

QTL mapping under truncation selection in homozygous lines derived from biparental crosses

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Abstract In plant breeding, a large number of progenies that will be discarded later in the breeding process must be phenotyped and marker genotyped for conducting QTL analysis. In many cases, phenotypic preselection of lines could be useful. However, in QTL analyses even moderate preselection can have a significant effect on the power of QTL detection and estimation of effects of the target traits. In this study, we provide exact formulas for quantifying the change of allele frequencies within marker classes, expectations of marker contrasts and the variance of the marker contrasts under truncation selection, for the general case of two QTL affecting the target trait and a correlated trait. We focused on homozygous lines derived at random from biparental crosses. The effects of linkage between the marker and the QTL under selection as well as the effect of selection on a correlated trait can be quantified with the given formulas. Theoretical results clearly show that depending on the magnitude of QTL effects, high selection intensities can lead to a dramatic reduction in power of QTL detection and that approximations based on the

infinitesimal model deviate substantially from exact solutions. The presented formulas are valuable for choosing appropriate selection intensity when performing QTL mapping experiments on the data on phenotypically preselected traits and enable the calculation and bias correction of the effects of QTL under selection. Application of our theory to experimental data revealed that selection-induced bias of QTL effects can be successfully corrected.

Introduction

Quantitative trait locus (QTL) mapping aims at the identification of significant associations between molecular marker loci and loci influencing quantitative traits for subsequent use in marker-assisted selection. In plant breeding, experimental QTL mapping studies are frequently performed on large experimental populations of randomly derived progenies (Schön et al. 2004). As a consequence, phenotypic and genotypic data are generated for a large number of progenies with limited genetic value. Different strategies have been proposed to increase the efficiency of QTL mapping using selected populations for QTL identification and estimation of effects. Lander and Botstein (1989) as well as other authors (e.g., Darvasi and Soller 1992; Gallais et al. 2007) demonstrated the usefulness of bidirectional selection (selection of both tails of the phenotypic distribution) with respect to saving genotyping costs, when only selected progenies were genotyped.

High-throughput genotyping has, however, become relatively cost efficient and today phenotyping of lines in multi-location field trials is the major bottleneck in genetic analyses as well as in commercial breeding. As a consequence, it would be highly useful if extensive QTL analyses could be performed as part of an ongoing breeding

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program on populations where selection has been performed either directly on the target trait with low intensity or on correlated traits at early selection stages. Further, QTL mapping in selected populations might be the only possible type of analysis if only one extreme of a population survives because of its exposure to a stressor, such as high salinity, temperature extremes, drought and disease (Lebowitz et al. 1987). Censored data are also common in situations where phenotyping is performed with technical equipment (sensor) unable to register values below a certain threshold (Foody et al. 2009).

In all these circumstances, the effects of selection on the power of QTL detection and unbiased estimation of QTL effects need to be taken into account, because (1) frequencies of the QTL and the marker alleles in the selected samples will deviate from the frequencies of the unselected (i.e., in the absence of selection) reference population, (2) expectations of marker contrasts will be biased due to the selection, (3) the genetic variance in the selected tail will be reduced, and (4) selection on correlated traits can affect the power of QTL mapping for the target trait due to pleiotropic or linked QTL.

The effect of truncation selection on the power of QTL detection compared to the case of no selection has been investigated in theoretical and computer simulation studies (Gallais et al. 2007; Mackinnon and Georges 1992; Navabi et al. 2009; Tanksley and Nelson 1996). Both, theoretical and simulation results showed that the power of QTL detection was reduced compared to equally sized random populations when only one tail of the distribution was analyzed. However, despite the reduced statistical power, QTL identification and characterization in selected populations can be of advantage to classical QTL mapping experiments if expenditures for genotyping and phenotyping can be reduced and QTL mapping can be integrated into ongoing breeding programs. While several authors gave approximate solutions for estimating the effects of bidirectional selection on QTL parameters (e.g., Bovenhuis and Spelman 2000; Darvasi and Soller 1992) to our knowledge no solutions have been presented for unbiased estimation of QTL parameters under truncation selection.

In this study, we derive exact formulas for expectations of the marker contrast and the variance of the marker contrast for truncation selection using probabilities of the marker genotypes in the selected lines considering the truncation selection point. The derivations are given for the case of fully homozygous lines such as recombinant inbred lines (RILs) or doubled-haploid (DH) lines in plant species derived from biparental crosses of homozygous parents. We present general analytical solutions to correct for the bias induced by selection of the target trait. In addition, we also consider the case of selection on a correlated trait. Based on these formulas, we compare the power of

QTL detection, the bias of QTL effects and the variance explained by QTL in the presence and absence of truncation selection. In addition, we present a numerical example illustrating the application of our results to obtain unbiased estimates of QTL effects under truncation selection.

Theory

Definitions and assumptions

We regard two correlated traits X^* and X and perform truncation selection on phenotypic data of X^* . Without loss of generality we assume selection of the upper tail of the distribution, which is subsequently employed for phenotyping and QTL mapping of X . We assume two linked QTL Q_i and Q_j which affect both X and X^* traits and a marker locus M_k linked to them. In addition, we assume that the phenotypic expressions of trait X^* and X are controlled by a large number of other genes acting independently of the two QTL. Given that X^* is a secondary trait used for indirect selection of X , we assume that the underlying QTL act pleiotropically on both traits.

We consider only homozygous lines derived from a heterozygous F_1 of the biparental cross $P_1 \times P_2$. Genotypes are identified by their corresponding haplotypes for simplification of our notation, and we use indices $r, s, t = 1, 2$ to denote if the alleles at Q_i, Q_j and M_k were derived from P_1 or P_2 , respectively. The notation used in this treatise is summarized in supplementary material S1.

In the absence of selection, the three loci genotype frequencies of DH lines with haplotype $Q_i Q_j M_k$ can be expressed as:

$$\gamma_{i,j,k_t} = [1 + (-1)^{r+s} \lambda_{ij} + (-1)^{r+t} \lambda_{ik} + (-1)^{s+t} \lambda_{jk}] / 8, \quad (1)$$

where $\lambda_{ij} = 1 - 2r_{ij}$ is the linkage value between loci i and j and r_{ij} is their recombination value (Schnell 1961). Further derivations in this treatise are given for DH lines, but the relationships hold also true for RILs, replacing λ_{ij} by $1/2(2 - \lambda_{ij})$, and in the general case of lines developed from intermated populations, replacing λ_{ij} by $4D_{ij}$, where D_{ij} denotes the linkage disequilibrium between the two loci as described by Frisch and Melchinger (2007).

