Simulation of marker-assisted selection utilizing linkage disequilibrium: the effects of several additional factors

W. Zhang, C. Smith

Centre for Genetic Improvement of Livestock, Department of Animal and Poultry Science, University of Guelph, Guelph, Ontario N1G 2W1, Canada

Abstract. Use was made of our published model and methods to investigate the effects of several additional factors on marker-assisted selection (MAS) utilizing linkage disequilibrium. The additional factors were: size of the sample used to estimate the marker quantitative trait locus (MQTL) association effects, the method used to estimate the MQTL effects, use of the average of the top MQTL estimates in selection rather than individual estimates, size of the selection population, and the crossing of duplicate selection lines to generate further linkage disequilibrium and further selection response. The average map distance between the quantitative trait loci (QTLs) and their nearest marker was 0.15 Morgans. Use of estimates of MQTL effects derived by least squares yielded smaller selection responses than estimates derived by mixed-model methods. Selection responses were also reduced by using a smaller sample for estimating the associations because MQTL effects were less well estimated. This applied to selection on the MQTL effects themselves and to selection combining the MQTL with phenotypic information. Thus, poorly estimated MQTL effects added noise to the system and reduced selection response in combined selection. Using the average of the top MQTL estimates, rather than individual estimates, also reduced selection response. New linkage disequilibrium, generated by crossing two lines selected from the same population, did not lead to additional selection response in the cross line. These results show limitations to MAS using linkage disequilibrium until close linkages of markers and QTLs are available.

Key words: Marker-assisted selection – Linkage disequilibrium

Introduction

The theoretical value of linkage disequilibrium between genetic markers and quantitative trait loci in selection was evaluated by Lande and Thompson (1990). With an increasingly large number of marker loci, very close linkages between markers and QTLs will become available, which will lead to high levels of linkage disequilibrium and eventually almost to the equivalent of selecting on the QTLs themselves (Zhang and Smith 1992). With a limited number of markers, the average map distance between a QTL and its nearest marker will not be small, linkage disequilibrium will not be large, and response to selection on MQTL effects will be limited.

The objective of the present paper was to use the model and methods of Zhang and Smith (1992) to investigate the effects on selection response of several additional factors in MAS using linkage disequilibrium. Two factors of obvious concern are the size of the sample used to estimate MQTL effects and the size of the selection population. Least-squares methods are often used to estimate gene effects, but the results may be biased (Kennedy et al. 1992), so comparison was made with mixed-model methods. Individual MQTL effects are not well estimated, but their average should be. Use of the average of selected top MQTL effects, rather than individual effects, was therefore investigated. Finally, results suggested by Zhang and Smith (1992), on the value of having and crossing duplicate selection lines to regenerate new marker QTL linkage disequilibrium, were developed and presented.

Methods

Zhang and Smith (1992) generated a base population from a cross (F_1) of two inbred lines. The F_2 and subsequent generations of the cross line then had genetic markers in linkage dis-

equilibrium with QTLs with known effects. From the base population, estimates of MQTL effects and linkage disequilibrium of the markers and the QTLs were derived. These estimates were used to calculate estimated breeding values (EBV) for all individuals. The EBV were used as a basis for selection. Thus selection was across the population rather than within families. A genome of 20 Morgans was simulated, made up of 20 chromosomes each one Morgan in length. One hundred QTLs were simulated, accounting for all the genetic variation associated with the trait (heritability 0.25). The QTLs were diallelic, and allocated five per chromosome at random along each chromosome. Initial gene frequencies were 0.5 at all loci. The gene effects were either normally distributed or distributed as a gamma distribution. The former were considered the standard case, but Mackay et al. (1992) recently presented evidence for the latter. One hundred genetic markers were also simulated and five were assigned at random per chromosome. These were also diallelic with an average initial frequency of 0.5. The average map distance between a QTL and its nearest marker was 0.15 Morgans. Levels of initial linkage disequilibrium were simulated, corresponding to the F_2 and F_{10} of the cross between the two inbred lines. The MQTL effects were estimated in a base population of 1,000 individuals with equal numbers of the two sexes. The associations were estimated by mixed-model methods as described in Zhang and Smith (1992). For the normal distribution, the top 20 estimated MQTL effects, and for the gamma distribution the top ten estimated MQTL effects, were used in selection. They were selected and then re-estimated in an independent data set to avoid the bias caused by their initial selection (Lande and Thompson 1990). The selection population consisted of 1,000 individuals per generation (500 males and 500 females). Thirty males and 30 females were selected for breeding per generation giving an effective population size of about 60. Selection was either on estimates of breeding values based on the MQTL associations (MAS) or on the best linear unbiased prediction (BLUP) of phenotype, or on a combination (COMB) of these.

