

Integrating genomic selection into dairy cattle breeding programmes: a review

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Extensive genetic progress has been achieved in dairy cattle populations on many traits of economic importance because of efficient breeding programmes. Success of these programmes has relied on progeny testing of the best young males to accurately assess their genetic merit and hence their potential for breeding. Over the last few years, the integration of dense genomic information into statistical tools used to make selection decisions, commonly referred to as genomic selection, has enabled gains in predicting accuracy of breeding values for young animals without own performance. The possibility to select animals at an early stage allows defining new breeding strategies aimed at boosting genetic progress while reducing costs. The first objective of this article was to review methods used to model and optimize breeding schemes integrating genomic selection and to discuss their relative advantages and limitations. The second objective was to summarize the main results and perspectives on the use of genomic selection in practical breeding schemes, on the basis of the example of dairy cattle populations. Two main designs of breeding programmes integrating genomic selection were studied in dairy cattle. Genomic selection can be used either for pre-selecting males to be progeny tested or for selecting males to be used as active sires in the population. The first option produces moderate genetic gains without changing the structure of breeding programmes. The second option leads to large genetic gains, up to double those of conventional schemes because of a major reduction in the mean generation interval, but it requires greater changes in breeding programme structure. The literature suggests that genomic selection becomes more attractive when it is coupled with embryo transfer technologies to further increase selection intensity on the dam-to-sire pathway. The use of genomic information also offers new opportunities to improve preservation of genetic variation. However, recent simulation studies have shown that putting constraints on genomic inbreeding rates for defining optimal contributions of breeding animals could significantly reduce achievable genetic gain. Finally, the article summarizes the potential of genomic selection to include new traits in the breeding goal to meet societal demands regarding animal health and environmental efficiency in animal production.

Keywords: genomic selection, breeding programme, dairy cattle, genetic gain, inbreeding rates

Implications

The practical use of genomic information to select animals, or genomic selection, is currently revolutionizing the organization of dairy cattle breeding schemes. The success of this new technology is because of increased genetic progress on both the bull and cow genetic pathways by reducing costs compared with conventional selection schemes, but also by the potential of using this rich source of information to manage genetic resources. Practical results of the implementation of genomic selection in dairy cattle breeding schemes are of great importance for other livestock species in which genomic selection is now under consideration.

Introduction

Use of molecular information to make selection decisions in breeding programmes was envisaged decades ago (Smith, 1967; Soller, 1978). Although conceptually simple, the implementation of genetic markers into breeding programmes has been rather limited for technological reasons. The recent availability in dense panels of single nucleotide polymorphism (SNP) markers has offered new opportunities to do so. The basic concept underlying such an approach is to use dense genetic markers as proxies to detect genome regions involved in a trait – the quantitative trait loci (QTL) – and exploit them for selection purposes. SNP genotyping technology has enabled profiling many animals for thousands of marker loci in a single analysis, thus with a low cost per marker (Williams, 2005). Capitalizing on this rich source of information permitted estimation of breeding values for young candidates with higher

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accuracy than before. The principle of genomic evaluation models is to take advantage of both genotypic and phenotypic data available in a training (also called 'reference') population to build prediction equations of the genetic merit of individuals (Meuwissen *et al.*, 2001). These equations can then be applied to selection candidates having genotypes but no phenotypes. Diverse approaches have been proposed to estimate genomically enhanced breeding values (GEBV), as reviewed by Hayes *et al.* (2009).

