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Evaluation of marker-assisted selection through computer simulation

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Abstract Computer simulation was used to evaluate responses to marker-assisted selection (MAS) and to compare MAS responses with those typical of phenotypic recurrent selection (PRS) in an allogamous annual crop species such as maize (*Zea mays* L.). Relative to PRS, MAS produced rapid responses early in the selection process; however, the rate of these responses diminished greatly within three to five cycles. The gains from MAS ranged from 44.7 to 99.5% of the maximum potential, depending on the genetic model considered. Linkage distance between markers and quantitative trait loci (QTLs) was the factor which most limited the responses from MAS. When averaged across all models considered, flanking QTLs within two marker loci produced 38% more gain than did selection based on single markers if markers were loosely-linked to a QTL (20% recombination). Flanking markers were much less advantageous when markers were closely-linked to a QTL (5% recombination), producing an advantage over single markers of only 11%. Markers were most effective in fully exploiting the genetic potential when fewer QTLs controlled the trait. Large QTL numbers exacerbated the problem of marker-QTL recombination by requiring more generations for fixation. In annual crop species, MAS may offer a primary advantage of enabling two selection cycles per year versus the 2 years per cycle required by most PRS schemes for the evaluation of testcross progeny. MAS thus appears to allow very rapid gains for the first 2–3 years of recurrent selection, after which time conventional methods might replace MAS to achieve further responses.

Key words Recurrent selection · Restriction fragment length polymorphisms · Marker-assisted selection · Computer simulation

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Introduction

Restriction fragment length polymorphisms (RFLPs) and isozymes have provided a rapid means of producing genetic maps of densely-spaced marker loci in numerous crop species (Ellis 1986; Helentjaris et al. 1986; Landry et al. 1987; Burr et al. 1988). Applications of RFLPs for basic genetic investigations and the mapping of linkage groups have been widespread during the past 5 years. Numerous applications of RFLPs to plant breeding also have been proposed in the literature. Beckmann and Soller (1983) include varietal identification, mapping of quantitative trait loci (QTLs), screening genetic resource strains for useful quantitative trait alleles, and marker-assisted introgression from the resource strains, as possible uses of RFLPs. General methodologies for mapping QTLs are discussed by Lander and Botstein (1989), Simpson (1989) and Knapp and Bridges (1990).

Molecular markers have been used successfully to detect QTLs for economically-important traits in several crop species (Nienhuis et al. 1987; Paterson et al. 1988; Keim et al. 1990). Edwards et al. (1987) and Stuber et al. (1987), using isozyme loci in maize, found that from less than 1% to more than 11% of the variation for yield and 24 yield-related traits was accounted for by genetic factors associated with individual marker loci in two F_2 populations. Stuber and Edwards (1986) showed that marker-facilitated genotypic selection was effective for

manipulating quantitatively-inherited traits in the two corn populations they studied. They noted that one generation of genotypic selection for yield, ear height, and ear number based on marker loci representing no more than 40% of the genome was as effective as one generation of mass selection. They concluded that increasing the number of markers to more thoroughly cover the genome should increase the effectiveness of marker-facilitated selection.

While most researchers involved in QTL mapping are optimistic about the usefulness of marker-assisted selection, little research has been done to evaluate its effectiveness. Lande and Thompson (1990) reported a theoretical evaluation of the merit of a single cycle of marker-based selection for a quantitative trait relative to phenotypic selection procedures. They found marker-based selection to offer potential for increases in gain under the conditions examined. Recently, Zhang and Smith (1992) used computer simulation to compare responses from marker-based selection (MAS) versus selection based on phenotypes of individuals and their relatives. Phenotypic selection was based on a best linear unbiased prediction model (BLUP), which is commonly used in animal breeding. They found that MAS, based only on the 20% of the QTLs with the largest detected effects, was rarely as effective as BLUP phenotypic selection. However, if the the QTL effects followed a Gamma distribution (with the top 20% of QTLs accounting for most of the genetic variance), MAS was more effective than BLUP provided MAS was initiated in early generations when linkage disequilibrium was greatest.

