Symposium review: Exploiting homozygosity in the era of genomics—Selection, inbreeding, and mating programs*

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ABSTRACT

The advent of genomic selection paved the way for an unprecedented acceleration in genetic progress. The increased ability to select superior individuals has been coupled with a drastic reduction in the generation interval for most dairy populations, representing both an opportunity and a challenge. Homozygosity is now rapidly accumulating in dairy populations. Currently, inbreeding depression is managed mostly by culling at the farm level and by controlling the overall accumulation of homozygosity at the population level. A better understanding of how homozygosity and recessive load are related will guarantee continued genetic improvement while curtailing the accumulation of harmful recessives and maintaining enough genetic variability to ensure the possibility of selection in the face of changing environmental conditions. In this review, we present a snapshot of the current dairy selection structure as it relates to response to selection and accumulation of homozygosity, briefly outline the main approaches currently used to manage inbreeding and overall variability, and present some approaches that can be used in the short term to control accumulation of harmful recessives while maintaining sustained selection pressure.

Key words: genomic evaluation, inbreeding, mating

INBREEDING AND GENOMIC INFORMATION

Genomic Selection as a Breeding Standard

After its initial implementation in the US dairy population (Wiggans et al., 2017), genomic selection has become a consolidated approach, which is now the standard in many breeding domains, including the vast majority of livestock (Georges et al., 2019), crop (Wallace et al., 2018), and forestry (Grattapaglia, 2017) species. Although genomic selection has been hailed as a revolutionary shift in animal breeding, it represents the latest in a series of iterations in the improvement of efficiency of selection, which spans a good part of 2 centuries. The discovery of single-gene transmission by Mendel (1965), the theorization of multiple gene inheritance by Fisher (1930), the introduction of pedigree relationships by Wright (1922), the formalization of the selection index by Hazel and Lush (1942), and the implementation of linear mixed models by Henderson (1953) all represent key innovations in the efficiency of discriminating among individuals on the basis of their genetic value that precede the use of genome-wide marker maps in prediction (Meuwissen et al., 2001).

Each of these incremental improvements increased the efficiency of selection. Similarly, and inevitably, these improvements have also resulted in an increase in inbreeding. The accumulation of inbreeding in selected populations is unavoidable, and it is the consequence of intense directional selection, the high disparity of reproductive success introduced by AI and other reproductive advancements, and of the use of BLUP and truncation selection, which favor the overrepresentation of a few elite families (Miglior and Beavers, 2014), leading to large variability in family size and the consequent reduction of the effective population size and higher rates of inbreeding.

How Genomic Selection Affects Inbreeding

Several authors have discussed the influence of genomic selection on inbreeding (Howard et al., 2017a; Varona et al., 2018; Baes et al., 2019). Here, we will briefly recap a few of the main concepts. On one side, under genomic selection, we can observe an increased rate of inbreeding per year due to shortening of the

generation interval. At the same time, the rate of inbreeding per generation should decrease because of our increased ability to discriminate Mendelian sampling among individuals, as well as the ability to access a larger pool of genotyped individuals compared with traditional progeny test schemes (Daetwyler et al., 2007). In general terms, all these phenomena are real. The net result of these combined processes, though, is that under genomic selection, homozygosity accumulates at a faster rate than under pedigree selection. Young bulls' pedigree inbreeding in Holstein has increased from 7.06% in 2012 to 9.59% in 2019. In the same period, genomic inbreeding has increased from 7.89 to 13.02%. Similar estimates can be seen for Jersey (from 6.49 to 8.76% pedigree and 8.93 to 10.87% genomic) and for Brown Swiss (from 7.30 to 9.22% pedigree, and from 8.20 to 10.87% genomic; CDCB April 2019, https://queries.uscdcb.com/eval/summary/inbrd.cfm). Another example of this phenomenon has been documented in French cattle, with a significant increase in pedigree inbreeding for Normande (0.059 to 0.088% per year) and Holstein (0.19 to 0.49% per year) and genomic inbreeding for Holstein (0.080 to 0.55% per year) under genomic selection compared with selection by progeny testing (Doublet et al., 2019).

WHAT DOES INBREEDING MEASURE?

In the previous section, we discussed how the process of selection affects the accumulation of inbreeding. Often, the implicit assumption made concerning inbreeding is that its accumulation is harmful *tout court*. It is important to note that, in itself, inbreeding is neither good nor bad. In selecting for the improvement of a particular trait (in most cases, we are interested in increasing the yield of a particular production trait), the accumulation of homozygosity at favorable variants is the primary objective. This, in turn, has implications for the amount of genetic variability and the response to selection in future generations, which will be discussed later. Accumulation of inbreeding depression is, for the most part, the unintended result of how selection is conducted in breeding programs.

Inbreeding and Inbreeding Depression

A working definition of inbreeding, following that of Malécot (1948), was given by Kimura and Crow (1963) as the probability that 2 random alleles at the same locus from 2 uniting gametes are identical by descent from a common ancestor. At a single locus, in a random mating population, the mean of a population is defined

as $\mu = a(p - q) + 2dpq$, where p and q are the allele frequencies of the locus and a and d are the genotypic values for additive and dominance, respectively (Falconer and Mackay, 1996). Under inbreeding, the previous equation is modified to $\mu = a(p - q) + 2d(1 - F)pq$, where F is the inbreeding coefficient. The population mean, therefore, under inbreeding, is reduced by a quantity of $-2pqFd$. This reduction is usually referred to as inbreeding depression. The first thing to notice is that the insurgence of inbreeding depression depends on dominance. If no dominance is present, the change in population mean will be zero, and inbreeding will not have an effect on the population. Conversely, for a single locus, if $d > 0$, inbreeding will decrease the mean of the population and if $d < 0$, inbreeding will increase it. If we generalize this to multiple loci, the insurgence of inbreeding depression requires dominance to be directional (dominance effects are, on average, negative). This agrees with empirical results, and recessive deleterious mutations and partial directional dominance are normally considered the drivers of inbreeding depression (Charlesworth and Willis, 2009) and are usually referred to as genomic or recessive load. Under this scenario, deleterious alleles are (partially) recessive and are generated by recurrent mutation so that deleterious alleles in the "base" population are present in the heterozygous state. Inbreeding increases the frequency of homozygotes for deleterious alleles as a result of selection and drift, which results in inbreeding depression (Falconer and Mackay, 1996).

