

Invited Review

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A review of inbreeding depression in dairy cattle: current status, emerging control strategies, and future prospects

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Abstract

Dairy cattle breeding has historically focused on relatively small numbers of elite bulls as sires of sons. In recent years, even if generation intervals were reduced and more diverse sires of sons could have been selected, genomic selection has not fundamentally changed the fact that a large number of individuals are being analyzed. However, a relatively small number of elite bulls are still siring those animals. Therefore inbreeding-derived negative consequences in the gene pool have brought concern. The detrimental effects of non-additive genetic changes such as inbreeding depression and dominance have been widely disseminated while seriously affecting bioeconomically important parameters because of an antagonistic relationship between dairy production and reproductive traits. Therefore, the estimation of benefits and limitations of inbreeding and variance of the selection response deserves to be evaluated and discussed to preserve genetic variability, a significant concern in the selection of individuals for reproduction and production. Short-term strategies for genetic merit improvement through modern breeding programs have severely lowered high-producing dairy cattle fertility potential. Since the current selection programs potentially increase long-term costs, genetic diversity has decreased globally as a consequence. Therefore, a greater understanding of the potential that selection programs have for supporting long-term genetic sustainability and genetic diversity among dairy cattle populations should be prioritized in managing farm profitability. The present review provides a broad approach to current inbreeding-derived problems, identifying critical points to be solved and possible alternative strategies to control selection against homozygous haplotypes while maintaining sustained selection pressure. Moreover, this manuscript explores future perspectives, emphasizing theoretical applications and critical points, and strategies to avoid the adverse effects of inbreeding in dairy cattle. Finally, this review provides an overview of challenges that will soon require multidisciplinary approaches to managing dairy cattle populations, intending to combine increases in productive trait phenotypes with improvements in reproductive, health, welfare, linear conformation, and adaptability traits into the foreseeable future.

Introduction

Inbreeding decreases the performance of dairy cattle by directly or indirectly affecting various productive and reproductive parameters (Gutiérrez-Reinoso *et al.*, 2020). During the 1970s, in countries such as the United States, the degree of inbreeding was recorded to be in the order of 3–6% in the Holstein breed (Young, 1984). This problem occurs because breeding programs in dairy cattle incentivize and reinforce matings between genetically related individuals, driving the phenomenon called inbreeding depression (Baes *et al.*, 2019). Even though estimates of genomic values have received much attention in recent years, estimates of inbreeding depression in dairy cattle are rare in the literature (Maltecca *et al.*, 2020). Several authors suggest a variable influence of genomic selection on the effect of inbreeding (Howard *et al.*, 2017; Baes *et al.*, 2019; Doekes *et al.*, 2019). In dairy cattle, the impact of inbreeding depression in recent generations is projected to drive very adverse effects compared to old inbreeding (distant generations) (Makanjuola *et al.*, 2020). However, inbreeding may exert a detrimental effect only on specific traits (Doekes *et al.*, 2019; Gutierrez-Reinoso *et al.*, 2021).

Implementing genomic evaluations has drastically changed how breeding systems are conducted in dairy cattle breeds (Howard *et al.*, 2017). Traditionally, pedigree-derived data was highly valuable for assessing the genetic diversity of non-genotyped individuals (Sonesson *et al.*, 2012). However, genomics has enabled more precise studies of the proportion of the inbreeding patterns across the genome (Howard *et al.*, 2017; Sell-Kubiak *et al.*, 2018).

Thus, genomics-based estimates started to be used to manage genetic diversity in animal selection programs, including dairy cattle (Sonesson *et al.*, 2012).

Inbreeding has been described as a cause of the reduced performance of productive and reproductive traits in dairy cattle by increasing the frequency of deleterious or non-deleterious recessive homozygous genotypes leading to the loss of genetic dominance and other non-additive effects (VanRaden, 1992; McParland *et al.*, 2009; Pryce *et al.*, 2014; Dezetter *et al.*, 2015; Gutiérrez-Reinoso *et al.*, 2020). Consequently, inbreeding depression can be reduced by minimizing overall inbreeding and avoiding the production of recessive homozygous offspring (Leroy, 2014; Pryce *et al.*, 2014).

The accumulation of annual genetic gain has gathered momentum for major dairy cattle breeds (Doublet *et al.*, 2019) due to the implementation of genomic selection during the last decades. Still, unfortunately, the annual loss of genetic diversity has increased considerably, reflecting the emergence of recent inbreeding (Makanjuola *et al.*, 2020). Therefore, understanding the impact of genomic selection on genetic diversity and the factors involved in different genetic traits (productive, reproductive, type, health, conformation, and adaptation, among others) as well as inbreeding rates based on genomics and pedigree estimations is critical for the development of dairy cattle selection programs (Pryce *et al.*, 2014; Doublet *et al.*, 2019; Gutiérrez-Reinoso *et al.*, 2021).

Despite the evident negative influence of inbreeding on several genetic traits in dairy cattle (McParland *et al.*, 2009; Pryce *et al.*, 2014; Dezetter *et al.*, 2015; Gutiérrez-Reinoso *et al.*, 2020), the mating of genetically related individuals continues to be carried out (Baes *et al.*, 2019). Breeding organizations continue to develop breeding programs involving very close or genetically related genetic lines, intending to fix different traits of interest (Gandini *et al.*, 2014). This issue has led to a vicious circle, negatively impacting genomic and phenotypic traits related to production, reproduction, conformation, health, and adaptability. For example, Holstein bulls show a higher annual genetic variability loss than other dairy breeds (Doublet *et al.*, 2019). To progressively generate understanding in the industry for the need to mitigate the negative inbreeding derived effects in dairy cattle breeds, urgent characterization, and dissemination of information on the extent of inbreeding and inbreeding coefficients of specific bulls are becoming extremely important.

