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A Simple Method to Calculate Resolving Power and Confidence Interval of QTL Map Location

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"Resolving power" is defined as the 95% confidence interval for quantitative trait locus (QTL) map location that would be obtained when scoring an infinite number of markers in a given constellation of a marker-QTL mapping experiment. Resolving power can serve as a close estimate of the confidence interval of QTL map location, as well as a guide to the lower efficient limit of marker spacing in an initial marker-QTL mapping experiment. In the present study, an extensive series of simulations was carried out to provide estimates of resolving power, for backcross (BC) and F_2 designs, over a wide range of experimental sizes and of gene effects and dominance at the QTL. From the simulation results, the remarkably simple expressions, $3000/(mNd^2)$ (where $m = 1$ for BC and $m = 2$ for F_2; N = population size, and d = allele substitution effect) and $530/Nv$ (in terms of v, the proportion of variance explained), were obtained for estimating resolving power. These expressions can provide a convenient guide to planning marker spacing in BC and F_2 marker-QTL linkage experiments and for placing confidence intervals about QTL map location obtained in such experiments.

KEY WORDS: Quantitative trait loci (QTL); confidence interval; resolving power; gene mapping.

INTRODUCTION

A large number of genetic traits, including behavioral traits, complex diseases, and economic traits in agricultural species, are quantitative in nature. Methods to detect and map quantitative trait loci (QTL) have been evolved significantly since Thoday's (1961) pioneering work. One currently used approach is interval mapping, using methods based on maximum likelihood (Lander and Botstein, 1989). Maximum-likelihood methods provide asymptotically unbiased estimates of the QTL map location but do not provide measures of the accuracy of the estimates (i.e., standard errors or confidence intervals). The estimated covariance matrix of the maximum-likelihood estimates, which can be obtained in this case, often provides inaccurate estimates for the standard error of the estimated QTL map location (Darvasi *et al.*, 1993). In practice a "support interval," defined as the interval delimited by a standard decrease in the LOD score value (the *level* of the support interval is defined by the magnitude of the decrease in the LOD score value), is often used as a rough guide to the accuracy of the estimated QTL map location (Lander and Botstein, 1989). However, simulation studies (Van Ooijen, 1992) showed that the same level of support interval can represent confidence intervals of different levels. Furthermore, Mangin *et al.* (1994) showed that this support interval ("classical confidence interval," as they termed it) can be very biased for QTL having small effect. Mangin *et al.* (1994) proposed a confidence interval based on principles similar to those underlying the support

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interval, but instead of the LOD score statistic they developed a novel statistic with asymptotic properties which do not depend on the QTL effect. In this, they were the first to provide an unbiased and feasible method for estimating confidence interval of QTL map location. In addition, Visscher *et al.* (1996) proposed a method based on bootstrapping. However, application of their methods for a *priori* estimates of confidence intervals require specific simulations.

We have previously defined "resolving power" of a marker-QTL mapping experiment, as the 95% confidence interval for the QTL map location, that would be obtained when scoring an infinite number of markers (Darvasi *et al.*, 1993). Extensive simulations revealed that resolving power, although calculated on the basis of an infinite number of markers, was generally similar to the 95% confidence interval of QTL map location, even when a moderate marker spacing (i.e., 10 to 20 cM) was used. Resolving power was also found to serve as a lower limit for marker spacing, below which further reductions do not significantly contribute to the accuracy of QTL map location.

In the current study a simple and general expression for resolving power of QTL map location is presented. Resolving power can serve both as an estimate of minimum useful marker spacing and as an estimate of the 95% confidence interval of QTL map location associated with a particular experimental constellation. This expression should be useful both in planning and in interpreting QTL mapping experiments.

THEORY

The model used to investigate resolving power consists of a 100 cM chromosome with a single QTL located at its center. The quantitative trait is assumed to have a normal distribution with equal variance, σ^2, for all QTL genotypes and standardized gene effects of $-d$, h, and d for the QTL genotypes qq, Qq, and QQ, respectively. The assumed "infinite number of markers" was represented in the simulation study by a marker located every 0.1 cM. Two experimental designs are considered, a backcross (BC) design and an F_2 design. Both designs are assumed to originate from a cross between two inbred lines with alternative alleles for all markers and for the QTL.

