(A)cross-breed Genomic Prediction

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ABSTRACT: Genomic prediction holds the promise to use information of other populations to improve prediction accuracy. Thus far, empirical evaluations showed limited benefit of multi-breed compared to single breed genomic prediction. We compared prediction accuracy of different models based on two closely related and one unrelated line of layer chickens. Multi-breed genomic prediction may be successful when lines are closely related, and when the number of training animals of the additional line is large compared to the line itself. Multi-breed genomic prediction requires models that are flexible enough to use beneficial and ignore detrimental sources of information in the training data. Combining linear and non-linear models may lead to small increases in accuracy of multibreed genomic prediction. Multitrait models, modelling a separate trait for each breed, appear especially beneficial when relationships between breeds are very low, or when the genetic correlation between breeds is negative.

Keywords: multibreed; genomic prediction

Introduction

Genomic selection alleviates the requirement to phenotype selection candidates and/or their close relatives. This holds the promise that genomic selection can be used across populations, such as different lines or breeds. Several simulation studies have supported this view by indicating that genomic selection across breeds or lines is effective (Ibanez-Escriche et al. (2009); Kizilkaya et al. (2010)), provided that the density of SNPs is sufficiently large, such that linkage disequilibrium (LD) is persistent across breeds (de Roos et al. (2009)). Based on these predictions, high density panels have been developed with 580,954 SNPs for chicken (Kranis et al. (2013)) and for cattle with 648,874 or 777,962 SNPs (Rincon et al. (2011)). Results from empirical studies confirm that using information of other breeds or lines hardly improves the accuracy of genomic prediction when a 50k SNP chip is used (Hayes et al. (2009); Pryce et al. (2011); Karoui et al. (2012); Hidalgo et al. (2014)). When using a higher density SNP panel, a somewhat higher increase in accuracy is observed (Erbe et al. (2012)), but the benefit of multi-breed over single-breed genomic prediction still appears to be limited.

One explanation for the discrepancy between the expectations of multi-breed genomic prediction based on simulation studies and the observed accuracies in empirical studies, is that most simulation studies oversimplified reality. Within breed genomic prediction relies heavily on family relationships, while multi-breed genomic prediction relies on similarities in allele frequencies, LD patterns and haplotypes (Wientjes et al. (2013)). If any of these factors is assumed similar across breeds in a simulation study, than the resulting accuracy will be higher than the accuracy in real life.

Considering differences in allele frequencies, LD and segregating haplotypes between breeds or lines, it is important that the used genomic prediction models are flexible enough to accommodate for those differences. In fact, models used for multi-breed genomic prediction should be able to make use of beneficial information of other breeds, while they should also be able to ignore detrimental information of other breeds. Such model ideally would yield the same accuracy as single-breed genomic prediction if the information of the other breeds is not useful, while it would be able to increase the accuracy when the information of the other breeds is useful. Below we briefly discuss different types of genomic prediction models that can be used for multi-breed genomic prediction

Most applications of multi-breed genomic prediction so far are based on linear genomic prediction models (Hayes et al. (2009); Simeone et al. (2012)). One drawback of such models is that the assumptions made are quite rigorous. By ignoring that animals originate from different breeds, the assumption is made that a trait is affected by the same QTL in different breeds, and that QTL effects are the same in different breeds. The assumptions made in linear models may be too rigorous, especially when breeds are very different. Non-linear models are actually able to avoid some of those assumptions, by putting more emphasis on information of animals that are closer to each other regardless of their origin.

Another appealing option to enable flexibility in linear genomic prediction models is by modelling one trait as separate, but correlated, traits for the different breeds or lines (Karoui et al. (2012); Olson et al. (2012)). Whether or not information of one breed is useful for another breed, follows from the estimated genetic correlation between those breeds. This genetic correlation is an important parameter, both from a modelling and a quantitative genetics perspective. In terms of modelling, the genetic correlation defines the shrinkage of information from one breed to another. In terms of the genetic relationship between breeds, it is a factor that should be used to multiply e.g. estimated genomic relationships between breeds to obtain “effective” relationships.

The objective of this paper is to compare several genomic prediction methods for multi-breed genomic prediction, to interpret their behavior in different scenarios, and to review in which situations multi-breed genomic prediction may be useful, depending on several factors impacting the accuracy of multibreed genomic prediction.

