The Efficiency of Mapping of Quantitative Trait Loci using Cofactor Analysis

G. Sahana[1], D.J. de Koning[2], B. Guldbrandtsen[1], P. Sorensen[1] and M.S. Lund[1]

[1] Danish Institute of Agricultural Sciences, Department of Animal Breeding and Genetics, Research Centre Foulum, DK-8830, Tjele, Denmark and [2] Division of Genetics and Genomics, Roslin Institute, Roslin, Midlothian, EH25 9PS, UK

ABSTRACT

Detection of QTL in outbred half-sib family structure has mainly been based on interval mapping of single QTL on individual chromosomes. Cofactor analysis builds a single model by combing information from individual analyses. Cofactor analysis is expected to have higher power due to decrease in residual variance by taking into account variance explained by cofactors. This experiment was designed to study the power and tape I error in QTL mapping including cofactor with varying family size, heritability of the trait, QTL effect, map density and threshold level of the cofactor to test two hypotheses using simulated data. Hypothesis I: using cofactors increases the power of QTL mapping, especially when there is very low power of experiment and liberal threshold for cofactor. Hypothesis II: using cofactors increases type I error in QTL mapping. With family size of 25, there was increase in power of identifying QTLs but also increase in false positive rate (FPR). When the power of the experiment was very high and with stringent threshold, cofactor analysis helps in reducing FPR. But in low power experiments the small increase in power was neutralized with increased false positives. Cofactor analysis was observed to increase type I error and increase was very high in low-power experiments and was worse for lower thresholds.

Introduction

The purpose of mapping quantitative trait loci (QTL) in livestock is to identify chromosomal regions affecting a quantitative trait and ultimately use existing variation in those chromosomal segments to select superior individuals from a population. A number of strategies have been proposed for QTL mapping (Lander and Botstein, 1989, Haley et al., 1994, Georges et al., 1995). Detection of QTL in outbred half-sib family structure has mainly been based on interval mapping of single QTL on individual chromosomes. These methods do not take possible QTL on other chromosomes into account. Jansen (1993, 1994) and Zeng (1994) proposed methods to account for linked and unlinked QTL by fitting markers as cofactors. These methods were developed for inbred line cross experiments, and Jansen et al. (1996, 1998) and Kao et al. (1999) described methods for multiple QTL mapping in outcrossing species. Zeng (1994) reported that when cofactors are used a larger part of the breeding value of offsprings is accounted for, which results in reduction of the residual genetic variance and consequently higher power in QTL detection.

Cofactor analysis, as described by De Koning et al. (2001), builds a single model by combing information from individual analyses. Iterating over the linkage groups, the trait scores are sequentially adjusted for identified QTL in previous linkage groups. Cofactor analysis is expected to have higher power than individual chromosome analysis and especially in experiment with lower power. The argument put forward to explain the increase in number of QTL detected was partly the decrease in the residual variance by taking into account variance explained by the cofactors. This results in lowering the residual variance and an increase in the test statistic, which is a function of residual variance and thereby increasing the chance of detecting QTLs, which were not identified when cofactors were not considered. The increase can be substantial, as putative QTL become part of the complete model in which all cofactor effects are estimated jointly to give the best fit of the data. De Koning et al. (2001) reported, using cofactor analysis, the initial number of five suggestive QTL had increased to eight significant QTL. Bennewitz et al. (2004) also observed 39% increase (from 18 to 25) in the number of QTL detected when cofactors were included in the model in comparison to analysis without cofactor. As the number of QTL detected is substantially high in cofactor analysis, it is crucial to investigate if the expected type I error rate is preserved in cofactor analysis. A critical question in QTL mapping studies is how many of the statistically significant QTL represent real QTL rather than type I errors. Further the initial effect of cofactor is overestimated as it is analyzed individually along with adjusting a nonexistent QTL effect in homozygous families may increase false positive rate.

