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Power of two- and three-generation QTL mapping experiments in an outbred population containing full-sib or half-sib families

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Abstract QTL mapping experiments involve many animals to be genotyped and performance tested. Consequently, experimental designs need to be optimized to minimize the costs of data collection and genotyping. The present study has analyzed the power and efficiency of experiments with two- or three-generation family structures containing full-sib families, half-sib families, or both. The focus was on data from one outbred population because the main interest is to locate genes that can be used for within-line selection. For a two-generation experiment more animals had to be typed for marker loci to obtain a certain power than for a three-generation experiment. Fewer trait values, however, had to be obtained for a two-generation experiment than for a three-generation experiment. A two- or three-generation family structure with full-sib offspring was more efficient than a two- or three-generation family structure with half-sib offspring. A family structure with full-sib grand-offspring, however, was less efficient than a family structure with half-sib grand-offspring. For the most-efficient family structure each pair of parents had full-sib offspring that were genotyped for the marker. For the most-efficient family structure each full-sib offspring had half-sib grand-offspring for which trait values were obtained. For equal power with a heritability of 0.1 and 100 grand-offspring per full-sib offspring, 30-times less marker typings were required for this most efficient family structure than for a two-generation half-sib structure in which marker genotypes and trait values were obtained for half-sib offspring. The effect of heritability and the type of analysis (single marker or interval analysis) on the efficiency of a family structure is described. The results of this study should help to design QTL mapping experiments in an outbred population.

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Introduction

Dense linkage maps consisting of highly polymorphic marker loci are available for most livestock species (Andersson et al. 1993; Barendse et al. 1994; Bishop et al. 1994; Crawford et al. 1994; Rohrer et al. 1994) and can be a powerful tool for mapping quantitative trait loci (QTLs) (e.g. Patterson et al. 1988; Stuber et al. 1992; Andersson et al. 1994; Georges et al. 1995). QTL-mapping experiments involve many animals to be genotyped and performance tested (Soller and Genizi 1978; Weller et al. 1990). Consequently, experimental designs need to be optimized to minimize costs of data collection and genotyping. In livestock, QTL mapping experiments can involve data from one outbred population or from a cross between populations (Soller 1991). An experiment involving a cross between populations will reveal genes that explain the variance between populations, whereas an experiment within one population will reveal genes that explain the variance within a population. Within an outbred population, genetic markers and putative QTLs are expected to be in linkage equilibrium; therefore analysis has to be done within families. Weller et al. (1990) computed the powers of experiments for balanced two- and three-generation half-sib designs for outbred populations. They quantified the influence on power of size of QTL effect, heritability, family size, and number of half-sib families. They focused on dairy cattle breeding in which the half-sib family structure is predominant. In poultry and pigs, however, full-sib family structures are feasible. For the mapping of markers, fewer animals are needed in an experiment with a full-sib family structure than in an experiment with a half-sib family structure. We expect that for QTL mapping a full-sib family structure has a higher efficiency than a half-sib family structure. The power of an experiment with a two-generation full-sib family structure or a three-generation

full-sib family structure is unknown. The present study analyzes the power and efficiency of experiments with two- or three-generation family structures with full-sib families, half-sib families, or both. We focus on data from one outbred population because the main interest is to locate genes that can be used for within-line selection.

Methods

Outbred population

Consider an outbred population in genotypic equilibrium for individual loci and genetic equilibrium for any pair of loci. Genetic variance in the population comprises the variance due to one quantitative trait locus (QTL) with two co-dominant alleles, having frequencies p and $1-p$, and the variance due to polygenic effects. The QTL genotype effects are a, 0 and $-a$. Flanking markers are at 0.1 M (10 cM) from the QTL. The map distance between the two flanking markers is denoted d. The QTL is at the midpoint between the two markers so that the map distance between a marker and the QTL is $0.5d$. The recombination rate between the two marker loci is denoted γ and the recombination rate between a marker and the QTL is denoted r. Map distance and recombination rate are related by the Haldane mapping function: $\gamma = 0.5(1-e^{-2d})$ and $r = 0.5(1-e^{-d})$.

The phenotypic expression of a trait is due to the effect of the QTL, a random normal polygenic effect, and a random normal residual effect. We denote polygenic variance as σ_u^2 and residual variance as σ_e^2. Further, $\sigma_p^2 = \sigma_u^2 + \sigma_e^2$ and heritability is $h^2 = \sigma_u^2/\sigma_p^2$. Note that QTL genotype effects are not included in σ_p^2 or h^2.

Family structures

In this paper, a parent is a first generation animal, an offspring is a second generation animal and a grand-offspring is a third generation animal.

Five family structures are considered that differ in the number of generations and the relations between animals. For each family structure a single pedigree will be described. An experiment can involve one of several pedigrees:

HS2. A two-generation half-sib structure. A sire has several unrelated mates and each mate has one offspring. Marker genotypes are obtained for the sire and the half-sib offspring, but not for the mates. Trait values for half-sib offspring are obtained.

FS2. A two-generation full-sib family structure. A pair of parents has several full-sib offspring. Each parent, male or female, has one mate. Marker genotypes are obtained for all animals. Trait values for full-sib offspring are obtained.

HS3. A three-generation half-sib family structure. A sire has several half-sib offspring. Each half-sib offspring is mated to several unrelated animals to produce one half-sib grand-offspring per mate per half-sib offspring. Marker genotypes are obtained for the sire and the half-sib offspring, but not for the mates of the sire, the mates of the half-sib offspring and the half-sib grand-offspring. Trait values for the half-sib grand-offspring are obtained. Weller et al. (1990) named a design with this family structure the 'grand-daughter' design.

FS3. A three-generation full-sib family structure. A pair of parents has several full-sib offspring. Each full-sib offspring is mated to one unrelated animal to produce several full-sib grand-offspring per full-sib offspring. Marker genotypes are obtained for the parents and the full-sib offspring but not for the mates of the full-sib offspring and the full-sib grand-offspring. Trait values for the full-sib grand-offspring are obtained.

FSHS. A three-generation full-sib offspring, half-sib grand-offspring family structure. A pair of parents has several full-sib offspring. Each full-sib offspring is mated to several unrelated animals to produce one half-sib grand-offspring per mate per full-sib offspring. Marker genotypes are obtained for the parents and the full-sib offspring but not for the mates of the full-sib offspring and the half-sib grand-offspring. Trait values for the half-sib grand-offspring are obtained.