Since the phenotypic expressions of trait X^* and X are controlled by the two QTL and also by a large number of other QTL acting independently of the two QTL, we termed the sum of these polygenic effects and random environmental effects as residual effect. This is assumed to follow a bivariate normal distribution with unit variance and correlation ρ . Thus, the joint distribution of

X^* and X has a mixture distribution of bivariate normal distributions

$$\begin{pmatrix} X^* \\ X \end{pmatrix} = \sum_{r=1}^2 \sum_{s=1}^2 \gamma_{irs} \begin{pmatrix} X^*(Q_i, Q_j) \\ X(Q_i, Q_j) \end{pmatrix} \text{ with} \\ \begin{pmatrix} X^*(Q_i, Q_j) \\ X(Q_i, Q_j) \end{pmatrix} \sim N \left(\begin{pmatrix} \mu_{irs}^* \\ \mu_{irs} \end{pmatrix}, \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix} \right) \quad (2)$$

and $\gamma_{irs} = \sum_{t=1}^2 \gamma_{irs k_t}$.

Without loss of generality, we assume $E \left(\begin{pmatrix} X^* \\ X \end{pmatrix} \right) = 0$,

i.e., $\sum_{r=1}^2 \sum_{s=1}^2 \gamma_{irs} \begin{pmatrix} \mu_{irs}^* \\ \mu_{irs} \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}$.

Expressing the means in terms of additive affects a_i^* , a_j^* , and a_i , a_j for QTL Q_i and Q_j , respectively, and denoting the epistatic interactions among them with aa_{ij}^* and aa_{ij} , we have

$$\begin{aligned} \mu_{irs}^* &= (-1)^{r+1} a_i^* + (-1)^{s+1} a_j^* + (-1)^{r+s} aa_{ij}^*, \\ \mu_{irs} &= (-1)^{r+1} a_i + (-1)^{s+1} a_j + (-1)^{r+s} aa_{ij}. \end{aligned} \quad (3)$$

We assume that truncation selection is practiced so that only lines with phenotypic values of X^* surpassing the point of truncation T are selected.

Marker allele frequencies under selection

With respect to the alleles r and s at QTL Q_i and Q_j , respectively, each DH line corresponds to the random variable $Q_i Q_j$ with realizations $Q_i Q_j$ ($r, s = 1, 2$). Hence, the four haplotypes $Q_i Q_j$ define a complete set of disjoint events in the entire sample space and with the theorem of total probability, we obtain

$$P(M_{k_t} | [X^* > T]) = \sum_{r=1}^2 \sum_{s=1}^2 P(Q_i Q_j M_{k_t} | [X^* > T]). \quad (4)$$

Since (1) truncation selection affects only the progeny generation (DH lines) and (2) meiotic recombination among loci happens only in the parental generation(s) and is unaffected by the genotype at the QTL and markers, both processes are stochastically independent from each other. Consequently, we have

$$P([X^* > T] | Q_i Q_j) = P([X^* > T] | Q_i Q_j M_{k_t})$$

and the probability of a DH line being selected, when its haplotype is $Q_i Q_j$, can be denoted as

$$\psi_{irs} = P([X^* > T] | Q_i Q_j) = P([X^*(Q_i, Q_j) > T]). \quad (5)$$

Finally, applying Bayes' formula (Mood et al. 1974, p. 36, Theorem 30) for each summand in Eq. 4, we obtain

$$p_{k_t} = P(M_{k_t} | [X^* > T]) = \frac{\sum_{r=1}^2 \sum_{s=1}^2 \psi_{irs} \gamma_{irs k_t}}{\alpha_T}, \quad (6)$$

where

$$\alpha_T = \sum_{r=1}^2 \sum_{s=1}^2 \sum_{t=1}^2 \psi_{irs} \gamma_{irs k_t} \quad (7)$$

is the proportion of the DH lines in the upper selected tail after truncation selection for X^* at point T .

Making use of the relationship $\gamma_{irs k_t} = \frac{1}{2} \gamma_{irs} + [(-1)^{r+t} \lambda_{ik} + (-1)^{s+t} \lambda_{jk}] / 8$, we obtain

$$\begin{aligned} p_{k_t} &= \frac{1}{2} + [\lambda_{ik}(\psi_{i_1 j_1} + \psi_{i_1 j_2} - \psi_{i_2 j_1} - \psi_{i_2 j_2}) \\ &\quad + \lambda_{jk}(\psi_{i_1 j_1} - \psi_{i_1 j_2} + \psi_{i_2 j_1} - \psi_{i_2 j_2})] / 8 \alpha_T. \end{aligned} \quad (8)$$

Thus, for the change in marker allele frequency M_{k_1} compared to the case of no selection we obtain the exact formula

$$\begin{aligned} \Delta p_{k_1} &= [\lambda_{ik}(\psi_{i_1 j_1} + \psi_{i_1 j_2} - \psi_{i_2 j_1} - \psi_{i_2 j_2}) \\ &\quad + \lambda_{jk}(\psi_{i_1 j_1} - \psi_{i_1 j_2} + \psi_{i_2 j_1} - \psi_{i_2 j_2})] / 8 \alpha_T. \end{aligned} \quad (9)$$

Marker class means and contrasts

We calculate $\zeta_{k_t} = E(X | M_{k_t}, [X^* > T])$, the expectation of X in marker class M_{k_t} after truncation selection for X^* at point T by making use of results on the expectation of conditional expectations (e.g., Mood et al. 1974, p. 158, Theorem 6):

$$\begin{aligned} E(X | M_{k_t}, [X^* > T]) &= E(E(X | Q_i Q_j, M_{k_t}, [X^* > T])) \\ &= \sum_{r=1}^2 \sum_{s=1}^2 P(Q_i Q_j | M_{k_t}, [X^* > T]) \\ &\quad E(X | Q_i Q_j, M_{k_t}, [X^* > T]) \end{aligned} \quad (10)$$

Application of the Bayes' formula yields the relative frequencies of haplotype $Q_i Q_j$ in marker class M_{k_t} of the selected fraction

$$\begin{aligned} \tau_{irs k_t} &= P(Q_i Q_j | M_{k_t}, [X^* > T]) \\ &= \frac{P([X^* > T] | Q_i Q_j) P(Q_i Q_j M_{k_t})}{\sum_{r=1}^2 \sum_{s=1}^2 P([X^* > T] | Q_i Q_j) P(Q_i Q_j M_{k_t})} \\ &= \frac{\psi_{irs} \gamma_{irs k_t}}{\sum_{r=1}^2 \sum_{s=1}^2 \psi_{irs} \gamma_{irs k_t}}. \end{aligned} \quad (11)$$

Based on the results on the selection gain in a correlated trait under truncation selection (Cochran 1951), we have

$$\begin{aligned} E(X | Q_i Q_j, M_{k_t}, [X^* > T]) &= E(X(Q_i, Q_j) | [X^*(Q_i, Q_j) > T]) \\ &= \mu_{irs} + \rho i(T - \mu_{irs}^*) \end{aligned} \quad (12)$$

where $i(T - \mu_{irs}^*)$ refers to the standardized selection differential with truncation selection at point $T - \mu_{irs}^*$.

