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Reinsch, Norbert

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Limitations of a moment method for mapping linked multiple QTL - Mayer,
Manfred

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Limitations of a moment method for mapping linked multiple QTL

Mayer, Manfred

Research Unit Genetics and Biometry, Research Institute for the Biology of Farm Animals, Dummerstorf, Germany

As an alternative to multiple interval mapping (Kao *et al.*, 1999) recently a moment method (Nakamichi *et al.*, 2001) was proposed to map linked multiple QTL. Their approach uses single interval mapping to obtain crude (biased) estimates of the additive genetic effect, the dominance effect and the population mean and residual variance. In a second step a moment method is applied to these crude estimates to remove the effects of the other QTL. The authors state, that this moment method may be less statistically efficient than multiple interval mapping, but the merit of the moment method is its simplicity and computational efficiency, especially in detecting closely linked QTL within a marker bracket; but also in mapping QTL in different marker intervals. In a simulation study the moment method was compared with multiple interval mapping. Two different models were used to simulate the data. In the first model 100 replicates of an F_2 population with 500 individuals were simulated and analyzed. Five QTL at the positions 8, 15, 25, 35, 42 cM on a chromosome of length 50 cM were postulated. The 5 QTL had the additive genetic effects $a_1 = -0.5$, $a_2 = 1.0$, $a_3 = -1.0$, $a_4 = 1.0$ and $a_5 = -0.5$, respectively. There were no dominance effects. The markers were located at the positions 0, 10, 20, 30, 40 and 50 cM, respectively. The residual variance was 0.1^2 . The second model was identical with the model used by Nakamichi *et al.* (2001) to demonstrate the behavior of their method for closely linked QTL. An F_2 population with sample size 500 was simulated and one hundred replicates were analyzed. Two QTL at the positions 43 and 47 cM on a chromosome of length 100 cM were assumed. The QTL had the effects $a_1 = 2.0$, $a_2 = -2.0$ and $d_1 = 1.0$, $d_2 = -1.0$. Markers were located every 10 cM on the chromosome, i.e. the 2 QTL were not separated by a marker. The residual variance was 1.0. In the moment method analyses for both models the default GA-controlling parameters of Nakamichi *et al.* (2001) were used. To study the influence of the distance between the two linked marker in a marker interval two further settings where the QTL were very close (position 43 and 44 cM for QTL 1 and QTL 2, respectively) and where the QTL were more far away (positions 43 and 49 cM) were simulated and analyzed. It is shown that the moment method may give poor results as compared to multiple interval mapping, irrespective whether the QTL are in the same or in different marker intervals, especially if linked QTL are in repulsion.

References

- Kao, C.-H., Z.-B. Zeng and R.D. Teasdale, 1999. Multiple interval mapping for quantitative trait loci. *Genetics* **152**: 1203-1216.

Nakamichi, R., Y. Ukai and H. Kishino, 2001. Detection of closely linked multiple quantitative trait loci using a genetic algorithm. *Genetics* **158**: 463-475.

Bootstrapping of Gene-Expression Data improves and controls the False Discovery Rate.

Meuwissen, Theo H.E.¹⁾ and Mike E. Goddard²⁾

¹⁾ *Institute for Animal Science, Agricultural University of Norway, 1432 Ås, Norway.*

²⁾ *Institute of Land and Food Resources, University of Melbourne, Parkville, 3052 Australia, and Victorian Institute of Animal Science, Attwood, Victoria, 3049 Australia.*

A non-parametric bootstrap-t-test was developed to discover up or down regulated genes in microarray gene-expression experiments. This test was compared to the ordinary and penalized t-test, least squares and Best Linear Unbiased Prediction in two publicly available data sets. Comparison was for the False Discovery Rate (FDR), ie. the fraction of falsely discovered genes, which was empirically estimated in a duplicate of the data set. The bootstrap-t-test yielded up to 80% lower FDRs than the alternative statistics, and its FDR was always as good as or better than any of the alternatives. Generally, the predicted FDR from the bootstrapped P-values agreed well with their empirical estimates, except when the number of mRNA samples is smaller than 16. In a cancer data set, the bootstrap-t-test discovered 200 differentially regulated genes at a FDR of 2.6%, and in a knock-out gene expression experiment 10 genes were discovered at a FDR of 3.2%. It is argued that, in the case of microarray data, control of the FDR takes sufficient account of the multiple testing, whilst being less stringent than Bonferoni-type multiple testing corrections. Extensions of the bootstrap simulations to more complicated test-statistics are discussed.