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Marker assisted selection for the improvement of two antagonistic traits under mixed inheritance

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Abstract – A Monte Carlo simulation was used to investigate the potential of Marker Assisted Selection (MAS) in a multiple-trait situation. Only additive effects were considered. The base population was assumed to be in linkage equilibrium and, next, the population was managed over 15 discrete generations, 10 males and 50 females were chosen out of the 100 candidates of each sex. Performance for two traits was simulated with an overall heritability of a given trait equal to 0.25 or 0.10 and the overall genetic correlation between traits was generally equal to −0.4 except in one case where it was equal to 0. The model involved one biallelic QTL, accounting for 10 or 20% of the genetic variance of a given trait, plus polygenes. Initial allelic frequencies at the QTL were generally equal to 0.5 but in one case were equal to 0.1 and 0.9. A marker with 120 different alleles in the 60 founder parents was simulated in the vicinity of the QTL. Two values of the recombination rate between these two loci were considered, 0.10 and 0.02. The genetic evaluation was based on a multiple-trait BLUP animal model, accounting (MAS) or not (conventional BLUP) for marker information. Two sets of simulations were run: (1) a "missing data" case, with males having no record for one of the traits, and (2) a "secondary trait" case, with one trait having a weight in the aggregate genotype 4 times less than the other trait and the QTL acting only on this secondary trait. In the first set, evaluation methods were found to mainly affect the accuracy of overall genetic values prediction for the trait with missing data. In comparison with BLUP, MAS led to an extra overall genetic response for the trait with missing data, which was strongly penalised under the conventional BLUP, and to a deficit in response for the other trait. This more balanced evolution of the two traits was obtained, however, at the expense of the long-term overall cumulated response for the aggregate genotype, which was 1 to 2.5% lower than the one obtained under the conventional BLUP. In the second set of simulation, in the case of low initial frequency (0.1) of the QTL allele favourable to the secondary trait, MAS was found to be substantially more efficient to avoid losing this allele than BLUP only when the QTL had a large effect and the marker was close. More benefits should be expected from MAS with more specific applications,

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such as early selection of animals, or by applying dynamic procedures *i.e.* letting the respective weights to QTL and polygenic values in the selection criterion vary across generation.

marker assisted selection / genetic response / mixed model methodology

1. INTRODUCTION

Recently, polymorphic genetic markers have been used in domestic animal species to detect loci responsible for a part of the variation of quantitative traits (QTL). Therefore, the potential interest of Marker Assisted Selection (MAS) has been questioned but the answers have been rather contrasting (see, for example, [1,10,15]). Studies on MAS in animal breeding have mainly focused on genetic gain for a single trait (*e.g.*, [18,20,28,29,42]) but, in practice, selection is applied to several traits, often based on a linear combination of estimated breeding values (EBVs) for each individual trait. De Koning and Weller [22] studied two-trait selection based on an index that included both phenotypes and genotypes (assumed to be known without error) at the involved QTL(s). As mentioned by the authors, under such conditions the results "should be considered as upper limits for the gains possible with MAS" in a two-trait situation. Applying the approach of Lande and Thompson [23] to the case of two positively correlated traits, Xie and Xu [40] investigated, over one generation, the efficiency of two-stage MAS, involving a first stage on molecular scores and a second stage on molecular scores and phenotypes, and one-stage MAS, based on a single selection on both sources of information. They showed that the relative efficiency of one-stage MAS with respect to the aggregate genetic gain could range from 100 to 278% in comparison with phenotypic selection, this advantage being slightly less for two-stage MAS. Long-term effects of two-trait MAS were investigated *via* simulation ([37] and unpublished results) in situations where, due to the full symmetry between traits (same heritability, same part of variance due to the QTL, same weight in the aggregate genotype, same amount of data), the aggregate genotype was equivalent to a single trait with more or less variance being due to the QTL. Under such conditions, general trends observed in single trait studies were confirmed: in comparison with the conventional BLUP, (i) MAS led to an additional gain in the aggregate genotype on the short term, due to an extra gain for the QTL, but to a long-term deficit, due to a polygenic lag, and (ii) the lower the heritability of the traits and the closer the marker to the QTL, the higher the extra short-term gain due to MAS.

The purpose of the present study was to investigate the value, on the short and long terms, of MAS when two antagonistic traits were considered, under two different situations: (1) the case of missing data in one sex for one trait, and (2) the case of a QTL involved in one of the traits only, this trait being secondary in the aggregate genotype. Several questions were addressed, dealing with the cumulated response for separate traits and for an aggregate genotype, the change of family structure and the risk of loss of a QTL allele that is favourable to a secondary trait. Monte Carlo simulation was used to compare two selection procedures based on multiple-trait animal model BLUP EBVs (i) ignoring and (ii) including marker information. The genetic model included

a single biallelic QTL, for which the genotype of the candidates was unknown but which was linked to a highly polymorphic marker, plus a large number of independent polygenes. Only additive gene effects were considered. In each case, genetic parameters were assumed to be known.

2. SIMULATION PROCEDURES AND SITUATIONS INVESTIGATED

2.1. Base population parameters, generation of data and observed results

Records for 2 traits were generated over 15 discrete generations. The breeding population consisted of $N_m(= 10)$ males and $N_f(= 50)$ females chosen out of $T(= 100)$ candidates per sex. Founder parents were randomly chosen within the base population and produced candidates in generation 1. Next, parents were selected on their estimated aggregate breeding value (see Sect. 2.2). For each generation, matings were random and hierarchical.

The only fixed effect considered was the overall mean (μ). When it existed, the phenotypic value of a given animal for trait k (y_k) was generated as follows:

$$y_k = \mu_k + a_k + e_k \tag{1}$$

where a_k is the overall genetic value and e_k the environmental effect. For a given trait, the environmental effect was drawn at random from a normal distribution, independent of the genetic value. Environmental effects for the two traits were assumed to be uncorrelated.

The QTL had two alleles with initial frequencies equal to 0.5:0.5 or 0.1:0.9, according to the case considered (see next). Genotypes were assumed to be in Hardy-Weinberg proportions in the base population. A highly polymorphic marker was simulated, with $2(N_m + N_f)$ different alleles in the founders distributed independently from alleles carried at the QTL. In addition, a neutral biallelic locus, independent from the QTL and from the marker, was simulated with the same initial frequencies as the QTL.

