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Palliating the impact of fixation of a major gene on the genetic variation of artificially selected polygenes

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Summary

Selective sweeps of variation caused by fixation of major genes may have a dramatic impact on the genetic gain from background polygenic variation, particularly in the genome regions closely linked to the major gene. The response to selection can be restrained because of the reduced selection intensity and the reduced effective population size caused by the increase in frequency of the major gene. In the context of a selected population where fixation of a known major gene is desired, the question arises as to which is the optimal path of increase in frequency of the gene so that the selective sweep of variation resulting from its fixation is minimized. Using basic theoretical arguments we propose a frequency path that maximizes simultaneously the effective population size applicable to the selected background and the selection intensity on the polygenic variation by minimizing the average squared selection intensity on the major gene over generations up to a given fixation time. We also propose the use of mating between carriers and non-carriers of the major gene, in order to promote the effective recombination between the major gene and its linked polygenic background. Using a locus-based computer simulation assuming different degrees of linkage, we show that the path proposed is more effective than a similar path recently published, and that the combination of the selection and mating methods provides an efficient way to palliate the negative effects of a selective sweep.

1. Introduction

DNA technologies are revealing an increasing number of loci controlling quantitative traits (QTLs; Andersson & Georges, 2004; Mackay & Lyman, 2005), which can potentially heighten the genetic improvement in selection programmes. The use of gene-assisted selection as a new source of breeding information can provide extra gains in short periods of time (Gibson, 1994). However, the selection of a gene with a major effect on the selected trait has two collateral effects. First, selection on the major gene reduces the intensity of selection applied at the level of unidentified genes, often denoted as polygenes. Second, as the major gene increases in frequency towards fixation, there is a hitchhiking of polygenes, particularly those closely linked to the major gene (Maynard-Smith & Haigh, 1974), implying a reduction in the effective size of the population. This selective sweep of polygenic variation implies, in turn, the loss of potential polygenic response to selection. Thus, the increased genetic gain from fixation of the major gene occurs at the cost of a reduced response from the polygenic variation (Gibson, 1994; Pong-Wong & Woolliams, 1998; Villanueva *et al*., 1999).

Recent developments in breeding theory aim to reduce this loss in polygenic response when selecting for a known gene of detectable effect. At the risk of oversimplification, we can distinguish between two major approaches among these recent developments. The first approach (hereafter "weighting method") consists of selecting on a performance aggregate of the estimated breeding value for the polygenes and the breeding value for the QTL, and where each aggregate's component is differentially weighted in order to maximize the aggregate's response at a given time horizon. Although early weighting methods

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assumed constant weights over generations (Gibson, 1994; Pong-Wong & Woolliams, 1998), others allowed the dynamic allocation of weights by the use of multiple-stage numerical optimizations (Dekkers & van Arendonk, 1998; Manfredi *et al*., 1998, Chakraborty *et al*., 2002; Dekkers *et al*., 2002; Villanueva *et al*., 2004). This latter advance offered a better compromise between short- and long-term gains than earlier methods with fixed weights. Yet the optimal allocation of weights is based on deterministic predictions for the gain with standard truncation selection.

The second approach (hereafter "path method") first defines a frequency path for the favourable gene at the QTL, which is fixed at a given time horizon, and then maximizes the marginal response for each frequency step of this path (Meuwissen & Sonesson, 2004). Although the objectives in both path and weighting methods are similar, that is to maximize cumulated response over a given time horizon, the way these objectives are achieved differs between the two methods. Whereas the weighting method does not control in a direct way the increase in frequency and the fixation time of the major gene, these are directly imposed in the path method. Under the weighting method, the time horizon over which the optimization operates might not necessarily coincide with the fixation time of the major gene. The weighting method simultaneously operates on the increase in frequency of the favourable gene at the QTL and on the polygenic response, by the choice of optimal QTL and polygene weights, for the best global (QTL and polygenic) response over the time horizon. In contrast, the path method looks at optimal QTL paths for the best polygenic response. This latter approach may be of special relevance when a favourable gene with identified genotypes, affecting either the selected trait or another trait, has been introgressed into the breeding population and is to be brought to fixation within a given desired time with minimum loss in the existing polygenic variation.

The path method circumvents the allocation of optimal weights of the weighting method, but it also raises a new question: that of the choice of the frequency path for the favourable gene. The frequency path proposed by Meuwissen & Sonesson (2004) is such that the selection intensity on the QTL remains constant over generations. Meuwissen & Sonesson (2004), however, did not provide a theoretical justification for the choice of this criterion other than the fact raised by Dekkers & van Arendonk (1998) in their simulation work on weighting methods, by which the implementation of optimal weights led to constant selection intensity on the QTL. Based on theoretical foundations alone, we address here the question of the choice of a frequency path, and present a new path method aimed at minimizing the loss of polygenic response due to a selective sweep, whose frequency path relies on a slightly different principle. We show by basic theoretical arguments that the impact of the QTL fixation on both the effective population size applicable to the polygenes and the selection intensity on the polygenic variation are minimized if the average squared selection intensity on the QTL across generations is minimal, rather than if the selection intensity is strictly constant, as proposed by Meuwissen & Sonesson (2004). Additionally, our path method combines a new feature involving a mating rule, by which mating occurs between carriers of the favourable QTL allele and non-carriers having the best available polygenic values. This mating system is analogous to the compensatory mating proposed by Santiago & Caballero (1995), and is intended to break the negative associations between the QTL and the polygenes by favouring the effective recombination between them.

As often highlighted in evolution studies (Maynard-Smith & Haigh, 1974; Braverman *et al*., 1985; Barton, 1998; Santiago & Caballero, 1998, 2005), the depletion of genetic diversity driven by selective sweeps of major genes may be amplified in a context of physical linkage. None of the existing methods, however, has considered the eventuality of physical linkage between the QTL and its polygenic background. To address this issue we evaluate the efficiency of the new path method under a range of linkage levels, by implementing a locus-based simulation model. The analysis allows us to focus not only on the polygenic response but also on the distribution of gene frequencies for individual polygenes, the percentage of favourable polygenes that are lost by drift during the selective sweep, and the identity of descent of individual neutral genes. Finally, we analyse and discuss the differences between the proposed path and that presented by Meuwissen & Sonesson (2004).

2. Frequency path for the QTL and mating system

Selection for a QTL has two main effects on the genetic variation and selection response from the polygenic background. First, it reduces the selection intensity applied on the polygenes and, accordingly, the genetic gain from selection. Second, it reduces the effective population size applicable to the polygenes, the loss of their variation from genetic drift contributing further to the loss in polygenic genetic response. Thus, the path of increase in gene frequency of the QTL should be derived taking into account both effects.

(i) *Minimization of the impact of fixation of a QTL on the selection intensity for polygenes*

The impact of the QTL fixation on the selection intensity of polygenes can be assessed by considering

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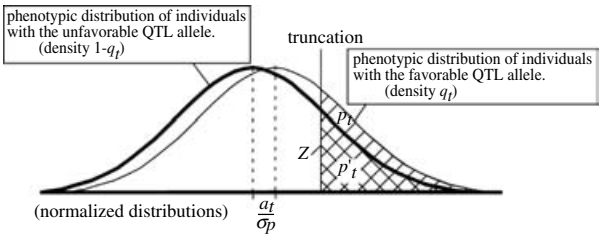

Fig. 1. Phenotypic distribution for the selected trait for carriers and non-carriers of the favourable QTL allele. a_t/σ_P, effect of the QTL in phenotypic standard deviations; p_t and p'_t, proportion of selected individuals carrying and not carrying the favourable allele at generation t, respectively; Z, height of the distribution at the truncation point; q, frequency of the favourable allele at generation t.

that the population has an infinite size. In order to simplify the derivation, let us first assume a haploid population (Appendix A shows the corresponding derivation for a diploid population). Every generation a proportion of individuals P is selected by truncation, that is, selection intensity i is constant over generations. If the QTL were absent, the expected response would be $R=i(\sigma_A^2/\sigma_P)$, where σ_P^2 and σ_A^2 are the phenotypic variance and the genotypic variance for polygenes, respectively.

