STRATEGIC OPTIMISATION OF SHORT- AND LONG-TERM GAIN AND INBREEDING IN MAS AND NON-MAS SCHEMES

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BACKGROUND

The first question that should be addressed is: why distinguish the optimisation of short- and long-term gain ($\Delta G$) in a breeding scheme? Why should a scheme that is optimal for short-term gain become sub-optimal for long-term gain? The answer is that the risks attached to achieving the objective of the breeding scheme will change with the perspective. Ignoring such risks in practical livestock breeding (where even the long-term is, say, ten generations) will tend towards solutions that argue for selecting the fewest possible males and females for breeding that reproductive biology will allow. Nevertheless there are clear risks in genetic selection that can be identified, even in the short-term. It is the procedures to manage these risks that provide the framework for much of the strategic optimisation to be described in this paper.

The merit of the offspring that are born as a result of selecting another generation of parents are genetically uncertain for all traits of importance, whether in traits measured and evaluated for the selection index, or in yet unrecognised traits that are important for fitness (e.g. diseases such as CVM and BLAD in dairy cattle). This uncertainty is the primary genetic source of risk in managing a breeding scheme. For evaluated traits in the selection index, parents are selected with imperfect accuracy, and consequently the genetic merit of the offspring may be much higher or much less than expected, and the latter can cause immediate problems to a breeding company in a competitive environment. Fitness traits, such as disease susceptibilities, are often recognised only retrospectively, by large changes in gene frequencies ($\delta q$). Unrecognised traits may be neutral with respect to the selection objective, yet the potential extent of undesirable changes in frequency is a problem that needs to be, and can be, managed.

Therefore whilst expected benefits are determined by the expected genetic changes, the risks are genetically determined by the distribution of potential genetic changes. A simple description of these deviations from their expected values is the variance. Therefore relevant genetic measures of risk are $V_{\Delta G}$, the error variance of predicted $\Delta G$, and $\Delta F$ which is associated with $\text{Var}(\delta q)$. This justification for managing $\Delta F$ as a design element is different from arguments that rely solely upon inbreeding depression and loss of genetic variation in the selected trait ($\sigma_A^2$). When calculated assuming the infinitesimal model, the impact of loss of $\sigma_A^2$ in the selected trait may be small over time horizons that are practical in livestock breeding, although in mutation models with selection the probability of loss of rare alleles with selective advantage increases with $\Delta F$ (Caballero and Santiago, 1998).
RISKS AND TIME HORIZONS

There are occasions when time-horizons are short: for example, where particular commercial lines may be developed for specific purposes and the anticipated lifetime of the line may be very few generations. In these circumstances the fitness of future generations within the line is less of a risk than failure to deliver the anticipated benefits, and $V_{AG}$ would be more relevant than $\Delta F$. $V_{AG}$ over 1 generation can be described as $c^T Ec$ (with a term depending on the Mendelian samplings which will reduce as the reciprocal of the total number of offspring), where $c$ is the vector of desired contributions to the offspring gene pool made by individual candidates (e.g. if $c_i = 0$, candidate $i$ is not used), and $E$ is the matrix of prediction error (co)variances for the estimated breeding values (EBV). Meuwissen and Woolliams (1994b) note that $E = (Z^T R^{-1} Z + A^{-1} \sigma^2_A)^{-1}$, where $R$ is the (co)variance matrix of environmental effects of records, $Z$ is the design matrix relating records to animals, and $A$ is the numerator relationship matrix. Since the risks in the longer term arise from more than the recorded traits, there is a need to down-weight of the component dependent on $R$, so the matrix tends to $A \sigma^2_A$ as the time horizon extends. The term $c^T Ac$ is twice the inbreeding coefficient of the next generation with fully random union of gametes. Thus the expansion of time horizons evolves, heuristically, from managing $E$ (and $V_{AG}$) to managing $A$ (and $\Delta F$) i.e. equivalent to moving from the matrix of prediction errors conditional on both data and pedigree to the matrix conditional on pedigree alone. It is also the case that the choice of constraint will reflect time horizons, so setting a generous constraint on $\Delta F$, or a low cost, reflects a greater risk preference.