In the base population, the genetic value (a) was generated as the sum of the values of both QTL genes (v' and v'') and the polygenic value (u):

$$a_k = v'_k + v''_k + u_k. \tag{2}$$

The values for trait k of the QTL genotypes were defined using the same scale as Falconer [11] (Chap. 7): the QTL had two alleles, called $\mathcal{A}$ and $\mathcal{B}$, and QTL values for trait k were set equal to $+\alpha_k$, 0 and $-\alpha_k$ for genotypes $\mathcal{AA}$, $\mathcal{AB}$ and $\mathcal{BB}$, respectively. Values of α_1 and α_2 were set according to the situation considered (see Sect. 2.3). Polygenic values (u_1 and u_2) were drawn at random and independently from the QTL values, from a binormal distribution with a correlation equal to ρ_u.

With the base population assumed to be at equilibrium, the variance of individual QTL values for a given trait was simply twice the variance of the QTL allelic effects:

$$\mathrm{Var}\,(v'_k + v''_k) = 2\sigma^2_{v_k} = 2pq\alpha_k^2 \tag{3}$$

where p and q are the initial allelic frequencies and α_k is defined as above. Due to the assumed independence between polygenic and QTL values in the base population, the overall genetic variance for trait k in the base population ($\sigma^2_{a_k}$) was the sum of the variance of individual QTL values and the variance of polygenic values ($\sigma^2_{u_k}$). Then, θ_k was defined as the portion of the overall genetic variance of trait k due to QTL segregation in the base population:

$$\theta_k = \frac{2\sigma^2_{v_k}}{\sigma^2_{a_k}} = \frac{2\sigma^2_{v_k}}{2\sigma^2_{v_k} + \sigma^2_{u_k}}. \tag{4}$$

In the same way, the overall genetic correlation between traits (ρ_a) may be expressed as a function of θ_ks, the correlation between QTL allelic values (ρ_v), and the correlation between polygenic values (ρ_u). In the case of pleiotropy of the QTL,

$$\rho_a = \rho_v \sqrt{\theta_1 \theta_2} + \rho_u \sqrt{(1-\theta_1)(1-\theta_2)}. \tag{5a}$$

In the case of no pleiotropy (say, $\alpha_1 \neq 0$ and $\alpha_2 = \theta_2 = 0$), ρ_v cannot be defined and

$$\rho_a = \rho_u \sqrt{(1-\theta_1)}. \tag{5b}$$

Note that in the case of pleiotropy, there are only two values for ρ_v, which are independent of the magnitude of α_1 or α_2, and are due to the presence of 2 alleles only: if the same allele is favourable to both traits, then ρ_v is equal to $+1$, and if the same allele is favourable to one trait and unfavourable to the other, then ρ_v is equal to -1. The consequence of the biallelic status of the QTL is that, in any case of pleiotropy of the QTL, the value of a gene for trait 2 (v_2) can be determined without error from its value for trait 1 (v_1):

$$v_2 = \rho_v \frac{\sigma_{v_2}}{\sigma_{v_1}} v_1. \tag{6}$$

For any offspring i, with sire s and dam d, the genetic value for trait k was generated as follows:

$$a_{k_i} = v^p_k + v^m_k + \frac{1}{2}u_{k_s} + \frac{1}{2}u_{k_d} + w_{k_i}$$

where v^p_k and v^m_k represent the values of the QTL allele of paternal (v^p_k) and maternal (v^m_k) origin respectively, and w_{k_i} represents the Mendelian sampling term for polygenic values. The values of w_{1_i} and w_{2_i} were drawn from a binormal distribution with a correlation equal to ρ_u, the variance of w_{k_i} being $\frac{1}{2}(1-\bar{F})\,\sigma^2_{u_k}$, where $\bar{F}$ is the mean of the coefficients of inbreeding of the two parents and $\sigma^2_{u_k}$ is the variance of polygenic values for trait k in the base population (see [14] for details). Transmission of alleles from parents to offspring was simulated at each locus according to Mendelian rules, taking into account the recombination rate (r) between the marker and QTL. Two values of r were compared: 0.10 and 0.02.

For each generation, the overall genetic mean and variance, and their QTL and polygenic components, were observed, as were correlations between the true and estimated values for QTL, polygenic and overall genetic values. For each generation, the average coefficient of inbreeding was computed from pedigree information. Each gene at an individual locus (QTL, marker or neutral locus) was labelled from 1 to $2(N_m + N_f)$ in the founder parents and the true probability of gene identity at a given locus was computed, at each generation, as the proportion of animals with two identical labels at this locus. The rate of inbreeding at a given generation (ΔF_t) was computed according to the classical formula:

$$\Delta F_t = \frac{F_t - F_{t-1}}{1 - F_{t-1}}$$

where F_t is the average coefficient of inbreeding from pedigree information, or the true probability of identity at a given locus, at generation t. The average rate of inbreeding was computed as the mean of ΔF_t for t from 2 to 15. Allelic frequencies and proportions of heterozygotes at the QTL were computed by direct counting. Allelic frequencies were not assessed at the marker. However, the effective number of marker alleles (*i.e.* the hypothetical number of alleles with equal frequencies which would provide the same Hardy-Weinberg proportion of heterozygotes as in the current population) was estimated from the true probability of gene identity at this locus.

2.2. Genetic evaluation and selection procedures

The aggregate genotype (H) was the selection goal, giving weight ω_k to trait k:

$$H = \omega_1 a_1 + \omega_2 a_2. \tag{7}$$

For each generation, candidates were selected based on their estimated value (I) for the aggregate genotype (H):

$$I = \hat{H} = \omega_1 \hat{a}_1 + \omega_2 \hat{a}_2$$

where $\hat{a}_k$ is the overall estimated breeding value (EBV) for trait k corresponding to multiple-trait BLUP solutions. Selection procedures differed in the way in which these multiple-trait solutions were obtained.

