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Advancing Genetic Improvement in Beef Cattle: Leveraging Genomics for Improved Heterosis Analysis and Utilization

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Biographical sketch (please do not exceed 250 words):

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Introduction

Genetic improvement strategies in beef cattle production traditionally leverage the breeding or additive genetic value to boost productivity and performance. In the United States 45% of beef cattle are found in the subtropical zones, predominantly across the southern and southeastern states. In these regions, cattle often encounter difficulties due to the hot and humid weather conditions (Cooke et al., 2020). These environments underscore the growing necessity for thermotolerant breeds, as traditional beef breeds may struggle to cope with increasing temperatures. This challenge has prompted the utilization of heat-adapted cattle, leading to a potential shift in breeding practices. Crossbreeding and the development of composite breeds have emerged as solutions to produce cattle that not only maintain high production levels but also thrive in harsh environments.

The genetic advancement in cross and composite breeds unfolds in two significant ways. The first is through breed complementarity, where the genetic merits of different breeds are combined to meet market demands effectively (Gregory and Cundiff, 1980). This complementarity is not just about meshing different breeds but also about optimizing the unique genetic contributions each breed brings to the table. The improvement of the different breeding or additive genetic value of the purebred parents can be optimized using genomic tools. Genomic selection in cattle and across different livestock species has shown great improvement in productivity (Meuwissen et al., 2016; Wiggans and Carrillo, 2022). The continued integration of genomic data promises to accelerate and refine the selection process, leading to more precise genetic improvements in beef production.

The second aspect is the role of heterosis. Introduced by Shull in 1914 (1948), heterosis or hybrid vigor, describes the superior biological and production traits observed in crossbred individuals compared to the average of their purebred counterparts. Heterosis is primarily

attributed to non-additive genetic effects, such as dominance and epistasis, and is crucial for enhancing traits related to fitness and profitability, including fertility, calf survival, and maternal ability (Dickerson, 1973).

This literature review delves into the use of genomics to track and maximize heterosis in beef cattle. With genomics, breeders can now more accurately identify and evaluate the potential for hybrid vigor of individual animals and breed combinations, thereby refining breeding strategies to sustain or even enhance hybrid vigor over generations. By exploring the current state of genomic applications in heterosis management, this review aims to illuminate the pathways through which genomics can synergize with traditional breeding practices to usher in a new era of genetic improvement in beef cattle production.

Review of Literature

Genomic Selection

Current advancements in genomic technology are geared towards enhancing genetic progress, with a focus on increasing accuracy in selecting animals and reducing the time between generations (Meuwissen et al., 2016). Central to these advancements are SNP (Single Nucleotide Polymorphism) chips. These chips are essential tools that scan the genome of cattle for specific genetic markers that help predict which animals will be the best parents for the next generation. These chips detect variations in the DNA sequence, pinpointing where cattle differ genetically. These differences are pivotal as they affect the appearance, growth, and environmental adaptability of the animals.

Genomic selection has significantly impacted dairy cattle breeding by enhancing genetic trends and improving breeding programs. Research indicates that genomic selection has been effective in predicting performance across various dairy cattle populations (Wiggans et al., 2017).

Beginning in 2010 there has been a notable increase in net merit, with an annual gain of \$85 compared to \$40 in the preceding five years (Wiggans and Carrillo, 2022). This improvement is attributable to the expanded number of genotyped dairy cattle and the widespread application of artificial insemination to better disseminate of superior genetics (Wiggans and Carrillo, 2022).

These developments illustrate that genomic selection is not only effective but also an economically viable strategy for achieving substantial genetic gains.

Genomic selection requires a reference population, which has been genotyped and phenotyped, and a breeding population which has been genotyped but lacks phenotypic information (Meuwissen et al., 2016). In the reference population, the genotypes and phenotypes are used to train a statistical model; this model establishes the relationship between SNP and the traits of interest. This model is then used to calculate the Genomic Estimated Breeding Value (GEBV) for animals in the breeding population, predicting their genetic worth without complete phenotypic records (Meuwissen et al., 2016).