Now let us consider that there is a QTL desired to be fixed in n generations. Selecting the QTL at generation t is equivalent to assigning it an effect a_t (Fig. 1). A proportion P and an effect of the marker a_t determine the selected proportions p_t and p'_t from the distributions with and without the QTL respectively. In fact, $Za_t/\sigma_p \approx p_t - p'_t$ (see Falconer & Mackay, 1996, pp. 199–201), where Z is the height of the ordinate at the point of truncation (Fig. 1). We can give a_t as a function of the selected proportions:

$$a_t \approx \frac{p_t - p'_t}{Z}\sigma_P = \frac{p_t - p'_t}{P}\frac{\sigma_P}{i}.$$

The proportions p_t and p'_t can be given as functions of the increase Δ_t in frequency (q_t) of the QTL:

$$\Delta_t = q_{t+1} - q_t = \frac{p_t q_t}{P} - q_t \ ;$$

thus

$$p_t = \left(1 + \frac{\Delta_t}{q_t}\right)P$$

and

$$p'_t = \left(1 - \frac{\Delta_t}{1-q_t}\right)P.$$

Then, $a_t \approx \dfrac{\Delta_t}{q_t(1-q_t)}\dfrac{\sigma_P}{i}$.

Considering the above QTL effect, then the expected response of polygenes will be reduced to

$$R_t^* = i\frac{\sigma_A^2}{\sqrt{\sigma_P^2 + q_t(1-q_t)a_t^2}} = i\frac{\sigma_A^2}{\sigma_P}\frac{1}{\sqrt{1+\frac{\Delta_t^2}{q_t(1-q_t)i^2}}}$$
$$\approx R\left(1 - \frac{\Delta_t^2}{2q_t(1-q_t)i^2}\right).$$

The total loss of response due to the increase in the QTL frequency until its fixation at generation n is then

$$\sum_{t=1}^{n}(R - R_t^*) \approx \frac{R}{2i^2}\sum_{t=1}^{n} V_t, \qquad (1)$$

where

$$V_t = \frac{\Delta_t^2}{q_t(1-q_t)} \qquad (2)$$

is the squared selection intensity applied to the QTL (note that Δ_t, the change in gene frequency, is the selection differential at the major gene, and $q_t(1-q_t)$ is the variance of allele frequencies). Therefore, in order to minimize the loss of response in the polygenic background, the average squared selection intensity at the QTL across generations ($\sum_{t=1}^{n} V_t$) has to be minimized.

(ii) *Minimization of the impact of fixation of a QTL on the effective population size*

The theory of effective population size (Robertson, 1961; Santiago & Caballero, 1995; Woolliams & Bijma, 2000) can be easily adapted to predict the consequences of selection of a favourable major gene on unlinked polygenes over consecutive generations. Again, in order to simplify the derivation, let us assume a haploid population (the derivation for a diploid population is given in Appendix B). The expected effective population size (Ne) for unlinked neutral genes resulting from selection on the QTL at generation t can be given as

$$Ne_t = \frac{N}{1 + Q^2 V_t}$$

(Robertson, 1961; Santiago & Caballero, 1995), where N is the constant number of reproductive individuals, Q^2 is the term accounting for the accumulation of selection advantages of individuals over generations (which will be considered nearly constant over generations), V_t is the variance of the contributions in QTL copies by individuals of generation t,

$$V_t = q_t\left(\frac{q_{t+1}}{q_t}\right)^2 + (1-q_t)\left(\frac{1-q_{t+1}}{1-q_t}\right)^2 - 1 = \frac{\Delta_t^2}{q_t(1-q_t)}$$

or, as above, the squared selection intensity applied to the QTL.

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The harmonic mean of the effective size ($\overline{Ne}$) over the selection process on the major gene, from the first generation to fixation at generation n, is

$$\frac{n}{\overline{Ne}} = \frac{1}{Ne_1} + \frac{1}{Ne_2} + \cdots + \frac{1}{Ne_n} = \frac{n + Q^2 \sum_{t=1}^{n} V_t}{N},$$

so that

$$\overline{Ne} = \frac{N}{1 + \frac{Q^2}{n} \sum_{t=1}^{n} V_t}. \quad (3)$$

Therefore, in order to maximize $\overline{Ne}$, again the average squared selection intensity at the QTL across generations ($\sum_{t=1}^{n} V_t$) must be minimized.

Thus, both the impact of the QTL fixation on the reduction of selection intensity and on the reduction of effective population size are minimized through the minimization of the average squared selection intensity at the QTL (see equations 1–3). This target makes the progression of the QTL through the pedigree theoretically distinguishable from that recently proposed by Meuwissen & Sonesson (2004). In this latter case, the target is similar but slightly different, to maintain a strictly constant selection intensity at the QTL (see Section 5 below). If the three genotypes of the major locus are distinguishable, the intended increments of frequency of the QTL can be achieved by selecting the appropriate number of homozygous and heterozygous carriers.

(iii) *System of mating to break the negative associations between the QTL and the polygenes*

The derivation of the previous section shows the procedure to obtain the QTL frequency path that maximizes the effective population size expressed in equation (3). This expression includes a term Q^2 accounting for the accumulation of selective advantages of individuals over generations (Robertson, 1961). As shown by Santiago & Caballero (1995), this term can be virtually cancelled out by the mating between individuals from the largest selected families to individuals from the smallest, which was called *compensatory mating* (see also Caballero *et al.*, 1996 and Sonesson & Meuwissen, 2000). In the present context of selection for a QTL, the equivalent procedure to be applied would consist of mating individuals carrying at least one copy of the major allele to non-carriers, as described in the next section. Under linkage, this mating method yields the additional advantage of increasing the effective rate of recombination between the major gene and polygenes.

3. Simulation methods

(i) *Model and parameters*

Simulations were carried out modelling a diploid population subject to contrasting breeding regimes. Their aim was to simulate the dynamics of a major gene and its linked polygenic background when they were subjected to selection across t generations. Directional selection proceeded on a quantitative trait, whose underlying genetic model comprised a biallelic QTL of large detectable selective effect, and 199 biallelic loci with minor effects (polygenes). Additive gene action was assumed within and between loci for both the QTL and the polygenes. Each of the polygenes had an effect of 1 unit, with genotypic values being 1, 0 and −1, for the favourable homozygote, heterozygote and unfavourable homozygote, respectively. The QTL had an effect A_{mg} (also defined as half the difference between the two homozygotes), which was measured in units of phenotypic standard deviations for the polygenes at the initial generation $t=0$ ($A_{\mathrm{mg}}=1$ or 1·5 phenotypic standard deviations). As a reference for comparisons, we used a model where the QTL is absent (denoted hereafter as *nmg* for "no major gene"). All favourable and unfavourable alleles of polygenic loci were set at intermediate frequencies of 0·5 at $t=0$, while only one copy of the favourable QTL was present at $t=0$. Mutation was assumed to be absent.

In the absence of the QTL, the selection criterion was the phenotypic value from polygenes, which was obtained as the sum of a genotypic value and an environmental deviation. This latter was sampled across generations as a normal deviate with mean zero and variance $\sigma^2_E=[\sigma^2_A(1-h^2)/h^2]$, where h^2 is the narrow-sense heritability for polygenic variation at $t=0$ (values of $h^2=0{\cdot}1$ and 0·4 were considered), and σ^2_A is the additive genetic variance at $t=0$. When a major QTL was considered, the selection criterion was the sum of its genotypic value and the phenotypic value from polygenes. Two contrasting methods based on this sum were applied, as will be explained in the next section.

An additional set of 200 neutral loci was included in order to allow for the calculation of probabilities of identity-by-descent across the pedigree, and the corresponding coancestry coefficients (Lynch & Walsh, 1998). The coancestry per generation was given by the average over all the entries of the matrix of coancestries, including self-coancestries and the reciprocals. At the founder generation, each individual carried two unique alleles per neutral locus. All polygenes and neutral loci were assumed to be uniformly distributed, equally spaced, and alternating across a single chromosome L cM long. The QTL was located in the centre of the chromosome. Several genome lengths were investigated, from $L=10$ to 300 cM, and $L=\infty$,

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which correspond to recombination rates between any two consecutive loci of 0·0005 to 0·005, and 0·5, respectively. Regardless of the level of physical linkage, crossings-over occurred without interference.