Materials and Methods

Data. The accuracy of multibreed genomic prediction with several models was investigated using data of three different lines of layers. Two of the lines, the brown layer lines B1 and B2, have been separated for at least 25 years and were more closely related to each other than the other white line (W1). The trait analyzed was number of eggs in the first production period. Phenotypes used in the analysis were pre-corrected for fixed effects of hatch week. In total, 3,753 female birds with phenotypes were genotyped with the chicken IIIumina Infinium iSelect Beadchip, that includes 57,636 SNPs. Genotype edits, performed across lines, included deleting SNPs with a call rate below 95%, a minor allele frequency below 2%, with no homozygote genotypes or with a Chi² value > 600 for a test of deviation from Hardy-Weinberg equilibrium. After these edits, 45,974 SNPs were available for 1,263 birds in line B1, 1,246 in line B2 and 1,244 in line W1.

Assessment of prediction accuracy. The data was split into training and validation sets, to enable evaluation of the accuracy of multi-breed genomic prediction. The validation sets comprised per line the youngest generation of 238-240 birds. The prediction accuracy of the validation animals was computed as the correlation between their estimated breeding values and observed phenotypes, divided by the square root of the heritability. Heritability values were obtained from routine genetic evaluations, being 0.41 for lines B1 and B2 and 0.51 for line W1. Seven training sets were used to evaluate the accuracy of genomic prediction (Table 1). Across training sets, the number of segregating SNP ranged from 30,508 to 45,974 (Table 1).

Table 1. Number of animals and segregating SNP for each training dataset

Training	# animals	# segregating SNP
B1	1,023	38,310
B2	1,008	37,729
W1	1,004	30,508
B1+B2	2,031	40,953
B1+W1	2,027	45,241
B2+W1	2,012	44,913
B1+B2+W1	3,035	45,974

Table 2. Estimated genetic correlations between the three layer lines (standard errors in brackets)

Line	B2	W1
B1	0.63 (0.14)	-0.26 (0.37)
B2		-0.55 (0.37)

Linear prediction models. The applied linear models comprised ridge regression BLUP (RRBLUP; (Habier et al. (2007))), principal component analysis followed by ridge regression (RRPCA), and BayesC (Habier et al. (2011)). RRBLUP was solved using the preconditioned conjugated gradient method implemented in the package MiXBLUP (Mulder et al. (2010)). The model RRPCA was implemented in MATLAB (Calus et al. (2014)). The model BayesC was implemented in a Gibbs sampler using right-hand-side updating (Calus (2014)). More details on the models are described in the references cited above.

Non-linear prediction models. In the context of multi-breed genomic prediction, most linear models assume that true allele effects are the same in different breeds. The assumption of linearity can be relaxed by using non-linear models depending crucially on similar animals. The applied non-linear models in our study comprised Radial Basis Function kernel regression (RBF) and Polynomial kernel regression (Poly). Both models use a kernel, that can be interpreted as a relationship matrix in the context of breeding value estimation models. For instance, the commonly used genomic relationship matrix is a type of linear kernel that can be used for linear regression. The polynomial kernel explicitly augments the input of regression model by the monomials of genotypes such that the similarity is measured by the inner product of polynomials of genotypes. The kernel used in RBF estimates the similarity by the distance between the genotypes of two animals. Only results of the RBF model are presented, because the results of the Poly model were very poor for all scenarios. More details on the non-linear models are described by Huang et al. (2014).

Multi-trait model. The applied multi-trait model was a straightforward GBLUP model that assumed that the trait analyzed was a different trait in each line. The first step involved applying the model using ASReml (Gilmour et al. (2009)), once for each pair of lines, to estimate the genetic correlations between lines. This first step used the inverse of a combined pedigree and genomic relationship matrix (Aguilar et al. (2010)). Using this combined relationship matrix, the number of training records per line increased from 1,004-1,023 to 24,906-27,896. Once the pairwise genetic correlations were estimated, they were used in a series of GBLUP models to predict genomic breeding values for all validation animals using all training data sets.