In both the BC and the F_2 designs, the maximum-likelihood estimator (MLE) for the QTL map location, in each simulation, was obtained as follows. At each marker, the likelihood and the MLE of the individual means for each QTL genotype, and the variance within QTL genotypes (assumed equal for all QTL genotypes) was calculated on the assumption that the QTL is located at the marker (i.e., that recombination did not occur between the marker and QTL). The marker with the highest likelihood value provided the estimate of QTL map location.

The parameter space analyzed by simulations consists of: population size, N = 100, 200, 500, 1000, 1500, and 2000; standardized (σ^2 = 1) gene effect, d = 0.125, 0.25, 0.5, 0.75, 1.0, 1.5, and 2.0; and dominance status, h = 0 for the BC design, and h = 0, 1/2d, and d, for the F_2 design. Note that the genetic variance contributed by the QTL, g, equals $(d + h)^2/4$ and $(2d^2 + h^2)/4$ for BC and F_2, respectively, and that the proportion of variance, v, that the QTL explains equals $g/(1 + g)$ (Falconer, 1989). Each parameter combination was simulated with 1000 replicates. In each individual replicate a MLE was obtained for the map location of the QTL, by maximizing the appropriate likelihood function (shown below). From the 1000 replicate simulations at each parameter combination, an empirical symmetric confidence interval was obtained as the interval that included the MLE of the map location in 95% of the simulations. Confidence intervals are presented hereon by the width of the interval in cM, rather than by the two points that define the interval.

This method of estimating confidence interval is appropriate for experimental cases where one is estimating QTL map location of a previously detected QTL, in an independent experiment, or if the power for QTL detection in the particular case involved is close to 1.0. The latter will comprise most of the cases when the main interest of the experiment is in obtaining an accurate map location for a QTL, since when the power is significantly less than 1.0 the confidence interval of map location is extremely large (Darvasi *et al.*, 1993). Thus, in most relevant cases the use of the above theory is straightforward. For cases where the QTL is detected with power significantly lower than 1.0, however, the presented procedure may be biased relative to confidence intervals appropriate to field data. The reason for this is that in any particular experiment, a confidence interval will be con-

Table I. Resolving Power (in cM) for the BC Design[a]

	Population size (N)					
$d+h$	100	200	500	1000	1500	2000
0.125	98.6	99.0	97.9	95.8	92.0	90.1
0.25	95.1	95.8	88.4	53.8	37.5	25.5
0.50	95.1	69.4	21.6	11.1	7.7	5.3
0.75	73.3	34.1	9.0	4.5	2.8	2.2
1.00	32.8	13.0	5.8	2.8	1.7	1.3
1.50	16.2	7.1	2.7	1.3	0.8	0.6
2.00	9.7	4.1	1.5	0.8	0.6	0.4

[a] Each value obtained from 1000 replicated simulations. $d+h$, allele substitution effect.

structed only for those QTL that were detected by the statistical test used, whereas in the present study all the 1000 replicate simulations are used. We here argue, however, that even when power is less than 1.0, the results based on total simulation, provide a close approximation to the actual confidence interval for those QTL which pass the significance threshold. Our reasoning is as follows. In an experiment with a power less than 1.0, only the more informative QTL will be detected. It can be shown that the estimated map location of the detected QTL will be more precise relative to the complete theoretical distribution of possible estimated QTL map locations, and therefore, the corresponding confidence interval will be smaller than obtained with the total simulation. At the same time, however, the gene effect of the detected QTL is overestimated relative to the actual gene effect (Hoeschele and Van Raden, 1993). Since the overestimated gene effect will be used to obtain the corresponding confidence interval [see expressions (1) and (2)], the estimated confidence interval will also be smaller than that which would have been obtained using the actual gene effect. Hence, the bias due to the use of all 1000 simulations (detected and not detected QTL) and the bias introduced by the use of the overestimated values of QTL gene effect tend to annul each other. This was examined by a simulation exercise.

RESULTS

Table I presents resolving power for various experimental constellations of the BC design. As expected, resolving power decreases as either the allele substitution effect, $d + h$, or the sample size, N, increases. A QTL with an allele substitution effect less than 0.5 can be located to a particular region of the chromosome, say, smaller than 20 cM, only when a large sample is used, i.e., $N > 1000$. For an allele substitution effect, $d + h = 0.125$, even a sample size of 2000 does not provide information as to the specific location of the QTL. In contrast, QTL having larger effects ($d + h > 0.5$) can be assigned to very small regions on the chromosome (~1 cM) when large sample sizes are used.