Combining this with the previous results, we obtain

$$\zeta_{k_i} = E(X|M_{k_i}, [X^* > T]) = \sum_{r=1}^2 \sum_{s=1}^2 \tau_{i_{rj_s k_i}} (\mu_{i_{rj_s}} + \rho i(T - \mu_{i_{rj_s}}^*)), \tag{13}$$

and for the contrast between the two marker genotypes we obtain

$$\delta_k = \zeta_{k_1} - \zeta_{k_2} = \sum_{r=1}^2 \sum_{s=1}^2 (\tau_{i_{rj_s k_1}} - \tau_{i_{rj_s k_2}}) (\mu_{i_{rj_s}} + \rho i(T - \mu_{i_{rj_s}}^*)). \tag{14}$$

This general formula simplifies for special cases described in Table 1. Case 1 assumes that one QTL (Q_i) affects only trait X^* and the other QTL (Q_j) affects only X . If none of the QTL shows pleiotropy, it is reasonable to assume absence of epistasis between them, i.e., $a_j^* = 0, a_i = 0, aa_{ij}^* = 0$ and $aa_{ij} = 0$. Thus, we get $\mu_{i_{rj_s}}^* = (-1)^{r+1} a_i^*$, $\mu_{i_{rj_s}} = (-1)^{s+1} a_j$ and $\psi_{i_{rj_s}} = \psi_{i_r}$ for $r, s = 1, 2$, and if we define $\Delta i(a_i^*) = i(T - a_i^*) - i(T + a_i^*)$, we obtain

$$\delta_k = \frac{2\lambda_{jk} a_j [(\psi_{i_1} + \psi_{i_2})^2 - \lambda_{ij} (\psi_{i_1} - \psi_{i_2})^2] + 4\lambda_{ik} \rho \Delta i(a_i^*) \psi_{i_1} \psi_{i_2}}{(1 - \lambda_{ik}^2) (\psi_{i_1}^2 + \psi_{i_2}^2) + 2(1 + \lambda_{ik}^2) \psi_{i_1} \psi_{i_2}}. \tag{15}$$

We will now proceed with special cases where we consider only one QTL ($Q_i = Q_j$), which acts pleiotropically on both traits X^* and X and we assume additionally

that M_k is located at the position of the QTL Q_i (Case 2, Table 1). With high-throughput genotyping available, it can be assumed that linkage between the QTL under selection and the marker will be almost complete. Hence, by inserting $a_i = a_j, a_i^* = a_j^*$, and $\lambda_{ij} = \lambda_{ik} = 1$, which implies $\lambda_{jk} = 1$, we obtain from Eq. 15

$$\delta_i = 2a_i + \rho \Delta i(a_i^*). \tag{16}$$

Equation 16 illustrates that the marker contrast is influenced by two components. The first part $2a_i$ reflects the effect of Q_i influencing the trait X . The second part reflects the effect of selection on X^* via QTL Q_i on the correlated residuals.

In Case 3, we assume $X^* = X$, i.e., the trait under selection is also used for QTL mapping (Table 1). Like in Case 2, we consider only one QTL (Q_i) lying directly on the marker ($M_k = Q_i$) and the additional restrictions $a_i = a_j = a_i^* = a_j^*$ and $\rho = 1$. Thus, we obtain

$$\delta_i = 2a_i + \Delta i(a_i), \tag{17}$$

from the results of Case 2. Since $\Delta i(a_i) < 0$ for $a_i > 0$, Eq. 17 shows that under truncation selection, δ_i does not yield an unbiased estimate of $2a_i$, but is biased downwards. The extent of the absolute value of the bias increases with larger values for a_i and T , i.e., smaller values of α_T . The relative bias in the estimates of the QTL effects, reflected by the ratio of the marker contrast δ_i divided by $2a_i$, is illustrated as a function of a_i and α_T in Fig. 1a for Case 3. The percentage of the phenotypic variance explained by

Table 1 Exact solutions for the expectation of the marker contrast (δ_k) and their variance (σ_k^2) for cases considered in this treatise together with the approximations for the marker contrast

Cases: trait(s)	Residual correlation	QTL	QTL effects ^a	Marker	Linkage values	Solution for δ_k see Eq.	Approximate solution for δ_k or δ_i
General: 2 QTL affecting two traits							
$X \neq X^*$	$\rho \neq 1$	$Q_i \rightarrow X, X^*$ $Q_j \rightarrow X, X^*$	^c	^c	^c	(14) (29)	
Case 1: 2 QTL affecting different traits							
$X \neq X^*$	$\rho \neq 1$	$Q_i \rightarrow X^*$ $Q_j \rightarrow X$	$a_i^* \neq 0$ $a_j \neq 0$ $a_j^* = 0$ $a_i = 0$	^c	^c	(15) ^d	$\delta_k \approx 2\lambda_{jk} a_j - 2\lambda_{ik} \rho \kappa(T) a_i^*$
Case 2: 1 QTL affecting different traits							
$X \neq X^*$	$\rho \neq 1$	$Q_i = Q_j \rightarrow X, X^*$	$a_i = a_j$ $a_i^* = a_j^*$	$M_k = Q_i$	$\lambda_{ij} = \lambda_{ik} = 1$	(16) (31)	$\delta_i \approx 2a_i - 2\rho \kappa(T) a_i^*$
Case 3: 1 QTL affecting one trait							
$X = X^*$	$\rho = 1$	$Q_i = Q_j \rightarrow X$	$a_i = a_j = a_i^* = a_j^*$	$M_k = Q_i$	$\lambda_{ij} = \lambda_{ik} = 1$	(17) (33)	$\delta_i \approx 2a_i(1 - \kappa(T))$

