Managing and Sustaining Genetic Diversity in Dairy Systems

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▪ Take Home Messages

‣ Inbreeding levels are increasing and this increase is unavoidable.

‣ The precision of inbreeding values depends on the depth and completeness of the available pedigree, and the inclusion or not of genomic information.

‣ Many consequences of inbreeding are still unknown.

‣ Mating decisions can be used to balance genetic gain with increases in inbreeding levels. In some cases, a sacrifice in genetic gain is required to conserve genetic diversity.

‣ Genetic diversity, economics, and societal acceptance will play an increasing role in how selection programs evolve.

▪ Introduction

Inbreeding occurs when related animals are mated, indicating that the two animals share a common ancestor in their pedigrees. The degree of inbreeding indicates how closely these relatives are related across the sire and dam lines. Mating two closely related animals results in a higher inbreeding coefficient than mating two distantly related animals. The traditional method of measuring inbreeding uses pedigree data that traces the pedigree back through multiple generations to identify common ancestors between the sire and dam. The precision of inbreeding values is thus highly dependent on the depth and completeness of the pedigree. A low inbreeding value may just be the result of a shallow or incomplete pedigree that excludes any shared ancestors. If the pedigree is traced further back, for example, three or four generations, there is a higher probability of finding a common ancestor that would contribute to a higher inbreeding coefficient.

▪ The Impact of Genomics on Diversity

The earliest data for comparing and selecting dairy cattle came from pedigree, dairy production recording programs, and a 'good eye.' With the passage of time, a greater knowledge of heredity in dairy cows evolved into breeding science. Major advances, such as the invention of selection index theory and best linear unbiased prediction, as well as the introduction of artificial insemination and other reproductive technologies, aided in the acceleration of genetic progress. Recently, genomic selection has transformed the way we breed cattle.

The development of genomic technologies has accelerated in the last decade. In contrast to genetics, which is the study of heredity using traditional, theoretical ideas and models, genomics gets closer to the function and structure of complete genomes using molecular information from an animal's DNA. Initially, different types of genetic markers were used for parentage verification and genetic defect testing. Nowadays, single nucleotide polymorphisms (SNP) are the markers of choice, because there are a lot of them in the DNA and they are relatively cost-effective to identify. SNP markers are now used to provide the information

needed for genomic selection because they are inexpensive, abundant in the bovine genome, stably inherited, and suited for rapid analysis. Additionally, they are often inherited together with genes controlling traits of economic importance, such as milk production, growth rate, and height. These markers can also be used to more accurately estimate the relationships that exist among animals.

The Illumina Bovine SNP50 chip, released in 2008, enabled genotyping of over 50,000 SNP at the same time, which changed the way we breed dairy cattle and now also many other livestock species. While these SNP account for only a small percentage of the overall genomic diversity in the genome, they provide important information for improving the accuracy of genetic evaluation models. The use of genomic selection in dairy breeding has increased genetic gain for many traits and has changed how we select the next generation of animals. The ability to correctly choose the best animals has improved greatly through the use of genomic information, but it will further improve as additional genomic technologies mature. There is still a long way to go before all of the information in the genome (about 3 billion base pairs per animal) can be understood and used in selection systems, but we're off to a great start. The information found in the DNA can be used to follow which alleles of the genes, i.e., alternate forms of the genes, have been passed on from sire and dam to offspring.

Although genomic information has altered how candidates are chosen and the rate at which genetic progress is made, Howard et al. (2017) argued that a similar degree of change has yet to be seen in the use of genomic information to manage genetic diversity and unfavourable inbreeding effects in dairy populations (Baes et al., 2019).