The five additional factors investigated in this paper are now described: (1) The size of the sample used to estimate the MQTL effects, either 1,000 (standard) or 100. (2) The size of the selection population, either 1,000 (standard) or 100 (50 males and 50 females). (3) The MQTL effects estimated either by mixed-model methods (standard) or by least squares. (The least-squares equations are the same as for the mixed-model equations in Zhang and Smith (1992), but with $A^{-1}\varepsilon$ dropped from the diagonals of the Z equations.) (4) Selection based on the individual top MQTL effects (standard) or on their average effect. (5) Selection response after crossing two replicate selection lines to generate new linkage disequilibrium after ten generations of selection and re-estimating the MQTL effects, compared for further genetic response with continued selection response in a single line (standard case). The effects of the individual factors were evaluated one at a time and compared with the standard case, rather than for all the possible combinations.

In this paper a heritability of 0.25 was used throughout, since the pattern of the results in Zhang and Smith (1992) was similar for a range of heritability. Genetic responses are measured in initial genetic standard deviation units. The total response possible by fixing all the favourable QTL alleles would be 12.3 genetic standard deviation units for the normal, and 4.1 for the gamma, distribution. The calculated selection responses listed are the averages of 30 replicates.

Results

The results are presented in terms of genetic response and its standard deviation for ten generations for each of the

Table 1. Genetic response and SD (in genetic SD) from MAS selection, with MQTL effects estimated by least-squares (LS) and mixed-model (MM) methods, for normal and gamma distributions of QTL effects, estimated and selected in F_2 and F_{10} populations of 1,000 individuals

Generation	LS	MM	LS	MM
	F_2 Normal distribution		F_{10} Normal distribution	
1	0.01 ± 0.10	0.00 ± 0.08	0.01 ± 0.10	-0.02 ± 0.10
2	0.52 ± 0.18	1.06 ± 0.14	0.25 ± 0.15	0.48 ± 0.15
3	0.59 ± 0.20	1.65 ± 0.17	0.30 ± 0.18	0.74 ± 0.20
4	0.66 ± 0.21	2.11 ± 0.22	0.34 ± 0.20	0.94 ± 0.21
5	0.76 ± 0.21	2.41 ± 0.24	0.36 ± 0.23	1.01 ± 0.19
6	0.85 ± 0.22	2.60 ± 0.27	0.38 ± 0.26	1.13 ± 0.23
7	0.94 ± 0.24	2.79 ± 0.27	0.39 ± 0.27	1.26 ± 0.27
8	0.97 ± 0.24	2.91 ± 0.28	0.40 ± 0.33	1.32 ± 0.28
9	1.02 ± 0.24	2.98 ± 0.32	0.41 ± 0.32	1.34 ± 0.30
10	1.05 ± 0.25	3.08 ± 0.32	0.42 ± 0.33	1.37 ± 0.31
	Gamma distribution		Gamma distribution	
1	0.01 ± 0.09	0.01 ± 0.12	0.01 ± 0.08	-0.01 ± 0.08
2	0.73 ± 0.16	1.74 ± 0.10	0.51 ± 0.13	0.69 ± 0.15
3	0.92 ± 0.22	2.03 ± 0.12	0.64 ± 0.18	1.24 ± 0.09
4	1.02 ± 0.21	2.18 ± 0.11	0.68 ± 0.20	1.53 ± 0.11
5	1.11 ± 0.23	2.29 ± 0.13	0.74 ± 0.24	1.68 ± 0.12
6	1.18 ± 0.20	2.36 ± 0.14	0.80 ± 0.31	1.79 ± 0.12
7	1.24 ± 0.21	2.38 ± 0.17	0.85 ± 0.31	1.89 ± 0.12
8	1.29 ± 0.23	2.40 ± 0.18	0.90 ± 0.32	1.96 ± 0.13
9	1.32 ± 0.23	2.40 ± 0.18	0.91 ± 0.32	1.98 ± 0.13
10	1.33 ± 0.22	2.41 ± 0.19	0.92 ± 0.32	2.00 ± 0.15

