Chapter 4

Genetic Improvement of Livestock for Milk Production

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http://dx.doi.org/10.5772/50761

1. Introduction

This chapter presents issues pertaining to genetic improvement of livestock for production. It covers aspects from basic population to quantitative genetics to molecular genetics, and their application in animal breeding. Genetics is the science of heredity which is concerned with physical and chemical properties of the hereditary material, how the material is transmitted from one generation to the next and how the information it contains is expressed in the development of an individual. Genetic make-up of animals control their structural configuration and productive abilities either via single genes or by multiple genes situated in different loci. Genes are compost of nucleotide sequences packaged into chromosomes in the nucleus. Milk production is largely affected by a combination of factors namely; genetic make-up in terms of the use of improved breeds selected for milk production, a favourable nutritional environment and improved managerial practices. Consequently, genetic make-up of dairy animals plays a great role in the variation of milk yield and composition. Milk production is, therefore, a factor of genotype-environment interactions. It is important to balance selection for both production (e.g., milk yield and composition) and functional (e.g., fertility, disease resistance, feed intake and body weight) traits. Techniques applied in molecular genetics in conjunction with conventional animal breeding techniques could be used to optimize animal breeding programmes, resulting in higher yields (i.e., greater genetic gains), as it is possible to determine the potential of an animal, even before the trait is expressed phenotypically. A genetic marker serves to favourably relate alleles for quantitative characteristics with information about the individual mode of action and their interaction of genes, helping to understand the quantitative variations and their practical use in animal husbandry. DNA markers present two possible future applications in animal selection; the combination of the best alleles of two or more breeds, and the selection of the best alleles within a breed or lineage. Commonly used genetic markers are the DNA-based markers; RFLPs and minisatellites,

and PCR-based markers like microsatellites, and SNP. DNA-based markers are more direct molecular markers that survey DNA variation itself rather than rely on variations in the electrophoresis mobility of protein that the DNA encodes. They allow the number of mutations between different alleles to be quantified. DNA containing genetic information identified to influence milk production traits can be artificially introduced into a dairy animal, using recombinant DNA technology, and then it must be transmitted through the germ line so that every cell, including germ cells, of the animal contain the same modified genetic material. Such techniques enable dairy animals to acquire desired milk production characteristics. However, use of such transgenic techniques attracts ethical questions. Generally, genetic marker approaches is a promising tool for milk production improvement. It is imperative that genetic improvement for milk production is approached holistically, taking into consideration all the factors that may affect a breeding programme.

2. Functional traits genetics

Functional traits are those traits that increase biological and economic efficiency not by higher outputs of products, but by reduced costs of production. Functional traits have become important for efficient breeding schemes in the dairy industries, due to increased costs of production relative to milk prices and consumers demand for safe, quality food and attention to animal welfare. Since dairy animals are bred in a wide range of local production conditions, the list of candidate functional traits may be large, including components of milk feed efficiency (body weight, feed intake and body reserves), reproduction traits (sexual precocity, out-of-season calving/lambing/kidding ability, female fertility), calf/lamb/kid meat production (suckling ability, prolificacy), milking ability (udder morphology, milking speed), resistance to disease (mastitis, scrapie, internal parasites), adaptation to local breeding conditions (fitness, wool, longevity), and others (Barillet et al., 2007). The relationships between milk production and functional traits are often null or antagonistic, illustrating the importance of knowledge of the genetic correlations between milk production and the functional traits of interest (Barillet et al., 2007).

Functional traits that increase efficiency not by higher output of products but by reduced costs of input, might have a greater impact on the profit of dairy farmers and should, therefore, be included in breeding programmes. Apart from economic reasons for including functional traits in the breeding programmes, there are several non-economic reasons, for example ethical and consumer concerns, which are becoming increasingly important (Olesen et al., 1999). The inclusion of functional traits in breeding programmes will likely have a major impact on the expected selection response of the functional traits, and will result in only small losses of the expected selection response of the production traits. Depending on the number of functional traits included in a breeding scheme, the relative importance of production versus functional traits varies from 70:30 to 30:70, sometimes even more. Relative weightings for the two groups of traits, production and functional, for the Estonian Holstein population were 79:21. In any of breeding scenarios tested, selection response in financial terms will come largely from production traits, because genetic parameters favour fat and protein yields (high heritability, high positive genetic correlation) (Pärnal et al., 2003).

