AGBU
ANIMAL GENETICS AND BREEDING UNIT
A joint unit of NSW DPI and UNE

Research in QTL Analysis

Searching for QTL in complex pedigrees with "The Gene Detective"

To date, most QTL detection effort has been directed towards designed experiments, where large groups of homogenous animals are bred, phenotyped and genotyped. This approach, while effective, ignores the vast quantities of pedigree and phenotypic data which have already been recorded. In addition, as more animals are genotyped at more loci, individual mapping experiments will become linked through complex pedigrees, and the ability to analyse these experiments jointly will become important.

With designed QTL mapping experiments, groups of full or half sib animals are bred, so that polygenic effects can be included with the error. The challenge then is to separate the QTL effect from the error. This is not possible in complex pedigrees, where the challenge is to separate the QTL effect from the polygenic effects. Assumptions made about polygenic variance components will have consequences for QTL effects, so for complex pedigrees, software needs to be able to simultaneously estimate fixed effects, polygenic variance components and QTL effects.

Without Markers

"The Gene Detective" is a software program designed to perform segregation analysis on complex pedigrees. Fixed effects, variance components and QTL effects are estimated concurrently, using a Markov chain Monte Carlo (MCMC) algorithm. An MCMC algorithm is required as iterative peeling based algorithms can produce biased results for pedigrees with marriage or inbreeding loops. For the sampling of QTL effects, a new algorithm, based on sampling descent graphs, has been developed by researchers at AGBU. By sampling descent graphs, mixing or moving around the space of QTL genotypes (and all other parameters), is improved. This algorithm is irreducible, even with more than two alleles.

With Markers

"The Gene Detective" can use any amount of marker information that is available in its analyses. At best, segregation analysis without marker data can only suggest that the data are consistent with a model including a major gene which adheres to Mendelian transmission rules. The inclusion of identity-by-descent probabilities for linked markers makes these analyses much more powerful. As the data are in a complex pedigree, it is unnecessary to produce a crop of animals of assumed genotypes, required in designed experiments. Existing pedigree and phenotype records can be used, along with any genotype data from any QTL mapping experiments that have been performed in the past or any other source. Extra genotypes can be obtained on animals for which DNA can be found. Importantly, this may include sires widely used in the past, if stored semen still exists. Even with a relatively small proportion of animals genotyped (such as sires only) regions of the genome, distant from QTL, can be excluded from further consideration. Multiple QTL, linked to multiple markers can be analysed.

Multiple Traits

"The Gene Detective" can simultaneously analyse several traits. Alleles that act positively on one trait may act negatively on another. It is important that any side effects of beneficial alleles are quantified before they are exploited.

Models

"The Gene Detective" can analyse traits with any or all of the following random effects: individual additive, maternal and permanent environmental effects. At present repeated records are analysed as highly correlated traits. Any parameters can be treated as known. This increases the efficiency of the algorithm by reducing the size of the parameter space. Various modes of inheritance/expression can be modelled, such as dominance, imprinting, multiple alleles, epistasis, and QTL for maternal effects.

Categorical Models

In segregation analysis, a model is fitted with different effects for different genotypes, with the genotypes adhering to Mendelian rules. In the absence of marker data, information in support of such a model is obtained from the pedigree and from the distribution of phenotypes. Non-normal, and in particular, multi-modal, distributions of phenotypes support a model including a QTL, unless the pedigree structure is sufficient to exclude a QTL model. This causes problems for traits with a categorical distribution. Accordingly, categorical data cannot be analysed using software designed for continuous data.

"The Gene Detective" analyses categorical traits by sampling variables from an unobserved underlying continuous distribution using the method of Albert and Chib (1993, JASA). Any number of categorical traits can be analysed with any number of continuously distributed traits.

Future Developments

"The Gene Detective" is being enhanced to

- analyse repeated records with a repeatability model
- analyse longitudinal data with covariance functions and changing temporal gene effects
- run more quickly.

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