Each simulation started as a base population with $N=40$ founder genotypes (half of each sex), assumed to be in linkage equilibrium, and reproduced for a variable number of non-overlapping generations maintaining the same breeding size and sex ratio. A number of $N/2$ mating couples were established each generation, following either of the two mating systems explained below. Each dam produced 10 full-sibs with equal numbers of male and female candidates for selection per family. One thousand replicates in which the QTL became fixed were analysed for each simulated case. Other replicates where the QTL was lost were discarded for analysis. Standard errors for the polygenic response and frequency at selective loci presented below were obtained from the variance between replicates of the corresponding estimates.

(ii) *Breeding systems*

Two contrasting selection methods were applied for comparison: truncation selection based on the sum of the QTL genotype and the polygenic phenotype (in brief TS), and a path selection scheme (PS) based on the number of favourable copies for the QTL and the polygenic phenotype. The TS scheme is equivalent to the standard gene-assisted selection, although with the particularity of using the polygenic phenotype instead of the estimated breeding value from standard BLUP. The PS scheme follows the frequency path that describes the increase in frequency of the favourable QTL up to a given fixation horizon (T_{fix} generations). This path was expressed in terms of the number of favourable copies for the QTL in the selected candidates per generation ($m_{(QTL)i}$ for $t=i$). Note that, under Mendelian segregation, the expected QTL frequency in the offspring before selection equals that of the mating parents, or selected candidates. The optimal vector of $m_{(QTL)}$ was obtained by applying the simulated annealing technique, well adapted to the solution of combinatorial problems (Press *et al*., 1992). The objective was to find the optimal allocation of gene copies from generation $t=1$ to $t=Tfix-1$ (note that $m_{(QTL)0}=1$ and $m_{(QTL)Tfix}=2N$ are constants), so that $\sum_{t=1}^{n} V_t$ is minimal: see equations 1–3).

Simulated annealing proceeded in a large sequence of iterations, each consisting of randomly changing the current vector of QTL frequencies by a single gene swap to create a new solution in the neighbourhood of the current solution. Once the new solution was created the corresponding change in $\sum_{t=1}^{n} V_t$ was computed to decide whether the newly created solution could be accepted as the current solution. When the change in $\sum_{t=1}^{n} V_t$ was negative the newly produced solution was directly taken as the current solution. Otherwise, it was accepted according to the Metropolis's criterion based on Boltzman's probability (Press *et al*., 1992). Once the vector of $m_{(QTL)}$ values was obtained, selection proceeded by finding the set of carriers that made up the required number of copies of the favourable QTL, and that had the maximum polygenic phenotype among all carriers (including homozygotes and heterozygotes). A maximization of the polygenic phenotype was also carried out among non-carriers of the favourable QTL, where the best non-carriers completed the remaining selections up to N. Whenever the resulting number of selected copies of the favourable QTL was one copy below the required number in $m_{(QTL)t}$, and only homozygotes at the QTL were available for subsequent selections, the decision on whether to select the last candidate as a carrier or non-carrier relied on which one of the two had the highest polygenic phenotype.

Two scenarios were considered regarding the mating strategy among selected individuals: random mating (in brief RM), and compensatory mating (CM). This latter is based on two complementary theoretical principles to limit the effects of hitchhiking of the QTL. First, the effective recombination rate between QTL and polygenes is favoured by mating carriers of at least one copy of the favourable QTL preferably with non-carriers. This was performed by ranking sires in ascending order according to the number of copies of the favourable QTL they carried, and their corresponding dam mates in descending order according to the same criterion. This assortment created a negative correlation between mates for the number of copies of the favourable QTL. The second theoretical principle is that the selection intensity on the favourable polygenes is increased when these genes appear preferably associated with the favourable QTL. In practical terms this was attained by mating the homozygotes for the favourable QTL with the best-performing non-carriers, and the heterozygotes with the second-best-performing non-carriers, thus creating a positive correlation between the number of copies of the favourable QTL of the selected carrier and the polygenic phenotype of its non-carrier mate. This CM scheme was applied from $t=0$ in all generations where non-carriers of the favourable QTL were available among the candidates for selection.

Regarding the two alternative mating patterns (RM and CM) and the two selection methods (TS and PS), four combinations of mating and selection procedures were compared. These combinations are denoted hereafter as RMTS, RMPS, CMTS and CMPS, respectively.

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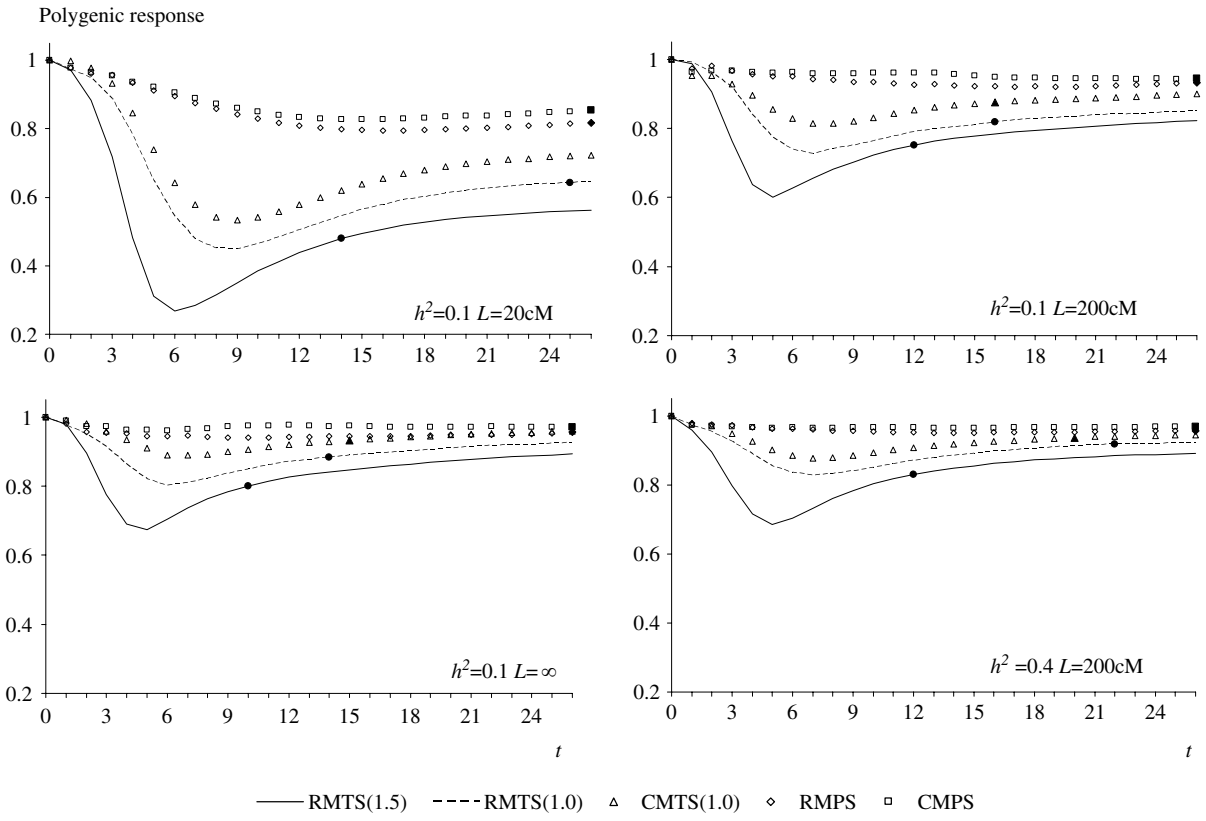

Fig. 2. Polygenic cumulated response of different selection and mating methods expressed as a ratio to the response of *nmg* (without QTL), for different QTL effects (A_{mg} = 1·0 and 1·5, in brackets), two values of heritability (h^2) and different levels of linkage in centimorgans (L). The black symbols denote the generation (t) at which the QTL is fixed. For RMPS and CMPS the fixation time of the QTL is established at T_{fix} = 26 and its effect is irrelevant. RM, random mating; CM, compensatory mating; TS, truncation selection; PS, path selection. Standard errors at t = 26: 0·006–0·0086 (h^2 = 0·1, L = 20 cM); 0·0042–0·0049 (h^2 = 0·1, L = 200 cM); 0·0035–0·0039 (h^2 = 0·1, L = ∞); 0·0025–0·0028 (h^2 = 0·4, L = 200 cM).