Genetic Variance Under Inbreeding

The relationship of inbreeding with genetic variance is nuanced. The total genetic variance under inbreeding as defined by Weir and Cockerham (1977) can be given by the formula

$$V_{GF} = (1 + F)V_A + (1 - F)V_D + \ldots,$$

where V_A and V_D are the additive and dominance variances and "..." are the remaining terms related to the covariance between additive and dominance as well as the variance of inbreeding depression itself; they are omitted here for simplicity but an extensive treatment of the subject can be found in Abney et al. (2000). It should be noted that in the absence of dominance variation, the total genetic variance is given by $(1 + F)V_A$ and is larger than that for the founder population. This holds only in the absence of dominance, and results with nonadditive variation are more complex (Walsh and Lynch, 2018).

PRIMARY QUESTION

Given what we have outlined above, it should be evident that inbreeding is an imperfect measure of the underlying recessive load of an individual because it cannot distinguish the accumulation of homozygosity for favorable variants, compared with neutral or deleterious loci. Some populations, such as US Jersey cattle, have even undergone purging inbreeding (Gulisija and Crow, 2007). Two individuals could therefore, in principle, have the same inbreeding coefficient but a different deleterious load, simply because inbreeding has been accumulated in different regions of the genome. A perfect inbreeding management strategy would allow discrimination between these 2 individuals based on the amount of deleterious recessive each carries.

Identifying Lethals and Sublethals

Genomic information has made the identification of lethal recessives extremely effective. To date, at least 16 known recessives are tracked in the US dairy population (Cole et al., 2018). This is partly due to the increased resolution that larger marker panels and sequence information provide, facilitating the detection of lethals via reverse genetic screening (Charlier et al., 2016), but it also stems from the fact that recessives can be identified, at least in the first instance, with simple statistical tools, essentially by tracking distortions from the expected genotypic frequencies (VanRaden et al., 2011a). When recessives are identified with a high degree of accuracy, then mating avoidance can be effectively deployed. Cole et al. (2016) estimated annual losses of at least $10.7 million due to known recessives. As the number of recessives identified increases, managing them through mating becomes more involved. Heuristic methods have been proposed by Cole (2015) to manage the total lethal recessive load. More recently, Johnsson and colleagues (2019) proposed the use of genome editing to remove deleterious recessives. When mutations in the population are partially dominant and harmful but have small to moderate-sized effects, methods based on genotype frequency distortions are not a viable solution. The identification of partially detrimental recessives then has to rely on the estimation of dominance effects. Unfortunately, this presents several challenges. The proportion of genetic variance at a causal variant that is captured by markers is ρ^2 for additive variants, but ρ^4 for dominant variants, where ρ is the allelic correlation (Zhu et al., 2015). Additive and dominance effects are, in general, not independent either because of linkage disequilibrium or by virtue of true covariance between the 2 effects (Huang and

Mackay, 2016). Finally, given the need for directionality of dominance variation, the effect of dominant variants should already be partially accounted for by inbreeding (Xiang et al., 2016). To the last point, a better formulation of models including dominance has been recently proposed by Vitezica et al. (2017), which makes dominance estimates free of inbreeding effects. In spite of this, the identification of partial dominance variants remains a difficult task. As the number of individuals genotyped and marker resolutions increase, our ability to identify partial dominance and partial recessives will also increase (e.g., Jiang et al., 2019). In the short term, heuristic approaches aimed at identifying haplotypes of negative effect (regardless of their mode of action), as proposed by Howard et al. (2017b), or, to a larger extent, methods to constrain homozygosity accumulation based on genome-wide measures of inbreeding will remain the most effective approaches.

Global Measures of Inbreeding and Recessive Load

Although estimates of genomic values have received a lot of attention in the past few years, estimates of inbreeding depression in dairy are less common in the literature. Miglior and colleagues (1995a,b) estimated the impact of inbreeding depression in health and production traits in Canadian dairy cattle using non-additive genetic models. A 1% increase in inbreeding resulted in a 0.01 increase in lactation SCS (Miglior et al., 1995a), 25.1 kg less milk, 0.9 kg less fat, 0.8 kg less protein, and an increase in fat and protein percentage of 0.05% (Miglior et al., 1995b). Smith et al. (1998) indicated that a 1% increase in the inbreeding coefficient of Holstein resulted in 37 kg less milk, 1.2 kg less fat, and 1.2 kg less protein per lactation, along with increases in first-calving age of 0.4 d and calving interval of 0.3 d, and a reduction in length of productive life of 13.1 d. More recent studies (Pryce et al., 2012; Cole, 2015; Doekes et al., 2019) have substantially confirmed these figures. In Table 1 are reported the current estimates of inbreeding depression used by the Council of Dairy Cattle Breeding and their impact on the Net Merit index. Table 2 reports the $-\log_{10}(P$-values) and estimates of pedigree genomic inbreeding depression obtained from yield deviations of a sample of approximately 15,000 Holstein cows born between 2013 and 2015. Estimates of inbreeding depressions were higher for all traits compared with those currently used in PTA correction, but that may reflect the small sample size in the analysis, rather than actual differences in population values. Interestingly, in all cases, the significance of genomic inbreeding was higher than that of pedigree inbreeding, suggesting that genomic