Smallholders, pastoralists and their animals often live in harsh environments which may be hot and dry, hot and humid, or high in altitude and cold. Moreover, these environments can be characterized by scarce feed and water resources and high disease pressure with large seasonal and annual variation. Adaptation to these factors is largely based on genetics, but animals can "learn" to live under such stressful conditions. To match genotype with the environment, breeders can follow two alternative strategies: adapt the environment to the needs of the animals as is the case in industrial animal production systems or keep animals that are adapted to the respective environment as is the case in low input smallholder and pastoral systems. Because of this, smallholders and pastoralists need different and diverse animal genotypes, species mix and types to enable animal husbandry in their specific physical environment locations and production systems (Mirkena et al., 2010).

3. Milk production traits genetic determinants

The phenotypic expression of milk production traits (e.g., milk yield and composition) are controlled by genes, which may or may not be transferred to the offspring. The genetic value of a trait indicates the likelihood that the genes responsible for that trait will be transferred to any offspring. Consequently, when dairy producers are selecting animals for breeding stock, they are typically more concerned with an animal's genetic value rather than its phenotypic value of a particular trait. The difference is that while the phenotypic value refers to the presence or absence of particular traits, the genetic value indicates the potential (or probability) that this animal, if bred, will give birth to calves with certain desired traits. The challenge of the dairy breeder is, therefore, to determine which cows and bulls to breed in order to obtain progeny with high quality milk production traits, as well as any other desirable attributes.

Two main reasons for the decline in fitness traits of cows associated with increased genetic merit for milk yield are: (i) fitness traits are ignored in the construction of selection indices because they are considered to have lower heritability or are not easy to record and (ii) use of inappropriate breeding programmes while the underlying genetic process (selection and inbreeding depression) is not well understood (Goddard, 2009). However, the low heritability of some fitness traits does not imply negligible genetic variance; often heritability is low because the phenotypic variance is rather larger than the genetic variance as evidenced by as high genetic coefficient of variation for fitness traits as for some production traits (Goddard, 2009).

The appropriate strategy for any breeding programme would, therefore, be to set suitable selection goals that match the production system rather than ambitious performance objectives that cannot be reached under the prevailing environment. Area-specific approach utilizing the existing resources and taking into account the prevailing constraints appears to be the only reasonable sustainable solution. Such approach would also enable *in situ* conservation of farm animal genetic resources, the only viable and practical conservation method in less developed countries compared to *ex situ* or cryopreservation approaches. This would support the importance of identifying the most adapted genotype capable of

coping with the environmental challenges posed by any particular production systems (Mirkena et al., 2010).

Karugia et al. (2000) analyzed the impact of crossbreeding zebu with temperate cattle breeds for dairy improvement in Kenya using sector- and farm-level approaches. The agricultural sector model showed that a dairy technology that involved crossbreeding and complementary improvements in nutrition and management has had a positive impact on Kenyan economy and welfare but this approach ignored important social cost components of crossbreeding. The farm-level approach, however, indicated that farm performance was little improved by replacing the indigenous zebu with exotic breeds. Conversely, this analysis indicated that a breeding programme that concentrates on improving the local zebu breeds would improve the financial performance of the farm level with important implications for the conservation of farm animal biodiversity.

4. Genotype by environment interactions

The external environmental stimuli (physical, chemical, climatic and biological) to which animals respond interact with their genotypes to determine level of performance. In the absence of genotype by environment interaction, the expected genetic correlation across environments is one. However, all species respond to changing natural environments through altering phenotype and physiology; in livestock production the situations become more complex since human intervention influences both genotype and external environment (King, 2006).

