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Potential for profitable use of DNA markers in the New Zealand Dairy Industry

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ABSTRACT

Annual genetic advance in merit of dairy cattle can be assessed from selection in four pathways: Bulls to breed Bulls (BB); Cows to breed Bulls (CB); Bulls to breed Cows (BC); and Cows to breed Cows. It is usually assumed that breeding merit is determined by actions of a very large number of genes, each having a small effect (infinitesimal model of inheritance). In practice, the number may be finite, with a few genes (known as QTLs) having large effects. DNA technologies allow young animals to be tested for particular QTLs using markers.

Benefits of marker assisted selection were calculated for one additive QTL over a range of sizes (allele values of 0.25, 0.38, or 0.5 genetic s.d.) and initial gene frequencies (0.01, 0.10, 0.35). Testing was conducted in the BB, BC and CB pathways. Strategies were compared using the Net Present Value of the stream of productive benefits less costs for a 30 year horizon, assuming one genetic s.d. is worth \$160.

Superior rates of advance were sometimes achieved at greater cost than benefits. At a cost of \$10 per genotype assessment it was never profitable to genotype small QTLs. The largest QTL could be profitably used to screen young bulls before progeny testing except at the lowest starting frequency. In some circumstances, selection for a QTL resulted in improved medium term response but reduced long-term response. Knowledge of the size and frequency of QTLs and a pre-defined time horizon will be essential to discriminate between profitable and costly applications of this technology.

Keywords: molecular genetics; DNA marker; genetic gain

INTRODUCTION

The annual advance in genetic merit of dairy cattle can be assessed from Rendel and Robertson's (1950) formula representing selection in four pathways: Bulls to breed Bulls (BB); Cows to breed Bulls (CB); Bulls to breed Cows (BC); and Cows to breed Cows (CC). In New Zealand, animals are selected on aggregate merit, known as Breeding Worth (BW) comprising estimates of breeding values for: milkfat; protein; milk volume; cow liveweight; and survival (Harris 1996). In calculating BW, these five breeding values are weighted by their relative economic values. Overall progress is affected by both the superiority of selected individuals in each pathway and their average age when progeny are born. The superiority of selected individuals relies on the selection intensity (related to the proportion selected) and the accuracy of selection.

It is usually assumed that the breeding values contributing to BW are determined by the action of a very large number of genes, each having a small effect (infinitesimal model of inheritance). In this model, reliable prediction of breeding values can only be achieved by analysis of lactational measurements on the cows of interest (CB and CC pathways) or on some 50 to 100 daughters of bulls of interest (BC and BB pathways).

In practice, the number of genes contributing to differences in performance between individuals may be finite, with a few genes (known as quantitative trait loci or QTLs) having relatively large effects. Should this prove to be the case, the approximate location and size of these QTLs may be detected with the use of a molecular map identifying the position of markers along the genome

(Georges 1996). In the short to medium term, markers may be identified that flank these QTL, but ultimately fine-mapping may allow the exact position of the QTL to be determined. Flanking markers have the disadvantage that crossing over may occur between the marker and the QTL, thereby breaking the correspondence between QTL alleles and the marker alleles. Furthermore, different associations would exist in different families. In this study, it was assumed that a marker could be used to perfectly discriminate between QTL alleles.

The discovery of perfect markers for QTLs will allow animals to be partitioned according to their QTL genotype in both sexes and at a young age, perhaps even as embryos. This could allow selection of parents at a younger age than currently practiced, reducing generation intervals. However, in the short-term, the cost and time-consuming nature of DNA collection, extraction and marker assessment is likely to limit the use of markers to bull parents. Accordingly, this study determined the impact of marker-assisted selection for a bi-allelic QTL in two scenarios with genotyping restricted to the bull pathways (BB, BC and CB). Relative to the existing selection strategy, the impact of the marker-assisted selection was determined from a genetic and economic perspective.

