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ORIGINAL ARTICLE

Inbreeding in genome-wide selection

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Summary

Traditional selection methods, such as sib and best linear unbiased prediction (BLUP) selection, which increased genetic gain by increasing accuracy of evaluation have also led to an increased rate of inbreeding per generation (ΔF_G). This is not necessarily the case with genome-wide selection, which also increases genetic gain by increasing accuracy. This paper explains why genome-wide selection reduces ΔF_G when compared with sib and BLUP selection. Genome-wide selection achieves high accuracies of estimated breeding values through better prediction of the Mendelian sampling term component of breeding values. This increases differentiation between sibs and reduces coselection of sibs and ΔF_G. The high accuracy of genome-wide selection is expected to reduce the between family variance and reweigh the emphasis of estimated breeding values of individuals towards the Mendelian sampling term. Moreover, estimation induced intraclass correlations of sibs are expected to be lower in genome-wide selection leading to a further decrease of coselection of sibs when compared with BLUP. Genome-wide prediction of breeding values, therefore, enables increased genetic gain while at the same time reducing ΔF_G when compared with sib and BLUP selection.

Introduction

Meuwissen *et al.* (2001) described genome-wide prediction (GWP) methods to estimate haplotype effects, assuming a high density genetic marker map across the entire genome. Their methods yielded high accuracies of estimated breeding values (EBV) based on genotypic information in newborn individuals without phenotypic records. Moreover, they showed that this high accuracy could then be maintained, with only minor loss, over subsequent generations when neither offspring nor parent had records.

In the past, methods proposed to increase accuracies of EBVs have resulted not only in accelerated rates of genetic gain (ΔG) but also in increased inbreeding rates per generation (ΔF_G). This was particularly true for methods that include information on relatives such as best linear unbiased prediction (BLUP) (Henderson 1975). When EBVs derived from BLUP were used in a traditional way, namely ranking the candidates on these EBVs and truncating the distribution to choose those with the highest values, ΔG was increased but so was ΔF_G (Belonsky & Kennedy 1988). This meant that short-term gain was greater at a cost to long-term gain (Quinton *et al.* 1992). While the long-term consequences of genetic variance reduction are often ignored in commercial breeding schemes, high ΔF_G also has more immediate effects. Monogenic recessive alleles can drift to high frequencies because of high usage of

one superior individual [e.g. complex vertebral malformation (CVM) in Holsteins, (Agerholm *et al.* 2001; Kearney *et al.* 2005)] and inbreeding depression can have increased impact because the degree of depression is empirically associated with ΔF_G (Wiener *et al.* 1992).

This experience with BLUP, coupled with the increased ΔF_G observed when selection intensity is increased, has led to an empirical association being perceived between gain and inbreeding. However, this association is much weaker in GWP. This paper has the objective of explaining why the increased accuracy of genome-wide methods leads to decreased ΔF_G when compared with sib and BLUP selection. Thus, GWP provides a method for achieving both the short-term goal of increased and sustained ΔG and the long-term needs for maintaining genetic variation. The approach taken will be to examine the existing quantitative genetic theory related to inbreeding and selection both for truncation selection and for methods using optimum contributions (Meuwissen 1997; Grundy *et al.* 1998).

Inbreeding with mass and BLUP truncation selection

It is useful to discuss in terms of the breeders equation, $\Delta G = i\rho\sigma_A$, how increasing ΔG has led to increased ΔF_G in mass and BLUP truncation selection. The additive genetic standard deviation (σ_A) is a constant for a trait in the short term and, therefore, advances in ΔG come from increasing the selection intensity (i) or the accuracy of EBVs (ρ).

The first option of increasing ΔG is by increasing i. However, reducing the proportion of individuals selected decreases the number of parents and invariably leads to increased ΔF_G. This is true for both mass and BLUP truncation selection as shown in Figure 1 for different values of heritability (h^2).

The second way to increase ΔG is to increase accuracy. Consider mass selection with a simple model of additive and independent environmental effects. Here, both accuracy and intraclass correlation among sibs are determined entirely by h^2 and there is a balance between two effects. Correlations among sibs increase as h^2 increases, leading to increased coselection of sibs and higher ΔF_G. In contrast, at higher h^2 the Bulmer effect reduces the between family genetic variance (σ^2_B) relatively more, reducing co-selection of sibs and ΔF_G. When h^2 is lower than intermediate values, ΔF increases because of the first effect, but when h^2 increases beyond intermediate values the balance shifts to the second effect and ΔF_G is decreased (Figure 1).