In a first set of simulations, marker information was not used, and $\hat{a}_1$ and $\hat{a}_2$ were obtained from a conventional multiple-trait animal model:

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_2 \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_2 \end{bmatrix} \begin{bmatrix} \mathbf{a}_1 \\ \mathbf{a}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix} \tag{8}$$

where, for a given trait k, $\mathbf{y}_k$ is the vector of data, β_k the overall mean, $\mathbf{a}_k$ the vector of overall genetic values, $\mathbf{e}_k$ the vector of errors, and $\mathbf{X}_k$ and $\mathbf{Z}_k$ are the corresponding incidence matrices. Under such a model, mixed model equations

involved the inverse of the additive relationship matrix between animals ($\mathbf{A}^{-1}$), and the overall genetic variance-covariance matrix between the two traits ($\mathbf{G}_0$):

$$\mathbf{G}_0 = \begin{bmatrix} \sigma^2_{a_1} & \rho_a \sigma_{a_1} \sigma_{a_2} \\ \rho_a \sigma_{a_1} \sigma_{a_2} & \sigma^2_{a_2} \end{bmatrix}.$$

In a second set of simulations, $\hat{a}_1$ and $\hat{a}_2$ were obtained as sums of the estimated allelic QTL values and polygenic values obtained from an extended animal model accounting for marker information. The model was:

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_2 \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_2 \end{bmatrix} \begin{bmatrix} \mathbf{u}_1 \\ \mathbf{u}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{W}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{W}_2 \end{bmatrix} \begin{bmatrix} \mathbf{v}_1 \\ \mathbf{v}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix}$$

where $\mathbf{u}$ and $\mathbf{v}$ are vectors of polygenic and QTL values, respectively, the $\mathbf{W}$s are the incidence matrices for QTL effects, and all the other terms are defined as in equation (8). Note that for a total number of N animals evaluated, $\mathbf{u}_k$ contains N elements and $\mathbf{v}_k$ contains $2N$ elements (corresponding to $2N$ genes). Since the QTL was biallelic, for a given animal and whatever the situation considered (see next), v_2 can be expressed as a linear function of v_1:

$$v_2 = \eta v_1.$$

In the case of pleiotropy, η is given by equation (6) and, in the case of no pleiotropy, $\eta = 0$. Therefore, the model can be rewritten as:

$$\begin{bmatrix} \mathbf{y}_1 \\ \mathbf{y}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{X}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{X}_2 \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} \mathbf{Z}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{Z}_2 \end{bmatrix} \begin{bmatrix} \mathbf{a}_1 \\ \mathbf{a}_2 \end{bmatrix} + \begin{bmatrix} \mathbf{W}_1 \\ \eta \mathbf{W}_2 \end{bmatrix} [\mathbf{v}_1] + \begin{bmatrix} \mathbf{e}_1 \\ \mathbf{e}_2 \end{bmatrix}. \tag{9}$$

Consider, for simplicity, the case where incidence matrices were the same for both traits:

$$\mathbf{X}_1 = \mathbf{X}_2 = \mathbf{X}, \quad \mathbf{Z}_1 = \mathbf{Z}_2 = \mathbf{Z}, \quad \text{and} \quad \mathbf{W}_1 = \mathbf{W}_2 = \mathbf{W}.$$

Letting $\mathbf{s}$ be the vector containing the factors affecting $\mathbf{W}$ ($\mathbf{s}' = [1, \eta]$), and setting $\boldsymbol{\beta}' = [\beta_1, \beta_2]$ and $\mathbf{u}' = [\mathbf{u}_1', \mathbf{u}_2']$, the mixed model equations were:

$$\begin{bmatrix} \mathbf{R}_0^{-1} \otimes \mathbf{X}'\mathbf{X} & & \text{sym} \\ \mathbf{R}_0^{-1} \otimes \mathbf{Z}'\mathbf{X} & \mathbf{R}_0^{-1} \otimes \mathbf{Z}'\mathbf{Z} + \mathbf{U}_0^{-1} \otimes \mathbf{A}^{-1} & \\ \mathbf{s}'\mathbf{R}_0^{-1} \otimes \mathbf{W}'\mathbf{X} & \mathbf{s}'\mathbf{R}_0^{-1} \otimes \mathbf{W}'\mathbf{Z} & \mathbf{s}'\mathbf{R}_0^{-1}\mathbf{s} \otimes \mathbf{W}'\mathbf{W} + \dfrac{1}{\sigma^2_{v_1}} \mathbf{G}_v^{-1} \end{bmatrix}$$

$$\times \begin{bmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{u}} \\ \hat{\mathbf{v}}_1 \end{bmatrix} = \begin{bmatrix} (\mathbf{R}_0^{-1} \otimes \mathbf{X}')\,\mathbf{y} \\ (\mathbf{R}_0^{-1} \otimes \mathbf{Z}')\,\mathbf{y} \\ (\mathbf{s}'\mathbf{R}_0^{-1} \otimes \mathbf{W}')\,\mathbf{y} \end{bmatrix}. \tag{10}$$

Due to the strict link between v_1 and v_2, $2N$ equations are saved. $\mathbf{U}_0$ is the polygenic variance-covariance matrix between the two traits:

$$\mathbf{U}_0 = \begin{bmatrix} \sigma^2_{u_1} & \rho_u \sigma_{u_1} \sigma_{u_2} \\ \rho_u \sigma_{u_1} \sigma_{u_2} & \sigma^2_{u_2} \end{bmatrix}$$

and $\mathbf{R_0}$ is the corresponding matrix for environmental values. Note that $\mathbf{s}'\mathbf{R}_0^{-1}\mathbf{s}$ is a constant scalar. $\mathbf{G}_v^{-1}$ is the inverse of the variance-covariance matrix of every QTL allelic effect, up to the base population. A simple method to compute $\mathbf{G}_v^{-1}$, just requiring that marker genotypes be known, was first proposed by Fernando and Grossmann [13]. In the present study, the extension of this method by Wang *et al.* [38], to accommodate situations when the paternal or maternal origin of marker alleles is uncertain, was used. Equation (10) was easily modified when the incidence matrices were not the same for both traits, as when some data were missing for one of the traits. Mixed model equations were solved by a bloc-iterative procedure: the first step consisted in solving $\hat{v}$s after the data were adjusted for $\hat{\beta}$s and $\hat{u}$s, the second step consisted in solving $\hat{\beta}$s and $\hat{u}$s after the data were adjusted for $\hat{v}$s.

Hereafter, the two selection procedures are called "BLUP" and "MAS", respectively, meaning selection on EBVs obtained from a multiple-trait animal model accounting (MAS) or not (BLUP) for marker information. The BLUP selection was run for 150 or 200 replicates. Solving mixed model equations required much more time to reach convergence for MAS than for BLUP. This was all the more true as the recombination rate (r) was small and when data were missing. Therefore, due to computing constraints, MAS was run for 50 to 150 replicates.

2.3. Genetic situations investigated

Whatever the situation considered in this paper, the two traits had the same initial overall genetic variance in the base population, chosen to be unity. In every case but one, their overall genetic correlation (ρ_a) was equal to -0.4. The desired value of ρ_a in the base population was obtained by choosing an adequate value for the polygenic correlation (ρ_u) according to the situation at the QTL [see eqs. (5.1) or (5.2)]. The aggregate genotype (H) was given by equation (7), and the ratio

$$\frac{\text{Var}(H)}{\text{Var}\,(\omega_1 y_1 + \omega_2 y_2)} = \frac{\text{Var}\,(\omega_1 a_1 + \omega_2 a_2)}{\text{Var}\,(\omega_1 a_1 + \omega_2 a_2) + \text{Var}\,(\omega_1 e_1 + \omega_2 e_2)}$$

was called the overall "heritability" of the selection goal. Two general situations were studied in this paper, which are summarised in Table I. Note that in Table I, as in further figures, the detailed cases are designed by a letter referring to the situation considered and to the percentage (θ) of variance of each traits, or of trait 1 only, due to the QTL.

