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Genomic selection for marker-assisted improvement in line crosses

N. Piyasatian · R. L. Fernando · J. C. M. Dekkers

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Abstract Efficiency of genomic selection with low-cost genotyping in a composite line from a cross between inbred lines was evaluated for a trait with heritability 0.10 or 0.25 using a low-density marker map. With genomic selection, selection was on the sum of estimates of effects of all marker intervals across the genome, fitted either as fixed (fixed GS) or random (random GS) effects. Reponses to selection over 10 generations, starting from the F_2, were compared with standard BLUP selection. Estimates of variance for each interval were assumed independent and equal. Both GS strategies outperformed BLUP selection, especially in initial generations. Random GS outperformed fixed GS in early generations and performed slightly better than fixed GS in later generations. Random GS gave higher genetic gain when the number of marker intervals was greater (180 or 10 cM intervals), whereas fixed GS gave higher genetic gain when the number of marker intervals was low (90 or 20 cM). Including interactions between generation and marker scores in the model resulted in lower genetic gains than models without interactions. When phenotypes were available only in the F_2 for GS, treating marker scores as fixed effects led to considerably lower genetic gain than random GS. Benefits of GS over standard BLUP were lower with high heritability. Genomic selection resulted in greater response than MAS based on only significant marker intervals (standard MAS) by increasing the frequency of QTL with both large and small effects. The efficiency of genomic selection over standard MAS depends on stringency of the threshold used for QTL detection. In conclusion, genomic selection can be effective in composite lines using a sparse marker map.

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N. Piyasatian
Department of Animal Production Technology,
King Mongkut's Institute of Technology Ladkrabang,
Bangkok 10520, Thailand

R. L. Fernando · J. C. M. Dekkers (✉)
Department of Animal Science and Center for Integrated Animal Genomics, Iowa State University, Ames, IA 50011, USA
e-mail: jdekkers@iastate.edu

Introduction

Selection on phenotype or on estimates of breeding values derived from phenotype has resulted in significant genetic improvement in many economically important traits in crops and livestock (Dekkers and Hospital 2002). Use of information on molecular markers associated with QTL for the trait through marker-assisted selection (MAS) can, however, increase rates of genetic improvement because marker information allows for an increase in selection accuracy, a reduction of generation intervals, or an increase in selection intensity (Soller and Beckmann 1983).

The standard strategy for MAS involves a two-stage approach (e.g. Lande and Thompson 1990): (1) conduct a genome scan to identify the most significant markers or QTL and estimates of their effects on phenotype, and (2) include those markers or QTL in genetic evaluation and MAS. A genome scan is, however, subject to false positives and negatives and estimates of the most significant markers or QTL tend to be biased (Beavis 1994, 1998) depending on the distribution of QTL effects, the power of the mapping design, and the stringency of the significance threshold used (Bost et al. 2001; Xu 2003a), and has been confirmed by experimentation (Melchinger et al. 1998). The impact of these factors on efficiency of MAS was

evaluated by Hospital et al. (1997), Moreau et al. (1998), Spelman and Garrick (1998), and Hayes and Goddard (2003). Several strategies have been investigated to ameliorate the impact of false negatives, false positives, and overestimation of effects on response to MAS, including re-estimation of effects in an independent data set (Lande and Thompson 1990; Zhang and Smith 1992), cross-validation (Whittaker et al. 1997), ridge regression (Whittaker et al. 2000), or mixed model and Bayesian approaches (Gianola et al. 2003).

All approaches just described involve selection of markers or QTL for inclusion in MAS. Meuwissen et al. (2001) suggested a one-step approach for implementation of MAS by using all markers for MAS, skipping selection of markers for inclusion in the model for marker-assisted genetic evaluation. To deal with the number of markers being large or even larger than the number of phenotypic observations, which would result in overparameterization and problems from colinearity when markers are fitted as fixed effects, they proposed fitting marker haplotypes for each region across the genome as independent random effects and used mixed model and Bayesian approaches for prediction of effects associated with each haplotype. Resulting estimates of haplotype effects were then used to select individuals in future generations using marker information alone, by selecting on estimates of breeding values derived by summing estimates of effects for each haplotype carried by the individual across the genome. They applied their approach, which they termed genomic selection (GS) to simulated populations representing outbred livestock populations with high-density marker genotype data and found correlations between true and estimated breeding values derived from marker data to be substantial, ranging from 0.73 to 0.85. Subsequent research has extended these results, but fitting individual marker genotypes rather than marker haplotypes (Solberg et al. 2006). Similar models fitting genotypes for all markers were used by Xu (2003b) for QTL mapping in line crosses.