A key element in this process is the Genomic Relationship Matrix (GRM), which helps understand the genetic links within the population (Hayes and Goddard, 2010; Goddard et al., 2011). The GRM quantifies the genetic similarities and differences between individuals based on their SNP profiles, providing a detailed and accurate representation of genetic relationships. This matrix is crucial for the accurate estimation of GEBVs, as it allows the statistical models to account for genetic variance and population structure more effectively. Incorporating the GRM into genomic selection models enhances the accuracy of the selection process, ensuring that the chosen parents are truly the best genetic contributors for the desired traits, thus accelerating genetic progress and efficiency in breeding programs.

Currently, genomic selection in animal breeding is based on additive genetic effects. By focusing on these additive effects, genomic selection aims to accumulate favorable alleles in the breeding population, thereby enhancing the overall genetic quality and performance of future generations. This additive model is fundamental to genomic selection, enabling breeders to make more precise and effective decisions in their breeding programs to accelerate genetic improvement and achieve desired production traits. However, these methods themselves cannot account for heterosis. Thus, the need to incorporate measures of heterosis using genomics is an area of interest.

Heterosis

Heterosis is the superior biological and production traits observed in crossbred individuals compared to the average of their purebred counterparts (Shull, 1948). Heterosis is the highest in first-generation (F1) crossbred cattle, primarily due to increased heterozygosity, which manifests as dominance effects (Dickerson, 1973). Higher heterozygosity can be achieved when crossing

more genetically distant breeds, which is where the highest heterosis is observed (Getahun et al., 2019). However, heterosis will diminish in subsequent crosses beyond the F1 generation as heterozygosity decreases. To gauge heterozygosity and its retention, various proxies are employed, among which the breed composition proxy is most prevalent.

Breed Composition

Approaches utilizing breed composition suggest that retained heterosis correlates with breed heterozygosity, which is dependent on the number and the different proportions of the breeds involved (Dickerson, 1973). Incorporating more breeds and genetically distinct breeds tends to enhance the benefits derived from heterosis. Wright (1922) first introduced a formula to illustrate this relationship, showing how varying breed proportions influence heterosis retention:

$$rhet_1 = 1 - \sum_{i=1}^n P_i^2$$

where P_i is the proportion of each n contributing breed.

VanRaden and Sanders (2003) modified this concept, calculating retained heterosis based on the breed proportions of both sire and dam:

$$rhet_2 = 1 - \sum_{i=1}^n (sire P_i^2 \times dam P_i^2)$$

where *sire* P_i and *dam* P_i denote the proportion of n contributing breed, in the sire and dam respectively.

Historically, these measures were based on pedigree information. However, in rotational crossbreeding systems, breed composition can fluctuate between generations, potentially causing significant performance variability among cattle if these changes are not meticulously managed (United States: Agriculture Department et al., 1999). This variability, coupled with pedigree inaccuracies and mendelian sampling errors often challenge the precise estimation of breed composition, prompting a shift towards genomic methods. Genomic analysis has become increasingly favored for estimating breed composition, offering a more accurate and reliable method to estimate breed composition. This is supported by studies performed by Gobena et al. (2018) which illustrate how inaccuracies in pedigree's can be identified using genomics.

Several studies have shown that traits such as carcass weight, carcass conformation and carcass fat have significant effects including these breed-based coefficient. A study performed on

multiple crossbred populations found a significant regression coefficient of 2.78 kg on carcass weight when fitting a breed-composition based heterosis coefficient (Kenny et al., 2022). Various studies have also found significant and positive effect on carcass fat in crossbred beef cattle using this breed-composition based heterosis coefficient (Akanno et al., 2017; Kenny et al., 2022). Despite its established contributions, there is a significant limitation in this proxy of heterosis. Given that these approaches utilizing breed composition are meant to be a proxy for retained heterozygosity, if genomic heterozygosity data is accessible, it should be utilized.

Genomic Heterozygosity – Observed Heterozygosity

Within the realm of genomic heterozygosity, two distinct measures exist to capture heterosis. The first assesses heterosis based on the presence of heterozygosity genome-wide and its subsequent impact on a specific trait. This is illustrated by the following equation,

$$\text{Observed Heterozygosity (OH)} = \frac{\# \text{ Heterozygous SNP calls}}{\text{Total \# of SNP}}$$