The present review sets out the primary objectives of providing a broader understanding of the importance of genomic analysis and exploring possible applications to mitigate the undesirable effects of inbreeding depression on different traits of production, reproduction, health and welfare, linear conformation and adaptability. We will address topics related to the use and influence of genomic analysis on genotypic traits affected by inbreeding in dairy cattle. This review paper is designed and organized as follows: a brief history of the emergence of the concept of inbreeding/endogamic depression, the impact of the negative effect of inbreeding on production traits, reproduction, animal health-welfare, linear conformation, and adaptability indices in different cattle operation systems, as well as causal and highly predictive genetic variants potentially key to the prediction of other complex traits. Furthermore, we will provide evidence that the control of inbreeding depression should focus on current methodologies applied to genomic selection. Promising new approaches to dairy cattle genomic selection based on genomic analysis show excellent potential to control the genetic gain of genomic

traits that influence different aspects of dairy cattle. These tools are essential to improve the prediction of the effects derived from increased homozygosity. However, considerable challenges exist to integrate a genomic analysis model that increases the accuracy of prediction for different genetic traits while at the same time detecting a greater or lesser increase in inbreeding depression. Therefore, monitoring the degree of homozygosity in dairy cattle becomes a critical factor, instrumental for controlling and determining the possible adverse effects derived from it. Consequently, follow-up of the phenomenon of homozygosity must be considered to counteract endogamic effects. This way, we can ensure a sustainable future and profitability during the productive life of dairy cattle across generations.

Inbreeding depression: history, background and current status

Inbreeding is the probability of two alleles in an individual being identical by descent due to mating-related individuals. The inbreeding rate is a function of the characteristics of the foundation stock as well as limited population sizes in subsequent generations (Possingham *et al.*, 2013). Inbreeding resulting from the mating between animals of standard genetic lines can be associated with a decrease or loss of the biological capacity called inbreeding depression. This concept is advanced by different authors who maintain that high levels of endogamy are undesirable because they diminish genetic diversity and yields of the future generations due to positive or negative influences over different traits (Miglior *et al.*, 2001; Croquet *et al.*, 2006; Doekes *et al.*, 2019; Doublet *et al.*, 2019) (Fig. 1). The first studies to demonstrate the effects of inbreeding depression were conducted in plants and, later, the concept was extrapolated to animal species.

Initially, evaluations of the degree and consequences of inbreeding in dairy cattle breeds were based on estimates of pedigree data. Consequently, predictions of inbreeding coefficients used to be fluctuating and imprecise (Howard *et al.*, 2017). Today, computerized animal selection programs have substantially improved the estimation of traits by reasonably limiting the degree of inbreeding in subsequent generations (Weigel and Lin, 2000). In parallel to these studies, a large number of meta-analyses have been conducted on various livestock species, demonstrating that reproductive traits are more severely depressed than other traits (McParland *et al.*, 2007; Ma *et al.*, 2019). Overall, for every 1% increase in the degree of inbreeding, an average decrease of 0.137% of some traits is estimated (Leroy, 2014), including production losses (McParland *et al.*, 2007; Dezetter *et al.*, 2015; Doekes *et al.*, 2019). In other cases, inbreeding depression has been observed to cause yield losses for production traits like for instance -32 to -41 kg of 305ME milk, -1.4 to -1.7 kg of 305ME fat, and -1.1 to -1.3 kg of 305ME protein by percent inbreeding (Dezetter *et al.*, 2015), or reducing fat and protein concentrations by 0.05% and 0.01%, respectively while somatic cell scores increased by 0.03–0.86 units (McParland *et al.*, 2007; Doekes *et al.*, 2019). (Table 1). Also, due to the effect of inbreeding, 2% more dystocia, 1% more stillbirths, 0.7% more male calves, an increase of calving interval of 8.8 d and increased age at first parturition of 2.5 d have been reported (McParland *et al.*, 2007; Ma *et al.*, 2019) (Table 2).

Despite the findings of several studies that suggest inbreeding negatively affects productive and other traits (Rokouei *et al.*, 2010; Dezetter *et al.*, 2015; Howard *et al.*, 2017; Martikainen *et al.*, 2017; Yurchenko *et al.*, 2018; Doublet *et al.*, 2019), other authors

