Selection, inbreeding and mating

Selection *Selection of breeding animals*	• Number of selected bulls - Genotyped → bought → reproductive start → large scale production • Number of selected females - Genotyped → contracted → reproductive start → large scale production • Average relationship in the different selection steps

Inbreeding *Inbreeding level*	• Rate of inbreeding (pedigree and genomic based) - Production population, breeding animals and reference population • Bull and female contribution • Yearly check new literature covering genomic information and inbreeding - Track changes (Genomic/pedigree)
Inbreeding *Control of lethal alleles*	• Plan to test, handle and control lethal alleles within and across breeds - Frequency in: population, breeding animals, reference population - Economic effect - Publish proved lethal alleles - Plan for usage of carriers in the breeding scheme • Yearly check law

Mating design	• Use minimum co-ancestry or minimizing the covariance between ancestral genetic contribution • Success rate with wanted matings - Time between semen released and enough breeding animals are inseminated • Variation in number of used sires - Mating programs - High index animals • Plan to handle and control lethal alleles - Mating programs - High index animals - Reproductive technology programs

Selection *Selection of breeding animals*	
Number of selected bulls Genotyped → bought → reproductive start → large scale production	Number of selected bulls in the different steps to track differences over years. To see weak points and rooms for improvements.
Number of selected females and average relationship in the different selection steps Genotyped → contracted → reproductive start → large scale production	Number of selected females in the different steps to track differences over years. To see weak points and rooms for improvements. Track average relationship in the different selection steps.

Inbreeding *Inbreeding level*	
Rate of inbreeding (pedigree and genomic based) - Production population, breeding animals and reference population	Rate of inbreeding (pedigree and genomic based) in production population, breeding animals and reference population. FAO upper guidance 1 % for a healthy population.
Bull and female contribution	Bull and female contribution to the inbreeding.
Yearly check new literature covering genomic information and inbreeding	To stay updated: check literature and talk to researcher about the topic.
Inbreeding *Control of lethal alleles*	
Plan to test, handle and control lethal alleles within and across breeds	Plan to test, handle and control for the different lethal alleles. Both within and across breeds to track them.
Plan for usage of carriers in the breeding scheme	Plan for usage of carriers in the breeding scheme

Frequency in: population, breeding animals, reference population	Track frequency in the population, breeding animals and reference population.
Economic effect	Estimated economic effect of the different lethal alleles.
Publish proved lethal alleles	Lethal alleles should be published so they can be avoided in the mating programs.

Mating design *Mating design*	
Use minimum co-ancestry or minimizing the covariance between ancestral genetic.	Use minimum co-ancestry or minimizing the covariance between ancestral genetic.
Success rate with wanted matings - Time between semen released and enough breeding animals are inseminated	Successful/all suggestions in the mating program. How much genetic gain if not all are successful. What is the average time between semen start and required number of breeding animals are inseminated?
Variation in number of used sires	Is there variation in number of use sires? In mating programs and high index animals.
Plan to handle and control lethal alleles	In mating programs, high index animals and reproductive technologies.
Plan to handle and control lethal alleles - Mating programs - High index animals - Reproductive technology programs	Plan to handle and control lethal alleles in the mating program, high index animals and in the reproductive technology programs.

Breeding scheme *Evaluation*	
Genetic trends for total merit	Track trends for total merit.
Check genetic trends for all breeding goal traits - Within and across countries	Track trends for all breeding goal traits. Are there differences between countries?
Phenotypic trends in main breeding goal traits	Phenotypic trends in main breeding goal traits over time to check breeding scheme.
Cost per dose of semen - Sold and produced	Could in cases be a good KPI to evaluate efficiency of the breeding scheme. Check both sold and produced.
Yearly track law changes - Impact on breeding scheme	Check law changes that could have impact on the breeding scheme. For example: You have to register a certain phenotype correct which could affect quality.
Action plan for ethical aspects	Plan for ethical aspects to be able to argue for decisions. Some examples: gen editing, cloning.