Prediction accuracies computed with selection index theory. Prediction of accuracy of multi-breed prediction, enables to derive whether two breeds can benefit from each other or not. A formula based on selection index theory to calculate accuracy when using one population to predict another, was derived by Wientjes et al. ((2014)). This formula can be applied when for the predicted breed limited genotypes and phenotypes are available and overcomes the need for cross-validation to investigate the accuracy. The accuracy of animal *i* is calculated as:

$$r_i = r_{A_{T,i}} \sqrt{\mathbf{g}'_{T,i} \left[\mathbf{G}_T + \mathbf{I} \frac{\sigma^2_{e_T}}{\sigma^2_{a_T}} \right]^{-1} \mathbf{g}_{T,i}}$$

where $r_{A_{T,i}}$ is the genetic correlation between the training animals and breed of the evaluated animal, $\mathbf{g}'_{T,i}$ is a vector containing genomic relationships between training animals and evaluated animal, $\mathbf{G}_T$ is the genomic relationship matrix of the training animals, $\mathbf{I}$ is a diagonal matrix, $\sigma^2_{e_T}$ is the residual variance in the training population, and $\sigma^2_{a_T}$ is the additive genetic variance in the training population. To calculate genomic relationship matrixes, genotypes of the training population were rescaled using allele frequencies in the training population, and genotypes of the validation

animals were rescaled using the allele frequency of the line of the validation animal. We applied this formula to all six scenarios where one line was used to predict another, using the genetic correlations estimated with the multi-trait model.

Results

Relationships and genetic correlations between populations. To visualize the relationships between the three populations, a heat map of the Euclidean distances between all animals is presented in Figure 1. Lines B1 and B2 are relatively closely related to each other, while line W1 animals have a very low relationship with B1 and B2 animals. Relationships within line W1 are higher than in lines B1 and B2, which is in agreement with the observation that white layers such as W1 are more inbred than brown layers (Qanbari et al. (2010)). The estimated genetic correlation of 0.63 between lines B1 and B2 confirms that those lines are closely related (Table 2). Its standard error shows that this genetic correlation is significantly greater than zero. The negative genetic correlations between lines B1 and B2 versus line W1, show that line W1 is very different from lines B1 and B2. The large standard errors of those estimates show that the estimated genetic correlation between line B1 and W1 is not significantly different from zero, while the correlation between B2 and W1 is significantly lower than zero.

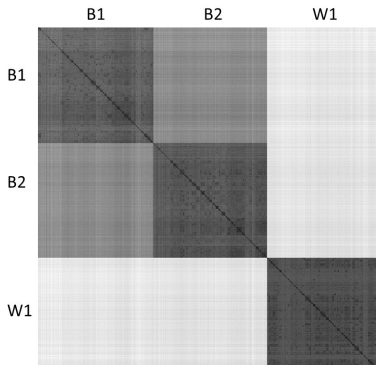

Figure 1. Euclidean distances between all animals. Black (light grey) indicates very small (large) distances.

Prediction accuracies across lines. Single line genomic prediction for line B1 yielded prediction accuracies of 0.45-0.50 across models (Table 3). Adding information from the other lines did not improve nor deteriorate its accuracy. Even using information from the related line B2 did not improve the accuracy, despite the observation that using information of B2 alone did result in accuracies ranging across models from 0.13-0.30 for line B1. Using information only from line W1 resulted in slightly negative accuracies for four out of five models, illustrating the large distance between B1 and W1. Single line genomic prediction for line B2 yielded prediction accuracies of 0.30-0.45 across models (Table 4), being somewhat lower than those for B1. Similar to the observation for line B1, using information from the related line B2 did not improve the prediction accuracy for B1, despite the observation that using information of B1 alone did result in accuracies ranging from 0.05-0.14 for line B1. Surprisingly, there was a small, but consistent, improvement in accuracy for the linear models when additionally using information of line W1. Single line genomic prediction for line W1 yielded prediction accuracies of 0.76-0.78 across models (Table 5), being substantially higher than those for B1 and B2. Using information from line B1 and/or B2 either left the prediction accuracy unchanged, or slightly decreased it. Using only information from line B1 and B2 separately or combined, led to negative accuracies in all scenarios with the most extreme value being -0.39.

Table 3. Accuracy of prediction using seven training data sets and five models[§] for line B1

Training	RRB	RRPCA	BayesC	RBF	MT
B1	0.453	0.447	0.452	0.460	0.441
B2	0.302	0.230	0.266	0.132	0.304
W1	-0.003	0.100	-0.093	-0.082	-0.058
B1B2	0.467	0.439	0.466	0.481	0.465
B1W1	0.438	0.436	0.429	0.463	0.441
B2W1	0.272	0.244	0.215	0.191	0.301
B1B2W1	0.452	0.432	0.447	0.482	0.466

[§]RRB = ridge regression BLUP, RRPCA = RR using principal components, RBF = RBF Basis Function kernel regression; MT=multitrait GBLUP