Computer simulation allows evaluation of a number of random genetic processes (Scheinberg 1968) and has been used to model genetic systems when testing genetic theory (Wells et al. 1987; Choo and Kannenberg 1988). We have used computer simulation to make comparisons of gains expected from marker-assisted selection (MAS) and phenotypic recurrent selection (PRS). The objectives were to examine the effects of the number of loci involved in trait inheritance, linkage distance between the markers and QTLs, and the use of single versus flanking markers in determining the usefulness of MAS for plant breeders.

Materials and methods

Observations were simulated for numerous genetic models to estimate response to MAS. Genetic parameters comprised a factorial of three variables: the crossover frequency between a trait locus and an adjacent marker locus (CO = 5, 10, 20 recombination units), the number of genes affecting the trait (G = 10, 15, 20, 25), and popultion size (N = 50, 100, 300 and 500). Computer programs were developed using the language PASCAL to simulate: (1) MAS using a single marker for each QTL, (2) MAS using flanking markers for each QTL, and (3) PRS. The genetic parameters were integrated as variables into programs which simulated responses to selection procedures. For each parameter combination, MAS was continued until all marker loci initially linked to favorable QTLs were fixed in the selected population. Genetic models used in the simulation of PRS consisted of a factorial of: the initial magnitude of narrow-sense heritability ($h^2 = 0.10$, 0.20, or 0.40), the number of genes (G = 10, 15, 20, or 25), and population size (N = 300, 500, or 850). Fifteen cycles of selection were completed for all PRS models. Ten percent of the population was selected in each cycle for each simulation model. Ten replicates of the entire selection process were run for each model to establish the response expectations. This number of replicates was as effective as were larger numbers examined in providing smooth average response curves across cycles. All subsequently presented data are averages across ten replicates of each simulation model.

Individual locus effects (selected parameter values) were allowed to have a range of magnitudes but, for ease of comparison between models, they were selected such that the sum of the values was 200 units in each of the models. The individual locus effects for models with 10, 15, 20, and 25 QTLs are listed in Table 1. No presumptions are made as to which distributional models best describe the "true" distributions of QTL effects in nature. Instead, the selected parameter values include some effects of large magnitude and many with smaller effects, modelled after results of a number of empirical investigations into QTLs in maize (Edwards et al. 1987, 1992; Abler et al. 1991). The genetic models in these programs employed additive gene action and random mating among selected individuals and did not consider epistasis.

Linkage groups in the MAS programs consisted of a marker(s) and a QTL. There was no linkage between QTLs. Therefore, any crossovers generated during the simulated selection served to degenerate the marker-QTL disequilibrium upon which MAS depends, but did not affect linkage between trait loci. Four gametic linkage types (hereafter designated as haplotypes) result between alternative QTL alleles (Q or q) and alleles at a single marker locus (M or m): (1, M-Q; 2, m-q; 3, M-q; and 4, m-Q) and eight haplotypes result when flanking markers are used (1, M-Q-M; 2, M-q-m; 3, m-Q-M; 4, M-Q-m; 5, m-q-M; 6, M-q-M; 7, m-Q-m; and 8, m-q-m). All initial populations are assumed to originate from a cross between two inbred lines; thus, the F_1 is heterozygous for the two parental haplotypes (M-Q and m-q or types M-Q-M and m-q-m for single markers or flanking markers, respectively). The other haplotypes result from crossovers between markers and QTLs.

In the MAS simulations which employed a single, linked marker for each QTL, individuals were generated at the beginning of each cycle by randomly assigning to them the four haplotypes at the frequencies they were contributed by the selected individuals from the previous generation. This was done, for each marker locus, as follows. First, the frequencies of M-Q/m-q and M-q/m-Q heterozygotes in the selected parental population were determined. These were then multiplied by the marker-QTL crossover frequency to determine the change in the number of each haplotype which would be passed from the progenitor to the progeny population. The adjusted frequencies were then multiplied by the population size to calculate the number of each haplotype to be assigned at random to the individuals (dependent observations) in the next generation. Thus, the genotypes of individuals were determined by independent random assignment of two haplotypes for each of the linkage groups (marker-QTL groups) in the genetic model under simulation.

