

Chapter 4. Statistical power to detect QTL, parameter confidence intervals, and optimization of experimental designs

4.1 Introduction

Statistical power to detect segregating QTL will depend on the number of individuals genotyped for the genetic markers and phenotyped for the quantitative traits, the magnitude of the Type I error allowed, the effect of the segregating QTL in comparison to the genetic and environmental variances, the recombination distances between the QTL and the genetic markers, the specific experimental design employed, and the method of statistical analysis. Since the number of possible combinations described is quite large, we will present only a few examples from the literature, and describe in general terms the effect of various parameters on the statistical power of the experiment. Parameter estimate variances and confidence intervals can be computed analytically for maximum likelihood estimation, as described in Chapter 3, but these are lower bounds. A few studies have also empirically estimated confidence intervals by repeat simulation, and these are generally close to the theoretical values for large samples. Examples will be presented.

Optimization of experimental designs, which we will define as obtaining maximum statistical power per unit cost, will be chiefly a function of the cost ratio of obtaining genotypes vs. trait records. We will consider the whole range of possibilities, from the dairy cattle situation, in which records are available for analysis at virtually no cost, to human diseases, in which the data set is of limited size and additional records cannot be obtained regardless of cost. We will assume that the cost of statistical analysis is negligible with respect to the cost of data generation. Although intuitively it would seem that statistical methodologies that are able to provide more accurate parameter estimates should also increase power of detection, this is generally not the case. ML, which utilizes all information in the data, should apparently be more powerful than ANOVA, which utilizes only the mean and variance of the distributions. Simulation results to this effect were in fact obtained (Simpson, 1989), but later retracted (Simpson, 1992). In most cases, power calculations based on t-tests or ANOVA for single traits analysis will generally also hold for maximum likelihood. Incomplete genotype data will be an exception. Multitrait analyses will be discussed in the next chapter.

4.2 Estimation of power in crosses between inbred lines

Different studies that estimate the power of QTL detection considered the substitution effect of QTL alleles in terms of either the phenotypic, the residual, or the genetic standard deviation. However, since residual and genetic variances only are known *a posteriori*, QTL effects will be given in units of the phenotypic standard deviation (SDU). Soller et al. (1976) computed the required number of offsprings required to obtain a given power for the BC and F-2 designs, based on a t-test. For the F-2 only the homozygotes were considered. The

required number of offsprings can be computed as follows:

$$n = \frac{2(Z_{\alpha} + Z_{\beta})^2}{(\delta/\sigma)^2} \quad \{4.1\}$$

Where: n = offsprings per marker class, Z_{α} and Z_{β} are the standard normal distribution values for a type I and type II errors of α and β , respectively, δ = expected contrast between marker groups, and σ is the residual standard deviation. The expectation of the contrasts, and required numbers of offsprings for $2a = 0.282\sigma$, $\alpha = 0.05$, $\beta = 0.1$, and $r = 0$, are given in Table 4.1. Power, $1-\beta = 0.9$. A locus of this magnitude is responsible for 1% of the phenotypic variance in the F-2 population.

Table 4.1. The expectation of the contrasts, and required numbers of offsprings to obtain statistical power of 0.9 for the BC and F-2 designs. ($2a = 0.282\sigma$, $\alpha = 0.05$, and $r = 0$).

Cross	Contrast	Sample size	Dominance		
			$d = -a$	$d = 0$	$d = a$
Backcross	$(a-d)(1-2r)$	$2n$	525	2100	∞
F-2	$2a(1-2r)$	$4n$	1050	1050	1050

The effects of the magnitude of the QTL, and the proportion of recombination between the marker and the QTL on sample size to achieve a given power will be quadratic. That is, for an effect of half the magnitude, it will be necessary to increase the number of individuals scored four-fold to achieve the same power. In either the F-2 or BC designs, the magnitude of the effect measured will decrease proportional to $1-2r$, as compared to complete linkage. Thus, to achieve power equal to the case of complete linkage, it will be necessary to increase the experiment size by a factor of $1/(1-2r)^2$. For example, for $r=0.1$ the sample size must be increased by a factor of 1.5625, that is 1641 individuals instead of 1050.

For the F-2, power can also be estimated by ANOVA including all three genotypes. The probability for the alternative hypothesis is computed based on the non-central F distribution. Power including the heterozygotes will be greater if $|d| > a/2$ (Soller et al., 1976).