In contrast to mass selection, BLUP makes use of information from all relatives, appropriately weighted to maximize accuracy. The higher accuracy leads to a stronger Bulmer effect, which reduces the σ^2_B. The Bulmer effect is less dependent on h^2 in BLUP than in mass selection and, therefore, has a relatively small impact on intraclass correlations. However, intraclass correlations are increased due to inclusion of sib information because of additional induced correlations which are due to using common information (i.e. residual terms averaged among relatives) (Wray *et al.* 1990). The high intraclass correlations increase coselection of sibs and ΔF_G. The emphasis on sib information is high at lower h^2 but decreases when h^2 increases and so the coselection of relatives always decreases as h^2

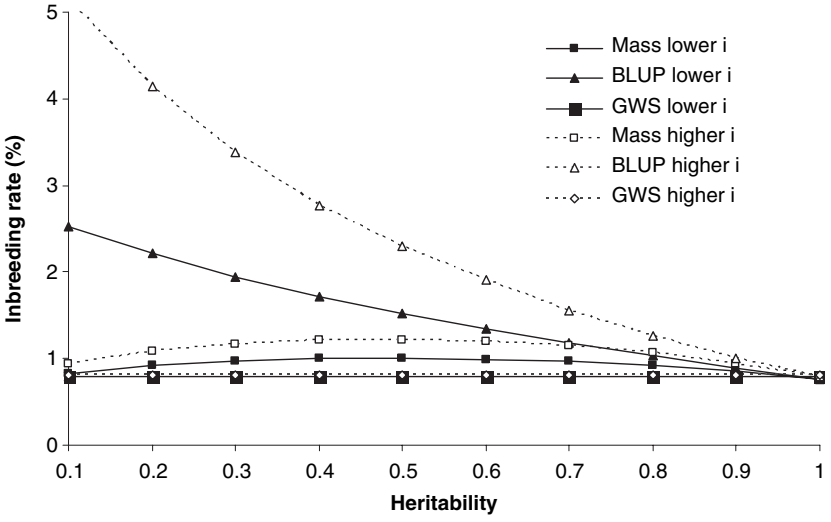

Figure 1 Inbreeding rates per generation from mass and best linear unbiased prediction (BLUP), and genome-wide selection (GWS) at two selection intensities (*i*) with heritability ranging from 0.1 to 1.0, predicted with SelAction (Rutten *et al.* 2002). SelAction input parameters: 20 males, 200 females, four male and four female offspring per dam, proportion selected = 0.05 males, 0.20 females (lower i), and 0.01 male, 0.1 female (higher i), mass used own performance, BLUP included information on own performance, full-sibs and half-sibs, GWS used only information on phenotypes in the marker trait, and GWS accuracy assumed was 0.85.

increases, in contrast to mass selection. Therefore, both elements (coselection and Bulmer effect) combine to produce the downward trend of ΔF_G as h^2 increases (Figure 1). As h^2 approaches 1, the use of sib information becomes unimportant when the phenotype is observed and the ΔF_G approaches that achieved with mass selection.

Three components of a breeding value

The breeding value of an individual can be conceived as having three components (Woolliams 2007): (i) the breeding value of the sire, (ii) the breeding value of the dam and (iii) the Mendelian sampling term, which is the aggregate deviation arising from sampling the segregation of alleles within the sire and within the dam (see Figure 2 for an illustration). Information on ancestors and collateral relatives increases accuracy through directly adding precision on the first two of these components. The accuracy of the Mendelian sampling term can be increased by using an individual's phenotypic record or progeny information. In practice, most BLUP selection schemes increase accuracy by capturing additional information on ancestors and collateral relatives, because progeny information is often not available at the time of selection. It becomes clear that, at the time of selection, BLUP relies heavily on increasing accuracy of σ^2_B to increase ΔG (Figure 2). In contrast, GWP utilizes the Mendelian sampling term more heavily and the consequences of this feature on ΔF_G will now be discussed further.

