The effect of discovery bias on genomic selection and why it can no longer be ignored

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Introduction

In the past, traditional breeding methods have concentrated mainly on genetic improvement by artificial selection and have contributed in large amount to the advancement of animal productivity over the past 50 years (Dekkers and Hospital, 2002). However, this traditional approach is based on the knowledge of genetic parameters such as heritabilities, genetic variances and correlations for an entire population, all of which can be estimated using statistical analysis of pedigree data (Dekkers and Hospital, 2002), but does not take advantage of an animal's genomic information.

Recent advancements in the field of molecular genetics have led to the identification of multiple genes and markers associated with economically relevant traits in livestock species (Dekkers, 2004). This discovery provides opportunities to further enhance response to selection, particularly in traits that are difficult to measure, have low heritabilities, are measured late in life, or are sex-limited (Dekkers, 2004; Garrick, 2009). The idea of genomic selection was first introduced by Meuwissen et al. (2001), who used dense marker maps to estimate the effects of ~50,000 haplotypes simultaneously using a limited number of phenotypic records. Meuwissen et al. (2001) suggested that by using a large number of markers, it becomes possible to estimate breeding values without having knowledge of their location on the genome. This is because dense marker maps are believed to have genetic markers covering the entire genome, and therefore all quantitative trait loci (QTL) are thought to be in linkage disequilibrium (LD) with at least one marker (Goddard and Hayes, 2007).

There are numerous advantages to utilizing an animal's genomic data to enhance selection decisions. Overall, genomic selection has given animal breeders the ability to enhance genetic improvement programs in livestock populations by direct selection on genes and genomic regions (Dekkers and Hospital, 2002). Perhaps the biggest advantage of genomic selection is the obvious possibility to increase the rate of genetic gain within a population.

Because genomic data, unlike phenotypes, can be collected early in an animal's life (Eggen, 2012), selection decisions can be made sooner. It then follows that bulls who can be bred at one year of age largely reduce generation intervals within a herd (Eggen, 2012; Goddard and Hayes, 2007; Schaeffer, 2006) causing an increase in selection intensity (Eggen, 2012). This is essential to the rate of genetic gain in the population.

Genomic selection can also reduce the cost of bull testing in cattle. The purpose of progeny testing a bull is to quantitatively measure how his offspring will perform to estimate his breeding value. In the context of carcass traits in beef cattle, progeny performance data is the only way to estimate a bull's performance. Utilization of genomic data will provide breeders with estimated values sooner as well as possibly reduce the cost.

Finally, the use of genomic selection is not sex limited (Eggen, 2012). It becomes possible to shift the emphasis of selection to the dam side of the pedigree (Schaeffer, 2006). New technologies such as flushing and embryo transfer allow animal breeders to take advantage and propagate the genetics of superior dams for an even further increase in genetic gain.

Although genomic selection seems very promising, the accuracy of the calculated molecular breeding values (MBV) will be the deciding factor in their successful implementation. The higher the accuracy of the MBV, the more successful the breeding program and the faster the rate of genetic change within a population.

The most important aspect of any experiment or trial is the ability to replicate the results. One of the main issues occurring in genomic studies is the inability to observe the same outcomes between populations (Goddard et al., 2009; Xaio and Boehnke, 2009; Xu et al., 2011). Calus (2010) suggests that the accuracy of the estimated marker effects depends heavily on the characteristics and size of the training population, how those animals are sampled, and the heritability of the trait being selected.

In genome wide association studies (GWAS), the goal is to test SNP for associations with a trait or phenotype (Goddard et al., 2009). However, the common occurrence seems to be the overestimation of the SNP effects, which tend to be larger in magnitude than the true effects (Goddard et al., 2009; Xiao and Boehnke, 2009). This causes the accuracy of MBV to be overestimated as well. This overestimation, or upward bias, causes any follow up study to fail (Xiao and Boehnke, 2009). It is believed that this type of discovery bias occurs because the

predictions are applied to the same animals, or data, from which model selection and parameter estimation were calculated (Xu et al., 2011).

This consistent over estimation of marker effects has been termed the "winner's curse" or "Beavis effect" in most of today's literature (Goddard et al., 2009; Xiao and Boehnke, 2009; Xu et al., 2011), but was perhaps first introduced by Göring et al. (2001). They believed that a sampling bias in reported test statistics of an analysis caused a sampling bias in the reported parameter estimates. This was based on the observation that follow-up studies give lower estimates of effect size. Because all tests of linkage or association are conceptualized mathematically, the estimation of any relationship between marker genotypes and trait phenotypes are subject to genome wide sampling bias.

