Comparison of Long-term Genomic Response under Restricted Inbreeding in Conventional and Modern Molecular Breeding Schemes: Review article

Shiva MAFAKHERI[1]
Navid GHAVI HOSSEIN-ZADEH[1] (✉)
Abdol Ahad SHADPARVAR[1]
Rostam ABDOLLAHI-ARPANAHI[2]

Summary

Reaction to selection in modern breeding programs has been expanded because of constant changes in the techniques for hereditary assessment. Without genomic data, hereditary assessment should center on amplifying the accuracy of evaluated breeding values (EBVs) and expanding the mean EBV of selected parents so there is no conspicuous chance to increase long-term response. The availability of single nucleotide polymorphism (SNP)-chips introduces new opportunities to optimize short versus long-term response under restricted inbreeding. Whenever frequencies and impacts of alleles underlying trait values can be assessed, an exchange between short and long-term optimum selection policies strategies will appear. Therefore, a technique to discover the optimum index to maximize long-term response is resulting from the weight given to a marker according to its frequency. It is probable that long-term genetic gain of genomic selection will be be improved by Jannink's weighting (JW) method, in which rare favorable marker alleles are weighted in the selection criterion. The JW technique was spread by including an additional factor to decrease the stress on rare favorable alleles over the time horizon and has been called dynamic weighting (DW). In comparison to unweighted genomic estimate, both DW and JW can improve long-term genetic gain and decrease inbreeding rate.

Key words

favorable minor allele, inbreeding, long-term genomic response, selection policy

[1] Department of Animal Science, Faculty of Agricultural Sciences, University of Guilan, Rasht, 41635-1314, Iran

[2] Department of Animal and Poultry Science, University of Tehran, Pakdasht, 3391653755, Iran

✉ Corresponding author: nhosseinzadeh@guilan.ac.ir

Received: May 19, 2018 | Accepted: December 11, 2018

Introduction

Selection patterns are usually designed to maximize genetic gain with no or a hidden limitation of rates of inbreeding. Some researchers have developed selection approaches that decrease inbreeding rates. For example, Grundy and Hill (1993) and Verrier et al. (1993) reduced family mean weight in their selection index relative to that in the best linear unbiased prediction–estimated breeding value (BLUP EBV), which decreased the probability of co-selection of relatives and therefore decreased inbreeding. Brisbane and Gibson (1994) and Wray and Goddard (1994) have selected animals while putting a charge on the average relationship of the selected animals. There is no assurance that these approaches yield the maximum genetic gains at some level of inbreeding. Furthermore, the actual rate of inbreeding is not recognized before the breeding pattern begins.

In a study, Goddard and Howarth (1994) have approved the application of dynamic selection rules in contrast to static designs of optimum breeding patterns. Dynamic rules optimize the selection of the actually available candidates and in this manner exploit openings that were not predicted when the reproducing program was arranged. For example, Meuwissen (1997) presented a dynamic selection rule that maximizes the genetic level of the selected parents while limiting their average association. This technique was developed for several generations and stable rates of genetic gain were achieved, which shows that the technique could control short and long-term impacts of selection on inbreeding. The technique can also be applied to oblige the variance of response by limiting the average prediction error variance of the selected animals (Meuwissen, 1997).

Inbreeding can be controlled at two levels. Firstly, the rate of inbreeding in a population as a whole can be limited to a preferred level while maximizing the rate of genetic gain, through optimizing the long-term contributions of a selected number of breeding animals (Wray and Goddard, 1994; Meuwissen, 1997). Secondly, at an individual level, avoiding large inbreeding coefficients in progeny through controlling mating it is very important to avoid reductions in fitness traits (Smith et al. 1998) and homozygous lethal recessive alleles. The control of inbreeding levels in progeny can be applied using mate allocation (Kinghorn, 1998).

Mate allocation can also be measured independently of mate selection. Although mating plans are normally used to control progeny inbreeding in farm animals, they can also be used to make culling decisions in young individuals and in situations where constraints, such as animal groups, exist (Kinghorn, 2011). Simulation investigations and some empirical evaluations of "genomic selection" (GS) (Meuwissen et al., 2001) or "genome-wide selection" (Bernardo, 2007) have indicated that prediction accuracies from GS are high enough to allow rapid gains from the selection (VanRaden et al., 2009; Lorenzana and Bernardo, 2009; Jannink, 2010; Hayes et al., 2009). Therefore, although scientists may have confidence that GS can accelerate short-term gain, no such confidence is acceptable for long-term gain (Jannink, 2010). Ideally, experimental investigations of long-term gain should be implemented empirically in model systems no matter how expensive necessary replicated investigations may be, and even in rapid cycling organisms, would not be accomplished in a near future. Stochastic simulation remains perhaps the only feasible choice to test hypotheses regarding the effect of selection approaches on a long-term gain (Hill and Caballero, 1992). Approaches for maximizing long-term genetic gain are different from those which have been used for maximizing short-term genetic gain. Although a quantitative trait locus (QTL) with a minor effect and/or with a low frequency of the favorable allele may not be essential for short-term gain, it possibly contributes more to long-term genetic gain through maintaining genetic variance over time. Therefore, over a longer time horizon, these alleles should be preserved in the population, for instance by unweighting them in the selection criterion. Goddard (2009) suggested an optimal index that is likely to maximize the long-term genetic gain with a two-QTL model example. It has been suggested that, in the genomic selection model, the optimum weight for each marker depends on its allele frequencies, such that a marker with a high (low)-frequency of the favorable allele obtains a low (high) weight in the index. Marker effects were not involved in this index (Goddard, 2009). Goddard's optimization was further applied by Jannink (2010), but, marker effects, as well as allele frequencies, were involved in the selection criterion, so it is unclear how accurately the marker effects are projected and whether the alleles are favorable or not. Furthermore, when there are many genes (compared to Goddard's two-loci example), it makes sense to arrange the loci based on their expected effect in order to offset random drift where it causes most problems. Jannink (2010), indicated that, as anticipated from Goddard (2009), selection on this index originally caused a lower accuracy of selection and genetic gain than selection on unweighted genomic prediction (GP). However, markers close to QTL stayed polymorphic much longer when the selection was on the index, leading to greater genetic variance and a further improvement in genetic gain in future generations (Jannink, 2010).