▪ Inbreeding Levels Are on the Rise

With all the benefits of genomic information, there are also some challenges. Genomic selection has resulted in higher rates of genetic gain, but it has also sped up the yearly increase of inbreeding (Figure 1).
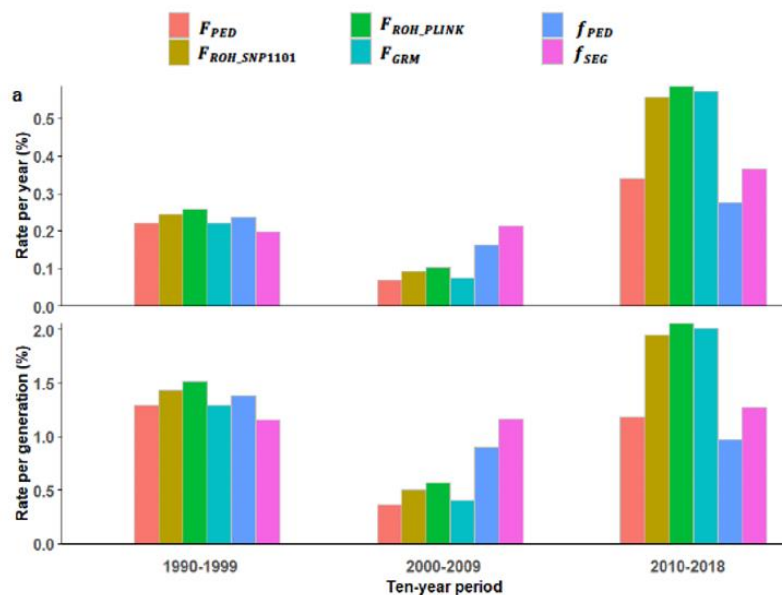

Figure 1: Rate of inbreeding and co-ancestry in North American Holsteins based on pedigree and genomic measures within ten-year periods from 1990 to 2018. F_{PED} = pedigree-based inbreeding; $F_{ROH\_SNP1101}$ = Genomic inbreeding based on Runs of Homozygosity) estimated using the software SNP1101; F_{ROH_PLINK} = Genomic inbreeding based on Runs of Homozygosity estimated using the software PLINK; F_{GRM} = Genomic inbreeding estimated using a marker-by-marker approach by subtracting one from elements of the genomic relationship matrix (fixed allele frequency of 0.5); f_{PED} = coefficient of co-ancestry using pedigree information; f_{SEG} = coefficient of co-ancestry using genomic information; adapted from Makanjuola et al., 2020.

This increasing rate of yearly inbreeding is mostly due to shorter generation intervals, which is an important consequence of the increased usage of genomically tested young sires (and younger animals in general), after 2009 (Figure 2). The decrease in generation interval is seen particularly in the male paths of selection (the age of sires of bulls and sires of cows decreased rapidly after 2009).
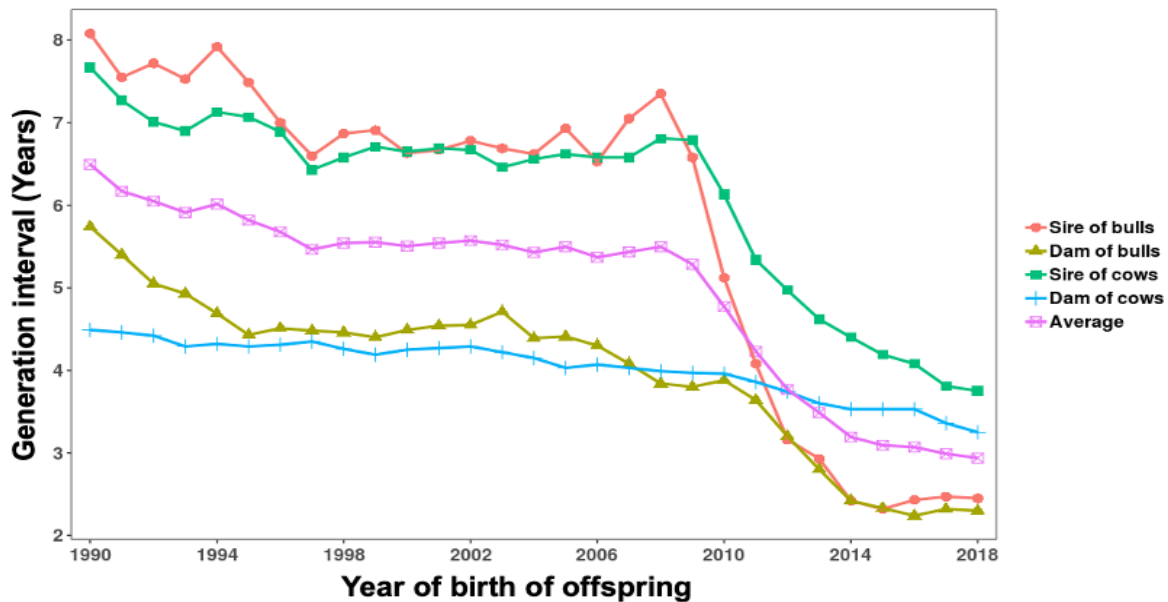

Figure 2: Length of generation interval (years) in North American Holsteins adapted from Makanjuola et al., 2020.