Breeding scheme *Evaluation*	• Genetic trends for total merit - Check genetic trends in main breeding goal traits - Within and across countries • Phenotypic trends in main breeding goal traits - Within and across countries - Females and bulls • Cost per dose of semen - Sold and produced • Yearly track law changes - Impact on breeding scheme • Action plan for ethical aspects - For example: gen editing, cloning

Comments:

Inbreeding – Literature review

Inbreeding has been shown to lower the mean phenotyping performance in the inbred animal and also increase the homozygosity levels in the whole population. In general traits associated with survival and fitness like reproduction and health are more susceptible (Miglior et al., 1995). Before the genomic era an increase in genetic gain has been associated with increased inbreeding. However, with genomic information the Mendelian sampling can be better predicted and full sibs can have different breeding values before phenotypic performance is available. The opportunity to select within families could result in less inbreeding (de Roos et al., 2011; Hayes et al., 2009a; Daetwyler et al., 2007).

Lillehammer et al. (2011) estimated that a juvenile scheme led to less inbreeding and higher genetic gain compared to a conventional progeny testing scheme. In general genomic relationships will obtain more information than pedigree-based relationships, due to the use of genetic markers. (Pryce et al., 2012b).

Lethal recessive defects may often be assumed when a homozygote is missing in a population (VanRaden et al., 2011). The access to genomic information from genotyped animals makes it possible to find and keep track of recessive genetic disorders. Several research groups have screened the genomic evaluation genotype pool and found recessive fertility haplotypes (HH1-HH5) in the Holstein breed. In homozygote form the haplotypes (HH1-HH5) can cause embryonic losses and thereby lead to decrease in fertility (VanRaden et al., 2011; Sahana et al., 2013; Cooper et al., 2013; Fritz et al., 2013).

Mating design for control of inbreeding – Literature review

Mating design structure is an important part of dairy cattle breeding to increase long term genetic gain (Caballero et al., 1996; Sonesson and Meuwissen, 2000). However, it has been suggested that mating designs have received less attention since the introduction of genomic (Henryon et al., 2014). Improved mating plans can improve long-term genetic gain by better family structure. Genomic information might have the possibility to separate genetic contribution more effectively than pedigree information (Henryon et al., 2014).

Liu et al. (2016) studied in a simulation study mating designed regarding inbreeding and genetic gain. The study compared two mating strategies with pedigree and genetic information. The two mating strategies were minimum co-ancestry (MC) and minimizing the covariance between ancestral genetic contribution (MCAC). The result showed that MC and MCAC with genomic information could without reducing genetic gain reduce inbreeding by 6% to 22% compared to MC and MCAC with pedigree information (Liu et al., 2016).

Selection – Literature review

Optimum-contribution selection (OCS) has been the choice for many conventional breeding schemes (Woolliams, 2007). The theory is that OCS maximizes long-term genetic gains by maximizing the weighted-genetic merit of selected parent and at the same time constraining the relationship between the parents (Wray and Goddard, 1994). Genomic information can contribute more information to OSC. It may trace inheritance of chromosomal segments and estimate more accurately relationships between animals. In practice this means that OCS could help to select candidates carrying favorable but different chromosomal segments from ancestral animals (Henryon et al., 2014).

Control of lethal alleles – Literature review

Pryce et al. (2012b) investigated 3 strategies for controlling estimated progeny inbreeding in dairy cattle mating plans. The strategies used pedigree inbreeding coefficients, genomic relationships or shared runs of homozygosity. The parameters were genetic gain, progeny inbreeding and the decrease of homozygosity of recessive alleles. Real pedigree genotypes with 43,115 SNP and LD genotypes with 3,123 SNP markers and GEBV from Holstein cattle were used. The study was replicated 50 times and herds consisted of 300 cows and 20 sires were available for mating. Each of the 300 cows were matched to the 1 of 20 sires, with the focus of maximize the genetic gain minus penalty for estimated progeny inbreeding. In addition, the sires could not be mated to more than 10% of the cows. The result showed that the strategies using a genomic relationship matrix (GRM) were more effective in reducing average estimated progeny inbreeding. The GRM strategies also resulted in fewer homozygous SNP. The results from the 43,115 SNP and the LD 3,123 SNP gave similar results. A 1% reduction of inbreeding valued as $5 per cow could be made with little compromise in the overall breeding objective (Pryce et al., 2012b). Cole et al. (2015) modified Pryce et al. (2012b) by also taking economic effects into account. The modified version showed similar effects in reducing estimated inbreeding and lethal alleles. However, the modified version outperformed regarding low-frequencies alleles with small economic effects (Cole et al., 2015).