The use of genomic information to make selection decisions, or genomic selection, was shown to greatly increase the technical and economic efficiency of dairy cattle breeding programmes (Schaeffer, 2006; König *et al.*, 2009). Indeed, genetic progress was achieved in conventional progeny testing (PT) schemes via the wide use of the very best progeny-tested bulls, which was enabled by means of artificial insemination (AI). Because selection in dairy cattle is undertaken on traits expressed by females, the PT step was necessary to generate a daughter group whose performance was used to predict the genetic merit of bulls with high accuracy. However, PT implies long generation intervals and huge costs related to bull maintenance and progeny-group constitution. Furthermore, only a limited number of young sires can be progeny tested each year owing to structural constraints. The choice of young males was therefore critical, whereas the accuracy of mid-parental Best Linear Unbiased Prediction (BLUP) breeding values was low at a young age. Because genomic selection alleviates some of these costs and technical constraints, the dairy cattle breeding industry has rapidly integrated genomic information into selection programmes. Many efforts have been devoted (so far) to improving the statistical models used for genomic evaluations (Hayes *et al.*, 2009). Research has also been undertaken to answer questions arising about the practical use of genomic selection in breeding programmes. Such questions are also likely to emerge in other populations in which application of genomic selection is being considered.

To date, two main approaches have been used to predict the response to genomic selection. Hence, the first objective of this review was to describe these methods, which rely on either infinitesimal or finite locus models (FLMs), and to discuss limitations in their application. The second aim was to summarize the main conclusions reached on the subject by considering the example of dairy cattle populations. Critical factors influencing the efficiency of genomic selection were reviewed, as were future challenges faced in designing breeding schemes. The present review mainly focused on factors affecting the technical efficiency of programmes that was assessed through three criteria, namely (i) the annual genetic gain (ΔG), (ii) the variability of this response and (iii) the impact of selection procedures on maintenance of genetic diversity accessed via inbreeding rates (ΔF).

Modelling the efficiency of genomic breeding programmes

Modelling genomic selection with the selection index theory
The selection index theory was proposed to model the overall gain in accuracy expected from using genomic

information at some selection stages (Lande and Thompson, 1990; Dekkers, 2007). To do so, SNP information of genotyped individuals is summarized into the direct genomic value (DGV). In practice, DGV is modelled as an infinitesimal indicator trait, which is highly heritable and genetically correlated with the selected trait. This indicator trait is modelled with a heritability of 1, meaning that genotyping errors are ignored and genotyped animals will receive no information from DGV of relatives. In this approach, the genetic correlation considered between the DGV and the selected trait reflects the desired level of accuracy for genomic predictions (Dekkers, 2007). Assuming the infinitesimal model and multivariate normal distribution of genotypic and phenotypic values, the selection index theory offers a convenient framework to optimally combine both information sources. Because no molecular data are simulated in this approach, the inbreeding rate generated by a scheme must be assessed with analytical formulas in deterministic models or with pedigrees in stochastic simulations. The main appeal of this approximate approach lies in its computational efficiency and straightforward implementation into existing software using either deterministic prediction models or stochastic simulations. It was extended to multi-trait selection by Dekkers (2007), and was also referred to as *pseudo-genomic selection* by Buch *et al.* (2012a).

Simulations based on FLMs

Another approach entails simulating individuals and their genotypes at a finite number of markers and QTL. This approach allows modelling the dynamics of genetic diversity at neutral markers and genetic variance at QTL by explicitly considering the discrete nature of genotypes and the finite size of genomes (Dekkers *et al.*, 2004). In FLM simulations, breeding programmes are generally not started from a founder population with genotypes sampled at random. It is recommended to first simulate an ancestral population that has reached equilibrium with respect to mutation and genetic drift to ensure that a realistic structure of linkage disequilibrium (LD) exists between syntenic loci (Muir, 2007). Before simulating the breeding scheme, a base population is constituted by sampling individuals from the ancestral population. The true breeding values (TBV) of individuals are obtained as the sum of effects of QTL alleles that they carry on their chromosomes plus a polygenic term, if simulated QTLs are not assumed to explain all of the genetic variance. Following conventional principles of stochastic simulations, phenotypic observations are reconstructed from TBV by adding a residual term sampled from known statistical distributions to achieve the desired heritability (Dekkers *et al.*, 2004). GEBVs are predicted by performing a genomic evaluation with simulated phenotypes and genotypes as inputs and by using the variance components assumed in the simulation. Hence, the accuracy of genomic predictions is not a prior in the model, but rather a result of simulations.