2.3.1. Missing data on one trait

In the first situation, equal heritabilities ($h_1^2 = h_2^2 = 0.25$), equal proportions of genetic variance due to the QTL ($\theta_1 = \theta_2 = 20\%$), and equal weights in the aggregate genotype ($\omega_1 = \omega_2 = 1$) were assumed for both traits. However, the traits were no longer symmetrical with respect to information available for genetic evaluation, because males had no data for trait 2. This situation was investigated to check the ability of MAS to compensate for the absence of data

Table I. Summary of the different situations considered.

	Weights in H		Overall heritability		Correlations			Part of genetic variance (%) due to QTL		Overall "heritability" of the selection goal	Part (%) of variance of H due to QTL
Designation	trait 1	trait 2	trait 1	trait 2	ρ_a	ρ_v	ρ_u	trait 1	trait 2		
Missing data											
M 20	1	1	0.25	0.25	−0.4	+1	−0.750	20	20	0.17	67
					0.0	+1	−0.250			0.25	40
Secondary trait and no pleiotropy											
S 10	1/4	1	0.10	0.25	−0.4		−0.422	10	0	0.19	0.7
S 20	1/4	1	0.10	0.25	−0.4		−0.447	20	0	0.19	1.4

in the case, for example, of a sex-limited trait. In order to evaluate this ability independently from the overall genetic correlation between traits, a null value of ρ_a was considered in addition to the value of -0.4 generally assumed in this paper. QTL alleles had an initial frequency of 0.5.

2.3.2. The QTL only affects a secondary trait in the aggregate genotype

There were notable differences between traits in this second situation. First of all, the QTL had an effect only on trait 1, with two values of θ_1 10 and 20% being compared, and no effect on trait 2 ($\theta_2 = 0$). Secondly, trait 1 was a secondary trait in the aggregate genotype ($\omega_1 = \frac{1}{4}\omega_2$). Finally, heritability was lower for trait 1 than trait 2 (0.10 *vs.* 0.25). Under such conditions, the portion of the variance of H due to the QTL was very small and the overall "heritability" of the selection goal was close to the heritability of the main trait. Therefore, the question addressed here, previously evoked by Colleau and Phocas [8] with an application to milk yield and longevity in dairy cattle, was the ability of MAS to avoid losing a QTL allele, that is favourable only to a secondary trait that is antagonistic to the main trait and more difficult to select for because of its lower heritability. For that prospect, two values of the initial frequency of the QTL allele favourable to trait 1 were compared: 0.5, which corresponds to a basic case, and 0.10, meaning a much higher probability of loss.

3. RESULTS

3.1. Missing data on trait 2

Table II shows genetic responses for each trait and for the aggregate genotype under conventional BLUP selection. Due to the chosen configuration ("positive" pleiotropy, same genetic parameters for both traits), the response at the QTL was exactly the same for both traits, and resulted in the fixation of the favourable allele in all replicates ($\rho_a = -0.4$) or in 98% of the replicates ($\rho_a = 0$). Polygenic responses were however different from one trait to another. Especially, with an overall genetic correlation of -0.4, which corresponded to a polygenic correlation (ρ_u) of -0.75 (see Tab. I), the polygenic response for trait 2 was negative. For two independent traits ($\rho_a = 0$, which corresponded to a polygenic correlation of -0.25), polygenic responses were more balanced and the overall response for the aggregate genotype was higher than for two antagonistic traits.

Figure 1 shows the plot of cumulated QTL and polygenic means for the aggregate genotype against time, for MAS over conventional BLUP. MAS provided higher QTL responses than BLUP during the first half of the process: the relative extra gain was more than 5% up to the 5th or 6th generation. No clear difference appeared between values of the overall correlation between traits for the extra-QTL responses due to MAS. MAS however led to polygenic responses almost equal or lower than BLUP, the polygenic lag being lower when both traits were independent. During approximately the first 7 generations (*i.e.* before fixation occurred in the majority of the replicates), there was a large and

Table II. Genetic means for both traits and for the aggregate genotype after 14 generations of selection with BLUP. The overall genetic standard deviation in the base population was equal to 1 for both traits and genetic means are expressed in this unit. Missing data case ($h^2 = 0.25, \theta = 20\%$), mean of 200 replicates. Standard deviation between replicates is null or almost null for QTL values, and ranges from 0.5 to 0.9 for other components.

ρ_a	Component	Trait 1	Trait 2	Aggregate genotype
−0.4	QTL	0.6	0.6	1.3
	Polygenes	3.1	−0.5	2.5
	Overall	3.7	0.1	3.8
0.0	QTL	0.6	0.6	1.3
	Polygenes	4.6	1.9	6.4
	Overall	5.2	2.5	7.7

significant ($P < 0.001$) effect of the selection method on the variability of the QTL mean, the variability being lowest under MAS with a low recombination rate between marker and QTL, and the highest under BLUP. There was however no clear effect of the selection method on the variability of the polygenic response.

As a consequence of its effects on both QTL and polygenic responses, MAS provided overall gains on the aggregate genotype which were higher than those obtained under BLUP on the short term, but almost equal or lower on the long run (results not shown). For two antagonistic traits ($\rho_a = -0.4$), the maximum extra relative gain on the aggregate genotype was observed in the third generation and was equal to +8% for a distant marker ($r = 0.10$), and +15% for a closer marker ($r = 0.02$). From the 5th generation, the cumulated mean for the aggregate genotype under MAS was 1 to 2.5% less than under BLUP. In the case of two independent traits ($\rho_a = 0$), the initial superiority of MAS was lower (around 5 or 10%), but remained for a longer time with a close marker (up to the 10th generation).

