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Marker-assisted recurrent selection for cumulating additive and interactive QTLs in recombinant inbred lines

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Abstract A computer program has been designed to manage marker information in recombinant inbred-line populations. The objective is to select pairs of inbred lines (either recombinant-inbred or doubled-haploid) to be intercrossed, in order to accumulate all or most favourable alleles, either with additive effects or with interactive effects. The population size required to have a 95% chance of obtaining the best line from a given cross is computed, taking into account the number of QTLs and the probability that no recombination event occurs in any of the QTL confidence intervals. It is shown that the accuracy of QTL location greatly affects selection efficiency and that a recurrent selection scheme is highly preferable for pyramiding many QTLs. An application to the bread-making quality improvement of wheat is presented.

Key words Molecular markers · Doubled-haploid · Molecular score · Confidence intervals

Introduction

The advent of molecular markers and the construction of saturated linkage maps in most crop plants has enabled the location of loci controlling quantitative traits or QTLs and the estimation of their additive, dominance or epistatic effects (Soller and Brody 1976; Lander and Botstein 1989). The use of genetic markers for improving selection efficiency has been proposed using two approaches. The first is a statistical one, which includes a molecular score into the selection index in addition to the phenotypic one (Lande and Thompson 1990). The efficiency of such marker-assisted selection (MAS) has been investigated either analytically (Lande and Thompson 1990; Gallais et al. 1997; Moreau et al. 1998) or by computer simulation (Zhang and Smith 1992, 1993; Gimelfarb and Lande 1994, 1995; Whittaker et al. 1995; Hospital et al. 1997). However, this approach is primarily focused on population improvement rather than the fixation of extreme genotypes. The second approach, known as genotype construction, simply considers and handles QTLs as Mendelian factors. This method has been considered mostly in the case of backcross breeding, as a mean of reducing linkage drag and optimising populations sizes (Tanksley 1983; Hospital et al. 1992; Vissher et al. 1996a; Hospital and Charcosset 1997). Recently, van Berloo and Stam (1998) proposed a selection-index method to select, among recombined inbred lines, those to be crossed to obtain single genotypes containing as many accumulated advantageous alleles as possible.

We have further improved their approach by including interactions among QTLs, and estimated the population size required to have a 95% likelihood of obtaining the best line from a given cross. We consider recurrent selection schemes, such as those proposed by Fouilloux (1980), as being economically more efficient for accumulating many QTLs than a single cycle requiring very large populations.

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Materials and methods

Computer algorithm

We considered a population of inbred lines (either recombined-inbred, RIL, assumed to be completely fixed, or doubled-haploid, DH) from a cross between two homozygous parents, as is currently practised in the breeding of selfing species such as cereals.

Contrary to van Berloo and Stam (1998), we considered that all markers located in the confidence interval (C.I.) of a QTL, and not only the flanking ones, should be taken into account, as suggested by Hospital and Charcosset (1997) in the back-cross case. This led us to consider that the genotype at a given QTL was known only when all markers in the C.I. originated from the same parent. In case of uncertainty, the unfavourable QTL allele or QTL combination is assumed, as explained in Table 1 for additive QTLs and in Table 2 for interactive QTLs. These index weights

Table 1 Coding of QTL information for constructing index weights for additive QTLs. QTL coding is as follows: –1 and 1 when all marker alleles in the C.I. of the QTL are of either the Chinese Spring (CS) or Courtot (Ct) type, respectively, and 0 when they are mixed, i.e. when the nature of the QTL allele cannot be ascertain. DHi (respectively j) is the actual or assumed QTL allele in line i (respectively j). In the case of uncertainty, the unfavorable QTL allele is assumed, which is a conservative approach (it led to overestimate the population size required to achieve fixation)

QTL effect	Actual DHi	Actual DHj	Assumed DHi	Assumed DHj	Weight (ij)	Segregation
+	1 (Ct)	1	1	1	1	N
+	1	–1	1	–1	1	Y
+	–1 (CS)	–1	–1	–1	–1	N
+	1	0	1	–1	1	Y
+	–1	0	–1	–1	–1	N
+	0	0	–1	–1	–1	N
–	1	1	1	1	–1	N
–	–1	1	–1	1	1	Y
–	–1	–1	–1	–1	1	N
–	1	0	1	1	–1	N
–	–1	0	–1	1	1	Y
–	0	0	1	1	–1	N