When genotypes have significant differences between the quantitative measures of the phenotypic plasticity, then there is a genotype by environment interaction. Plastic genotypes are known by highly variable phenotypes across environments, whereas robust or stable genotypes are known by relatively constant phenotypes across environments. Differences in the phenotypic plasticity could be explained by the fact that some alleles may only be expressed in some specific environment due to change in some gene regulations depending on the environment; favorable genes in some environments may become unfavorable under other environmental conditions. Developing countries in the tropics often rely on exotic germplasm for breeding purposes. They, however, have climatic conditions, production systems and markets that are different from those where animals were evaluated. Consequently, the genotype-environment interactions can cause reduced efficiency of their genetic improvement programmes. When genotype by environment interactions exists and the environment is under the control of the breeders (i.e., genotype by ration or genetic by housing interaction), it would be easier for breeders to modify the environment to allow optimum expression of the genotype. However, when environments are beyond the breeders' control, they have to choose the genotypes able to adapt to those environments (Hammami et al., 2008). In low input systems, the best alternative to circumvent the consequences of genotype by environment interactions is to select for adaptive traits.

According to Mirkena et al. (2010), imported improved temperate breeds produce more than indigenous tropical breeds if supplied with high quality feed; however, they lose weight

and fail to survive when fed poor quality grass or straw, whereas adapted indigenous animals still grow, give some milk and reproduce. Adapted tropical animals recycle nutrients more efficiently than do improved temperate breeds and can also reduce their basic metabolism during periods of weight loss (Bayer and Feldmann, 2003). Leitóna et al. (2008) observed that the average genetic variance for 305-d milk yield in Costa Rican populations of Holstein and Jersey cows was near 20%. The environmental and genetic trends for milk production in both breeds were positive, although the proportion attributable to genetic improvement was low compared to the phenotypic increase. The genotype by environment interaction had a significant effect on milk production in both breeds, but was particularly marked for the Holstein breed. The study concluded that these were probably caused by the lack of control over import of genetic material into Costa Rica and how it was used, which implied that dairy producers needed to reconsider the genetic improvement strategy based almost exclusively on importing genetic material.

In Zebu cattle, Freitas et al. (2010), in a preliminary study involving Gyr dairy cattle, observed the effect of herd on milk production of daughters of sires with different breeding values, pointing out for the possibility of G-E interaction. In another study, Ayalew et al. (2003) compared productivity of indigenous breeds of goats (Hararghe Highland and Somali) with that of crossbred (Anglo-Nubian X Somali) goats in Ethiopia and concluded that the crossbreds did not improve households' income in the mixed crop–livestock production system. The study indicated that there were increased net benefits per unit of land or labor from mixed flocks (i.e. both indigenous goats and Anglo-Nubian crosses) under improved management compared with indigenous goats under traditional management. In flocks using an improved management package, the crossbreds did not produce more net benefits than indigenous goats either in mixed or separate flocks. The improved management package, however, increased net benefits of farmers keeping indigenous goats; these findings that explained the low adoption rate of exotic crosses by smallholder farmers and superior adaptability of indigenous goats to the prevailing production system (Mirkena et al., 2010). It is, therefore, imperative that the genetic improvement of locally adapted breeds will be important to realizing sustainable production systems.

5. Genetic variations

Allele frequencies and, therefore, genotypic frequencies do not change on their own accord. They will tend to remain the same generation after generation, and each progeny generation will tend to resemble its parental generation. Counteracting this tendency is a number of processes that can change allele frequency and thereby lead to the genetic modification of progeny. In the long term, the most important of the modifying processes is natural selection, the process in which the most adapted to survive and reproduce in their environment and, subsequently, contribute more than an equal share of alleles to the next generation; when repeated over a course of many generations, a disproportionate contribution of alleles, even if small, will significantly increase the frequency of alleles responsible for the superior adaptation. Other causes of change in the frequency of alleles

are as follows: mutation that occurs when a DNA gene is damaged or changed in such a way as to alter the genetic message carried by that gene and/ or changes in sequences of introns and/ or promoter regions; migration, the movement of individuals among subpopulations within a larger population; random genetic drift that results from random undirected changes in all population and, especially, occurring in small populations. These four processes account for most or all of the changes in allele frequencies that occur in populations. They form the bases for cumulative change in the genetic characteristics of populations, leading to descent with modification.

Interestingly, mutation can result due to replication errors caused by both endogenous and exogenous factors. Endogenous factors consist of transversion, spontaneous depurination of bases, deamination of cytosine and sometimes adenine residues, yielding uracil and hypoxanthine, respectively. Exogenous reactions for mutations include dimerization of pyrimidine bases induced by ultra violet light, various chemicals such as alkylating agents forming adducts with DNA bases, reactive oxygen species damaging pyrimidine and purine rings and ionizing radiation causing DNA strand nicking and breakage. The majority of these modifications are generally recognized and corrected by the DNA repair system.