A comparison of achieved overall genetic responses is shown for each trait in Figure 2. Here, the raw difference between MAS and BLUP is given, because when ρ_a was equal to −0.4, the overall response on trait 2 under BLUP was close to zero (see Tab. II) and therefore the MAS over BLUP ratio became meaningless. Figure 2 clearly shows that MAS generally provided higher responses than BLUP for the trait with missing data (trait 2) and lower responses for the other trait. For any trait, differences between MAS and BLUP (both positive and negative) were greater when the marker was closer to the QTL. The difference between MAS and BLUP for trait 1 showed approximately the same picture for both values of the overall genetic correlation between traits, except that when both traits were independent, the effect of MAS remained close to zero for a longer time. In fact, during the first four generations, the initial reduction due to MAS in the correlation between the selection criterion and the true polygenic value for trait 1 was relatively small when $\rho_a = 0$ (−2 and −6% for $r = 0.10$ and 0.02, respectively) and was balanced by the extra-gain on the QTL. This initial

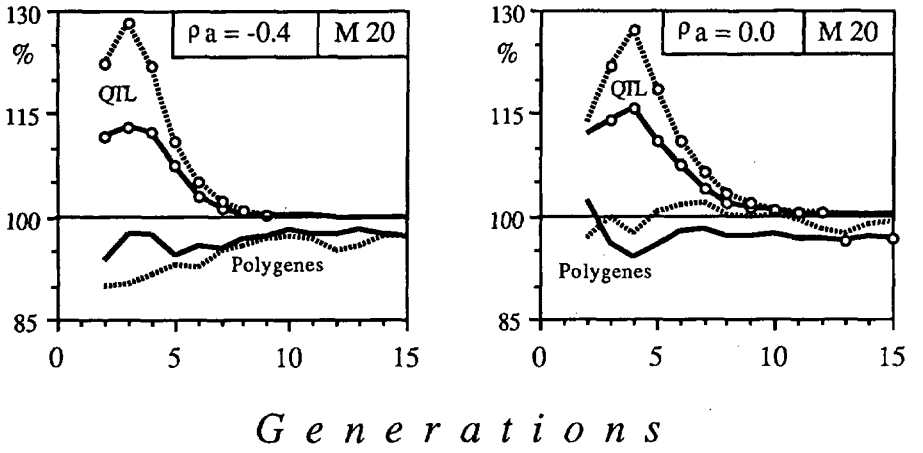

Figure 1. Genetic means for the aggregate genotype, for polygenes and at the QTL, obtained under MAS, expressed as a percentage of the mean obtained under BLUP. Missing data case with a QTL accounting for 20% of the genetic variance of each trait ($M20$) and with two values of the overall genetic correlation (ρ_a). Thin straight line = BLUP (mean of 200 replicates). Wide straight line = MAS [$r = 0.10$] (mean of 100 replicates). Wide dotted line = MAS [$r = 0.02$] (mean of 50 replicates). Open circles = difference MAS *vs.* BLUP statistically significant ($P < 0.05$).

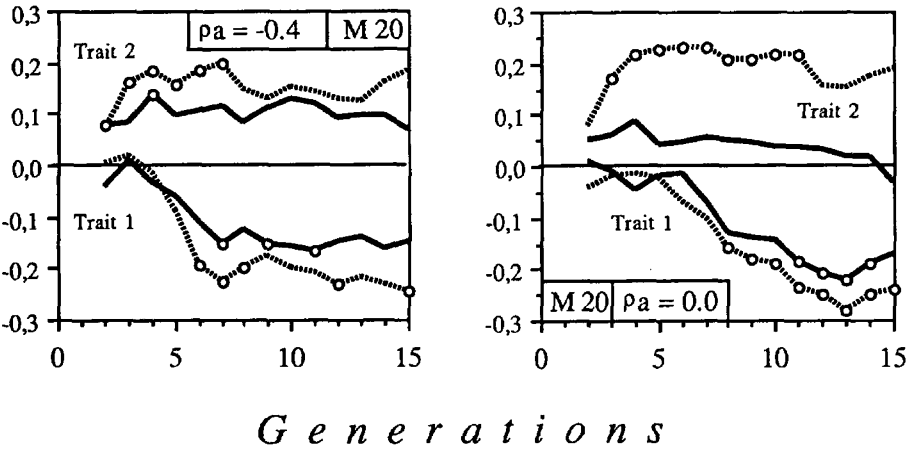

Figure 2. Overall genetic mean for both traits obtained under MAS, expressed as a deviation from the mean obtained under BLUP. Missing data case, same legend as in Figure 1.

deficit was substantially larger when $\rho_a = -0.4$ (-11 and -16%, respectively). The contrast between values of ρ_a was however, more important for trait 2. In particular, with a recombination rate of 0.10, the difference between MAS and BLUP in overall response for trait 2 was smaller and never significant when the two traits were independent. Also, the difference between cumulated gains

Table III. Correlation, averaged across the generations of selection, between true genetic values and predicted values (all components) of candidates for separate traits in the case of missing data. Mean of 200, 100 and 50 replicates for BLUP, MAS [$r = 0.10$] and MAS [$r = 0.02$], respectively (in a given generation, standard deviation between replicates ranges from 0.07 to 0.12). In brackets: correlation expressed as the percentage of the value obtained under BLUP. For the QTL component, the correlation is the same for both traits, and it is given only for the first four generations due to the fast rate of fixation of the QTL "favourable" allele.

Component	ρ_a	Trait	BLUP	MAS [$r = 0.10$]	MAS [$r = 0.02$]
Overall (a)	−0.4	1	0.584	0.589 (101.0 %)	0.601 (102.8%)
		2	0.537	0.541 (100.8%)	0.552 (103.0%)
	0.0	1	0.550	0.553 (100.6%)	0.550 (100.1%)
		2	0.470	0.474 (100.8%)	0.476 (101.3%)
Polygenic (u)	−0.4	1		0.590	0.596
		2		0.555	0.557
	0.0	1		0.544	0.542
		2		0.473	0.467
QTL (v) (four first generations only)	−0.4			0.383	0.441
	0.0			0.391	0.484

for trait 2 obtained under MAS with the two values of the recombination rate was large and significant ($P < 0.05$ from generation 3 to 6) only in the case of overall genetic independence between the two traits.

Table III shows the accuracy of the prediction of genetic values of candidates for each trait, averaged across generations. In all cases, there was a significant decrease of accuracy over generations. Under BLUP, the accuracy of the overall genetic value prediction was lower for the trait with missing data (trait 2). For both traits, the accuracy under BLUP was lower when $\rho_a = 0$, because data on a given trait were not informative for the genetic value of the other trait. Under MAS, the accuracy of QTL component prediction was strongly affected by the value of the recombination rate between the marker and the QTL. However for the polygenic component, differences in the accuracy of prediction between the two values of the recombination rate were rather small or almost null. In general, for a given trait, MAS led to higher accuracies of prediction of overall genetic values than BLUP. However, differences between MAS and BLUP were not very large, the largest being observed with a close marker. In the case of two independent traits, the advantage of MAS was more appreciable for the trait with missing data than for the other trait. The superiority of MAS was even larger in the case of two antagonistic traits ($\rho_a = -0.4$) but no clear

differences were observed between traits in such a case. Finally, it should be noticed that, for two antagonistic traits, this accuracy for overall genetic values under MAS was always lower than the one achieved under conventional BLUP with full data and with the same parameters, which was around 0.61 for both traits (unpublished results).