Table 1 Magnitudes of effects of hypothetical genes employed in the marker-assisted selection models with QTL numbers of 10–25 genes affecting the trait undergoing selection

Number of QTLs in the model	Individual locus effects
10	4, 10, 15, 18, 20, 22, 25, 25, 29, 32
15	3, 6, 6, 8, 9, 10, 12, 12, 13, 14, 15, 19, 20, 23, 30
20	2, 3, 5, 6, 7, 8, 8, 9, 9, 10, 10, 10, 11, 11, 12, 13, 13, 15, 18, 20
25	1, 2, 2, 3, 4, 4, 5, 6, 6, 7, 7, 8, 8,8, 8, 9, 9, 10, 10, 11, 12, 13, 14,15, 18

The apparent genotypic values of individuals were obtained by summing over marker loci the coded genotypic weights (the trait parameter values as indicated in Table 1) for the marker genotypes of each individual (M/M = + genotypic weight; M/m = 0; and m/m = − genotypic weight). The top 10% of the individuals in each generation were then selected, based only on this "net" marker score. The frequencies of each haplotype at each linkage group among the selected individuals were used to start the process of recombination and the procedure of generating the population for the next cycle of selection. The true genotypic values of individuals in the new population were determined by summing the coded genotypic weights for each individual, based on the genotype at each QTL and irrespective of the linked marker genotype. The population averages were then used to assess gain from each cycle of selection.

Simulations employing flanking markers for MAS were conducted as described above with two exceptions. First, there are eight haplotypes and two crossover frequencies for each linkage group. Second, linkage groups having a haplotype resulting from a single crossover between flanking markers (M-q-m, m-Q-M, M-Q-m or m-q-M) were given a value of zero when computing the individuals selection criterion (marker score). M-M/M-M and m-m/m-m individuals were assigned values like those for the corresponding M/M and m/m genotypes, respectively, for MAS with single linked markers.

The PRS program generates individuals at the beginning of each cycle by assigning the two QTL allele types for each locus, at their respective frequencies, to individuals at random. Again, this was done for all QTLs in the model and the frequencies were determined from the selected individuals. Genotypic values for each individual were calculated, based on the genotype and weight for each locus, by summation over loci. Environmental variance was simulated by randomly choosing error values from a normal distribution with a mean of zero and variance set to give a desired heritability using the function: $\sigma_e = ((1.0 - h^2)/h^2)^{1/2} * \sigma_g$, where σ_e is the standard deviation which was used to generate a distribution from which environmental error terms were sampled, h^2 is the desired heritability, and σ_g is the standard deviation of the genotypic values which was calculated from the array of random genotypes generated in the simulation. A randomly-selected error value from the specified distribution was added to the genotypic value of each individual to produce a phenotype consistent with the heritability being simulated. The environmental variance was set in the first generation and remained constant thereafter: thus heritability decreased as genetic variance was exhausted through selection. The 10% of the individuals having the greatest phenotypic values were selected in each cycle, and allelic frequencies in the selected group were determined. Another cycle of selection was then initiated by randomly assorting alleles, at the newly-determined frequencies, to generate a progeny population.

Results and discussion

Single-marker-assisted selection

Population size did not affect the rate of gain from selection. Smaller population sizes exhibited a greater variance in the rate of response across replicates of the selection process. However, average responses for the various population sizes were equal, due to the use of a constant selection intensity of 10%.