All tables: 30 replicates, $h^2 = 0.25$, 30 males and 30 females selected. Estimation population size 1,000, selection population size 1,000

different methods of selection. In each case one parameter is varied at a time, and the response is compared with the standard case. In Table 1 the genetic responses from MAS using MQTL effects estimated by the least-squares and by the mixed-model methods are compared. The least-squares estimates yielded much smaller responses than the mixed-model estimates in agreement with theoretical results and the simulations of Kennedy et al. (1992). They concluded that the least-squares methods tend to overestimate QTL effects and to increase prediction error-variance. The mixed-model method treats QTL effects as random effects and regresses them back towards zero (Kennedy et al. 1992).

Reductions in response using least-squares compared with mixed-model estimates were greater for the normal distribution of QTL effects than for the gamma distribution (Table 1). Thus, there was less difference between the methods for large QTL effects (as with the gamma distribution) but the mixed-model methods were better than least squares when the QTL effects were moderate or small (as with the normal distribution).

Table 2. Genetic response and SD (in genetic SD) from MAS selection, with MQTL effects estimated by mixed-model methods for a normal distribution of QTL effects. The first number (B) denotes the size of the base population to evaluate MQTL effects, the second number (S) denotes the size of the selection population

Gener-ation	B S $1,000-1,000$	B S $100-1,000$	B S $1,000-100$	B S $100-100$
	Base population F_2			
1	0.00 ± 0.08	0.01 ± 0.14	0.02 ± 0.10	0.01 ± 0.12
2	1.06 ± 0.14	0.51 ± 0.15	0.57 ± 0.11	0.21 ± 0.15
3	1.65 ± 0.17	0.76 ± 0.15	0.88 ± 0.13	0.35 ± 0.15
4	2.11 ± 0.22	0.92 ± 0.17	1.14 ± 0.15	0.50 ± 0.17
5	2.41 ± 0.24	1.07 ± 0.16	1.41 ± 0.17	0.57 ± 0.22
6	2.60 ± 0.27	1.22 ± 0.17	1.62 ± 0.17	0.65 ± 0.21
7	2.79 ± 0.27	1.31 ± 0.18	1.80 ± 0.19	0.76 ± 0.22
8	2.91 ± 0.28	1.37 ± 0.20	1.96 ± 0.21	0.83 ± 0.20
9	2.98 ± 0.32	1.45 ± 0.21	2.08 ± 0.23	0.86 ± 0.21
10	3.08 ± 0.32	1.51 ± 0.21	2.19 ± 0.21	0.94 ± 0.21
	Base population F_{10}			
1	-0.02 ± 0.10	-0.01 ± 0.10	0.02 ± 0.11	0.01 ± 0.09
2	0.48 ± 0.15	0.28 ± 0.15	0.25 ± 0.12	0.16 ± 0.13
3	0.74 ± 0.20	0.37 ± 0.17	0.42 ± 0.15	0.23 ± 0.14
4	0.94 ± 0.21	0.43 ± 0.20	0.62 ± 0.16	0.28 ± 0.15
5	1.01 ± 0.19	0.51 ± 0.19	0.73 ± 0.18	0.33 ± 0.16
6	1.13 ± 0.23	0.59 ± 0.21	0.86 ± 0.19	0.40 ± 0.18
7	1.26 ± 0.27	0.67 ± 0.19	1.00 ± 0.20	0.44 ± 0.21
8	1.32 ± 0.28	0.73 ± 0.22	1.08 ± 0.23	0.47 ± 0.23
9	1.34 ± 0.30	0.80 ± 0.24	1.17 ± 0.24	0.50 ± 0.24
10	1.37 ± 0.31	0.84 ± 0.26	1.26 ± 0.28	0.53 ± 0.26

Table 3. Genetic response and SD (in genetic SD) from MAS selection, with MQTL effects estimated by mixed-model methods for a gamma distribution of QTL effects. The first number (B) denotes the size of the base population and the second number (S) denotes the size of the selection population