Table 1. Inbreeding (F) depression and Net Merit value for US dairy

Trait	Inbreeding depression (1%)	Trait value in Net Merit, $	Value, $ (1% F)
Milk (lb)	−63.90	−0.004	0.30
Fat (lb)	−2.37	3.56	−8.40
Protein (lb)	−1.89	3.81	−7.20
Productive life (mo)	−0.26	21.00	−5.50
SCS	0.004	−117.00	−0.50
Daughter pregnancy rate	−0.13	11.00	−1.40
Cow conception rate	−0.16	2.20	−0.40
Heifer conception rate	−0.08	2.20	−0.20
Cow livability	−0.08	12.00	−1.00
Net Merit $	−25.00	1.00	−25.00

inbreeding might better capture the underlying true recessive load, in accordance with what was shown by Forutan and colleagues (2018).

MANAGING INBREEDING GLOBALLY AND LOCALLY WITH THE USE OF GENOMIC INFORMATION

Every breeding program aims at maintaining genetic diversity and limiting the inbreeding accumulation while maximizing the response to selection. This is achieved by maximizing the effective population size and minimizing the rate of inbreeding. Currently, inbreeding in the US dairy is controlled at the population level with the use of expected future inbreeding or genomic future inbreeding (Sun et al., 2014). These quantities are the average (pedigree/genomic) inbreeding expected when a bull is mated to a random sample of cows in the population so that the higher the ratio of expected to genomic future inbreeding, the more related the bull is to the current population (VanRaden et al., 2011b). Minimization of progeny inbreeding (Pryce et al., 2012), linear programming (Weigel, 2001), look-ahead mate selection (Shepherd, 2005), selection against lethal alleles (Van Eenennaam and Kinghorn, 2014; Cole et al., 2016; Upperman et al., 2019), index selection including Mendelian variance (Santos et al., 2019), and genomic selection including dominance (Sun et al., 2014) have all been proposed as methods to controlling inbreeding.

One of the most effective methods to manage genetic variability and inbreeding over the long term is optimum contribution selection (**OCS**; Meuwissen, 1997). Optimum contribution selection assigns the contributions from each potential parent by minimizing the global coancestry between prospective parents weighted by their contributions. Although OCS has been available since the 1990s, its practical use has been limited in dairy cattle populations. There are several reasons for its limited adoption, but probably the main limiting factor resides in the structure of dairy breeding. In vertically integrated industries, such as swine or poultry breeding, decisions are centralized at the nucleus level. However, the dairy industry remains fragmented, and breeding decisions ultimately rest with individual farmers. This makes the application of systemic approaches logistically challenging. With the adoption of genomics, though, the dairy genetic industry is slowly reshaping, moving toward scenarios more similar to those of other livestock where tighter control of the population size and structure is possible. Within this context, OCS is probably destined to regain momentum. To this extent, the availability of genomic data offers an opportunity to apply OCS with a broader range of options com-

Table 2. Significance $[-\log_{10}(P\text{-value})]$ and regression coefficients for 1% increase in genomic or pedigree inbreeding (F)

| Trait	Pedigree F		Genomic F	
	$-\log_{10}(P\text{-value})$	Regression coefficient (1%)	$-\log_{10}(P\text{-value})$	Regression coefficient (1%)
Milk (lb)	4.95	−78.1	8.06	−81.2
Fat (lb)	4.67	−3.63	9.96	−3.58
Protein (lb)	3.18	−1.81	7.47	−2.86
Productive life (mo)	0.33	−0.56	1.5	−0.85
Daughter pregnancy rate	0.57	−0.12	0.8	−0.02
SCS	0.11	−0.08	0.14	∼0

pared with pedigree information (Clark et al., 2013). Genomic-derived breeding value estimates can explain a portion of Mendelian sampling variation and, therefore, can explain more than the parent-average EBV. Previous research has shown that using genomic relationships to control inbreeding, as an alternative to pedigree relationships, resulted in no additional genetic gain, except in the case of very large full-sib families (Clark et al., 2013). Engelsma et al. (2011) showed that the benefits of using either the pedigree or the genomic relationship in OCS algorithms vary across the genome. Still, on average, the difference between the two is small. In all of these cases, though, little was done to track the actual recessive load of individuals. Recent inbreeding produces long stretches of DNA shared by individuals. These, in turn, will be enriched with deleterious variants that have been exposed to purging opportunities for less time. Runs of homozygosity (**ROH**) have been proposed as a measure to track recent autozygosity and better capture recent inbreeding that is more related to the actual recessive load of individuals (Doekes et al., 2019). Howard and colleagues (2017a), among others, have discussed the use of alternative metrics to measure inbreeding, yet little is known about the long-term impact of using pedigree, genomic, or ROH measures on genetic gains, or about the accumulation of harmful mutations in a population.

CASE STUDIES

### Case Study 1: Simulation Study on the Optimal Contribution

In this section, we present a case study in which we have investigated the use of alternative metrics of ancestry in OCS for simulated scenarios using genomic information. A production trait and a fitness trait were generated with GenoDiver (Howard et al., 2017c) software following typical genetic architectures of dairy populations. We simulated a polygenic yield trait ($h^2 = 0.45$; 1,000 QTL). A fitness trait was simulated under partial dominance, with a proportion of lethal loci of 5% of the total number of fitness trait loci (**FTL**); then, OCS was simulated for 30 generations. At each generation, genomic information was used to obtain breeding values of individuals, whereas different measures were used for the optimal contribution portion; namely, relationships based on pedigree, genomic, and 2 different types of ROH (5 and 10 Mb). Selection was performed only on the production trait. Genetic progress for all scenarios was measured at the end of the 30 generations, along with fitness parameters, which included homozygosity and segregating sublethal alleles.