Table 4. Accuracy of prediction using seven training data sets and five models[§] for line B2

Training	RRB	RRPCA	BayesC	RBF	MT
B1	0.129	0.143	0.111	0.054	0.126
B2	0.359	0.448	0.338	0.403	0.349
W1	0.142	0.109	0.106	0.003	-0.134
B1B2	0.373	0.476	0.318	0.400	0.382
B1W1	0.176	0.185	0.139	0.049	0.072
B2W1	0.369	0.463	0.354	0.386	0.333
B1B2W1	0.390	0.494	0.357	0.399	0.367

[§]RRB = ridge regression BLUP, RRPCA = RR using principal components, RBF = RBF Basis Function kernel regression; MT=multitrait GBLUP

Table 5. Accuracy of prediction using seven training data sets and five models[§] for line W1

Training	RRB	RRPCA	BayesC	RBF	MT
B1	-0.252	-0.247	-0.235	-0.005	0.217
B2	-0.192	-0.249	-0.224	-0.015	0.218
W1	0.761	0.775	0.759	0.768	0.769
B1B2	-0.393	-0.352	-0.355	-0.157	0.329
B1W1	0.743	0.748	0.737	0.763	0.773
B2W1	0.762	0.772	0.757	0.767	0.768
B1B2W1	0.742	0.747	0.739	0.763	0.773

[§]RRB = ridge regression BLUP, RRPCA = RR using principal components, RBF = RBF Basis Function kernel regression; MT=multitrait GBLUP

Prediction accuracies across models. Comparing the models amongst each other, clearly showed that the RBF model did behave different than the linear models. In general, it performed as well as the linear models for single line genomic prediction. When using only information from the related line, however, the accuracy of the RBF model had a value that was 50% lower compared to the linear models. In the specific situation where lines B1 and/or B2 were used to predict W1, RBF appeared to be more robust than the linear models, in the sense that both classes of models resulted in negative accuracies, albeit that RBF had much less extreme values. The multitrait GBLUP model, however, was able to overcome the negative accuracies when only B1, B2 or both were used to predict W1. In fact, it yielded positive accuracies that had a similar absolute value as the other linear models, due to considering the (sign of) the genetic correlation between lines in the model..

To investigate potential complementarity between models, correlations between estimated DGVs are presented in Figure 2. This figure shows that the models cluster in four groups: 1) the linear models RRBLUP, BayesC, and multitrait GBLUP, 2) RRPCA, and 3) RBF. Considering that these groups of models achieved reasonably similar accuracies, the correlations between estimated DGV suggest that both RRPCA and the non-linear model RBF use part of the variance that is not used by the other linear models and vice versa. To investigate the potential of combining features of both types of models, we evaluated the prediction accuracy of weighted combinations of the predictions obtained with RR-PCA and RBF (Figure 3). The patterns of those prediction accuracies indicate that there was a slight benefit of combining methods, up to an increase in accuracy of ~0.02, when the combined models yielded a similar prediction accuracy. Whenever there was a difference in prediction accuracy between models of at least 0.05, then combining predictions yielded an accuracy very similar to the highest accuracy obtained with one of the two models.

Line B1

	RRBLUP	BayesC	MT	RRPCA	RBF
RRBLUP	1	0.98	0.96	0.93	0.87
BayesC	0.98	1	0.94	0.90	0.85
MT	0.96	0.94	1	0.90	0.91
RRPCA	0.93	0.90	0.90	1	0.87
RBF	0.87	0.85	0.91	0.87	1

Line B2

RRBLUP	1	0.98	0.95	0.93	0.90
BayesC	0.98	1	0.92	0.91	0.88
MT	0.95	0.92	1	0.89	0.93
RRPCA	0.93	0.91	0.89	1	0.88
RBF	0.90	0.88	0.93	0.88	1

Line W1

RRBLUP	1	0.99	0.99	0.98	0.92
BayesC	0.99	1	0.98	0.97	0.93
MT	0.99	0.98	1	0.96	0.93
RRPCA	0.98	0.97	0.96	1	0.90
RBF	0.92	0.93	0.93	0.90	1

Figure 2. Correlations between breeding values estimated with five different models for each of the three lines, based on the training data including all three lines.