In this study, we first review challenges to obtain more long-term genetic response in traditional selection, then we discuss how the optimal contribution selection (OSC) has been improved and finally we survey the dynamic of long-term response in genomic selection and find the optimum weights in a selection index to apply to each marker to maximize long-term response.

Challenges of Long-Term Genetic Gain with Traditional Selection

Traditional genetic gain has relied on using the recorded phenotype of each individual together with the data of its pedigree to predict its breeding value (BV), most often using statistical methods, known as the best linear unbiased selection (BLUP) (Henderson, 1984). This approach has been successful, leading to genetic gains in most livestock (Van Vleck et al., 1986; Havenstein et al., 1994). Despite this success, there has been an interest in using simply inherited genetic markers to rise the rate of genetic gain (Dekkers and Hospital, 2002) and although some genes with known polymorphisms affecting quantitative traits have been discovered (Grisart et al., 2002; Jeon et al., 1999; Wilson et al., 2001), in general they have not added greatly to the efficiency of selection based on EBVs calculated from phenotypes and pedigrees (Boichard et al., 2006; Dekkers, 2004).

There are at least three causes. Firstly, there are generally many genes affecting a trait, so the proportion of the variance clarified by one gene is very small. Meuwissen and Goddard (1996)

indicated that the gain in selection response from using individual genes was proportional to the variance they explained, so if only a few of the genes explaining a small proportion of the variance are known, the gain will be too small. Secondly, as there are many genes influencing a trait, their effects are typically small and thus hard to estimate precisely. For example, polymorphisms in casein genes have been recognized for years to affect milk yield in dairy cattle. However, the projected effects of these polymorphisms are small and differ from one experiment to another (Bouvenhuis and Weller, 1994; Goddard and Wiggans, 1999). Thirdly, we identify a few genes that are responsible for variation in vital traits. Although a gene might be recognized to have a role in physiology, it does not mean that there is a genetic variation in this gene that has a significant effect on physiological function. In addition, genes are usually revealed to affect a trait that was not previously suspected from their identified function (Goddard, 2009). For example, Moffatt et al. (2007) have found that ORMDL3 affects asthma, but this gene had not been involved in asthma. Modern molecular biology promises to overcome this shortage in the current knowledge.

Fernando and Grossman (1989) developed a general method for estimating BVs using markers in linkage equilibrium with QTL. However, in practice, the gains were small and this method of marker-assisted selection was rarely used. By saturating a QTL region with additional markers, the causal mutation has infrequently been discovered (Grisart et al., 2002). Only when it explained an unusually large proportion of genetic variance did Meuwissen and Goddard (1996) indicate that the gain in selection response from marker-assisted selection was nearly proportional to the proportion of genetic variance explained by the markers. Thus, a new kind of marker-assisted selection was required to utilize all QTL and that did not require linkage phase to be determined for each family.

Meuwissen et al. (2001) revealed that a dense panel of markers covered the whole genome and in linkage disequilibrium (LD) with QTL could lead to large increases in response to selection. This type of marker-assisted selection has been known as genomic selection. It became achievable with the availability of thousands of SNPs that could be genotyped at a reasonable cost. It has been widely used in dairy cattle breeding (Dalton, 2009) and is expected to revolutionize all livestock genetic improvement programs and can also be extended to plants (Bernardo and Yu, 2007; Heffner et al. 2009; Zhong et al. 2009), aquaculture (Sonesson and Meuwissen, 2009) and prediction of genetic risk in humans (Wray et al., 2007).

Aran Ardebili et al. (2016) assessed that the genetic gain from a progeny testing program corresponding to the characteristics of Holstein population and an equivalent genomic selection program in terms of number of needed male and female parents was compared and the effect of number of young bulls on genetic gain in these two programs was evaluated. Selection objective included the milk production. Genetic gain for milk production from four path selection was estimated using gene flow method over 150 years. The results indicated that the progeny testing and genomic selection varied in terms of selection accuracy, through selection intensity and generation interval. The annual genetic gain from progeny testing was 114.7 and from genomic selection was 173.7 kg suggesting that the genetic gain obtained from genomic selection could be higher than that of progeny testing by more than 50% due to a shorter generation interval.