^a Except for the general case, absence of epistasis is assumed

^b $Q_i \rightarrow X$ stands for QTL Q_i that affects trait X

^c No restriction

^d Must be derived from the general case with restrictions on the model parameters

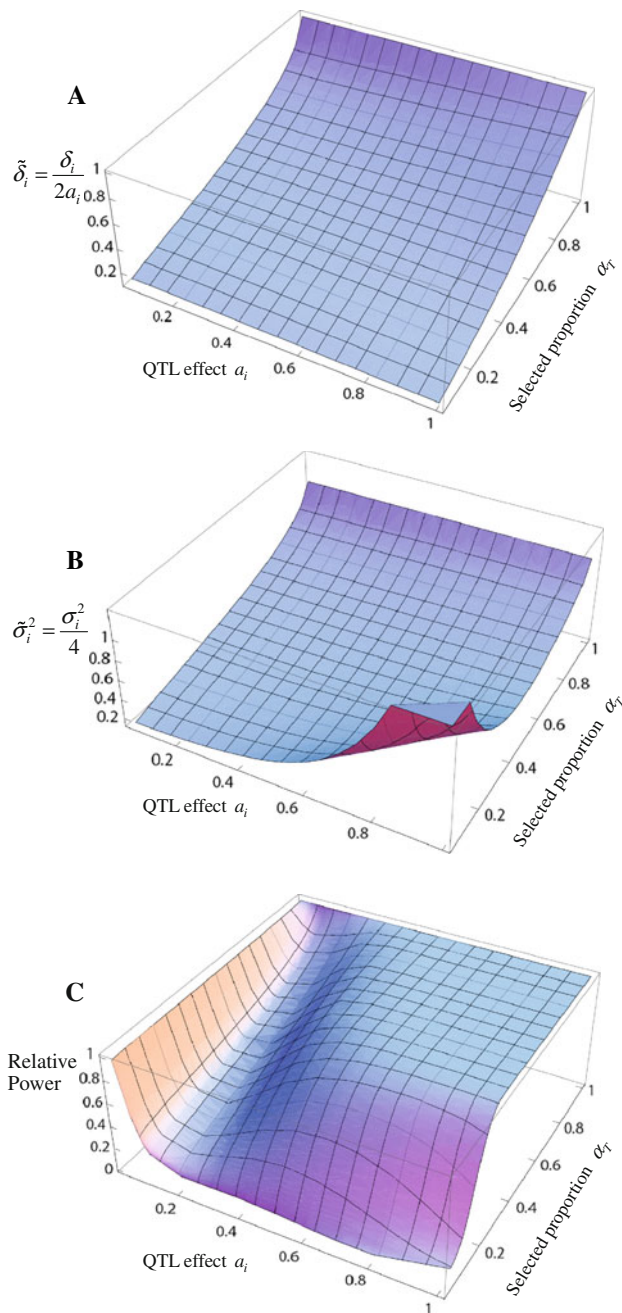


Fig. 1 **a** Expected marker contrast (δ_i) under selection, **b** expected variance of the marker contrast (σ_i^2) under selection and **c** power of the F test ($1 - \beta$) under selection, all expressed relative to their corresponding statistics in the absence of selection for Case 3 (one QTL lying on the marker and affecting one trait). All graphs are presented as a function of the true QTL effect a_i and the selected proportion α_T of the DH lines under truncation selection

the QTL in the graph equals $a_i^2 / (a_i^2 + 1)$, where 1 is the sum of the polygenic and error variance (i.e., residual variance).

Assuming the distribution of the trait under selection to follow a normal probability density function and considering the Taylor expansion of $\Delta i(a_i)$ in terms of a_i , which yields

$$\Delta i(a_i) = -2\kappa(T)a_i + o(a_i^3), \tag{18}$$

where $\kappa(T) = i(T)(i(T) - T)$ and $o(a_i^3)$ denotes the remainder term of the Taylor expansion, we obtain for small values of a_i or for moderate selection, the following approximation

$$\Delta i(a_i) \approx -2\kappa(T)a_i. \tag{19}$$

The expectation of the marker contrast can be approximated for the different cases in Table 1 using Taylor expansions for $\Delta i(a_i)$, $(\psi_{i_1} + \psi_{i_2})^2$ and $(\psi_{i_1} - \psi_{i_2})^2$ and rationale functions of these functions. Combining these results, we obtain the approximations of δ_k given in Table 1, based on the first two terms of the Taylor expansion. Approximately unbiased estimates of a_i can be obtained from these equations.

In Case 3 (one QTL affecting one trait), we can obtain from Eq. 17 an unbiased estimate of a_i by solving the non-linear Eq. 17 for a_i using Newton’s rule or any other suitable method (Deuffhard 2004). Alternatively, by solving Eq. 17 in combination with Eq. 19 for a_i , we obtain the following estimate for a_i

$$\hat{\omega}_i = \frac{\hat{\delta}_i / 2}{1 - \kappa(T)} \tag{20}$$

where $\hat{\delta}_i$ is the marker contrast of the truncated selected population. Application of this formula is provided with a numerical example subsequently.

In Case 2 (one QTL affecting different traits), one must first obtain an unbiased estimate of a_i^* using the bias correction of Eq. 20 in QTL mapping of X^* and then use this value together with $\kappa(T)$ and an estimate of ρ to calculate

$$\hat{\omega}_i = \hat{\delta}_i / 2 + \hat{\rho}\kappa(T)\hat{a}_i^*. \tag{21}$$

For a QTL with small effect a_i^* , the residual correlation ρ is closely approximated by the phenotypic correlation of X^* and X . Using the same procedure and an estimate of the linkage value between Q_i and Q_j , one can calculate unbiased estimates of a_i for Case 1 (2 QTL affecting two traits).

Beside the three cases in Table 1, we considered additional cases and gave solutions for the expectation of the marker contrast and their approximation in supplementary material S2 and S3. Briefly, Case 1a is a simplification of Case 1 because it considers the marker M_{k_i} located directly at the position of QTL Q_i . Cases 2a and 3a assume the same conditions as Cases 2 and 3, respectively, but the marker M_{k_i} is not located directly at the position of the QTL Q_i .