Power to detect segregating QTL is a function of the number of individuals genotyped for the genetic markers and phenotyped for the quantitative traits, effect of segregating QTL, heritability of the trait, type I error allowed and marker density as well as residual variance (Van Der Beek et al., 1995; Weller, 2001). The threshold level for inclusion as cofactor will also influence the power as well as type I error. Therefore, this experiment was designed to study the power and tape I error in QTL mapping including cofactor with varying family size, heritability, QTL effect, map density and threshold level of the cofactor to test the following two hypotheses. Hypothesis I: using cofactors increases the power of QTL mapping, especially when there is very low power of experiment and liberal threshold for cofactor. Hypothesis II: using cofactors increases type I error in QTL mapping.

Materials and Methods

Simulation of data: The phenotypes and marker data were simulated for 15 sire families based on a half-sib design. The parameters for nine different scenarios are presented in Table 1. Marker alleles were sampled from 12 tetra-allelic markers with equal frequencies placed with a distance of 5 cM between loci. Except in the sparse-marker density scenario where 4 markers were placed at 20 cM intervals. QTL alleles were simulated on five chromosomes situated halfway between markers 7 and 8. Except in the sparse-marker density scenario where the QTL location was halfway between markers 3 and 4. The QTL alleles were assumed to have equal frequency. Each QTL (scenarios 1-6) explained 10% of the genetic variance adding up to a total of 50% of the genetic variance

explained by five QTLs. 50% of the genetic variance was due to polygenes. In scenario 7 (large QTL effect) two QTLs with large effect were simulated each explaining 25% of the total genetic variance. 50% of the genetic variance was due to polygenes. In scenario 8 (uneven QTL effect I), five QTLs with diminishing effects were simulated, biggest 13.3%, 2nd 11.7%, 3rd 10.0%, 4th 8.3% and 5th 6.7% such that the smallest QTL explained half the variance as the biggest QTL and thereby jointly explained half of the genetic variance. Similarly in 9th scenario (uneven QTL effect II), the five QTLs had 12, 11, 10, 9, 8 percent of genetic variance, respectively, so that the smallest QTL explained two-third of the variance of the biggest QTL.

Table 1. Parameters for default and alternative simulated population

Scenario 1 (Default population)	
No. of sires	15
No. of sons per sire	100
No. of chromosomes	15
Length of each chromosome	55
Markers per chromosome	12
Distance between adjacent markers (cM)	5
No of chromosome with QTL	5
Position of QTL	Halfway between markers 7 and 8
QTL effect (individual)	10% of genetic variance
Phenotypic variance	100
Additive effect of QTL allele	1
Threshold level for cofactor	0.05
Scenario 2 (Medium family size)	
No. of sons per sire	50
Scenario 3 (Small family size)	
No. of sons per sire	25
Scenario 4 (Stringent threshold)	
Threshold level for cofactors	0.01
Scenario 5 (Liberal threshold)	
Threshold level for cofactors	0.10
Scenario 6(sparse-marker density)	
Length of the chromosome (cM)	60
No. of markers	4
Distance (cM) between adjacent markers)	20
Position of QTL	Halfway between markers 3 and 4
Scenario 7(large QTL effect)	
No of chromosomes with QTL	2
QTL effect (individual)	25% of genetic variance
Scenario 8 (uneven QTL effect I)	Smallest QTL explains half of the
Uneven QTL effect	variance of what the biggest QTL does
Scenario 9 (uneven QTL effect II)	Smallest QTL explains two-third of the
Uneven QTL effect	variance of what the biggest QTL does

Parameters for alternative populations are the same as the default except for those specified here

The total phenotypic variance of the trait was assumed to be 100. Each of nine scenarios was simulated for two heritabilities, 0.90 and 0.30. The phenotypes were directly

simulated on sons. Therefore the heritability 0.90 resemblance a granddaughter design with a heritability about 0.30 for yield traits in the granddaughters. Similarly a heritability 0.30 resemblance the low heritability of disease traits in a granddaughter design. Three family sizes were considered with 100, 50 and 25 sons per sire. There were three threshold levels for considering cofactors in the analysis: 0.05, 0.01 and 0.10.