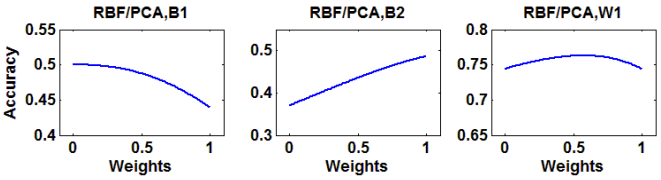

Figure 3. Prediction accuracy of weighted combinations of the models RR-PCA and RBF. The X-axis gives the weight for the first method in the header of the plot.

Prediction accuracies computed with selection index theory. Prediction accuracies of all six scenarios where one line was used to predict another, were calculated based on selection index theory, using genomic relationships and estimated genetic correlations between lines (Table 2). Those calculated accuracies are plotted against the empirical accuracies obtained with RRBLUP (Figure 4). The regression line through those six data points indicates that the calculated accuracies are fairly unbiased predictors of the empirical accuracies. The two scenarios that deviate most from the regression line, are the scenarios where line W1 is used to predict B2, and when line B1 is used to predict W1. In these scenarios, the selection index and empirical accuracies have opposite signs.

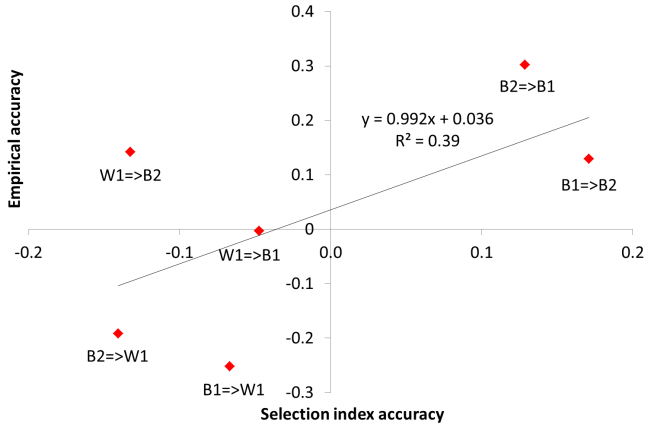

Figure 4. Selection index theory and empirical prediction accuracies for all six scenarios where one line was used to predict another. Data labels indicate "training line" => "predicted line".

Discussion

Several studies have shown that using information from one population to genomically predict another, gives poor results, depending on the relationship between the popoulations (Andreescu et al. (2010); Kachman et al. (2013)). In our data, using information of B1 to predict B2, or vice versa, did result in accuracies with values op to 0.30. Nevertheless, using both lines as training hardly improved the prediction accuracy compared to single line genomic prediction. This illustrates that closely related lines or breeds indeed may harbor useful information, but whether this actually improves the prediction may depend on the relative amount of information that is added on top of the information that is available for the line or breed itself. So for lines or breeds for which already a lot of

information is available, it will be very difficult to improve prediction accuracy by using information of other breeds (Simeone et al. (2012)). It also means that multi-breed genomic prediction still may be especially useful for numerically smaller breeds, provided that a flexible model is used that utilizes useful information and ignores potentially detrimental information.

One reason for the limited benefit of using information of multiple breeds when predicting animals from one breed, is that the relative contribution to prediction accuracy is much smaller for an animal from a different breed. For instance, theoretical predictions indicated that the training data consisting of animals from a different breed may need to be ~15 times as large to reach a reliability (squared accuracy) of 0.6 compared to using a reference population of the breed itself (Wientjes et al. (2013)). In such a scenario, however, the prediction model has to be able to use the information of a large breed on top of the information of small breed, while avoiding that the large breed overwhelms the prediction. When breeds are closely related such as lines B1 and B2 in our data, the assumption of linearity may still be valid, or at least not be detrimental to the predictions. When breeds are unrelated, such as B1 and B2 versus W1, using non-linear models or a multi-trait model appears to be useful to control the potential negative impact of the additional breed. Our results suggest that there is scope for combining features of linear and non-linear models, to build a prediction model that is more flexible than either model by itself, while bringing together features of both models.

One important question is how the "relationship" between breeds can be evaluated. One way is to compare the value of relationships between breeds versus those within breeds. In the data that we analyzed, it was clear that the highest relationships between B1 and B2 animals were in the range of within line relationships of either line. For line W1, however, relationships with the other lines were clearly outside the range of relationships within the line itself. Another feature that is closely related with differences in relationship, is the difference in allele frequencies between lines. In the data used in our study, the correlations between allele frequencies were 0.35, -0.11, and -0.09, respectively, for lines B1 and B2, B1 and W1, and B2 and W1 (Calus et al. (2014)). In addition, LD consistency between lines is closely related with the relationship between lines (Andreescu et al. (2007)). Finally, the genetic correlation between lines or breeds is also a useful parameter (Karoui et al. (2012)) Due to how this genetic correlations is estimated, it reflects the similarities in estimated SNP-effects for different lines, but also includes similarities in terms of LD between lines.