We consider balanced designs. All parents are heterozygous (Mm) for marker loci and 50% of the offspring inherit marker allele M and 50% of the offspring inherit marker allele m. Each family has the same number of offspring. In a three-generation design each offspring has the same number of grand-offspring. Offspring are divided into two groups. In one group are the offspring that inherit marker allele M, and in the other group are the offspring that inherit marker allele m. Grand-offspring are also divided into two groups. In one group are the grand-offspring that descend from offspring that inherit marker allele M from the parent. In the other group are the grand-offspring that descend from offspring that inherit marker allele m from the parent.

Computation of power: single-marker analysis

We assume that the QTL mapping experiment is analyzed with a linear model. In this model, the effect of the marker is nested within the parent. The model for a design with a HS2 family structure is given as an example:

$$y_{ijk} = s_i + m_{ij} + e_{ijk} \tag{1}$$

where y_{ijk} is the trait value for the k-th offspring inheriting marker allele j of sire i, s_i is the effect sire i, m_{ij} is the effect of marker allele j of sire i, and e_{ijk} is the residual effect of offspring k. For a sire with marker genotype Mm, m_{i1} is the effect of allele M and m_{i2} the effect of allele m.

Let $(m_{i1} - m_{i2})$ be the marker contrast (MC) for sire i. Inferences about the presence of a QTL linked to the marker are based on the marker contrast. The marker contrast is expected to be zero if no QTL is linked to the marker or if a parent is homozygous for the linked QTL. The marker contrast is expected to be *non-zero* if a QTL is linked to the marker and the sire is heterozygous for the linked QTL. Thus, the presence of a linked QTL can be found by testing for significantly non-zero marker contrasts. The square of the marker contrast divided by the square of the standard error (SE) of the marker contrast is used to compute a test-statistic with a value (Weller et al. 1990):

$$\sum_{i=1}^{n_p} \mathrm{MC}_i^2/\mathrm{SE}_i^2 \tag{2}$$

where n_p is the number of parents for which a marker contrast is computed (for an experiment with a HS2 family structure, n_p is equal to the number of sires), MC_i is the marker contrast for the i-th parent, SE_i is the standard error of MC_i. If the standard error can be computed from a priori known phenotypic variance then this test statistic is a chi-square statistic (Geldermann 1975). We assume that the phenotypic variance is known and use the chi-square statistic. Under the null hypothesis of no linked QTL the statistic has a central chi-square distribution. The null hypothesis is rejected when the statistic is larger than threshold T. Threshold T is the $(1-\alpha)$ percentile of the central chi-square distribution where α is the type-I error. The power of a QTL mapping experiment is equal to the probability that the null hypothesis is rejected, i.e. the probability that the chi-square statistic exceeds threshold T. Under the alternative hypothesis of a linked QTL, the chi-square statistic has a non-central chi-square distribution. The non-centrality of this distribution depends on the expectation for the marker contrast, the standard error of the marker contrast, and the number of parents that are heterozygous for the linked QTL.

Given the definitions and assumptions described above, the power of an experiment is computed as (Weller et al. 1990):

$$\text{power} = \sum_{x=0}^{n_p} \mathrm{pr}(x)\, \mathrm{p}[\chi^2(\mathrm{NC}(x), n_p) > \mathrm{T}] \tag{3}$$

where x is the number of parents that are heterozygous for the QTL, n_p is the number of parents for which a marker contrast is computed, $\mathrm{pr}(x)$ is the binomial probability that x out of n_p parents are heterozygous for the QTL, $\chi^2[\mathrm{NC}(x), n_p]$ is a non-central chi-square variable with n_p degrees of freedom and with non-centrality parameter $\mathrm{NC}(x)$, $\mathrm{NC}(x)$ is the non-centrality parameter for the distribu-

tion under the alternative hypothesis given that x parents are heterozygous for the QTL, and $p[\chi^2(NC(x), n_p) > T]$ is the probability that the non-central chi-square variable exceeds threshold T. The non-centrality parameter is computed as:

$$NC(x) = x\, E^2(MC)/SE^2(MC) \quad (4)$$

where $E^2(MC)$ is the square of the expectation of a marker contrast for a parent that is heterozygous for the QTL and $SE^2(MC)$ is the square of the standard error of this marker contrast. $E^2(MC)$ and $SE^2(MC)$ depend on the design of an experiment as will be shown below.

If a parent is homozygous at the linked QTL then the marker contrast is expected to be zero. If a parent in heterozygous at the linked QTL then for a two-generation family structure (HS2, FS2) (Soller 1991):

$$E^2(MC-2) = a^2(1-2r)^2 \quad (5)$$

where $E^2(MC-2)$ is the square of the expected marker contrast for a parent of a two-generation family that is heterozygous for the linked QTL, and a and r as described earlier.

For a three-generation family structure (HS3, FS3 or FSHS) the marker contrast is the difference between the two groups of grand-offspring. The marker allele of the parent for which the marker contrast is computed is transmitted to 50% of the grand-offspring so the marker contrast of a three-generation design is expected to be half the marker contrast of a two-generation design (Weller et al. 1990). If a parent is heterozygous at the QTL then for a three-generation family structure:

$$E^2(MC-3) = 1/4\, a^2(1-2r)^2 \quad (6)$$

where $E^2(MC-3)$ is the square of the expected marker contrast for a parent of a three-generation family that is heterozygous for the linked QTL. Note that $E^2(MC)$ denotes the square of the expected marker contrast in general, while $E^2(MC-2)$ and $E^2(MC-3)$ are specific notations for two- and three-generation family structures.

$SE^2(MC)$, the other parameter necessary to compute the non-centrality parameter, depends on heritability, family structure and number of animals. For a HS2 family structure:

$$SE^2_{HS2} = \mathrm{var}\left(\frac{2}{n_o}\sum_{k=1}^{n_o/2} y_{ijk} - \frac{2}{n_o}\sum_{k=1}^{n_o/2} y_{i2k}\right) = \frac{4-h^2}{n_o} \quad (7)$$

where n_o is the number of offspring per parent. A full derivation of SE^2_{HS2} is given in Appendix 1. Table 1 gives the SE^2 of the marker contrast for the five family structures.