As expected, differing gene numbers did influence the rate of response to marker-based selection. Selection plateaus were reached, on average, in three selection cycles with ten-gene models and in six cycles with 25-gene models. These plateaus occurred when all marker loci were fixed in the populations. Figure 1 illustrates the response to selection for four genetic models consisting of a factorial combination of two gene numbers (10 and 25) and two linkage distances (5 and 20 recombination units). Selection in models with ten genes resulted in greater selection responses than were achieved in models with 25 genes. Ten-gene models produced gains which were 3.9 (CO = 5%) and 5.6 (CO = 20%) percent of the genetic potential greater than did 25-gene models. The higher selection responses seen when fewer genes were involved resulted from less recombination between markers and the QTLs during the entire selection process. The reduced recombination occurred as a result of more rapid fixation of desirable linkage groups.

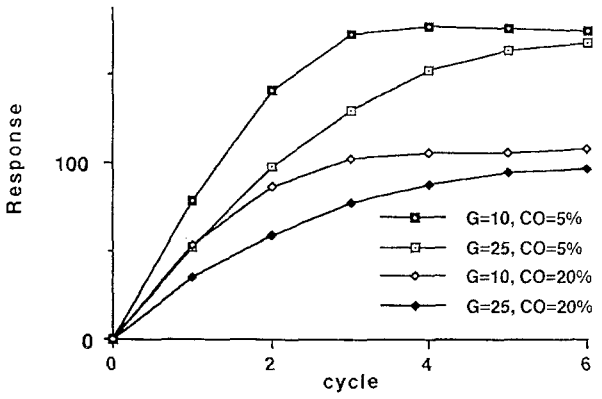
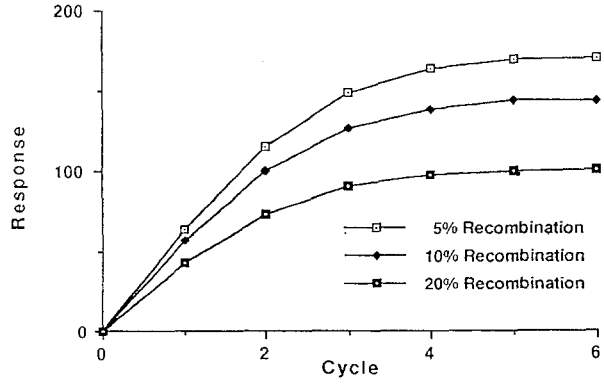


Fig. 1 Responses to selection on marker score with two gene numbers (10 and 25 QTLs) and two crossover frequencies (5 and 20%) between marker loci and single adjacent markers averaged across population size (50–500 entries)

Linkage distance between markers and QTLs was the most important factor affecting the amount of gain achieved using MAS in these simulations. Figure 2 illustrates the selection response curves for three models, each with 25 genes. The selection plateaus for the models with 5, 10, or 20% recombination between QTLs and markers, averaged over the four population sizes, were 168, 139.3, and 97.7 units respectively. These responses indicate that increase in the selection plateau of 20.8 and 14.3% of the total genetic effect was achieved when

Fig. 2 Effect of recombination frequency between single markers and adjacent QTLs (5, 10 or 20%) on selection responses averaged over population sizes (50–500 entries)



marker-QTL recombination was decreased from 20 to 10% and from 10 to 5%, respectively. Changes in the number of QTLs under selection had little effect on these relationships when selecting with single markers (Table 2). When averaged over gene number and population size, selection on markers 5, 10, and 20 recombination units from QTLs resulted in selection gains of 85.5, 71.8, and 50.8% respectively, of the maximum genetic potential. These results demonstrate the need for tight marker-QTL linkages in order to achieve appreciable response from MAS with single markers.