The cofactor analysis followed the procedure described by De Koning et al. (2001, 2004). First, all the chromosomes are analyzed individually to identify candidate regions by interval mapping. In the second stage, the candidate positions are identified based on significance levels. Candidate regions that exceed a given threshold are included as cofactor in the further analyses. Subsequently, all linkage groups are reanalyzed by interval mapping including the cofactors as covariate. If it reveals additional or candidate regions different from earlier round, the set of cofactors is modified and the effects re-estimated. This step was repeated five times uniformly in each simulated data set. The number of significant QTL ($P<0.05$) were counted in the first round (without cofactor) and the fifth round and the locations of true QTLs was recorded. An identified QTL was considered to be a true positive when it was identified to reside on a chromosome where a QTL was simulated. Each scenario was replicated 100 times. Significance thresholds were determined empirically by 1000 permutations (Churchill and Doerge, 1994; Doerge and Churchill, 1996). For a type I error of 0.05, a sample of 1000 permutations is usually regarded as sufficient (Churchill and Doerge 1994, Piepho, 2001). A putative QTL was included as cofactor when it exceeded the given level of threshold fixed under the scenario. The expected theoretical power of each scenario was calculated as described by Van Der Beek et al. (1995).

Results

The results of QTL analysis with varying family size scenarios, each over 100 replicates, are presented in table 2. In cofactor analysis there was no change the in power to locate true QTLs in the large family size scenario but there was small increase in power in case of medium and small family size scenarios. However, in all the scenarios there were increases in false positive rate (FPR), which is realized type I error, except in large family with the high heritability situation, where it decreased by 5%. In cofactor analysis in small family size scenario, there were 13% and 21% increases in the number of true QTL identified in high- and low heritability conditions respectively but also 49% and 45% increase in FPR. Out of a total of 47 new significant positions found in cofactor analysis in small family size with high heritability, 24 were false positives. The theoretical power calculated (table 7) based on the population design and the parameters used to simulated the data was very close to the power observed for both individual and cofactor analysis in high heritability conditions and the observed power was little lower in low heritability conditions. The accuracy of QTL location estimates remains very similar in both individual and cofactor analysis (table 3). With small family size (25 sons/sire) the power of detection of true QTL increased in cofactor analysis in both high- and low heritability conditions.

Three levels of threshold: 0.01, 0.05 and 0.10 were considered for a chromosomal position to qualify as a cofactor. The effect of all these three thresholds on QTL detection was studied with high- and low-heritability situations. The number of true QTL detected and the FPR are presented in table 4. The stringent threshold (0.01) and liberal threshold (0.10) were compared with the default scenario i.e. threshold level of 0.05. It was observed that when the stringent threshold level was used, with the high-heritability there was 13% decrease in FDR in cofactor analysis, though the power to identify true QTL was the same as observed in individual analysis. However, in the case of small family size and high heritability there was a 34% increase in FPR. Out of 21 new locations, which became significant in this scenario with cofactor analysis, only six were true QTLs and rest false positives. With low heritability and liberal threshold levels for cofactors at 0.10, there was a 13% increase in power. However, FPR increased for both stringent- and liberal threshold scenarios. The biggest increase in FPR (41%) was in the case of a liberal threshold in this situation. The comparison of theoretical power estimates and observed power under individual and cofactor analysis is present in table 7. Out of three levels of threshold used the power was only increased in cofactor analysis in comparison to individual QTL mapping in low heritability and liberal threshold scenario. The accuracy of the estimates of QTL location was very similar in both individual and cofactor analysis (data not shown).

The results of QTL analysis presented so far had five QTLs each explaining the same amount of variance. Two scenarios, 8 and 9, were simulated with ‘uneven QTL effect’ and QTL mapping results are presented in table 5. With high heritability these two ‘uneven QTL effect’ scenarios and the default scenario had similar power for both individual and cofactor analysis. Similar to the default scenario of high heritability situation, there was 7% decrease in FPR in scenario 9 (uneven QTL effect II) scenario with cofactor analysis. However, 15% increase in FPR was observed in case of scenario 8 (uneven QTL effect I) scenario. With low heritability, there was an increase in FPR in both scenarios 8 and 9. The observed powers in both cases were lower than in the default situation (equal QTL effect). No significant changes in QTL location estimates were observed when cofactors were included in the analysis in comparison to when they were not included (data not presented here).