In all cases, the within-line QTL genetic variance decreased dramatically, due to fixation, especially under MAS. For both traits, and regardless of the selection method, the evolution of the within-line polygenic variance showed the same well-established picture due to linkage disequilibrium and genetic drift (see [4,35]). After 14 generations of selection, more than half the initial polygenic variance was lost. The polygenic variance tended to be less eroded for the trait with missing data than for the other one, regardless of the selection method. This difference between traits was larger for two independent traits than for two antagonistic traits. The realised effective size, computed from the average rate of inbreeding, was between 13 and 15 depending on the selection method and regardless of the value of ρ_a *i.e.* 2.2 to 2.5 times less than the theoretical value under pure drift with the same number of parents ($N_e = 33$ in this case). This phenomenon was due to the effect of selection on family structure (see [27,35,38]). Rates of inbreeding computed at the QTL were higher than those from pedigree (+10 to +176%), especially under MAS and for two antagonistic traits. Eventually, the highest average rates of inbreeding under MAS were observed for the marker, since selection was directly operating on it. This phenomenon dramatically affected the polymorphism at the marker. Starting from an initial value of 120 (in the base population), the effective number of marker alleles quickly reached a value lower than 2 (from the 7th generation with $\rho_a = -0.4$ and $r = 0.02$ to the 13th generation with $\rho_a = 0$ and $r = 0.10$) and next reached values close to 1, *i.e.* not far from fixation.

3.2. No pleiotropy, the QTL acting only on a secondary trait

Table IV shows genetic responses cumulated for each trait and for the aggregate genotype, under conventional BLUP selection. Responses on the QTL were slightly positive, due to the low part of variance of the aggregate genotype due to this locus (*cf.* Tab. I). However, regardless of the case considered, polygenic responses were largely positive for trait 2 and negative for trait 1, because the main selection pressure was put on trait 2. Similar trends were observed under MAS (results not shown). When comparing selection methods, the main result was that in any situation, differences between BLUP and MAS for the cumulated overall mean of the aggregate genotype were small (only exceptionally higher than ±3% of the value under BLUP) and never significant. In fact, differences were observed only for the trait governed by the QTL, with QTL and polygenic responses affected in opposite directions (see next).

As expected, no significant change in allelic frequencies was observed at the neutral locus, but some changes in frequencies occurred at the QTL (Fig. 3). In general, the frequency of the favourable QTL allele increased over time. This change, however, was much greater when the QTL effect was larger. No significant difference between selection methods was found in the case of a small QTL effect ($\theta_1 = 10\%$). With a large QTL effect ($\theta_1 = 20\%$), MAS only

Table IV. Genetic means for both traits and for the aggregate genotype after 14 generations of selection with BLUP, expressed in the same units as in Table II and as deviations from the base population (the starting point differed for QTL values depending on initial allelic frequencies). Secondary trait and no pleiotropy case. $f(+)$ = initial frequency of the favourable allele at the QTL. θ_1 = part of genetic variance of trait 1 due to the QTL. Mean of 150 replicates. The standard deviation between replicates of the genetic mean at the 14th generation ranges from 0.2 to 0.4 for QTL values, and ranges from 0.6 to 0.9 for other components.

$f(+)$	θ_1	Component	Trait 1	Trait 2	Aggregate genotype
0.5	10%	QTL	0.06		0.02
		Polygenes	−2.70	7.78	7.10
		Overall	−2.65	7.78	7.12
	20%	QTL	0.12		0.03
		Polygenes	−2.80	7.77	7.07
		Overall	−2.68	7.77	7.10
0.1	10%	QTL	0.05		0.01
		Polygenes	−2.73	7.75	7.06
		Overall	−2.68	7.75	7.08
	20%	QTL	0.07		0.02
		Polygenes	−2.86	7.79	7.08
		Overall	−2.79	7.79	7.09

led to a significantly higher frequency of the favourable allele than BLUP for a marker close to the QTL ($r = 0.02$), and starting at the 5th or 6th generation.

With initial frequencies of 0.5, allele loss at the identified loci occurred in very few replicates (results not shown). At the neutral locus, the "+" allele was lost in 4 to 6% of the replicates, and at the QTL, the favourable allele was lost in only 0 to 5% of the replicates. The only case where the favourable QTL allele was never lost was the situation with the largest QTL effect and the smallest recombination rate. With an initial frequency of 0.1 for the favourable QTL allele or the "+" neutral allele, loss occurred at a much higher rate, in 1/3 to 2/3 of replicates (Tab. V). Under BLUP, the rate of loss was slightly lower for the QTL than the neutral locus. No clear difference between selection methods was found for the rate of loss at the neutral locus. Similarly to the effect on allelic frequencies, MAS led to a substantially lower rate of loss at the QTL than BLUP only with a QTL of large effect and a close marker.

Change in allelic frequencies and allele loss/fixation at the QTL only had direct consequences on genetic responses for the trait governed by the QTL. So, in some cases (see Fig. 3), MAS led to an extra QTL response for this trait which was, however, generally balanced by a polygenic lag. The variability in QTL response between replicates was greatly affected by allele loss or fixation. In cases with intermediate initial frequencies, the allele loss was rare and no difference in the selection method for the variability of QTL response was found.