Variations of marker class means and contrasts

For our derivations, we make use of a theorem from statistical theory about the conditional variance (e.g.,

Mood et al. 1974, p. 159, Theorem 7). Accordingly, we can express

$$\begin{aligned} \sigma_{k_t}^2 &= \text{var}(X|M_{k_t}, [X^* > T]) \\ &= \text{var}(E(X|Q_iQ_j, M_{k_t}, [X^* > T])) \\ &\quad + E(\text{var}(X|Q_iQ_j, M_{k_t}, [X^* > T])). \end{aligned} \tag{22}$$

The first term on the right-hand side of Eq. 22 refers to the variance between the four QTL haplotypes in marker class M_{k_t} within the selected fraction. Making use of Eqs. 11 and 12, we obtain

$$\begin{aligned} &\text{var}(E(X|Q_iQ_j, M_{k_t}, [X^* > T])) \\ &= \sum_{r=1}^2 \sum_{s=1}^2 \tau_{i_rj_sk_t} (\mu_{i_rj_s} + \rho i(T - \mu_{i_rj_s}^*) - \xi_{k_t})^2. \end{aligned} \tag{23}$$

The second term on the right-hand side of Eq. 22 refers to the residual variance of the QTL-marker haplotype class Q_i, Q_j, M_{k_t} . Making use of Cochran’s (1951) result on the variance of a correlated trait y after truncation selection for x in the case of a bivariate normal distribution, we have $\text{var}(X|Q_i, Q_j, M_{k_t}, [X^* > T]) = 1 - \rho^2 \kappa(T - \mu_{i_rj_s}^*)$ and obtain

$$\begin{aligned} &E(\text{var}(X|Q_iQ_jM_{k_t}, [X^* > T])) \\ &= \sum_{r=1}^2 \sum_{s=1}^2 \tau_{i_rj_sk_t} (1 - \rho^2 \kappa(T - \mu_{i_rj_s}^*)). \end{aligned} \tag{24}$$

Using the relationship $\sum_{r=1}^2 \sum_{s=1}^2 \tau_{i_rj_sk_t} = 1$ for $t = 1, 2$, which follows directly from Eq. 11, and combining Eqs. 23 and 24, we obtain for the general case

$$\begin{aligned} \sigma_{k_t}^2 &= 1 + \sum_{r=1}^2 \sum_{s=1}^2 \tau_{i_rj_sk_t} \\ &\quad [(\mu_{i_rj_s} + \rho i(T - \mu_{i_rj_s}^*) - \xi_{k_t})^2 - \rho^2 \kappa(T - \mu_{i_rj_s}^*)]. \end{aligned} \tag{25}$$

For Case 1, we have $\kappa(T - \mu_{i_rj_s}^*) = \kappa(T + (-1)^r a_i)$ and consequently

$$\sigma_{k_t}^2 = 1 + \frac{\sum_{r=1}^2 \sum_{s=1}^2 \psi_{i_r} \gamma_{i_rj_sk_t} [((-1)^{s+1} a_j + \rho i(T + (-1)^r a_i^*) - \xi_k)^2 - \rho^2 \kappa(T + (-1)^r a_i^*)]}{\sum_{r=1}^2 \psi_{i_r} \gamma_{i_rk_t}}. \tag{26}$$

For Case 2, we obtain

$$\sigma_{i_r}^2 = 1 - \rho^2 \kappa(T + (-1)^r a_i^*) \tag{27}$$

The two terms in this equation reflect the total variance of residual effects in X after truncation selection for X^* . The reduction in the variance, compared to the variance of

the residual effects $X(Q_iQ_j)$ in the absence of selection, is attributable to the correlated response caused by the effect of selection on the residuals of $X^*(Q_iQ_j)$.

Likewise, for Case 3 we have

$$\sigma_{i_r}^2 = 1 - \kappa(T + (-1)^r a_i) \tag{28}$$

as expected from Eq. 10 of Cochran (1951).

Turning now to the variance of marker contrasts, we have to take into account that if the selected fraction comprises a total of N DH lines, we expect a proportion of p_{k_1} to carry the marker allele M_{k_1} and $p_{k_2} = 1 - p_{k_1}$ to carry the marker allele M_{k_2} . Hence, the expected variance between the difference of \bar{X}_{k_t} , the mean of X in marker class M_{k_t} ($t = 1, 2$), is

$$\text{var}(\bar{X}_{k_1} - \bar{X}_{k_2}) = \frac{1}{Np_{k_1}} \sigma_{k_1}^2 + \frac{1}{Np_{k_2}} \sigma_{k_2}^2 = \frac{1}{N} \sigma_k^2, \tag{29}$$

where

$$\begin{aligned} \sigma_k^2 &= \frac{p_{k_2} \sigma_{k_1}^2 + p_{k_1} \sigma_{k_2}^2}{p_{k_1} p_{k_2}} \\ &= \frac{4}{1 - 4\Delta p_{k_1}^2} \left[\frac{\sigma_{k_1}^2 + \sigma_{k_2}^2}{2} + \Delta p_{k_1} (\sigma_{k_2}^2 - \sigma_{k_1}^2) \right] \end{aligned} \tag{30}$$

with Δp_{k_1} as defined in Eq. 9.

Figure 1b shows a graph of the variance of the marker contrast relative to its expectation in the absence of selection as a function of the effect of the QTL a_i and the selected fraction α_T for Case 3, based on the exact solution in Eq. 30.

In the general case and also for Case 1, the formula for σ_k^2 cannot be simplified. However, for Case 2, we obtain from Eq. 27:

$$\begin{aligned} \sigma_i^2 &= \frac{4}{1 - 4\Delta p_{i_1}^2} \left\{ 1 - \rho^2 \left[\frac{\kappa(T + a_i^*) + \kappa(T - a_i^*)}{2} \right. \right. \\ &\quad \left. \left. + [\kappa(T - a_i^*) - \kappa(T + a_i^*)] \Delta p_{i_1} \right] \right\}, \end{aligned} \tag{31}$$

where $\Delta p_{i_1} = (\psi_{i_1} - \psi_{i_2})/2(\psi_{i_1} + \psi_{i_2})$. Using a Taylor expansion for σ_i^2 in terms of a_i^* , we obtain the following approximation:

$$\sigma_i^2 \approx 4[1 - \rho \kappa(T)] \tag{32}$$

and for Case 3, we get from Eq. 28

$$\sigma_i^2 = \frac{4}{1 - 4\Delta p_i^2} \left\{ 1 - \left[\frac{\kappa(T + a_i^*) + \kappa(T - a_i^*)}{2} + [\kappa(T - a_i^*) - \kappa(T + a_i^*)]\Delta p_i \right] \right\} \quad (33)$$