For QTL bracketed by two markers, the effect measured will not be reduced by recombination (except for double cross-overs), but, in a simple linear model analysis, recombinant individuals will be deleted. The proportion of recombinants for the F-2 and BC designs will be $(1-R)^2$ and $(1-R)$, respectively, where R is the recombination frequency between the markers. Power with a marker bracket, therefore, will be reduced by this factor

relative to complete linkage. Assuming $R = 2r_1$, which is the optimum case for a marker bracket, power with a marker bracket will be increased by (1-R) for the BC design, and will be equal to a single-marker analysis for the F-2 design (Weller, 1992). Darvasi et al. (1993) compared power for a single marker t-test to power obtained by a likelihood ratio test with marker brackets. Maximum difference in power was obtained with wide marker brackets, and the QTL located in the middle of the bracket. Even with a distance of 50 cM between markers, the difference in power between the two methods was at most 8%. Similar results were found by Haley and Knott (1992).

4.3 Replicate progeny in crosses between inbred lines

In Chapter 2 we also considered analysis of recombinant inbred lines produced by selfing of BC or F-2 individuals. Soller and Beckmann (1990) considered F-3, and F-4 generations, recombinant inbred lines (RIL), vegetative clones, and double haploid lines (DHL). In the F-3 design each F-2 individual is selfed. It is assumed that only the F-2 individuals are genotyped, but quantitative trait records are recorded on the F-3 individuals. Similarly for the F-4 design, the F-3 individuals are selfed, and the F-4 individuals are phenotyped, but not genotyped. Genotype data from the F-2 generation is analyzed. In both these designs recombination in the additional generations does not affect the analysis, because only the F-2 individuals are genotyped. RIL are produced by several generations selfing, starting with the F-2 individuals. At the final generation, a group of individuals from each line are scored for the quantitative trait, but only a single individual is genotyped for the markers. Since each line is now nearly completely homozygous and isogenic, it is only necessary to genotype a single individual for the genetic marker, and genetic variance within each RIL will tend to zero. However, because the RIL individuals are genotyped after several generations of inbreeding, the recombination between the markers and the QTL relative to the F-2 is increased. Vegetative clones produced from F-2 individuals are similar to RIL in that genetic variance within each clone is zero, but no additional recombination has occurred. Doubled haploid lines have the same statistical features as RIL when recombination between the marker and the QTL tends to zero, as described below.

The effect of replicate progeny on statistical power for all these designs can be derived by the analysis of the following model:

$$Y_{ijk} = A_i + B_j + L_k + \epsilon_{ijk} \quad \{4.2\}$$

where: Y_{ijk} = record of individual l from "line" k with genotype i with "block" effect j , A_i = effect of genotype i , B_j = effect of the j^{th} "block", L_k = effect of "line" j nested within genotype i , and ϵ_{ijk} is the random residual. This model differs from the model of Equation {2.1} in the inclusion of a line effect. Significance of a segregating QTL can be tested by an F-test of the ratio of the mean squares of A and L times the number of inbred lines. This can be computed as follows: The expectation of the mean squares of L will be: $\sigma_G^2 + \sigma_e^2/n$, where σ_G^2 = genetic variance between lines, σ_e^2 = residual variance, and n = number of individuals per line. The expectation of the mean squares for A for the F-2 design with codominance at

the QTL and complete linkage will be: $a^2 + \sigma_G^2/m + \sigma_e^2/(mn)$, where m = number of inbred lines. Thus, the ratio of the MS of A and L times n will have a central F distribution under the null hypothesis that $a^2 = 0$. (An F-test of the ratio of the MS of the marker effect to the residual MS as done for the model of Equation {2.1} will give erroneous results. A similar situation is encountered for the granddaughter design, and was discussed by Ron et al., (1994).)

σ_G^2 will be a function of the heritability, dominance, and the specific mating strategy considered. The advantage of inbred lines is greatest when σ_G^2 is large compared to σ_e^2 . Following Soller and Beckmann (1990), the between- and within-progeny group variance components, and the required number of lines relative to the F-2 design to obtain equal power are given in Table 4.2.

The variance between lines will be h^2 for all the replicate progeny designs considered above, except RIL and DHL, which will have a variance component of $2h^2$. The saving in genotyping can be quite significant. For example, for $h^2=0.2$, and $n = 10$, only 0.29 as many genotypes are required by the F-3 design as compared to the F-2. For all designs, except RIL, with large n , the number of lines required will be a direct function of the heritability. For RIL, the power will also be a function of r , as noted above. Recombination between the marker and the QTL for RIL will tend towards: $r_1 = 2r/(1+2r)$. Thus, the power for RIL will be proportional to $1/(1-2r_1)^2$ as compared to $1/(1-2r)^2$ for the F-2 design.