4. Results

(i) *Polygenic gain*

Polygenic response is given hereafter in units of measurement of the selected trait. Fig. 2 shows the polygenic cumulated response over generations for models that consider the presence of the QTL, two values of heritability and several linkage levels, expressed as a ratio of the cumulated polygenic response in the absence of the QTL (*nmg* model). Thus, the lower a line is below the value of 1, the higher is the loss of polygenic response with the corresponding breeding method. The figure also shows the fixation times of the QTL, which were within 26 generations, except for CMTS with h^2 = 0·1 and L = 20 cM that was at generation 28. The polygenic response was particularly depressed under RMTS, especially during the period of maximum change of the QTL frequency, i.e. at intermediate frequencies of the QTL. This depression was not entirely recovered in later generations, and was especially conspicuous with large effects for the QTL, strong linkage and low heritabilities. Although following a similar pattern to that of RMTS, the loss in polygenic response was reduced under CMTS (a similar result was observed comparing CMTS and RMTS for a QTL of effect 1·5; not shown). Unlike these previous methods, RMPS and especially CMPS showed little loss in polygenic response, both resulting in the closest levels of response to those of *nmg*. Therefore, both mating and selection tools (CM and PS) brought improvements in polygenic response over RMTS. Yet the highest advantages were observed under the combination of both breeding tools in CMPS. The ranking of breeding alternatives for the highest polygenic response (i.e. CMPS > RMPS > CMTS > RMTS) remained unchanged across the different parametric scenarios considered (not shown).

Unlike Fig. 2, which shows results for a selection horizon of 26 generations, Fig. 3 illustrates a case comparing different fixation times (*Tfix*) for the QTL with CMPS versus RMTS. Two results can be highlighted. First, the benefit of CMPS does not depend exclusively on the choice of a *Tfix* for the favourable QTL longer than those characteristically shown by RMTS. For instance, at equal fixation times for the QTL (compare RMTS(1·0) and CMPS(16), for which the QTL is fixed at t = 16), the advantage of CMPS

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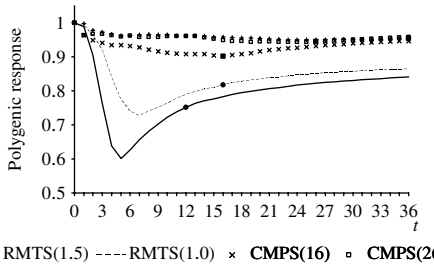

Fig. 3. Polygenic cumulated response of different selection and mating methods expressed as a ratio to the response of *nmg* (without QTL). In brackets, the effect of the QTL (RMTS) or the fixation time (CMPS) in generations (t). Initial heritability $h^2 = 0{\cdot}1$ and linkage $L = 200$ cM. Standard errors at $t = 26$: 0·0033–0·0035 (CMPS); 0·0037–0·0039 (RMTS).

over RMTS was still substantial and did not decrease after the fixation of the favourable QTL. Second, longer selection paths for the QTL brought some extra polygenic response, particularly during the early generations. No further improvement, however, was attained with the longest horizon, $Tfix = 36$, compared with that obtained with $Tfix = 26$. In general, the difference in polygenic response between paths using different fixation horizons under CMPS was substantially smaller than the difference in response between RMTS and CMPS.

Fig. 4 shows the proportion of favourable polygenic alleles that were lost before the fixation of the favourable QTL (Fig. 4*a*), and the level of polygenic response (Fig. 4*b*) and additive genetic variance for polygenes (Fig. 4*c*) at the time of a QTL's fixation, all as a function of chromosome lengths. The polygenic response (Fig. 4*b*) and the additive variance (Fig. 4*c*) are taken as the ratio between the corresponding values assuming the presence of the QTL and those for the *nmg* model (absence of QTL). The proportion of lost alleles at the polygenes can be taken as a measure of the available variability for selection and, therefore, as a predictor of the long-term potential gain from polygenes. Results in Fig. 4*a* indicate that this available variability was substantially reduced with linkage, and that this reduction was more important under RMTS than with CMPS, which showed levels close to those found in the absence of the QTL (*nmg*). Similarly, close linkage reduced substantially the level of polygenic response (Fig. 4*b*), although this reduction was always more important under RMTS than with CMPS. This disadvantage in response of RMTS could be partially attributed to allele losses during the selective sweep, as seen previously in Fig. 4*a*. The same cause, however, cannot be advocated with equal support for the difference in response between *nmg* and CMPS, given the relatively slight differences in percentage of lost alleles between the two procedures. Regarding the levels of additive genetic variance (Fig. 4*c*), CMPS always showed the highest variances, and RMTS the lowest, across the range of chromosome lengths. The difference between CMPS and RMTS was larger the closer the linkage, suggesting that CMPS was particularly efficient in preserving polygenic diversity from selective sweeps under close linkage.

Fig. 5 shows the frequency of favourable polygenic alleles across the chromosome at the time of fixation of the favourable QTL for CMPS and RMTS. For comparison, the average allele frequency is also plotted in the case where the QTL is absent (*nmg*) at the same time period (horizontal broken line). The selective sweep driven by the QTL caused a larger frequency depression under RMTS than with CMPS. The extent of this depression increased with linkage and was particularly important in the vicinity of the QTL. For CMPS, this "damage" in frequencies was less important and more localized around the QTL than with RMTS.

(ii) *Genetic drift and inbreeding*

The lower polygenic response and genetic variance of RMTS relative to CMPS can be partially attributed to genetic drift. Fig. 6 shows the extent of genetic drift for polygenes and neutral loci around the QTL, both for CMPS and RMTS. The quantities represented are the variance of favourable allele frequencies between replicates, for polygenes, and identity-by-descent probabilities, for neutral loci. The same estimates are given for the *nmg* model for the sake of comparison. Both the allelic frequency variance and identity-by-descent showed similar patterns for the two methods, resulting in a conspicuous drift peak centred on the QTL. RMTS resulted in higher drift levels than CMPS across the chromosome, with an increasing difference between the two methods with linkage. CMPS restricted efficiently the extent of the drift peak caused by the QTL, attaining drift levels at the base of the peak similar to or even lower than those shown by *nmg*.

5. Discussion

The selective sweep of variation caused by the increase in frequency of a major selected gene has two collateral effects. The first is the reduction in selection response from polygenes, which can be attributed to a diminution in the selection intensity that is applied to them (Pong-Wong & Woolliams, 1998). The second is the decrease in effective population size (Robertson, 1961; Santiago & Caballero, 1995; Woolliams & Bijma, 2000) caused by the selection of the QTL which, in turn, further affects the long-term polygenic response. This effect is exacerbated for the polygenes closely linked to the selected QTL (Santiago &