6. Molecular genetic technologies

Molecular genetics is the study of the genetic makeup of individuals at the DNA level; it is the identification and mapping of genes and genetic polymorphisms. There are opportunities for using molecular genetics to identify genes that influence milk production traits. Armed with this information, it would be possible to select improved livestock on the basis of their genetic makeup. If applied with care, the use of molecular information in selection programmes has the potential to increase productivity, enhance environmental adaptation and maintain genetic diversity (Naqvi, 2007). The first task is to understand the genetic control of the trait of interest and then to identify the genes and genotypes involved.

Molecular genetic technologies have been used to identify loci or chromosomal regions that affect single-gene traits and quantitative traits. Single-gene traits include genetic defects, genetic disorders, and appearance. For the purposes of quantitative traits loci (QTL) detection and application, quantitative traits can be categorized into (a) routinely recorded traits; (b) difficult to record traits (e.g., feed intake and product quality); and (c) unrecorded traits (disease resistance). Each of these can be further subdivided into traits that are (i) recorded on both sexes; (ii) sex-limited traits; and (iii) traits that are recorded late in life. The ability to detect QTL depends on the availability of phenotypic data and decreases in the order a, b, c and within each of those in the order i, ii and iii. For related reasons, genome scans, which require more phenotypic data than candidate gene analyses, are often used to detect QTL for traits in category a, whereas candidate gene approaches are more often used to identify QTL for traits that are not routinely recorded (b and c) (Meuwissen and Goddard, 1996).

The use of molecular genetic technologies potentially offer a way to select breeding animals at an early age (even embryos); to select for a wide range of traits and to enhance reliability in predicting the mature phenotype of the individual. The broad categories of existing gene

technologies based options include; molecular analysis of genetic diversity, animal identification and traceability, reproductive enhancement; transgenic livestock; germ line manipulation and; marker/ gene based trait selection; animal health: diagnosis, protection and treatment; ruminant and non-ruminant nutrition and metabolism (Naqvi, 2007).

7. Genetic markers

Recent developments in molecular biology and statistics have opened the possibility of identifying and using genomic variation and major genes for the genetic improvement of livestock. Molecular techniques allow detection of the existence of variation or polymorphisms among individuals in the population for specific regions of the DNA. These polymorphisms can be used to build up genetic maps and to evaluate differences between markers in the expression of particular traits in a family that might indicate a direct effect of these differences in terms of genetic determination on the trait (Montaldo et al., 1998).

Application of molecular genetics for genetic improvement relies on the ability to genotype individuals for specific genetic loci. Genetic markers can be used to identify specific regions of chromosomes where genes affecting quantitative traits are located, i.e., QTL (Davis and DeNise, 1998). These techniques can directly confirm the potential parent-to-offspring transfer of those genes associated with a desired trait (Akhimienmhonan and Vercammen, 2007). For these purposes, three types of observable polymorphic genetic loci can be distinguished: (i) direct markers: loci that code for the functional mutation; (ii) LD markers: loci that are in population- wide linkage disequilibrium with the functional mutation; and (iii) LE markers: loci that are in population wide linkage equilibrium with the functional mutation in outbred populations; linked markers can be used within families segregating marker and QTL alleles following the establishment of the phase relationship (Davis and DeNise, 1998). The LE markers can be readily detected on a genome-wide basis by using breed crosses or analysis of large half-sib families within the breed. Such genome scans require only sparse marker maps (15 to 50 cM spacing, depending on marker informativeness and genotyping costs; to detect most QTL of moderate to large effects (Darvasi et al., 1993). The LD markers can be identified using candidate genes (Rothschild and Soller, 1997) or fine-mapping approaches (Andersson, 2001). Direct markers (i.e., polymorphisms that code for the functional mutations) are the most difficult to detect because causality is difficult to prove and, consequently, a limited number of examples are available, except for single-gene traits (Andersson, 2001). Direct markers where a linkage analysis has been performed and a zero recombination rate found between the markers and the QTL, or where sequence data have verified the exact location of the genetic change in a number of individuals. Direct markers can be used across families after prediction of an allelic effect for a given genetic background. Both markers can be used in MAS programmes that incorporate other pedigree and phenotypic information for the genetic evaluation of animals (Davis and DeNise, 1998).

