PREDICTING GENETIC INTERACTIONS WITHIN AND ACROSS BREEDS

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INTRODUCTION

Evaluations for U.S. dairy cattle recently were revised to account for inbreeding, and a multi-breed model that accounts for heterosis has been tested. In many species, breeds are evaluated separately on bases that are not easily compared. For dairy cattle, a few multi-breed evaluations have modeled general heterosis (Harbers, 1997) or specific heterosis (Harris, 1994) or even heterosis and recombination loss between the Holstein and Friesian strains within a breed (Van der Werf and de Boer, 1989). One of the earliest all-breed evaluations was for U.S. dairy goats (Wiggans, 1989). Multi-breed evaluations have also been proposed in poultry (Wei and van der Werf, 1995), swine (Lutaaya *et al.*, 2002), and beef (Arnold *et al.*, 1992). Genetic interactions within breed also may be important (Hayes and Miller, 2000), and those interactions were predicted from milk yield and productive life data of U.S. Holsteins. Strategies were compared for modeling genetic effects and accounting for genetic interactions within and across breeds.

INBREEDING AND HETEROSIS

Because heterozygosity decreases when relatives are mated and increases when breeds are mixed, inbreeding is unfavorable and heterosis is favorable for most traits. Meuwissen (1997) proposed optimal selection and mating strategies to balance additive gain and inbreeding loss within a breed, but the proposed formulas are not optimal unless the estimated breeding values (EBV) are adjusted to 0 inbreeding (EBV_0) as in VanRaden and Smith (1999). Progeny testing and random mating result in official EBV that already account for an average effect of inbreeding because the records include inbreeding depression. Proper accounting for inbreeding may require access to both EBV and EBV_0. When selection and mating are done in separate steps, breeders should select on EBV rather than EBV_0 unless sires are used for crossbreeding. Meuwissen's (1997) formulas might be extended to crossbred populations by using an across breed relationship matrix (VanRaden, 1992) and adjusting EBV to the more remote, non-inbred population that existed before relationships accumulated within breeds. Miller and Goddard (1998) presented further ideas on this topic.

If non-additive effects are subtracted and only additive effects are reported, selection may not be optimal. When North American Holsteins were introduced in Europe, heterosis and recombination effects with Friesians were estimated in several countries and subtracted from the EBV (Boichard *et al.*, 1993; Harbers, 1997; van der Werf and de Boer, 1989). In early generations, most European cows were Friesians. Holstein sires provided both additive and heterosis advantages over Friesian sires when mated to pure Friesian cows, but EBV of Holstein sires included only a portion of their advantage. Today, most potential mates are nearly pure Holstein. Thus, Friesian sires now can provide heterosis, and Friesian EBV should include both the additive and heterosis effects when expressed on a Holstein base. Non-additive effects are genetic, and their expected values for the target population of mates need to be added back if subtracted in the model (VanRaden and Smith, 1999). Beginning in 2005, U.S. dairy evaluations subtract past inbreeding effects in the model and add expected future inbreeding effects to the EBV. Computer mating programs (Weigel and Lin, 2000) should also be used to help control inbreeding.

DOMINANCE AND EPISTASIS
Specific heterosis among breeds and specific combining abilities within breeds are analogous effects. If some breed combinations have few observations, models might estimate general heterosis as a fixed effect and specific heterosis as a random deviation from general heterosis. Similarly, within breed models that contain fixed effects for inbreeding depression plus dominance effects as random and related can estimate specific inbreeding losses for each sire or animal. These specific losses are estimated from the interactions of related mates.

Non-additive effects within breed often are partitioned into separate dominance and epistatic effects. In traditional across-breed models, heterosis is modeled as the sum of the dominance and epistatic effects expressed in the first generation (F1) cross and recombination loss as the difference between the epistatic and dominance fractions in other crosses. Equivalent across-breed models with separate dominance and epistatic effects may be easier to understand (Hill, 1982) and could simplify the math needed to unify within- and across-breed genetic effects (Miller and Goddard, 1998). Breed differences contain additive, dominance, and epistatic effects that are confounded if only two breeds are considered but that can be separated using data from multiple breeds and crossbreds. For example, outstanding performance of a particular pure breed is non-additive if that breed performs poorly in crosses with several other breeds. If the breeds crossed are widely divergent, recombination losses can be large (Rutledge, 2001).