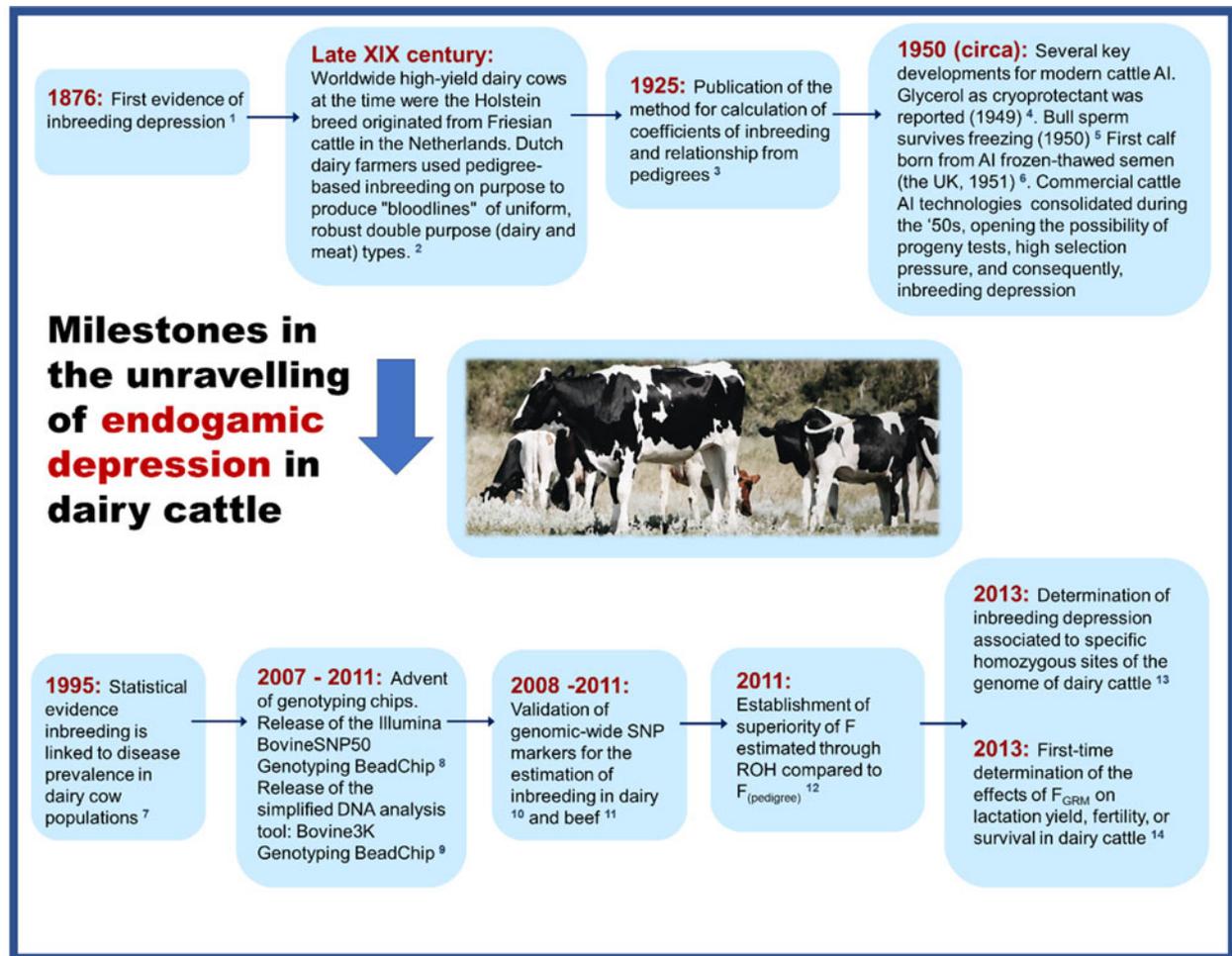


Fig. 1. Milestones in the unravelling of endogamic depression in dairy cattle. AI = artificial insemination; $F_{(pedigree)}$ = coefficient of inbreeding estimated through pedigree; ROH = Runs of homozygosity; F_{GRM} = Inbreeding coefficient based on the genomic relationship matrix. References: (1) (Darwin, 1876); (2) (Theunissen, 2008); (3) (Wright and McPhee, 1925); (4) (Polge and Rowson, 1952); (5) (Bailey, 2017); (6) (Leibo *et al.*, 1994); (7) (Miglior *et al.*, 1995); (8) (BovineSNP50 DNA Analysis Kit, 2021); (9) (Data Sheet: DNA Analysis, 2021); (10) (VanRaden *et al.*, 2011); (11) (Hayes and Goddard, 2008); (12) (Keller *et al.*, 2011); (13) (Pryce *et al.*, 2014); (14) (Bjelland *et al.*, 2013).

indicate that inbreeding is unlikely to cause large losses (McParland *et al.*, 2007). Although overdominance and epistasis may contribute to inbreeding depression in dairy cattle, partial dominance is expected to account for the more significant proportion of inbreeding depression. Thus, the degree and timing of inbreeding do not always seem to be negative, considering that recent inbreeding is more detrimental than old inbreeding (Doekes *et al.*, 2019). In dairy breeds such as Holstein and Jersey, these effects would be accompanied by an increased frequency of unfavorable homozygous recessive genotypes (Pryce *et al.*, 2014). Therefore, the estimation of genomic homozygosity seems to be a more accurate tool than the pedigree-based inbreeding coefficient (Kardos *et al.*, 2015; Baes *et al.*, 2019).

There is a consensus that the effect of inbreeding at undesirable levels seriously affecting genetic variability, as well as the performance in generations of dairy cattle (Croquet *et al.*, 2006; Doekes *et al.*, 2019; Doublet *et al.*, 2019; Miglior *et al.*, 2001) is associated to specific genomic regions (Pryce *et al.*, 2014). This implies that inbreeding coefficients vary and are inaccurate when their predictions are based solely on pedigree data (Howard *et al.*, 2017). One summarizing remark from the above studies is that the continuous use of genomic evaluation as a

routine method in bovine genetic improvement programs is highly relevant to positively impact the reduction of the degree of inbreeding in the future generations (de Oliveira Seno *et al.*, 2018). However, estimation of genomic homozygosity appears to be a more accurate tool (Kardos *et al.*, 2015; Baes *et al.*, 2019), so linking these two factors (genomics and pedigree) significantly improves the estimation of prediction for the most desirable traits of interest in dairy cattle (Weigel and Lin, 2000).

Inbreeding depression in dairy cattle: production, reproduction, health and welfare, linear conformation and adaptability

Impact of inbreeding depression on production

One of the main advantages of bovine genome sequencing is that it has contributed significantly to the analysis and interpretation of the functionality of genes. This advance leads to opportunities to answer the problem of the overuse of existing genetic lines in dairy breeds that has generated an increase in the consanguinity index (Doekes *et al.*, 2019). The reported incidence of inbreeding and, consequently, inbreeding depression is evident in several

Table 1. Regression coefficients of inbreeding depression for production and conformation for production traits per 1% increase in inbreeding in dairy cattle (genomics vs. pedigree)