MANAGEMENT OF $V_{AG}$

Methodology. Woolliams and Meuwissen (1993) formulated the problem as:

$$\text{find } c \text{ to maximise } c^T g - \lambda c^T Ec, \text{ subject to } 0 \leq c_i \leq \frac{1}{2}, \text{ and } \sum c_i = 1 (1)$$

where $g$ is the vector of estimated breeding values (EBV), and $\lambda$ may be either a cost factor for error variance, or a Lagrange multiplier that can be chosen to constrain $c^T Ec$ to be less than some predetermined value. This formulation introduces the idea of a ‘quadratic index’ as a tool for managing risks, so called since the selection criterion $c^T g - \lambda c^T Ec$ is technically a ‘quadratic form’ in $c$. Note, as mentioned above, that if $\lambda = 0$ and risk is ignored, the selection would result in 1 male and 1 female being selected, both with the maximum $g_i$ for their sex. Thus the selection of more than one individual per sex points to an implicit risk policy.

Application. Woolliams and Meuwissen (1993) found that in a simple dairy-breeding scheme, more gain could be obtained by favouring higher prediction errors (i.e. $\lambda > 0$ in Eqn. 1) although this was achieved only with a substantial increase in $V_{AG}$. Therefore Meuwissen and Woolliams (1994a) developed a full deterministic model to examine the need for maintaining a formal system of progeny testing compared to relying on young bulls from a nucleus system, and making comparisons at the same CV for $\Delta G$. The conclusions were that schemes with formal progeny testing gave more gain when compared at the same CV than those without testing and were therefore more robust. For a CV of 0.05 over a 10-year period, the progeny test gave approximately 10% more response. This benefit reduced as the CV increased and for very large CVs may reverse.
MANAGEMENT OF ∆F

Using the A-matrix. The methodology for managing ∆F can be developed by substituting A for E in equation (1) and this was the route followed by Wray and Goddard (1994), Brisbane and Gibson (1994), and Meuwissen (1997) i.e.

\[
\text{find } c \text{ to maximise } c^T g - \lambda c^T A c, \text{ subject to } 0 \leq c_i \leq \frac{1}{2}, \text{ and } \sum c_i = 1
\] (2)

At each time, it is necessary to find the value of \( \lambda \) that allows \( \frac{1}{2}c^T A c \) (the group kinship) to satisfy the constraint on ∆F. If at time t the group kinship of the selected parents was \( C_t \), then at time t+1, the group kinship must be \( C_t + \Delta F(1-C_t) \). With these modifications the breeding scheme will have a constant rate of ∆F, and at each stage the gain is maximised by the algorithm of solution. Meuwissen (1997) gives such an algorithm together with some near-optimal modifications to cater for other constraints, such as fixed equal contributions for females. With more complex constraints the solutions can be found using genetic algorithms and Kinghorn (in this Congress) discusses the opportunities for such solutions. The solutions, \( c \), of (2) are often referred to as ‘optimal contributions’; they are contributions to the next cohort but should not be confused with long-term contributions (see later).

Equation (2) does not include all the information that is required to maximise gain with a constraint on ∆F in breeding schemes (as will be shown later). Some understanding of why this is so, and what modifications are required arises from examining the problem via theory of genetic contributions, which also provides a route for strategic optimisation.

Unified Theory of Genetic Contributions. Woolliams and Thompson (1994) introduced the theory of genetic contributions. The long-term genetic contribution of an individual (\( r_i \)) is the proportion of genes it contributes in the long-term to the population and they showed that:

(i) \( \Delta F = \frac{1}{4} \sum r_i^2 \) and (ii) \( \Delta G = \sum r_i a_i \) (3)

where \( a_i \) is the Mendelian sampling term of i. Grundy et al. (1998) showed that the optimal solution for the problem of maximising AG at a fixed ∆F, was to linearly allocate individuals according to their Mendelian sampling term, i.e. \( r_i = 0 \), if \( a_i < u \) and \( r_i = b(a_i - u) \) otherwise. As ∆F becomes more restrictive then \( u \) decreases and \( b \) decreases. See Figure 1(a).