Genome Architecture. A total of 54,240 biallelic markers (minor allele frequency = 0.10) were generated
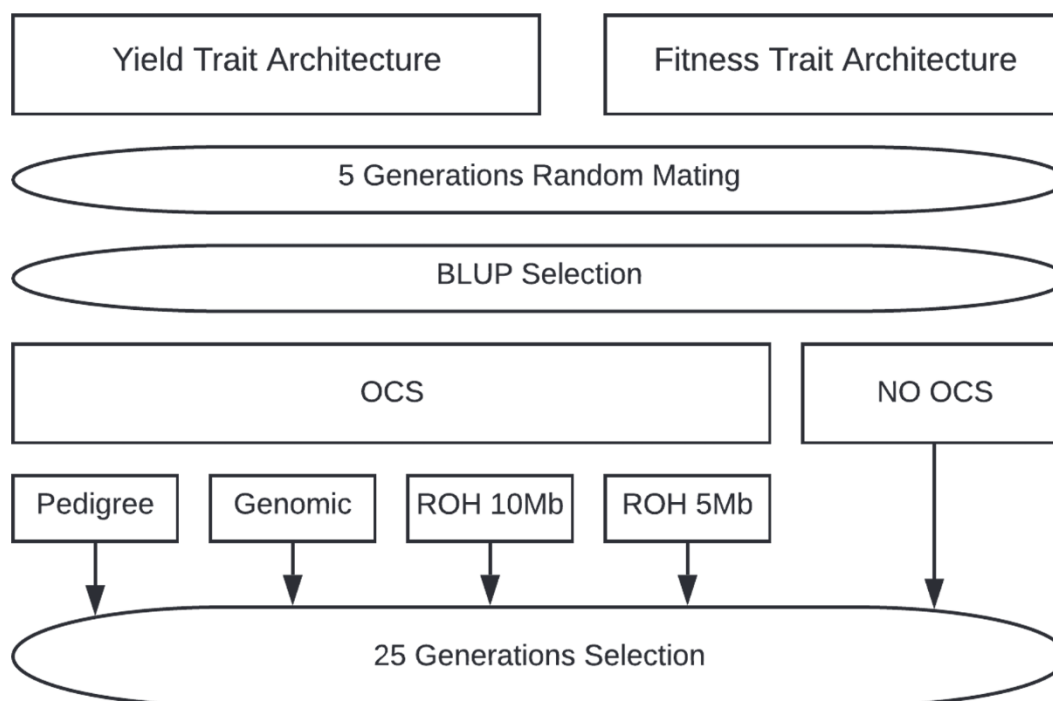
Figure 1. Simulation architecture of case study of alternative metrics of ancestry in optimum contribution selection (OCS) using genomic information. Each simulation was repeated 10 times. ROH = runs of homozygosity.
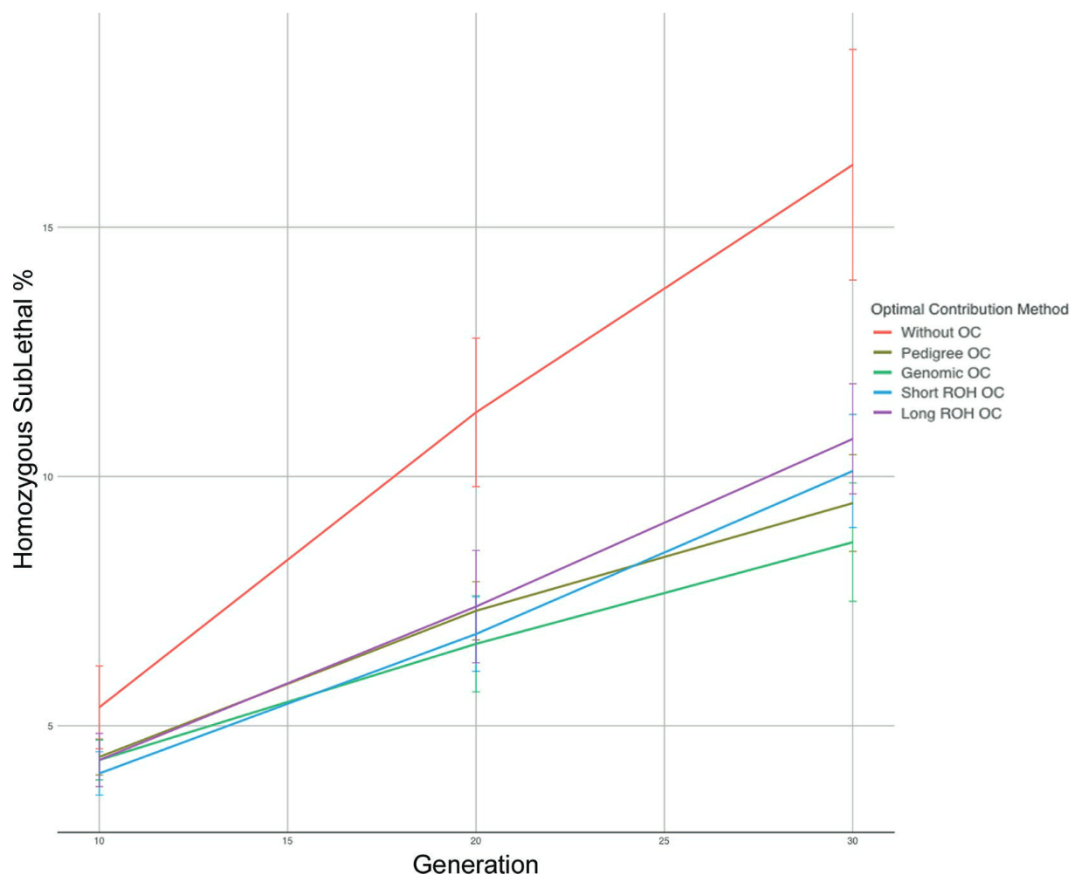
Figure 2. Increase in overall population homozygosity in the simulated scenarios. Without OC = no optimal contribution selection (OCS); pedigree OC = pedigree OCS; genomic OC = genomic OCS; short ROH OC = 5-Mb runs of homozygosity (ROH) OCS. Long ROH OC = 10-Mb ROH OCS.