Computation of power: interval analysis

Instead of performing single-marker analysis, markers can be analyzed in pairs to detect a QTL in the interval between two markers (Lander and Botstein 1989). We assume that a QTL is located at the midpoint of the interval between marker loci M and N. Let a parent be heterozygous for marker loci M and N; the ordered genotype of the parent is MN/mn. Offspring can inherit four marker haplotypes (MN, Mn, mN or mn), two of which are non-recombinant (MN, mn) and two recombinant (Mn, mN) with respect to the two markers. Offspring inheriting a recombinant haplotype provide no information to detect a QTL if that QTL is at the midpoint of the interval (Lander and Botstein 1989). Therefore, only information on offspring inheriting non-recombinant haplotypes is used. This information is analyzed with a linear model. The model for a HS2 family structure is given as an example:

$$y_{ijl} = s_i + h_{ij} + e_{ijl} \quad (8)$$

where y_{ijl} is the trait value of the l-th offspring inheriting non-recombinant haplotype j of sire i, s_i is the effect of sire i, h_{ij} is the effect of the j-th non-recombinant haplotype of sire i, and e_{ijl} is the residual effect of offspring l. Let $(h_{i1}-h_{i2})$ be the haplotype contrast (HC) for sire i. The presence of a linked QTL is identified by testing for significantly non-zero haplotype contrasts using the square of the haplotype contrast divided by the square of the standard error of the haplotype contrast. The power of this test is computed using equation (3). For interval analysis, the non-centrality parameter is:

$$NC(x) = E^2(HC)/SE^2(HC) \quad (9)$$

where $E^2(HC)$ is the square of the expected haplotype contrast for a parent that is heterozygous for the QTL, and $SE^2(HC)$ is the square of the standard error of this haplotype contrast.

If a parent is homozygous at the linked QTL, then the haplotype contrast is expected to be zero. If a parent is heterozygous at the linked QTL, then for a two-generation family structure (see Appendix 2):

$$E^2(HC-2) = a^2(1-2r)^2/(1-\gamma)^2 \quad (10)$$

where a, r and γ are as described earlier. Using equation (4):

$$E^2(HC-2) = E^2(MC-2)/(1-\gamma)^2 \quad (11)$$

If a parent is heterozygous at the QTL, then for a three-generation family structure:

$$E^2(HC-3) = 1/4\, a^2(1-2r)^2/(1-\gamma)^2, \quad (12)$$

and using equation (5):

$$E^2(HC-3) = E^2(MC-3)/(1-\gamma)^2. \quad (13)$$

The portion $(1-\gamma)$ of the offspring that inherits a non-recombinant marker haplotype is used to compute the haplotype contrast. All offspring are used to compute the marker contrast. In general, the squared standard error of a mean is inversely proportional to the number of observations used to compute the mean. The standard error of the haplotype contrast of a parent is therefore larger than the standard error of the marker contrast of that same parent. In particular:

$$SE^2(HC) = SE^2(MC)/(1-\gamma). \quad (14)$$

Relative efficiency (RE) and relative effect of doubling (RED)

The power of an experiment is determined by n_p, pr(x), NC(x) and T [equation (3)]. The parameter n_p is defined by the design of an experiment; pr(x) depends on n_p and the heterzygosity at the QTL, and T is directly related to α. Each other variable that determines the design of an experiment influences the power of an experiment via the influence it has on NC(x). To measure the relative effect on the power of a variable, we define two paratmeters: relative efficiency (RE) and relative effect of doubling (RED). RE is used to compare family structures, to compare interval analysis with single marker analysis, or to determine the effect of changing the value of one variable. RE is defined only if designs A and B have an equal number of offspring per family and is:

$$RE(A/B) = [NC^A(1) \times \#C^A]/[NC^B(1) \times \#C^B] \quad (15)$$

Table 1 Squared standard error of the marker contrast (SE^2) for five family structures

Family structure	SE^2
HS2	$(4-h^{2a})/n_o^b$
FS2	$(4-2h^2)/n_o$
HS3	$[0.75h^2+(4-h^2)/n_{og}^c]/n_o$
FS3	$[1.25h^2+(4-h^2)/n_{og}]/n_o$
FSHS	$[0.25h^2+(4-h^2)/n_{og}]/n_o$

[a] h^2 is heritability
[b] n_o is number of offspring
[c] n_{og} is number of grand-offspring per offspring

where RE(A/B) is the efficiency of an experiment with design A relative to the efficiency of an experiment with design B, $NC^Y(1)$ is the non-centrality per marker or haplotype contrast for an experiment with design Y, $\#C^Y$ is the number of marker or haplotype contrasts per family for an experiment with design Y. The use of RE can be illustrated by a simple example. If RE(A/B) is 2 and for experiments A and B the same number of marker contrasts are computed, then experiments A and B have equal power if the number of offspring per experiment is two-times larger for experiment B than for experiment A.

First, the RE to compare family structures is described. To compare FS2 with HS2:

$$\mathrm{RE(FS2/HS2)} = \left(\frac{a^2(1-2r)^2}{(4-2h^2)/n_o} \times 2\right) \Big/ \left(\frac{a^2(1-2r)^2}{(4-h^2)/n_o} \times 1\right)$$
$$= 2 \times \frac{4-h^2}{4-2h^2} = 2 + \frac{h^2}{2-h^2}. \quad (16)$$

The RE among family structures HS2, FS2, HS3, FS3 and FSHS are in Table 2.

A second use of RE is to compare interval analysis (I) with single-marker analysis (S). Using equations (4) and (9):

$$\mathrm{RE(I/S)} = \mathrm{NC^I(1)/NC^S(1)} = \frac{\mathrm{E^2(HC)}}{\mathrm{SE^2(HC)}} \Big/ \frac{\mathrm{E^2(MC)}}{\mathrm{SE^2(MC)}}. \quad (17)$$

Using equations (11), (13) and (14):

$$\frac{\mathrm{E^2(HC)}}{\mathrm{SE^2(HC)}} \Big/ \frac{\mathrm{E^2(MC)}}{\mathrm{SE^2(MC)}} = \frac{\mathrm{E^2(MC)}/(1-\gamma)^2}{\mathrm{SE^2(MC)}/(1-\gamma)} \Big/ \frac{\mathrm{E^2(MC)}}{\mathrm{SE^2(MC)}} = \frac{1}{1-\gamma}. \quad (18)$$

Third, RE is used to evaluate the effect of changing the value of a variable. We use RE to evaluate the effect of changing heritability and the effect of changing the map distance between two marker loci. For heritability, RE for a HS2 family structure is:

$$\mathrm{RE}(h^2 = y/h^2 = z) = \left(\frac{\mathrm{E^2(MC)}}{(4-y)/n_o}\right) \Big/ \left(\frac{\mathrm{E^2(MC)}}{(4-z)/n_o}\right) = \frac{4-z}{4-y}. \quad (19)$$

Table 3 gives $\mathrm{RE}(h^2 = y/h^2 = z)$ for the five family structures.