Egger-Danner et al. (2014) studied genetic defects in Austrian Fleckvieh and what effect erasing lethal alleles carriers from the breeding programs would have on the genetic gain and discounted profit. The allele frequency varied from 0.5% to 7% and the study included 6 genetic disorders. When all bulls were erased from both herdbook cows and mating plans the losses summed up to 7% AMGG and 9% discounted profit.

Selection – Optimal breeding scheme

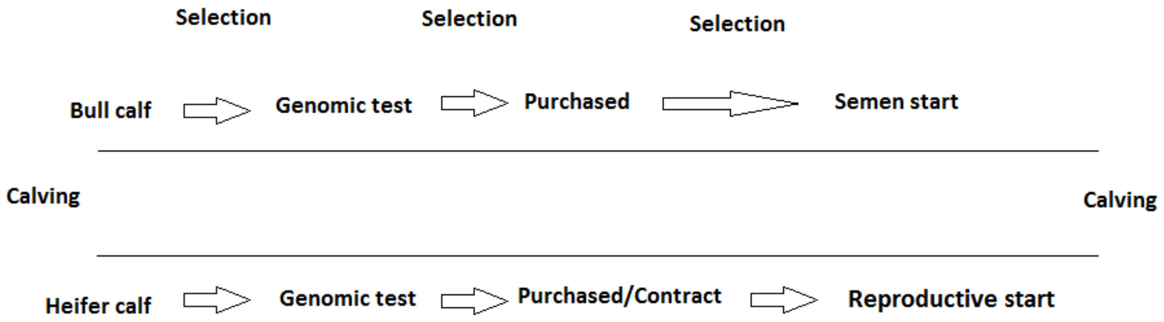

Figure 2. Selection steps for breeding animals. The selection can be divided into different steps. From what calves to genotype to reproductive start and further also a new calving.

In each selection step in *figure 2* there will be a selection decision. The selection could be divided into two phases. The first phase defines how many to select in each step and the second define what animals to choose to maximize long-term genetic gain. The first step in the first phase is to define the number of genotypings. An increasing amount of genotypings (males+females) the optimal proportion off these to spend on females is increased. The value of genotyping females also increase when MOET and OPU are used (Sørensen & Sørensen, 2009). However, females could also be genotyped for different purposes than further breeding (*figure 1*). Regarding the number of genotyped bulls, the farmer has no direct interest in genotyping bull calves, instead this cost will fall on the breeding organizations. In a breeding scheme, where both dams and sires are genotyped it should be possible for a breeding organization with some quite accurate pre-screening. The cost for genotyping bulls could possibly be even more reduced if the breeding scheme is more nucleuses based and thereby you can surround the animals you want to genotype.

The second step in the first phase is to decide how many to buy. In the female case, contracts for MOET or mating suggestions on farm could be solutions. Thereafter, the next step is to choose animals for reproductive animals. There might be changes in breeding values due to new information. Some animals will fall off due to reduced replicability or diseases. Further, there will be a culling decision. However, the most important part is in the start of the reproductive period, where the best animals should be mated which will reduce generation interval as far as possible.

In the second phase the most optimal is to use optimum-contribution selection (OCS), which maximizes the genetic merit of a cohort of animals while constraining the average relationship of the current generation (Henryon et al., 2014). The benefit of OCS, besides reducing the risks of inbreeding, genetic drift, and changes in gene frequencies, is that it can maximize long-term genetic gain. The software program “Eva” (Evolutionary Algorithm) is one example of a program that can help to control of inbreeding and adequate balancing of selection and inbreeding in populations. The program has been developed at DJF (Faculty of Agricultural Sciences) at Aarhus University, Denmark. From an optimal breeding scheme view, those kind programs will help a lot to optimize and balance selection of breeding animals. The challenge with OCS and genomic information is to define measurements that constrain losses of genetic variation and relationship between parents (Henryon et al., 2014).