Table 2 Coding of QTL information for constructing index weights for pairs of interactive QTLs (QTLA and QTLB, respectively). Interactive effect are + when the association of two alleles from the same parent is favourable to the trait. X replaces either 1 or –1, for the sake of space

Interaction	Actual DHi	Actual DHj	Assumed DHi	Assumed DHj	Weight ij	Segregation
+	QTLA X QTLB X	QTLA X QTLB X	QTLA X QTLB X	QTLA X QTLB X	1	N
+	QTLA X QTLB X	QTLA X QTLB -X	QTLA X QTLB -X	QTLA X QTLB -X	–1	N
+	QTLA X QTLB X	QTLA -X QTLB X	QTLA X QTLB X	 QTLA -X	1	Y
+	QTLA X QTLB X	QTLA 0 QTLB X	QTLA X QTLB X	QTLA -X QTLB X	1	Y
+	QTLA X QTLB -X	QTLA 0 QTLB X	QTLA X QTLB -X	QTLA X QTLB X	1	Y
+	QTLA X QTLB 0	QTLA 0 QTLB X	QTLA X QTLB -X	QTLA -X QTLB X	1	Y
+	QTLA X QTLB 0	QTLA 0 QTLB -X	QTLA X QTLB -X	QTLA X QTLB -X	–1	N
+	QTLA 0 QTLB X	QTLA 0 QTLB X	QTLA -X QTLB X	QTLA -X QTLB X	–1	N
+	QTLA 0 QTLB 0	QTLA 0 QTLB 0	QTLA X QTLB -X	QTLA X QTLB -X	–1	N
–	QTLA X QTLB X	QTLA X QTLB X	QTLA X QTLB X	QTLA X QTLB X	–1	N
–	QTLA X QTLB -X	QTLA X QTLB -X	QTLA X QTLB -X	QTLA X QTLB -X	1	N
–	QTLA X QTLB X	QTLA -X QTLB X	QTLA X QTLB X	QTLA -X QTLB X	1	Y
–	QTLA X QTLB X	QTLA 0 QTLB X	QTLA X QTLB X	QTLA X QTLB X	–1	N
–	QTLA X QTLB -X	QTLA 0 QTLB X	QTLA X QTLB -X	QTLA X QTLB X	1	Y
–	QTLA X QTLB 0	QTLA 0 QTLB X	QTLA X QTLB X	QTLA X QTLB X	–1	N
–	QTLA X QTLB 0	QTLA 0 QTLB -X	QTLA X QTLB -X	QTLA X QTLB -X	–1	Y
–	QTLA 0 QTLB X	QTLA 0 QTLB X	QTLA X QTLB X	QTLA X QTLB X	–1	N
–	QTLA 0 QTLB 0	QTLA 0 QTLB 0	QTLA X QTLB X	QTLA X QTLB X	–1	N

Table 3 Extract of marker data associated with additive QTLs for the first two DH lines of Courtot×CS, with an illustration of the construction of the index weight for a pair of lines. Marker data are –1 and 1 for CS and Courtot marker alleles, respectively. Individuals are coded –1, 1 and 0 if they have CS, Courtot or an unknown QTL allele, respectively. Additive QTL effects are positive when allele 1 is favourable to the trait. Marker locations are given in cM from the origin of the linkage group. The number of markers for each QTL depends on C.I. length and marker density

QTL	Probe	Location	Effect	DH 1	DH 2	QTL1	QTL2	Pair1–2	Segreg.
1	bcd738	1A-63.7		1	1				
1	mta17	1A-70.6		1	1				
1	fba92	1A-79.0	+21.8	1	1	1	1	1	N
2	ksuH9c	1A-90.3		1	1				
2	fbb255c	1A-117.2		–1	1				
2	fba266b	1A-134.7	–15.6	–1	1	0	1	–1	N
3	mta14	1B-0.0		1	–1				
3	fbb234	1B-17.6		–1	–1				
3	cdo99	1B-27.5	+16.8	–1	–1	0	–1	–1	N
4	ksuE3b	3B-37.4		1	–1				
4	fba189a	3B-75.2		1	1				
4	ksuF34	3B-96.0	+16.8	–1	1	0	0	–1	N
5	tam75	5A-110.7		1	1				
5	glk510a	5A-120.0		1	1				
5	fbb166	5A-132.9	–12.4	1	1	1	1	–1	N
6	ksuE2	5A-193.5		1	–1				
6	ksuG30b	5A-217.9	+10.9	1	1	1	0	1	Y
7	mta10	5D-0.0		1	–1				
7	gwm190	5D-18.4	+26.7	1	–1	1	–1	1	Y
8	fbb82a	6B-111.7		1	1				
8	fbb250b	6B-116.1	–16.4	1	1	1	1	–1	N