MATERIALS AND METHODS

A deterministic simulation model was developed to account for the four pathways of selection allowing representatives from each of three QTL genotypes (QQ, Q+ and ++) in each pathway. Sub-populations by genotype and pathway were further partitioned by year of birth to account for overlapping generations and to allow tracking of

annual changes in QTL frequency. This model represents an extension of the approach described by Ducrocq and Quaas (1988), the extension comprising allowance for the three genotypes.

The additive effect of the favourable Q allele was varied between runs from 0.25, to 0.38 and 0.5 genetic s.d. The QTL alleles were introduced at frequencies of 0.01, 0.1 or 0.35 with the genotype frequencies reflecting Hardy-Weinberg equilibrium and linkage equilibrium with polygenic background effects.

The simulation was modelled around the existing breeding scheme for the Holstein-Friesian breed in New Zealand. This comprises some 1.6 million cows, of which only 169,000 (known as the active cows) are eligible for use as bull dams. Eligibility for selection as a bull dam requires cows to be herd tested and to have identified three generations of breeding to AB-sires of the same breed. The top 455 of these active cows are selected each year in order to produce the 140 young bulls that are annually progeny tested using 85 daughters. Bulls are five years old when their progeny test evaluations are available. Two percent of bulls die each year. The best ten (proven) bulls still living at 5, 6 or 7 years of age are used as bulls to breed cows. The best two proven bulls (dead or alive) are used to inseminate the 455 elite active cows. Bulls and cows used as parents were selected on the basis of truncation selection of their estimated breeding worth. No selection was assumed on the CC pathway.

Control scenario.

In each selection pathway, truncation selection was applied across subpopulations representing years of birth and QTL genotype. The QQ subpopulations have an elevated average genetic merit relative to the Q+ subpopulations which have elevated genetic merit relative to the ++ subpopulations. Selection will favour QQ and Q+ individuals, but breeding worths will be biased towards the average in all three subpopulations. In the case of cows with lactation records, their lactational deviation relative to contemporary animals is regressed towards the average with the regression coefficient relating to the heritability of the trait (assumed 0.3), the repeatability (0.6) and the number of lactations (one per year). In the case of sires with progeny test breeding worth the average progeny deviation is regressed by a lesser amount, determined by the heritability and the number of progeny of the sire. The regression of that component of the lactational deviations resulting from effects of the QTL introduces bias in the breeding worths, this bias being greater for cows than for sires.

In both the following alternative scenarios, control selection was first undertaken for 60 years to ensure that the historical effects of selection on the average merit by birth year was established prior to introduction of marker-assisted selection.

Selecting bull parents on aggregate genotype. (MAS 1)

In this situation, active cows and all proven bulls were assessed for the DNA marker and their QTL geno-

type was therefore known without error. Truncation selection was applied on aggregate genotype, defined as the sum of the (known) QTL effects and the polygenic background effects. In contrast to the control situation, the aggregate genotypes or breeding worths are not biased in each of the subpopulations. Selection in this case will be more effective at increasing the frequency of the favourable QTL allele than was the case in the control setting. Exceptional parents without the favourable QTL allele will still be used for breeding young bulls.

Progeny-testing only QQ and Q+ bulls. (MAS 2)

This scenario attempted to increase the frequency of the favourable QTL allele as rapidly as possible. At low frequencies of the favourable QTL, many young bulls were excluded from progeny testing on the basis of their QTL genotype (++)

For each of the three scenarios, selection was continued for a thirty year time horizon (following the sixty years of control selection). Annual genetic means in each of the marker-assisted strategies were compared to the control situation. The benefits from increased productivity returns in the entire population, less the genotyping costs (\$10 per animal) were accumulated on an annual basis. The Net Present Value (NPV) of this income stream was calculated, using a discount rate of 6.5% and including a startup \$4 million research grant for identification of the markers to the QTL.