![Figure 1](image-url)

Figure 1. (a) shows the ideal relationship between \( r_i \) and \( a_i \); whereas (b) shows the inevitable compromise in selection schemes.
However the Mendelian sampling terms are not known and so the best that can be hoped for is that the individuals are utilised in relation to their estimated Mendelian sampling terms. In multiple generations it is not possible to independently manage the long-term contribution of individuals. Changing the contribution of an individual alters the contributions of all its ancestors, and importantly changing the contribution of a sire through his offspring alters the contribution of at least one of its mates. Therefore the compromise that is arrived at will be similar to Figure 1(b): the deviations from the line shown in Figure 1(b) may be regarded as unavoidable ‘contribution errors’, the sum of these squared deviations represents the portion of $\sum\tau_i^2$ that is not generating gain efficiently. Efficient schemes will minimise the squared deviations allowing $u$ to be greater, the regression line steeper, thereby generating more gain.

Grundy et al. (1998) showed that solving equations (3) for each generation and using selection alone to maximise gain with $\Delta F$ constrained, was equivalent to the quadratic index in equation (2) with $A$ substituted by a matrix $A^*$, broadly similar in construction to $A$ (see reference for details). With $A^*$, the constraint at time $t+1$ is simply $C_t + \Delta F$. Providing the constraints are correctly applied the methods of Meuwissen (1997) and Grundy et al. (1998) though different, are both effective in managing $\Delta F$ and give very similar solutions. Grundy et al. (1998) showed in theory, and Avendaño shows empirically (unpublished results) that at all times (from initial selection through to convergence of $r_i$) the quadratic index in equation (2) is attempting to manage individual contributions in relation to the best available information on their Mendelian sampling term not their breeding value i.e. as shown in Figure 1(b).

**Implications and applications for selection.** The quadratic index provides a flexible way of making selection decisions that allows the management of $\Delta F$. This has been shown by the publications listed above, but the details of findings will not be described here. Nevertheless the following points should be noted:

(i) There is no doubt that if a breeding scheme uses truncation selection based upon BLUP then the breeding scheme will have a greatly increased $\Delta F$. Ad hoc corrections for this can remove all the anticipated benefits of BLUP (Smith and Quinton, 1993). This is particularly a problem when a numerically small breed is dispersed and needs to rely on BLUP to provide dependable estimates. The use of quadratic indices completely removes this dilemma: BLUP is used as it should be (best prediction) and the quadratic index manages selection in line with the policy for $\Delta F$ for the population.

(ii) Quadratic indices will give $\geq$ gain compared to truncation selection using BLUP when compared at the same $\Delta F$. This is an important point for commercial companies, in that the same $\Delta G$ can be achieved with less $\Delta F$, so active management of genetic variation can be achieved whilst maintaining competitiveness. This extra gain is achieved since $c_i$ is allowed to vary among those selected for use.

(iii) Caballero and Santiago (1998) point out that rare but beneficial mutations are more frequently lost using BLUP evaluation and selection. Since the quadratic index is managing individual contributions in relation to the Mendelian sampling term of an individual, it follows that a new beneficial mutation would be favoured by the quadratic index.

(iv) Methods have been extended to overlapping generations (Grundy et al. 1997, Meuwissen and Sonnesson, 1998), and are capable of optimising generation intervals to achieve a given $\Delta F/generation$ (Grundy et al. 2000). Meuwissen and Sonesson (1998) showed that with $\Delta F$,
as with $V_{AG}$, progeny testing in dairy cattle delivers more gain than young bull schemes when compared at the same risk.

**Selection and mating.** It has been established (Woolliams, 1989; Caballero *et al.* 1996; Sonesson and Meuwissen, 2000) that the mating policy of selected individuals, as well as the selection itself, plays a role in the strategic optimisation of long-term gain. In particular these papers show that Minimum Coancestry Mating (MC) and Compensatory Mating can be beneficial compared to random mating. In the context of managing genetic contributions these can be viewed as speeding the convergence of contributions towards their desired values i.e. a retrospective tidying up of ancestral contributions among the descendants. However Sonesson and Meuwissen (2000) also note that MC will tend to produce as many offspring as possible from a good pair, contrary to the ideas of factorial mating, which favours producing half-sibs rather than full-sibs. They show that in some schemes considerable extra $\Delta G$ may be made by a combination of the two.