Finally, inbreeding rates can be estimated in FLM simulations by using either recorded pedigrees or marker information. Although the pedigree-based estimator of inbreeding

ignores the effects of linkage and selection around QTL regions, its use is expected to give accurate estimations of ΔF for long genomes, that is, $>10\text{ M}$ (Villanueva *et al.*, 2005). However, the use of pedigree-based inbreeding estimates does not provide information about reductions in genetic diversity around QTL regions under selection (Sonesson *et al.*, 2010). An advantage of FLM simulations is that they provide information at simulated markers to monitor the evolution of autozygosity along the genome. Indeed, the proportion of simulated marker loci that is homozygous by descent with respect to the base population gives an expectation of the 'realized' inbreeding coefficient.

Limits of application

Pseudo-genomic selection and FLM simulations rely on different genetic models. Given a certain genetic architecture, the FLM simulation is expected to be the most accurate approach because it models the effects of biological processes and selection procedures on both genetic diversity and genetic variance. Although most breeding programme simulations have focused on additive effects, sophisticated architectures can be simulated with QTL exhibiting dominance and epistatic effects. However, the choice of parameters is expected to influence the level and maintenance of genetic variance and diversity (Hu and Li, 2006). Hence, it is safe to test the sensitivity of predictions to different architectures when using this prediction method.

Pseudo-genomic selection is an approximate approach that requires a set of assumptions with various consequences on predictions. First, it assumes the infinitesimal model and multivariate normal distribution of DGV and phenotypic values to combine them optimally into a genomic selection index. This supposes that the genetic architecture of selected traits complies with the hypotheses of the infinitesimal model, that is, traits are controlled by a large number of genes with individually small additive effects (Bulmer, 1980). Research on model species confirmed the relevance of using the infinitesimal model to describe the genetic mean and variance of a population for most quantitative traits because QTL alleles with large effects are rare and most of genetic variation is generally due to many loci with small effects (Mackay *et al.*, 2009). Thus, this model is valid over a short to medium time period, ignoring long-term changes in genetic variance due to fluctuations of allele frequencies. In addition, when dense marker maps are used, DGVs are expected to follow a multivariate normal distribution as a result of the central limit theorem (Lande and Thompson, 1990).

Second, in pseudo-genomic selection, the accuracy of GEBVs is a prior in the model and assumed to remain constant over time and to be the same for all individuals. In practice, GEBV accuracy is expected to increase depending on the size of the training population. Fixing GEBV accuracies to currently achieved values consequently depicts a rather pessimistic scenario, which is safe when genomic schemes are compared with conventional schemes. However, accuracy of GEBVs was shown to be sensitive to many

intermingled parameters comprising the genetic architecture of traits (Daetwyler *et al.*, 2010), the LD existing between markers and QTL (Goddard, 2009; Goddard *et al.*, 2011), the statistical model of genomic evaluation (Daetwyler *et al.*, 2010; Bastiaansen *et al.*, 2012), the frequency of updating prediction equations (Muir, 2007) and the composition of the training population and its relationship with selection candidates (Lillehammer *et al.*, 2011; Pszczola *et al.*, 2012). As a consequence, different designs of genomic schemes can lead to different evolutions of GEBV accuracy (Lillehammer *et al.*, 2011). Because pseudo-genomic selection ignores the influence of all of these parameters on GEBV accuracy, this approach may lead to biased comparisons of genomic schemes on the basis of predictions of genetic gain.

Finally, computational requirements to achieve calculations also influence the choice of prediction method. Pseudo-genomic selection makes the optimization of breeding schemes more tractable than in FLM simulations, especially when selection is carried out on a breeding objective that includes several genetically correlated traits. However, Meuwissen (2009) showed that it was possible in FLM simulations to scale down by the same factor the effective size of the population, the genome size and the number of training records without modifying the achieved level of GEBV accuracy. This allows comparison of expected genetic gain from different genomic selection schemes at lower computational expense.