Flanking-marker-assisted selection

The effects of population size and gene number on response to selection, when using flanking marker genotypes as a selection criterion, were very similar to the effects seen when single markers were used. Selection response was similar for all population sizes at a given linkage distance. The effect of gene number is illustrated in Fig. 3. Once again, at any given linkage distance, models with fewer genes affecting the trait had greater responses at the selection plateau. However, this trend was less pronounced than that observed when using single markers, particularly with tight marker-QTL linkages. The response plateau for a ten-gene model was only 2.9% of the total genetic effect higher than that of a 25-gene model when flanking markers were five recombination units from the QTL and 16.2% greater with 20% marker-QTL recombination. Thus, flanking markers allow selection to exploit greater numbers of QTLs due to a greater ability to preserve linkage disequilibria within marker-flanked regions.

As with selection based on single markers, the effect of linkage distance between markers and QTLs had the largest impact on the selection response. For example, the selection response curves for models with 25 genes affecting a trait and marker-QTL linkage distances set at 5, 10, or 20% recombination are shown in Fig. 4. The increases in efficiency resulting from reduced marker-QTL linkage distances were much smaller for flanking marker selection than for single marker selection (Table 2). This result was due to a reduction in the number of recombinant gametes among selected progeny when flanking markers were employed in selection.

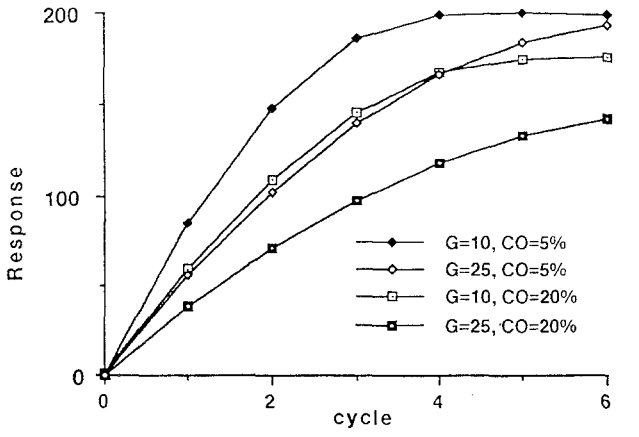


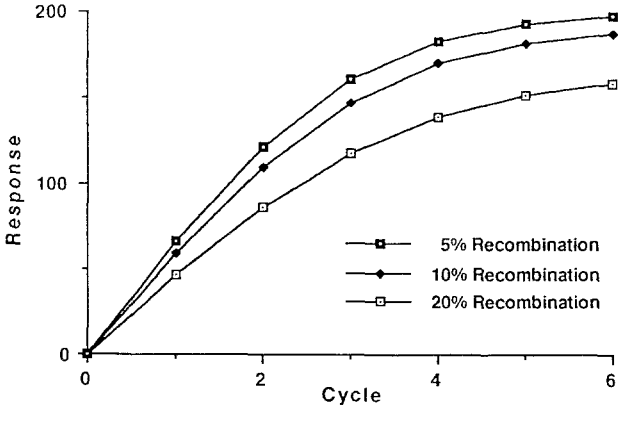
Fig. 3 Responses to selection using flanking markers on a factorial combination of two gene numbers (10 and 25 QTLs) and two recombination frequencies (5 and 20%) between each of two flanking markers and the intervening QTLs

Table 2 Responses at the selection plateau for selection on single-marker-linked QTLs and marker-flanked QTLs. Models consider varying QTL numbers (10–25) controlling the hypothetical trait with varying marker-QTL linkage intensities (5–20% recombination between markers and QTLs)

QTL #	% Recomb.[a]	Gain at plateau[b]		Sgl/flk[c]
		Single	Flanking	
10	20	54.5	87.9	62.0
	10	74.4	96.1	77.4
	5	87.8	99.6	88.1
15	20	50.2	81.6	61.5
	10	72.0	95.3	75.5
	5	86.9	99.4	87.4
20	20	49.8	76.0	65.5
	10	71.2	93.9	75.8
	5	83.8	98.7	84.9
25	20	48.8	71.3	68.4
	10	69.6	89.3	77.9
	5	84.0	96.7	86.8
Avg.[d]	20	50.8	79.2	64.1
	10	71.8	93.6	76.7
	5	85.5	98.6	87.0