Table 4.2. Between and within progeny group variance components, and the required number of lines relative to the F-2 design for equal power, as a function of the heritability (h^2) and the number of individuals per line (n).

Progeny type	Variance component		Required number of lines relative to the F-2
	Between lines	Within lines	
F-2	h^2	$(1-h^2)$	1
F-3	h^2	$(1-h^2/2)/n$	$h^2+(1-h^2/2)/n$
F-4	h^2	$(1-h^2/4)/n$	$h^2+(1-h^2/4)/n$
Vegetative clones	h^2	$(1-h^2)/n$	$h^2+(1-h^2)/n$
Recombinant inbred lines	$2h^2$	$(1-h^2)/n$	$[h^2+(1-h^2)/2n][1-2r^2]/[1-4r/(1+2r)]^2$
Doubled haploid lines	$2h^2$	$(1-h^2)/n$	$h^2+(1-h^2/2)/2n$

4.4 Estimation of power for segregating populations

Soller and Genizi (1978) estimated power for the daughter design assuming a nested ANOVA

analysis. Weller et al. (1990) estimated power for the daughter and granddaughter design assuming a Chi-squared test, first proposed by Neimann-Sorensen and Robertson (1961). With large samples the two methods give virtually identical results. Weller et al. (1990) assumed that the squared sum of the within family paternal allele contrasts would have a central Chi-squared under the null hypothesis, and a non-central Chi-squared distribution under the alternative hypothesis. Their calculations were based on the assumption of two QTL alleles with equal frequency segregating in the population. Thus, half of the sires would be homozygous for the QTL, and expected paternal allele contrast for these families are zero. They also assumed complete linkage, and considered substitution effects of 0.1, 0.2 and 0.3. With no dominance at the QTL, the substitution effect is equal to a (half the difference between the homozygote means). For the daughter design, power of 0.7, with a type I error of 0.01, is obtained for a QTL with a substitution effect of 0.2 SDU if 400 daughters of each of 10 sires are analyzed for a trait with heritability of 0.2 (Weller et al., 1990). This entails genotyping 4000 individuals. An extensive table for various combinations of substitution effect, number of sires, and number of daughters is given in Weller et al. (1990). Power is maximum when the frequency of the two QTL alleles is equal. For a codominant allele the allele frequency effects power only through the expected frequency of heterozygous sires, which will be close to 0.5 over the range of 0.3 to 0.7. Thus, within this range, allele frequency has only a small effect on power for a codominant locus.

The situation with the granddaughter design is similar to the F-3 design considered above, in that the sons are genotyped, while records from their progeny are analyzed. Similar to the F-3 design, power for the granddaughter design is increased per individual genotyped, because many phenotypes are analyzed for each individual genotyped. Also power is not affected by an additional generation of recombination. Unlike the F-3 design, both the QTL contrast and the common polygenic effect passed to the grandprogeny are halved. As in the case of inbred lines, increasing the number of granddaughters will reduce the residual variance, but not between-son genetic variance. Thus, the advantage of the granddaughter design is greatest for low heritability traits. With heritability of 0.2 and a type I error of 0.01, power is 0.74 to detect a segregating with a substitution effect of 0.2 SDU if genetic markers are analyzed on 100 sons of each of 10 grandsires, with 50 quantitative trait-recorded granddaughters per son (Weller et al., 1990). Comparing this example to the example above for the daughter design, greater power is obtained to detect an effect of the same magnitude with the granddaughter design, even though only one-fourth as many individuals are genotyped (4000 vs. 1000). An extensive table of power for the granddaughter design is also given in Weller et al. (1990). The following conclusions can be drawn from the daughter and granddaughter design power tables:

1. For both the daughter and granddaughter designs with equal number of genotypes, power is greater for a few big families than for many small ones.
2. With heritability of 0.2 power equal to the daughter design can be obtained by the granddaughter design with only 1/4 as many genotypings.
3. For a given substitution effect measured relative to the phenotypic SD, power for granddaughter design decreases with increase in heritability.
4. Similar to replicate progeny, designs for inbred lines, increasing number of granddaughters

per son above 50 increases power only marginally.