The estimated genetic correlations using the multi-trait model are based on SNP data, while ideally they should reflect the correlation between allele substitution effects on the QTL. This indicates that differences in LD across lines could unintentionally have affected the estimated genetic correlation and that they are in fact depending on the density of the used SNP chip. The high genetic correlation between the lines B1 and B2 indicates that both QTL effects and LD are reasonably consistent across those lines. The negative genetic correlation between lines B1 and B2 versus W1 might be due to large differences in LD, due to differences in QTL effects or due to a combination of those factors. The formula to calculate the accuracy based on selection index theory is using the actual genetic correlation, i.e. the correlation between QTL effects. Due to differences in LD between SNP and QTL, the estimated genetic correlation might underestimate the actual genetic correlation, which results in an underestimation of the actual accuracies. Besides that, standard errors of the estimated genetic correlations were large. Those factors together can explain the differences between calculated and actual accuracy per scenario, but on average, both accuracies were in good agreement.

The results showed that prediction accuracies for line B2 were always positive when using only information from line W1 in the prediction. The reciprocal situation, where only line B2 was used to predict W1, yielded however negative accuracies. This might be related with the observation that LD extends across larger distances in white layers (Megens et al. (2009)). Therefore, using W1 as a training population results in spreading QTL effect across a large number of SNPs whose phase with the QTL may not be persistent across lines. In the B2 line, inbreeding was less, resulting in more short-range LD, whose persistency of phase across breeds may be higher. This is an interesting hypothesis, and stresses that strong relationships within training data may be undesirable for multibreed prediction.

In agreement with findings in the literature, our results showed limited differences between e.g. RRBLUP and BayesC, despite the expectation that variable selection methods should be better able to put more weight on SNPs associated with QTL. This raises the question whether such models should be further refined. One feature that has received little attention in the context of multibreed genomic prediction, is whether genotypes should be scaled with breed specific allele frequencies, or average allele frequencies across breeds. Results with a single step GBLUP model indicated that different ways of scaling have limited impact (Makgahlela et al. (2014)), but this has not been investigated when using variable selection models.

In practice, the objective of poultry and pig breeding programs is to improve performance of crossbred production animals. Traditionally, selection is taken place in the purebred breeding animals, assuming a reasonable genetic correlation between purebred and crossbred performance. Nevertheless, this correlation is usually smaller than unity, and extreme values as low as 0.6 in poultry (Wei and Vanderwerf (1995); Besbes and Gibson (1998); Cavero et al. (2010)) and 0.3 in pigs (Lutaaya et al. (2001); Merks and De Vries (2002)) have been reported. This implies that selection based on purebred performance is suboptimal in many cases. Genomic prediction enables to link phenotypic information from crossbred production animals back to purebred breeding animals. Several simulation studies have shown promising results with this strategy (Dekkers (2007); Ibanez-Escriche et al. (2009); Zeng et al. (2013)). It was shown that accounting for line-of-origin, which can be determined for alleles observed in crossbred animals (Bastiaansen et al. (2014)), hardly increased the accuracy. The benefit of using line-of-origin in prediction models may be much larger in real data,

because differences between breeds or lines appear to be much larger in real data than compared in simulation studies, as we discussed earlier on.

Conclusion

Multi-line genomic prediction may be effective when lines are closely related, albeit that the added benefit strongly depends on the amount of information used from the additional line. Multi-breed genomic prediction may therefore be especially useful for numerically smaller breeds, provided that a flexible model is used that does enable using useful information and ignoring potentially detrimental information. When breeds are unrelated, such as B1 and B2 versus W1 in our study, using non-linear models or a multi-trait model is useful to control the potential negative impact of the additional breed, while straightforward linear models may be used when lines are closely related. Furthermore, linear and non-linear models are proven to be complementary to each other, and combining their predictions resulting in a combined prediction in fact may slightly improve the accuracy.

Relatedness of lines can be investigated by evaluating: prediction accuracy when using one line to predict another, relationships between breeds, similarity of allele frequencies and LD between lines, and the genetic correlation between breeds.

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