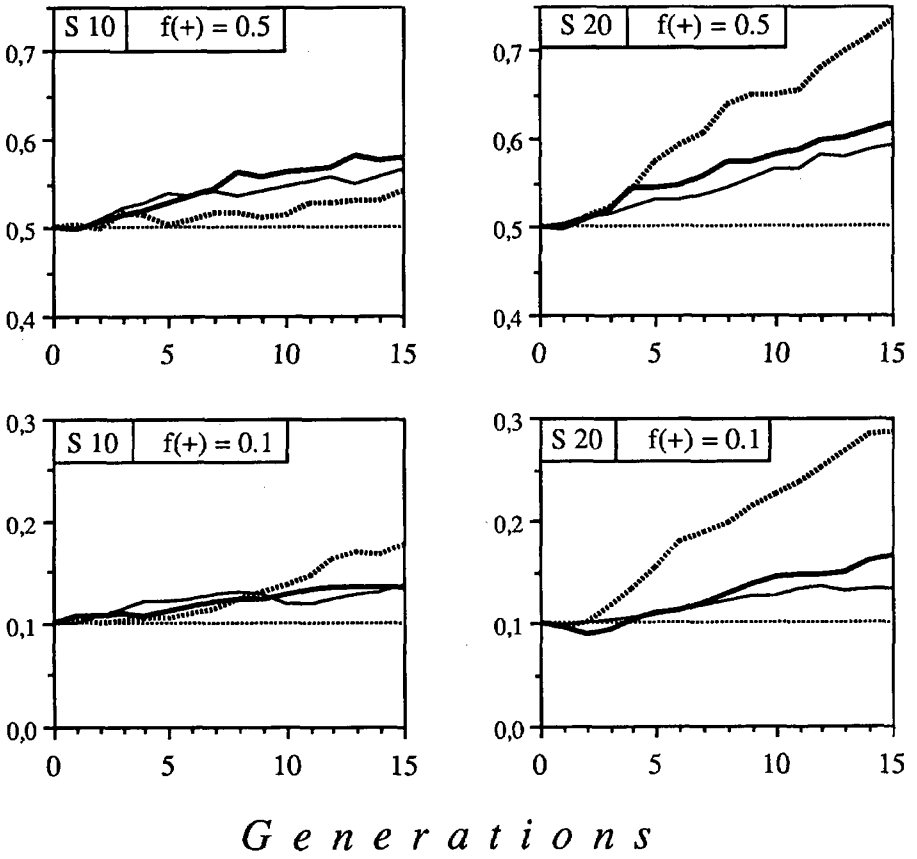

Figure 3. Evolution of the frequency of the QTL allele favourable to the secondary trait. No pleiotropy case, with a QTL explaining 10 (S10) or 20% (S20) of the genetic variance of the secondary trait. $f(+)$ = initial frequency of the favourable allele. Thin straight line = BLUP (mean of 150 replicates). Wide straight line = MAS [$r = 0.10$] (mean of 150 replicates). Wide dotted line = MAS [$r = 0.02$] (mean of 75 replicates). Note that the vertical scale is not the same for the two values of the initial frequency.

Table V. Percentage of replicates where the "+" allele was lost during the whole process of selection, when its initial frequency was 0.1. Secondary trait and no pleiotropy case. θ_1 = part of genetic variance of trait 1 due to the QTL. r = recombination rate between the marker and the QTL. Total number of replicates = 150, 150 and 75 for BLUP, MAS [$r = 0.10$] and MAS [$r = 0.02$], respectively.

Observed locus	θ_1	BLUP	MAS [$r = 0.10$]	MAS [$r = 0.02$]
Neutral locus	10%	56	61	62
	20%	61	62	65
QTL	10%	52	53	56
	20%	53	55	37

When the initial frequency was equal to 0.1, this allele loss occurred to a large extent and the higher the rate of loss of the favourable allele, the lower the variability between replicates in the QTL response, because a larger part of replicates were located at exactly the same QTL mean. However, no significant effect of the selection method was found for the variability between replicates in polygenic or overall responses.

Under BLUP, all average rates of inbreeding (computed from pedigree, at the neutral locus or at the QTL) were similar. No difference between selection methods was found for inbreeding from pedigree, the realised effective size being around 15 for all cases. At the QTL, MAS led to a higher average rate of inbreeding than BLUP (+8 to +18%) but only in some circumstances, particularly when the marker was close ($r = 0.02$).

4. DISCUSSION

4.1. Value of BLUP methodology when marker information is available

Other evaluation methods than the one considered in this study could be used for MAS within populations starting from equilibrium [6,12,17]. However, it was confirmed that, when taking into account marker information, mixed model methodology is an efficient tool for the estimation of QTL allelic effects despite the fact that basic assumptions (such as normal distribution of allelic effects) are not met in the base population (for a detailed discussion, see [12] and [28]). This point could be of practical importance: including marker information in BLUP evaluations according to the method first proposed by Fernando and Grossman [13] is one of the available efficient ways to apply MAS in outbred populations.

4.2. Value of MAS for partially compensating lack of data

The results presented in this paper show that, in a multiple-trait context, MAS can partially (but not fully) compensate the lack of data in the case, for example, where the breeding goal includes a sex-limited trait, as shown for a single-trait situation by Ruane and Colleau [29]. In this two-trait study, under conventional BLUP, the main part of the genetic gain was achieved on the trait with full data, whereas the response on the other trait was much lower or even almost null. In comparison with BLUP, MAS led to more progress for the trait with missing data and less progress for the other trait. So, one of the main interests of MAS in such a context is to provide a more balanced evolution of the selected traits, especially when there is a genetic antagonism between these traits. This result, however, was obtained at the expense of the cumulated gain on the aggregate genotype on the long term. As a matter of fact, MAS provided extra gain for the overall breeding goal in the first generations, mainly because this selection is more efficient in fixing the favourable allele and in limiting random fluctuations of QTL allelic frequencies. This initial extra QTL response from MAS was penalised, but not offset, by the loss in polygenic response, as shown and discussed in detail by Ruane and Colleau [28,29]. The long term

overall response was lower under MAS than under BLUP because it was not possible to cancel out the polygenic lag even after fixation of the favourable allele at the QTL, as predicted by Gibson [16]. Therefore, in a multiple-trait context with at least one sex limited trait, benefit from MAS is expected on the short term and/or if a balanced evolution of the traits is of interest, especially if there is a constraint for the evolution of trait(s) with missing data and when this(these) trait(s) is(are) strongly opposite to the other traits.

4.3. Value of MAS in order to avoid gene loss for a secondary trait

Differences between selection methods were only observed when the initial frequency of the allele of interest was low. If the process was extended for a longer term, differences would probably have been observed even with intermediate initial frequencies. However, it is only when the QTL effect was large and the marker was close to the QTL, that MAS was found to increase the frequency of the favourable allele faster than BLUP, and to be more efficient against the loss of this allele. In particular, a value of 10% for the recombination rate between the marker and the QTL seems to be too high to allow MAS to be efficient in that aspect. It should be noted that the advantage of MAS in avoiding allele loss is an intrinsic property of the method, because no difference between selection methods was observed for the change of family structure. This advantage of MAS comes from its ability to more frequently select animals carrying favourable allele(s), although differences in QTL genotype induce only very small differences in the overall value for the aggregate genotype. From a practical point of view, an important result is that this effect of MAS was not provided at the expense of the overall genetic response for the aggregate genotype: in comparison with BLUP, the extra gain in QTL response was strictly balanced by an equivalent deficit in polygenic response. In order to avoid loss of alleles in small selected populations, other procedures are of interest, such as decreasing the selection intensity or putting more emphasis on the within-family deviations in the selection criterion. These procedures were checked *via* simulation in single-trait situations [5,19,30,36] and were found to significantly decrease the risk of gene loss, over a term between 10 and 30 generations, but with a substantial lag in genetic response, at least in the medium term (first 10 to 15 generations). Finally, with small unselected populations, such as rare breeds under conservation programmes, the results by Toro *et al.* [32,33], clearly show the efficiency of using markers for monitoring genetic variability and avoiding gene loss, especially in the vicinity of the markers themselves.