Resolving power was empirically found to be inversely proportional to sample size and to the square of $d + h$. Thus, these simulations show that for a backcross design resolving power of a QTL mapping experiment, which is equivalent to the 95% confidence interval, CI, can be expressed in the form of the following simple expression:

$$\mathrm{CI} = \frac{k}{N\delta^2} \qquad (1)$$

where $\delta = d + h$.

In order to define the constant k, each entry in Table I was multiplied by its sample size and the square of its gene effect. An average of $k = 2999.1$ was obtained (range, 2362.5 to 3880.0; SD, 425.8). This average was obtained by taking into account only the entries in Table I with resolving power below 70 and above 1 cM. The 70-cM upper limit was set since resolving power larger than this becomes strongly influenced by the chromosome length; the 1-cM lower limit was set since smaller resolving powers are inaccurate relative to their size, because of the 0.1-cM step that was used in the simulations. In order to increase the accuracy of the estimated k, the entries in Table I with values between 1 and 20 cM, which represent the most relevant cases, were simulated again, with 10,000 replicates each. A similar estimate of k was obtained. Thus setting $k = 3000$ in Expression (1) presents a simple and general method to obtain resolving power or confidence interval in a backcross population. Note that in the BC design, dominance at the QTL affects resolving power only by its influence on the allele substitution effect, $d + h$. Depending on the direction of the cross, dominance can increase or decrease the allele substitution effect and, hence, increase or decrease resolving power.

Table II presents resolving power for various experimental constellations of the F_2 design. When $h = 0$, the resolving power decreases inversely to the sample size and inversely to d^2, as in the BC

Table II. Resolving Power (in cM) for the F_2 Design[a]

		Population size (N)					
d	h/d	100	200	500	1000	1500	2000
0.125	0	99.2	99.5	96.6	89.8	76.6	56.8
	1/2	98.8	98.9	96.9	89.5	73.1	46.6
	1	98.7	98.7	92.1	78.6	50.9	30.6
0.25	0	98.1	95.7	62.5	26.2	14.9	10.5
	1/2	97.3	92.9	56.1	21.3	12.0	8.9
	1	94.4	83.2	35.1	12.6	7.5	5.2
0.50	0	76.7	43.9	12.1	5.4	3.2	2.4
	1/2	75.5	30.8	9.0	4.0	3.2	2.2
	1	53.4	17.1	5.6	2.5	2.0	1.3
0.75	0	34.1	13.1	4.7	2.3	1.3	1.2
	1/2	27.5	11.9	3.4	2.0	1.4	1.0
	1	18.0	7.6	2.9	1.3	0.9	0.6
1.00	0	15.2	6.8	2.8	1.3	0.9	0.7
	1/2	14.9	6.5	2.5	1.2	0.8	0.4
	1	9.7	4.7	1.9	0.9	0.6	0.4
1.50	0	7.5	3.3	1.3	0.6	0.4	0.4
	1/2	7.1	3.4	1.2	0.6	0.4	0.2
	1	6.6	3.0	1.2	0.6	0.4	0.2
2.00	0	4.8	2.1	0.9	0.4	0.2	0.2
	1/2	4.6	2.6	0.9	0.4	0.2	0.2
	1	6.1	2.8	1.0	0.5	0.3	0.2

[a] Each value obtained from 1000 replicated simulations. d, h, additive and dominance effect at the QTL.

population. Thus, again, for F_2 and when $h = 0$,

$$CI = \frac{k'}{Nd^2} \qquad (2)$$

The average value of $k' = 1512.1$ (range, 1200.0 to 1953.1; SD, 266.6) was obtained from Table II in the same manner as for k in Table I. It should be noted that for mapping purposes the number of informative meiosis, rather than the population size, defines the mapping accuracy. In an F_2 the number of informative meiosis is 2N for a codominant gene. Thus substituting N in expression (2) by $2N$ provides an estimate of $k' = 3024.2$, which is virtually equal to the constant k obtained in the BC design.