Application of genomic selection to outbred populations, as in Meuwissen et al. (2001), requires large numbers (thousands) of markers because linkage disequilibrium (LD) extends over only short distances (Dekkers and Hospital 2002). Although costs of genotyping have reduced significantly, this may still be prohibitive for routine application. However, because of the much more extensive LD, this would not be the case for line crosses and genomic selection could be implemented with a limited number of markers. Thus, the objective of this study was to evaluate the efficiency of genomic selection in a cross between inbred lines. Several alternative models for estimation of marker effects were evaluated, including fitting markers as fixed or random, inclusion of polygenic effects, and inclusion of interactions between marker effects and generation. The impact of availability of phenotypic information in later generations and level of heritability was also considered.

Materials and methods

Genetic model and population structure simulated

A cross between two inbred lines (1 and 2) was simulated stochastically. The genome consisted of 18 chromosomes of 100 cM, with markers at an interval of 20 cM that were informative for line origin. A random 50% of the intervals was simulated to contain a QTL, with position within the interval assigned at random. Effects of the biallelic additive QTL were sampled from a standard normal distribution and rescaled relative to a random normally distributed environmental effect that was added, to result in an overall heritability of 0.1 and a phenotypic standard deviation of 14.14. Presence of the favorable QTL allele in parental line 1 or 2 was sampled with either equal (50/50) or unequal (75/25) probabilities. An alternative scenario with marker intervals of 10 cM was also simulated by adding an informative marker to the center of each 20 cM interval. Each generation, 5% of males and 25% of females were selected, mated at random, and produced 8 offspring per female, resulting in 400 progeny per generation. Individuals were genotyped for all (108 or 198) markers, starting in the F_2. Phenotypes were observed in each generation or only in the F_2.

Models for marker-assisted genetic evaluation for genomic selection

For each marker interval and each individual, a marker score (MS = 0–4) was computed as the number of alleles at the flanking markers that originated from line 1. If phenotypes were recorded beyond the F_2, each generation the data from that and all previous generations, starting from the F_2, were included in the analysis. The model used for MA-genetic evaluation in generation k was:

$$y_{jk} = \text{generation}_k + \sum_{i=1}^{N} \beta_i \text{MS}_{ijk} + u_{jk} + e_{jk},$$

where MS_{ijk} is the MS for interval i of individual j of generation k, β_i is the effect associated with interval i, u_{jk} is the residual polygenic breeding value of individual j of generation k; N is the number of marker intervals ($N = 90$ and 180 for marker intervals of 20 and 10 cM, respectively); e_{jk} is a random environmental deviation which was assumed to be normally distributed with mean zero and

variance $(1-h^2)\sigma_P^2$, where h^2 is the true heritability (total genetic variance/phenotypic variance) in the F_2 and σ_P^2 is the phenotypic variance in the F_2. Polygenic variances used for MA-genetic evaluation were varied to 0, 10, 25 and 50% of V_G, where $V_G = h^2\sigma_P^2$, i.e. the true genetic variance in the F_2. Use of a polygenic variance of zero, means that the model contained only marker scores. This was used when phenotypes were available in the F_2 only because only marker information would be available for candidates in later generations. The above model assumes the effect associated with an interval (β_i) was the same for each generation. A model in which a separate effect was fitted for each generation was also fitted for cases where phenotype was available each generation by replacing β_i by β_{ik}.

Effects associated with the marker score for each marker interval (β_i) were either treated as fixed (=fixed GS) or as independent normally distributed random variables (=random GS). For random GS, each marker interval was assumed to contribute equal variance V, which was equal to (see "Appendix" for derivation) $V = \frac{V_G}{(N\times\sum_{i=0}^{4} i^2 P_{MS=i})}$, where $P_{MS=i}$ is the probability that the markers score is equal to i (i = 0 to 4), which was derived ignoring double recombinants (see "Appendix").

Selection was on the sum of estimates of marker interval effects across the genome, plus the estimated polygenic effect (if fitted), resulting in the following selection criterion for individual j of generation k: $I_{jk} = \sum_{i=1}^{N} \hat{\beta}_i \mathrm{MS}_{ijk} + \hat{u}_{jk}$, where $\hat{\beta}_{ijk}$ are the estimated marker interval effects; and $\hat{u}_{jk}$ is from the estimated breeding value for residual polygenes.