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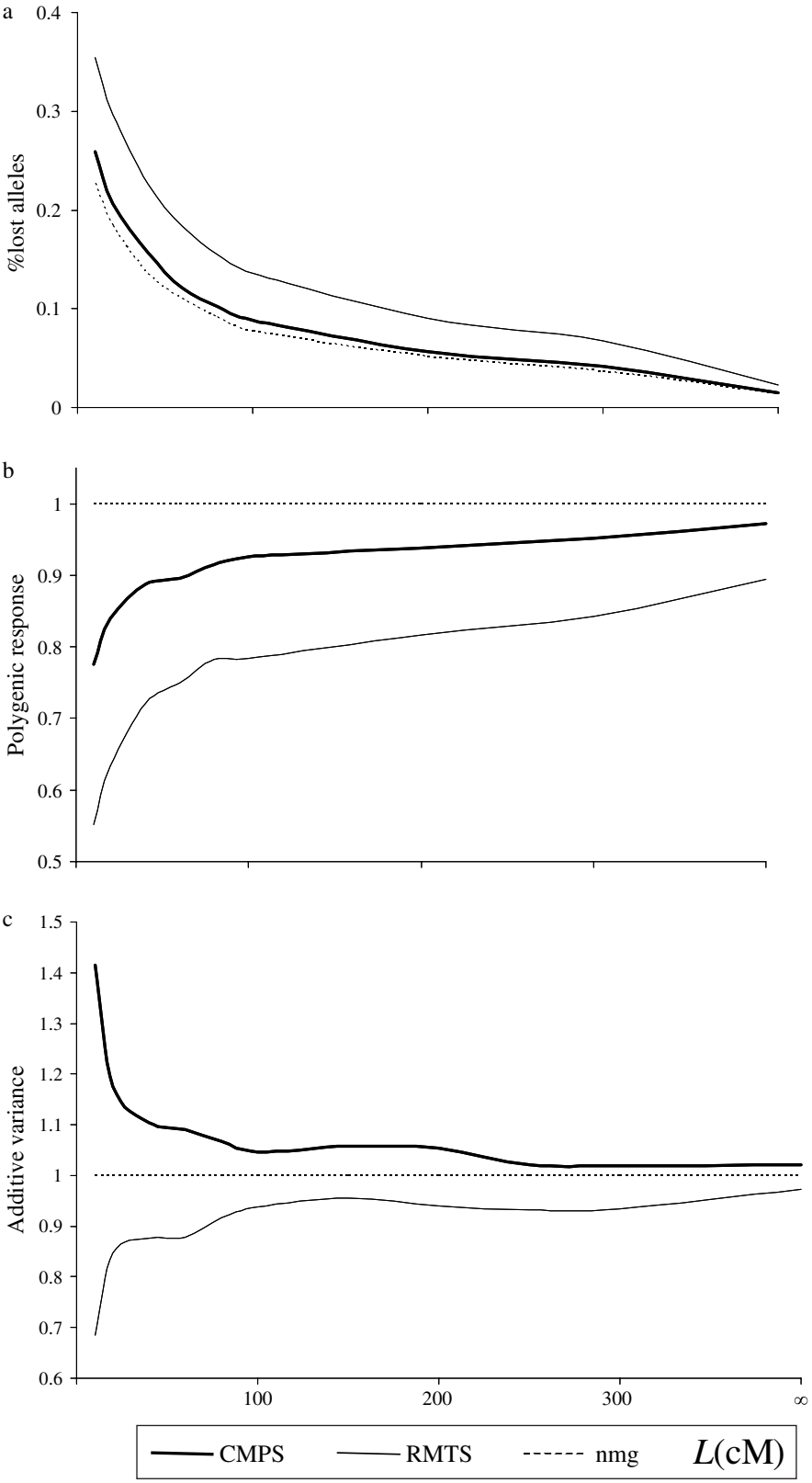

Fig. 4. (*a*) Proportion of favourable polygenic alleles that are lost at the time of fixation of the favourable QTL ($T_{fix}=26$ for CMPS, variable for RMTS), and at $t=26$ for *nmg*, as a function of the level of linkage in centimorgans (L). (*b*) Polygenic cumulated response at the QTL fixation time ($T_{fix}=26$ for CMPS, variable for RMTS), and $t=26$ (*nmg*), relative to the response with *nmg*. (*c*) Additive polygenic variance at the QTL fixation time ($T_{fix}=26$ for CMPS, variable for RMTS), and $t=26$ (*nmg*), relative to the variance with *nmg*. Initial heritability $h^2=0{\cdot}1$. RMTS with QTL effect $A_{mg}=1{\cdot}0$. Standard errors of polygenic cumulated response at the time of fixation of the favourable QTL for RMTS: 0·0039 ($L=\infty$) – 0·0077 ($L=10$ cM); for CMPS: 0·0029 ($L=\infty$) – 0·007 ($L=10$ cM).

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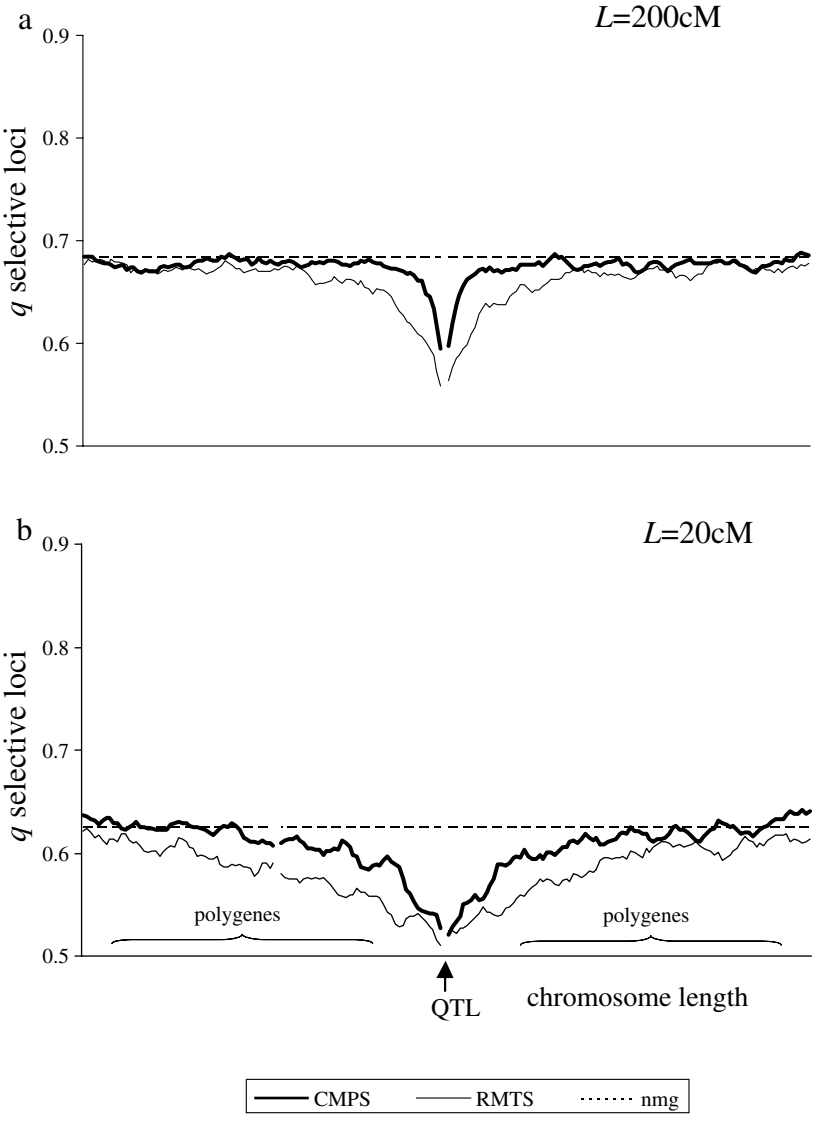

Fig. 5. Spectrum of frequencies of favourable polygenic alleles across the chromosome length (*x*-axis) at generation 26 for RMTS (with a QTL at the centre of the chromosome with effect $A_{mg}=1{\cdot}0$) and CMPS. The horizontal broken line is the average allele frequency across the chromosome for *nmg* at $t=26$. Initial heritability $h^2=0{\cdot}1$ with two levels of linkage in centimorgans (L). Standard errors at $t=26$: 0·015 (chromosome's centre), 0·01 (extremes) with 200 cM; 0·016 (centre), 0·012 (extremes) with 20 cM.

Caballero, 1998; this paper). Whereas the first effect has been the focus of most previous studies of QTL selection, the second has received less attention. Our results showed that selective sweeps driven by a major known QTL are responsible for substantial permanent losses in neighbouring polygenic variability, and that they might also affect more distant loci for larger QTL effects. The development of specific breeding tools to palliate these eventual losses is, therefore, fully justified.