The best explanation of the winner's curse is perhaps given by Bazerman and Samuelson (1983), who explain the occurrence in terms of an auction. For example, if an item is up for auction, participants who have no concept of the item's actual value place unbiased bids. However, these are imprecise estimates of the item's true value causing the final selling price to be higher than its actual value. This upward bias occurs because the winning bid is contingent on being the highest of the unbiased bids. This carries over into GWAS because an initial positive finding is based on a SNP having a higher effect than the rest, resulting in estimates of its effect size being upwardly biased (Xiao and Boehnke, 2009). But where exactly does this occur in beef cattle genomic selection? It is possible that the cause comes in part from the use of "training" and "validation" populations.

Literature Review

Genomic information was first introduced into the National Cattle Evaluation (NCE) by the American Angus Association (AAA) in 2009. Upon this initial incorporation, the identification of animals in training populations was unknown, causing the relationship between them and the target populations to be unknown (Spangler, 2013). It was discovered that the use of a known training population, in conjunction with a validation population was the most efficient way to calculate MBV. According to Garrick and Saatchi (2013), the development of MBV requires a group of historic animals that have both genomic data and information related to their true breeding values, known as a training population. Phenotypes and genotypes from the training population are used to develop MBV prediction equations using the individual SNP

additive effects of loci that show the strongest association with the trait of interest (Van Eenennaam et al., 2009). Using various statistical approaches to this procedure, an MBV is calculated for each animal within the population. Once the MBV prediction equations are created, they are then the focus of a validation study (Van Eenennaam et al., 2009). Another group of representative animals are selected and genotyped and the resulting MBV are compared to their phenotypes to assess their accuracy (Goddard and Hayes, 2007). As expected, prediction equations perform "best" when used in discovery populations in which the SNP associations were discovered or where the SNP effects were estimated (Van Eenennaam et al., 2009). Because the SNP effects are optimized to fit the data in the training populations, their estimated accuracies are higher, but not necessarily representative of the actual accuracy.

Methods of molecular breeding value calculation

One of the first methods used to estimate an animal's MBV is termed genomic best linear unbiased prediction (GBLUP) and is described my Meuwissen et al. (2001) at the same time genomic selection was introduced. This GBLUP follows the assumption that each locus explains variance equal to V_g/n where V_g is the total genetic variance and n is the number of loci (i.e. an equal amount of variance), making the process unweighted. The main difference between using GBLUP over pedigree BLUP is instead of a numerator relationship matrix (**A**), the relationship matrix becomes the genomic relationship matrix (or realized relationship matrix, **G**) derived from the markers (Meuwissen et al., 2011; Erbe et al., 2012). An alternative to this method is weighted GBLUP, where the markers are weighted by their effects (Zhou et al., 2014).

A second method of calculating MBV is the use of Markov Chain Monte Carlo (MCMC) algorithms to implement Bayesian models. Unlike GBLUP, in Bayesian models the variance explained by the ith locus, V_{gi}, is assumed to be drawn from a prior distribution, meaning the variance can differ across loci (Meuwissen et al., 2001). This idea is more realistic than BLUP, which assumes the variance is fixed. Bayesian models include BayesA, BayesB, BayesC, BayesCπ, BayesR, and BayesRC. While all of these Bayesian models are slight variations of each other, their most important aspect is that they assume the variance accounted for by each locus is different.

The final method of calculating MBV is the use of heterogeneous variance with restricted maximum likelihood. This requires the use of Expectation-Maximization (EM) algorithms instead of MCMC estimation, which are common in Bayesian Regression techniques, to speed

up computation time (Sun et al., 2012). Sun et al. (2012) termed this EM algorithm "fastBayesA", as it follows a BayesA method but uses EM algorithms in place of MCMC. The fastBayesA approach predicts random SNP effects and estimates SNP variances by restricted maximum likelihood (REML), whereas BayesA bases predictions on posterior means of effects. In each EM iteration, BLUP estimates of SNP effects are predicted from a mixed linear model that incorporates a weighted marker-based realized relationship matrix.