Impact of genomic selection on selection response and its variability

Description of investigated genomic selection schemes

Most studies have compared genomic selection schemes with the conventional PT scheme, which was the norm in dairy cattle populations until recently. Genomic selection was integrated into breeding schemes in two different ways, leading to genomic pre-selection (PS) and genomic juvenile (JS) schemes. The PS scheme entails using GEBVs to pre-select young males for PT. All subsequent steps for the selection of males remain the same as in PT schemes. Compared with PT schemes, PS schemes allow increasing the selection accuracy of young male candidates by using their genotypic information. In JS schemes, the use of genomic information is more aggressive. AI sires are selected by using GEBVs among young genotyped males able to produce semen. Although GEBVs of young sires are less accurate than conventional breeding values estimated for progeny-tested bulls, the loss in selection accuracy is compensated by a huge reduction in generation intervals, as there is no need for progeny testing. Genetic gain is then rapidly cumulated over shortened generations. In both genomic schemes, females can be genotyped to increase both accuracy and intensity for the selection of females.

Large variations in predicted ΔG were found across studies, as described by Pryce and Daetwyler (2012). Compared with conventional schemes, gains in ΔG ranged from +9% for PS schemes to more than +100% for JS schemes.

However, these figures must be interpreted with caution, considering the specific set of parameters used in each study, for example, the heritability of the trait, the accuracy of GEBV and the number of genotypings allocated to males and females. For instance, for a trait with moderate heritability (0.3) – typical of a production trait – setting up a PS scheme increased ΔG by 9% (Lillehammer *et al.*, 2011), 13% (Buch *et al.*, 2012a) and 16% (Pryce *et al.*, 2010) compared with the former PT scheme. JS schemes were shown to generate higher selection response, with increases of 29% (Lillehammer *et al.*, 2011), 59% (Pryce *et al.*, 2010), 65% (Buch *et al.*, 2012a) and 86% (Colleau *et al.*, 2009) compared with PT schemes.

Increases in ΔG because of genomic selection were the largest when selection was carried out on traits of low heritability, because genomic data added relatively more information to predict breeding values for these traits. Compared with a traditional PT scheme, Lillehammer *et al.* (2011) showed that ΔG was increased by 29%, 40% and 70% in JS schemes for heritability values of 0.30, 0.05 and 0.01, respectively. However, levels of GEBV accuracy remained generally moderate to low for traits of low heritability. Phenotypic information of an indicator trait genetically correlated with the selected trait and recorded on a large scale can be integrated in the genomic evaluation model to improve the accuracy of predictions for traits of low heritability when the genetic correlation between both traits is large, that is, >0.5 (Calus and Veerkamp, 2011; Buch *et al.*, 2012a).

GEBV reliabilities larger than 0.5 to 0.6 are already achieved in homogeneous dairy cattle populations with large reference populations (e.g. Holstein populations) for traits with moderate to high heritability (Harris and Johnson, 2010; Su *et al.*, 2010). By contrast, reliabilities of at least 0.8 are obtained for breeding values estimated for progeny-tested bulls. In breeds with large effective sizes or small reference populations, reliability of GEBVs is generally lower (<0.5) even for production traits.