Rapid methods for obtaining inverses of within-breed dominance (**D**) and additive-by-additive (**A*A**) matrices can be extended across breeds in the same way that within-breed additive inverses ($\mathbf{A^{-1}}$) were extended across breeds. In $\mathbf{A^{-1}}$, each animal contributes a 3 x 3 matrix to the additive inverse if unknown parents groups are used and a smaller matrix if parents are unknown and groups are not used. In dominance inverses ($\mathbf{D^{-1}}$), each sire-dam subclass contributes a matrix of maximum size 9 x 9 to the dominance inverse (Hoeschele and VanRaden, 1991). If individual parent interactions are unknown, the coefficients would instead be added to specific heterosis effects among parent breeds. Schaeffer (2003) suggested alternative computations that may be more efficient if **D** is very sparse. Models may need to account for the covariances between additive and dominance effects that arise in inbred populations (Miller and Goddard, 1998). Interactions for related mates usually are unfavorable, and models that include **D** or **A*A** relationship matrices should also include regressions on inbreeding and heterosis coefficients to account for changes in both means and variances.

GENETIC EVALUATION
Multi-breed models enable across-breed selection and mating programs by calculating EBVs for crossbred animals and providing routine estimates of breed differences and heterosis. Breed differences can be estimated by defining unknown parent groups separately by breed (Wiggans, 1989) or by including regressions on breed fractions (Harris, 1994). Models with unknown parent groups are simpler to set up, but regressions on breed fractions may still be needed for environmental factors or genotype by environment interactions. For example, if age effects differ by breed, age effects for crossbreds may be intermediate between the parent breed effects.

A multi-breed model that includes general heterosis was tested with U.S. dairy cattle data for yield, somatic cell score, longevity, and daughter pregnancy rate. The largest analyses included records from >22 million cows; about 1% of recent cows were F1 crossbreds. Crossbred animals were assumed to be non-inbred, but an earlier proposal to consider purebred base animals as related within breed (VanRaden, 1992) was not used. Convergence of the multi-breed model was similar to that for the current within-breed animal model, and correlations between EBV from across- and within-breed models were >0.99 for Holsteins and slightly <0.99 for other breeds. Predicted transmitting abilities may be converted back to the current

within-breed bases for purebred animals or to the breed of sire base for crossbred animals so that most breeders will not be impacted by the change to a multi-breed model.

Interactions among sires and maternal grandsires (MGS) also were predicted from U.S. national data. An analysis of first lactation milk yield included records for 5.5 million Holstein cows, an additive relationship matrix for their 4263 sires and MGS, and a dominance relationship matrix for 1.6 million sire-MGS interactions. Computing time was 30 minutes to form $\mathbf{D^{-1}}$ and 16 hours per trait to solve the equations. Maximum number of cows in an individual sire-MGS subclass was 6830; 55 such subclasses contained >1000 cows. Dominance variance estimates were from Van Tassell *et al.* (2000). The largest sire-MGS interactions within breed were not quite as large as the estimate of general heterosis across breeds, which was 3.4% of mean yield (VanRaden and Sanders, 2003). For productive life, the largest sire-MGS interactions were about 4% of mean yield and were larger than the estimated heterosis. Interactions for younger bulls can be predicted by separate post-processing (Varona and Misztal, 1999) or by including them in $\mathbf{D^{-1}}$; such predictions have smaller ranges. Table 1 provides example interactions.

Table 1. Numbers of observations (below diagonal) and predicted interactions excluding effect of inbreeding (above diagonal) for 305-day milk yield (kg) for bulls of interest.

Bulls	Duster	Manfred	Durham	BW Marshall	Garter
Duster		+86	-35	+125	-11
Manfred	200		+39	+69	-22
Durham	245	46		-90	+7
BW Marshall	183	123	161		+71
Garter	51	60	18	15	

CONCLUSIONS
Genes interact, but most genetic evaluation models have included only additive effects. This approach simplified selection by allowing breeders to just choose animals with the best breeding values within breed. Models that include genetic interactions such as inbreeding, heterosis, dominance, and epistasis can be more accurate but also more confusing because both selection and mating must be considered rather than just selection. Genetic interactions are not just nuisance terms to subtract from models but can provide useful predictions if presented carefully. Breeders should continue selecting for additive merit but can also improve non-additive merit by considering interactions in mating programs.

Multi-breed evaluations for U.S. dairy cattle are expected in the near future. Inbreeding adjustments began last year. Computer mating programs that limit inbreeding and recessive defects, account for non-linear economic values of traits, and assign easy calving service sires to heifers are widely used by the dairy industry. Programs to manage crossbreeding and to predict within-breed genetic interactions could be profitable, but breeders that use such tools may require more expert assistance than was required for traditional selection on highest EBV or index within breed. Genotype by environment interactions can cause the same animals to rank differently across herds, climates, and countries. Genotype by genotype interactions also can cause animals to rank differently depending on the individual mate or mate population.

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