4.4. Limits of the present results and perspectives

A number of conditions of this study were *a priori* favourable to MAS in comparison with conventional BLUP: a highly polymorphic marker, pleiotropy of the QTL which acted in the same direction as the selection goal, genotyping of all animals and assuming all genetic parameters were known. Obviously, if one of these conditions was not fulfilled, the QTL response under MAS would be

expected to be substantially affected. However, some conditions of this study were *a priori* not so favourable to MAS: especially in the secondary trait case, all animals in both sexes were performance-recorded, and in all cases, no delay for measurements was considered, which did not allow to check the value of MAS for an early selection and then shorten the generation interval. Ignoring fixed effects was another condition specific to this study but not relevant in practice: further research is needed to check the impact of such effects on the efficiency of MAS, especially if allelic frequencies at the QTL(s) are not the same for all fixed effect classes.

With the same value for the overall genetic correlation as in the present study (−0.4), but with a "negative" pleiotropy of the QTL (*i.e.* a QTL acting in opposite directions on the two traits), simulation results ([37] and unpublished results) showed that the advantage of MAS on overall response appeared only with low heritability traits, a QTL with a large effect on both traits and a marker close to the QTL. To date, most published detected QTL in livestock species are based on single-trait analysis and, when a chromosome interval is involved in several traits, there is generally no power to make the distinction between a pleiotropic locus or linked loci. Despite this, most published results show that when a chromosome interval is found to induce variations for two traits, its effect on the two traits follows the overall genetic correlation (see, for example, [3,41] for dairy cattle, and [2] for pigs). Therefore, in practice, MAS for the improvement of two antagonistic traits would mainly correspond to a "negative" pleiotropy situation, requiring marker(s) very close to the QTL. A notable exception was found in pigs, where the same interval on chromosome 7 was found to act on both backfat thickness and intramuscular fat content, which are positively correlated ($\rho_a = +0.3$ to $+0.5$), and where the "Meishan allele", in comparison to a "Large-White allele", was found to be unfavourable for the first trait and favourable for the second trait [2]. Such a case would roughly correspond to the missing data case of the present study, because the pleiotropy of the detected chromosome interval is in the same direction as the selection goal (decreasing backfat thickness and increasing intramuscular fat content) and because it is not possible to measure the second trait on selection candidates. The present results indicate that, in such a situation, MAS could be useful, provided special emphasis would be paid to the avoidance of too large a polygenic lag (see next). In practice, traits to be improved may be positively correlated. In such a case, according to the results by Koning and Weller [22] (obtained with genotypes at the perfectly known QTL), the advantage of MAS would be lower than in the present study, probably because this situation is favourable for simultaneously increasing the two traits, regardless of the selection method. Similarly, the advantage of MAS would be higher if the environmental correlation (always null in the present study) is opposite to the overall genetic correlation, a case which is relatively rare in animal breeding.

Considerations about loss of QTL alleles and polygenic lag strengthen the interest of dynamic selection procedures. In the case where the genotype at a major gene is known, it was shown [9,24] that maximisation of middle or long term overall response requires putting little emphasis on the genotype for this gene at the beginning of the selection and increasing it in successive generations. Applying such a procedure in the context of a BLUP evaluation

accounting for a marker is straightforward. For each trait k, a modified EBV (I_k) could be computed for each candidate from solutions for each component of the genetic value:

$$I_k = \zeta_v \left(\hat{v}'_k + \hat{v}''_k\right) + \zeta_u \hat{u}_k \tag{11}$$

where $\hat{v}'_k$, $\hat{v}''_k$ and $\hat{u}_k$ are solutions of (10) for paternal and maternal QTL gene effects and polygenic value, respectively, and ζ_v and ζ_u are weights given to these values. Restricting the polygenic lag simply requires choosing a value of 1 for ζ_u and increasing the value of ζ_v over time, from values close to 0 to values close to 1. If gene loss at the QTL is to be avoided, starting from low values of the frequency of the favourable allele, dynamic selection may be achieved by choosing during the first generations a higher weight for QTL values than for the polygenic value ($\zeta_v > \zeta_u$). The efficiency of such procedures should be checked. In particular, methods to find the optimal weights (ζ_v and ζ_u) according to what is to be optimised and the time horizon is a problem of its own.

An important problem, which will be met in practice, lies in the estimation of genetic parameters. In a single-trait situation, it has been shown [29] that using incorrect estimates of the QTL variance led to a reduction of the extra gain from MAS. In a multiple-trait situation, this unfavourable effect of using incorrect parameters would probably be magnified and, so, providing unbiased and accurate parameters will be at least as important as for a single-trait case but, undoubtedly, much more difficult, especially properly estimating the correlation structure of the QTL. As pointed out by Moreau *et al.* [26], these considerations should also moderate the conclusion about the higher value of MAS when the heritability of the trait(s) is lower, because in practice, the lower the heritability, the lower the power of QTL detection and the more difficult the estimation of the related genetic parameters.

5. CONCLUSION

This study confirmed that the interest of MAS in comparison to conventional selection methods largely depends on the genetic context and the selection goal. Especially, as already shown in single-trait situations, the closer the linkage between the marker and the QTL is and the less informative phenotypes are, the more valuable MAS is, provided that genetic parameters are estimated without bias and accurately. In a multiple-trait view, it was shown that MAS could be useful for including in the aggregate genotype traits that are difficult or impossible to measure in one sex. This could be of particular interest if such traits are secondary in the selection goal and the purpose would mainly be to avoid loss of favourable QTL alleles or if a balanced evolution of the different traits (traits with full data and sex limited traits) is required. More benefits should be expected from MAS for specific applications, such as the early selection of animals, and the use of dynamic procedures: further research is needed in these fields. As stressed by Colleau [7] or Spelmann and Garrick [31], special attention is to be paid to the choice of the step(s) within the selection programme when marker information is to be used, the choice of animals to be typed, and how MAS is to be combined with other tools, such as modern reproduction technologies, depending on genotyping costs.

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