The RE for map distance between two marker loci depends on the type of statistical analysis. If the QTL is at the midpoint between the two markers, then for single-marker analysis:

$$\mathrm{RE}(d = y/d = z) = ((1-2r_y)^2 a^2/\mathrm{SE^2})/((1-2r_z)^2 a^2/\mathrm{SE^2})$$
$$= (1-2r_y)^2/(1-2r_z)^2 = e^{-2y}/e^{-2z} \quad (20)$$

where r_y is the recombination rate between a marker and the QTL if y is the map distance between the two marker loci. Recombination rate r_y is computed from map distance y using the Haldane mapping function. For interval analysis:

$$\mathrm{RE}(d_y/d_z) = ((1-2r_y)^2/(1-\gamma_y))/((1-2r_z)^2/(1-\gamma_z))$$
$$= (e^{-2d_y}/e^{-2d_z}) \times [(1+e^{-2d_z})/(1+e^{-2d_y})]. \quad (21)$$

The relative effect of doubling (RED) is a second measure to compare the efficiency of designs. It is defined as:

$$\mathrm{RED}(y, z) = [\mathrm{NC(1)} \mid 2y, z]/[\mathrm{NC(1)} \mid y, 2z] \quad (22)$$

where $\mathrm{RED}(y, z)$ is the change in NC due to doubling the value of variable y, relative to the change in NC due to doubling the value of variable z; $[\mathrm{NC(1)} \mid 2y, z]$ is the value of NC(1) for the design of a certain experiment if the value of y is doubled and $[\mathrm{NC(1)} \mid y, 2z]$ is the value of NC(1) for the design of the same experiment if the value of z is doubled. Two forms, $\mathrm{RED}(a^2, n_o)$, and $\mathrm{RED}(n_o, n_{og})$, will be described. For a HS2 family structure:

$$\mathrm{RED}(a^2, n_o) = \left(\frac{(2a^2)(1-2r)^2 \times n_o}{4-h^2}\right) \Big/ \left(\frac{a^2(1-2r)^2 \times 2n_o}{4-h^2}\right) = 1. \quad (23)$$

Similarly, it can be shown that $\mathrm{RED}(a^2, n_o)$ is 1 for all five family structures. For all family structures, doubling a^2, and thus doubling the variance due to the QTL, has the same effect on the non-centrality parameter, and thus power, as doubling the number of offspring per family. The second form, $\mathrm{RED}(n_o, n_{og})$, is defined for designs with a three-generation family structure. For a HS3 family structure:

$$\mathrm{RED}(n_o, n_{og}) = \frac{\mathrm{E^2(MC-3)} \times 2n_o}{0.75h^2 + (4-h^2)/n_{og}} \Big/ \frac{\mathrm{E^2(MC-3)} \times n_o}{0.75h^2 + (4-h^2)/(2n_{og})}$$
$$= 1 + \frac{0.75h^2}{0.75h^2 + (4-h^2)/n_{og}}. \quad (24)$$

The $\mathrm{RED}(n_o, n_{og})$ for HS3, FS3, and FSHS family structures are in Table 4.

Table 2 Relative efficiency (RE) between family structures HS2, FS2, HS3, FS3 and FSHS

RE(FS2/HS2)	$2 + h^{2a}/(2-h^2)$
RE(HS3/HS2)	$(1-0.25h^2)/[0.75h^2 + (4-h^2)/n_{og}^b]$
RE(FS3/HS2)	$(2-0.5h^2)/[1.25h^2 + (4-2h^2)/n_{og}]$
RE(FSHS/HS2)	$(2-0.5h^2)/[0.25h^2 + (4-h^2)/n_{og}]$
RE(FS3/HS3)	$2-(h^2-2h^2/n_{og})/[1.25h^2 + (4-2h^2)/n_{og}]$
RE(FSHS/HS3)	$2 + h^2[0.25h^2 + (4-h^2)/n_{og}]$
RE(FSHS/FS3)	$1 + (h^2 - h^2/n_{og})/[0.25h^2 + (4-h^2)/n_{og}]$

[a] h^2 is heritability

[b] n_{og} is number of grand-offspring per offspring

Table 3 The efficiency of heritability at y relative to the efficiency of heritability at z $[\mathrm{RE}(h^2 = y/h^2 = z)]$ for five family structures. n_{og} is number of grand-offspring per offspring

HS2	$(4-z)/(4-y)$
FS2	$(2-z)/(2-y)$
HS3	$[0.75z + (4-z)/n_{og}]/[0.75y + (4-y)/n_{og}]$
FS3	$[1.25z + (4-2z)/n_{og}]/[1.25y + (4-2y)/n_{og}]$
FSHS	$[0.25z + (4-z)/n_{og}]/[0.25y + (4-y)/n_{og}]$

Results

The power of an experiment with a two-generation family structure

The power of experiments with a HS2 or a FS2 family structure for a QTL that explains 1% of the phenotypic variance and that has a heterozygosity of 50%, for various number of families, various number of offspring per family, and for two heritabilities ($h^2 = 0.1$ and

Table 4 The effect of doubling the number of offspring (n_o) relative to the effect of doubling the number of grand-offspring per offspring (n_{og}) $[\mathrm{RED}(n_o, n_{og})]$ for family structures HS3, FS3 and FSHS. h^2 is heritability

Family structure	RED
HS3	$1 + 0.75h^2/[0.75h^2 + (4-h^2)/n_{og}]$
FS3	$1 + 1.25h^2/[1.25h^2 + (4-2h^2)/n_{og}]$
FSHS	$1 + 0.25h^2/[0.25h^2 + (4-h^2)/n_{og}]$

$h^2 = 0.4$) of the observed trait, are given in Table 5. First, Table 5 is used to compare HS2 and FS2 family structures. An experiment with a FS2 family structure and n families had about the same power as an experiment with a HS2 family structure and $2n$ families for all values of n. For a heritability of 0.1, an experiment with five full-sib families and 800 offspring per family had a power of 0.59 and an experiment with ten half-sib families and 800 offspring per family had a power of 0.57. This example shows that an experiment with a FS2 family structure and n families had the same power as an experiment with a HS2 family structure and $2n$ families. RE(FS2/HS2) reflects this. RE(FS2/HS2) was close to 2:2.06 for $h^2 = 0.1$ and 2.25 for $h^2 = 0.4$

The power of an experiment with a two-generation family structure increased with an increasing number of families and with an increasing number of offspring per family (Table 5). Increasing the number of offspring per family was more efficient than increasing the number of families, e.g. for a h^2 of 0.1, an experiment with ten full-sib families and 200 offspring per family had a power of 0.43 whereas an experiment with 20 full-sib families and 100 offspring per family had a power of 0.27. The non-centrality parameter doubled by doubling the number of families and also doubled by doubling the number of offspring per family. Doubling the number of families, however, doubled the degrees of freedom, whereas doubling the number of offspring per family did not influence the degrees of freedom.