Genome-wide prediction of breeding values

Meuwissen *et al.* (2001) demonstrated that GWP increases the accuracy of EBV prediction. The important issue is how the increased accuracy is achieved, namely using the markers to explain the Mendelian sampling terms. In the past, physiological indicator traits, which were genetically correlated to a particular trait of interest, were used to select young animals and increased ΔG by giving an early indication of an animal's Mendelian sampling term (Woolliams & Smith 1988). Genotyping technology provided another tool that could be used to gain insight into an animal's unique ability, as individuals could be genotyped at birth or even as an embryo. Marker

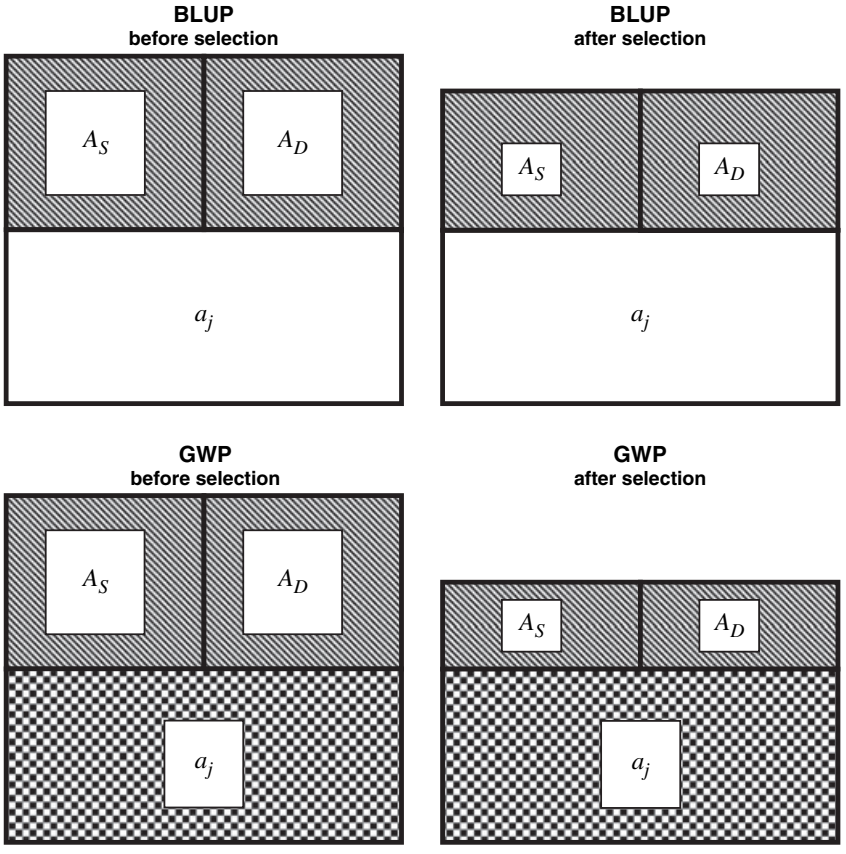

Figure 2 Representation of the sources of information utilised (shaded areas) and their proportions before and after selection (i.e. selection reduces the between family variance) when using best linear unbiased prediction (BLUP) and genome-wide prediction (GWP) to predict the estimated breeding value of a newborn with no phenotypic record. A_S is the sire breeding value, A_D is the dam breeding value, and a_j is the Mendelian sampling term.

assisted selection (MAS) was found to increase ΔG because each genetic marker explained a part of the within family variance (Mendelian sampling variance, σ^2_M) (Meuwissen & Van Arendonk 1992). Preselecting young dairy sires with MAS increased ΔG and offered a method to select within families (Mackinnon & Georges 1998). While the number of markers is dramatically increased with dense marker maps, the principle is the same. Thus GWP offers the possibility that an individual's Mendelian sampling term can be estimated with great accuracy early in its life.