Observed heterozygosity is the number of heterozygous SNPs from a SNP panel of genotypes. Studies have suggested that genomic heterozygosity could be a superior predictor of heterosis over breed-based measures. For example, a study based on a crossbreeding herd found *OH* to be more indicative of heterosis for carcass weight than breed-based coefficients (Kenny et al., 2022). However, in the same study it was discovered that for other traits such as carcass conformation and carcass fats both *rhet*₂ and *OH* were significant when analyzed concurrently, indicating they capture different aspects of the phenotypic variation (Kenny et al., 2022). This observation implies that these proxies are not directly interchangeable and may represent distinct underlying genetic factors. Akanno et al. (2017) found that *OH* was significant for average daily gain, yearling weight, lean meat yield and USDA yield grade, whilst *rhet*₁ was not significant. Similar results were found by Bolormaa et al (2015) who found significant effects for live weight, and traits related to reproduction

Genomic Heterozygosity – Dominance

The second measure to capture heterosis considers the expression of heterozygosity through dominance values, where dominance, akin to heterosis, quantifies the differential effect between heterozygous and homozygous genotypes. Dominance in genetics can manifest in various forms, including partial, complete, and over-dominance, as illustrated in Figure 1. These effects can be integrated into genomic evaluations through the concept of dominance deviation. Consider an

additive genetic effect represented by 'a', where one homozygote genotype's value is -a and the other's is +a. In this scenario, the expected value for a heterozygote would be zero, representing the midpoint between the two homozygotes.

In Figure 1, assuming 'a' equals +1 for all scenarios, setting the expected value for the heterozygote at zero in each case. The deviation from this expected value, denoted as 'd', signifies the dominance deviation. Figure 1 demonstrates how dominance deviation varies with different gene actions. In a scenario of pure additive gene action, there is no deviation from the expected value for the heterozygote, so 'd' equals zero. For partial dominance, there is a slight deviation from zero, where 'd' equals 0.5 in our example, indicating the heterozygote performs slightly similar to one of the homozygotes. In the case of complete dominance, 'd' equals 1, showing that the heterozygote performs as well as the superior homozygote. Lastly, over-dominance is depicted where 'd' equals 1.5, indicating the heterozygote outperforms both homozygotes.