In one of the approaches followed, which we have called the weighting method, the objective is to achieve the maximum accumulated genetic gain over a time horizon from both the QTL and polygenes (Dekkers & van Arendonk, 1998; Manfredi *et al*., 1998; Villanueva *et al*., 2004). In general, the weighting method does not explicitly control the QTL path through the selection process, although Settar *et al*. (2002) carried out an explicit constraint on the QTL frequency where the QTL path is set by the user to meet particular demands, like economic targets. The weighting method depends on the availability of long-term deterministic predictions for the genetic gain. These predictions, developed for the case of recurrent conventional truncation selection (Dekkers & Chakraborty, 2001), are needed to evaluate the feasible sets of QTL weights over the optimization process for genetic gain maximization.

The alternative approach, which we have called the path method, assumes a fully detectable QTL, which allows the application of an explicit path for the progression of the QTL allele over generations up to the

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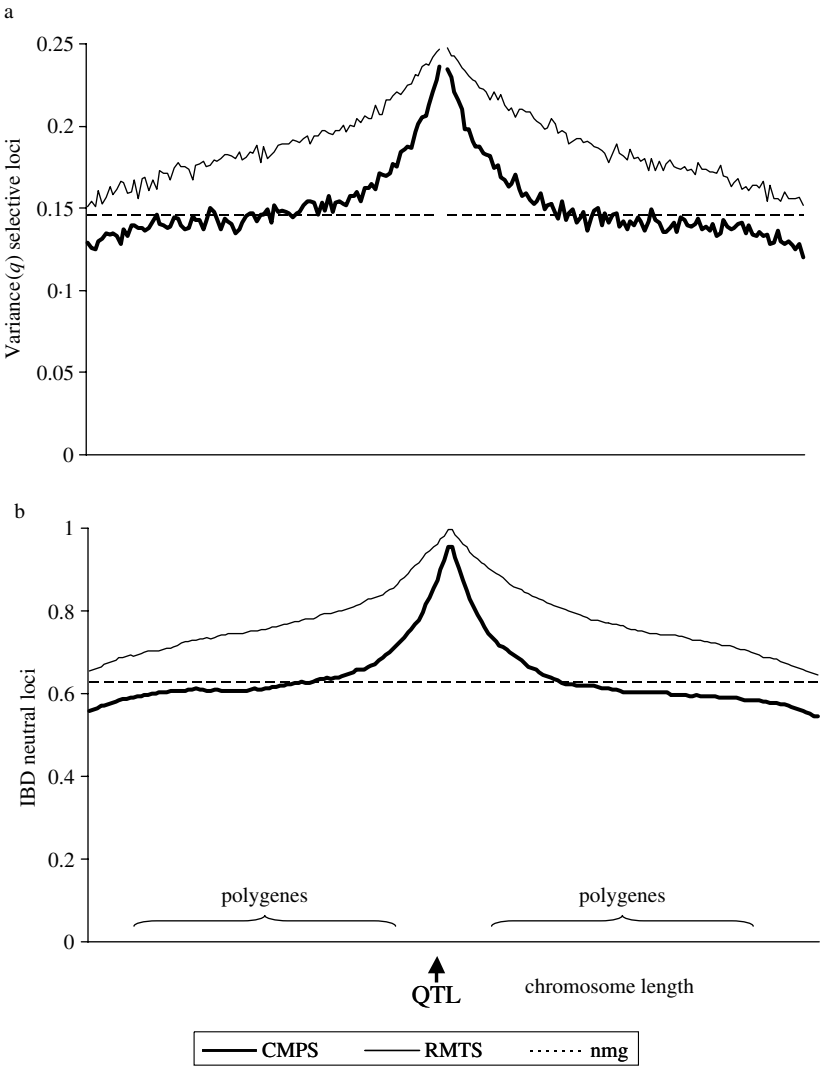

Fig. 6. Spectrum of the variance between replicates of allelic frequencies at selective polygenic loci across the chromosome length (*x*-axis) (graph *a*), and identity-by-descent (IBD) at neutral loci (graph *b*), both at the time of fixation of the favourable QTL, for a level of linkage of 20 cM and for breeding methods RMTS (with a QTL at the centre of the chromosome with effect $A_{mg}=1{\cdot}0$) and CMPS (with fixation time $T_{fix}=26$). The horizontal broken line corresponds to the average levels for *nmg* at $t=26$. Initial heritability $h^2=0{\cdot}1$. Standard errors: 0·0017 (chromosome's centre), 0·0074 (extremes) with RMTS; 0·003 (centre), 0·0073 (extremes) with CMPS.

fixation horizon (Meuwissen & Sonesson, 2004). This method circumvents the need for determining the optimal QTL weights, as the fixation of the favourable QTL is decided *a priori* without dependence on the polygenic background. The path proposed by Meuwissen & Sonesson (2004) was derived in such a way that a constant selection intensity is applied at the QTL for a given selection horizon. The reasoning behind this choice was the simulation evidence by which the optimization of QTL weights over generations leads to approximately constant selection intensity at the QTL, first noticed by Dekkers & van Arendonk (1998).

The method presented here shares the same principle as that of Meuwissen & Sonesson (2004) (denoted hereafter the M&S path), thus to decide the progression of the QTL allele up to its fixation. However, our principle, relying on effective population size and selection response theory (hereafter the PS path), is slightly but functionally different. The rationale of the PS path is to minimize the average squared selection intensity at the QTL across generations, whereas that of the M&S path is to keep a strictly constant value. Thus, whereas the PS path is equivalent to minimizing the sum of $\sum_{t=1}^{n} V_t = \sum_{t=1}^{n} \Delta_t^2 / [q_t(1-q_t)]$ (see equations 1–3), the M&S path is equivalent to minimizing the variance among all the terms $\Delta_t^2 / [q_t(1-q_t)]$. The M&S path was derived by the recurrent deterministic approach based on equation 5 of Meuwissen & Sonesson (2004). In order to compare the two paths on identical grounds, the M&S path was also obtained by simulation, by using an annealing

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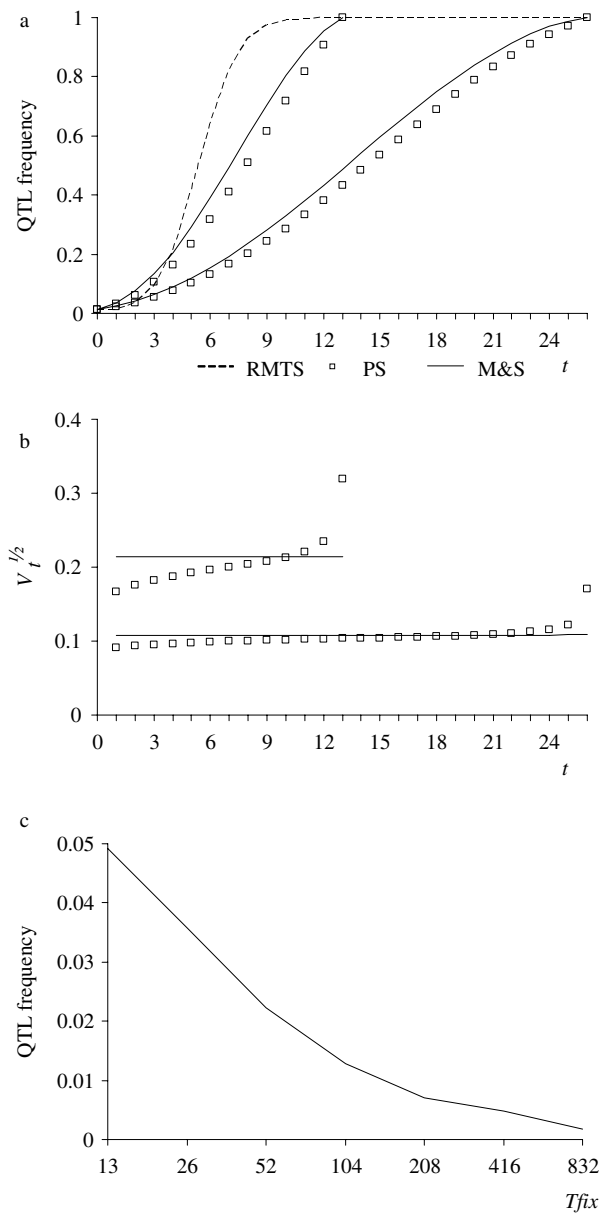