Comparison of analysis models

Responses to genomic selection (GS) were compared with selection on standard estimated breeding values (EBV) derived from only phenotypic data using animal model BLUP (Henderson 1975). For GS, phenotypes were either available each generation, in which case $\hat{\beta}_i$ were re-estimated each generation using data from all generations, or available in the F_2 only. Results with a model that included a polygenic effect were also compared to those of two-stage MAS, in which MAS was on marker intervals that were found to be significant in the F_2, along with estimates of polygenic effects. This approach, which is described in Piyasatian et al. (2006) involved identification of significant marker intervals by backward selection, starting from a model that included all intervals, using a p-value threshold of 0.05 to remove intervals.

The efficiency of alternate models for genetic evaluation and methods of selection was evaluated based on cumulative response in each generation k (CR_k) and cumulative discount response in generation k ($CDR_k = (\sum_{i=1}^{k} \frac{1}{(1+r)^i} CR_i)$, where r is a discount rate and was set to 10% per generation), over ten generations (F_2–F_{11}). The CR and CDR were presented as percentage *superiority* over responses to phenotype BLUP selection. Rates of increase in frequencies of favorable QTL alleles were evaluated also. Results were based on 100 replicates.

Results

Responses to selection

Table 1 shows the impact of alternate selection strategies on CR and CDR with an equal distribution of favorable QTL alleles across parental lines and a marker interval of 20 cM. Extra responses to GS over selection on BLUP from phenotype were greatest for the first round of selection (F_3), giving up to 109% greater response, but decreased over generations (Table 1). Treating marker effects as random instead of fixed resulted in substantially greater responses in early generations but differences were not significant in later generations. Allowing for the effects of marker scores to change over generations by including interactions between marker scores and generation, reduced responses. When compared to MAS on significant markers (10 marker intervals) only (Piyasatian et al. 2006), random GS resulted in significantly higher CR in all generations.

Responses to GS tended to be affected by the level of residual polygenic variance used for genetic evaluation but differences were not large (Table 1). In general, setting polygenic variance equal to zero tended to result in greatest responses for random GS but was slightly inferior for fixed GS. From now on, results from genetic models for GS will be based on models without interaction and zero polygenic variance.

Table 2 shows the effects of size of marker intervals, distribution of favorable QTL effects across parental lines, and availability of phenotypes on CR and CDR. The size of marker intervals had a larger impact on CR and CDR for fixed GS than for random GS (Table 2), especially when phenotypes were available only in the F_2. Unlike random GS, fixed GS performed noticeably better for the larger marker intervals. In contrast, random GS gave higher CR and CDR when the size of the marker intervals was smaller. This was true when phenotypes were available in all generations and only in the F_2.

Table 1 Cumulative and cumulative discounted (10% interest) responses (CDR) from genomic selection for alternate levels of polygenic variances used for genetic evaluation, availability of phenotypic data and having interactions between marker effects and generations, for a trait with heritability 0.1, 20 cM marker intervals and equal distribution of favorable QTL effects across parental lines

Model of analysis		Phenotype availability for GS	Cumulative responses (% over BLUP)				CDR (% over BLUP)
Marker effects	Polygenic variance[a]		F_3	F_5	F_8	F_{11}	
Fixed	0	All	69	31	21	13	23.3
	10	All	69	30	20	14	23.0
	25	All	70	33	23	16	23.0
	50	All	70	34	25	19	27.7
Random	0	All	109	46	27	14	31.7
	10	All	98	34	22	14	26.3
	25	All	96	37	24	16	28.3
	50	All	94	37	24	17	28.7
Fixed with Interaction	0	All	69	16	5	0	9.1
	10	All	69	17	5	1	9.3
	25	All	70	19	6	1	11.0
	50	All	70	19	8	3	11.8
Random with Interaction	0	All	109	31	12	4	18.2
	10	All	98	23	10	4	15.2
	25	All	96	26	14	6	18.3
	50	All	94	24	14	8	18.2
MAS on significant QTL only[b]							
Fixed without Interaction	True polygenic variance	All	77	21	11	7	15.4
Fixed with Interaction	True polygenic variance	All	77	19	4	−2	8.9

Results from selection on true breeding values and from GS using only significant marker intervals (threshold = 0.05) are presented also for comparison

[a] Polygenic variance used as a % of total genetic variance in the F_2

[b] MAS using significant marker intervals in genetic evaluation (Piyasatian et al. 2006)

When phenotypes were available in all generations with 10 cM marker intervals, both fixed and random GS outperformed BLUP (Table 2). This was true for both the 50/50 and 75/25 probability cases. Although with the 75/25 probability case with phenotypes in all generations, all strategies gave higher *absolute* responses to selection than the 50/50 probability case, it tended to give lower CR and CDR (% over BLUP) than the 50/50 probability case.