Maximizing Genetic Gain at the Desired Rate of Inbreeding (OCS)

Wray and Goddard (1994) and Brisbane and Gibson (1994) described methods that decrease inbreeding by maximizing the objective:

$$c_t'EBV_t - k\, c_t'A_t c_t,$$

where EBV_t = vector of BLUP estimated breeding values of the candidates for selection in generation t, ct = vector of genetic contributions of the selection candidates to generation t+1, A_t = the matrix of additive genetic relationships between selection candidates in generation t and k = a cost factor. They applied optimization algorithms that did not guarantee to find the optimum c_t. However, the optimum solution for the cost factor method was found by replacing λ_0 with k in equation (Meuwissen, 1997).

$$c_t = A_t^{-1}(EBV_t - Q\lambda)/2\lambda_0$$

or

$$Q'\, A_t^{-1} Q\lambda = Q'A_t^{-1} EBV_t - 1\lambda_0$$

where λ_0 and λ are LaGrangian multipliers (λ = a vector of two LaGrangian multipliers). **Q** = known incidence matrix for sex (the first column yields ones for males and zeros for females, and the second column yields ones for females and zeros for males); and 1/2 = a vector of halves of order 2.

Wray and Goddard (1994) find optimum c_t, within a group of animals which have been selected by their optimization algorithm. The cost factor k is commonly unknown, although Wray and Goddard (1994) computed a cost factor based on inbreeding depression, variance reductions because of inbreeding, and a time horizon. The presumption made here was that practical breeders do approximately know which rates of inbreeding are acceptable, although they do not have a feel for cost factors and therefore are willing to accept only cost factors that result in acceptable rates of inbreeding. Hence, the cost factor λ is calculated from the acceptable rate of inbreeding by the following equation:

$$\lambda_0^2 = \frac{EBV_t' \left(A_t'^{-1} - A_t'^{-1} Q \left(Q' A_t'^{-1} Q\right)^{-1} Q' A_t'^{-1} \right) EBVt}{8\ \bar{C}_t - 1'\left(\left(Q' A_t'^{-1} Q\right)^{-1} 1\right.}$$

Meuwissen (1997) anticipated that acceptable rates of inbreeding are approximately known. Breeding schemes were simulated to test whether the intended rate of inbreeding was achieved and to compare rates of gain with BLUP selection. For all the breeding schemes mating was considered as random. Meuwissen (1997) was going to maximize the genetic level of the next generation of animals within every round of selection using optimal genetic contributions to the next generation. In optimal contributions, the average coefficient of co-ancestry of the parents of the generation (t) is limited to (t-1) ΔF for t=2, ..., 10, where ΔF=0.025 per generation. The average co-ancestry constraint was obtained in all generations without reduction of rates of genetic gain in later generations. The initial reduction in genetic gain was due to reduced genetic variances on account of the selection (Bulmer, 1981). In the next generations, rates of genetic gain

slightly increased. However, this increase was small in relation to standard error and was not statistically significant. An explanation is that the inbreeding constraint becomes less stringent. The rates of gain and inbreeding of the optimal selection methods to rates obtained from the selection on BLUP-EBV (BLUP selection) were compared. With BLUP selection, it was found that the rate of inbreeding strongly depends on the number of sires and dams selected, whereas the results of schemes that optimize the selection of sires and dams with equal contributions of the selected sires and the selected dams, were close to the numbers based on Wright's (1931) inbreeding formula for random mating: $\Delta F = 1/8n_s + 1/8n_d$, where ns ($n_d$) = the number of sires (dams) selected. The results obviously showed the superiority of the optimal contribution methods in comparison to BLUP selection (Meuwissen, 1997).

The optimal contribution method of selection attains, on average, a predefined rate of inbreeding. The realized rates of inbreeding fluctuate around this desired rate. This might be due to the fact that the realized contributions of the parents fluctuate around the optimal contributions due to the variance of family sizes. However, because the average relationship between the selected parents did not vary around their predefined levels, the standard deviation of the inbreeding level in the last generation was much lower than BLUP selection. The present method limited the average co-ancestry of the selected parents instead of the average inbreeding coefficient of their offspring. When co-ancestry was limited, it was not difficult to achieve the predefined rate of inbreeding during the course of selection; the rates of gain did not decline and numbers of animals selected did not enhance, which suggests that previous selections affect future inbreeding only through affecting the present co-ancestry (Meuwissen, 1997).