Fig. 7. (*a*) QTL frequency path across generations for RMTS with QTL effect $A_{mg}=1{\cdot}0$ and $L=20$ cM. Other strategies (with a QTL fixation time of $T_{fix}=13$ or 26) are: PS, minimum average of the squared selection intensity; M&S, constant selection intensity obtained by minimum variance of the squared selection intensity (equivalent to the recurrent deterministic approach of Meuwissen & Sonesson, 2004). (*b*) Selection intensity on the QTL allele ($V_t^{1/2}$; see equation 2) across generations for the same cases of PS and M&S as in (*a*). (*c*) Average difference per generation in gene frequency between the PS and M&S paths for different times to fixation of the QTL.

function for minimizing the variance of terms in $\sum_{t=1}^{n}\Delta_t^2/[q_t(1-q_t)]$. The resulting path was identical to that obtained by the recurrent deterministic approach. Both M&S and PS were implemented assuming random mating. The two paths are plotted in Fig. 7*a* for QTL fixation times of 13 and 26 generations, together with the path described by a QTL allele under RMTS, as a reference.

The M&S path describes an approximately symmetrical curve from the initial $p=1/2N$ to $p=1$, where an equal number of generations occur before and after $p=0{\cdot}5$. The PS path, however, is asymmetrical relative to $p=0{\cdot}5$, showing a slower rate of increase of the QTL allele during the initial two-thirds of the QTL segregation period, with faster increases during the last generations before fixation. The explanation can be seen in Fig. 7*b*, which shows the selection intensity ($V_t^{1/2}$) applied to the QTL for each of the paths. Whereas the M&S path applies a constant intensity, the PS path applies a lower intensity in the early stages and a higher intensity in the later ones. Due to the counteracting effect between the selection pressure on the QTL and that on the polygenes, less selection pressure on the QTL corresponds to a greater emphasis of the selection pressure on the polygenes. Thus, the PS path favours the progression of the polygenes relaxing the pressure on the QTL during the first stages of the process, when the risk of loss caused by drift and hitchhiking is highest (Caballero *et al*., 1996), and increases the pressure on the QTL, relaxing that on the polygenes, when most of the favourable polygenic variability has been efficiently ensured.

The two paths become closer to each other the longer the fixation time of the QTL, as the average selection intensity on the QTL becomes smaller. This is shown in Fig. 7*c*, which presents the average difference in frequency between the two paths per generation for increasing fixation times of the QTL. An infinite time to fixation is equivalent to assuming a continuous time process, in which case the two paths are identical (J. A. Woolliams, pers. comm.). However, for a realistic finite-generation discrete model, the two paths differ from each other as shown in Fig. 7*a*, *b*.

These differences in QTL paths between the two methods can have consequences in terms of the management of the polygenic variation. To illustrate this, we show in Fig. 8*a* and *b* the difference in polygenic gain and coancestry per generation, respectively, between the PS and M&S paths, together with filled symbols to indicate when the difference was significantly larger than zero. Both the differences and the standard errors of the differences were obtained from replications of the simulated populations. Without linkage ($L=\infty$), PS obtained higher polygenic response than M&S once the favourable QTL became fixed (Fig. 8*a*), also accumulating less coancestry (Fig. 8*b*). With $L=20$ cM, the advantage in polygenic response of PS over M&S was more important than that observed with $L=\infty$, and covered most of the generations previous to the QTL's fixation. This latter happened at the cost of less important differences in

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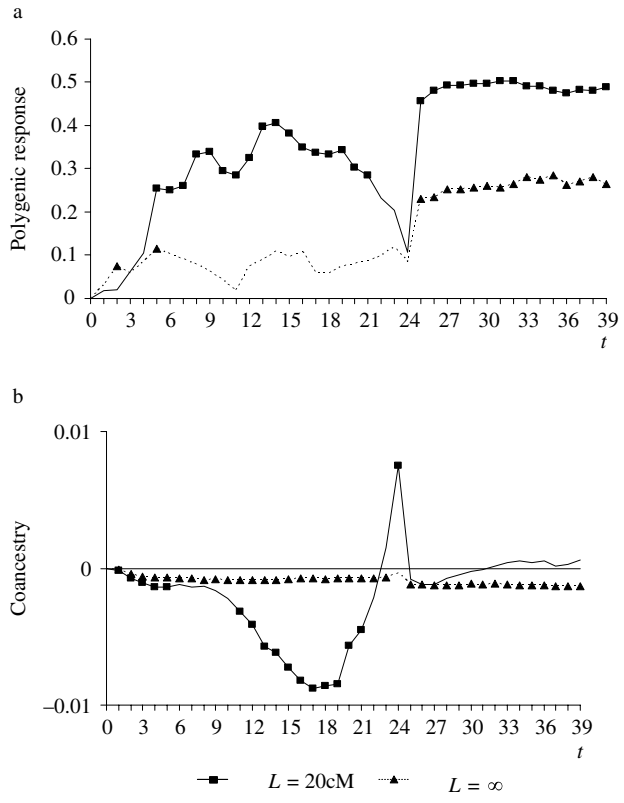

Fig. 8. (*a*) Difference in polygenic response between PS and M&S across generations, for two levels of linkage in centimorgans (L) and QTL fixation time $T_{fix}=26$. (*b*) Difference in coancestry between PS and M&S across generations. Initial heritability $h^2=0{\cdot}1$. Filled symbols in graphs (*a*) and (*b*) indicate differences significantly larger than zero at a 5% level.

coancestry after the QTL's fixation. The temporal reduction of the advantage in polygenic response of PS around the QTL's fixation, when the increase in frequency of the QTL is at a slower rate with M&S than with PS, was not enough to reverse the PS's cumulated advantage attained earlier. In conclusion, PS was more efficient than M&S in converting polygenic variation into genetic gain, especially under strong linkage, as higher levels of polygenic gain were obtained without impairing the coancestry levels.

An aspect often ignored in the optimization of breeding schemes is the possibility of applying non-random mating designs (Caballero *et al.*, 1996). Santiago & Caballero (1995) suggested the compensatory mating system, by which negative assortative mating is imposed such that males of the largest selected families are mated with females of the lowest selected families, to minimize the rapid progression driven by directional selection of successful lineages. Here, we applied the same principle of compensatory mating in the CM strategy, where the successful lineages are those carrying the favourable QTL. The CM strategy is expected to be more efficient at intermediate frequencies of the QTL, when the number of carriers approximately equals that of non-carriers. It also improves its efficiency the longer the time to fixation of the QTL, as more generations are available to accomplish the mating system. Our results suggest that CM is beneficial both if applied alone or in combination with PS selection. Its benefits are also larger under linkage (cf. RMTS and CMTS in Fig. 2*a*, *c*). The reason is that CM increases the frequency of heterozygotes (Santiago & Caballero, 1995) and, hence, favours the efficiency of recombination.

Manfredi *et al.* (1998) carried out one of the few mixed inheritance studies considering a mating structure according to the parental genotypes of a biallelic QTL. They optimized the proportion of descendants born from each of the nine classes according to the genotypes of the mating parents, in order to maximize the cumulated discounted genetic gain of QTL and polygenes over a given time horizon. Contrary to CM, the strategy of Manfredi *et al.* (1998) favours the mating between carriers, driven by a discount rate, while penalizing the mating between carriers and non-carriers. As a result, a rapid fixation of the favourable QTL was obtained, often before six generations under the conditions of their simulations, resulting in a high weight given to the short-term performance over longer periods. It is likely that this method would not prevent the negative effects of selective sweeps in the long run, and high levels of inbreeding would be expected, especially if the favourable QTL starts at low frequencies.

We have shown the way by which the optimal frequency path for a QTL should be obtained given its initial frequency and its final frequency (fixation is not a requisite for the model). There is a single optimal path for a particular final QTL frequency, which maximizes genetic gains for polygenes. Under this perspective, the problem of maximizing the global response for a function of QTL and phenotypic weights is equivalent to the problem of finding the final QTL frequency that maximizes the global response for that function. It is thus possible to ascertain what is the most appropriate QTL frequency at the time horizon so as to balance the earlier and later gains.