[a] Percent recombination between each QTL and the marker(s) by which the QTL is manipulated in selection
[b] Percent of the maximum genetic potential realized at the selection plateau
[c] Response at selection plateau for single markers as a percent of the response for flanking markers
[d] Average responses across the gene numbers: 10–25

Fig. 4 Response to selection on flanking markers for 25 QTLs at 5, 10 or 20% recombination between each of two flanking markers and the intervening QTLs, averaged across population sizes of 50–500 entries per selection cycle



Overall, the use of flanking markers required a few more cycles of selection to fix all the loci because twice as many marker loci were involved in making selections as was the case with single markers. However, linkage disequilibrium was maintained longer (due to selection against recombinant haplotypes), resulting in a greater selection response for flanking MAS. As linkages between markers and QTLs became tighter, the advantage of flanking markers over single markers diminished. For example, the advantage of flanking markers over single markers for 25 genes with 5% recombination was only 12.7% of the total genetic effect, whereas at 20% recombination the advantage was 22.5% (Table 2). Economic considerations, as well as the density of markers available for use in a cross, will determine if single markers, flanking markers, or a combination should be used. Use of flanking markers in selection requires the expense characterizing twice as many marker loci as when using single markers. Therefore, single markers may be more cost effective when dense maps (and closer linkages, on average) are available. However, flanking markers may be preferred when markers are widely-spaced in the genome or on a chromosome region. Use of flanking markers in these situations will decrease the chance of losing the linkage disequilibrium between markers and distant QTLs. Obviously, initial analysis for the purpose of identifying putative QTLs may well benefit from use of flanking markers, even if it is decided that subsequent manipulation of identified QTLs is best done with single markers.

Comparison of phenotypic recurrent and marker-assisted selection

Comparison of selection responses attained through MAS with responses from PRS illustrate some of the genetic conditions necessary to justify the use of MAS. Figure 5 illustrates the selection responses from three single-marker-assisted selection models and three PRS models. The response curves from MAS are truncated at the cycle in which marker loci are fixed and whereupon no further gains are possible. All six models employed 25 QTLs. With MAS, the QTLs were 5, 10, or 20 recombination units from the markers and with PRS, responses are shown given heritabilities of 0.10, 0.20, and 0.40. Simulations were run to determine optimum population size and selection intensity to maximize the response and minimize the cost of MAS. A population size of 50 individuals and a selection intensity of 6% were determined to be optimum for the above stated genetic model. We estimated that approximately three times as many individuals could be handled with equal expense in the PRS program, thus we simulated responses with a population size of 150. Six percent selection was found to optimize the selection response with PRS, as well.

MAS with 5% recombination between markers and QTLs (CO = 5%) resulted in faster initial gain than did PRS under these genetic models. MAS with 10% recombination showed an advantage over PRS for traits with heritabilities at or below 20%. MAS had no advantage relative to PRS when recombination between markers and QTLs reached 20%. PRS response with a trait having a heritability of 0.20 surpassed responses from MAS under 20, 10, and 5% recombination between markers and QTLs in 1, 5, and 10 cycles, respectively. Responses to PRS for traits of low heritability ($h^2 = 0.10$) remained below responses from MAS under tight linkage (5% recombination) for more than 15 cycles, but surpassed MAS under loose linkages (10 and 20% recombination) in 2–12 cycles of selection.

The value of MAS for quantitative traits will depend on how much more efficient the procedure is than PRS, in terms of gain per year. Several additional assumptions are made here to lay a basis for comparison between methods. First, we assume that investigations to determine marker-QTL linkages will be estimated in S_3 progenies, thus the initiation of MAS will lag behind PRS by 1 year. Second, we assume that PRS requires 2 years per cycle (for selfing-testcross-evaluation-recombination) and MAS requires 1/2 year per cycle of selection. Since markers are unaffected by the environment,