The scenario 6 was simulated with sparse marker density in comparison to the default scenario. Here the distance between markers was 20 cM in comparison to 5 cM marker interval in default case. These scenarios were simulated to study the effect of marker spacing on power of QTL with cofactor analysis and the results are presented in table 6. With high heritability, the power of sparse-marker scenario was 0.86 for individual analysis compared to 0.97 observed in the default situation. About 81 percent of QTLs were located in the correct marker intervals but this is due to very large maker interval in this scenario. There was also a 7% decrease in FPR when cofactors were added to the analysis. Similar to the default scenario the power did not change with cofactor analysis. With low heritability the power did not change with cofactor analysis but 16% increase in FPR was observed in this scenario.

Scenario 7 (large QTL) was simulated with two large QTLs each one explaining 25% of the genetic variance. As expected from theoretical expectations, the power to identify QTL was 100% with high heritability scenario and 0.91 with low heritability for both individual and cofactor analysis (table 6). However, with respect to FPR the two levels of heritability had opposite effects. With high heritability there was a 23% decrease in FPR and with low heritability there was a 34% increase in FPR.

DISCUSSION

In this paper we have compared the efficiency of QTL mapping using cofactor analysis with respect to that of individual analysis. There were small or no increase in power of QTL mapping with cofactor analysis, except in small family size and liberal threshold level for cofactors. For large family size and high heritability the power without cofactor was very high (0.97) leaving very small scope for further improvement in power. Similarly fixing a stringent threshold for cofactor did not improve the power in both high- and low heritability conditions. Similar results were observed with 'uneven QTL effect', sparse marker density and large QTL scenarios. The very small decreases in power for cofactor analysis in a few scenarios may be attributed to Monte Carlo variation. Zeng (1994) reported that when cofactors were used a larger part of the breeding value of offsprings was accounted for, which results in a reduction of the residual genetic variance and consequently higher power in QTL detection. De Koning et al. (2001) observed an increase in number of QTL detected in combined analysis, which was also explained as partly caused by the decrease in residual variance by taking into account variance that is explained by the cofactors. However, in the present study, there was no or very small increase in power in most of the scenarios except with small family size and a liberal threshold. Therefore, this study does not support the first hypothesis, i.e that cofactor analysis improves power.

The false discovery rate was another parameter studied to compare QTL mapping with cofactor analysis and the results are presented in table 8. QTL mapping only identifies the chromosomal regions that are statistically significant at the level fixed for the experiment. A critical question in QTL mapping is how many of the QTL found are type I errors instead of true QTL. In the present study we have used a uniform threshold level for QTLs at 0.05. On an average 5% of chromosomes without QTL in the study will be called significant. At this significant level we expect to get the FPR on average 50 in each scenario, as in 100 replications there were a total of thousand chromosomes without QTL. Expected FPR in large QTL was around 65. The reason of not fixing more stringent threshold levels for QTL was that we wanted to examine if QTL mapping with cofactors helps in reducing FPR. It was observed that FPR increased in the majority of the scenarios except some cases where power was very high. The biggest increase in FPR was observed in low power scenarios and was about 50% for small family scenario. The largest decrease in FPR was observed with QTL with large effect and high heritability where the power to detect QTL was 100%. With low heritability trait, the FPR increased in cofactor analysis in all the scenarios. Overall results for various scenario suggest the second hypothesis i.e. cofactor analysis increases FPR.

In the present study we have covered a wide range of scenarios with varying effects on power and FPR for the use of cofactors. The high heritability design has a good power to detect QTL (table 7). The 'heritability' of 0.90 in this 2-generation design resembles a granddaughter design where the EBVs of the sires are estimated with an accuracy of 0.90, which is achieved for most traits that are routinely measured in progeny testing of AI bulls in dairy cattle. The power of the low heritability design is very modest (table 7) and in practice this would not be a fruitful design for QTL detection. The simulations show that using cofactors will not improve the analyses of designs with low a priori power to detect QTL. To what degree our simulations mimic 'real' experiments is unclear but because of the large number of scenarios some of the conclusions are expected to be of general relevance.