This implies that nonrandom mating cannot control inbreeding because the relationships between the selected parents will be converted into inbreeding in later generations. Nonrandom mating can postpone the time until the close relationships are transformed into inbreeding, but, cannot prevent it. Conversely, nonrandom mating, in which the selected animals with many co-selected relatives are mated to those with few co-selected relatives, decreases the cumulative effect of multiple generations of selection on inbreeding by decreasing the variance of long-term genetic contributions (Santiago and Caballero, 1994). The effect of decreasing the co-selection of relatives (Meuwissen, 1997) and compensatory mating on inbreeding is additive (Grundy et al., 1994), hence, both BLUP selection and the present method can equally benefit from it. Findings revealed that the constrained selection achieves the genetic gain by changing the contributions of young ancestors rather than those of old ancestors. The contributions of old ancestors are hardly changed and do not contribute to rates of inbreeding (Meuwissen, 1997).

This agrees with Woolliams and Thompson (1994), who computed that the changes in genetic contributions of old ancestors added much more to the rate of inbreeding than to the genetic gain and should be avoided when rates of inbreeding are supposed to be reduced. Thus, at equal rates of inbreeding, selection differentials are higher when the contributions of the selection differentials are optimized in comparison to applied BLUP selection.

A dynamic selection rule was offered and yielded 21-60% greater selection response than best linear unbiased prediction selection at the same rate of inbreeding, which may be due to increased selection differentials (Meuwissen, 1997). In optimal contribution selection (OCS), the contribution of a parent is the result of a trade-off among its genetic merit and its relationship to other individuals (Fernández et al., 2011; Woolliams et al., 2015).

Sonesson et al. (2010) have shown that with finite locus models (FLM), simulations in which OCS is not able to maintain genetic diversity across the whole genome in selected populations, relationship coefficients can be estimated from pedigree information. In fact, it leads to a strong reduction in diversity around QTL regions by favoring alleles with the largest effects. To circumvent this flaw, the authors proposed using marker-based relationships as they reflect genome sharing between individuals more accurately than pedigree-based expectations.

Sánchez-Molano et al. (2016) demonstrate that the use of optimum contribution strategies in a genomic context effectively decreases the rate of increase in inbreeding while ensuring genetic gain for traits of interest in a wide range of scenarios. The inbreeding impact on fitness was clearly included, thus allowing the maintenance of fitness levels and, therefore, genomic-based optimum contribution strategies can be recommended both from conservation and animal genetic improvement perspectives.

Attaining the optimal genetic contributions of females would require high female reproductive rates, which may be possible in poultry, pigs, or in cattle by the use of Ova Pick Up (Kruip et al., 1994). For example, when the number of selected sires exceeds the number of dams, the optimal solution requires mating of one dam to several sires. Such flexible female reproductive methods may not be existing and often a predefined number of dams is selected, say n_d, with equal genetic contributions per dam. In this situation, we may simply select the n_d, dams with the highest optimal contributions.

Ghavi Hossein-Zadeh (2010) evaluated the genetic trend of milk yield in multiple ovulation and embryo transfer (MOET) populations of dairy cows using stochastic simulation and concluded that all four MOET breeding schemes could result in larger genetic responses than the realized and theoretical genetic gains from the current artificial insemination (AI) progeny testing populations. This progress was achieved in spite of having a small size, closed scheme and restrictions on inbreeding in some cases. The small population without restrictions on inbreeding accumulated a high level of inbreeding. Such restrictions are not usually worthwhile in terms of genetic gain for the time horizon studies. Moreover, selection would become ineffective due to reductions in genetic variation caused by inbreeding. Regardless of population size, higher selection intensity led to a higher degree of linkage disequilibrium. The reduction in genetic variation due to linkage disequilibrium was as important as that due to the accumulation of inbreeding. Large population size led to lower random genetic drift.

Wang et al. (2017) noticed that maintaining genetic originality is essential for conserving native breeds. It was shown that using an OCS approach can effectively maintain the diversity of native alleles and genetic originality, while ensuring genetic gain. Although traditional OCS provided the greatest breeding

values under classical kinship restriction, the extent of migrant contribution in the progeny generation was not controlled. When migrant contribution was limited or minimized, the kinship at native alleles increased compared to the reference scenario. Therefore, in addition to limiting migrant contribution, limiting kinship at native alleles is needed to ensure that native genetic diversity is kept. When kinship at native alleles was constrained, the classical kinship was automatically lowered in most cases and more sires were selected (Hartwig et al., 2014; Wang et al., 2017).

Genomic Information and Selection Decisions

Applying molecular information to make selection decisions in breeding programs was envisaged decades ago (Smith, 1967; Soller, 1978). Marker-assisted selection is the most useful method for traits which cannot be recorded on an individual prior to the (minimum) age of breeding (Meuwissen and Goddard, 1996). For example, traits which are only displayed in females or only observable late in life or after slaughter would benefit. Traits such as milk yield, which is not displayed by bulls, have been improved by progeny testing bulls based on their daughters' milk yield. This leads to an accurate estimate of the bulls' BV but at the expense of a long generation interval. The advantage of genomic selection is that bulls and heifers can be selected early in life and the generation interval leads to approximately double genetic gain per year (Schaeffer, 2006; König et al., 2009; Pryce et al., 2010).

Application of genetic markers and genomic selection helps us in selecting the best bulls when they are born and breed from them at 1-year of age instead of waiting until they have completed a progeny test at 5-years of age. However, the implementation of genetic markers into breeding programs has been limited due to technological reasons (Goddard et al., 2010).