Power for replicate progeny designs decreases with increase in heritability, if the QTL effect is measured relative to the phenotypic SD. Although it is the phenotypic SD that is economically relevant, it is the genetic variance that must be explained by segregating QTL. With the QTL measured relative to the genetic SD, there is virtually no relationship between heritability and power, if the number of granddaughters is large.

As mentioned in Chapter 2, very large samples will be required in the sib-pair design of Haseman and Elston (1972) to obtain reasonable power for QTL of the magnitude considered above. Most of the calculations for the full sib design have assumed loci of much larger magnitude (Srihney and Swift, 1992), and most calculations have been for dichotomous disease traits. Tens of thousands of individuals will be required to obtain power greater than 0.5 for loci with substitution effects in the range of 0.2.

4.5 Confidence intervals for QTL parameters

As shown in Equation {3.16}, for MLE the estimation error variance-covariance matrix can be estimated from the inverse of the ML matrix of second differentials. This is also the case for linear model estimation. Lander and Botstein (1989) alternatively proposed estimating "support intervals" for QTL location, based on the ML estimates for the other parameter with map location fixed. These estimates do not account for variation in other parameters, or the possibility that the QTL is outside the marker bracket (Martinez and Curnow, 1992). They do account for the possibility that the confidence interval is asymmetric. Mackinnon and Weller (1995) also proposed to estimate confidence intervals and standard errors by computing the expectation of the likelihood function as a function of each parameter with the other parameters held constant. As noted previously, the difference of the log ML to the log likelihood with one parameter fixed has a $1/\chi^2$ distribution with one degree of freedom. Based on the expectation of the likelihood function and the χ^2 distribution, the 95% confidence interval for each parameter can be determined.

Darvasi et al. (1993) estimated estimation error variances based on Equation {3.16} and by repeat simulation for the BC design with marker brackets, and also directly estimated the 95% confidence intervals by repeat simulation. All methods were very accurate for estimation of QTL variances. Estimates based on the second differential matrix tended to slightly overestimate standard errors for QTL means relative to the empirical estimates, especially for large spacing between markers. Neither the QTL effect or marker spacing had any appreciable effect on confidence intervals for QTL means. The effect of sample size was quadratic, as expected. That is, doubling the sample decreased the confidence interval by a factor of about the square root of two.

For QTL map location, the estimates based on the empirical 95% confidence interval, and estimates based on four times the empirical standard error were generally similar. However, estimates based on the second differential matrix tended to underestimate the confidence interval for small marker intervals, and overestimate the confidence interval for large marker

intervals. Differences were in some cases more than double. Clearly, for this parameter the asymptotic properties of the second differential matrix do not hold. Thus, the "support interval" method, despite the deficiencies considered above, may be the method of choice for estimation of map location. For the BC design and a single marker, the matrix of second differentials tended to overestimate error variance for all parameters, even though by theory the opposite should occur. It should be noted though, that even for very large samples, the error variance estimated by the matrix of second differentials is correct only at the point of maximum likelihood. The likelihood function can behave marked differently for other parameter values.

Maekinnon and Weller (1995) estimated parameter standard errors both empirically and by the matrix of second differentials for the daughter design for a single marker, and also deterministically computed the 95% confidence intervals, as described above. In addition to QTL means, r , and the residual variance, they also estimated the QTL allele frequencies. Deterministic estimates based on assuming that all other parameters were fixed tended to underestimate the standard errors derived by either repeat simulation or the matrix of second differentials. As for the BC design with a single marker, the matrix of second differentials tended to overestimate the standard errors, even though the opposite was expected. Discrepancies increased with decrease in sample size. Confidence intervals were largest for recombination rate. The standard error for r with a substitution effect of 0.5 was about 0.1 with 2000 individuals. For the BC design and a marker bracket of 50 cM, a similar SE was obtained with only 1000 individuals, although, in both cases the number of QTL genotypes performed was the same.

4.6 Optimization of Experimental Designs

The major cost elements of QTL detection are producing the individuals for analysis, scoring the quantitative traits, genotyping for the genetic markers, and data analysis. Optimization of experimental designs to obtain maximum power per unit cost will depend on the relative costs of these factors. Genotyping individuals for the genetic markers is often the most expensive part of the experiment. Furthermore, if the analysis is based on existing records, marker genotyping is the only significant expense.