More emphasis placed on bull dam selection

In schemes integrating genomic selection, an important part of genetic gain is achieved through the selection of bull dams (Schaeffer, 2006). Indeed, the reliability of breeding values is strongly increased for genotyped females to a level comparable with that achieved for genotyped males. Furthermore, GEBVs of bull dams are expected to be less biased, because genomic information reduces the weight attributed to own performance, which may be subject to preferential treatment. With a training population of sufficient size, large gains are expected from a more accurate selection of breeding cows, even when only a small proportion is genotyped (Sørensen and Sørensen, 2009). Therefore, it is relevant to define strategies to optimally allocate genotyping capacities between young males and females in order to maximize genetic gain. Sørensen and Sørensen (2009) showed that allocating larger proportions of genotypings to females than males resulted in larger selection responses. Indeed, the proportion of males kept for reproduction is small in dairy cattle populations. If extra genotyping

capacity is spent on males, the second best males according to parent average will be genotyped, although they have a lower chance of being selected. On the contrary, if extra genotyping capacity is spent on females, there are greater chances of detecting interesting females among the cow population to generate high genetic merit bull calves.

Influence of reference population constitution on genomic prediction accuracies

The need for large reference populations to increase GEBV accuracy has encouraged collaboration between breeding organizations and countries to exchange genotypic data (Lund *et al.*, 2011; Wiggans *et al.*, 2011). Collaboration has quickly appeared to be one of the cheapest ways to achieve higher GEBV reliabilities, although competitive interests often impeded the process (VanRaden *et al.*, 2009). In such collaborations, all genotypes of selected and unselected candidates have to be shared to avoid biases in the estimation of genomic breeding values, at both the national and international scales (Patry *et al.*, 2011).

Constitution of the reference population also influences the level of GEBV accuracy (Habier *et al.*, 2007) and its persistence over time (Lillehammer *et al.*, 2011). Hence, breeding programmes should be designed to minimize the average relationship within the reference population and maximize relationships between candidates and the reference population (Pszczola *et al.*, 2012). On the basis of FLM simulations of scenarios with reference populations of equivalent sizes, Lillehammer *et al.* (2011) showed that PS and JS schemes led to different levels of GEBV accuracy. Indeed, in PS schemes, all sires of male candidates have been progeny tested and are included in the reference population. This implies larger genetic ties between candidates and reference bulls than in JS schemes, in which only grandsires of candidates and older ancestors are included. Reducing the number of progeny-tested bulls in PS schemes led to a decrease in GEBV accuracy because fewer bulls with daughter information could be added each year to the reference population. However, Lillehammer *et al.* (2011) showed that the resulting loss in ΔG could be compensated by increasing the progeny group size. Thus, in PS schemes, maintaining maximal testing capacity is required to ensure accurate EBVs for bulls in the training population, and subsequently, accurate GEBVs for candidates, especially for traits of low heritability.

Including cows in the reference population has recently been suggested to further increase the reliability of genomic predictions because the number of AI sires is generally limited in dairy cattle populations (McHugh *et al.*, 2011; Buch *et al.*, 2012b). Such a strategy is gaining some interest given the increasing popularity of genomic selection in the industry and the decreasing costs of genotyping (Strauss, 2010). Actually, the recent release of cheaper SNP platforms is likely to extend the use of genomic selection to a wider female population. Use of imputation techniques makes it feasible to use sparser SNP chips to estimate GEBVs with only moderate losses in prediction accuracy (Weigel *et al.*, 2010;

Dassonneville *et al.*, 2011). However, before practical inclusion of female information in reference populations, the issue of preferential treatment, which frequently occurs with elite cows, must be tackled because it can introduce bias in the estimation of SNP effects, potentially decreasing the accuracy of genomic predictions.

Impact on variability of selection response

In PT schemes, the risk of using a bull with poor genetic merit is minimized because of PT. In PS schemes, this risk is further reduced owing to the genomic pre-selection step, which allows distinguishing with higher accuracy the best young males within families before PT (Buch *et al.*, 2012a). In JS schemes, the accuracy of breeding values used to select AI sires is lower than that obtained after PT. Considering a fixed number of AI sires selected each year, the variability of selection response obtained by implementing a JS scheme is increased relative to conventional schemes (Buch *et al.*, 2012a). Thus, in practice, increasing the number of AI sires in JS schemes is recommended to mitigate the risk of using bulls with poor genetic merit. Another recommendation is to use young sires in 'teams' because the reliability of the mean GEBV of a group of bulls increases with group size. Schefers and Weigel (2012) reported that a team of five young bulls, each having a GEBV with a reliability of 0.70, will have an average GEBV with a reliability of 0.94.