Direct markers can be identified by use of candidate gene approach. Candidate gene approach proposes that a significant proportion of quantitative genetic variation of a given trait is contributed by segregation of functional alleles of one or more of the candidate genes for the trait (Rothschild and Soller, 1997). Candidate genes are genes that play a role in the

development or physiology of a trait of economic importance. At the DNA level, a candidate gene comprises a contiguous tract of DNA, including introns, exons, and upstream and downstream regulatory regions concerned with biosynthesis of a single protein or via alternative processing to produce related proteins. Allelic variation at a candidate gene sequence can cause a change in protein production or efficiency in a metabolic process that will influence a specific trait. The candidate gene approach can be very powerful and can detect loci even with small effect, provided that the candidate gene represents a true causative gene. However, there are often many candidate genes for the trait of interest and it may be more time-consuming to evaluate all of these than performing a genome scan. Furthermore, the candidate gene approach might fail to identify a major trait locus simply because of the gap in knowledge about a gene function. Candidate gene tests must be interpreted with caution because spurious results can occur because of linkage disequilibrium to linked or non-linked causative genes or because the significant thresholds have not been adjusted properly when testing multiple candidate genes. Once the chromosomal location of a trait locus has been determined, this information can be applied in breeding programmes by using Marker-Assisted Selection (MAS). Candidate genes can be sequenced and analyzed in animals manifesting divergent expressions of a given trait of interest. Sequence analysis provides highest resolution of DNA variation; provides the fundamental structure of the gene systems. It is a vital tool in the analysis of gene structure and expression (Drinkwater and Hazel, 1991).

Quantitative trait loci have been detected in experimental and commercial populations of cattle, swine and sheep. In dairy cattle, linked markers have been reported for milk and component yields (Georges et al., 1995) and cheese yield (Graham et al., 1984).

8. Genetic marker technologies applied in animal breeding

Recent developments in molecular biology and statistical methodologies for QTL mapping have made it possible to identify genetic factors affecting economically important traits. Such developments have the potential to significantly increase the rate of genetic improvement of livestock species, through MAS of specific loci, genome-wide selection, gene introgression and positional cloning (Andersson, 2001). Instead of conventional animal breeding programmes solely relying on phenotype and pedigree information, the incorporation of detected QTL into genetic evaluation provides a great potential to enhance selection accuracies, which expedites the genetic improvement of animal productivity (Jiang et al., 2010).

Genetic marker technologies, like MAS, parentage identification, and gene introgression can be applied to livestock selection programmes. Highly saturated genetic maps are now available for cattle, swine and sheep to provide the genetic framework for developing MAS programmes (Davis and DeNise, 1998).

8.1. Marker-assisted selections (MAS) and gene-assisted selections (GAS)

Genetic improvement involves selection of outstanding individuals from a population to produce better yields in future generations. For a long time, dairy breeders have used

genetic evaluations to identify superior animals. Selective use of these animals improved phenotypic measures for milk production and milk components, especially in Holstein cattle. However, there are some limitations to selecting on predicted breeding values. This selection approach has limited ability to improve lowly heritable traits without adversely affecting production. Lowly heritable traits often include those associated with disease resistance, reproduction, duration of productive life, and some conformation traits correlated with fitness (Sonstegard et al., 2001). Most breeding schemes do not account for population effects on genetic diversity, and selection is optimized for genetic response in the next generation rather than the highest long-term response (Meuwissen, 1997). Information from genetic markers that identify desirable alleles of economically important traits could be used with breeding values to guide mating decisions, resulting in genetic gains over a broader range of traits. Additionally, MAS could be used to select the most desirable phenotypes affected by non-additive gene action or epistatic interactions between loci (Sonstegard et al., 2001). Marker-assisted selection is a selection approach in which the relative breeding value of a parent is predicted using genotypes of markers associated with the trait. However, Lande and Thompson (1990) showed that genetic information cannot entirely replace phenotypic information. They developed a model combining phenotypic and genotypic information to be used in a selection programme, in which the selection index was constructed once every three generations. Before MAS can be applied in commercial dairying, economic trait loci (ETL) must be identified, validated, and characterized for utility in improving genetic gain (Sonstegard et al., 2001).