With microsatellites it is now possible to develop virtually unlimited numbers of markers. For a complete genome search, the total number of genotypes will be the number of individuals genotyped times the number of markers genotyped for individual. Darvasi and Solter (1994) considered a number of experimental designs, and cost ratios of genotyping to phenotyping. If both the numbers of individuals and markers available for genotyping are unlimited, and costs of phenotyping are low relative to genotyping costs, then marker spacing of close to 80 cM between will give maximum statistical power per unit cost for crosses between inbred lines or half-sib families. Of course at these distances the markers will be unlinked. For RIL, optimum spacing will be about 50 cM. Even if the cost of obtaining trait

records, including producing the recorded individuals if necessary, is one-hundred fold the cost of each marker genotype, optimum marker spacing is still 30 cM for designs other than RIL. In any event, decreasing marker spacing below 20 cM has virtually no effect on power (Darvasi et al., 1993).

In addition to replicate progeny, which we considered above, several other techniques have been proposed to increase statistical power to detect segregating QTL as a function of the number of genotype assays performed: selective genotyping, sample pooling, and sequential sampling. All of these techniques require increasing the number of individuals produced and scored for quantitative traits, as compared to designs in which all individuals scored for the quantitative traits are also genotyped. Unlike replicate progeny, these other techniques are trait specific.

Selective genotyping was first proposed by Lebowitz et al. (1987), and elaborated by Lander and Botstein (1989), and Darvasi and Solter (1992). Most of the information with respect to QTL detection for any given trait is derived from the individuals with the extreme phenotypic values. Thus, if the sample of individuals recorded for the quantitative trait is large, power per individual genotyped can be increased by selectively genotyping those individuals with the highest and lowest trait values. With selective genotyping it is possible to obtain the same statistical power by genotyping only one-fourth as many individuals as compared to a random sample (Darvasi and Solter, 1992). The disadvantages of this method are, first, that a much larger sample of individuals must be scored for the quantitative trait. Second, if there are several quantitative traits of interest, it will be necessary to genotype a different sample for each trait. Selective genotyping with multiple traits will be considered in more detail in the following chapter. In general, though, this technique is only useful if the number of traits of interest is low. Third, estimates of the QTL effect will be biased by a linear model analysis, although unbiased estimates can be derived as a function of the selection intensity (Darvasi and Solter, 1992). Unbiased estimates can also be derived by ML if all phenotypic individuals are included in the analysis. Finally, power to detect QTL variance effects is reduced (Weller and Wylter, 1992).

The number of genotypings that must be performed can be reduced further by up to two orders of magnitude by sample pooling (Plotsky et al., 1993, Darvasi and Solter, 1994a). That is, instead of genotyping each individual separately, genetic material from several individuals with similar phenotypes for the quantitative trait can be combined prior to assay. In this case a linked QTL is detected by band intensity when pools of individuals with "high" and "low" phenotypes are compared. For this method to be effective, it must be possible to determine accurately the number of individuals of each genotype in a pool from the band intensity. Sample pooling must be applied together with selective genotyping. Thus, this method is most useful if the number of quantitative traits of interest is relatively low. Since there will be some degradation of information when genetic material of individuals is pooled, more individuals must be scored for the quantitative trait, as compared to selective genotyping without sample pooling to obtain the same statistical power.

Finally, Motro and Solter (1993) suggested sequential sampling as a further tool to reduce the number of individuals genotyped. Rather than genotyping a sample large enough to obtain the desired statistical power, a smaller sample is genotyped. Further genotyping will not be

required for those markers that either clearly show no significant effect or that show a significant effect. Additional individuals will be genotyped only for those markers that display "borderline" significance. By this method it is possible to reduce the total number of genotypings required by nearly half for a single trait. However, if the number of traits is large, nearly every marker will have borderline significance for at least one quantitative trait. Thus, like selective genotyping and sample pooling, this method is useful only if the number of traits under consideration is small.

4.7 Summary

Numerous misconceptions with respect to the power of QTL detection and experiment design optimization are prevalent. In most cases power to detect a segregating QTL of a magnitude likely to be segregating in the population will require genotyping at least 500 individuals, and often many more. Most experiments have been too small to find effects of the magnitude that could be reasonably expected. Unless the phenotyping costs are very high relative to genotyping costs, experimental designs with very wide marker spacing are optimum, and decreasing marker intervals below 20 cM will have virtually no effect for most experimental designs. Power per individual genotype can be dramatically increased by replicate progeny, selective genotyping, sample pooling and sequential sampling, and the effect of these techniques are cumulative. Except for replicate progeny, these other techniques are trait specific, and are therefore most appropriate for experiments that consider only a few traits.

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