As an example of the potential of GWP, consider the EBV accuracy achieved by Meuwissen *et al.* (2001). An individual with only parent information and no record has an EBV ($\tilde{A}$) that is equal to $\tilde{A}_i = (0.5)\tilde{A}_S + (0.5)\tilde{A}_D$, where $\tilde{A}_S$ and $\tilde{A}_D$ are the sire and dam EBVs respectively. The accuracy of the EBV ($\rho_{A\tilde{A}}$) is $\rho_{A\tilde{A}} = \sigma_{A\tilde{A}}[\sigma_A\sigma_{\tilde{A}}]^{-1}$, where $\sigma_{A\tilde{A}}$ is the covariance between true breeding value and EBV and $\sigma_{\tilde{A}}$ is the EBV standard deviation. Assuming that the parent EBVs have an accuracy of 1 (i.e. $\tilde{A} = A$), then $\sigma_{A\tilde{A}} = (0.5)\sigma^2_A = \sigma^2_{\tilde{A}}$, and $\rho_{A\tilde{A}} = (0.5)\sigma^2_A[(0.5)\sigma^2_A\sigma^2_A]^{\frac{-1}{2}} = 0.71$, which is the upper bound of accuracy for an animal at birth when using conventional BLUP. The GWP Bayesian method achieved an accuracy of 0.85 (Meuwissen *et al.* 2001). Hence, the difference in accuracy of 0.14 observed in GWP and the upper bound in conventional BLUP must originate from the increased accuracy of the Mendelian sampling term estimate (Woolliams *et al.* 2002).

The accuracy of the Mendelian sampling terms ($\rho_{M\tilde{M}}$) in GWP can be approximated for this example. Assuming that σ^2_B was explained precisely (i.e. $\sigma^2_B = (0.5)\sigma^2_A$), then the proportion of the Mendelian sampling variance explained by the GWP EBV ($\rho^2_{M\tilde{M}}\sigma^2_M$) is

$$\rho^2_{M\tilde{M}}\sigma^2_M = \rho^2_{A\tilde{A}}\sigma^2_A - (0.5)\sigma^2_A,$$

where $\rho^2_{A\tilde{A}}$ is the proportion of σ^2_A explained by the EBV. If $\rho_{A\tilde{A}}$ is 0.85 in GWP, then the $\rho_{M\tilde{M}}$ of GWP is

$$\begin{aligned}\rho_{M\tilde{M}} &= (\rho^2_{A\tilde{A}} - 0.5)^{\frac{1}{2}}\sigma_A[(0.5)\sigma^2_A]^{\frac{-1}{2}} \\ &= (0.85^2 - 0.5)^{\frac{1}{2}}\sigma_A[(0.5)\sigma^2_A]^{\frac{-1}{2}} = 0.67\end{aligned}$$

The approximated increase of 0.67 in the accuracy of $\rho_{M\tilde{M}}$ of GWP is very large when compared with $\rho_{M\tilde{M}} = 0$ in conventional BLUP. However, it is unlikely that σ^2_B is explained precisely. A more plausible scenario would be that $\sigma^2_B < 0.5\sigma^2_A$ and, if overall GWP $\rho_{A\tilde{A}}$ is still 0.85, this would result in $\rho_{M\tilde{M}} > 0.67$. Conventional BLUP EBVs are parent averages when an animal has no record of its own, whereas GWP identifies and uses the new Mendelian sampling variation that is generated in each generation. This exploitation of new variation is the major source of increased ΔG of GWP over conventional approaches. Utilizing Mendelian variation is key to achieving sustained genetic progress (see Figure 2) and reducing ΔF_G (Woolliams & Thompson 1994; Woolliams *et al.* 1999).

Inbreeding with truncation genome-wide selection

In GWP, ΔF_G can be much lower than in mass or BLUP for comparable resources and there are several reasons why this is the case. First, GWP breeding values are less correlated between sibs because they rely more on Mendelian sampling information (Figure 2). The increased accuracy of Mendelian sampling terms in GWP allows for better differentiation within families and leads to lower coselection of sibs, which reduces ΔF_G. Second, GWP achieves higher accuracy for all values of phenotype h^2 and, therefore, a strong Bulmer effect is induced by selection and reduces σ^2_B. Due to the Bulmer effect, GWP further re-weights the offspring EBV towards the Mendelian sampling term (Figure 2), which further reduces coselection of sibs and ΔF_G. This is repeated in successive generations where an individual's breeding value has less influence on selection of descendents. The above processes decrease ΔF_G because the Mendelian sampling term arises from the random sampling of alleles carried by the parents, and the variance of these terms is regenerated in each generation. In the long-term, the Mendelian sampling variance is reduced by the loss of alleles due to inbreeding.