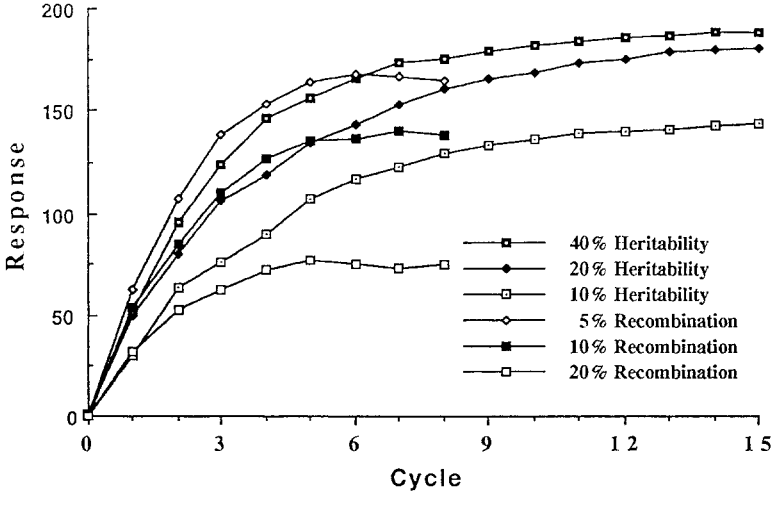


Fig. 5 Comparison between responses to selection on single, QTL-linked markers (MAS) and phenotypic recurrent selection (PRS). MAS models consider markers exhibiting 5, 10 or 20% recombination between the adjacent QTLs. PRS responses simulate 10, 20 and 40% heritability for the trait under selection. All models involve populations of 500 entries per selection cycle

MAS can be carried out in the greenhouse allowing completion of two cycles per year if plants can be genotyped before they reproduce.

Selection responses under all of these assumptions, for six genetic models involving 25 QTLs, are illustrated in Fig. 6. The initial response to MAS was very rapid relative to PRS in all models. Despite the rapid response from MAS, its advantage over PRS was not maintained in the case of loose marker-QTL linkages (20% recombination). Even with a low trait heritability ($h^2 = 0.10$), the PRS response exceeded the MAS response in just over 2 years after the MAS response plateau.

With tighter marker-QTL linkages, MAS was notably superior to PRS. Although MAS responses were markedly affected by the genetic distance between markers and QTLs, all three MAS models reached a selection plateau at about cycle five (in 3.5 years). PRS with a trait of $h^2 = 0.40$ required about 8 years (an excess of 4 years) to exceed the performance level of the MAS plateau with 10% recombination, and 12 years (an excess of 8 years) to exceed the MAS plateau with 5% recombination. The major benefit of MAS was that of greatly accelerating the selection response in these models where two cycles of MAS were conducted per year.

With traits of heritability lower than 0.40, MAS (even with loose marker-QTL linkages) provided a substantially higher population performance at the time of plateau than did PRS at the same point in time. In these cases MAS might be employed for the initial four or five cycles, followed by PRS as the MAS response diminishes. An alterenative would be to choose an individual from the MAS population and use it in an improvement cross with an unrelated parental line as soon as the MAS response begins to decline. This new population could again be evaluated with genetic markers and subjected to MAS, enabling "rapid" cycles of MAS-based selection to exploit the phase of maximum genetic disequilibrium.

The results from this study are consistent with those of Zhang and Smith (1992) in indicating the overwhelming importance of close linkages between markers and the QTLs they identify in order for MAS to be competitive with PRS. This work further examines the usefulness of flanking markers in selection as an alternative to dependence upon a highly-saturated marker map to assure close linkages between single markers and QTLs. The two studies are also consistent in demonstrating rapid decreases in response from MAS over generations, as the linkage disequilibrium between markers and QTLs is exhausted.