With availability of phenotypes in the F_2 only, GS had greater *CR* than BLUP (which had phenotypes for all generations) up to the F_4 when treating marker effects as fixed, but up to the F_6 when treating them as random (Table 2). Fixed GS with phenotypic data only in the F_2 resulted in substantially lower CDR than BLUP, but random GS was just as good as BLUP. With 10 cM marker intervals, fixed and random GS for the 50/50 probability case outperformed BLUP until the F_3 and F_7, which were sooner (F_4) and later (F_6) than those with 20 cM (Tables 2). Furthermore, with 10 cM marker intervals, fixed and random GS for the 75/25 probability case outperformed BLUP until F_3 and F_8, respectively.

QTL frequencies

Tables 3 shows the effects of selection strategy, size of marker intervals with an equal distribution of favorable QTL effects across parental lines on average frequencies of favorable QTL alleles in the F_5 and F_{11}, as a function of magnitude of QTL effects. The 20 and 10 cM marker intervals resulted in 50% of QTL having zero effects, as expected (Table 3). For the 75/25 probability case, 75% of QTL had zero effects (results not shown). The average frequencies for the zero QTL effects represented average frequencies of alleles from line 1, rather than favorable average frequencies. Average frequencies of QTL with zero effects did not change for the 50/50 probability case (Table 3), but increased slightly over generations for the 75/25 probability case (results not shown) because of linkage drag. Average frequencies increased with magnitude of the QTL effect for all strategies. In the F_{11}, QTL with very large effects (2–3.5) were nearly fixed (frequency > 0.95) for all strategies and all scenarios, except for GS strategies that used only F_2 data with 20 cM marker

Table 2 Effect of the distribution of favorable QTL alleles and size of marker intervals on cumulative and cumulative discounted (10% interest) responses (CDR) from genomic selection for selection strategy, size of marker intervals, and availability of phenotypic data, for a trait with heritability 0.1 and equal (50/50) and unequal (75/25) distributions of favorable QTL effects across parental lines

% of favorable QTL alleles from line 1	Size of marker intervals (cM)	Models	Phenotype availability for GS	Cumulative responses (% over BLUP)				CDR (% over BLUP)
				F_3	F_5	F_8	F_{11}	
50	20	Fixed	All	69	31	21	13	23.3
		Fixed	F_2 only	69	−10	−28	−39	−22.4
		Random	All	109	46	27	14	31.7
		Random	F_2 only	109	20	−6	−20	1.7^{NS}
50	10	Fixed	All	42	18	16	16	17.5
		Fixed	F_2 only	42	−29	−48	−54	−40.7
		Random	All	112	49	30	23	36.7
		Random	F_2 only	112	25	−2	−13	7.3
75	20	Fixed	All	65	25	17	11	20.6
		Fixed	F_2 only	65	−13	−33	−41	−24.7
		Random	All	103	38	22	13	28.1
		Random	F_2 only	103	17	−7	−18	2.2
75	10	Fixed	All	39	13	16	14	15.3
		Fixed	F_2 only	39	−32	−48	−54	−41.3
		Random	All	106	43	32	23	36.4
		Random	F_2 only	106	22	3	−8	10.1

Results from selection on true breeding values are presented also for comparison

NS not significantly different from BLUP ($P > 0.05$)

intervals. Average QTL frequencies were greater with 10 than 20 cM intervals for all strategies, except for fixed GS with phenotypes available in only the F_2. The distribution of favorable QTL effects across parental lines had a limited impact on average QTL frequencies for all models (some results not shown).