Gener-ation	B S $1,000-1,000$	B S $100-1,000$	B S $1,000-100$	B S $100-100$
	Base population F_2			
1	0.01 ± 0.12	0.01 ± 0.12	0.03 ± 0.09	0.02 ± 0.10
2	1.74 ± 0.10	1.09 ± 0.16	1.04 ± 0.09	0.53 ± 0.13
3	2.03 ± 0.12	1.32 ± 0.17	1.46 ± 0.10	0.85 ± 0.10
4	2.18 ± 0.11	1.49 ± 0.15	1.63 ± 0.10	1.04 ± 0.11
5	2.29 ± 0.13	1.59 ± 0.14	1.72 ± 0.12	1.06 ± 0.13
6	2.36 ± 0.14	1.65 ± 0.12	1.82 ± 0.13	1.13 ± 0.13
7	2.38 ± 0.17	1.74 ± 0.12	1.91 ± 0.14	1.20 ± 0.14
8	2.40 ± 0.18	1.80 ± 0.13	1.98 ± 0.13	1.23 ± 0.14
9	2.40 ± 0.18	1.80 ± 0.12	2.00 ± 0.14	1.24 ± 0.13
10	2.41 ± 0.19	1.81 ± 0.13	2.01 ± 0.16	1.25 ± 0.13
	Base population F_{10}			
1	-0.01 ± 0.08	-0.01 ± 0.10	0.02 ± 0.06	0.01 ± 0.09
2	0.69 ± 0.15	0.62 ± 0.15	0.57 ± 0.07	0.37 ± 0.15
3	1.24 ± 0.09	0.89 ± 0.17	0.94 ± 0.09	0.55 ± 0.14
4	1.53 ± 0.11	1.16 ± 0.20	1.25 ± 0.13	0.69 ± 0.16
5	1.68 ± 0.12	1.32 ± 0.19	1.43 ± 0.12	0.79 ± 0.16
6	1.79 ± 0.12	1.41 ± 0.21	1.56 ± 0.10	0.85 ± 0.14
7	1.89 ± 0.12	1.48 ± 0.19	1.65 ± 0.11	0.89 ± 0.14
8	1.96 ± 0.13	1.55 ± 0.22	1.73 ± 0.10	0.93 ± 0.15
9	1.98 ± 0.13	1.56 ± 0.24	1.74 ± 0.09	0.97 ± 0.16
10	2.00 ± 0.15	1.57 ± 0.26	1.75 ± 0.09	0.98 ± 0.18

As expected, overall responses decreased appreciably as linkage disequilibrium decreased, as shown by comparing responses in the base population from the F_{10} with that from the F_2 (Tables 1–4).

Effects of size of the estimation population and of size of the selection population on genetic response are shown in Tables 2, 3 and 4. The effectiveness of MAS was substantially higher when the MQTL estimates were from the estimation population of 1,000 compared with the small estimation population of 100 individuals. As expected, responses were also appreciably lower when selection was in a small population, selecting the same number (30) of males and females as before, so that the selection intensity was greatly reduced. Finally, with both factors, the responses were even smaller. These results agree with those of previous authors (Smith 1967; Soller 1978; Smith and Simpson 1986) which indicate that large sample sizes are needed to estimate QTL and MQTL effects accurately enough to be of value in selection.

Results for MAS selection for the gamma distribution of QTL effects are presented in Table 3. The pattern is similar to that for the normal distribution effects except that responses with a small base (estimation) sample were reduced less. This indicates that the larger MQTL effects in the gamma distribution were better estimated in the

Table 4. Genetic responses and SD (in genetic SD) from *combined* selection on mixed-model estimated MQTL effects and on phenotype for a normal distribution of QTL effects. The first number (B) denotes the size of the base population and the second number (S) denotes the size of the selection population