The issue of appropriate threshold level for a candidate region to be included as a cofactor was examined in the present study. However in the liberal scenario there were increases in both power and FPR. Though the power may increase with less stringent threshold but often new QTL detected are false positives. De Koning et al. (2001) used the chromosome-wise threshold level of 5%. Jansen (1994) and Zeng (1994) suggested backward elimination and stepwise regression respectively, to select the cofactors using an ad hoc threshold based on nominal significance level. In practice it is advisable to use different thresholds for picking cofactors and for declaring a significant QTL. A cofactor could be selected at f.i. the 5% chromosome-wide level, while for declaring that cofactor as a QTL, genome-wide thresholds would be applied (de Koning et al. 2004)

In the present study the power of detecting QTL was lower when the marker spacing was 20 cM in comparison to marker spacing at 5 cM interval. Similarly, Van Der Beek et al. (1995) showed that power is a function of the distance between markers. Darvasi et al. (1993) performed a simulation study on the effect of marker density and concluded that with respect to the power that reducing marker spacing below 10 cM or 20 cM does not provide additional gains, regardless of the population size and gene effect. Piepho (2000) observed that the power of detection of QTL is stable between spacing of 0 and 20 cM.

Overall there was no or little increase in power in cofactor analysis. The cofactor methods showed small advantage in terms of reducing FPR in scenarios with high heritability because most of the genetic variance can be controlled and removed from the residual variance in the model. For traits with low heritability, the gain of fitting cofactors in the model in the way of detecting more QTLs was neutralized by an increase in false positive rate. There was a reduction in FPR in five scenarios but all of them in high heritability situation. Though the power was lower with larger marker intervals in comparison to a dense map but the power of detecting QTL was similar with both individual and cofactor analysis. Though there was decrease in FPR with large QTL effect in high heritability situation with cofactor analysis but it was opposite in low heritability situation. Hence, this study could not establish any generalized advantage of cofactor analysis for QTL mapping.

Table 2. Number of QTL simulated and identified with different **family size**

h^2	Family size	Individual Analysis			Cofactor Analysis			Change in true QTL	Change in FPR
		True	False	Total	True	False	Total	(%)	(%)
High	Large	483	59	542	482	56	538	-0.21	-5.08
	Medium	356	55	411	383	60	443	7.58	9.09
	Small	174	49	223	197	73	270	13.22	48.98
Low	Large	211	57	268	211	63	274	0.0	10.53
	Medium	93	56	149	94	66	160	1.08	17.86
	Small	57	51	108	69	74	143	21.05	45.10

Total 500 QTLs were simulated

Table 3. Accuracy in QTL location estimation with different **family size**

h^2	Family size	Individual Analysis						Cofactor Analysis					
		A	0	±1	±2	±3	>3	A	0	±1	±2	±3	>3
High	Large	96.6	51.1	37.7	5.6	3.7	1.9	96.4	53.7	34.0	7.1	3.3	1.9
	Medium	71.2	35.4	37.4	11.8	9.3	6.2	76.6	32.6	39.2	14.4	7.1	6.8
	Small	34.8	24.1	32.8	17.2	15.5	10.3	39.4	26.4	26.9	18.3	17.8	10.7
Low	Large	42.2	15.2	32.2	18.5	17.5	16.6	42.2	16.1	34.6	15.2	18.0	16.1
	Medium	18.6	20.4	22.6	21.5	21.5	14.0	18.8	20.2	20.2	26.6	18.1	14.9
	Small	11.4	7.0	19.3	21.1	28.1	24.6	13.8	7.2	26.1	15.9	24.6	26.1

A – Percentage of simulated QTL identified; Proportion (%) of QTL identified in the correct, ±1, ±2, ±3, and beyond 3 maker interval