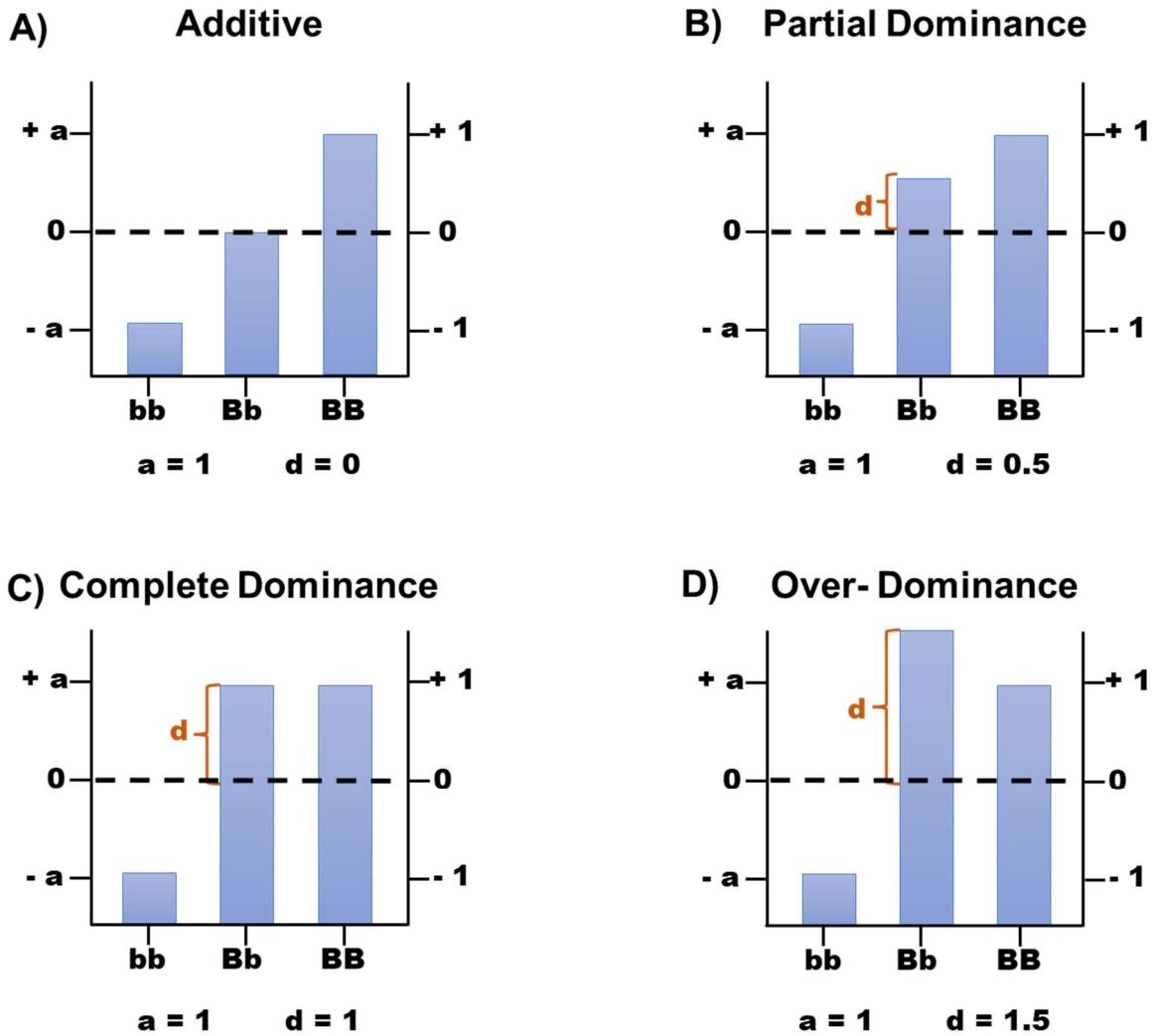


Figure 1) Bar plots illustrating different mode of gene action, including additive (a) and the dominance deviation (d). The genotype designations BB and bb represent the homozygous alleles, while Bb indicates the heterozygous condition. Part A. depicts pure additive gene action, where the phenotype of the heterozygote Bb is an intermediate with no observed dominance effect. Part B shows partial dominance, where the heterozygote Bb exhibits a phenotype closer to that of the BB homozygote. Part C illustrates complete dominance, with the heterozygote Bb expressing a phenotype equivalent to the dominant BB homozygote. Part D represents over-dominance, in which the phenotype of the heterozygote Bb surpasses those of both the BB and bb homozygotes.

This method not only accounts for additive genetic contributions but also allows for the identification of potential dominance effects, suggesting that heterosis is influenced by these dominance effects, not solely by retained heterozygosity. Genome-wide association studies have been employed to identify markers with dominance effects, providing evidence for the varied influence of dominance in genetic expression. In crossbreed cattle, several QTLs with a

dominance gene action have been identified for carcass traits (Kenny et al., 2022). A pleiotropic QTL on BTA2 had significant dominance effects on carcass weight, carcass confirmation and carcass fat in a population of crossbreed cattle (Kenny et al., 2022). An analysis looking at several growth traits in crossbreed cattle identified several QTLs with dominance effect, which when compared to the same analysis done in their purebreds yielded a higher number of dominance effects indicating genes with dominance gene action are more prevalent in crossbreed populations contributing too heterosis (Akanno et al., 2018b).

Dominance deviation is typically modeled in genomic evaluations using a Dominance relationship matrix (DRM), which is considered alongside an additive genomic relationship matrix (Sun et al., 2013). Some studies have emphasized the benefits of incorporating this DRM, although there is not unanimous agreement on its impact. Furthermore, when DRM is combined with measures of retained heterozygosity derived from genomic heterozygosity, it becomes apparent that these two measures may not explain the same variation in heterosis, indicating the complexity and multifaceted nature of genetic interactions in heterosis. Several traits related too growth and reproduction had significant effects from DRM and *OH* in crossbreed beef cattle (Bolormaa et al., 2015). This observation has also been made for multiple different production traits, where alongside the DRM different measures of heterosis (*OH*, *rh_{et1}*) were also fit (Akanno et al., 2018a) . The common explanation for this is the presence of dominance and overdominance effects does not directly translate to the presence of heterosis unless dominance and overdominance effects are directional (Akanno et al., 2018a).