The power of an experiment with a two-generation family structure increased with increasing heritability if the effect of the QTL, expressed in phenotypic standard deviation units, remained constant (Table 5). For an experiment with five half-sib families and 800 offspring per family, the power was 0.34 for $h^2 = 0.1$, and power was 0.38 for $h^2 = 0.4$. The effect of h^2 could be explained from RE($h^2 = 0.4/h^2 = 0.1$). RE($h^2 = 0.4/h^2 = 0.1$) was 1.08 for a HS2 family structure and 1.19 for a FS2 family structure.

The power of an experiment with a three-generation family structure

The power of experiments with a three-generation family structure (HS3, FS3 or FSHS) for a QTL that explains 1% of the phenotypic variance and that has a heterozygosity of 50%, for various number of families, for various number of offspring per family, for various number of grand-offspring per offspring, and for two heritabilities ($h^2 = 0.1$ and $h^2 = 0.4$), is given in Table 6.

The power of an experiment with a HS3 family structure was similar to the power of an experiment with a FS3 family structure if n_f, n_o, and n_{og} were equal for the two-family structures (Table 6). For a heritability of 0.1, the power for a FS3 family structure was 1- to 1.2-times the power for a HS3 family structure, whereas

Table 5 The power of experiments[a] with a two-generation half-sib (HS2) or two-generation full-sib (FS2) family structure for a QTL that explains 1% of the phenotypic variance and that has a heterozygosity of 50%, for various number of families (n_f), various number of offspring per family (n_o), and two heritabilities ($h^2 = 0.1$ and $h^2 = 0.4$)

n_f	n_o	$h^2 = 0.1$		$h^2 = 0.4$	
		HS2	FS2	HS2	FS2
5	50	0.02	0.02	0.02	0.02
	100	0.03	0.04	0.03	0.04
	200	0.05	0.09	0.06	0.11
	400	0.13	0.24	0.15	0.31
	800	0.34	0.59	0.38	0.69
10	50	0.02	0.03	0.02	0.03
	100	0.04	0.05	0.04	0.07
	200	0.08	0.15	0.09	0.19
	400	0.23	0.43	0.26	0.54
	800	0.57	0.86	0.62	0.92
20	50	0.03	0.03	0.03	0.04
	100	0.05	0.09	0.06	0.11
	200	0.14	0.27	0.16	0.36
	400	0.42	0.72	0.47	0.83
	800	0.85	0.99	0.88	0.99
40	50	0.03	0.05	0.04	0.06
	100	0.08	0.15	0.09	0.21
	200	0.26	0.51	0.30	0.64
	400	0.71	0.95	0.76	0.99
	800	0.99	0.99	0.99	0.99

[a] For all experiments the power is for interval analysis assuming that markers have a heterozygosity of 1

Table 6 The power of experiments[a] with three-generation family-structures (HS3, FS3 or FSHS) for a QTL that explains 1% of the phenotypic variance and has a heterozygosity of 50%, for various number of families (n_f), various number of offspring per family (n_o), for various number of grand-offspring per offspring (n_{og}), and for two heritabilities ($h^2 = 0.1$ and $h^2 = 0.4$)

n_f	n_o	n_{og}	$h^2 = 0.1$			$h^2 = 0.4$		
			HS3	FS3	FSHS	HS3	FS3	FSHS
5	25	10	0.02	0.02	0.02	0.02	0.02	0.02
		50	0.04	0.04	0.11	0.02	0.02	0.05
		100	0.06	0.06	0.22	0.02	0.02	0.07
	50	10	0.03	0.03	0.04	0.02	0.02	0.04
		50	0.10	0.11	0.30	0.03	0.03	0.14
		100	0.15	0.15	0.55	0.04	0.03	0.14
	100	10	0.06	0.08	0.11	0.04	0.04	0.09
		50	0.26	0.31	0.67	0.08	0.07	0.38
		100	0.37	0.41	0.88	0.09	0.07	0.51
10	25	10	0.02	0.02	0.03	0.02	0.02	0.03
		50	0.06	0.07	0.18	0.02	0.02	0.08
		100	0.09	0.09	0.39	0.03	0.02	0.12
	50	10	0.04	0.05	0.06	0.03	0.03	0.06
		50	0.17	0.19	0.53	0.05	0.04	0.25
		100	0.26	0.27	0.82	0.05	0.05	0.36
	100	10	0.09	0.13	0.18	0.06	0.06	0.15
		50	0.45	0.54	0.91	0.12	0.11	0.65
		100	0.62	0.68	0.99	0.14	0.12	0.79

[a] For all experiments the power is for interval analysis assuming that markers have a heterozygosity of 1

for a heritability of 0.4 the power of a FS3 family structure was 0.85-to 1-times the power for a HS3 family structure. The power of an experiment with a FSHS family structure was higher than the power of an experiment with either a HS3 or a FS3 family structure. For a heritability of 0.1, the power of an experiment with a FSHS family structure was 1- to 4-times the power of an experiment with a HS3 or a FS3 family structure, and for a heritability of 0.4 the power of an experiment with a FSHS family structure was 1- to 6-times the power of an experiment with a HS3 or a FS3 family structure. For example, for a heritability of 0.1, an experiment with ten families, 50 offspring per family, and 100 grand-offspring per offspring, had a power of 0.82 for a FSHS family structure, a power of 0.26 for a HS3 family structure, and a power of 0.27 for a FS3 family structure.

The RE for the HS3, FS3 and FSHS family structures depended on h^2 and n_{og} as is shown in Table 7 which gives the RE among HS3, FS3 and FSHS family structures for h^2 values of 0, 0.1 or 0.4 and an n_{og} of 10, 50 or ∞. RE(FS3/HS3), RE(FSHS/HS3) and RE(FSHS/FS3) were larger than 1 for all combinations of values of h^2 and n_{og}. RE(FS3/HS3) decreased, and RE(FSHS/HS3) and RE(FSHS/FS3) increased, with increasing h^2 and with increasing n_{og}. Maximum values were 2 for RE(FS3/HS3), 5 for RE(FSHS/FS3), and 6 for RE(FSHS/HS3).

The power of an experiment with a three-generation family structure increased with an increasing number of families and an increasing number of offspring per family (Table 6). Similar to two-generation experiments, the power increased more by doubling the number of offspring per family than by doubling the number of families.