Gener-ation	B S $1,000-1,000$	B S $100-1,000$	B S $1,000-100$	B S $100-100$
	Base population F_2			
1	0.01 ± 0.08	0.01 ± 0.09	0.03 ± 0.09	0.02 ± 0.08
2	1.42 ± 0.21	1.00 ± 0.16	0.80 ± 0.13	0.29 ± 0.11
3	2.18 ± 0.23	1.56 ± 0.20	1.18 ± 0.15	0.47 ± 0.12
4	2.98 ± 0.25	2.05 ± 0.23	1.63 ± 0.16	0.72 ± 0.12
5	3.60 ± 0.29	2.48 ± 0.24	2.13 ± 0.15	0.86 ± 0.13
6	3.90 ± 0.26	2.87 ± 0.24	2.44 ± 0.16	0.97 ± 0.12
7	4.10 ± 0.24	3.09 ± 0.26	2.68 ± 0.17	1.13 ± 0.14
8	4.23 ± 0.24	3.42 ± 0.24	2.88 ± 0.18	1.22 ± 0.13
9	4.34 ± 0.25	3.52 ± 0.25	3.03 ± 0.19	1.25 ± 0.15
10	4.42 ± 0.26	3.71 ± 0.26	3.19 ± 0.18	1.37 ± 0.14
	Base population F_{10}			
1	-0.01 ± 0.10	-0.01 ± 0.09	0.02 ± 0.08	0.01 ± 0.08
2	1.20 ± 0.23	0.92 ± 0.15	0.73 ± 0.11	0.26 ± 0.10
3	2.00 ± 0.24	1.47 ± 0.18	1.06 ± 0.13	0.42 ± 0.12
4	2.58 ± 0.25	1.96 ± 0.19	1.48 ± 0.12	0.66 ± 0.13
5	3.01 ± 0.25	2.30 ± 0.21	1.78 ± 0.13	0.74 ± 0.14
6	3.36 ± 0.27	2.60 ± 0.23	2.04 ± 0.14	0.89 ± 0.13
7	3.66 ± 0.25	2.89 ± 0.22	2.31 ± 0.15	1.09 ± 0.14
8	3.86 ± 0.25	3.13 ± 0.24	2.56 ± 0.14	1.16 ± 0.16
9	4.04 ± 0.25	3.37 ± 0.24	2.81 ± 0.14	1.21 ± 0.14
10	4.21 ± 0.27	3.55 ± 0.25	3.02 ± 0.13	1.28 ± 0.16

Table 5. Genetic response and SD (in genetic SD) from MAS selection, with MQTL effects estimated by mixed-model methods for a normal distribution of QTL effects. Selection was based on the top 20 estimated MQTL effects using the individual (IND) estimates or the average (AV) estimate

Generation	IND	AV
1	0.00±0.08	−0.01±0.09
2	1.06±0.14	0.87±0.17
3	1.65±0.17	1.32±0.17
4	2.11±0.22	1.70±0.18
5	2.41±0.24	1.98±0.18
6	2.60±0.27	2.23±0.20
7	2.79±0.27	2.47±0.21
8	2.91±0.28	2.64±0.18
9	2.98±0.32	2.73±0.21
10	3.08±0.32	2.89±0.25

Estimation population size 1,000, selection population size 1,000. F_2 base population

smaller sample than the moderate effects in the normal distribution.

Genetic responses using both the MQTL effects and the phenotypic information in *combined* selection are given in Table 4. With the best linear unbiased prediction (BLUP), the average response from 30 replicates was 4.11 ± 0.06 genetic standard deviations after ten generations of selection (Zhang and Smith 1992). These results with combined selection show, as expected, that large genetic responses were obtained for large population sizes irrespective of linkage disequilibrium. This result implies that either the MQTL effects were reasonably well estimated or else that information on phenotype may offset any deficiencies in the estimates of the marker effects. However, when population size for estimation was small, responses were reduced indicating that MQTL information introduced noise into the system, and so confounded the phenotypic information and resulted in smaller responses. When the effects of small population size for estimation and selection were both acting, responses were further reduced.

While individual effects of the MQTLs may not be well estimated, the average of the best MQTL effects should be. Genetic responses obtained by using individual MQTL estimates and using the average estimate for these MQTLs, are compared in Table 5. This table shows that the response achieved from using the average effect was less than that from using individual effects, so there was no advantage from using the average value.