are slightly different from those of van Berloo and Stam (1998), as they only account for the possibility of accumulating the QTLs in the progeny of a given pair cross, no matter how many QTLs are still segregating. In other words, for additive QTLs, a pair was given a weight of one when at least one line bears the favourable allele. Positive weights were given to the favourable allele, which ever parent it comes from. Consequently, these weights had to be multiplied by the absolute value of the QTL effect. The type of QTL interaction considered here is the classical 2×2 contrast, with the usual statistical constraint of centering by row and by column to ensure the uniqueness of estimates. The consequence is that, for a pair of loci, the interaction table is diagonally symetrical, with only two opposite values. By convention, we have chosen to assign a positive value to such interaction when the favourable effect was associated with a combination of two alleles from a common parent (coupling), and negative values to a recombined association of alleles having a favourable effect on the trait. Owing to the possibility of fixing the favourable combination, and taking into account the unknown QTL allele in a pessimistic way, many more cases have to be considered for pairs of interactive QTLs compared with addive ones (Table2).

It should be noted that all interactive QTLs are supposed to be different from the additive ones. Had a given QTL both an additive and an interactive effect, it would be counted twice by the algorithm, which would lead to an overestimate of the population size required (see below). This problem can easily be avoided in the following way: when only one of the interactive QTLs has an additive effect, one might consider that the second one has also an additive effect of the same value as the interaction, conditional to the favourable allele which should be fixed in the first QTL. If the two QTLs show both an additive effect and an interaction, the latter can be split for each QTL and added algebraically to the additive value. In other words, a pair of interactive QTLs has to be considered only when neither of them also has an additive effect.

Line pairs were then sorted by decreasing index values. A threshold can be placed on the population size to be derived from each cross for having a 95% likelihood of obtaining the best line, and additional aids to selection can be computed, such as the overall genetic distance between parents and their difference in flowering date. Whenever the maximum attainable value is not reached by any pair, the allelic composition of the best possible line is computed and re-introduced as a new entry into the programme. It is even possible to use a recursive "while" loop, by setting a limit to the number of recurrent generations to avoid infinite looping.

Numerical example

In our example we have considered a set of 110 doubled-haploid lines of bread wheat derived from the cross between cv 'Courtot' and cv 'Chinese Spring', for which a fairly saturated map has been obtained (Cadalen et al. 1997). Several QTLs for bread-making traits have been found in this population (Cadalen 1996; Perretant et al. 1999). In its present form, the algorithm is univariate, although a linear combination of different traits could be considered as well. We illustrate the effectiveness of the algorithm on the deformation energy of dough, estimated by the Chopin alveograph, and symbolised by W. Eight QTLs with additive effects and two additional pairs of QTLs showing only interaction effects were identified using marker regression (Kearsey and Hyne 1994) and its extension to interactive QTLs (Charmet et al. 1998) at a nominal α risk of 1%, and their confidence intervals were estimated through 500 bootstrap re-samples (Vissher et al. 1996a).

Results and discussion

Marker data and QTL coding is illustrated for the first two DH lines in Tables 3 and 4, for additive and interactive QTLs, respectively. The algebraic sum of all favourable QTL alleles equals 179.3, and represents the predicted value of the best possible line. This value is the deviation from the grand mean of the population, since QTL effects are centred. As a comparison, the individual

Table 4 Extract of marker data associated with pairs of interactive QTLs for the first two DH lines of Courtot×CS, with illustration of the construction of the index weight for a pair of lines. Marker data are –1 and 1 for CS and Courtot marker alleles, respectively. Individuals are coded –1, 1 and 0 if they have CS, Courtot or an unknown QTL allele, respectively. Interactive QTL effects are positive when both alleles of the pair come from the same parent. Marker locations are given in cM from the origin of the linkage group. QTLs are coded in arabic characters within pairs coded in roman characters. (NA represents missing data)

QTL	Probe	Location	Effect	DH1	DH2	QTL1	QTL2	Pair1–2	Segreg.
I-1	fba393	1A-10.6		–1	1				
I-1	fba285	1A-18.4		–1	1				
I-1	ksuG9	1A-27.7		NA	1	0	1		
I-2	glk163	1B-69.5		1	–1				
I-2	ksuG34a	1B-79.6		–1	–1				
I-2	ksuA1c	1B-88.7	21.7	–1	–1	0	0	–1	N
II-1	fba342	5A-36.0		–1	1				
II-1	bcd207	5A-51.4		–1	1				
II-1	glk407	5A-66.5		1	1	0	1		
II-2	ksuA5	7A-122.7		1	–1				
II-2	ksuG12b	7A-132.2		1	–1				
II-2	fba69	7A-149.3	20.0	1	–1	1	0	1	Y

