accepted that the allelic effects might differ as a result of differences in background genotypes or environmental conditions. These interactions are accounted for in the BLUP approach because allelic effects can be different in different families and are allowed to change within a family as a result of recombination.

## MARKER ASSISTED SELECTION

Marker assisted selection is expected to increase genetic response by affecting time, intensity and accuracy of selection (Soller and Beckman, 1982; Smith and Simpson, 1986). More recently, Kashi *et al.* (1990) used genetic markers to select young bulls prior to progeny testing and calculated the effect of preselection on the frequency of favorable QTL alleles. With a proportion preselected of 0.25, the average genetic merit of bulls increased by $.30\sigma_a$ to $.53\sigma_a$. Meuwissen and Van Arendonk (1992) predicted the fraction of within-family variance that can be explained by tracing markers transmitted from grandsire to grandsons. A 20% increase in annual genetic change was found in an open nucleus scheme in which sires were selected at 2 years of age and

markers explained 10% of the within-family genetic variance. The fraction of within-family variance that can be explained by markers is of critical importance. To predict 10% of the within-family variance in grandoffspring informative genotypes on 500 daughters of both grandsires are needed for a large number of markers. Van der Beek and Van Arendonk (1994) found a 2% to 4% higher genetic gain by using markers assisted selection in a poultry breeding programme. The lower benefit of marker assisted selection compared to that found in the former study, can be explained by the smaller family sizes and the lower selection intensities in males. The large differences in results between studies illustrate the need for more research in this area.

## VALUE OF CLOSE MARKERS

Due to recombination, associations between a marker and a QTL has to be used within families and such associations will erode over time. Closer linked markers will help to predict allelic effects at QTL more accurately. Smith and Smith (1993) concluded that the main advantage of closer markers is an increase in linkage disequilibrium between markers and QTL, which would allow marker assisted selection across the population. Linkage disequilibrium across the population rather than within specific families would make evaluation and selection simple and general. The question, however, is whether a small recombination rate implies linkage disequilibrium across the population. In a population recently derived from a cross of distinct lines, which is the situation studied by Lande and Thompson (1990), this might be realistic. But within a segregating population such a relationship can only result from random drift. It is known that the four casein genes in cattle are located on a chromosomal segment of less than 200 kilobase pairs of DNA (Threadgill and Womack, 1990), which corresponds approximately to a recombination rate of 0.4% between the casein genes (Copeland *et al.*, 1993). Despite this very close linkage, genotypes for the different casein genes are not far from linkage equilibrium (Bovenhuis *et al.*, 1992). In conclusion, close linkage is expected to be advantageous but will not lead to across population linkage disequilibrium within most livestock populations.

A different situation arises, however, when we know the genotype for the QTL itself. For finding the functional genes, the genome maps of human and mouse are expected to be useful (Copeland *et al.*, 1993). An important application of the comparative map is the transfer of linkage information and genome resources from "map-rich" to "map-poor" species. By mapping a well-defined set of evolutionarily conserved loci across mammalian genomes, it should be possible to use these conserved loci to transfer linkage information from "map-rich" species, such as humans and mice, to "map-poor" species, such as cow, pig, and sheep, and thereby expedite genome research. In mice, several mutations have been cloned by positional cloning, that is, chromosomal walking from nearby genetic markers (Copeland *et al.*, 1993) This approach has become practical due to the large number (>3000) of markers and the development of efficient walking methods and large insert libraries. The rate-limiting step in positional cloning has now become the generation of large numbers of backcrossed animals needed to define recombination events in close proximity to the mutation of interest. With the genetic analysis of single-gene traits becoming increasingly straightforward, the challenging frontier in mouse genetic studies will begin to shift to the study of polygenic traits (Copeland *et al.*, 1993).

The detection of markers linked to the Booroola gene for fecundity is a recent example of using comparative maps and modern mapping tools in livestock (Montgomery *et al.*, 1993). Isolation of the gene using positional cloning strategies will be retarded by the lack of candidate genes in the homologous human region and by the lack of high density linkage maps for sheep (Hetzel, 1993). Most biologically and economically important traits are polygenic. Detection of genes responsible for differences in these traits is important both for a better understanding of the underlying processes as well as for practical selection purposes. But we are more likely to find markers than the genes and it is therefore worthwhile to invest also in more sophisticated methods to determine genotypes of animals and to use this information in selection programmes.

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