Once MBV have been calculated they must be combined with EBV to produce a genome enhanced estimated breeding value (GE-EBV). The MBV do not include any information from phenotypes collected, and the inclusion of the EBV will help to increase the accuracy of the GE-EBV (Garrick and Saatchi, 2013).There are various ways in which this is done, including blending, the correlated trait method, one-step GBLUP, one-step random regression, and treating the MBV as an external EPD with corresponding accuracy.

Using the blending method, the American Hereford Association (AHA) released their first GE-EBV in the fall of 2012 (Ward, 2013). This method only impacts the genotyped animals because it is done post genetic evaluation (Spangler, 2013). Using selection index principles, the variance-covariance structure among the selection criteria, P, and the covariance between the same criteria and objective, g, are blended with the MBV (Garrick and Saatchi, 2013). Straightforward matrix calculation can be used to determine the weighting factors, b, once P and g are defined by solving Pb = g. The GE-EBV, along with a relationship matrix, can be used to derive a pedigree-imputed direct genomic value (DGV) for relatives of genotyped animals. This DGV is then blended with EPD to produce separate GE-EBV.

The American Angus Association (AAA) utilizes the correlated trait method to incorporate calculated MBV into EBV (Northcutt, 2013). This method was proposed by Kachman (2008) and used by MacNeil et al. (2010). It assumes that the calculated MBV could be fitted as a correlated indicator trait in already existing multiple-trait models and also allows for genomic information to influence the predictions of animals in a pedigree without genotypes (Spangler, 2013). Because marker scores are based on marker genotypes, their residual variances are expected to be small relative to their genetic variance (Kachman, 2008).

Another variation of incorporating MBV into NCE is considering the MBV as an external source of information following the approach of Quaas and Zhang (2006). The benefit of this concept is that it allows for varying accuracy of MBV, unlike blending and the correlated trait

method (Spangler, 2013). This follows the idea that MBV do not predict the genetic merit of every animal within a population with the same degree of accuracy, mainly due to their relationship with the training population.

A single step implementation of GBLUP (SS-BLUP) has been proposed based on linear mixed models and pedigree relationship matrices combined with genomic information (Vitezica et al., 2011). The SS-BLUP method modifies the numerator relationship matrix **A** to $\mathbf{H} = \mathbf{A} + \mathbf{A}_{\Delta}$, where $\mathbf{A}_{\Delta}$ includes deviations from expected relationships (Misztal et al., 2009). Creation of **H** can be interpreted as a projection of marker phenotypes from genotyped to non-genotyped animals using their pedigree relationships (Vitezica et al., 2011). However, using MME, it is necessary to calculate $\mathbf{H}^{-1}$ which may prove to be more difficult for larger pedigrees (Miztal et al., 2009).

In similar fashion to SS-BLUP, single-step Bayesian Regression (SSBR) combines phenotype, genotype and pedigree information (Fernando et al., 2014). Unlike SS-BLUP, where the **H** matrix is difficult to invert in large data sets, SSBR does not require computing **H** or its inverse. Single-step Bayesian Regression is also not limited to normally distributed marker effects and can be implemented using the BayesB or BayesCπ models.

How to calculate accuracy

The reliability of an MBV can be defined as the squared correlation between an animal's true breeding value and their calculated MBV (Kachman, 2013). The reliability is then a function of the variance of the true breeding value, the variance of the MBV, and the covariance between them. The reliability of an MBV is important because it impacts both an animal's EBV and the GE-EBV; the greater the reliability of an MBV, the greater the weight and the greater the resulting increase in reliability of the GE-EBV. Habier et al. (2010) discovered that the reliability of an MBV suffers as the genetic relationship between the training population and the animals under evaluation decreases.

There has been a progression of methods used to evaluate genomic tests. Van Eenennaam et al. (2007) described application of the "validation" concept based on independent confirmation of associations to various genomic tests. However, Thallman et al. (2009) shifted the emphasis to quantifying "how well" a genomic test works through estimation of the (co)variances used to incorporate MBV into NCE. Thallman et al. (2009) showed that the proportion of additive genetic variation accounted for by a genetic test is the square of the REML

estimate of the genetic correlation in a two-trait animal model including the target trait and the MBV as the second trait. It was suggested by Kachman (2008) that the proportion of additive genetic variation due to MBV is directly related to the (co)variances required for incorporation of MBV into NCE.