New opportunities to monitor and preserve genetic diversity

Impact of genomic selection on inbreeding rates

Exploiting genomic information enables estimation of the Mendelian sampling term of young individuals without any phenotypic information. Therefore, genomic selection is expected to reduce the weight of family information in selection decisions by placing the emphasis on Mendelian sampling information of young candidates (Daetwyler *et al.*, 2007). The largest reductions in inbreeding rates due to the use of genomic selection were observed 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 also facilitates the identification of the least related animals having high genetic merit with a higher accuracy than before. In particular, McHugh *et al.* (2011) showed that genotyping a large number of females had a very beneficial impact on ΔF reduction.

The use of genomic selection to pre-select males for PT (i.e. PS scheme) resulted in a clear reduction of per generation inbreeding rates compared with PT 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.*, 2012a). Setting up JS schemes also generally led to reductions in per generation ΔF compared with PT schemes. However, because the generation interval was reduced as well, annual ΔF may not be decreased compared with conventional schemes (Lillehammer *et al.*, 2011; Buch *et al.*, 2012a). Increasing the number of young AI sires used in

JS schemes is an option to curb inbreeding rates without markedly reducing genetic gain (Lillehammer *et al.*, 2011).

Differentiating the number of matings 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). Finally, schemes with mixed use of proven and young genomic bulls were studied by Colleau *et al.* (2009) to mimic the situation in which some breeders did not accept the risk of using young AI bulls having a GEBV of moderate reliability. The authors showed that allocating 50% of inseminations in a JS scheme to the 20 best bulls having milking daughters led to a small increase in genetic gain and a large increase in inbreeding rate. Thus, this practice was harmful for genetic diversity unless strict rules were defined for the management of genetic resources.

The conclusions about the impact of genomic selection schemes on genetic diversity critically depend on the time unit chosen to express inbreeding rates. In practice, the inbreeding rate should be kept under 1% per generation in conservation and breeding schemes to avoid undesirable effects of inbreeding on fitness (Food and Agriculture Organization (FAO), 1998). This recommendation indicates that an effective population size of at least 50 individuals is required so that factors such as natural selection, recombination and mutation – which intervene at every generation – can counterbalance effects of inbreeding depression (FAO, 1998). When the selected trait and fitness were not genetically correlated, Meuwissen and Woolliams (1994) estimated that a critical effective size of 30 to 250 individuals was required in a selection scheme so that natural selection could overcome the effects of inbreeding depression on fitness, which is consistent with FAO recommendations. However, when the selected trait and fitness were negatively correlated, even weakly (-0.2), Meuwissen and Woolliams (1994) showed that it was almost impossible to prevent a decline in fitness. In such situations, shortening the generation interval makes the accumulation of inbreeding depression effects bigger. Thus, in our opinion, it is safe to compare breeding schemes by using annual inbreeding rates. In addition, the inbreeding rate can be considered a measure of the risk of a scheme. Therefore, it seems relevant to express it on the same time scale as genetic gain, that is, on an annual basis.

Although the design of breeding schemes is important to limit the rise in inbreeding in a population, there is also a need to develop efficient recording systems that are able to detect emerging genetic defects (Agerholm *et al.*, 2001). In particular, when the generation interval is shortened, it is essential to take rapid measures to control the spreading of the defect by restricting the use of bulls carrying it. The example of Holstein BLAD, CVM and Brachyspina genetic defects illustrated how fast a lethal mutation can spread in a population of small effective size.

Including genomic information in the optimal contribution selection (OCS) method

In the near future, JS schemes will likely be preferred to other designs because they generate larger genetic gain at

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