The power of an experiment with a three-generation family structure decreased with increasing heritability. If n_f was 10, n_o was 50, and n_{og} was 100, then for a FSHS family structure the power of the experiment was 0.82 for $h^2 = 0.1$ and 0.36 for $h^2 = 0.4$. The effect of h^2 could be explained from RE($h^2 = 0.4/h^2 = 0.1$). Table 8 gives the RE($h^2 = 0.4/h^2 = 0.1$) for experiments with three-generation family structures with 10, 50 or 100 grand-offspring per offspring. All RE($h^2 = 0.4/h^2 = 0.1$) values in Table 8 were smaller than 1, i.e. the power was lower for $h^2 = 0.4$ than for $h^2 = 0.1$ for all combinations of three-generation family structure and the number of grand-offspring per family. The RE($h^2 = 0.4/h^2 = 0.1$) was lowest for a FS3 family structure and highest for a FSHS family structure. The RE($h^2 = 0.4/h^2 = 0.1$) was lowest for $n_{og} = 100$ and highest for $n_{og} = 10$.

The power of an experiment with a three-generation family structure increased more by doubling the number of offspring than by doubling the number of grand-offspring per offspring (Tables 6 and 9). Table 9 gives RED(n_o, n_{og}) values for three-generation family structures with $n_{og} = 10$, 50 or 100 and with $h^2 = 0.1$ or 0.4. Table 8 shows that the RED(n_o, n_{og}) increased with increasing heritability and with increasing n_{og}. The RED(n_o, n_{og}) was lowest for a FSHS family structure and highest for a FS3 family structure.

Comparing experiments with two- and three-generation family structures

In Table 5 are the powers of experiments with two-generation family structures and in Table 6 are the powers of experiments with three-generation family structures. For a given number of families, more offspring per family are needed to obtain a certain power for experiments with two generations than for experiments with three generations. For example, if $h^2 = 0.1$ then an experiment with ten two generation full-sib families with 800 offspring per family had a power of 0.86, whereas an experiment with ten families with a FSHS family structure, with 100 full-sib offspring per family and 50 half-sib grand-offspring per full-sib offspring, had a power of 0.91.

Besides directly comparing power, experiments were also compared by relative efficiency (RE). In Fig. 1 are the efficiencies of five family structures relative to the efficiency of a HS2 family structure for $h^2 = 0.1$ and $h^2 = 0.4$, for values of n_{og} ranging from 0 to 100. The RE showed that three-generation experiments were more efficient than two-generation experiments, especially for traits with low heritability and if many grand-offspring per offspring are available. The RE(FSHS/HS2) was 30 for $h^2 = 0.1$ and $n_{og} = 100$.

Table 7 Relative efficiency (RE) among experiments with three-generation family structures (HS3, FS3 or FSHS) for heritability (h^2) of 0, 0.1 or 0.4 and a number of grand-offspring per offspring (n_{og}) of 10, 50 or ∞

h^2	n_{og}	RE(FS3/HS3)	RE(FSHS/HS3)	RE(FSHS/FS3)
0	10	2	2	1
	50	2	2	1
	∞	2	2	1
0.1	10	1.84	2.24	1.22
	50	1.54	2.96	1.95
	∞	1.2	6	5
0.4	10	1.6	2.86	1.78
	50	1.32	4.32	3.27
	∞	1.2	6	5

Table 8 The efficiency of heritability at 0.4 relative to the efficiency of heritability at 0.1 [RE($h^2 = 0.4/h^2 = 0.1$)] for experiments with three-generation family structures (HS3, FS3 or FSHS) with a number of grand-offspring (n_{og}) of 10, 50 or 100

n_{og}	HS3	FS3	FSHS
10	0.70	0.62	0.90
50	0.41	0.36	0.60
100	0.34	0.31	0.47

Table 9 The effect of doubling the number of offspring (n_o) relative to effect of doubling the number of grand-offspring per offspring (n_{og}) [RED(n_o, n_{og})] for three-generation family structures with a number of grand-offspring per offspring of 10, 50 or 100 and with a heritability (h^2) of 0.1 or 0.4

n_{og}	$h^2 = 0.1$			$h^2 = 0.4$		
	HS3	FS3	FSHS	HS3	FS3	FSHS
10	1.16	1.25	1.06	1.43	1.65	1.22
50	1.49	1.62	1.24	1.79	1.90	1.58
100	1.66	1.77	1.39	1.89	1.95	1.74

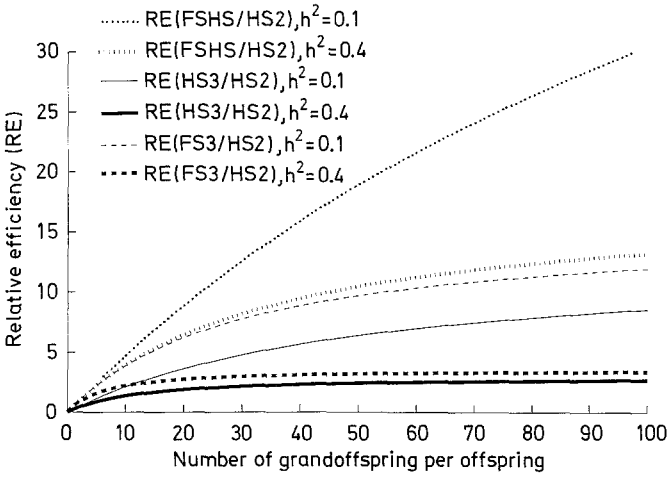


Fig. 1 Efficiency of five family structures relative to the efficiency of a HS2 family structure for two heritabilities ($h^2 = 0.1$ and $h^2 = 0.4$)

Discussion

In this paper we have used power and relative efficiency to compare the efficiency of designs of QTL mapping experiments. Although power determines the value of a design, it has its limitations to compare designs because the relation between power and the size of an experiment is non-linear. Tables 5 and 6 showed that the effect of increasing the size of an experiment on power depended on the initial power. Relative efficiency is independent of initial power and the size of an experiment. Relative efficiency can be directly translated to the relative number of marker genotypes that have to be determined in experiments whereas power cannot be used for this purpose.

We showed that family structure is an important factor in designing QTL mapping experiments. For a two-generation experiment, more offspring were required for a certain power than for a three-generation experiment. Consequently, more animals had to be typed for marker loci for a two-generation experiment than for a three-generation experiment. Fewer offspring per two-generation experiment, however, were required than grand-offspring per three-generation experiment. Thus, fewer trait values had to be obtained for a two-generation experiment than for a three-generation experiment. In deciding on a design, the cost of typing a marker and the cost of obtaining a trait value have to be considered as well as the time required to collect all the information. The cost of obtaining a trait value is low if a trait is routinely collected for management or breeding purposes, such as milk production in dairy cattle. Furthermore, the family structure of the commercial dairy cattle population enables experiments with a three-generation half-sib family structure. The three-generation half-sib family structure is used in QTL mapping experiments in dairy cattle (Da et al. 1994; Georges et al. 1995). A trait like meat quality measured on carcasses, however, is expensive to assess and usually not collected routinely. In such a case the cost of measuring meat quality should be balanced against the cost of typing markers.