Table 5 Extract of the output of the first run of the program, sorted by decreasing pair-index, whithout any limit on population size required. Pair-index refers to the QTL-predicted value of the best possible line from the cross, Segregating QTLs represent the number of additive QTLs or pairs of interactive QTLs which are segregating among the two crossed lines, Pop size 95% is the population size required to have a 95% likelihood to fix the best possible line. Ct is the Courtot parent, Dhx are the segregating DH lines

Pair cross	Pair-index	Segregating QTLs	Pop size 95%
Ct×DH25	179.3	9	17930
Ct×DH34	179.3	7	4464
Ct×DH93	179.3	8	11439
DH17×DH98	179.3	7	3680
DH26×DH98	179.3	8	12019
DH31×DH55	179.3	8	8571

value of the 110 DH lines range from –151.6 to 125.2, while that of the better parental line, cv Courtot, is 90.5. A substantial genetic gain can thus be expected from accumulating complementary QTLs, not yet associated in this first set of RIL. A first run of the algorithm, without any threshold on population size, shows that this maximum value of 179.3 can be obtained from 13 crosses, the first six being shown in Table 5, but at the expense of large population sizes.

When a maximum population size of 200 lines for each cross is imposed, only six crosses are selected, and the value of the best line is now only 154.5. The six best lines, one from each cross, were re-introduced into the algorithm (omitting the QTL coding step). Table 6 shows that the recursion stopped after two generations of selection. The maximum attainable value is reached in five crosses, all of them involving the better parent of the population, cv Courtot. In the most favourable case, the best line can be obtained by making 159 lines from (Courtot×DH 98) and 52 lines from (DH98×DH102) in the first generation, then 79 lines from the cross between the two best lines derived from each of the above mentioned crosses.

The proposed algorithm provides a useful aid for selecting pairs of lines to be crossed for accumulating favourable alleles at QTLs. Indeed this task may appear obvious, and feasible by hand, when only a few QTLs are considered together. However, our program has the advantage of being of general use, with no upper limit on QTL number, and also able to deal with interactive QTLs, which has not yet been reported. The population

Table 6 Output of the recursive algorithm, which stopped after two runs, with a limit on the population size required of 200. The best possible line from each cross in step *n* is re-introduced for crossing in step *n*+1

Pair cross	Pair-index	Segregating QTLs	Pop size 95%
First step			
Ct×DH98	154.5	4	159
DH98×DH102	137.6	3	52
DH102×DH123	137.6	4	180
DH34×DH102	137.6	4	190
DH34×DH123	137.6	4	142
DH86×DH159	137.6	4	115
Second step			
(Ct×DH98)×(DH98×DH102)	179.3	3	79
(Ct×DH98)×(DH102×DH123)	179.3	3	79
(Ct×DH98)×(DH34×DH102)	179.3	3	106
(Ct×DH98)×(DH34×DH123)	179.3	3	136
(Ct×DH98)×(DH86×DH159)	179.3	3	136

Table 7 Population size required to have a 95% likelihood of obtaining the best possible line, as a function of the number of additive QTLs (QTLA), the number of pairs of interactive QTLs (QTLI) and the length of the confidence intervals for QTL location (C.I. in cM), assumed to be all identical