Unlike the simulations of Zhang and Smith (1992), all QTLs were "exposed" to MAS selection in these simulations. This makes it difficult to compare results with those of their investigation, wherein only 20% of the QTLs were exposed to marker-based selection pressure. However, as in the current simulation, Zhang and Smith also demonstrated MAS responses exceeding those of their "check" selection method (BLUP) under some circumstances. They found MAS to be most effective in cases where the distribution of gene effects was such that much of the total genetic variance was generated by the top 20% of the QTLs and, therefore, subjected to MAS in their simulations.

The QTL effects simulated herein are based on results of empirical investigations in maize which suggest that numerous effects of large magnitude will segregate even in crosses among elite lines (Abler et al. 1991). This differs from Zhang and Smith's presumption that "if QTLs of moderate to large effects exist, past selection would have used them, and they would be at high frequency or fixed". Further information on the distribution of QTL magnitudes is required to corroborate either assumption.

The above scenario represents an effort to compare expected gains under the constraint of equal cost per cycle of selection using current RFLP technologies and common maize breeding procedures. Many other scenarios are possible and perhaps more relevant to other crops and breeding strategies. Considerations such as time needed to determine marker-QTL associations and time required per selection cycle are certain to vary.

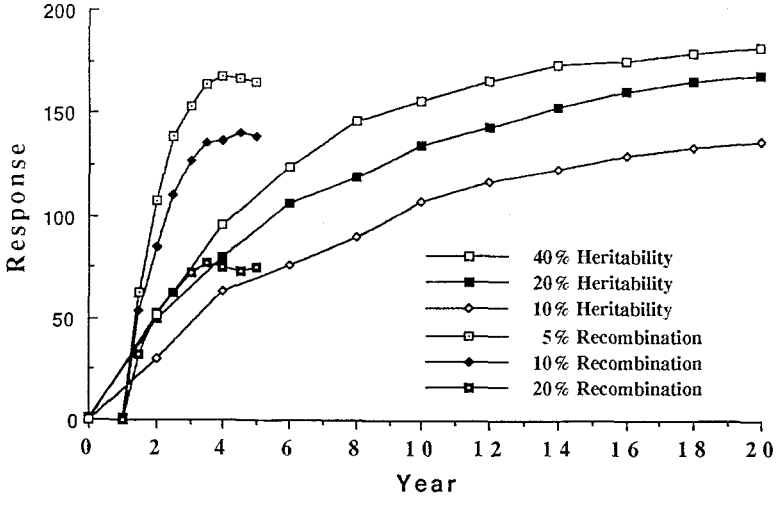


Fig. 6 Comparisons between MAS and PRS under assumptions designed to simulate comparable input costs per cycle. MAS models involve 50 entries per selection cycle, a selection intensity of 6%, and recombination frequencies of 5, 10 or 20% between single marker loci and adjacent QTLs. PRS models involve population sizes of 150 entries per cycle, a selection intensity of 6%, and heritabilities of 10, 20 or 40% for the trait under selection. All models involve 25 effective QTLs and PRS is assumed to initiate 1 year earlier but to require 2 years per selection cycle versus MAS at 6 months per cycle

These simulations have considered relative efficiencies of MAS versus PRS for trait manipulation assuming knowledge of the genetic control of the trait. In practice, the QTL must be identified experimentally. Errors of omission and misestimation will occur in this process as a function of the degree of coverage of the genome with markers, the experimental approach, the choice of Type I and Type II error rates for hypotheses, and unforeseen complexities of gene action which underlie quantitative trait inheritance.

Further investigations are required to establish optimum procedures for QTL estimation and to examine the effects of estimation errors on MAS responses. The results above illustrate some of the potentials and limitations of indirect selection with linked marker loci which will be superimposed upon limitations of the QTL-estimation process. Computer simulation will continue to be a useful tool for addressing many of the issues in MAS which require further investigation as the technology develops. Since there are many parameters invoked in computer simulation of selection responses about we have limited knowledge (for example, the number of QTLs, the distribution of their magnitudes of effect, their genomic organization, the degree to which they interact with one another, etc.), data is needed from empirical efforts to employ markers in quantitative trait selection.

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