distributed over 29 autosomes using GenoDiver v. 3.0. Parameters were chosen to obtain a base population and effective population size of approximately 100. A population of 400 males and 1,000 females was then created and retained as a base for the remaining of the simulations.

Yield Trait Architecture. One thousand QTL with additive effects were generated randomly across the 29 autosomes. All QTL were generated from a gamma distribution with shape and scale of 0.4 and 1.66, respectively. A minor allele frequency of 0.05 was adopted for QTL in the base populations. Genetic architecture was completely determined by the QTL with an h^2 of 0.45.

Fitness Trait Architecture. The generation of FTL was split among lethal and sublethal recessives. For both categories, fitness was defined as relative fitness and parameterized in terms of selection coefficient (s) and dominance coefficient (h) (Wright, 1931). Selection coefficients were generated from a gamma distribution with different parameters for lethal and sublethal variants. As a result, sublethal loci had a mean frequency

0.03 with a mean selection coefficient of 0.013 and a mean degree of dominance of 0.296. An upper threshold on sublethal loci frequency in the base population was placed at 0.08. Conversely, lethal alleles had a mean frequency of 0.013, a mean selection coefficient of 0.72, and mean degree of dominance of 0.001. An upper threshold on lethal loci frequency was placed at 0.05. One thousand FTL were generated for the fitness trait.

Covariance Between Fitness and Quantitative Traits. A pleiotropic covariance between the quantitative and fitness trait of 0.2 was simulated using a trivariate reduction algorithm.

Selection and OCS. At each generation, 50 males and 200 females were selected and mated based on their genomic breeding values obtained through genomic BLUP (VanRaden, 2008). The replacement rate for each generation was 0.8 for sires and 0.3 for females. Each mating resulted in 3 progenies (this was done to ensure that enough individuals were available for replacement at each generation). At each generation, optimal contribution selection was performed using the software "eva"

(Berg et al., 2006). Four different metrics were used for the OCS portion of the simulation. Relationships were constrained based on pedigree; a realized genomic relationship obtained using the VanRaden algorithm number 2 (VanRaden, 2008), with allele frequencies obtained from the base population after the random mate stage; or ROH relationship matrices (Luan et al., 2014) for ROH of 5 and 10 Mb, respectively. Details on how these were obtained can be found in Howard et al. (2016). Each scenario was replicated 10 times. A pictorial schematic of the overall simulation is reported in Figure 1.

Results. In all cases, performing no OCS resulted in higher inbreeding, with homozygosity levels approximately 10% higher for "no OCS" scenarios compared with all other scenarios (Figure 2). As expected, when comparing the different inbreeding metrics used in OCS, genomic information obtained from the diagonal of the genomic relationship matrix was best at constraining the increase of homozygosity, whereas pedigree information was the worst. The ROH measures were intermedi-

ate between pedigree and the GRM. Again, this was expected because ROH minimizes only the portion of homozygosity that resides in long, contiguous stretches of the genome, not the overall homozygosity.