with the approximation

$$\sigma_i^2 \approx 4[1 - \kappa(T)] \quad (34)$$

Effects of selection on power of QTL detection

In the regression approach for QTL mapping (Haley and Knott 1992; Martinez and Curnow 1992), an F test $F_k = MS_k/MSE_k$ is used for testing the presence of a QTL at marker M_k , where MS_k is the mean square between the two marker classes and MSE_k the weighted error mean squares within marker class M_k . In the case of DH lines, there are only two marker classes and consequently, MS_k follows a χ^2 distribution with one degree of freedom. Under truncation selection with a sample size N of the selected fraction, the variance $\sigma_{k_i}^2$ within each marker class M_{k_i} can differ between the two marker classes. Therefore, MSE_k follows approximately a central χ^2 distribution with expectation

$$MSE_k = \left(\frac{\sigma_{k_1}^2}{p_{k_1}} + \frac{\sigma_{k_2}^2}{p_{k_2}} \right) \frac{1}{N} = \frac{\sigma_k^2}{N} \quad (35)$$

with $\sigma_{k_i}^2$ and p_{k_i} defined in Eqs. 25 and 8, and the expected degrees of freedom calculated according to Satterthwaite (1946)

$$n_k = \frac{N(\sigma_k^2)^2}{\frac{(\sigma_{k_1}^2)^2}{p_{k_1}^2(p_{k_1} - \frac{1}{N})} + \frac{(\sigma_{k_2}^2)^2}{p_{k_2}^2(p_{k_2} - \frac{1}{N})}} \quad (36)$$

Thus, under the null hypothesis H_0 : $\delta_k = 0$, the test statistic is $F_k \sim F(1, n_k; 0)$, i.e., a central F distribution. Under the alternative hypothesis H_1 : $\delta_k \neq 0$, F_k follows a non-central F distribution $F_k \sim F(1, n_k; \phi^2)$, with non-centrality parameter ϕ^2 . Adopting results on the non-centrality parameter in a one-factor design analysis of variance given by Graybill (1976, p. 518) we obtain for truncation selection:

$$\phi^2 = \frac{\delta_k^2 N}{\sigma_k^2 8}, \quad (37)$$

with δ_k^2 and σ_k^2 as defined in Eqs. 14 and 30, respectively. Hence, for a given Type 1 error α , the power $(1 - \beta)$ of the F test F_k to detect a QTL with a Type 2 error of β is

$$1 - \beta = 1 - P(F_k < F_{\alpha}(1, n_k)) \quad (38)$$

where $F_{\alpha}(1, n_k)$ denotes the α quantile of a central F distribution with 1 and n_k degrees of freedom (Kendall and Stuart 1979, page 269). Equation 38 can be used to

compare the power of QTL detection under truncation selection with that in the absence of selection. Likewise, Eq. 38 can be used to calculate the sample sizes required under truncation selection for achieving the same power of QTL detection as achieved for a sample size N in the absence of selection.

Using the approximations of δ_k and σ_k^2 for Case 3 in Eqs. 17 and 34, we obtain for truncation selection

$$\phi^2 \approx a_i^2 [1 - \kappa(T)] \frac{N}{2}, \quad (39)$$

and $n_k \approx N - 2$. By comparison, in the absence of selection we have

$$\phi^2 = a_i^2 \frac{N}{2}. \quad (40)$$

Consequently, the power of the F test F_k is reduced with truncation selection compared to QTL mapping in the absence of selection.

The theoretical power of the F test statistic in the absence and presence of selection was calculated for Case 3 for different QTL effects using Eqs. 37 and 40, respectively. Numerical results are shown in Fig. 1c.

Numerical example

We demonstrate application of our theory with experimental data of a study by Martin et al. (2011). Briefly, 150 random DH lines developed from the cross UH006 \times UH007 were genotyped with 129 SSR markers and phenotyped for Giberella ear rot resistance (GBR) in four environments with heritability = 0.77. Using composite interval mapping according to established procedures and a LOD threshold of 3.8, we detected two QTL explaining 17.7 and 18.1% of the genetic variance for GBR (Table 2). For investigating the effects of truncation selection, we analyzed the subset of the 75 most resistant DH lines based on GBR entry means across environments, corresponding to $\alpha_T = 50\%$ and selection intensity $i = 0.798$. A QTL analysis was performed with software PLABQTL (Utz and Melchinger 1996) at fixed QTL positions taken from the QTL analysis of the reference set to avoid inflation of QTL estimates due to model selection. For both QTL, the additive effects a_i estimated from the selected subset, corresponding to $\hat{\delta}_i/2$, were about one-third in magnitude compared to the QTL effect \hat{a}_i estimated from the unselected reference set. This illustrates the substantial downward bias in QTL estimates under truncation selection even with moderate selection intensity. Treating both QTL independently according to the procedure outlined for Case 3, the QTL effects $\hat{\delta}_i/2$ estimated from the selected subset were corrected using the approximation given in Eq. 20,

Table 2 Parameters estimated in QTL mapping of Giberella ear rot resistance (GBR, % of ear surface covered with mycelium) using the unselected population of 150 DH lines (reference set) from crossUH600 × UH007 (see, Martin et al. 2011) and the subset of 75 DH lines (selected subset) obtained under truncation selection with $\alpha_T = 50\%$

Chromosome	Position in cM	Reference set ($N = 150$)		Selected subset ($N = 75, \alpha_T = 50\%$)	
		Explained % of genetic variance	Additive effect \hat{a}_i (%)	Estimated effect $\hat{\delta}_i/2$ (%)	Corrected estimated effect $\hat{\omega}_i$ (%)
1	238	17.67	8.22	2.82	7.78
2	42	18.12	7.55	2.77	7.65

with $1 - \kappa(T) = 0.363$, calculated from Eq. 26. For both QTL, the corrected QTL effect estimates ($\hat{\omega}_i$) deviated from \hat{a}_i by less than 5%, which illustrates the correction to work well. A second example of bias correction in a selected subsample is given in supplementary material S4 and S5.

Discussion

In general, all DH lines are phenotyped and marker genotyped for conducting QTL analysis, even though a large part of them is discarded later in the breeding process. In many cases, however, phenotypic preselection of lines could be useful. Complex traits like yield or physiological traits are often correlated with morphological, disease resistance and quality traits. Moreover, in hybrid breeding, costly production and evaluation of testcross progenies should only be performed for lines that meet minimum requirements with respect to these traits. However, even moderate preselection can have a significant effect on the power of QTL detection and estimation of the effects of the target traits. Consequently, statistical methods that take into account the consequences of selection are required for unbiased estimation of QTL effects.