There are three phases in the development of MAS programmes. In the detection phase, DNA polymorphisms are used as linked or direct markers to detect QTL segregating in particular populations with specific allele frequencies. One or more markers associated with QTL are identified, and the size of the QTL allele effects and the location of the QTL in the genome are estimated. In the evaluation phase, the linked markers are tested in target populations or families to determine whether the detected QTL are segregating in those populations. In the implementation phase, linked markers shown to be predictive in a population are used within families and direct markers are used across families to produce a database of genotypes. These data are combined with phenotypic and pedigree information in genetic evaluation for the prediction of genetic merit of individuals within the population (Davis and DeNise, 1998).

In livestock, there are basically four design possibilities for marker QTL linkage analysis; (i) using F2 populations crossing two similar F1 populations, or a backcross between the F1 and one of the original populations; (ii) using a half-sib sire design on which heterozygous sires for the markers are mated to a random sample of females and all the progeny is genotyped; (iii) using instead a grand-daughter design on which a sire and their sons evaluated by progeny testing are genotyped; (iv) using crosses of individuals with extreme phenotypes for one trait or trait combination. Animals from divergently selected lines or from populations with wide variation for important traits are also used. Method (i) allows detecting QTL already fixed in one breed. Methods 2 and 3 are more suitable for prediction of QTL effects for within-population selection (Montaldo and Meza-Herrera, 1998). The

challenge of the design of a breeding programme is to balance selection emphasis among traits to maximize response in the overall objective. With the availability of genetic markers and tests, there is need to balance emphasis on molecular versus quantitative genetic information. This also holds for selection against genetic defects, the emphasis on which must be balanced against selection on quantitative traits. Extra genetic gains from MAS, therefore, depend on the effect of direct selection on individual loci on genetic progress at other loci (polygenes) and for other traits that affect overall genetic merit. Although tandem selection results in the most rapid fixation of the gene(s) that are targeted by the molecular score, it results in the greatest loss in response for polygenes and for traits that are not included in the molecular score and may, therefore, result in less response in the trait and the overall breeding goal. The choice between tandem and index selection (and other alternatives) also depends on other factors, like market and cost considerations. Tandem and index selection apply to the use of molecular information in a given stage of selection (Montaldo and Meza-Herrera, 1998).

Marker-assisted introgression programmes are based on tandem selection in a multigenerational backcrossing programme, in which a marker selection (MS) based on the presence of donor breed alleles at or around the target gene is used in the first selection step (foreground selection), followed by background selection on a MS based on presence or absence of recipient alleles at markers spread over the genome, on phenotype, or an index of the two (Dekkers, 2004). A major gene in another population can be introduced through the process of introgression by means of backcrosses assisted by molecular markers. In this case, it does not seem to exist advantage in using a single genetic marker information, in comparison with the use of only phenotypic information when the characteristic is continuous and the considered genetic effects are additives (Groen and Smith, 1995). Classical introgression schemes (introgressing specific QTL alleles) are most likely to be successful when combined with deliberate selection for the specific favorable alleles, known to exist in the donor line, or by selection on closely linked markers. Using genomic selection, all marker alleles in LD with favourable QTL alleles are potentially selected for; this method may, therefore, be especially relevant in situations where a number of QTL underlie the genetic variation of the trait. During the backcrossing process, donor alleles are likely to be lost or at low frequencies unless favoured by selection within the crossbred line. Crossing can be used for introgression of favourable novel alleles and may be worthwhile even when there are considerable differences in the genetic levels of the recipient and donor lines (Ødegard et al., 2009).

Whereas initial applications of MAS in livestock populations may have been on *ad hoc* bases, it is clear that successful implementation of a MAS program requires a comprehensive integrated approach that is closely aligned with business goals and markets. Implementation of MAS requires development and integration of procedures and logistics for DNA collection and storage, genotyping and storage, and for data analysis. This must be supported by a systematic approach to quality control and must support day-to-day decision making (e.g., on which animals to genotype or regenotype in case of errors, which animals to phenotype, etc.) (Dekkers, 2004). Meuwissen & Goddard (1996) showed that

response to MAS is maximal at the starting generations. The decrease in response to MAS throughout the subsequent generations may result from increased frequency of recombination events that leads to linkage equilibrium and, consequently, decreases the MAS efficiency (Lahav et al., 2006). The main application and potential for use of markers to enhance genetic improvement in livestock is through within-breed selection. This requires markers that trace within-breed variability (Dekkers, 2004).