Overall homozygosity measures do not truly reflect the recessive load of the populations under different scenarios. Figure 3 reports the average percentages of sublethal alleles carried at homozygous state. In this case No_OCS resulted in a higher accumulation of recessive load. All OCS methods constrained the accumulation of sublethal homozygous effectively. The ROH measures were intermediate between pedigree and genomic. Genetic progress for the simulated scenarios is reported in Figure 4. No OCS resulted in the highest genetic gain, followed by ROH, genomic OCS, and pedigree OCS. It should be noted that in this respect the simulation is simplistic because it assumes that no new additive (or dominance) variation is generated and that genomic architecture remains constant over time. This might not be the case in real scenarios and results need to be interpreted with caution. Furthermore, as
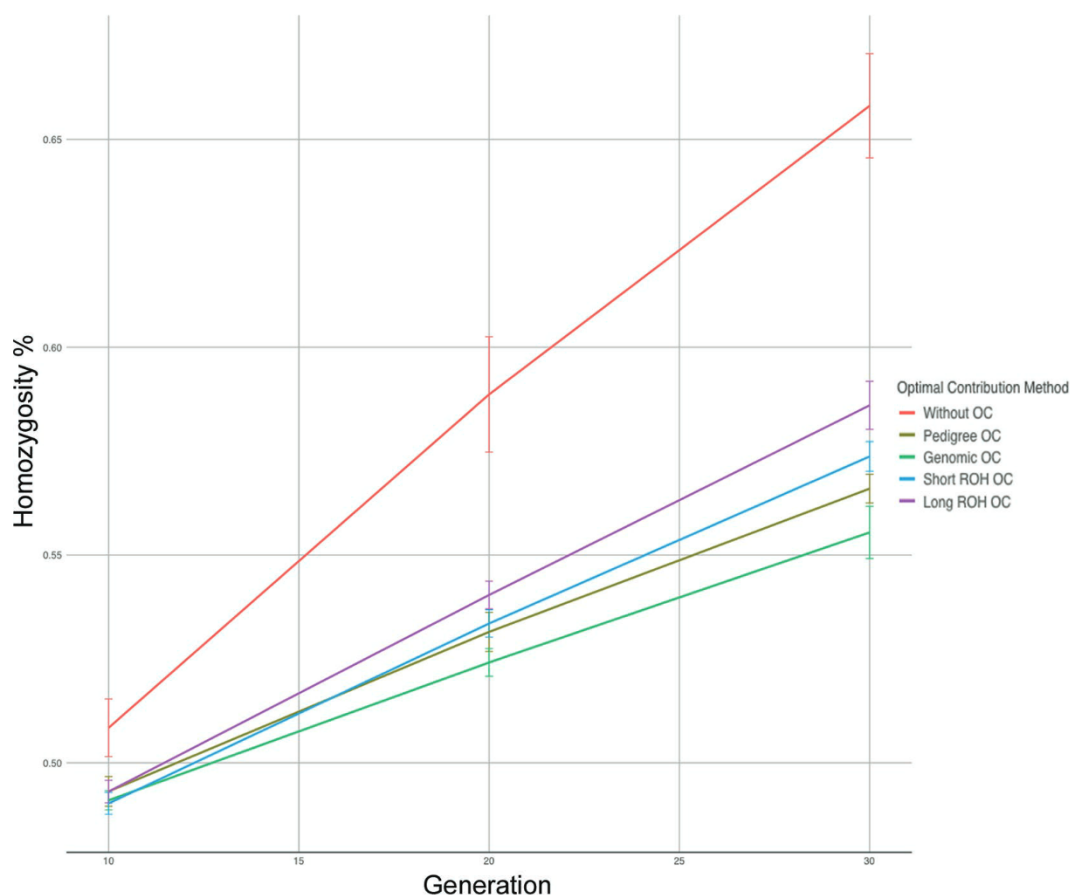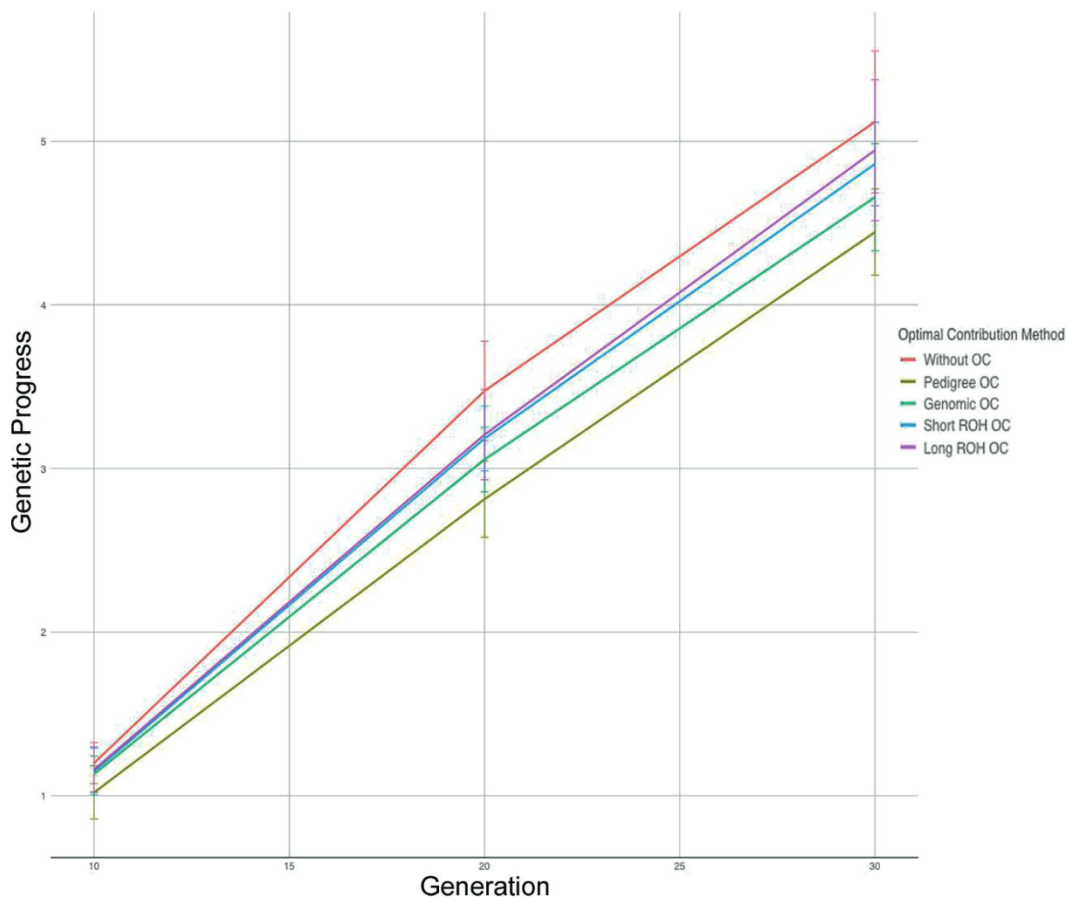

Figure 3. Increase in homozygous sublethal over generations in the simulated scenarios. Without OC = no optimal contribution selection (OCS); pedigree OC = pedigree OCS; genomic OC = genomic OCS; short ROH OC = 5-Mb runs of homozygosity (ROH) OCS. Long ROH OC = 10-Mb ROH OCS.

a consequence of this simplification, the exhaustion of current genetic variability reflects the "success" in selection.