The genetic responses and linkage disequilibrium generated by crossing replicate selection lines from the same base population after ten generations of selection, are examined in Tables 6 and 7. With an effective population size of about 60, and selection of the top MQTL, genetic drift should be small. New linkage disequilibrium generated by crossing the lines was indeed very small and

Table 6. Genetic response and SD (in genetic SD) and linkage disequilibrium from MAS selection in two selection lines crossed at the 10th generation and the new line (1 × 2) selected for another ten generations. The QTL effects are normally distributed, the MQTL effects were estimated by mixed-model methods. The top 20 estimates were used

Generation	Line 1	Line 2	Generation	Line 1 × 2
	Genetic response			
1	0.00±0.08	0.00±0.12	11	3.12±0.14
2	1.06±0.14	1.08±0.16	12	3.23±0.12
3	1.65±0.17	1.76±0.19	13	3.28±0.15
4	2.11±0.22	2.16±0.23	14	3.29±0.13
5	2.41±0.24	2.44±0.26	15	3.30±0.13
6	2.60±0.27	2.62±0.27	16	3.30±0.15
7	2.79±0.27	2.86±0.28	17	3.31±0.14
8	2.91±0.28	3.06±0.30	18	3.32±0.13
9	2.98±0.32	3.10±0.33	19	3.32±0.15
10	3.08±0.32	3.16±0.34	20	3.33±0.14
20	3.39±0.28	3.42±0.29		
	Linkage disequilibrium			
1	0.141±0.013	0.138±0.012	11	0.035±0.005
2	0.124±0.012	0.124±0.010	12	0.022±0.004
3	0.104±0.011	0.102±0.011	13	0.017±0.003
4	0.084±0.010	0.086±0.010	14	0.017±0.003
5	0.065±0.012	0.065±0.011	15	0.016±0.004
6	0.048±0.011	0.049±0.010	16	0.015±0.004
7	0.042±0.011	0.043±0.010	17	0.016±0.004
8	0.033±0.012	0.036±0.010	18	0.017±0.003
9	0.032±0.010	0.034±0.009	19	0.017±0.003
10	0.031±0.008	0.032±0.008	20	0.015±0.002

Estimation population size 1,000, selection population size 1,000. F_2 base population

further selection responses after re-estimating the MQTL effects and selecting the crossbred population were also quite small and less than if selection had been continued in the original lines. These results show, as mentioned in Zhang and Smith (1992), that crossing of selected lines and regeneration of linkage disequilibrium (Lande and Thompson 1990) is unlikely to be a useful method of achieving further genetic response. In addition, with a fixed testing capacity, selection response in two sublines will be less than in one line, due to smaller selection differentials and greater inbreeding. Moreover, differential responses in the two lines (Nicholas 1980) cannot be exploited because the two lines must be crossed to generate the cross line and new linkage disequilibrium. With combined selection, on BLUP of MQTL effects and phenotype, responses (Table 7) in the first ten generations were larger than for selection on BLUP of phenotype alone (4.11 genetic standard deviations). Some further response was achieved in the second ten generations of selection by both methods, reaching 5.61 ± 0.16 with combined selection compared at generation 20 compared with 5.46 ± 0.14 by selection on BLUP of phenotype alone, so the advantage was limited.

Table 7. Genetic response and SD (in genetic SD) and linkage disequilibrium from combined selection in two selection lines, crossed at the 10th generation and the new line (1 × 2) selected for another ten generations. The QTL effects are normally distributed and combined selection, on mixed-model estimates of MQTL effects and on phenotype, was practiced

Generation	Line 1	Line 2	Generation	Line 1 × 2
	Genetic response			
1	0.00 ± 0.08	0.00 ± 0.11	11	4.28 ± 0.11
2	1.20 ± 0.21	1.24 ± 0.20	12	4.47 ± 0.12
3	2.00 ± 0.23	2.09 ± 0.23	13	4.63 ± 0.13
4	2.58 ± 0.25	2.64 ± 0.25	14	4.78 ± 0.13
5	3.01 ± 0.29	3.07 ± 0.28	15	4.92 ± 0.14
6	3.37 ± 0.26	3.42 ± 0.25	16	5.06 ± 0.14
7	3.66 ± 0.24	3.75 ± 0.24	17	5.19 ± 0.14
8	3.86 ± 0.24	3.93 ± 0.24	18	5.30 ± 0.14
9	4.04 ± 0.25	4.12 ± 0.26	19	5.42 ± 0.15
10	4.21 ± 0.26	4.30 ± 0.27	20	5.51 ± 0.14
20	5.58 ± 0.22	5.63 ± 0.23		
	Linkage disequilibrium			
1	0.064 ± 0.003	0.060 ± 0.003	11	0.021 ± 0.001
2	0.058 ± 0.004	0.056 ± 0.004	12	0.014 ± 0.001
3	0.053 ± 0.004	0.051 ± 0.005	13	0.013 ± 0.001
4	0.046 ± 0.004	0.045 ± 0.005	14	0.014 ± 0.001
5	0.039 ± 0.005	0.038 ± 0.005	15	0.012 ± 0.001
6	0.032 ± 0.005	0.031 ± 0.006	16	0.012 ± 0.001
7	0.026 ± 0.005	0.027 ± 0.006	17	0.011 ± 0.001
8	0.023 ± 0.006	0.024 ± 0.006	18	0.011 ± 0.001
9	0.021 ± 0.006	0.022 ± 0.006	19	0.011 ± 0.001
10	0.020 ± 0.005	0.021 ± 0.006	20	0.010 ± 0.001