Accuracy Results

Habier et al. (2007) discovered that the presence of genetic relationships captured by markers have an effect on the accuracy of MBV calculations, causing the MBV of individuals with progeny in the training population to have higher accuracy. Genomic relationships cause the accuracy of prediction of MBV both across and within different families or lines to be different. Habier et al. (2010) showed that the accuracy of MBV is not constant, but can vary depending on the number of relatives in training and the degree of additive-genetic relationships. Overall, discovery bias caused by related animals may explain the variation in accuracies being observed.

There are many published studies documenting the increase in accuracy when using a weighted GBLUP compared to unweighted (Snelling et al, 2011; Su et al., 2014; Tiezzi and Maltecca, 2014; Zhang et al., 2014). Snelling et al. (2011) brings up the point that although increased accuracy occurs within the population being studied, this accuracy may not carry over to predictions of unrelated animals. Banos and Coffey (2010) determined that LD patterns are not consistent between selected lines of the same breed, meaning the weights given to SNP of one population may not be optimal when attempting to predict in an unrelated population. The weighting of selected SNP for use in GBLUP leads to bias in the estimated accuracy. The animals more closely related to the training population are more likely to have the LD patterns used to weight the SNP. This may be the cause of the increased accuracy.

When genomic selection was first suggested by Meuwissen et al. (2001), BLUP, BayesA and BayesB were used to calculate MBV and their accuracies were compared. These methods were selected to compare the effects of variance component estimation. Both BayesA and BayesB calculate variance at each locus separately, whereas BLUP assumes that all variances are equal across the genome. The main difference between BayesA and BayesB is that BayesB assumes some loci have no genetic variance. Results showed that while BLUP had reasonable accuracy, BayesA resulted in ~9% more accuracy and BayesB resulted in ~16% more accuracy, suggesting that BayesB was the superior method. Another study by Meuwissen and Goddard (2010) supports this hypothesis, stating that BLUP estimation does not take full advantage of the

high-density marker data, giving BayesB the higher accuracy. Because BayesB gives separate variances to each locus, it (as well as Bayes A) is able to put more weight on causative SNP, resulting in a higher accuracy (Meuwissen et al., 2001; Meuwissen and Goddard, 2010).

Comparisons of GBLUP to Bayesian regression report similar results. The GBLUP method is preferred by some because of its simplicity and low computational requirements (Gao et al., 2013), but its estimates are not as accurate as Bayesian regression. Gao et al. (2013) found that a Bayesian mixture model, most similar to BayesB, increased the reliabilities of MBV by anywhere from 2 to 6.2 percentage points, depending on the training and validation populations used. The increase in accuracy between Bayesian models over GBLUP increased as the relationship between the training and validation populations decreased. Although GBLUP has been proven to exploit LD, additive-genetic relationships and cosegregation to capture relationships of QTL, it does not capture the short-range LD as well as Bayesian regression (Habier et al., 2011; Habier et al., 2013; Gao et al., 2013). However, unweighted GBLUP avoids marker selection and marker weighting, leading to less bias (an accuracy that is closer to the true accuracy). A study by Erbe et al. (2012) found that BayesR outperformed GBLUP as well, with an average increase in accuracy across three traits of 5%. Because of this, Bayesian methods are expected to perform better than GBLUP (Habier et al., 2011; Habier et al., 2013). What has yet to be determined, however, is whether this increase in accuracy is due to the statistical method, or the presence of discovery bias within the analysis.

In comparing SS-BLUP to GBLUP, Aguilar et al. (2010) found similar accuracies, but stated that advantages of SS-BLUP over GBLUP were its simplicity and automatic weights for the various sources of information used to calculate MBV. One of the largest disadvantages of GBLUP as well as SS-BLUP is the necessity to calculate the dense inverse of the **G** matrix (Koivula et al., 2012). A study by Koivula et al. (2012) found that SS-BLUP had slightly higher accuracies of validation populations over that of GBLUP. However, SS-BLUP includes information of non-genotyped animals in the genomic predictions of related animals with genotypes.

Using SS-BLUP methodology, Fernando and Garrick (2013) proposed a single step Bayesian Regression procedure (SSBR). They believed that the limitations of SS-BLUP could be overcome using SSBR to accommodate those animals without genotypes. Because the computational burden of Bayesian regression methods increases linearly with the number of

genotyped animals, SSBR has a computational advantage over SS-BLUP. Another computational advantage of SSBR over SS-BLUP is that dense matrix inversion is not required; but this comes at the expense of having to use MCMC methods instead (Fernando et al., 2014). Furthermore, unlike SS-BLUP, SSBR marker effects do not have to be normally distributed (Fernando and Garrick, 2013; Fernando et al., 2014). The Bayesian regression allows use of t-distributed marker effects as in BayesA, as well as mixture models such as BayesB and BayesCπ (Fernando et al., 2014). An innovative aspect of SSBR is that it uses a marker model for genotyped animals and an animal model for ungenotyped animals, drawing upon the advantages of each model for the animals to which it is applied.