Relative efficiency and a comparison of power showed that a two- or three-generation family structure with full-sib offspring was more efficient than a two- or three-generation family structure with half-sib offspring. With full-sib offspring, two marker contrasts can be computed per family while with half-sib offspring only one marker contrast can be computed. A family structure with full-sib grand-offspring, however, was less efficient than a family structure with half-sib grand-offspring. The standard error of a marker contrast was larger when full-sib grand-offspring were used than when half-sib grand-offspring were used.

The power of three-generation experiments decreased with increasing heritability if the effect of the QTL, expressed in *phenotypic* units, was constant. In a three-generation experiment, information comes from the average trait value on grand-offspring. This average represents the breeding value of the offspring plus a residual. The part of the breeding value that is due to the QTL of interest decreases with increasing heritability if the QTL effect is constant in phenotypic units. Therefore, those grand-offspring averages become less informative with increasing heritability, and power decreases. In our statistical method only one QTL is considered. Recently, multi-marker methods have been developed that allow for several QTLs simultaneously (Zeng 1993; Jansen and Stam 1994). In these methods a larger part of the breeding values of offspring is accounted for, which results in a reduction of the residual genetic variance in grand-off spring averages and consequently in a higher power. Our results can be used to infer the effect of multi-marker methods on the power of three-generation experiments. The effect of a reduction of residual genetic variance is similar to that of a reduction in heritability in a single QTL method. If markers explain, say, half the genetic variance then we could simply take the power for a situation where the heritability is halved.

For two-generation experiments the effect of heritability was small. For the range of heritabilities we studied, standard errors on marker contrasts in the two-generation designs are almost entirely determined by environmental errors. This suggests that for two-gener-

ation experiments multi-marker experiments are less beneficial.

So far, we have compared full-sib families and half-sib families for a given family size. Due to limitations in female reproductive capacity, family size is more limited with full-sib than with half-sib families. This is particularly true is cows and pigs, but less so in poultry and fish. It would be fair to compare an experiment with a few large half-sib families to an experiment with many smaller full-sib families. Table 5 showed that an experiment with five half-sib families and 800 offspring per family had a higher power than an experiment with 40 full-sib families and 100 offspring per family. This illustrates that practical limitations have to be considered in designing an experiment.

The power of experiments was given for various family structures and also family sizes and the heritability of the trait was varied. Other parameters that also determine power, such as marker heterozygosity, were held constant. The effect on power of some other parameters will now be discussed.

The RE(I/S) in this study is for a linear model but was equal to the efficiency of interval mapping relative to the efficiency of single-marker mapping for a likelihood model as given by Lander and Botstein (1989). The RE(I/S) was $1/(1-\gamma)$. This means that an experiment with x offspring per family that is analyzed by interval analysis has the same power as an experiment with $x/(1-\gamma)$ offspring per family that is analyzed by single-marker analysis, assuming that only the number of offspring per family and the type of analysis differ between the experiments. For example, a FS2 experiment with five families with 800 offspring per family had a power of 0.59 for $h^2 = 0.1$ with interval analysis. For single-marker analysis, a FS2 experiment with five families with $800/(1-\gamma) = 800/(1-0.165) = 958$ offspring per family would have had a power of 0.59 for $h^2 = 0.1$. The RE(I/S) was computed for a QTL at the midpoint of the interval between two markers. The difference between single-marker analysis and interval analysis decreases if the QTL is closer to the bounds of the interval (Darvasi et al. 1993; Mackinnon et al. 1995).

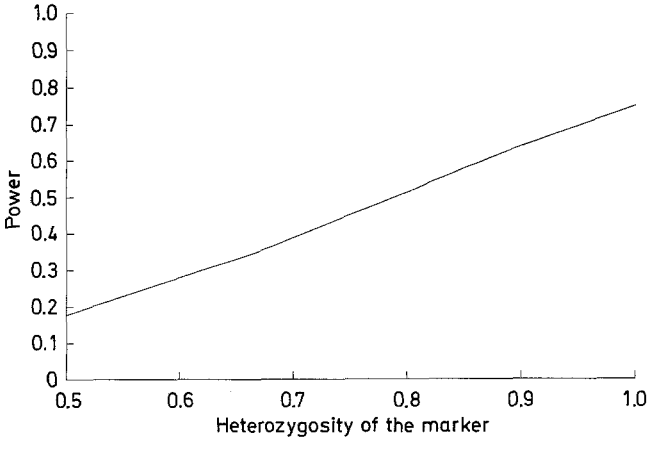
Not only the location of the QTL but also the variance explained by the QTL is important. The variance depends on a^2 and the heterozygosity of the QTL. The equation for RED (a^2, n_o) showed that doubling a^2 had the same effect on power as doubling n_o. Because the effect of doubling n_o is given in Tables 5 and 6, the effect of doubling a^2 can also be derived from these tables. Heterozygosity at the QTL was 0.5 in this study. For a QTL with two alleles this is the maximum heterozygosity in a population that is in genetic equilibrium. For lower heterozygosity at the QTL, more families will be needed for equal power. The relation between heterozygosity at the QTL and the required number of families is about linear (Weller et al. 1990).

We showed that the map distance between the markers that flank the QTL determines the efficiency of interval analysis relative to the efficiency of single-marker analysis. Map distance also has a direct influence on efficiency. The efficiency of a design with $d = 0.2$ relative to a design with $d = 0.1$ [RE($d = 0.2/d = 0.1$)] was 0.89. Thus, an experiment with $d = 0.2$ and n_o offspring per family has the same power as an experiment with $d = 0.1$ and $0.89 \times n_o$ offspring per family.

The heterozygosity at the marker was 1 in this study because, due to the abundance of highly polymorphic microsatellite loci, it is expected that a set of almost perfect markers will become available. A recent study in chicken (Groen et al. 1994), however, showed that the average heterozygosity of microsatellite markers was 0.28 in commercial layer populations and 0.55 in commercial broiler populations. At such a level of heterozygosity the power of an experiment is lower than for a heterozygosity at the marker of 1. Figure 2 illustrates this for one design of an experiment. The power is decreased because a marker or haplotype contrast can only be computed for a heterozygous animal; moreover at lower marker polymorphism it will be less often possible to determine which marker allele is transferred from a parent to an offspring (Soller 1991). The latter problem will be larger in a half-sib family in which one parent is untyped than in full-sib family in which both parents are typed for the marker (Soller 1991). If heterozygosity of the marker loci is not close to 1 then an alternative to analysing markers one by one, or in pairs, is to simulatneously use many linked markers which increases the power of an experiment (Haley et al. 1994).