Parameters	Means estimates per every 1 % increase in inbreeding (genomics)	References	Means estimates per every 1 % increase in inbreeding (pedigree)	References
<i>Production</i>				
305-d milk (kg)	-36.30	Doekes <i>et al.</i> (2019)	-19.68	Croquet <i>et al.</i> (2006)
Somatic cells (CFUs)	0.86	Doekes <i>et al.</i> (2019)	0.52	Croquet <i>et al.</i> (2006)
305-d Fat (kg)	-2.42	Doekes <i>et al.</i> (2019)	-0.96	Croquet <i>et al.</i> (2006)
Protein yield (kg)	-1.20	Bjelland <i>et al.</i> (2013)	-0.69	Croquet <i>et al.</i> (2006)
<i>Conformation for production</i>				
Stature	-0.06	Bjelland <i>et al.</i> (2013)	-0.24	Croquet <i>et al.</i> (2006)
Body depth	-0.14	Bjelland <i>et al.</i> (2013)	-0.48	Croquet <i>et al.</i> (2006)
Loin strength	-0.19	Bjelland <i>et al.</i> (2013)	-0.14	Croquet <i>et al.</i> (2006)
Foot angle	-0.04	Bjelland <i>et al.</i> (2013)	-0.47	Croquet <i>et al.</i> (2006)
Rear leg rear view	-0.14	Bjelland <i>et al.</i> (2013)	-0.62	Croquet <i>et al.</i> (2006)
Udder depth	0.06	Bjelland <i>et al.</i> (2013)	0.30	Croquet <i>et al.</i> (2006)
Udder support	0.04	Bjelland <i>et al.</i> (2013)	-0.13	Croquet <i>et al.</i> (2006)
Front teat placement	0.18	Bjelland <i>et al.</i> (2013)	0.16	Croquet <i>et al.</i> (2006)
Teat length	-0.13	Bjelland <i>et al.</i> (2013)	-0.13	Croquet <i>et al.</i> (2006)
Rear udder height	-0.05	Bjelland <i>et al.</i> (2013)	-0.03	Croquet <i>et al.</i> (2006)
Rear udder width	-0.05	Bjelland <i>et al.</i> (2013)	-0.28	Croquet <i>et al.</i> (2006)
Rear teat placement	0.12	Bjelland <i>et al.</i> (2013)	0.01	Croquet <i>et al.</i> (2006)
Overall fore udder	-0.02	Bjelland <i>et al.</i> (2013)	0.03	Croquet <i>et al.</i> (2006)
Overall dairy trait	-0.03	Bjelland <i>et al.</i> (2013)	-0.05	Croquet <i>et al.</i> (2006)

Estimates were readjusted as standardized linear regression coefficients.

traits, particularly in production traits (Pryce *et al.*, 2014). Thus, inbreeding generates a substantial effect on milk, fat, and protein derived-traits, and an alteration of the somatic cell count as evaluated through genealogical information of sires and dams of different dairy breeds (Croquet *et al.*, 2007; Rokouei *et al.*, 2010; Bjelland *et al.*, 2013; Dezetter *et al.*, 2015). In another study involving Jersey animals in which different degrees of inbreeding were estimated over time and their relationship with production and genealogical data was quantified, a greater negative presence of inbreeding in animals of early ages and at the beginning of lactation was found (Thompson *et al.*, 2000). Also, in other breeds such as Ayrshire, this time introducing genomic analysis, harmful homozygous recessive alleles have been identified to be responsible for the increase in inbreeding depression affecting production traits in general (Martikainen *et al.*, 2020). When identical haplotypes are inherited from both parents, inbreeding seems to be related to continuous lengths of homozygous genotypes (runs of homozygosity, ROH). These may be formed with deleterious (lethal) recessive alleles and could be associated with inbreeding depression and consequently with a decreased phenotypic performance. In the Ayrshire dairy breed, several ROHs have been reported to adversely affect production and reproductive traits (Martikainen *et al.*, 2020). However, not all ROHs in a region may have negative effects on the trait of interest. Therefore, more efficient control of inbreeding depression could

minimize the occurrence of unfavorable haplotypes as homozygous status in breeding programs.

According to Doekes *et al.* (2019), inbreeding in Dutch Holstein-Friesian cows decreases animal performance traits (inbreeding depression), but inbreeding may not always be detrimental. In the Holstein breed, the effect of the degree of ancestral and current inbreeding ratifies the harmful effects of inbreeding on production traits (McParland *et al.*, 2009). Over time the frequency of deleterious (lethal) alleles decreases due to a selection process called genetic purging, and recent inbreeding may be more harmful than old inbreeding. In both production and reproductive traits, long and short ROHs contributed to inbreeding depression (Doekes *et al.*, 2019).

Genomics has recently emerged as a tool for the evaluation of inbreeding depression. Several genomic studies have detected the continuous increase of inbreeding indexes associated with deleterious homozygous recessive alleles, responsible for the rise of inbreeding depression affecting production traits in several dairy breeds (Croquet *et al.*, 2007; Rokouei *et al.*, 2010; Bjelland *et al.*, 2013; Dezetter *et al.*, 2015; Doekes *et al.*, 2019), such as the Ayrshire (Martikainen *et al.*, 2020), Jersey (Thompson *et al.*, 2000) and Holstein (McParland *et al.*, 2009). Therefore, the implementation of genomic analysis is essential to understand the functionality and potential of some genes to influence productive traits and establish the size of the association of

Table 2. Regression coefficients of inbreeding depression for reproduction and conformation for ease of calving traits per 1% increase in inbreeding in dairy cattle (genomics vs. pedigree)

Parameters	Means estimates per every 1 % increase in inbreeding (genomics)	References	Means estimates per every 1 % increase in inbreeding (pedigree)	References
<i>Reproductive</i>				
AFS_H (d)	0.35	Makanjuola <i>et al.</i> (2020)	0.44	Makanjuola <i>et al.</i> (2020)
NS_Hc	0.99	Makanjuola <i>et al.</i> (2020)	0.96	Makanjuola <i>et al.</i> (2020)
NRR_Hc	−0.19	Makanjuola <i>et al.</i> (2020)	−0.01	Makanjuola <i>et al.</i> (2020)
FSTC_H (d)	0.31	Makanjuola <i>et al.</i> (2020)	0.29	Makanjuola <i>et al.</i> (2020)
CTFS_C (d)	0.02	Makanjuola <i>et al.</i> (2020)	0.07	Makanjuola <i>et al.</i> (2020)
NS_Cc	0.70	Makanjuola <i>et al.</i> (2020)	0.45	Makanjuola <i>et al.</i> (2020)
NRR_Cc	−0.33	Makanjuola <i>et al.</i> (2020)	−0.29	Makanjuola <i>et al.</i> (2020)
FSTC_C (d)	0.19	Makanjuola <i>et al.</i> (2020)	0.16	Makanjuola <i>et al.</i> (2020)
Calving interval (d)	0.48	Doekes <i>et al.</i> (2019)	0.18–0.7	Pryce <i>et al.</i> (2014)
Ease of calving	0.04	Bjelland <i>et al.</i> (2013)	0.06	Rokouei <i>et al.</i> (2010)
<i>Conformation parameters for ease of calving</i>				
Rump angle	−0.14	Bjelland <i>et al.</i> (2013)	0.01	Croquet <i>et al.</i> (2006)
Rump width	−0.03	Bjelland <i>et al.</i> (2013)	−0.33	Croquet <i>et al.</i> (2006)