Moreover, in species where only males can attain high accuracies (through progeny tests) and have a high number of selected offspring, GWP is expected to shift the selection emphasis from males towards females because males and females will have more similar accuracies. This leads to more evenly distributed long-term contributions among male ancestors and, therefore, decreases ΔF_G when BLUP and GWP are compared at the same ΔG. This would be the effect of the shift in emphasis from sires to dams in dairy cattle pointed out by Schaeffer (2006).

Inbreeding and genetic gain with optimum contribution genome-wide selection

The previous section has examined how genome-wide selection (GWS) may affect ΔG and ΔF_G when the design parameters are fixed (i.e. truncation

selection). However, a more appropriate approach is to consider how to maximise ΔG with fixed resources and fixed ΔF_G by optimizing long-term genetic contributions of the selection candidates (Meuwissen 1997; Grundy *et al.* 1998).

Optimum contribution selection is attempting to allocate contributions of candidates and ancestors in relation to the best estimate of the Mendelian sampling term of each individual (Avendano *et al.* 2004). The optimum solution is, beyond a threshold value, to have a linear relationship between the long-term contribution of an individual and its (true) Mendelian sampling term (Grundy *et al.* 1998). In reality, however, this optimum cannot be attained for two reasons. First, contributions of distinct individuals cannot always be changed independently, for example it is not possible to change the contribution of an individual without changing that of its parent. Second, because Mendelian sampling terms are estimated with limited precision, the true optimum contributions are also known with limited precision. Hence, the solution is a compromise repeated each generation as more accurate information on Mendelian sampling terms becomes available. This was confirmed by Avendano *et al.* (2004), who showed by simulation that the major component by which optimum contribution algorithms keep ΔF_G at a predefined level, while maximizing ΔG, is the estimated Mendelian sampling term. Grundy *et al.* (1998, 2000) showed that with optimum contributions, ΔG is proportional to Mendelian sampling term estimate. It therefore follows directly that a more accurate estimate of the Mendelian sampling term will lead to more ΔG while not affecting ΔF_G. Hence, the use of optimum contribution procedures and GWP together will always result in more ΔG when compared at the same ΔF_G. Quantifying the full benefit of GWP in relation to inbreeding will require further development of methods to predict the accuracy of the Mendelian sampling term (Avendano *et al.* 2005).

Implications on inbreeding of frequency of haplotype effect re-estimation

There are other considerations in GWP that reinforce why GWP is expected to reduce ΔF_G, but these may depend on how GWP is implemented. Two cases can be considered: (i) where haplotype effects are estimated in either earlier generations or, conceivably, in related but distinct populations, and (ii) where haplotype effects are re-estimated each generation or whenever new phenotypic information is available as part of a continuous process.

No updating

When GWS is used with previously estimated haplotype effects with no updating, then the EBV is a sum of haplotype values which do not change over generations. In this case, the marker based genome-wide EBV can be treated as a classical trait with h^2=1 and its genetic correlation with the original phenotypic trait is equal to the accuracy of GWP (Schrooten *et al.* 2005; Dekkers 2007a,b). Thus, genome-wide truncation selection is expected to have a similar ΔF_G to those achieved by mass and BLUP selection at h^2=1. Figure 1 shows that there is no distinction in this case between mass selection and BLUP, as BLUP ΔF_G tends towards mass selection ΔF_G as h^2 increases. This trend is substantiated by the fact that a lower ΔF_G can be achieved in BLUP by artificially increasing the trait h^2 which reduces the reliance on relatives (Toro & Perez-Enciso 1990; Grundy *et al.* 1994). When predicted with SelAction (Rutten *et al.* 2002), the ΔF_G of GWS is similarly low as BLUP at h^2=1 and, in addition, stays at this low and constant level regardless of the h^2 of the original phenotypic trait (Figure 1).

Another property of traits with h^2=1 is that increasing selection intensity by reducing the proportion of candidates selected, while increasing the total number of candidates, has only a small effect on ΔF_G. This scenario would be equivalent to genotyping more individuals but still selecting the same number of parents to increase selection intensity. In Figure 1, while BLUP shows a large increase in ΔF_G at lower h^2, GWS (when treated as a trait with h^2=1) results only in a small and constant increase in ΔF_G regardless of phenotypic trait h^2. Therefore, when applying GWS with no updating of haplotypes, selection intensity can be increased in this way with relatively little consequence on ΔF_G.