The recent advances in SNP markers have offered new opportunities to do so. SNP markers can cover the genome with high density. SNP genotyping technology has enabled us to profile many animals for thousands of marker loci in a single analysis with the minimum cost per marker (Williams, 2005).

The principle of genomic evaluation models is to take benefit of both genotypic and phenotypic data available in a training (also called 'reference') population to build prediction equations of the genetic quality of individuals (Meuwissen et al., 2001). These equations can be used to select candidates having genotypes but not phenotypes. Diverse approaches have also been proposed to estimate genetically enhanced breeding values (GEBV), as reviewed by Hayes et al. (2009).

The use of genomic data to make selection decisions, or genomic selection, has greatly increased the technical and economic efficiency of dairy cattle breeding programs (Schaeffer, 2006; König et al., 2009). The selection index theory was suggested to model the overall gain in accuracy expected from using genomic data at some selection stages (Lande and Thompson, 1990; Dekkers, 2007; Dagnachew et al., 2016).

Atefi et al. (2016) have found that models with additive gene action Reproducing Kernel Hilbert Spaces (RKHS) method such as BayesA and BayesL did not perform better than parametric methods, and besides that RKHS is more complicated and time-consuming. Comparison of these methods for non-additive models should be done under different simulation and real data. Marker density is one of the most important factors that affect the genomic prediction accuracy and fortunately by new progress in genotyping technologies, the high-density SNP panels with low cost are available and could apply easily in getting an accurate genomic prediction. Preventing decay of accuracy due to recombination across time is one of the most important benefits of dense marker panels, so when the highest number of markers (1000) was used, the lowest accuracy decay was found. In this study, the decreasing trend of accuracy across generations was not affected by marker effect estimation methods. In high heritability traits, increase in the number of markers had a slight effect on accuracy but for low heritability trait, increase in the number of markers increased accuracy; therefore, using the dense marker panels is imperative for low heritability traits. There was the same association between heritability and the interval between validating and testing sets so that getting away from validating sets somehow declined the accuracy of high heritability trait but the decline was severe for low heritability trait.

Impact of Genomic Selection on Inbreeding Rates

Exploiting genomic data helps to estimate the Mendelian sampling term of young individuals without having any phenotypic data. Therefore, genomic selection is expected to reduce the weight of family data in selection decisions by placing the emphasis on Mendelian sampling information of young candidates (Daetwyler et al., 2007). The largest decreases in inbreeding rates due to the use of genomic selection were sighted for traits of low heritability (Lillehammer et al., 2011) and when a large part of variance was explained by markers (de Roos et al., 2011). By screening a large population of candidates, genomic selection facilitates the identification of the least related animals having high genetic merit with a higher accuracy than before.

In particular, McHugh et al. (2011) indicated that genotyping of a large number of females had a very beneficial impact on ΔF reduction. However, even though the rate of inbreeding should be lower per generation from genomic selection compared with progeny testing, and the Mendelian sampling can be estimated at the time of selection more accurately (Daetwyler et al., 2007), shorter generation intervals can lead to an enhancement in the rate of annual rate of inbreeding (e.g., Lillehammer et al., 2011). In addition, there is a risk that genomic selection could result in large homozygous segments of chromosome surrounding QTL in the selected population (Sonesson et al., 2010). For these reasons, approaches to control the rate of inbreeding using genomic selection schemes are essential. Differentiating the number of mating per young bulls on the basis of GEBVs is not a sustainable option; it leads to a slight increase in genetic gain at the expense of a drastic increase in ΔF (Sørensen and Sørensen, 2009).

Pryce et al. (2012) compared three strategies for controlling progeny inbreeding in mating plans. The strategies used data from pedigree inbreeding coefficients, genomic relationships, or shared runs of homozygosity. The results presented here show that using a genomic relationship matrix (GRM) instead of pedigree in a mating plan is an effective way to decrease the expected inbreeding in progeny. The reduction in inbreeding using a GRM calculated using 43,115 SNP (G), a GRM calculated using 3,123 SNP (G3k), and pedigree relationships (A) was dependent on the way in

which inbreeding was assessed. For instance, the performance of G was superior when progeny inbreeding was measured using G and A was superior to G when progeny inbreeding was measured using A. This shows that the method of measuring inbreeding is important when assessing different strategies to control inbreeding. However, in none of these examples the measurement scale independent of the method was used to control inbreeding (Pryce et al., 2012; Gómez-Romano et al., 2016).

Sonesson et al. (2012) have found when the data used to estimate breeding values and to constrain rates of inbreeding were either both pedigree-based or both genome-based, rates of genomic inbreeding were close to the desired values and the identical-by-descent profiles were reasonably uniform across the genome. But, with a pedigree-based inbreeding constraint and genome-based estimated breeding values, genomic rates of inbreeding were much higher than expected rates. With pedigree-instead of genome-based estimated breeding values, the impact of the largest QTL on the breeding values was much smaller, resulting in a more uniform genome-wide identical-by-descent index but genomic rates of inbreeding were still higher than expected, based on pedigree relationships because they measure the inbreeding at a neutral locus not linked to any QTL. Neutral loci did not exist where there were 100 QTLs on each chromosome. With a pedigree-based inbreeding limitation and genome-based estimated breeding values, genomic rates of inbreeding substantially exceeded the value of its limitation. By contrast, with a genome-based inbreeding constraint and genome-based estimated breeding values, marker frequencies changed. However, this change was limited by the inbreeding constraint at the marker position.