Table 4. Number of QTL simulated and identified with different **threshold level**s for cofactors

h^2	Threshold level for cofactor	Individual Analysis			Cofactor Analysis			Change in true QTL	Change in FPR
		True	False	Total	True	False	Total	(%)	(%)
High	0.05	483	59	542	482	56	538	-0.21	-5.08
	0.01	470	61	531	472	53	525	0.43	-13.11
	0.10	481	44	525	487	59	546	1.25	34.09
Low	0.05	211	57	268	211	63	274	0.0	10.53
	0.01	201	51	252	198	58	256	-1.49	13.74
	0.10	224	51	275	255	72	327	13.84	41.18

Table 5. Number of QTL simulated and identified with **uneven QTL effect**

h^2	Uneven QTL effect	Individual Analysis			Cofactor Analysis			Change in true QTL	Change in FPR
		True	False	Total	True	False	Total	(%)	(%)
High	Default (high- h^2)	483	59	542	482	56	538	-0.21	-5.08
	Half (8-I)	479	46	525	484	53	537	1.04	15.22
	Two-third (8-II)	473	57	530	475	53	528	0.42	-7.02
Low	Default (low- h^2)	211	57	268	211	63	274	0.0	10.53
	Half (8-I)	179	52	231	178	62	240	-0.56	19.23
	Two-third (8-II)	191	49	240	195	60	255	2.09	22.45

Table 6. Number of QTL simulated and identified with **sparse marker and large QTL** effect

h^2	Marker density and large QTL	Individual Analysis			Cofactor Analysis			Change in true QTL	Change in FPR
		True	False	Total	True	False	Total	(%)	(%)
High	Default (high- h^2)	483	59	542	482	56	538	-0.21	-5.08
	Marker interval 20cM	430	56	486	428	52	480	-0.47	-7.14
	Large QTL*	200	71	271	200	55	255	0.0	-22.54
Low	Default (low- h^2)	211	57	268	211	63	274	0.0	10.53
	Marker interval 20cM	139	57	196	132	66	198	-5.04	15.79
	Large QTL*	181	56	237	181	75	256	0.0	33.93

***** Total 200 QTLs were simulated

Table 7. Comparison of theoretical expected powers based on experimental designs and empirical powers with and without cofactor analysis.

Scenarios	High h^2			Low h^2		
	Expected	Realized		Expected	Realized	
		Individual Analysis	Cofactor Analysis		Individual Analysis	Cofactor Analysis
Scenario 1 Default population	0.98	0.97	0.96	0.53	0.42	0.42
Scenario 2 Medium family size	0.81	0.71	0.77	0.26	0.19	0.19
Scenario 3 Small family size	0.47	0.35	0.39	0.14	0.11	0.14
Scenario 4 Stringent threshold	0.98	0.94	0.94	0.53	0.40	0.40
Scenario 5 Liberal threshold	0.98	0.96	0.97	0.53	0.45	0.51
Scenario 6 Sparse-marker density	0.96	0.86	0.86	0.45	0.28	0.26
Scenario 7 Large QTL effect	1.00	1.00	1.00	0.92	0.91	0.91
Scenario 8 Uneven QTL effect-I	0.97	0.96	0.97	0.46	0.36	0.36
Scenario 9 Uneven QTL effect-II	0.97	0.95	0.95	0.49	0.38	0.39

Table 8. Comparison of expected FPR and observed FPR individual and cofactor analysis.

Scenarios	High h^2			Low h^2		
	Expected	Realized		Expected	Realized	
		Individual Analysis	Cofactor Analysis		Individual Analysis	Cofactor Analysis
Scenario 1 Default population	50	59	56	50	57	63
Scenario 2 Medium family size	50	55	60	50	56	66
Scenario 3 Small family size	50	49	73	50	51	74
Scenario 4 Stringent threshold	50	61	53	50	51	58
Scenario 5 Liberal threshold	50	44	59	50	51	72
Scenario 6 Sparse-marker density	50	56	52	50	57	66
Scenario 7 Large QTL effect	65	71	55	65	56	75
Scenario 8 Uneven QTL effect-I	50	46	53	50	52	62
Scenario 9 Uneven QTL effect-II	50	57	53	50	49	60

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