AFS_H: Age at first service for heifers, NS_H: Number of services for heifers, NRR_H: 56-day non-return rate for heifers, FSTC_H: First service to conception for heifers, CTFS_C: Conception to the first service for cows, NS_C: Number of service for cows, NRR_C: 56-d non-return rate for cows, FSTC_C: First service to conception for cows. Estimates were readjusted as standardized linear regression coefficients.

conventional traits regarding new traits included in genetic improvement programs in recent years.

Effects of inbreeding depression on reproduction

Increased inbreeding rates have been associated with reduced reproductive capacity in major dairy breeds (Martikainen *et al.*, 2020). In the Holstein breed, it has been shown that classic, ancestral and future inbreeding has detrimental effects on fertility and survival traits (McParland *et al.*, 2009). For decades, the analysis to determine the degree of inbreeding has been performed relying on genealogical data, and adverse effects on reproduction have been reported (Hermas *et al.*, 1987). For example, pedigree-based estimations of the inbreeding coefficients in the Ayrshire breed show important differences derived from inbreeding depression on the fertility indexes, the prediction through genomic analysis being more precise (Martikainen *et al.*, 2017). Moreover, studies using solely genealogical data show that the estimation of the inbreeding coefficient had no significant effects on traits such as birth weight and calving ease (McParland *et al.*, 2007). In contrast, a study in adult Holstein cattle showed that inbreeding, assessed by pedigree data, affected the calving interval trait and detected an increased incidence of difficult calvings (Rokouei *et al.*, 2010). Evaluations of inbreeding depression from genomic data have shown a more accurate and significant prediction of reproductive traits (Martikainen *et al.*, 2018) such as decreased oocyte and embryo competition (Perez *et al.*, 2017), fetal death (Hinrichs and Thaller, 2011), udder health traits and overall fertility rates (Doekes *et al.*, 2019) as well as days open and calving ease (Bjelland *et al.*, 2013).

Genomic regions have also been identified that harbor harmful recessive mutations associated with decreased calving rates (Fritz

et al., 2013) and lethal recessive mutations associated with embryonic death (VanRaden and Miller, 2006). Hence, the effects of inbreeding rates on different reproductive traits should be considered in genetic improvement programs in dairy cattle (Martikainen *et al.*, 2017). For such evaluation, genomic evaluation techniques should be prioritized due to their predictive capacity and greater precision. Although the results of inbreeding estimation using pedigree data are similar to those estimated by genomics for some reproductive traits, certainly genomic estimations are more efficient and accurate (Weller *et al.*, 2017). Some authors even claim that there is now evidence of increased predictive accuracy using genomic analyses in dairy cattle breeds in this respect (Martikainen *et al.*, 2018, 2020). Through genomic methods, the different regions in the genome that have been identified as harboring harmful recessive mutations associated with negative phenotypic effects involve calving rates (Fritz *et al.*, 2013), embryonic death (VanRaden and Miller, 2006), fertility (Martikainen *et al.*, 2017), calving interval, dystocic parturition (Rokouei *et al.*, 2010; Bjelland *et al.*, 2013), decreased oocyte/embryo competence (Perez *et al.*, 2017), early fetal death (Hinrichs and Thaller, 2011), lower fertility rates (Doekes *et al.*, 2019), and increased open days (Bjelland *et al.*, 2013). In contrast, other studies mention that inbreeding had no significant effect on specific traits such as birth weight and calving ease (McParland *et al.*, 2009). We consider that the negative impact generated by inbreeding on most reproductive traits is evident. However, these effects would be presented in greater or lesser proportion to the levels of inbreeding present in each individual studied and directly proportional to the number of genomic regions harboring recessive mutations (Fritz *et al.*, 2013) and lethal recessive mutations (VanRaden and Miller, 2006). These effects have been increasing simultaneously with the evolution of higher yields in

dairy cattle (Cole *et al.*, 2016). In this sense, from the genotyping of genomic regions affected by inbreeding, further studies are suggested to identify a more significant proportion of regions to propose strategies to reduce the effects of inbreeding and maintain a balance between production levels, reproduction and inbreeding coefficients.

Influence of inbreeding depression in health and welfare

Health indices are fundamental factors in dairy farming as they directly influence animal welfare. In recent years, genomic evaluations of dairy cattle have incorporated new traits related to animal welfare that had not previously been considered. These traits play a major role in the overall health of the individual. In that sense, several studies give importance to the effect of inbreeding depression on health and animal welfare traits associated with dairy cattle longevity (Baes *et al.*, 2019).

An increment of the inbreeding coefficient is a serious factor that increases the risk of activation of harmful recessive genes potentially influencing the cattle's immune system (Macedo *et al.*, 2014). Thus, increased inbreeding coefficients would be directly associated with the expression of recessive genes that impair the overall immune system, even affecting mitochondrial DNA (Macedo *et al.*, 2014; Baes *et al.*, 2019), udder health (Doekes *et al.*, 2019), linear conformation traits, dairy temperament, survival, general health status, individual vigor and strength (Cassell *et al.*, 2003). Doekes *et al.* (2019) also observed that inbreeding depression due to recent, compared to old inbreeding, significantly affected udder health. Health and animal welfare traits are strongly linked to the longevity of dairy cows, thereby increasing the time they remain in dairy operations, which impacts profitability. Therefore, these desirable health trait genotypes should be included in all dairy cattle evaluation, selection, and breeding systems to transmit them to future generations. We also emphasize that those dairy systems that maintain longevity traits in present populations will be highly profitable in the medium and long term.