In Table II, the influence of h is not constant. For small values of d, dominance decreases resolving power significantly. For example, with a sample size of $N = 500$ and $d = 0.5$, complete dominance gives a resolving power of 5.6 cM, whereas exact intermediate dominance ($h = 0$) provides a resolving power of 12.1 cM. However, as d increases, the influence of h is reduced, becoming negligible for values of d greater than 1.0. This effect is caused because as d increases, a higher value of h does not provide a significant increase in the proportion of variance explained by the QTL (Falconer, 1989).

In view of the complex effect of dominance in an F_2 experiment, it seems reasonable to use expression (2) with $k' = 1500$ for planning F_2 experiments. If on the basis of the actual estimates obtained, h turns out to be significantly differ from 0, adjustment of the confidence interval can be made with the aid of Table II. That is, for $d < 0.75$ and absolute dominance, confidence intervals will be about half of the confidence interval obtained by expression (2); for $d > 1.0$, expression (2) is appropriate for any dominance status; and for $0.75 < d < 1.0$, the confidence interval obtained from expression (2) should be adjusted by a factor of 0.5 to 1.0 according to the degree of dominance and relative estimate of d between 0.75 and 1.5.

Comparing the results in Table I and Table II, it can be seen that the preferred design depends on dominance. When complete dominance is present at the QTL ($h = d$), a BC design will generally provide slightly better resolving power than an F_2 design. For example, with $N = 1000$, $d = 0.25$, and $h = d$, the BC design provides a resolving power of 11.1 cM, whereas the F_2 design provides a resolving power of 12.6 cM (note that the allele substitution effect in this case is $d + h = 0.5$). This, however, holds only if the direction of dominance is known, so that the BC can be generated by backcrossing to the recessive line. If exact intermediate dominance is present at the QTL ($h = 0$), an F_2 design will provide significantly better resolving power than a BC design. For example, with $N = 200$ and $d = 0.75$ and $h = 0$, the resolving power of the BC and F_2 designs are 34.1 and 13.1 cM, respectively. For partial dominance ($h = 1/2d$), similar resolving power is obtained for the BC and F_2 designs. From a practical point of view and when multiple regression on all markers is applied, the BC design present a possible advantage since in an F_2 the number of parameters to be estimated will be twice that in a BC.

Considering these results as representing 95% confidence intervals in a specific experiment (Darvasi *et al.*, 1993), they indicate that in an experiment of achievable size, say, $N = 1000$, only QTL with extremely large effects (i.e., $d + h > 1$), will be located to a region small enough (~1 cM) to

Table III. Effect of Threshold on Simulation Analysis[a]

Gene effect	LOD score threshold[b]	Average estimated gene effect	Average 95% confidence interval (cM)[c]	Percentage of confidence intervals including the QTL[d]
0.25	0.0 (1000)	0.25	88.4	96.8
	1.0 (901)	0.26	82.4	96.5
	2.0 (607)	0.29	76.6	95.2
	3.0 (293)	0.32	68.6	92.5
	4.0 (130)	0.36	54.8	93.2
0.5	0.0 (1000)	0.51	24.6	95.1
	4.0 (930)	0.53	22.8	95.0
1.0	0.0 (1000)	1.01	6.0	95.9
	4.0 (1000)	1.01	6.0	95.9

[a] Obtained from 1000 replicate simulations of a 500 BC population.
[b] In parentheses the number of simulations found significant at that threshold.
[c] Obtained from the average of all the estimates at each of the 1000 replicate simulations.
[d] Where each confidence interval was obtained using expression (1) with the estimated gene effect.

proceed with physical mapping techniques for positional cloning of the gene. Considering these results as representing a reasonable marker spacing for use in a given experiment, they indicate that for QTL with moderate effects ($d + h \leq 0.5$) and population size $N \leq 1000$, a marker spacing of about 20 cM will usually be efficient for estimating the QTL map location.

It should be noted that the constants k and k' depend on the confidence level. That is, the values of $k = 3000$ and $k' = 1500$ are appropriate for a 95% confidence levels. Corresponding values for other levels of confidence can be easily obtained by similar simulations.