With phenotypes available for all generations and the 50/50 probability case, fixed and random GS for 20 cM marker intervals resulted in very similar average frequencies in the F_{11} for all QTL classes, whereas random GS for 10 cM marker intervals resulted in higher average frequencies in the F_{11} for QTL with medium effects (0.5–1.5) than for fixed GS (Table 3). These results are consistent with the similar responses of random and fixed GS in the F_{11} (Table 2). For the 75/25 probability case, random GS resulted in slightly higher average frequencies than fixed GS in the F_{11} for small QTL (>0–0.5) with 20 cM marker intervals and for small to medium QTL (>0–1.5) with 10 cM marker intervals (results not shown).

Random GS with phenotypes in only the F_2 resulted in greater frequencies than BLUP for all QTL classes in the F_5 (Table 3). In contrast, with the 50/50 probability case, fixed GS with phenotypes in only the F_2 had lower frequencies than BLUP in the F_5 for larger QTL (effect >1) and similar frequencies for smaller QTL (effect <1) for 20 cM marker intervals, but had smaller frequencies than BLUP for all QTL classes for 10 cM marker intervals. In addition, with the 75/25 probability case, fixed GS with phenotype in only the F_2 had lower frequencies than BLUP in the F_5 for medium to large QTL (0.5–3.5) for 20 cM and for all QTL effect classes for 10 cM marker intervals.

Effect of heritability

Table 4 shows the effects of the sizes of marker intervals, the distribution of favorable QTL effects across parental lines, and the availability of phenotypes for alternate selection strategies on CR and CDR for a trait with a heritability of 0.25. Compared to heritability equal to 0.1 (Table 2), the larger heritability led to the higher *absolute* responses for all models including BLUP (results not shown) but in lower extra responses over BLUP. CR in F_3 were smaller with $h^2 = 0.25$ than with $h^2 = 0.1$ for all models, although the pattern of responses to selection was not affected by heritability.

A higher heritability decreased the benefit of random GS over fixed GS in the F_{11} when the size of marker intervals was small, but it increased the performance of fixed GS in the F_{11} over random GS. However, random GS gave similar CDR to fixed GS ($P > 0.05$) with 20 cM marker

Table 3 Average frequencies of favorable QTL in the F_5 and F_{11} from genomic selection depending on selection strategy, availability of phenotypic data, and size of marker intervals, for a trait heritability was 0.1 and equal distribution of favorable QTL alleles across parental lines

Marker interval (cM)	QTL effect range	% of QTL	Average QTL effect	BLUP	Fixed GS		Random GS	
				All[a]	All	F_2 only	All	F_2 only
Average frequency of favorable[b] QTL alleles in F_5								
20	0	50.3	0	0.50 [b]	0.50	0.50	0.50	0.50
	>0–0.5	19.2	0.24	0.52	0.53	0.52	0.54	0.53
	0.5–1.0	16.2	0.74	0.57	0.60	0.57	0.61	0.59
	1.0–1.5	8.5	1.22	0.63	0.67	0.61	0.69	0.65
	1.5–2.0	4.1	1.71	0.67	0.73	0.66	0.75	0.71
	2.0–3.5	1.6	2.32	0.74	0.78	0.69	0.81	0.76
Average frequency of favorable[b] QTL alleles in F_{11}								
	0	50.3	0	0.49 [b]	0.49	0.50	0.49	0.50
	>0–0.5	19.2	0.24	0.57	0.60	0.54	0.60	0.54
	0.5–1.0	16.2	0.74	0.69	0.74	0.61	0.74	0.64
	1.0–1.5	8.5	1.22	0.82	0.86	0.68	0.86	0.75
	1.5–2.0	4.1	1.71	0.89	0.93	0.76	0.93	0.83
	2.0–3.5	1.6	2.32	0.96	0.96	0.80	0.96	0.89
Average frequency of favorable[b] QTL alleles in F_5								
10	0	75.1	0	0.50 [b]	0.50	0.50	0.49	0.49
	>0–0.5	10.1	0.24	0.53	0.53	0.51	0.54	0.53
	0.5–1.0	7.7	0.74	0.58	0.59	0.55	0.61	0.60
	1.0–1.5	4.3	1.22	0.63	0.66	0.59	0.70	0.66
	1.5–2.0	1.9	1.71	0.67	0.70	0.63	0.75	0.70
	2.0–3.5	0.9	2.32	0.75	0.79	0.68	0.84	0.81
Average frequency of favorable[b] QTL alleles in F_{11}								
	0	75.1	0	0.50 [b]	0.50	0.50	0.49	0.49
	>0–0.5	10.1	0.24	0.57	0.59	0.53	0.60	0.56
	0.5–1.0	7.7	0.74	0.71	0.75	0.57	0.79	0.67
	1.0–1.5	4.3	1.22	0.82	0.88	0.65	0.91	0.78
	1.5–2.0	1.9	1.71	0.89	0.94	0.70	0.95	0.84
	2.0–3.5	0.9	2.32	0.97	0.98	0.77	0.98	0.94

[a] Generations with phenotypic data

[b] For QTL with zero effects, line 1 alleles were considered favorable

intervals and $h^2 = 0.25$ whereas higher *CDR* than fixed GS with 10 cM marker intervals (Table 4).