Limitations of current approaches

A critical limitation of genomic heterozygosity measures as proxies for heterosis is their underlying assumption that heterozygotes are exclusive to crossbred animals. In reality, many genetic markers are not fixed within purebred populations and can also be present with varying levels of heterozygosity, challenging the uniqueness of heterozygosity in crossbreds. Thus, the occurrence of a heterozygote in a crossbreed is not necessarily unique to the crossbreds. For instance, in multi-breed genetic evaluations aimed at detecting heterosis, purebred cattle exhibiting genomic heterozygosity could misleadingly appear to benefit from heterosis. This observation has been noted in multiple studies (Akanno et al., 2017). Some studies have tried to address this issue by adjusting the genomic heterozygosity scale so that purebreds register zero

genomic heterozygosity (Hayes et al., 2023). Yet, this approach does not fully resolve the issue, as it remains difficult to determine whether a heterozygote in crossbred animals results from interbreed inheritance or from receiving alleles from the same breed.

Future Directions: Breed of Origin of Alleles (BOA) and Epigenomics

A viable approach to addressing the limitations of SNP/genetic marker-based heterozygosity is to determine the haplotypic origins of alleles in crossbred populations, thereby refining the calculation of heterozygosity. The term breed-of-origin of allele (BOA) denotes the haplotype origin of genetic markers in individuals (Sevillano et al., 2016; Sevillano et al., 2017). The BOA concept was first implemented in swine genetics, a field predominantly reliant on crossbreeding strategies (Sevillano et al., 2016; Sevillano et al., 2017). In these systems, selection of purebred parents is informed by the performance of their crossbred offspring. This approach necessitates tracing the allele origins in the crossbred individuals, enabling the recalibration of breeding values for the purebred parents.

The application of BOA has also shown promise in dairy and beef cattle, where studies have demonstrated its potential to enhance genomic selection in crossbreeding programs (Eiríksson et al., 2021; Guillenea et al., 2023). For instance, research incorporating BOA has revealed benefits in more accurately assessing genetic contributions and improving selection strategies (Warburton et al., 2023). A particular study on fertility traits indicated that integrating genetic markers with their BOA led to a more accurate and less biased genetic evaluation (Warburton et al., 2023).

The use of BOA is poised to offer a more comprehensive control for heterosis, as it integrates conventional heterozygosity metrics with breed-specific genomic information. This dual approach not only incorporates breed information but also enriches it with detailed genomic heterozygosity data, offering a more nuanced view of how animals benefit from heterosis.

Theoretically, BOA could also enhance the detection of non-SNP inheritance patterns between breeds, shedding light on breed-specific gene and epigenetic expression. Given the variability in gene and epigenetic expression across breeds, and their inheritance, BOA could serve as a tool to capture these differences. Furthermore, the role of epigenetic expression in contributing to heterosis has been hypothesized, suggesting that BOA could be instrumental in unraveling the genetic intricacies underlying heterosis. Future work should investigate the use of BOA in

measuring heterosis, and the use of transcriptomics and epigenomics too measure genes that contribute toward heterosis.

Conclusions & Implications to Genetic Improvement of Beef Cattle

This review has thoroughly explored the advancement in genomic applications within beef cattle breeding for the management of heterosis. Genomic selection and the assessment of genomic heterozygosity have emerged as pivotal tools in enhancing beef cattle productivity by optimizing genetic gain and heterosis retention. The integration of genomic data has refined the understanding and exploitation of heterosis, moving beyond traditional breed composition metrics to more precise genomic measures.

The distinction between observed heterozygosity and dominance effects in genomic heterozygosity underlines the complexity of genetic interactions contributing to heterosis. While genomic selection has primarily focused on additive genetic effects, the incorporation of dominance relationship matrices and breed-specific genomic information, such as BOA, has provided deeper insights into the multifaceted nature of heterosis.

The challenges of accurately quantifying heterosis, particularly in crossbred populations, highlight the limitations of relying solely on SNP-based heterozygosity measures. The occurrence of heterozygosity in purebreds complicates the interpretation of genomic heterozygosity as a proxy for heterosis, necessitating more nuanced approaches.

Looking ahead, the potential of BOA and the exploration of epigenomic influences on heterosis open new avenues for research. The integration of transcriptomic and epigenomic data could illuminate the gene expressions and epigenetic modifications contributing to heterosis, offering a more comprehensive understanding of the genetic underpinnings of this phenomenon.

In conclusion, the use of genomic technologies and new statistical methodologies promises to enhance the genetic improvement strategies in beef cattle breeding. By more accurately identifying and leveraging heterosis, these advancements pave the way for sustainable, efficient, and productive breeding program.

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