Consequences of inbreeding depression on linear conformation

There is still some controversy regarding the impact of inbreeding on the conformation of dairy cows. The highly specialized conformation in high-yield dairy cattle has demanded the use of strongly related genetic lines initially derived from only about ten sires (Battagin *et al.*, 2013). Several authors claim that in dairy breeds such as Holstein, the high levels of inbreeding brought about by the convergence of genetic lines negatively affect several traits including linear conformation (morphological lines) (Croquet *et al.*, 2006; Rokouei *et al.*, 2010; Battagin *et al.*, 2013). These traits would be strongly associated with longevity, production, and reproductive capacity (Smith *et al.*, 1998; Sewalem *et al.*, 2006). The reason for this is because adaptability traits, including conformation, longevity, and even disease resistance traits, show low heritability and decrease as levels of milk production per cow increase over time (Mirkena *et al.*, 2010). However, the importance of these characteristics derived from high inbreeding could be genotypically and phenotypically more related to longevity, production, and reproductive ability (Sewalem *et al.*, 2006) than conformation. Another study showed that the degree of inbreeding had little effect on conformation traits but more adverse effects on production traits (Smith *et al.*, 1998). However, several studies based on a genealogical analysis in

Holstein sires and dams regarding linear conformation traits showed that the degree of inbreeding significantly influences height, chest width, body depth, udder size and height, median suspensory ligament, udder depth, and teat placement (Rokouei *et al.*, 2010).

Repercussions of inbreeding depression on adaptability

The adaptability of dairy cattle to different environments has been the result of century-old natural evolution. Therefore the real adaptability of cattle to different current production systems and new environments is debatable. For example, a study conducted in nine native Russian cattle breeds identifying candidate known genes and other new genes related to domestication and production traits such as milk production (e.g. *DGAT1*, *ABCG2*), growth (e.g. *XKR4*), reproduction (e.g. *CSF2*) and environmental adaptation (e.g. *AQP5*, *RAD50*, *RETREG1*) showed highly variable results (Yurchenko *et al.*, 2018). This way, during the last centuries, human beings have constantly been working out the specialization of dairy cattle to obtain a high-performance phenotype in the process of continuous matings of genetically related lineages with the accompanying increase in inbreeding rates (Refoyo-Martínez *et al.*, 2019). Therefore, evaluating the individual inbreeding coefficient is crucial for the progress of animal adaptation, evolution, and conservation biology (Kardos *et al.*, 2015). Consequently, the degree of endogamy generated and the specialization of dairy cattle reached so far could have a considerable influence on the capacity of adaptability of dairy cattle to new environments and different production systems, for which additional research is necessary.

The breeding success and the improved adaptability of dairy cattle to different environments is controversial as this trait has low heritability (Strandén *et al.*, 2019). This natural evolutionary trait takes several centuries to become fixed in cattle (Åby and Meuwissen, 2014). Yet, the specialization of dairy breeds has led to an increase in inbreeding rates (Refoyo-Martínez *et al.*, 2019), with variable heritability estimates observed regarding genes of domestication, production, reproduction, growth, and environmental adaptability (Yurchenko *et al.*, 2018). The adequate and permanent monitoring of both individual and population inbreeding in dairy cattle is necessary to mitigate detrimental genetic effects related to cattle adaptability to different environments and production systems in the near future (Kardos *et al.*, 2015).

Accordingly, the need for the adaptation of dairy cattle to imminently emerging environments is a current concern. A recent study compared selection strategies in dairy cattle correlating productive traits (moderately heritable) with adaptive traits (low heritability) using simulations (Strandén *et al.*, 2019). This study concluded that genomic introgression (gene movements) produced more positive genetic change for both production and adaptive traits depending on the weight given to the adaptive or production traits during selection. Furthermore, this genomic introgression system seems to generate a lower risk of inbreeding. In general, results from simulations suggest that genomic selection can effectively introgress a low heritable trait into a target high-production population when the traits, i.e. the introgressed trait and production, are polygenic and genetically non-correlated (Åby and Meuwissen, 2014; Gaspa *et al.*, 2015). Therefore, in the face of constant environmental changes that characterize current times, it is essential to highlight that one solution would point to introducing local adaptive genes in the most important

dairy breeds (Nardone *et al.*, 2006; Hoffmann, 2010) (Berman, 2011; Hoffmann, 2013). This genetic input could be an efficient strategy to introduce adaptive traits into commercial breeds (Strandén *et al.*, 2019; Hoffmann *et al.*, 2021).

It is also important to remark that dairy cattle populations must be prepared for future adaptive scenarios arising from the ongoing climate change. Therefore, the adaptability of animal populations to future environments will be vital for the proper performance of dairy breeds, suggesting that both adaptive and production traits can be simultaneously improved through genomic introgression (Strandén *et al.*, 2019). Therefore, introducing adaptive genes from donor dairy breed populations into less adapted recipient populations should be a central strategy. This introduction of genes would be a compelling way to increase genetic variability and avoid an increase in inbreeding depression and associated adverse effects on different genomic and phenotypic traits.