Although our theoretical model is of simple conception, with some basic assumptions, we do not expect this simplicity to distort the outcome fundamentally. First, comparisons were made between systems of similar complexity (i.e. M&S and PS). Second, transient effects of selection on genetic variability, which are not explicitly taken into account in the model, are not expected to be essentially different between the alternative paths considered here. Our greatest assumption was probably to deduce the selective effect of the major gene from its quantitative effect and selection pressure. Here, we followed standard theoretical arguments in Falconer &

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Mackay (1996). Our simulations did not consider the possibility of applying optimum contribution selection (Villanueva *et al*., 2004; Meuwissen & Sonesson, 2004) in our PS scheme, but the good performance of the QTL frequency path in PS is inherent to the path itself, and it is therefore unlikely to be diminished by using that selection tool. Finally, the study only considered a single QTL, but the main principles behind PS could be applied to multiple QTLs. *A priori*, an optimal path could be drawn for each newly identified gene, and optimization could be developed to best fit selection to the multiple paths.

Appendix A. Minimization of the impact of fixation of a QTL on the selection intensity for polygenes: a diploid model

Let us assume an infinite population of diploid individuals. A quantitative trait is controlled by an infinite number of unlinked and additive genes (polygenes). The phenotypic variance for the trait is $\sigma^2_P=\sigma^2_A+\sigma^2_E$, where σ^2_A and σ^2_E are the additive and the environmental variances, respectively. The selection intensity i is constant over generations. At any generation t, the expected response due to polygenes is $R=i(\sigma^2_A/\sigma_P)$. At generation $t=0$, there is a known major QTL with alleles M and m (M at frequency q_0) that is desired to be at frequency q_n in n generations. The frequencies of the three genotypes MM, Mm and mm are those expected at Hardy–Weinberg equilibrium. Selection induces additive (a_t) and dominance (d_t) effects on the QTL. If we take into account these effects, the expected response of polygenes will be reduced to

$$R^*_t=i\frac{\sigma^2_A}{\sqrt{\sigma^2_P+\sigma^2_{Mat}+\sigma^2_{Mdt}}},$$

where $\sigma^2_{Mat}=2q_t\,(1-q_t)\,\alpha_t^2$ and $\sigma^2_{Mdt}=(2q_t\,(1-q_t)\,d_t)^2$ are the variances of the additive and dominance effects induced by the QTL, respectively. The term α_t is the average effect of the gene, $\alpha_t=a_t+d_t\,(1-q_t)\,q_t$ (see Falconer & Mackay, 1996).

The additive variance σ^2_{Mat} can be also given as a function of the observed increase in QTL frequency Δ_t from generation t to $t+1$. To do this, we equate the expected response with the observed response of the QTL given in phenotypic units,

$$i\frac{2q_t(1-q_t)\alpha_t^2}{\sigma_{P^*}}=2\alpha_t\Delta_t,$$

where $\sigma^2_{P^*}=\sigma^2_P+\sigma^2_{Mat}+\sigma^2_{Mdt}$. Then,

$$\alpha_t=\frac{\Delta_t}{q_t(1-q_t)}\frac{\sigma_{P^*}}{i}$$

and

$$R^*_t=i\frac{\sigma^2_A}{\sqrt{\sigma^2_P+2\frac{\Delta_t^2}{q_t(1-q_t)}\frac{\sigma^2_{P^*}}{i^2}+\sigma^2_{Mdt}}}.$$

The term σ^2_{Mdt} does not contribute to the increase in QTL frequency but it reduces the response of polygenes. This non-additive variance can be virtually cancelled out by selecting a proportion of heterozygotes Mm that is equal to the average of the selected proportions of the two homozygotes. Thus,

$$R^*_t=i\frac{\sigma^2_A}{\sqrt{\sigma^2_P+2\frac{\Delta_t^2}{q_t(1-q_t)}\frac{\sigma^2_{P^*}}{i^2}}}\approx i\frac{\sigma^2_A}{\sigma_P}\frac{1}{\sqrt{1+\frac{2\Delta_t^2}{q_t(1-q_t)i^2}}}\approx R\left(1-\frac{\Delta_t^2}{q_t(1-q_t)i^2}\right).$$

The total loss of response over the term of selection of the marker is

$$\sum_{t=1}^{n}(R-R^*_t)\approx\frac{R}{i^2}\sum_{t=1}^{n}\left(\frac{\Delta_t^2}{q_t(1-q_t)}\right),$$

as for the haploid model (equation 1), except for a factor of 2.

Appendix B. Minimization of the impact of fixation of a QTL on the effective population size: a diploid model

We shall use the same terminology as in Appendix A. Here, a finite population of full-sib families is assumed, but the population size is large enough to consider that the effect of drift on the polygenic variation is small, i.e., σ^2_A is constant over the time to fixation of the QTL. If the effect of the QTL on *Ne* is not considered,

$$Ne_t=\frac{N}{1+Q_t^2C^2}=\frac{N}{1+Q^2i^2\rho}=\frac{N}{1+Q^2i^2\frac{\frac{1}{2}\sigma^2_A}{\sigma^2_p}}$$

(Santiago & Caballero, 1995).
We also assume that the cumulated effect of selection on *Ne* (Q^2) is nearly constant over generations. C_t^2 is the variance of the contributions from generation t to $t+1$, and ρ is the intraclass correlation of full sibs.

Now, we take into account the additive and the dominance effects of the QTL. Then, the variance of the contributions increases, and *Ne* decreases to

$$Ne^*_t=\frac{N}{1+Q^2i^2\frac{\frac{1}{2}\sigma^2_A+\frac{1}{2}\sigma^2_{Mat}}{\sigma^2_{p^*}}+i^2\frac{\frac{1}{4}\sigma^2_{Mdt}}{\sigma^2_{p^*}}}=\frac{N}{1+Q^2i^2\frac{\frac{1}{2}\sigma^2_A+\frac{\Delta_t^2}{q_t(1-q_t)}\frac{\sigma^2_{P^*}}{i^2}}{\sigma^2_{p^*}}+i^2\frac{\frac{1}{4}\sigma^2_{Mdt}}{\sigma^2_{p^*}}},$$

where the asterisks imply that the QTL is included. Note that Q^2 is only associated with the additive

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component of the variance of the contributions. The dominant variance σ^2_{Mdt} does not contribute to the increase in QTL frequency but it reduces *Ne*. This variance can be cancelled out by selecting a proportion of heterozygotes *Mm* that is the average of the selected proportions of the two homozygotes. Thus, the equation is simplified to

$$Ne_t^* = \frac{N}{1+Q^2 i^2 \frac{\frac{1}{2}\sigma^2_A + \frac{\Delta_t^2}{q_t(1-q_t)}\frac{\sigma^2_{p*}}{\beta^2}}{\sigma^2_{p^*}}} = \frac{N}{1+Q^2 i^2 \frac{\sigma^2_A}{2\sigma^2_{p^*}} + Q^2 \frac{\Delta_t^2}{q_t(1-q_t)}}.$$

Now, we shall calculate the average effect over the time of selection of the QTL assuming that σ^2_{p*} is nearly constant over generations,

$$\frac{n}{\overline{Ne^*}} = \frac{1}{Ne_1^*} + \frac{1}{Ne_2^*} + \cdots + \frac{1}{Ne_n^*} = \frac{n + nQ^2 i^2 \frac{\sigma^2_A}{2\sigma^2_{p*}} + Q^2 \sum_{t=1}^{n}\left(\frac{\Delta_t^2}{q_t(1-q_t)}\right)}{N}.$$

Therefore,

$$\overline{Ne^*} = \frac{N}{1+Q^2 i^2 \frac{\sigma^2_A}{2\sigma^2_{p^*}} + Q^2 \frac{1}{n}\sum_{t=1}^{n}\left(\frac{\Delta_t^2}{q_t(1-q_t)}\right)},$$

which is analogous to equation (3) for the haploid model.

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