Continuous updating

When GWP is applied with continuous re-estimation of haplotype effects, then the process of estimation might be considered as inducing correlations due to the averaging of residual terms of relatives just like the estimation of sire and dam EBVs in BLUP. This applies particularly in a simple pedigree with only parents and offspring. In BLUP, all offspring of a parent are averaged to provide an estimate of the parent EBV, so differences between EBVs of sires

(dams) are contrasts between sire (dam) family means. This is the origin of the intraclass correlation leading to coselection of sibs in BLUP that is described above. In GWP, if haplotypes are re-estimated continuously then contrasts are made across the population as a whole comparing carriers and non-carriers of particular alleles both between and within families. Thus, the estimation-induced intraclass correlations act much less strongly as sources of coselection of sibs. This would reduce ΔF_G when compared with BLUP.

It should be noted that continuous re-estimation of haplotype or marker effects must be more effective in generating ΔG for a trait than not updating effects. This follows because re-estimating marker effects with additional phenotype information must result in at least as good accuracy compared with ignoring it. In each generation, novel additive genetic variation is generated which is not captured by the original estimate of the haplotype effects. This is due to the decay of linkage disequilibrium between markers and to changes in allele frequencies which are associated with mutation, dominance and epistasis. The cost of collecting some phenotypes might prohibit regular updating of haplotype effects and so allowing some loss of accuracy (and ΔG) may be a cost-effective option.

Impact of linkage on inbreeding

In this paper, all comparisons of ΔF_G between different selection methods are based on inbreeding as calculated from the pedigree. Differences do exist between inbreeding calculated from pedigree information and inbreeding computed from genotypic data.

The pedigree based method is an expectation assuming neutral loci and, therefore, the two alleles of the same neutral locus on two homologous chromosomes have an equal chance of being selected. This ignores that the two alleles present in non-neutral loci on either chromosome may have different effects on a trait which leads to unequal selection probabilities between the two alleles of the neutral locus when there is linkage (Santiago & Caballero 1998). The proportion of loci that is actually neutral, when neutral is defined as not under selection directly or indirectly (i.e. linked to an allele under selection), is unknown. However, while it was found that the assumption of no linkage is violated in small genomes (<10 Morgans), it becomes progressively more appropriate as genomes become larger (Fernandez *et al.* 2000; Villanueva *et al.* 2005). Thus, in farm animal species which typically have genome sizes of 20–30 Morgans, accurate average inbreeding rates across the whole genome can be predicted from pedigree records.

When inbreeding is calculated from genotypic data, the expectation is adjusted with identity-by-state probabilities at the marker loci to yield actual inbreeding at specific locations across the genome (Pong-Wong *et al.* 2001; Liu *et al.* 2002; Roughsedge *et al.* 2006). The increasing amount of genotypic data available will lead to new methods for calculating inbreeding which could give an indication of the effect of linkage on the accumulation of localized inbreeding across the genome. The potential exists, therefore, to get a more complete picture of inbreeding with genotypic methods than with pedigree based methods.

Practical issues of implementing genome-wide selection

This article has discussed an important benefit of GWS, namely increased gain with no cost to inbreeding. Other potential benefits that GWS offers to livestock breeders are (i) overcome age limitations whilst offsetting additional costs through changes in structure; (ii) overcome or reduce sex limitations, or more generally limitations caused by measuring only special subsets e.g. expensive or destructive testing; (iii) use in non-pedigreed populations and (iv) a direct link between the genetic evaluation and the genome. Nevertheless, the relevance and benefits described will vary among sectors and depend on practical issues related to the implementation of GWS.

Generation interval

Genome-wide selection is expected to increase ΔG and reduce ΔF_G due to the high accuracy of the Mendelian sampling term. However, it would be expected that there are opportunities to reduce the generation interval with GWS, as a substantial increase in accuracy is available in the newborn. In dairy cattle, it has the potential to reduce the generation interval of sires of bulls and dams from 6 to 2 years, as progeny tests may become unnecessary (Schaeffer 2006). This may increase the annual inbreeding rate (ΔF_A). However, the biological risks of inbreeding depression and deleterious alleles are more relevant in the context of ΔF_G, because balancing processes, such as mutation, also occur per generation. Optimum contributions with constrained

ΔF_G (Grundy *et al.* 1998, 2000) could be used to manage the transition to shorter generation intervals. Whether or not the scheme would evolve into that of Schaeffer (2006) remains unknown. However, in a truncation scheme an increase in ΔF_A may occur, but the arguments above would be expected to remain valid and more gain achieved with GWS if compared with BLUP at same ΔF_G per generation.