In this study, we provide exact formulas for quantifying the change of allele frequencies within marker classes, expectations of marker contrasts and the variance of the marker contrasts under truncation selection for two QTL (Q_i, Q_j) affecting the same or a correlated trait. The formulas are very powerful because they are valid for a wide range of genetic models. The underlying theory does not make assumptions about the degree of interference in crossover formation, the linkage phase of the two QTL, or the presence or absence of epistasis and pleiotropy. For the general case of two QTL affecting the target trait and a correlated trait, for arbitrary values of linkage between the QTL and the marker as well as for the genetic correlation between the investigated traits, exact formulas have been derived, which allow the calculation of the power of QTL detection under selection as well as the calculation of the selection bias in QTL effects. Our approach can also be

extended to distributions other than the bivariate normal distribution as long as the regression of X^* on X is linear. For Case 3, where one normally distributed trait is considered we provided two numerical examples that show how the formula for bias correction can be applied in practical situations. Our numerical examples showed that under moderate selection ($\alpha_T = 50\%$) the selection induced bias of QTL effects can be successfully corrected with Eq. 20 for a wide range of effects explaining from 2 to 18% of the genetic variance (Table 2; Supplementary material S5).

Selection-induced bias

Mackinnon and Georges (1992) were the first to demonstrate the effects of truncation selection on linkage analysis of quantitative traits. They provided theoretical predictions but did not give analytical solutions for the expected means, the contrast of marker classes and the corresponding variances. In a comprehensive discussion of the causes of the selection induced bias, they demonstrated that both, the means of the (unknown) QTL genotype classes and the mix of QTL genotypes within the marker genotype classes are influenced by selection. The formulas presented here allow the quantification of these factors ($\Delta i(a_i)$ and ψ_i) as a function of the selected proportion α_T for the case of homozygous lines derived from biparental crosses. In addition, the effects of selection on a correlated trait can also be derived with the formulas. For both the general and the different special cases that we reported, the bias induced by truncation selection is mainly caused by a selection asymmetry of the DH lines belonging to the two marker classes M_{k_1} and M_{k_2} .

For the special case of direct selection on the trait for which QTL mapping is performed and complete linkage between the marker and the QTL (Case 3), the marker contrast, its corresponding variance, and the power of the F test, were quantified and illustrated in Fig. 1, relative to their corresponding statistics in the absence of selection. All graphs are presented as a function of the true QTL effect a_i and the selected proportion α_T . Under truncation selection, the relative bias in the expectation of the marker

contrast ($\delta_i/2a_i$) depends almost exclusively on the selected proportion (α_T) and is hardly affected by the size of the QTL effect a_i . Only for mild selection ($\alpha_T > 0.7$), does the relative bias in $\delta_i/2a_i$ for QTL of small effects exceed that for QTL of large effects, where it is almost a linear function of α_T . The reduction in the variance of the marker contrast under selection relative to the corresponding variance in the absence of selection ($\sigma_i^2/4$) follows the same trend for QTL of small effects ($a_i < 0.4$) or values of $\alpha_T > 0.5$. However, for larger values of a_i and smaller values of α_T , the ratio increases again and surpasses 1.0 (Fig. 1b). This is attributable to the fact that under these conditions, truncation selection leads to large differences in the proportion of DH lines represented in the two marker classes so that the term $\Delta p_{k_1}^2$ in Eq. 30 outweighs the reduction in the variances $\sigma_{k_1}^2$ and $\sigma_{k_2}^2$. Moreover, the two variances $\sigma_{k_1}^2$ and $\sigma_{k_2}^2$ become more heterogeneous as α_T decreases, due to the strong selection asymmetry among the DH lines carrying alternative marker classes.

The asymmetry introduced by truncation selection also complicates the calculation of the non-centrality parameter ϕ^2 and the degrees of freedom necessary for the determination of the power. The power of the F test was determined relative to the power of an unselected population as a function of a_i and the selected fraction α_T with a constant number ($N = 200$) of DH lines (Fig. 1c).

Similarly to the marker contrast and its corresponding variance, the power decreases when α_T decreases.

For QTL of large effects ($a_i > 0.6$) the curve of the relative power is flat and equal to 1.0 for a wide range of α_T ($0.3 < \alpha_T < 1$) and it decreases almost linearly for $\alpha_T < 0.3$. For QTL of medium effects ($0.02 < a_i < 0.6$) the curve of the relative power decreases smoothly with decreasing α_T , and it approaches zero at higher selection intensities as compared to QTL of larger effects. Therefore, under strong selection the relative power of QTL detection is higher for QTL of small than of large effects. This result is due to the fact that when large QTL effects are segregating in the population under study and extreme selection is applied, the number of DH lines in the two marker classes is extremely unbalanced, while both marker classes M_{k_1} and M_{k_2} are almost equally represented in the selected fraction when smaller QTL effects are considered. For QTL of small effects ($a_i < 0.02$) the power of QTL detection is similar in the truncated and in the unselected population approaching zero in both cases. As a consequence their ratio is close to 1.0, as illustrated in the left side of the graph (Fig. 1c).

Since the power of the F test depends on the population size, we also determined the relative power for 100 and 400 DH lines (N) present in the selected fraction α_T (results not shown). The graphs in these cases have similar shape

compared to that in Fig. 1c. However, for $N = 400$, the curve of the relative power is flat and equal to 1.0 for a wider range of α_T and a_i than that found for $N = 200$, while the opposite holds true for $N = 100$.

Taken together, these results suggest that the power of QTL analysis under truncation depends on the population size, the selected proportions, and the genetic architecture of the quantitative trait. To optimize the power of QTL detection in truncated populations all these parameters have to be taken into account simultaneously.

Effects of incomplete linkage between the marker and the QTL

With high-throughput genotyping having become available at reasonable costs for many species, it is realistic to assume that linkage between the QTL under selection and the marker will be tight. Thus, for many scenarios the complexity of the given formulas can be reduced by assuming complete linkage ($\lambda_{ik} = 1$, Cases 1a, 2, 3). In some cases, however, incomplete linkage between the marker and the QTL must be considered (Cases 1, 2a 3a), e.g., when performing QTL analysis in species with limited polymorphism of genetic markers and/or a large genome size. Variation in linkage also needs to be taken into account, when validating the effects of previously identified QTL with large confidence intervals in independent but selected populations.