A step in the right direction

Perhaps the first step in addressing discovery bias can be seen in the form of K-fold validation. K-means clustering is used to split the animals used in an analysis into equal groups while attempting to maximize relatedness within each group and minimize relatedness between groups (Saatchi et al., 2012). Once the groups are established, analyses exclude one group and train on the others to estimate marker effects which are in turn used to predict the MBV of animals in the excluded group (validation population) (Saatchi et al., 2011). This process is repeated until every animal has a predicted MBV obtained without using its own DEBV.

Using the predicted MBV a bivariate model is used with the DEBV as the second trait (Garrick and Saatchi, 2013). Fitting this model allows for the estimation of the genetic correlation between the trait and its respective MBV (Saatchi et al., 2012). The **G** matrix consists of non-zero elements of **A** among individuals in the same group, but sets the covariances between individuals in different groups as zero. This method leads to predictions of accuracy that are pooled predictions from each fold (Garrick and Saatchi, 2013). The resulting variance components should show an MBV heritability near one as proposed by Kachman (2008), a DEBV heritability near the trait heritability and the genetic correlation between the two whose square represents the average proportion of genetic variance accounted for by the MBV (Garrick and Saatchi, 2013). K-fold validation has been used to assess the accuracy of MBV for the Angus, Simmental and Limousin breeds (Saatchi et al., 2011; Saatchi et al., 2012).

Conclusion

Finding ways to reduce the effects of discovery bias on the accuracy of GE-EBV is critical to the advancement of genomic prediction. While current methods of prediction that include genomic information are superior to traditional breeding methods, consistent accuracies have not been found. Ways in which to close the gap between true and calculated accuracy have been discussed with emphasis being placed on training and validation populations and minimizing the amount of relatedness between the two. Most importantly, discovery bias and the "winner's curse" are pivotal issues that must be addressed if true accuracy is to be calculated. This increase in true accuracy will help increase the accuracy of selection, decrease generation interval, and increase selection intensity (Miller, 2010), all of which are critical to increasing the rate of genetic gain. While this issue is important for all breeds who compute GE-EBV to consider, it is even more crucial for smaller breed associations, in which all animals must be used for both training and validation. The ideal solution is to statistically adjust predictions for discovery bias.

The relationship between discovery bias and accuracy can be confusing. The GBLUP method has appeal because it does not seem to be subject to discovery bias, but that appeal comes at the cost of giving up some accuracy. Methods that use the data to improve the model (e.g. select or weight markers) are subject to the winners curse. The consequences are 1) accuracy is improved and 2) accuracy is estimated to be improved by even more than it really is. The latter is discovery bias. The cost of discovery bias is that genomics gets more weight relative to pedigree and phenotypes than it truly deserves. Nonetheless, the improved accuracy of the genomic part of GE-EBV that comes from weighting markers optimally is probably better than unweighted GBLUP. But, accounting for the discovery bias and weighting optimal genomic predictions more appropriately with pedigree and phenotype should yield still better GE-EBV.

The ultimate goal of any genetic evaluation or selection decision is to positively impact a population of animals, beef cattle or otherwise. The bottom line is always the impact that it has on the industry as a whole. Genomics provides new insights into the growth, nutrition, and overall health of animals while enabling a better understanding of traits of interest (Eggen, 2012). It provides breeders, breeding organizations, and members of the livestock industry the opportunity to increase efficiency and productivity of animal breeding (Eggen, 2012). Since first suggested by Meuwissen et al. (2001), the idea that a large number of SNP can give a reasonable

amount of information about the genomic make up of an animal has led to substantial progress in genomic selection (Miller, 2010). This is true especially for traits that are difficult to measure, have low heritabilities, are measured late in life or are sex limited (Dekkers, 2004; Garrick, 2009). However, in order to further this advancement, discovery bias can no longer be ignored. It is critical that new statistical methods be derived to address the issue so that unbiased estimates of accuracy can be calculated. Should this be accomplished, a profound increase as well as possible consistency in MBV could be observed.

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