Genomics has aided in the promotion of a larger range of pedigrees by allowing more testing and selection of the best individuals rather than families, as well as by providing more expansive breeding goals, with increased emphasis on health, reproduction, and additional new traits that are difficult to measure and evaluate using traditional methods and reproductive traits. However, it is still common for a few elite related individuals to contribute the most to future generations. It does not take much detective work to see that most bulls on the top lists are related, but that does not mean relatedness cannot be managed.

▪ Consequences of Inbreeding

There is still a lot to learn about the impacts of inbreeding and there is no set limit for how much inbreeding is acceptable or when major issues are likely to occur. Inbreeding can elicit a variety of responses. In general, we know that the buildup of inbreeding in dairy cow herds has unfavourable consequences. That being said, any kind of direct selection will result in inbreeding, so it will not go away any time soon.

Lowered performance due to inbreeding, known as inbreeding depression, often has the greatest influence on fitness characteristics, leading to decreased fertility or health, although production can also be reduced. The impacts of inbreeding can be minor or serious, and in severely inbred animals, can result in large economic losses.

While inbreeding does not result in the creation of unwanted alleles, it does raise the likelihood that an animal may acquire two copies of the same unfavourable allele of a gene, which will be expressed in its homozygous form. Genomics has enabled the discovery of multiple recessive haplotypes. These haplotypes are genomic regions on the same chromosome carrying the recessive alleles with significant impact on economically important traits. The knowledge of these haplotypes can assist in the avoidance of mating of two carriers. Advances in genomics have also brought further insight into how we can detect these problems and can help to describe inbreeding and its varied repercussions. While pedigree-based inbreeding is based on expectations and average probabilities and is limited by pedigree depth, genomic inbreeding gives a more precise look at realized inbreeding or homozygosity at the genome level.

Inbreeding is not always harmful. In fact, the genetic gain we have seen in economically important traits has been the result of controlled inbreeding over many generations. As more genomic information becomes available, researchers are now finding specific regions of the genome where inbreeding has an impact on performance in various traits. This type of research could lead to more advanced breeding practices.

▪ Managing Diversity

Directional selection increases uniformity for desirable traits, but by increasing uniformity in general, there can be a negative consequence of reducing diversity for fitness traits. Inbreeding in a purebred population is largely unavoidable, but it can and should be managed. Inbreeding does not pass down to progeny in the same way that genes do, so an inbreeding coefficient of a potential bull does not tell you much about the inbreeding coefficient of that bull's offspring.

When a bull with a high inbreeding coefficient is mated with a distantly related female who is not closely related to him, the resulting calves will not be highly inbred. If that same bull is mated with a highly related female, its progeny will have a high inbreeding coefficient. It is important to keep track of pedigree information to avoid accidental mating between close relatives. This can be done, for example, by maintaining good records and registering your herd with a breed association, such as Holstein Canada, who will keep track of the pedigree information for you.

When considering which bull to use on your farm, the relationship-value (R-value) is a more relevant piece of information for the breeder than is the inbreeding coefficient of the bull, since the R-value represents the percentage of DNA the bull shares with active females of the same breed. A critical component of inbreeding management is to identify each animal accurately, to establish the correct sire and dam, and to keep the overall pedigree integrity. Selecting bulls with lower R-values maintains a higher level of diversity within the breed as a whole.

As mentioned earlier, registration also makes it possible to track the herd's pedigree, and therefore its inbreeding rate. The cost of registration is approximately $2.80/cow/year, which includes registration cost and Holstein Canada and provincial membership fees (Info Holstein, 2021. Underestimating the inbreeding rate by 1% can result in a loss of income of $9.60 per cow per year due to inbreeding depression (Holstein Canada, 2021), so it pays to keep track of your inbreeding rates.

Breeding decisions can be made in a way that considers the progeny's inbreeding level to help manage inbreeding at the farm level. Lactanet provides breeders with several tools, such as the inbreeding calculator on the website, to analyze the inbreeding level of the resulting progeny from mating different females in their herd to various sires (see https://lactanet.ca/en/genetic-evaluations/inbreeding-calculator/). Matings that produce offspring with an inbreeding coefficient higher than a given threshold can be avoided in this way. There is a point where sacrificing some genetic gain is required to preserve genetic diversity of the breed as a whole, and to decrease inbreeding at the farm level.