As is well known from single-marker analysis of variance in unselected populations, the conditional probabilities of the QTL genotypes within the marker classes are a linear function of the linkage value between the marker and the QTL and consequently, estimates of the additive genetic effect at the QTL are biased downward, if linkage is incomplete (Soller et al. 1976). The same applies to the estimation of the marker contrast under truncation selection. For $\lambda_{jk} < 1$ and $\lambda_{ik} < 1$ the estimated marker contrast is reduced irrespective of the selection intensity. Under truncation selection, however, the marker contrast is additionally reduced by Δi (see Eq. 15), which is always smaller than 1 for $a_i^* > 0$. This reduction of the marker contrast is caused by unequal frequencies of the marker classes M_{k_1} and M_{k_2} for $\lambda_{ik} > 0$ (Eq. 9) and is specific to the case of truncation selection. In maize, significant changes in marker allele frequency were found for marker loci located in the vicinity of QTLs in a population of F4 independent families after two cycles of recurrent selection on phenotype (Moreau et al. 2004). This change in marker allele frequency in response to selection can be useful for finding markers associated with QTL in an approach called unidirectional selective genotyping (Gallais et al. 2007; Navabi et al. 2009). With unselected populations of homozygous lines from biparental crosses or selection of both tails of

their distribution, as is performed in bidirectional selective genotyping (Lebowitz et al. 1987), frequencies of marker classes are expected to be identical, if the variables $X^*(Q_i, Q_j)$ have a symmetric distribution around the mean and identical proportions are selected in each tail. Thus, the difference in the effective recombination rate between the marker and the QTL within marker classes only needs to be accounted for under truncation selection.

The effects of incomplete linkage between the marker and the QTL on the variance of the marker contrast are complex and formulas become unwieldy (results not shown). In this study, we provide approximations of the variance of the marker contrast for models assuming $\lambda_{ik} = 1$. Special cases of having restrictions on the linkage parameter, e.g., when linkage between the marker and the QTL is known from previous studies can be derived from the general formula (Eqs. 29, 30). For the special case of a half-sib design common in animal breeding, the combined effect of selection and linkage on the variance of the marker contrast has been shown by Mackinnon and Georges (1992) using computer simulations.

Effect of selection on correlated traits

A selection-induced bias in QTL analyses of correlated traits can be the result of linkage or pleiotropy. If two QTL are linked and affect different traits (Case 1), a selection bias is introduced also in the marker contrast for the trait that was not selected for. This bias is the result of the correlation between the residual effects and the marker genotype means and is a function of the strength of the correlation ρ between the two traits and the linkage phase between the two QTL. From Eq. 42 (Supplementary material S2), it can be seen that the selection bias will lead to a reduction of the estimated marker contrast, if QTL Q_i and Q_j are in coupling phase linkage and the correlation of the residuals is positive. However, if the residual correlation and the product of the effects at the two QTL have opposite signs, then the selection bias of the marker contrast will lead to an inflation of the estimate δ_k compared to its absolute value in the absence of selection. With pleiotropy, the same principles apply because pleiotropy can be considered a special case of two QTL affecting different traits in complete linkage (Case 2). Thus, we can conclude that truncation selection on trait X^* affects the power of QTL detection also for the correlated trait X and leads to biased estimates of QTL effects.

Goodness of the approximations

The formulas presented here can be approximated using restrictions on the model parameters. We give approximate

solutions for the marker contrasts (Table 1) and their corresponding variance assuming normal probability density functions for two traits, QTL with small effects and/or moderate selection intensities as well as complete linkage between the marker and the QTL. The difference between the expected marker contrast obtained with the approximation in Eq. 19 and with the exact formula in Eq. 17, relative to the marker contrast in the absence of selection ($2a_i$) is shown in supplementary material S6 as a function of the proportion selected α_T and the size of the QTL effect a_i . As illustrated, the approximation gives satisfactory results even with extreme values of a_i and α_T .

For the variance of the marker contrast σ_k^2 , however, approximations based on the infinitesimal model deviate substantially from exact solutions for QTL with large effects and low values of α_T . Thus, under the hypothesis of a geometric distribution of QTL effects and small values of α_T , QTL estimates and their standard errors must be calculated using exact formulas presented here.

The approximations given for the different cases provide also a means of relating our results with those presented in the literature. For the case of only one QTL Q_i with an effect on X^* , i.e., $a_j^* = 0$, $aa_{ij}^* = 0$, and using a Taylor expansion for ψ_{i_1} and ψ_{i_2} as a function of a_i^* , we obtain from Eq. 8 the following approximation:

$$\Delta p_{i_1} \approx \frac{1}{2} i(T) a_i^* \quad (41)$$

When accounting for the fact that selection is twice as effective when performed in DH lines compared to an F_2 population, this approximation translates directly to the approximation for the change of allele frequency under truncation selection given by Falconer (1989, Chap. 11). Results obtained for bidirectional selection by Darvasi and Soller (1992) and Bovenhuis and Spelman (2000) have been derived using an analogous approach. Assuming QTL with small effects, approximate bias corrections can be derived for the marker contrast and the corresponding variance based on a linear regression approach. In bidirectional selection, the bias is positive and analogous to the case of truncation selection, it is also a function of the change in variance of the selected fractions compared to the original population.

Bovenhuis and Spelman (2000) demonstrated with computer simulations that the employed approximation is quite robust with respect to the size of the QTL if the selection intensity at both tails of the phenotypic distribution is not too high ($\alpha_T = 10\%$ selection at each tail). However, results from bidirectional selection are not directly applicable to the case of truncation selection, because differences in marker genotype frequencies are specific to truncation selection and need not be considered in bidirectional selection for symmetric trait distributions.

This fact adds significantly to the complexity of the formulas for the calculation of the marker contrast and its variance, as well as the calculation of the degrees of freedom and the non-centrality parameter of the corresponding χ^2 distribution.

Conclusions

For a wide range of genetic models the effect of truncation selection on the selection bias in QTL effects as well as on the power of QTL detection has been derived for the case of homozygous lines derived from biparental crosses. The theoretical results and numerical examples clearly show that depending on the magnitude of QTL effects, high selection intensities ($\alpha_T \leq 50\%$) can lead to a dramatic reduction in the power of QTL detection and that approximations based on the infinitesimal model deviate substantially from exact solutions. The problem of reduced power of QTL detection with incomplete linkage between the marker and the QTL is aggravated by truncation selection due to different effective recombination rates between the marker and the QTL within each marker class. Truncation selection on correlated traits also reduces the power of QTL detection and introduces a selection bias in estimated QTL effects. The presented formulas allow quantification and correction of the selection bias of marker contrasts, opening the possibility of obtaining unbiased QTL effect estimates even from phenotypically preselected data.

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