Higher heritability increased CDR for fixed GS with phenotypes available only in the F_2. Fixed GS with small number of marker intervals performed as well as random GS with high heritability due to two reasons. First, accuracy of selection was already high with high heritability. Second, random GS did not have much advantage over fixed GS when the number of marker intervals was not so high, i.e. 90 marker intervals for 20 cM in length (Table 4).

Higher heritability resulted in higher average QTL effects (1–3.5) and in a higher percentage of QTL from medium to large effects (1 to 3.5) but had no significant effect on the pattern of the average QTL frequencies, regardless of the distribution of favorable QTL effects across parental lines or size of marker intervals. Higher heritability, however, resulted in slightly lower average QTL frequencies for all scenarios (results not shown).

Discussion and conclusions

The efficiency of genomic selection in a composite line using low-density marker maps with alternative analysis models was presented. Owing to the development of molecular technologies, the amount of genetic marker information that can be available for genetic evaluation has markedly increased, leading to insufficient phenotypic data to estimate parameters. Lande and Thompson (1990) and Zhang and Smith (1992) used splitting a data set to select a subset of markers linked to QTL and to calculate marker scores using multiple regression. However, there are a few problems with the regression approach. First, splitting data may cause suboptimal use of information (Meuwissen et al. 2001). Second, having too many parameters to be estimated using regression leads to colinearity and results in poor estimates and marker scores (Whittaker et al. 2000). In addition, signs of the regression estimates of marker effects can be different, although the true effects have the

Table 4 Responses to genomic selection for a trait heritability of 0.25, showing effect of selection strategy, the distribution of favorable QTL alleles and size of marker intervals on cumulative and cumulative discounted (10% interest) responses (CDR)

Percent of favorable QTL alleles from line 1	Size of marker intervals (cM)	Models	Phenotype availability for GS	Cumulative responses (% over BLUP)				*CDR* (% over BLUP)
				F_3	F_5	F_8	F_{11}	
50	20	Fixed	All	40	19	12	6	14.19
		Fixed	F_2 only	40	−6	−22	−31	−16.62
		Random	All	52	20	8	2	12.27
		Random	F_2 only	52	4	−14	−23	−7.40
50	10	Fixed	All	27	15	13	11	13.84
		Fixed	F_2 only	27	−22	−37	−42	−30.62
		Random	All	54	24	16	10	19.09
		Random	F_2 only	54	8	−7	−15	−1.58
75	20	Fixed	All	40	19	12	6	13.86
		Fixed	F_2 only	40	−5	−21	−30	−15.16
		Random	All	50	22	11	3	14.41
		Random	F_2 only	50	8	−9	−18	−3.04
75	10	Fixed	All	25	15	14	11	14.02
		Fixed	F_2 only	25	−20	−34	−40	−28.00
		Random	All	50	26	17	11	20.02
		Random	F_2 only	50	11	−2	−10	2.84

Results from selection on true breeding values are presented also for comparison

same sign (Gianola et al. 2003). Finally, a certain extent of false positive and false negative errors has to be borne in mind.

False negatives can occur when the QTL have marginally larger *P* values than an assigned threshold. As a result, they are not detected. In addition, cancellation of adjacent QTL with opposite signs of effects may also result in not detecting the QTL. False positives and negatives from high power QTL detection designs (i.e. less stringent threshold), result in high numbers of detected QTL with zero effects. These QTL with zero effects bring about an overestimated variance explained by QTL and thus, overestimated genetic improvement. Using genomic selection can be beneficial because it can avoid the problem of false positives and negatives. Both large and small QTL effects are included in the selection criteria, as seen via increased QTL frequencies across QTL effects.