Case Study 2: Characterization of the Age of Inbreeding

The premise of using ROH as a measure of inbreeding is related to the need to control recent inbreeding, the one for which deleterious variants had a relatively short purging opportunity. Among the disadvantages of ROH measures of inbreeding is the need to establish an arbitrary cutoff delimiting the ROH (and, therefore, the time considered). Often, this threshold is based on the a priori expectation of the investigator. Druet and Gautier (2017) presented an alternative, elegant, and self-contained approach to this problem. In their work, they aimed at identifying segments of the genome that are homozygous by descent (**HBD**). These segments occur when individuals inherit copies of an ancestral chromosome. As for ROH, the length of the HBD depends on the number of generations and the population's structure. But unlike ROH, HBD are explicitly modeled through a hidden Markov model. The result is that the overall inbreeding can then be divided into different age classes, and these classes can then be related to the total depression load based on their age. In Figure 5, the HBD distribution of the 15,000 Holsteins described in previous sections is reported. Individuals had genotypes available for 67,904 SNP markers. For this analysis, the R package "RZooRoH" (Bertrand et al., 2019) was used, which implements the method of Druet and Gautier (2017) described above. Partial homozygosity was obtained for a power of 2 series, including inbreeding from approximately 1 to 256 generations ago. In Figure 5, it can be seen that most of the inbreeding in the individuals is concentrated between 4 and 16 generations ago. It is also evident that considerable variability in class distribution is present among individuals. This can be better observed

Figure 4. Genetic progress (in yield units) in the simulated scenarios. Without OC = no optimal contribution selection (OCS); pedigree OC = pedigree OCS; genomic OC = genomic OCS; short ROH OC = 5-Mb runs of homozygosity (ROH) OCS. Long ROH OC = 10-Mb ROH OCS.

in Figure 6, in which a random sample of individual partial inbreeding coefficients are depicted based on their age of inbreeding. It is evident that for different individuals with similar overall inbreeding, the contribution of partial inbreeding of different age can vary dramatically. To explore the potential effect of age of inbreeding on inbreeding depression, we regressed these partial coefficients on yield deviations, as outlined in the previous section. In Table 3 we report the partial regression coefficients for inbreeding grouped from 1 to 4 generations ago and from 4 to 64 generations. The grouping was, in this case, done arbitrarily to explore old versus new inbreeding; inbreeding of >64 generations ago was excluded under the assumption that it would need to be mostly free of deleterious variants and in recognition of the small sample of individuals used. More in-depth analysis with a larger collection of individuals, possibly across breeds, would need to account explicitly for all partial inbreeding coefficients. In all cases, inbreeding depression estimates were higher for more recent inbreeding than for older inbreeding. Estimates were also higher than those obtained by both pedigree and genomic information, possibly highlighting that partial inbreeding estimates tend to overestimate real inbreeding depression because they are likely not independent. In addition, a scaling effect might result in different levels of inbreeding depression, given that partial inbreeding estimates might have different variances. Finally, as inbreeding in different classes is also a function of marker density, it is possible that denser marker density would be needed to capture smaller segments (and their associate effects). More research in this area is needed to highlight the possible use of age-related HBD partial inbreeding coefficients.