McHugh et al. (2011) indicated that genotyping of a large number of females had a very beneficial impact on ΔF reduction. The use of genomic selection to pre-select males for progeny testing resulted in a clear diminution of per generation inbreeding rates compared with progeny testing schemes, for only slight modifications of the generation interval (Pryce et al., 2010; de Roos et al., 2011; Lillehammer et al., 2011; Buch et al., 2012).

The use of genomic information will greatly develop the understanding of the genetic architecture of inbreeding depression in terms of the identification of lethal haplotypes and regions of the genome that are sensitive to inbreeding. The management of the associated haplotypes is likely to become increasingly complex (MacArthur et al., 2012). As outlined by Van Eenennaam and Kinghorn (2014), as the number of lethal loci increases, selection or mating strategies will need to optimize the balance among accordance in genetic gain and decreasing the effect of inbreeding depression. A large number of either lethal or unfavorable haplotypes across multiple economically important traits will finally be identified. Therefore, methods need to be developed that effectively take into account the probability of occurring within an individual or progeny, along with their individual importance to the overall breeding objective (Van Eenennaam and Kinghorn, 2014).

Dynamics of Long-Term Response Genomic Selection

In a simulation looking at several generations, Muir (2007) has displayed that the accuracy of genomic prediction reduces much more quickly if used for selection than if followed by random mating. This result and the putative mechanisms outlined suggest that a careful look at long-term selection using GS is required to detect mechanisms having an important effect on its performance and to give research directions to improve GS. There is also a practical need for both crop and animal breeding programs. Therefore, insight into the long-term consequences of GS deployment would be useful (Jannink, 2010).

In particular, Heffner et al. (2009) have suggested that GS separates the breeding process into two cycles; the selection cycle and model training cycle. The model training cycle is much more constrained than the selection cycle because it needs adequate phenotyping data. Therefore, regardless of species, it appears likely that the frequency of model updating will be lower than that of selection cycles. This limitation raises the questions of how accurate GS can be in selection cycles if it has not been improved, and to what extent long-term selection will be adversely affected.

Another limitation for GS is the necessity of assembling the initial training population (TP) for the model. In simulations using population-wide LD, rather large TP has been used (Meuwissen et al., 2001; Habier et al., 2007; Zhong et al., 2009). In GS on bi-parental cross populations, much smaller populations have been effective, though these populations have never been suggested for long-term selection (Lorenzana and Bernardo, 2009; Wong and Bernardo, 2008).

Azizian et al. (2016) demonstrated that accomplishing higher accuracies by increasing the size of training set would not necessarily lead to the maximum economic efficiency. The optimal value of genomic selections accuracy and the corresponding number of animals in the training set should be estimated according to the economic and breeding situation of the target population. In Iran's condition, the optimal accuracy of genomic selection is about 0.63 which would be achieved by allocating 1,000 individuals in the training set. The cost of genotyping had a little effect on the optimal accuracy and the size of the training set. Variation of heritability did not affect the optimal accuracy and the size of the training set, while this factor increased the economic efficiency.

Eventually, different GS prediction models have proposed the impacts which may differ on short and long terms periods. In simulations of generations promptly after the TP, models that assume all marker effects are distributed with equal variance (i.e., ridge regression), have been found to be as or more accurate than models that assume some markers do not explain any variance (e.g. BayesB) (Meuwissen et al., 2001). However, the accuracy of the former decays more quickly over generations than that of the latter (Habier, 2007).

To examine the questions of the long-term success of GS, the impact of initial training population size, the timing of additions of new phenotypes to the training population, and on GS analysis method, long-term selection for a quantitative trait using GS was simulated. This practice strongly increased primary selection gains but also caused the loss of many favorable QTL alleles, leading to loss of genetic variance, loss of GS accuracy, and a low selection plateau. Placing an additional weight on low-frequency favorable marker alleles, however, allowed GS to increase their frequency earlier on, causing an initial increase in

genetic variance. This dynamic led to higher long-term gain while relieving losses in short-term gain. Weighted GS also enhanced the maintenance of marker polymorphism, ensuring that QTL-marker linkage disequilibrium was higher than in unweighted GS. Losing favorable alleles that are in weak linkage disequilibrium with markers is maybe unavoidable when using GS. Placing an additional weight on low-frequency favorable alleles, however, may reduce the rate of loss of such alleles to below that of phenotypic selection. Applying such weights at the beginning of GS implementation is critical (Jannink, 2010).

A useful feature of genomic selection is that the long-term response is predictable because the marker allele frequencies are well known. This conclusion ignores non-additive effects of the QTL which may cause a change in the gene substitution effect of the QTL, and thus in the apparent effect of the marker, as the selection changes gene frequencies. Of course, it would be possible to continually re-estimate marker effects and involve new markers which had been divested in the primary index (Goddard, 2009).