When marker information is available, selecting on all marker regions regardless of significance resulted in greater responses to what was observed in a previous study (Piyasatian et al. 2006), which considered only markers that were significant following a QTL scan within the same cross of inbred lines. The magnitude of the difference between genomic selection and MAS following QTL detection depends on the stringency of the threshold used for QTL detection.

Similar to what was found by Meuwissen et al. (2001) for genomic selection in an outbred population with a high-density map, genomic selection was found to substantially outperform BLUP selection within a cross. Accuracy of selection increased when marker density increased, and is dependent on the type of markers used (Solberg et al. 2006). With a heritability of 0.5, the use of SNPs required a 4–5 times denser map than when using microsatellites for genomic selection in an outbred population (Solberg et al. 2006). One limitation of the Meuwissen et al. (2001) method is that they could not fit all markers (haplotypes) as fixed effects because their number was greater than the number of observations. This was not the case in this study. In this study, only a sparse marker map (10 and 20 cM intervals) is required because of the extent of LD that exists within the cross.

With a large number of confounded parameters to be estimated, regression leads to colinearity and to poor estimates. Ridge regression has been used to improve the precision of estimates in a linear model by using an informative prior distribution of estimates. With ridge regression, the usual estimates $\hat{\beta}$ are shrunk towards zero, to the degree of a specified scalar (Whittaker et al. 2000). The use of genome-wide dense marker maps and ridge regression was exploited in an outbred population by Meuwissen et al. (2001). In one approach, Meuwissen et al. (2001) suggested the use of equal variance for each interval, calculated as V_G/N, where V_G = total genetic variance and N = the number QTL loci. A similar approach was used in the present study, but with the degree of shrinkage determined by the expected variance contributed by the region. Instead of using V_G/N directly, the variance

accounted for recombination rates between markers and QTL. Here, we also assumed each interval to be independent and to contribute equal variance, which does not represent the real situation. Equal variance not only prevents zero QTL effects to have too extreme estimates, but also prevents large QTL effects to have near true estimates beyond the variance. However, the advantage of having incorrect prior (equal variance) outweighs the disadvantage of not having a prior at all due to the small number of large QTL effects relative to the number of QTL with small or zero effects. Methods can be further improved by Bayesian methods similar to Meuwissen et al. (2001), which estimate the variance associated with each interval. In addition, a covariance structure could be imposed across intervals.

Both fixed and random GS outperformed selection on BLUP EBV estimated from phenotype in the initial generations. There was strong evidence that the use of ridge regression (random $\hat{\beta}$) outperformed the usual multiple regression (fixed $\hat{\beta}$), especially in early generations. Treating marker scores as fixed resulted in substantially lower responses in all generations than treating marker scores as random effects, except when trait heritability was 0.25 and size of marker intervals was 20 cM for both distributions of favorable QTL alleles. Ridge regression has great potential in GS, especially with a small set of data. Random GS also outperformed fixed GS when phenotypes were only available for the F_2, again demonstrating the better behavior of the random estimates, which will be beneficial for traits that are difficult or expensive to measure. Using GS is also advantageous when phenotypes are recorded in only one sex, such as milk yield, or only on culled animals, such as meat quality traits or after selection (Visscher et al. 2000; Goddard and Hayes 2002).

Heritability of the trait affected the magnitude of the extra gain obtained from GS over selection on BLUP using only performance records. The lower the heritability, the greater the benefit of GS over BLUP. This is because when heritability is low, phenotype contains less information for estimation, leading to inaccurate marker effects and less response for GS. Treating marker scores as fixed for a large number of marker intervals (90) resulted in poor estimates caused by colinearity and led to lower responses than treating marker scores as random. The extent of colinearity was greater when the number of marker intervals increased (180). As a result, fixed GS gave lower responses (% over BLUP) whereas random GS gave higher response (% over BLUP) when the number of marker intervals increased. Fixed GS gave even lower response when phenotypes were available only in the F_2.

Unequal distribution of favorable QTL alleles across parental lines increased *absolute* genetic gains in all strategies due to an increase in positive QTL effects lying on the same chromosome. However, benefits of GS over BLUP selection were greater for equal distribution of favorable QTL effects across parental lines (i.e., 50/50), except for fixed GS with phenotype available only in the F_2.