Estimation population size 1,000, selection population size 1,000. F_{10} base population

Discussion

The method employed to generate linkage disequilibrium between markers and QTL was to cross inbred lines and use the F_2 and F_{10} populations as the base populations for identifying MQTL associations and for selection, (Zhang and Smith 1992). In practice, in out-breeding selection lines, there would also be statistical linkage disequilibrium (gametic-phase disequilibrium) due to previous selection (Bulmer 1971), which would cause spurious linkage associations. This would reduce the efficiency of MAS using estimated MQTL effects. On the other hand, genetic map distances were used in the simulation, assuming no interference in recombination among adjacent loci. The actual recombination rate with interference would be less than that simulated, which would slightly enhance MAS.

The results presented here, as for any simulation, depend on the model and parameters used, and are indicative rather than general. However, the responses achieved were reasonable and effects of the various factors on the responses can be understood. Dealing with diallelic markers and QTLs at initial frequencies of 0.5 ensured considerable heterozygosity, but heterozygosity may occur in practice with the multiple allelic markers now being detected. With 100 markers and 100 QTLs, average distance from a QTL to its nearest marker was 0.15 Morgans. If more markers were available, average distance would be less and linkage disequilibrium would be greater. Alternatively, having established a MQTL association, it may be possible by pulse-field gel electrophoresis (Old and Primrose 1990) to identity markers closer to the QTL with more linkage disequilibrium. Comparison of responses were made for a single trait and for selection on individuals with their own performance (phenotypic) record. For some traits, such as sex-limited traits or traits measured after puberty or after slaughter, marker-assisted selection may have additional advantages. Selection here has dealt with a single trait, whereas economic merit usually involves a number of traits. Some MQTL effects may be favourable for some traits and unfavourable for others, which would reduce the value of MAS in selecting for overall economic merit. Other MQTL effects may be appreciable for some traits and have no effect on others, but nevertheless would all involve sampling variances of estimates and so add noise to the system. MQTL associations will thus have to be estimated for all of the traits, and all the information combined optimally in selection. These results, and those in Zhang and Smith (1992), show limitations to MAS using linkage disequilibrium until close linkages of markers and QTLs are available.

References

Bulmer MG (1971) The effect of selection on genetic variability. Am Nat 105:201–211

Kennedy BW, Quinton M, van Arendonk JAM (1992) Estimates of effects of single genes on quantitative traits. J Anim Sci 70:2000–2012

Lande R, Thompson R (1990) Efficiency of marker-assisted selection in the improvement of quantitative traits. Genetics 124:743–756

Mackay TFC, Lyman RF, Jackson MS (1992) Effects of P-element insertions on quantitative traits in *Drosophila melanogaster*. Genetics 130:315–332

Nicholas FW (1980) Size of population required for artificial selection. Genet Res 35:85–105

Old RW, Primrose SB (1990) Principles of gene manipulation. 4th edn. Blackwell, Oxford, England

Smith C (1967) Improvement of metric traits through specific genetic loci. Anim Prod 9:349–358

Smith C, Simpson SP (1986) The use of polymorphisms in livestock improvement. J Anim Breed Genet 103:205–217

Soller M (1978) The use of loci associated with quantitative effects in dairy cattle improvement. Anim Prod 27:133–139

Zhang W, Smith C (1992) Computer simulation of marker-assisted selection utilising linkage disequilibrium. Theor Appl Genet 83:813–820