Mating - Optimal breeding scheme

Mating design structure is an important part of dairy cattle breeding schemes to increase long term genetic gain (Caballero et al., 1996; Sonesson and Meuwissen, 2000). In an optimal breeding scheme mating design optimize family structures. Liu et al. (2016) showed that MC and MCAC with genomic information could without reducing genetic gain reduce inbreeding by 6% to 22% compared to MC and MCAC with pedigree information (Liu et al., 2016). However, it requires that both animals are genotyped. MC and MCAC might also be hard to execute from a farmer perspective, especially with genomic information. Therefore, it should be preferable if the breeding companies control as much as possible of the mating structure.

Logistics and optimization - Optimal breeding scheme

With genomic information and the possibility for more accurate breeding values for young animals there are potentials for better decision making from a very young age or animals that are not even born. This makes it possible for optimizations before an animal is used for breeding. For example, feed optimization could help a bull to start producing semen earlier or a heifer could be mature for MOET earlier. It is also possible to make sure that the right animals are at the right place at the right time. Those factors could for example help to reduce the generation interval and thereby increase genetic gain. However, those factors are rarely captured by the literature but could have considerable effect on an optimal breeding scheme.

There might be need for closer collaborations between breeding companies and farmers. With the need of more accurate phenotypes and genotyping collaboration, the partnerships between farmers and breeding organizations have to be strengthened. This situation is new and will require increased knowledge in the whole community about genomic selection and its effect on the breeding schemes. Further, the breeding scheme should also be regularly evaluated and adjusted when phenotypic trends gets available. It does not matter how theoretical optimal the breeding scheme if the breeding scheme does not add extra value for the farmers.

Inbreeding - Optimal breeding scheme

In an optimal breeding scheme a healthy level of inbreeding is kept which allows for long-term genetic gain. According to FAO, an inbreeding level below 1% per generation is recommended in order to avoid undesirable effects of inbreeding (FAO, 2007). Inbreeding lowers the mean phenotyping performance in the inbred animal and also increases the homozygosity level in the population. Traditional BLUP-selection uses pedigree information to construct relationship matrices and to constrain the progeny inbreeding. The development of molecular genetics has enabled genotyping of animals and using genomic relationships in the selection process. Pryce et al. (2012b) showed that the strategies using a genomic relationship matrix

(GRM) were more effective in reducing average progeny inbreeding. A 1% reduction in progeny inbreeding (valued at around $5 per cow) could be made with very little compromise in the overall breeding objective (Pryce et al., 2012b). Also, Lillehammer et al. (2011) suggested that a breeding scheme with genomic information led to less inbreeding compared to a conventional breeding scheme.

There are no arguments to adventure the long-term the genetic gain by intensively use of individual bulls. One major key to achieve as little inbreeding as possible is accurate breeding values. To succeed with accurate breeding values in the genomic era the design of reference population is again the important discussion topic. Genomic information may also help to control inbreeding through trace inheritance of chromosomal segments and estimate more accurately relationships between animals. This would help to select candidates carrying favorable but different chromosomal segments from ancestral animals (Henryon et al., 2014). The literature gives no clear suggestion how this is done in the best way. It is however clear that there are more to explore regarding within inbreeding and how to maximize long-term genetic gain in the genomic era. The best thing from an optimal breeding scheme should then be to continuously evaluate new research and thereafter implement it.

Control of lethal alleles - Optimal breeding scheme

The access to genomic information has also led to detection of recessive genetic disorders. With shorter generation intervals the changes of different alleles frequencies also goes much faster. Therefore, it is important in an optimal breeding scheme with a strategy to control them. Depending of the frequency and economic value of the unwanted recessive allele and each one of them has to be handled differently. Instead of working for full elimination of all harmful alleles, it might be more optimal if animals used for breeding are tested for their breed’s most common lethal recessives and by publishing the data, at-risk mating can be avoided.