▪ From Genotypes to Phenotypes

In the age of genomic selection, the ability to identify exact regions of DNA that affect a particular trait is improving. The genome-wide association study is a tool used frequently in the past decade to identify and map SNP and haplotypes with a significant effect on a given trait. These studies can be used to find 'good alleles' and also recessive alleles of genes that cause problems when two copies are inherited, one from each parent (in this case, an animal is "homozygous" for a specific recessive haplotype). With the increased use of young genomic bulls, some of these recessive haplotypes may arise and spread throughout the population very rapidly.

In Holsteins, the recently identified haplotype for cholesterol deficiency (HCD) provides a first-class example of the danger of haplotypes containing a deleterious mutation in homozygous form. Animals heterozygous for HCD (heterozygous = the animals carry two different haplotype versions) have a reduced amount of cholesterol in their blood, but homozygote HCD animals (those that receive two identical copies of the

same, detrimental haplotype) have no cholesterol and only survive a few months (Kipp et al., 2015). The defective haplotype is difficult to track because a neutral version and a recently mutated version are both very frequent, and the available SNP surrounding the mutation are identical. Other harmful haplotypes, often referred to as haplotypes affecting fertility, have been found in Holstein, Jersey, Brown Swiss, and Ayrshire animals. There are likely many more detrimental haplotypes in dairy cattle; however, they are yet to be identified. Genomic information can help track down these recessive haplotypes quickly.

Similarly, the capacity to detect lengthy segments of homozygous DNA (known as 'runs of homozygosity,' or ROH) and connect such areas with traits of interest is also increasing rapidly (e.g., Howard et al., 2017). Such studies will aid in determining whether areas of the genome have a detrimental or positive influence on characteristics of interest when ROH are present. Figure 3 shows homozygous areas on bovine chromosome 11 that influence several calving and fertility traits. Some areas are related to a variety of traits impacting calving and fertility in both heifers and first parity cows. These areas can now be identified and further investigated with more powerful analyses to find the specific causal mutations.
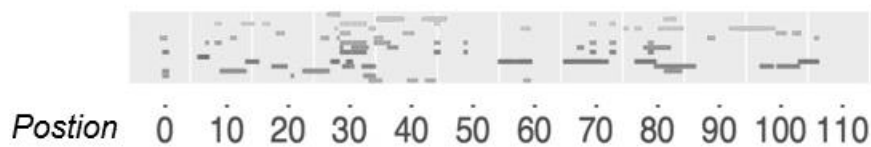
Figure 3. Location of runs of homozygosity (ROH) on chromosome 11 with an effect on various fertility traits. Lines represent traits as follows (from top to bottom: ac0 & ac1 = age at calving (heifer & 1st parity, respectively); afs0 = age at first service (heifer); ctfs1 = calving to first service (1st parity); cz0 & cz1 = calf size (heifer & 1st parity, respectively); do1 = days open (1st parity); fstc0 & fstc1 = first service to calving (heifer & 1st parity, respectively); gl0 & gl1 = gestation length (heifer & 1st parity, respectively); ns0 & ns1 = number of services (heifer & 1st parity, respectively); sb0 & sb1 = still birth (heifer & 1st parity, respectively) (Makanjuola et al., 2020)

▪ Conclusions

New technologies, both those applied to studying the molecular basis of inheritance, and those used to measure various physical characteristics of animals, have had, and will continue to have, disruptive effects on livestock breeding practices. Advances in technologies are being made at an unprecedented rate and large-scale implementation of these technologies will affect both genetic diversity of future livestock populations and the economics of genetic improvement. Furthermore, with active, information-seeking consumers entering the marketplace, past breeding goals centred on production may no longer be attractive and new phenotypes will need to be collected on a large scale. The implications of increasing the use of reproductive and genomic technologies and applying novel technologies and methods in livestock breeding populations must be carefully considered. In particular, the effects on genetic diversity of livestock populations, the financial implications for all stakeholders, and the societal acceptance of these technologies and their wide-spread use must be evaluated. Despite these caveats, the use of these technologies, together with their integration in breeding, could contribute to sustainable and further genomic improvement if properly managed.

▪ Acknowledgements

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