Dekkers and van Arendonk (1998) investigated selection for one QTL in combination with phenotypic selection. They explained that long-term response could be increased by modifying the selection pressure applied to the QTL as its allele frequency changes. To obtain the maximum long-term response, it is necessary to change the index weights as selection earnings (Dekkers and van Arendonk, 1998). Goddard (2009) indicated that this should be done by making the index weights proportional to $1/\sqrt{p(1-p}$ where p is the gene frequency. The use of this index, and the transformation of allele frequencies (p) to $z = \arcsin\sqrt{p}$, turns a problem with non-constant selection response but linear objective into a problem with a steady selection response but a non-linear objective. The optimum long-term index can then be calculated using procedures developed to deal with non-linear profit functions. This provides an index that puts increased weight on rare favorable alleles. This increases their frequency more quickly than the optimum short-term index and so increases the genetic variance due to them and thus increases the future genetic gain as well. This index is similar to the one obtained by Dekkers and van Arendonk (1998) and Meuwissen and Sonesson (2004) for selection on a single QTL plus a polygenic component. They ignored LD between the QTL and when this is taken into account, a slightly better index may result (Dekkers and van Arendonk, 1998; Sanchez et al., 2006).

Improving Long-Term Response by Focus on Favourable Minor Alleles

Goddard (2009) and Jannink (2010) anticipated that selection was performed for an adequate amount of time to fix all favorable alleles. However, when making decisions for optimum selection, the end of the time horizon might be previous to a selection limit (Wray and Goddard, 1994). If the time horizon is short, increased importance of rare favorable alleles are no longer essential to enhance genetic gain, and therefore, the short-term genetic gain should be maximized. Liu et al. (2014a) assumed that long-term genetic gain can be maximized by slowly decreasing weights on the rare favorable alleles as the population approaches the end of the time horizon. Furthermore, Goddard's optimization (Goddard, 2009) and Jannink's implementation (Jannink, 2010) assume that marker effects are known without error and that markers are in perfect linkage disequilibrium (LD) with QTL.

However, Bijma (2012) reasoned that even if the true effects of alleles are known and selection is for the optimal combination of all true allele effects, drift should be computed for because of Mendelian sampling, linkage, and recombination. Therefore, by chance, certainly favorable alleles will inevitably be absent in the selected individuals. Bijma (2012) argued that the optimum weights of rare favorable alleles should be larger than the optimum weights of Goddard (2009). By doing so, rare favorable alleles would be promptly selected towards higher frequency, thus decreasing the probability of losing them from the population.

Liu et al. (2014a) extend the Jannink's weighting (JW) method by including an additional parameter to reduce the emphasis on rare favorable alleles over the time horizon, with the purpose of further improving the long-term genetic gain. They called this new method dynamic weighting (DW). Compared to unweighted genomic prediction, both dynamic weighting and Jannink's weighting can increase long-term genetic gain and decrease rate of inbreeding with a time horizon of 40 generations. The long-term genetic gain when using dynamic weighting was 30.8% greater than that of unweighted genomic prediction, and also 8% greater than Jannink's weighting, although at the cost of a lower short-term genetic gain. With a time horizon of 15 generations, the long-term genetic gain of dynamic weighting can be supported to be at least as high as that of unweighted genomic prediction, whereas Jannink's weighting cannot. Consequently, dynamic weighting is a promising method that is expected to result in high long-term genetic gain within a fixed time frame.

Results demonstrated that without weighting methods, Bayesian lasso (BL) is superior to ridge regression (RR) in keeping genetic variance and controlling inbreeding, and therefore can result in higher long-term genetic gain, regardless of the length of planning horizon and the number of QTL influencing the trait. The number of QTL also varied in Liu's simulations since it might influence the accuracy of various prediction models. By contrast to prior expectations, the relative superiority of BL over RR was larger when the number of QTL was larger and long-term response was the scale for comparison. The results indicated that the number of QTL mainly affected the loss of favorable alleles and the loss of genetic variance, which was greater with RR than with BL. This may be due to the fact that with more QTL, the selection pressure on each QTL is smaller, and the drift therefore becomes relatively more important. The number of QTL did not affect the rate of inbreeding since, here, the rate of inbreeding was measured based on pedigree information only (Liu et al. 2014a). Mating programs such as positive assortative mating can also enhance variance by introducing positive co-variances among breeding values of selected mates (Fernando and Gianola, 1986; Breese, 1956; Wilson, 1965).