Soerensen (in this Congress) shows that the benefits of using factorial mating will (i) depend on the presence of selective advantages for the mates (e.g. there is no benefit from factorial mating in random selection, and its impact will depend on the form of the advantages) and (ii) arise from the ‘contribution errors’ shown in Fig. 1(b) i.e. factorial mating gives a greater flexibility to refine individual contributions in the future. Therefore there are two components to the impact of mating in selection schemes: one retrospective and the other prospective. As a consequence the formulation of mating based on $A$ for the candidates alone is accounting only for the first of these and possibly the minor component. Currently there is no framework to identify the optimal mating strategy. Some authors (e.g. Shepherd and Kinghorn, 1998) advocate solving equation (2) and the subsequent mating allocation within the same algorithm, without explicitly solving (2). It is unclear whether or not this is capable of providing an optimal solution, since the optimum may itself depend on the explicit solution of equation (2).

**Deterministic Optimisation.** Deterministic methods have been developed for strategic optimisation of breeding programmes with constrained inbreeding. These utilise equation (3) and follow the results of Woolliams *et al.* (1999), Woollamis and Bijma (2000), Bijma *et al.* (2001); in particular, $\Delta F = \frac{1}{2} \sum \mu_i^2$, where $\mu_i = E[r_i | s_i]$ and $s_i$ is the selective advantage of the individual. These deterministic methods allow for predictions of $\Delta G$, the associated gene flow, and $\Delta F$ (and consequently their strategic optimisation) in schemes with truncation selection and overlapping generations, and with general indices including BLUP. The methods encompass variation other than additive genetic, and Ronnegard (in this Congress) shows results from extending these methods to a combination of maternal and direct additive genetic variation.

Whilst many problems have been solved in deterministic prediction, the challenges for deterministic optimisation arise from quadratic indices. The most important gap in knowledge is the prediction of $\Delta G$ when $\Delta F$ is constrained, since it is difficult to predict the selection intensity achieved. Limits to $\Delta G$ have been derived (Grundy *et al.*, 1998) in terms of total offspring born/sex/cohort ($T$) and $\Delta F$: $\Delta G = i k^{-1} \sqrt{h^2}$ where $i$ and $k$ are selection intensity and variance reduction parameters for a selection proportion satisfying $(8T\Delta F)^{\frac{1}{2}} = 2p(i-x)^{(1+x^2-i)}$. 

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The maximum ultimate accumulated gain when assuming the infinitesimal model is a classic problem of optimising the short-term initial gains with the longer term: with high selection intensities and indices using family information, the initial gains are relatively large, but the high $\Delta F$ rapidly erodes $\sigma^2_A$ and the ultimate accumulated gain is relatively low. Villanueva and Woolliams (1997) show with the deterministic model that maximum gain is obtained from indices close to phenotypic selection, with selection proportions of approximately 2/3. This solution is different from that proposed by Robertson assumed $\Delta F$ to be the same as random selection and is distinct from within-family selection.

**GENE ASSISTED SELECTION (GAS)**

The use of the QTL genotypes in genetic evaluation results in a greater accuracy in the breeding value estimates and, thereby, a higher $\Delta G$. However, Gibson (1994) observed short-term $\Delta G$ made by utilising a known QTL was at the expense of long-term $\Delta G$, when compared with selection based on phenotype only. This reduced long-term $\Delta G$ is mainly due to a lower intensity of selection applied to the polygenic component and, to a lesser extent, a higher $\Delta F$ in early generations and a linkage disequilibrium built up between the QTL and the polygenic effects (Pong-Wong and Woolliams, 1998). However, this lower long-term $\Delta G$ is not necessarily large or unavoidable. When using BLUP evaluation with truncation selection or quadratic indices this antagonism was substantially reduced and, in some cases, avoided (Villanueva et al., 1999), and the quadratic indices resulted in a greater $\Delta G$ when compared at the same $\Delta F$.