Models without interactions between generation and marker score outperformed those with interactions. The reason is because the amount of data points available to estimate individual effects was greater for models without interactions. With large marker intervals (20 cM), allowing marker score effects to be different across generations had a much larger impact on limiting the amount of data and accuracy of marker score estimates. The accuracy of estimating marker effects is the key to quantifying genetic variance explained by QTL and accuracy of MAS selection (Goddard and Hayes 2002). Recombination rate between marker and QTL is one of the factors to indicate accuracy of estimates of marker score effects based on LD generated by a cross, especially in later generations of a breeding program. Interactions may be beneficial when using dense marker maps.

The efficiency of GS was identified by using the percentage of the superiority of cumulative response (CR) and cumulative discounted response (CDR) over selection on BLUP from phenotype (% over BLUP). The CDR is the CR over a time horizon weighted by an interest rate. The idea of CDR is to put more emphasis on genetic improvement made in the early generations, rather than in the later generations. In this study, a 10% discounted rate was applied to a simulated pig population, which is suitable for species with short generation intervals such as poultry or pigs (Dekkers and Chakraborty 2001). A higher interest rate can be used for a species with a longer generation interval such as cattle (Dekkers and Chakraborty 2001).

Early selection in a cross of inbred lines capitalizes on the LD that exists between markers and QTL alleles. The amount of useable LD decreases over generations, depending on recombination rates between the QTL and markers. The results presented here show that LD is still substantial after a few generations, as seen when phenotypic data were available only in F_2.

A polygenic effect was included in the genetic model to in addition to marker effects to investigate the efficiency of GS. As a result, the expanded selection criteria would be the sum of estimated marker scores and estimated breeding values. Different polygenic variances for genetic evaluation were used. Adding a polygenic effect had limited impact on results observed for crosses between inbred lines.

We simulated a cross between two inbred lines but methods can in principle be extended to multi-breed crosses by allowing for different effects for alleles derived from different lines. Also, when crossing inbred lines, all genetic variance present in the cross originates from QTL differences between the lines and can be captured by markers that are informative for breed origin. When

crossing outbred breeds, as would be the case for livestock, genetic variance in the cross is a combination of between and within-breed variances. In this case, only variance generated by between-breed differences is amenable to the strategies proposed here with selection on markers based on line origin. As a result, the benefit of GS using between-breed LD will be smaller than observed here. Nevertheless, breed crosses between commercial lines have shown to result in substantial numbers of QTL based on between-breed LD, which would be amenable to GS using the approach suggested here. In such crosses, to capitalize on within-breed variation, a polygenic effect should be fitted in addition to marker score effects. In addition to capturing linkage disequilibrium generated by the cross, markers can also be used to follow the co-segregation of markers and QTL within families by adding a random QTL variable, following (Perez-Enciso and Varona 2000).

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Appendix

The complete derivation is given below.

Using

$$V(A) = \underset{B}{E}[V(A|B)] + V[\underset{B}{E}(A|B)].$$

Let

$$A = \beta_i \times \mathrm{MS}_{ijk} \quad \text{and} \quad B = \mathrm{MS}_{ijk}.$$

It was assumed that marker intervals were independent and each marker interval contributed equal variance.

Then

$$V(\beta_i \times \mathrm{MS}_{ijk}) = V_\mathrm{G}/N,$$

where N = number of marker intervals (90 or 180).

$$V(A) = \underset{\mathrm{MS}}{E}[V(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)] + V[\underset{\mathrm{MS}}{E}(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)],$$

where

$$\underset{\mathrm{MS}}{E}[V(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)] = \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times V(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i) = \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times i^2 \times V(\beta_i)$$

and

$$V[\underset{\mathrm{MS}}{E}(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)] = \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times [E(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)]^2 - \left[\sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times E(\beta_i \times \mathrm{MS}_{ijk}|\mathrm{MS}_{ijk} = i)\right]^2 = \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times [i \times E(\beta_i)]^2 - \left[\sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times i \times E(\beta_i)\right]^2 = 0$$

because $E(\beta_i) = \dfrac{\mu_{\mathrm{Phen\_Line1}} - \mu_{\mathrm{Phen\_Line2}}}{N}$,

which in our case is equal to zero because the expected means of the two lines are equal. This would be true for the 50/50 case but not for the 75/25 case.

Hence,

$$V_\mathrm{G}/N = \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i) \times i^2 \times V(\beta_i) \quad \text{and}$$

$$V(\beta_i) = V_\mathrm{G}/[N \times i^2 \times \sum_{i=0}^{4} P(\mathrm{MS}_{ijk} = i)]$$

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