Fernando and Gianola (1986) simulated 20 generations and found that selection with assortative mating can have a sizable (10 to 20%) long-term benefit over selection with the random mating of parents when heritability is high, the allele frequency of base population is low and proportion selected is large. Hallander et al. (2007) revealed that the genetic variance could be sustained or even increase in the presence of non-additive genetic effects. Consequently, simulations that consider non-additive effects with a large number of QTL need additional understanding of

the influence of the quantity and distribution of these effects. Furthermore, even when epistatic effects exist, this does not reduce the importance of maintaining genetic variance and rare favorable alleles by weighting methods. It should be noted that the aim of the previous studies was to investigate the main mechanisms that have consequences in long-term selection programs. DW showed a lower accuracy and a lower short-term genetic gain than JW, which may be relevant for practical breeding programs. Besides, another common way of increasing selection limits is to switch the selection rule from truncation selection to optimum contribution selection (OCS). OCS works by optimizing the genetic contribution (i.e. number of mating) of each selection candidate, conditional on EBV and average co-ancestry. By doing so, the genetic gain is expected to be maximized and, meantime, the rate of inbreeding is limited. This method has been well studied in dairy cattle, pig, and fish breeding and has proven to be promising in terms of long-term genetic gain (Gandini et al., 2012; 2014; Nielsen et al., 2011; Liu et al., 2014b; Dagnachew et al., 2016). Therefore, it will be worthwhile to compare DW with OCS in subsequent studies. Combining DW with OCS may result in a lower rate of inbreeding and higher genetic gain compared to each procedure used alone.

Sun and VanRaden (2014) suggest simple, improved formulas for weighting favorable minor alleles to enhance long-term progress from the genomic selection with less reduction of short-term progress. The prior formula used nonlinear weights based on square root of the frequency of the favorable allele. Prior formulas to implement FMA selection used arcsin (Goddard, 2009) or square root (Jannink, 2010) to adjust weights for favorable alleles.

Goddard (2009) argued that the index weight for long-term response alters as the gene frequencies alters due to selection, and using a transformation of $\zeta=\arcsin\sqrt{f}$ leads to a response on the transformed scale ζ that is constant regardless of gene frequency. The arcsin formula considered only selection direction and allele frequency (*f*) but not effect size, and therefore was not applicable for variable effect sizes (Jannink, 2010).

The square root formula is closely proportional to arcsin over a range of allele frequencies and also includes allelic effect, hence, it has no parameter to balance long-term gains with short-term losses. Two new formulas to enforce FMA selection were derived. The first used nonlinear weights and the quare root of the frequency of the favorable allele as done by Jannink (2010), but also included a parameter δ that could vary from 0 to 1 to balance long- and short-term progress. The new formula is identical to Square root if δ= 1. When 0< fj <1. The second formula involved a parameter δ that could vary from 0 to 2, but simple linear weights were applied with more weight for favorable minor and less weight for favorable major alleles proportional to frequency variation from 0.5 (Jannink, 2010).

The formulas were examined by simulation of 20 generations (population size of 3,000 for each generation) with direct selection on 3,000 QTLs (100 per chromosome). The prior formula had a slower response than unweighted selection in primary generations and did not recover by generation 20. The long-term response was slightly greater with the new formulas than with unweighted selection; the linear formula may be best for routine use because of more progress in primary generations compared with nonlinear formula. Official and adjusted U.S. evaluations based on actual genotypes and projected marker effects were correlated by 0.994 for Holsteins and Jerseys and 0.989 for Brown Swiss using a linear weighting of allele frequency, which was higher than nonlinear weighting. The difference between adjusted and official evaluations was highly correlated negatively with an animal's average genomic relationship to the population. Therefore, strategies to reduce genomic inbreeding may obtain almost as much long-term progress as a selection of favorable minor alleles (Sun and VanRaden, 2014).

Studies have shown that, when performing selection for many generations, GS increases the risk of losing favorable QTL alleles compared with phenotypic selection (Toosi et al., 2009), predomonantly in the first few generations. Some of these alleles are rare and inevitably lost due to low linkage disequilibrium (LD) with any marker (Lu et al., 2003). The remaining favorable QTL alleles are essential to maintaining long-term genetic variance and response to selection (Liu et al., 2014a).

Conclusion

Mating plans could be planned to control the rate of inbreeding in a subset of individuals in the next generation. If maximizing long-term genetic gain while controlling inbreeding in the entire population is the desired outcome, then approaches that select candidates including data on co-ancestry among the selection candidates should be used. As there is no need for the use of a pedigree when sequence data is available, it would seem reasonable to apply the current population as a reference point. Difference in identity between individuals could then simply be realized in terms of covariance among breeding values. The strategy combining wGEBV with OCS was very promising, as it provided higher gain and/or lower true inbreeding than using each of them alone in genomic breeding schemes. That's why using wOCSG has been recommended as not only did it boost the cumulative genetic gain, but also it restricted the increase in true inbreeding across the genome. The OCS with limitations imposed during optimization realizes most of the long-term genetic gain realized by OCS without restrictions. Realizing 67 to 99% of the additional gain with many of limitations demonstrates that OCS is a strong selection method. Its strength has been evident even with multiple limitations, where several limitations that remove solutions from the solution space are imposed at the same time. Dynamic weighting was described as a novel genomic selection technique to maintain genetic variance and raise long-term genetic gain. This technique is made upon Jannink's weighting technique, in which low-frequency favorable alleles obtain a high weight. Jannink's weighting technique was proven to be successful in increasing the long-term genetic gain compared with unweighted GP.

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aCS84_29