	QTLI=0	QTLI=1	QTLI=2	QTLI=3	QTLI=4	QTLI=5
C.I.=0 cM						
QTLA=1	4	10	22	46	94	190
QTLA=2	10	22	46	94	190	382
QTLA=3	22	46	94	190	382	765
QTLA=4	46	94	190	382	765	1532
QTLA=5	94	190	382	765	1532	3066
QTLA=6	190	382	765	1532	3066	6134
QTLA=7	382	765	1532	3066	6134	12269
QTLA=8	765	1532	3066	6134	12269	24540
QTLA=9	1532	3066	6134	12269	24540	49081
QTLA=10	3066	6134	12269	24540	49081	98163
C.I.=10 cM						
QTLA=1	5	15	39	98	243	600
QTLA=2	13	35	88	219	540	1333
QTLA=3	31	79	197	487	1201	2959
QTLA=4	71	177	439	1082	2667	6568
QTLA=5	160	395	975	2403	5919	14576
QTLA=6	356	879	2166	5335	13137	32345
QTLA=7	792	1952	4808	11840	29153	71775
QTLA=8	1759	4334	10672	26276	64692	159270
QTLA=9	3906	9618	23682	58307	143552	353419
QTLA=10	8669	21345	52553	129385	318541	784234
C.I.=20 cM						
QTLA=1	6	21	67	208	637	1945
QTLA=2	17	54	168	516	1575	4804
QTLA=3	44	136	417	1276	3891	11863
QTLA=4	110	338	1033	3152	9609	29293
QTLA=5	273	836	2553	7783	23728	72329
QTLA=6	677	2067	6305	19220	58588	178587
QTLA=7	1674	5107	15568	47458	144660	440944
QTLA=8	4136	12611	38442	117178	357176	1088719
QTLA=9	10215	31138	94917	289321	881890	2688112
QTLA=10	25223	76885	234357	714353	2177439	6637107
C.I.=30 cM						
QTLA=1	7	29	113	426	1598	5976
QTLA=2	21	82	311	1168	4371	16341
QTLA=3	60	227	854	3197	11953	44682
QTLA=4	166	624	2338	8743	32683	122172
QTLA=5	456	1710	6395	23907	89366	334046
QTLA=6	1250	4677	17487	65368	244346	913352
QTLA=7	3421	12791	47815	178733	668094	2497291
QTLA=8	9356	34975	130738	488694	1826706	6828098
QTLA=9	25583	95631	357467	1336190	4994584	18669393
QTLA=10	69952	261478	977389	3653414	1365619	51045869

size required to give a 95% likelihood to obtain the best line takes into account the length of QTL confidence intervals, through the probability (conditioned by the C.I. length) that no recombination event occurs between any marker in these intervals in order to be certain of the allelic QTL status of the selected lines. This constraint was not always taken into account in some reports (e.g. Howes et al. 1998), although Hospital and Charcosset (1997) did consider it in the case of backcrosses.

The length of the confidence intervals for QTLs has a huge effect on population size. Table 7 gives the sizes required in an ideal case of all confidence intervals being of equal length. There is clear evidence that, for a C.I. of 30 cM, which is a likely value for QTLs of moderate heritability detected with a population of about 200 recombinant lines (Hyne and Kearsey 1995), it would be difficult to cumulate more than 3–4 segregating QTLs in one generation. It is much more efficient to use a recurrent selection scheme. The one described in this paper is very similar to that proposed by Fouilloux (1980) who considered the expected number of QTLs (whatever their effect, or setting them as equal) that can be fixed, according to population size and the number of recurrent generations. Fouilloux reported, for example, that two cycles with a population size of 200 should be as efficient as a one cycle with a size 4000. Although we considered the extreme value rather than the expected one, our conclusions from the experimental study are very similar to those of Fouilloux (1980).

There are some limitations in the present release of our program. The first is that all QTLs are assumed to be unlinked, as we observed in our biological example. If this assumptions does not hold, this would affect the

population size required: by a decrease if the two favourable alleles are in coupling phase in the parents, by an increase if they are in repulsion. However, for tightly linked QTLs this situation is not very likely to happen, since with the population sizes currently used in QTL studies, two QTLs linked by less than 30 cM would hardly be detected (Hyne and Kearsey 1995; Goffinet and Mangin 1998).

We have chosen one strategy for the recurrent selection, which proved to be efficient in practice. However, many alternative strategies are possible, and their efficiency could be explored by means of simulation as in the papers of van Berloo and Stam (1998) or Hospital et al. (1997). For example, it should be possible to compute indices for *n*-uplets of lines, rather than pairs, in order to directly select for three-way or double crosses. However, this would require a much more sophisticated algorithm and increased computing time.

Conclusion

This paper presents a pragmatic approach to the problem of accumulating or pyramiding QTLs for pure-line construction. The given example is for an autogamous crop, for which additive QTLs relate directly to line value. However, the algorithm can also be applied to inbred lines selected for hybrid value, provided QTLs for general combining ability are identified. An extension to nonnbred lines is possible, although less straightforward. Moreover, the present program applies to recombinant populations from a single cross, and extensions to broad-based populations more often worked out by recurrent selection would be highly desirable, as has been recently proposed by Hospital et al. (1999). The Splus (Becker et al. 1988) script of the reported computer-programme is available upon request.

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