The success of the quadratic index is not surprising since equations (2) and (3) do not necessarily assume the infinitesimal model, and the framework extends very largely intact to the use of major genes and markers, with EBVs ($g$) in equation (2) provided by the best and most appropriate method available. Dekkers and van Aren donk (1998) took a different approach, using control theory to provide explicit solutions that optimise the weight given to the identified QTL (Chakraborty et al. (2002) include dominance for the QTL) to maximise total gain over a fixed time horizon. Although considerations of $\Delta F$ were ignored, they showed that this methodology was effective in eliminating the antagonism between short and long time horizons. Using the optimised weights given to the QTL combined with quadratic indices to manage $\Delta F$ was yet more effective (Villanueva, in this Congress). The extra $\Delta G$ was mostly due to the management of $\Delta F$ whilst the optimum weight assigned to the QTL had a greater impact in avoiding any loss in the long-term response. Nevertheless one implication is that the gains from control theory appear to lie outside the framework of equation (2).

**MAS WITH LOCAL MARKERS**

When only genotypes of linked marker(s) are known, the QTL can still be accounted for in the evaluation, provided the QTL position and its variance are known. QTL effects are included as a random effect, with a covariance structure proportional to identical-by-descent (IBD) probabilities (Fernando and Grossman, 1989). Several methods to calculate IBD matrices given linked marker(s) are available (e.g. Pong-Wong et al., 2001; Windig, in preparation). Pong-Wong (in this Congress) considers MAS in more detail, and conclusions about short- and long-term gain, and the management of $\Delta F$, described above for GAS, are also relevant to MAS. However there are two additional conclusions. Firstly, the effectiveness of MAS using realistic
marker information, biallelic QTL and marker linkages was much less dramatic than might be inferred from Meuwissen and Goddard (1996). This was primarily due to the limitations of traceability provided by the markers. Secondly, even when markers were tightly linked the short-term performance of MAS was much less than GAS e.g. a very narrow flanking marker interval of 0.1cM resulted in less than half the short term gain obtained with GAS. This latter problem can be overcome (Pong Wong, in this Congress) by providing prior information into the evaluation on the genotype effects of each (some) individual. It is conceivable that methods based upon Fernando and Grossman (1989) can be made to mimic bi-allelic (additive) QTL by creating covariance between allelic effects in the base population either estimated from assumptions on IBD based on haplotypes and presumed population disequilibrium, or other prior information.

There are two further issues arising in strategic optimisation with MAS. Firstly, convincing, general deterministic predictors for MAS have yet to be developed. The information index of Soerensen et al. (2002) may provide a starting point for future development of strategic planning tools. Secondly, the availability of locally dense markers allows both an increase in accuracy where they are indicative of QTL variance (through $g$), and a refinement in the management of genetic variance (with IBD matrices replacing $A$ in Eqn (2)). Thus the markers in one region may be used to increase accuracy of $g$, while the markers in another region to manage local variation. More than one IBD matrix may be used for managing variation in several regions, although obtaining solutions would become more demanding.

**MAS WITH GENOME-WIDE HIGH-DENSITY MARKERS**

Meuwissen et al. (2001) provided intriguing results from considering the potential of utilising high-density markers that are distributed and genotyped genome wide. They assume a distribution of gene effects affecting the trait that had been derived empirically from QTL studies. Mutations for both these genes, and for the markers scattered throughout the genome, were allowed to accumulate and drift for 1000 generations of random selection. After this the population had 2 generations of genotyping and recording and newborn individuals were then evaluated with genotypes but no records. Bayesian techniques were used to estimate a genetic value for each marker interval, and the breeding value was calculated as a sum of genetic values for all marker intervals, irrespective of magnitude or statistical significance. The results showed that for a heritability of 0.5 the newborn were evaluated with accuracies of 0.85 and 0.74 when the markers were 1cM and 4cM apart respectively.

The high accuracies of the results are striking, and are achieved by taking an approach that (unlike the one above) is not concerned over whether a QTL exists in a marker interval or not, or how much of the variance is explained, but is directly concerned with estimating breeding values. However of great relevance to the topic of this paper is the observation that if the breeding values of both parents had been known precisely then the maximum accuracy would have been 0.71, and consequently, a substantial component of this increased accuracy is an increased precision of estimating the Mendelian sampling term. (The opportunity to track Mendelian sampling using markers has been a major justification for their use in dairy breeding). An approximate calculation suggests an accuracy of 0.71 for the Mendelian term. Whilst this study has still to be tested with real data, it’s impact is exciting, since it is clear...
from Fig 1(b) that increasing the precision of estimating the Mendelian sampling term at an early stage before selection is the key to unlocking genetic gain at the same time as managing and conserving genetic variation.

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