The need to manage pedigrees

Genome-wide selection does not fully remove the impact of pedigree on ΔF_G. Parents come as packages of haplotypes, and with truncation selection, parents with good packages will tend to have more offspring selected even though individual haplotypes are being evaluated. While GWS decreases ΔF_G when compared with BLUP, it is not inbreeding free. Breeding programmes are competitive and are expected to push for more ΔG by, for example, increasing selection intensity through a reduction in the number of parents which would increase ΔF_G. Therefore, the need to manage inbreeding using tools such as optimum contributions to maximize ΔG in relation to ΔF_G remains.

Conclusion

This paper has outlined why GWS is expected to result in lower ΔF_G than BLUP selection. The main reason for this reduced ΔF_G is that GWP will result in an increased estimation accuracy of the Mendelian sampling term. This allows for better differentiation within families and leads to lower coselection of sibs, which reduces ΔF_G. The between family portion of the additive genetic variance in GWS is reduced quickly due to the high EBV accuracy and shifts the emphasis of selection in favour of the Mendelian sampling term which has no effect on inbreeding as it is regenerated in each generation. Haplotype effects which are used for several generations without re-estimation will resemble a trait with $h^2=1$ and result in low and constant ΔF_G regardless of the original trait h^2. When haplotype effects are re-estimated in each generation, contrasts between haplotypes are made both between and within families, thereby reducing coselection through reduced estimation induced correlations between sib EBVs. Mendelian sampling terms are also used in optimum contribution procedures which could be used to maximize ΔG at a preset rate of ΔF_G.

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References

Agerholm J.S., Bendixen C., Andersen O., Arnbjerg J. (2001) Complex vertebral malformation in Holstein calves. *J. Vet. Diag. Invest.*, **13**, 283–289.

Avendano S., Woolliams J.A., Villanueva B. (2004) Mendelian sampling terms as a selective advantage in optimum breeding schemes with restrictions on the rate of inbreeding. *Genet. Res.*, **83**, 55–64.

Avendano S., Woolliams J.A., Villanueva B. (2005) Prediction of accuracy of estimated Mendelian sampling terms. *J. Anim. Breed.Genet.*, **122**, 302–308.

Belonsky G.M., Kennedy B.W. (1988) Selection on individual phenotype and best linear unbiased predictor of breeding value in a closed swine herd. *J. Anim. Sci.*, **66**, 1124–1131.

Dekkers J.C.M. (2007a) Marker-assisted selection for commercial crossbred performance. *J. Anim. Sci.*, **85**, 2104–2114.

Dekkers J.C.M. (2007b) Prediction of response from marker-assisted and genomic selection using selection index theory. *J. Anim. Breed. Genet.*, **124**, 331–341.

Fernandez B., Santiago E., Toro M.A., Caballero A. (2000) Effect of linkage on the control of inbreeding in selection programmes. *Genet. Sel. Evol.*, **32**, 249–264.

Grundy B., Caballero A., Santiago E., Hill W.G. (1994) A note on using biased parameter values and nonrandom mating to reduce rates of inbreeding in selection programs. *Anim. Prod.*, **59**, 465–468.

Grundy B., Villanueva B., Woolliams J.A. (1998) Dynamic selection procedures for constrained inbreeding and their consequences for pedigree development. *Genet. Res.*, **72**, 159–168.

Grundy B., Villanueva B., Woolliams J.A. (2000) Dynamic selection for maximizing response with constrained inbreeding in schemes with overlapping generations. *Anim. Sci.*, **70**, 373–382.

Henderson C.R. (1975) Best linear unbiased estimation and prediction under a selection model. *Biometrics*, **31**, 423–447.

Kearney J.F., Amer P.R., Villanueva B. (2005) Cumulative discounted expressions of sire genotypes for the complex vertebral malformation and beta-casein loci in commercial dairy herds. *J. Dairy Sci.*, **88**, 4426–4433.