RESULTS

Selecting bull parents on aggregate genotype. (MAS 1)

The rate of genetic gain assessed by annual changes in the mean breeding worth of the commercial population of cows for the thirty year horizon was always superior in MAS 1 compared to the control situation. The extent of superiority of MAS 1 over the control was greater for larger-sized QTL effects. The strategy was profitable only for the largest QTL (0.5 genetic s.d.). Given the large QTL, the profitability was greater when the starting QTL frequency was increased. The break-even time horizons when accumulated benefits equalled accumulated costs equalled 21 and 17 years for starting frequencies of 0.1 and 0.35, respectively. Net Present Values for MAS 1 including the startup research costs are in Table 1.

Given that research costs are expended prior to discovery of the QTL, it may be argued that the \$4 million

TABLE 1: Economic returns (\$NPV) from selection of bull parents on the sum of QTL genotype and polygenic background effects for a 0.5 σ_G QTL at three starting frequencies, three time horizons and a 6.5% discount rate.

Years	QTL starting frequency		
	0.01	0.1	0.35
20	-4,087,852	-67,853	901,778
25	-3,762,803	1,087,514	2,220,487
30	-3,413,862	1,995,953	3,198,508

investment costs should be ignored in the calculation of the NPV. This would have the effect of making all three QTL sizes profitable providing the starting QTL frequency was sufficiently high.

Long-term losses as a result of selection for the QTL did manifest but not until well beyond the 30-year time-frame reported in this study, even for the largest QTL size.

Progeny testing only QQ and Q+ young bulls. (MAS 2)

Genetic superiority of MAS 2 relative to the control strategy was sensitive to the initial QTL allele frequency. At low starting frequency, selection for QQ and Q+ bulls was at considerable expense in terms of lost selection differential. At high starting frequency, there was reduced benefit from rapidly increasing QTL frequency as many individuals already carried at least one copy of the favourable allele. The maximum superiority for a QTL of size 0.5 s.d. therefore occurred at the intermediate starting frequency of 0.1. The financial benefits from this strategy are in Table 2.

TABLE 2: Economic returns (\$NPV) for progeny testing only QQ and Q+ bulls with 0.5 σ_G QTL at three starting QTL frequencies, three time horizons and a 6.5% discount rate.

Years	QTL starting frequency		
	0.01	0.1	0.35
20	-19,012,200	1,543,580	908,383
25	-19,382,418	3,687,987	2,182,218
30	-19,007,713	5,339,519	3,077,351

DISCUSSION

The simulation model assumed a perfect marker to the QTL alleles was available. In practice, it is more likely that flanking markers will be available. This would require at least twice the genotyping effort on an ongoing basis, although with multiplexed markers the costs may not increase. However, any crossing over between one or other of the markers and the QTL would break the association, requiring that the phase of the favourable QTL in relation to the marker alleles be reassessed in subsequent generations. Accordingly, the genotyping costs are likely to increase and/or the benefits may be reduced, for example by incorrectly ranking animals on putative QTL genotype.

The scenarios considered in this study represent only minor changes to the existing breeding scheme design. These changes incorporated marker assessment of sires and active cows or young bulls, with no changes to the number or ages of animals at selection. Relative to current practice, a substantial improvement in gain would be achieved if generation intervals could be reduced without eroding the accuracies of selection. Alternative breeding schemes could be designed where greater attempt is made to reduce generation intervals such as by using unproven (young) bulls in either one or both of the BC or BB pathways. Furthermore, larger teams of bulls might be used, thereby reducing the risk associated with chance sampling of bulls at either extreme.

The benefits of marker-assisted selection may require concomitant application of advanced reproductive techniques. It can be shown (beyond the scope of this paper) that as a result of gametic phase disequilibrium, the best Q carrying gametes will be sourced from heterozygous (Q+) bulls. Accordingly, embryo genotyping might offer opportunities for better exploiting markers.

The results of this study indicate that there are opportunities for improving the rate of genetic advance such that resulting productive benefits exceed the costs associated with the new scheme. However, the value of any economic benefit is sensitive to the size of the QTL, the starting frequency of the QTL in the population and the time horizon for which benefits are assessed.

The break-even time horizon for benefits from these techniques were beyond the framework used by many business organisations. This may limit opportunities for routine application of marker-assisted selection as proposed in this paper.

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