Strategic priorities to control inbreeding depression

Considering the increase in the annual loss of gene variability in studies involving Holstein sires (Doublet *et al.*, 2019), recent work proposes that inbreeding should be controlled through evaluations based on genotyping because this control will be much more rigorous in genomic-based breeding programs than in those using pedigree for this purpose (Howard *et al.*, 2017; Mäntysaari *et al.*, 2020). Genomic selection has become an established approach and the standard in numerous dairy cattle production systems (Wiggans *et al.*, 2017). Likewise, genomics has now paved the way for an extraordinary increase in genetic progress for most dairy cattle populations by drastically reducing the generation interval (Maltecca *et al.*, 2020). Under genomic selection systems, an increase in the annual cumulative inbreeding rate has been observed due to the shortening of the generation interval through the use of genetic material from genetically related sires (Maltecca *et al.*, 2020). This increase has favored the homozygosity effect to rapidly build up in dairy cattle populations (Howard *et al.*, 2017). Therefore, a better understanding of how homozygosity and recessive load are related will ensure continuous genetic improvement, reduce the accumulation of harmful recessive genes and maintain genetic variability at the population level in dairy cattle (Maltecca *et al.*, 2020). Regrettably, the accumulation of inbreeding depression is the unintended result of how selection has been performed in breeding programs over the past decades (Doekes *et al.*, 2019). Thus, the inbreeding rate per generation could decrease, since genomic selection can be used in a larger pool of candidates as we are not restricted by the limitations of traditional progeny testing systems, which allows only the testing of fewer candidates (Daetwyler *et al.*, 2007; Yurchenko *et al.*, 2018). The degree of inbreeding is an imperfect measure of an individual's underlying recessive load because the accumulation of homozygosity for beneficial variants, compared to neutral or deleterious loci, cannot be distinguished (Gulisija and Crow, 2007). However, information derived from the current genomic analysis methods has identified 18 lethal recessive loci (Cole *et al.*, 2016). Therefore, the possibility to identify such loci with high accuracy may prevent adverse phenotypic effects in future matings, avoiding high inbreeding rates by identifying partial dominance and partial recessives (Jiang *et al.*, 2019).

Estimates of future inbreeding evaluated through pedigree are more subjective and show a greater degree of underestimation (Sell-Kubiak *et al.*, 2018). However, the fact that genomic evaluation of inbreeding is more accurate than inbreeding levels

obtained from pedigrees suggests that genomic inbreeding could better predict the actual recessive load to be taken into account in different dairy cattle breeding programs (Forutan *et al.*, 2018). Therefore, it is essential to highlight the need for the association of genomic and pedigree data to improve the estimation in the prediction of the traits, allowing us to perform matings with open lines of sires and consequently decreasing the degree of inbreeding (Gutiérrez-Reinoso *et al.*, 2020; VanRaden, 2020).

Several state-of-the-art methods, such as those based on high-density single nucleotide polymorphisms (SNPs), are currently emerging as tools for identifying recessive lethal load, and therefore, for the selection of individuals carrying recessive genes (Cole *et al.*, 2016; Maltecca *et al.*, 2020) (Fig. 2). This fact could be considered a possible complementary tool to genome editing when variants are recessive (Cole, 2015). However, a better formulation of different models, including dominance, has recently been achieved. This approach makes dominance estimates free of harmful effects arising from inbreeding (Vitezica *et al.*, 2017).

On dairy farms in different countries, including the USA, inbreeding control programs have been implemented at the population level using projections of expected future inbreeding or future genomic inbreeding (Sun *et al.*, 2014). However, one of the most effective methods for managing long-term genetic variability and inbreeding is optimum contribution selection (OCS). This has been available since the 1990s, although the practical use of this tool has been minimal (Maltecca *et al.*, 2020). Therefore, it is essential to consider which selection allocates the contributions of each potential parent to minimize the overall weighted co-ancestry between prospective parents weighted by their contributions (Meuwissen, 1997).

One of the most important advances obtained to date has been the implementation of several computer methods such as the genomic best linear unbiased predictor (BLUP) of a single step (ssGBLUP) to perform studies of genome-wide association (GWAS), genomic prediction and estimation of several traits, taking into account the inbreeding index (Strandén *et al.*, 2017; Kang *et al.*, 2018). It has also been shown that the use of genomic relationships for inbreeding control is more efficient when assessing very large families of full siblings as opposed to single individuals (Clark *et al.*, 2013). Thus, runs of homozygosity (ROHs) have been proposed as a measure to track autozygosity and recent inbreeding that would be related to the actual recessive load of individuals (Clark *et al.*, 2013; Doekes *et al.*, 2019) (Fig. 2).

Conclusions and future perspectives

Although genome editing technologies facilitate efficient cattle breeding without introducing transgenes, it can be difficult for the public to understand their possible benefits. However, we are currently witnessing that the use of strategies to eliminate deleterious alleles by genome editing is becoming real in cattle breeding, and it promises to be very advantageous. Thus, genome editing could prove helpful in eliminating deleterious recessive alleles identified by bioinformatics screening methods, which use sequence conservation and prior biological information about protein function. Genomics as a tool to control the harmful effects of inbreeding depression will continue to be the methodology of reference in the coming years. It will be increasingly used as an efficient set of methods to control and restrict the accumulation of genome homozygosity in dairy cattle. Breeding programs aim to maintain genetic diversity and limit the buildup of inbreeding, thus maximizing the response to selection. This