Confidence Intervals on Detected QTL Only

We now examine, by simulation, the question of whether the confidence intervals provided by Table I and Table II [or expressions (1) and (2)] are appropriate in instances where power is lower than 1.0 so that QTL are detected in only a proportion of the runs. A BC population of 500 individuals and a QTL with an effect of $d = 0.25$, 0.5, and 1.0 are considered. Since an approximate threshold for QTL detection will depend on number of markers and traits scored and on *a priori* information (Lander and Botstein, 1989; Hoeschele and Van Raden, 1993; Rebai *et al.*, 1994), a range of thresholds with corresponding range of power was examined. Table III present the results of 1000 replicate simulations yielding significant effects. At each individual significant simulation of the 1000 replicates (according to the various threshold values), an estimate of gene effect was obtained. The numbers in parenthesis, in the first column, presents the number of detected QTL at the appropriate threshold. The second column in Table III presents the average of these single estimates. For each individual significant simulation, an estimated confidence interval was obtained by substituting in expression (1), the estimated gene effect as obtained in that simulation. The average of all confidence intervals estimated in this way is presented in the third column in Table III. Knowing the true location of the gene, it was then determined, for each significant individual simulation whether the estimated confidence interval contained the gene. The percentage of cases for which the confidence interval indeed contained the gene is presented in the last column in Table III. For $d = 0.5$ and $d = 1.0$, power is high even for a 4.0 LOD threshold (0.93 and 1.0, respectively). Consequently, estimates of gene effect are practically unaffected by threshold and the use of expression (1) indeed provides a close 95% confidence. For $d = 0.25$, as expected, gene effects are increasingly overestimated as higher thresholds are used. It can be seen that the average estimated gene effect increases from an unbiased estimate (0.25) for a LOD threshold of 0.0 (i.e., all the simulations are considered) to an overestimated value of up to 0.36 for a threshold of 4.0 LOD score (i.e., only simulations that exceeded the 4.0 LOD threshold are considered).

Again, as expected, the confidence interval (third column in Table III) decreases as a higher threshold is used. The percentage of simulations that comprised the gene decreases slightly at higher thresholds but does not deviate appreciably from the expected value of 95% over the wide range of thresholds examined. Consequently, it would appear that the use of expression (1), as obtained from the total set of 1000 replicated simulations, is appropriate for approximating the true confidence interval for the set of statistically significant estimates.

Generalized Expressions

Expression (1) and (2) can be combined to give a general expression for resolving power or a 95% confidence interval, both for F_2 (with $h = 0$) and BC:

$$CI = \frac{3000}{m \cdot N \cdot \delta^2} \qquad (3)$$

where m is the relative number of informative meiosis ($m = 1$ for BC and $m = 2$ for F_2) and other notations are as previously defined. In Fig. 1 all the entries in Table I and Table II (with $h = 0$) at the range of 1–20 cM are plotted against their expected values using expression (3). It can be seen that expression (3) is generally a close approximation to the simulated values. It should be noted that expression (3) is valid for all relevant range of QTL effects (i.e., a gene effect of $0 < d < 2.0$, or proportion of variance explained of up to 75%). Larger gene effects can be considered as Mendelian genes for which expression (3) is no longer valid. It should be also noted that, in practice, the confidence interval might be truncated to one of its sides by the end of the chromosome.

The expected confidence interval can also be expressed in terms of ν, the proportion of variance explained by the QTL, instead of the gene effect δ. The squared gene effect, δ^2, is approximately linear to the proportion of variance explained ν. Thus the expected confidence interval can be expressed as

$$CI = \frac{530}{N \cdot \nu} \qquad (4)$$

The constant 530 was obtained from the simulations in the same manner as the constant 3000 for expression (3). Expression (4) is appropriate both for BC and for F_2 also when $h \neq 0$. In Fig. 2 all the entries in Table I and Table II (including $h \neq 0$) at the range of 1–20 cM are plotted against their expected values using expression (4). Expression (4), as compared to expression (3), tends to overestimate the expected CI for values < 10 cM and underestimate the expected CI for values > 10 cM.

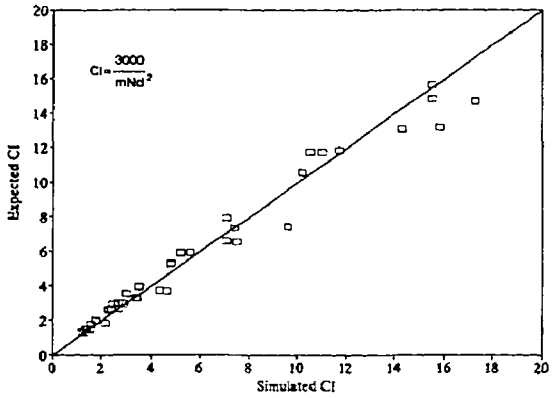

Fig. 1. Expected confidence intervals using Expression (3), as a function of the simulated confidence interval. Presented for all the results of BC and F_2 (with $h = 0$), where CI < 20 cM.