Liu Y., Jansen G.B., Lin C.Y. (2002) The covariance between relatives conditional on genetic markers. *Genet. Sel. Evol.*, **34**, 657–678.

Mackinnon M.J., Georges M.A.J. (1998) Marker-assisted preselection of young dairy sires prior to progeny-testing. *Livest. Prod. Sci.*, **54**, 229–250.

Meuwissen T.H.E. (1997) Maximizing the response of selection with a predefined rate of inbreeding. *J. Anim. Sci.*, **75**, 934–940.

Meuwissen T.H., Van Arendonk J.A. (1992) Potential improvements in rate of genetic gain from marker-assisted selection in dairy cattle breeding schemes. *J. Dairy Sci.*, **75**, 1651–1659.

Meuwissen T.H., Hayes B.J., Goddard M.E. (2001) Prediction of total genetic value using genome-wide dense marker maps. *Genetics*, **157**, 1819–1829.

Pong-Wong R., George A.W., Woolliams J.A., Haley C.S. (2001) A simple and rapid method for calculating identity-by-descent matrices using multiple markers. *Genet. Sel. Evol.*, **33**, 453–471.

Quinton M., Smith C., Goddard M.E. (1992) Comparison of selection methods at the same level of inbreeding. *J. Anim. Sci.*, **70**, 1060–1067.

Roughsedge T., Pong-Wong R., Villanueva B. (2006) Optimised selection restricting coancestry at a specific location on the genome. In: Proceedings of the Eighth World Congress of Genetics Applied to Livestock Production, Belo Horizonte, Brazil. CD-ROM Communication no. 30–07.

Rutten M.J.M., Bijma P., Woolliams J.A., Van Arendonk J.A.M. (2002) SelAction: software to predict selection response and rate of inbreeding in livestock breeding programs. *J. Hered.*, **93**, 456–458.

Santiago E., Caballero A. (1998) Effective size and polymorphism of linked neutral loci in populations under directional selection. *Genetics*, **149**, 2105–2117.

Schaeffer L.R. (2006) Strategy for applying genome-wide selection in dairy cattle. *J. Anim. Breed. Genet.*, **123**, 218–223.

Schrooten C., Bovenhuis H., Van Arendonk J.A., Bijma P. (2005) Genetic progress in multistage dairy cattle breeding schemes using genetic markers. *J. Dairy Sci.*, **88**, 1569–1581.

Toro M., Perez-Enciso M. (1990) Optimization of selection response under restricted inbreeding. *Genet. Sel. Evol.*, **22**, 93–107.

Villanueva B., Pong-Wong R., Fernandez J., Toro M.A. (2005) Benefits from marker-assisted selection under an additive polygenic genetic model. *J. Anim. Sci.*, **83**, 1747–1752.

Wiener G., Lee G.J., Woolliams J.A. (1992) Effects of rapid inbreeding and of crossing of inbred lines on conception rate, prolificacy and Ewe survival in sheep. *Anim. Prod.*, **55**, 115–121.

Woolliams J.A. (2007) Genetic contributions and inbreeding. In: K. Oldenbroek (ed.), Utilisation and Conservation of Farm Animal Genetic Resources. Wageningen Academic Publishing, AE Wageningen, pp. 147–165.

Woolliams J.A., Smith C. (1988) The value of indicator traits in the genetic-improvement of dairy-cattle. *Anim. Prod.*, **46**, 333–345.

Woolliams J.A., Thompson R. (1994) A theory of genetic contributions. Proceedings of the Fifth World Congress on Genetics Applied to Livestock Production 19, Guelph, Canada, pp. 127–133.

Woolliams J.A., Bijma P., Villanueva B. (1999) Expected genetic contributions and their impact on gene flow and genetic gain. *Genetics*, **153**, 1009–1020.

Woolliams J.A., Pong-Wong R., Villanueva B. (2002) Strategic optimisation of short- and long-term gain and inbreeding in MAS and non-MAS schemes. In: Proceedings of the Seventh World Congress of Genetics Applied to Livestock Production, Montpellier, France. CD-ROM Communication no. 23–02.

Wray N.R., Woolliams J.A., Thompson R. (1990) Methods for predicting rates of inbreeding in selected populations. *Theoret. Appl. Genet.*, **80**, 503–512.