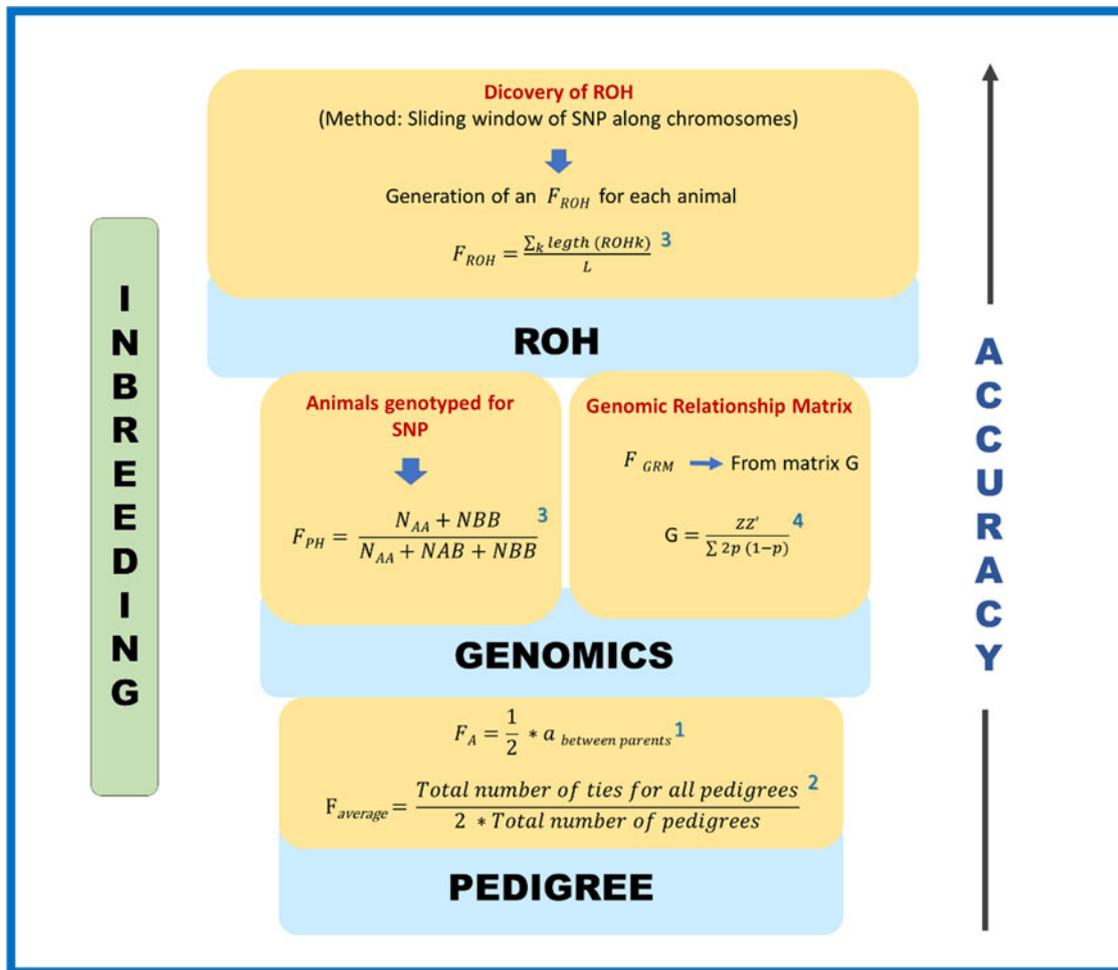


Fig. 2. Main methods for the determination of inbreeding. The inbreeding coefficient (F) has been estimated from the pedigree of animals since around 100 years ago. $A = \text{animal} = \text{offspring}$; $a = \text{additive genetic relationship}$. $F_A \rightarrow [0-1]$, is the probability for each locus of the offspring evaluated to be homozygous because their parents received the same alleles from a common ancestor (Oldenbroek and Waaij, 2014)¹; (Young and Seykora, 1996)². Genomic methods are based on SNPs (Single nucleotide polymorphisms) and provide higher accuracy to F estimation. Besides, the pedigree of animals does not need to be known. F_{PH} = percentage of homozygosity of all SNP. N_{AA} , N_{AB} , N_{BB} = number of SNP classified as AA, AB and BB, respectively. F_{PH} does not distinguish between IBD (Identical by Descent, which what we aim F to be based on, represented by alleles descended from a common ancestor in a base population and IBS (identical by state, identical alleles regardless of whether they are inherited by a recent ancestor or not) (Bjelland *et al.*, 2013)³ G = matrix that contains allele frequencies, in rows $\rightarrow 0 - 2p$ (homozygotes); $1 - 2p$ (heterozygotes); $2 - 2p$ (opposite homozygotes). Columns correspond to each marker. p = allele frequency (VanRaden *et al.*, 2011)⁴. ROH = Runs of homozygosity. F_{ROH} can be estimated genomically. ROHs are a specific number of consecutive homozygous SNP. Inbreeding is characterized by high homozygosity and is highly clustered in the genome sequence space. Therefore, ROHs are long runs of homozygous SNP that become inherited together (Bjelland *et al.*, 2013)³. F_{ROH} is more accurate in the sense that it better detects IBD. F_{ROH} is higher when ROHs are long, and this will be associated with a short distance to common ancestors in the pedigree line (chromatin will not have had time to fragment during meiosis through more generations as would happen when related animals are further back in the pedigree), (Bjelland *et al.*, 2013)³; $\sum_k \text{length}$ = number of ROH discoveries per animal; L = Total genome length (in kilobases, Kb). References: (1) (Oldenbroek and Waaij, 2014) (2) (Young and Seykora, 1996) (3) (Bjelland *et al.*, 2013) (4) (VanRaden *et al.*, 2011).

goal can be achieved by maximizing the effective population size and minimizing the rate of inbreeding through control methods. With the adoption of genomics, the dairy genetics industry is slowly transforming and moving toward scenarios similar to those of other species in which control of population size is critical for inbreeding control in contrast to the information obtained from pedigree data. The combined use of data from pedigree-based relationships, genomics, OCS and ROH, among other methods, will help to improve accuracy at identifying the different lethal recessive loci of full and partial dominance, as well as other loci affecting other full and partial recessive traits. Also, inbreeding more closely related to overall recessive load could be determined either through the use of ROH or age-related partial inbreeding coefficients. Although managing lethal mutations

has become more effective in recent years, considerable economic losses are associated with partial recessive loci of small effect. The significant amount of information gathered in recent years, based on several million individuals genotyped, offers an excellent opportunity to investigate partial recessive load and functional inbreeding depression, thus discriminating homozygosity and its potentially detrimental effects. The identification of truly deleterious partial recessives remains a long-term challenge in dairy cattle. The preservation of genetic diversity in future generations of dairy cattle is necessary to maintain current and future production in different environments. The application of intense genetic improvement and genetic introgression will guarantee increases in the frequency of favorable additive alleles and gene migration between donor and recipient populations. All these pieces of

evidence suggest that genomic evaluation can be a standard tool in programs of reproduction, selection, and genetic improvement of dairy cattle.

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