The power was computed for an experiment with a balanced design. The power of an experiment with a balanced design is, however, a good inidcator for the power of an experiment design that is unbalanced with respect to the number of offspring per family, the num-

Fig. 2 The effect of heterozygosity of the marker on the power of an experiment with a two-generation half-sib family structure with 20 families and 800 offspring per family for a QTL that explains 1% of the phenotypic variance and has a heterozygosity of 0.5, for a heritability of 0.1. The power is computed for single-marker analysis as the weighted average of the powers of experiments with 0 to 20 heterozygous parents. The heterozygosity of the marker is varied by the number of equiprobable marker alleles



ber of grand-offspring per offspring, or the number of offspring per marker allele per parent (Wang et al. 1995). The chi-square method to compute power is approximate because error variance and heritability have to be known whereas in a real experimment these parameters have to be estimated from the data. Values computed with the chi-square method are, however, close to exact values (Wang et al. 1995). For the situation studied by Wang et al. (1995) the maximum difference between the approximate and the exact value was 0.034.

We studied experiments within one outbred population. The efficiency of an experiment with a cross between populations is higher (Soller 1991). Genes of large effects are expected to segregate at higher frequencies in a cross than within an outbred population and also a high level of heerozygosity of the marker is more likley if a cross between populations is used. If in a cross a marker is found that explains the between-population variance, then possibly this marker also explains within-population variance. Whether this is true or not remains uncertain until within-population studies are performed. If the goal is to understand and exploit the variation within commercial popuplations, then QTL mapping experiments within the populations are necessary. The present study should help to design such experiments.

Appendix 1

Standard error of marker contrast

The linear model for an experiment with a HS2 family structure is:

$$y_{ijk} = s_i + m_{ij} + e_{ijk} \tag{A1}$$

where y_{ijk} is the trait value for the k-th offspring inheriting marker allele j of sire i, s_i is the effect of sire i with $\sigma_s^2 = 0.25\,\sigma_u^2$, m_{ij} is the effect of marker allele j of sire i, and e_{ijk} is the residual effect of offspring k with $\sigma_e^2 = \sigma_p^2 - \sigma_s^2$. Let σ_p^2 be 1 then $\sigma_s^2 = 0.25h^2$ and $\sigma_e^2 = 1 - 0.25h^2$.

For a sire with marker genotype Mm, m_{i1} is the effect of allele M and m_{i2} the effect of allele m. Let the expected value of the marker contrast be $(m_{i1} - m_{i2})$ and the realized value:

$$\mathrm{MC}_i = \frac{2}{n_o}\sum_{k=1}^{n_o/2} y_{i1k} - \frac{2}{n_o}\sum_{k=1}^{n_o/2} y_{i2k} \tag{A2}$$

where MC_i is the marker contrast for the sire i, n_o is the number of offspring per sire and $n_o/2$ is the number of offspring per marker allele.

The squared standard error of the marker contrast is:

$$\mathrm{SE}^2_{\mathrm{MC}} = \mathrm{E}[\mathrm{MC} - \mathrm{E}(\mathrm{MC})]^2.$$

Rewriting A2 using A1 gives:

$$\begin{aligned}\mathrm{MC}_i &= \frac{2}{n_o}\sum_{k=1}^{n_o/2}(s_i + m_{i1} + e_{i1k}) - \frac{2}{n_o}\sum_{k=1}^{n_o/2}(s_i + m_{i2} + e_{i2k}) \\ &= \left(s_i + m_{i1} + \frac{2}{n_o}\sum_{k=1}^{n_o/2} e_{i1k}\right) - \left(s_i + m_{i2} + \frac{2}{n_o}\sum_{k=1}^{n_o/2} e_{i2k}\right) \\ &= m_{i1} - m_{i2} + \frac{2}{n_o}\sum_{k=1}^{n_o/2}(e_{i1k} - e_{i2k}).\end{aligned}$$

we can derive that:

$$\begin{aligned}\mathrm{E}[\mathrm{MC}_i - \mathrm{E}(\mathrm{MC}_i)]^2 &= \mathrm{E}\left[(m_{i1} - m_{i2} + \frac{2}{n_o}\sum_{k=1}^{n_o/2}(e_{i1k} - e_{i2k})\right] \\ &\quad - (m_{i1} - m_{i2})^2 = \mathrm{E}\left[\frac{2}{n_o}\sum_{k=1}^{n_o/2}(e_{i1k} - e_{i2k})\right]^2 \\ &= \frac{4}{(n_o)^2}\sum_{k=1}^{n_o/2} 2\sigma_e^2 = \frac{4}{(n_o)^2} n_o \sigma_e^2 = \frac{4 - h^2}{n_o}.\end{aligned}$$

Appendix 2

Expected haplotype contrast

Let M and N denote two markers and Q a QTL. The recombination rate between M and Q is r_1, between Q and N is r_2, and between M and N is γ. Let the ordered genotype of a parent be MQN/mqn. The haplotype contrast is defined as the average trait value of offspring that inherit non-recombinant haplotype MN from the parent, minus the average trait value of offspring that inherit non-recombinant marker haplotype mn from the parent. The expected haplotype contrast is the expected trait value of offspring that inherit non-recombinant haplotype MN minus the expected value of offspring that inherit non-recombinant haplotype mn from the parent.

Offspring that inherited MN, inherited marker-QTL haplotype MQN from the parent with the probability $(1-r_1)\times(1-r_2)/(1-\gamma)$ and will have inherited marker-QTL haplotype MqN form the parent with the probability $r_1 \times r_2/(1-\gamma)$. The expected trait value of offspring that inherited MN is $(1-r_1)\times(1-r_2)/(1-\gamma)\times a/2 + r_1 \times r_2/(1-\gamma)\times -a/2 = (1-r_1-r_2)/(1-\gamma)\times a/2$. Offspring that inherited mn have inherited marker-QTL haplotype mQn from the parent with the probability $r_1 \times r_2/(1-\gamma)$ and have inherited marker-QTL haplotype mqn from the parent with the probability $(1-r_1)\times(1-r_2)/(1-\gamma)$. The expected trait value of offspring that iniherited mn is $r_1 \times r_2/(1-\gamma)\times a/2 + (1-r_1)\times(1-r_2)/(1-\gamma)\times -a/2 = (r_1+r_2-1)/(1-\gamma)\times a/2$. Thus, the expected haplotype contrast is $(1-r_1-r_2)/(1-\gamma)\times a/2 - (r_1+r_2-1)/(1-\gamma)\times a/2 = (1-r_1-r_2)/(1-\gamma)\times a$. For $r_1 = r_2 = r$ the expected haplotype contrast is $(1-2r)/(1-\gamma)\times a$.

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