FINAL REMARKS

The adoption of genomic information as standard practice in dairy breeding has facilitated considerably increased genetic progress, yet it poses a challenge for the maintenance of long-term variability and the accumulation of harmful mutations. Average losses due to known recessives affecting fertility are currently estimated at $5.77, $3.65, $0.94, and $2.96 in Ayrshire, Brown Swiss, Holstein, and Jersey, respectively (Cole et al., 2016). Although management of lethal mutations has become more effective in recent years, a large proportion of these economic losses is tied to partial recessives of small effect. The incredible amount of information accumulated in recent years, with more than 2 million cows genotyped, offers a unique opportunity to investigate partial recessive load and functional inbreeding depression, thus discriminating homozygosity on the basis of its potential detrimental
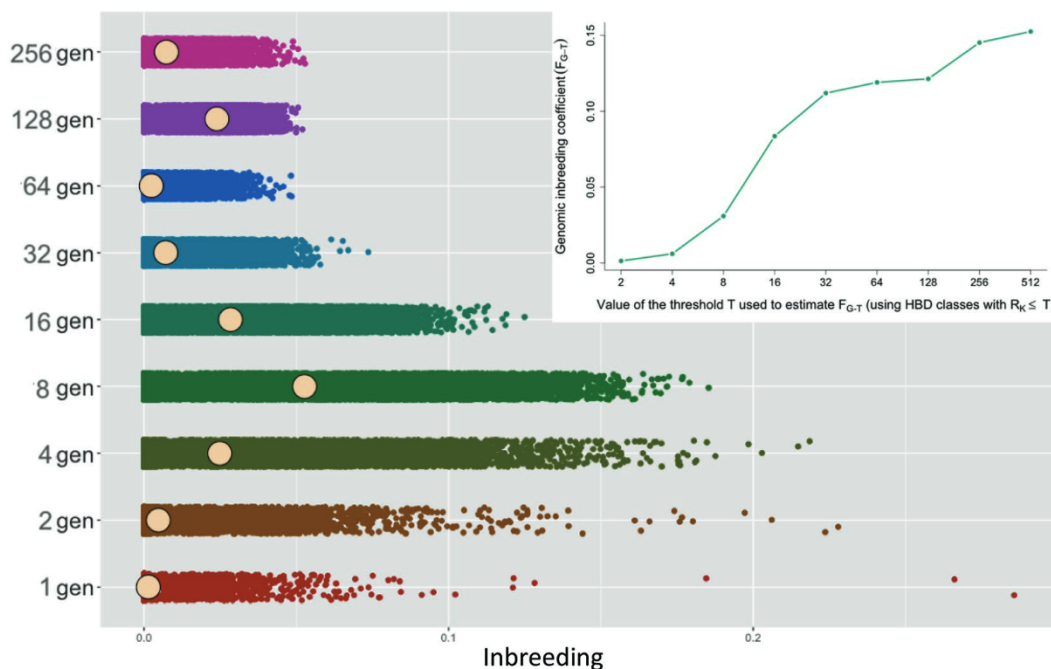
Figure 5. Distribution of partial inbreeding coefficients (F) for age of inbreeding; gen = generation; HBD = homozygous by descent; R_K = no. of generations threshold.
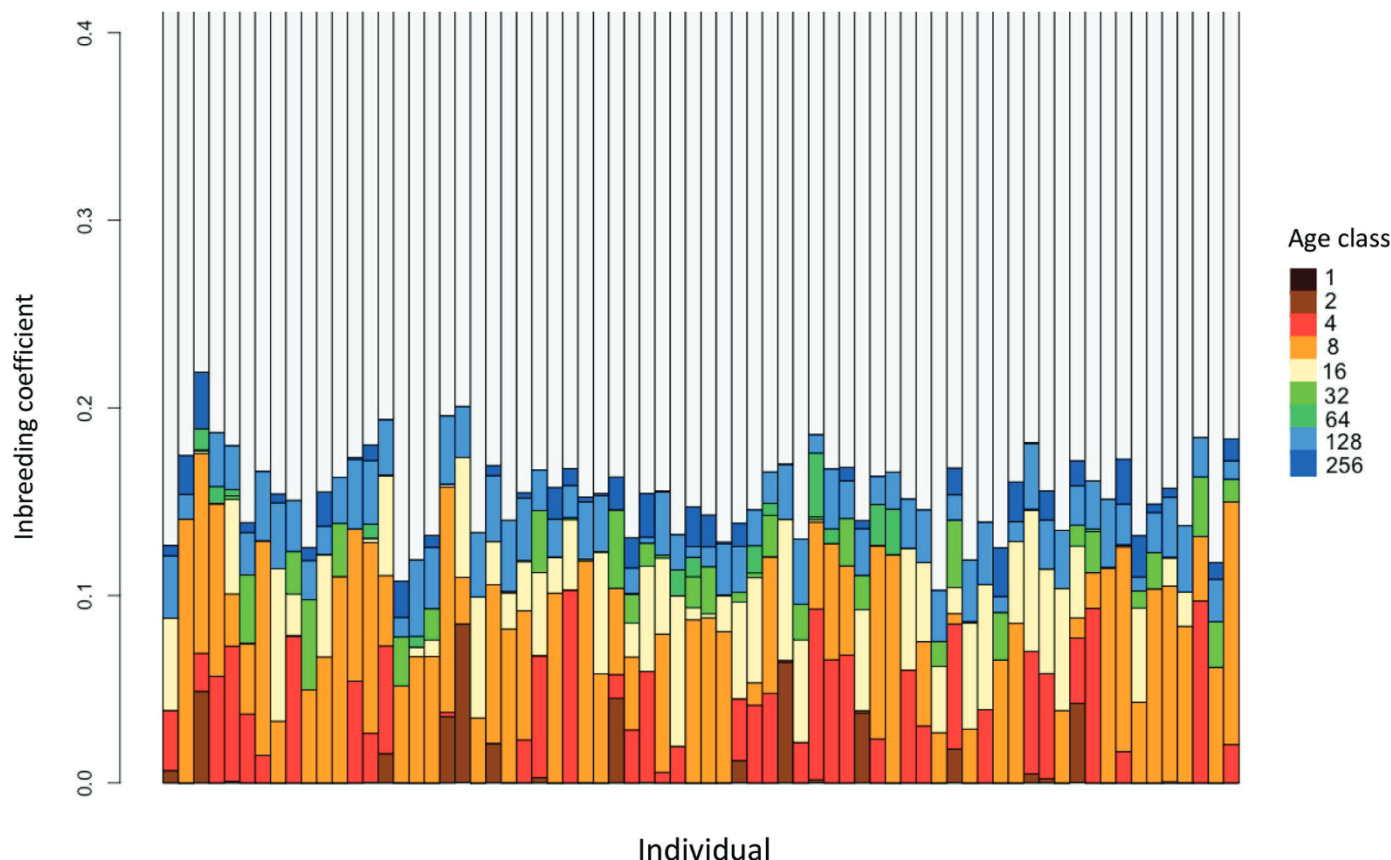
Figure 6. Distribution of class of inbreeding, based on age for a sample of Holstein cows. Age class represent age of inbreeding.

effect. The identification of true deleterious partial recessives remains a long-term challenge. To this point, an important contribution to the understanding of the basic mechanisms of inbreeding depression and heterosis in the dairy population will be made by the growing number of crossbred individuals that are currently being genotyped. In the short term, measures of overall inbreeding more closely related to the overall recessive load could be used, either through the use of ROH or age-related partial inbreeding coefficients.

Table 3. Regression coefficients for a 1% increase in genomic homozygous-by-descent inbreeding classes for generations 1 to 4 and 4 to 8

Trait	Partial inbreeding regression coefficient	
	Generations 1–4	Generations 4–8
Milk (lb)	−118.3**	−78.3**
Fat (lb)	−4.4**	−3.82**
Protein (lb)	−3.38*	−2.60*
Productive life (mo)	−0.83*	−0.32*
Daughter pregnancy rate	−0.14*	−0.04
SCS	0.003	0.002

**$P < 0.01$; * $P < 0.05$.

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