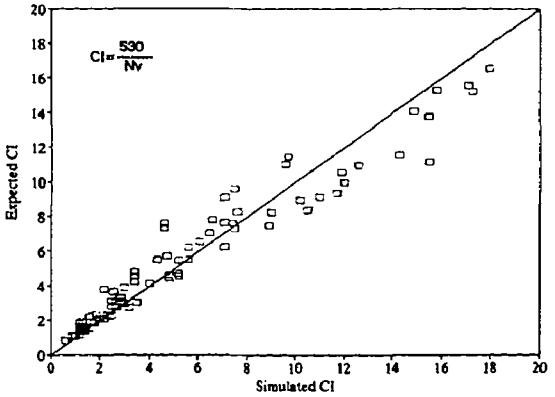

Fig. 2. Expected confidence intervals using Expression (4) as a function of the simulated confidence interval. Presented for all the results of BC and F_2 (with $h = 0$ and $h \neq 0$), where CI < 20 cM.

DISCUSSION

In this study a large number of simulations were carried out to define the resolving power of

QTL mapping experiments. It was found that the simple expression (3) or (4) provide good approximation for the resolving power. The expressions show that resolving power is inversely proportional to sample size and to the square of the QTL gene effect (or to the proportion of variance explained). The inverse relation of resolving power to sample size implies that major steps toward fine-mapping of QTL can be provided by simple increasing sample size. For a given gene effect and population size, resolving power indicates the maximal accuracy of estimating the QTL map location. Usually the value of the resolving power sets a lower useful limit for marker spacing in initial marker-QTL linkage experiments (Darvasi *et al.*, 1993). Therefore, resolving power can be useful for defining the marker spacing that should be used *a priori* in a particular marker-QTL mapping experiment. Furthermore, resolving power can serve as a useful method for obtaining a confidence interval for estimates of QTL map location, after a particular marker-QTL linkage experiment is implemented. As previously described (Darvasi *et al.*, 1993), resolving power with infinite number of markers, is an accurate estimate of confidence interval even when wider marker spacing is used, so long as marker spacing is equal or less than resolving power.

The 95% confidence interval obtained in this manner represents the distribution of all estimated QTL map locations. This is appropriate for most QTL mapping experiments, since experiments that provide reasonable QTL map location estimates, are carried out at a power close to 1.0 (Darvasi *et al.*, 1993). When statistical power is less than 1.0, not all QTL will be detected. In this case, the estimated gene effect will be overestimated causing a reduction in the estimated confidence interval relative to that obtained from expression (3). In Table III a numerical example was presented illustrating that the effect of using a given LOD threshold causes an overestimation of gene effect, which, in turns, appropriately reduces the estimated 95% confidence interval. Thus, using the entire set of simulations to estimate the confidence interval appears to be a close approximation to the actual confidence interval that would be found in field data. Consequently, for a given population size and estimated gene effect, in a BC or F_2 design, resolving power and confidence interval can be obtained directly from expression (3) or (4). This can be easily incorporated in standard QTL mapping software packages, as a means of providing reasonable estimates of the confidence intervals in specific experiments.

The F_2 design should be generally preferred over the BC design in a marker-QTL linkage experiment aimed at estimating QTL map location. With complete dominance at the QTL and backcrossing to the recessive line, a BC design can provide a more accurate estimate of the QTL map location than an F_2 design. This, however, requires *a priori* knowledge as to the direction of the dominance and, even then, only a slight improvement in mapping accuracy is obtained.

The model of an infinite number of markers is a simple one for investigating situations other than the common BC and F_2 designs. The simplicity results from the fact that calculating the likelihood of the QTL being at a particular marker does not involve a recombination proportion, so that the ML procedure reduces to a standard ANOVA. This is computationally less complicated than maximizing the likelihood function for QTL map location using an interval mapping procedure with a possibly complex pedigree. Thus, following the concepts described here, it should not be difficult to carry out the appropriate simulations for any desired experimental design.

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