MAS/ GAS versus conventional selection methods

Conventional animals breeding programmes depend on selection programmes based on phenotypic selection where traits are measured directly and animals with superior performance in the traits are used as breeding stock where the trait is limited, like milk production, progeny test schemes have allowed the genetic merit of the sex not displaying the trait to be estimated. Several problems are associated with phenotypic selection, and include: (i) narrowing the genetic base of a population; (ii) the approach can only be applied to traits that are easily measured; and (iii) high costs. In traits that are displayed only in adults, which comprise most of the production traits, it is necessary to raise a large number of individuals for which the trait is recorded, so that a few can be chosen for breeding. In case of progeny testing for milk production, the costs are very high, as the test sires have to be raised and then the daughters themselves raised and bred before the trait can be measured and the elite sires selected (Naqvi, 2007). Marker and gene assisted selection technique can efficiency solve problems associated with the conventional selection methods.

There is considerable marketing hype associated with emerging technologies, with predictions by the patent holders that gene marker selection techniques will soon entirely replace conventional breeding methods. Nevertheless, such efficiency gains will depend on the rate of scientific advancement in gene marking. Since economically important traits in dairy cattle, like milk yield and composition, are influenced both by a combination of genes and management factors. That only a handful of the more than 30,000 genes in cattle have been marked suggests that DNA-based seed stock selection, which relies on the small number of available markers, is unlikely to produce sizeable efficiency gains in the very near future. Furthermore, scientists and industry experts are concerned that a rapid substitution of gene marker selection for conventional breeding will result in unanticipated efficiency losses in the long term bases (Akhimienmhonan and Vercammen, 2007).

Economic benefits of MAS/ GAS on improvement of livestock genetics

Molecular genetics allows studying the genetic make-up of individuals at the DNA level. The main reasons why molecular genetic information can result in greater genetic gain than phenotypic information are: (i) assuming no genotyping errors, molecular genetic information is not affected by environmental effects and, therefore, has heritability equal to 1; (ii) molecular genetic information can be available at an early age, in principle at the embryo stage, thereby allowing early selection and reduction of generation intervals; (iii) Molecular genetic information can be obtained on all selection candidates, which is

especially beneficial for sex-limited traits for example milk yield, traits that are expensive or difficult to record, or traits that require slaughter of the animal (carcass traits) (Naqvi, 2007).

It is believed that MAS could be particularly profitable in dairy cattle. Because this species concentrates many conditions unfavourable to phenotypic selection and, therefore, favourable to MAS; most traits of interest are sex-limited; the generation interval is long; AI bulls should be progeny tested before extensive use, which is a long and costly step; the breeding schemes are more and more designed with bull dams selected before their first lactation on pedigree information only, in order to reduce the generation interval; last but not least, functional traits, like disease resistance or fertility, have a low heritability but are more and more important in the breeding goal (Boichard, 2002). When AI is used predominantly, the number of key animals in the breeding scheme is limited and makes MAS relatively easy to implement. Although MAS could be oriented towards increasing the genetic trend on breeding objective or modifying the breeding objective by efficiently including low heritability traits, the breeders can use it to decrease the cost of the breeding programme by reducing the number of bulls sampled (Boichard, 2002).

According to Dekkers (2004), opportunities for increases in genetic gain through MAS on a given QTL differ depending on whether the QTL is marked by LE, LD, or direct markers; whereby genetic gains from MAS are lower for LE markers than for direct markers. The difference is caused by the accuracy of estimates of the molecular score, which is lower for LE markers because of the limited information that is available to estimate effects on a within-family basis, whereas for direct markers, effects are estimated from data across families. In that study, differences were reduced but far from eliminated when marker spacing was reduced to 1 or even 0.05 cM. Greater differences between the two types of markers are expected if phenotypic and/ or genotypic data is not available on all individuals, which will limit the accuracy of molecular scores based on LE markers for individuals in families with limited data, in particular if marker-QTL distances are considerable. Furthermore, the LD markers also enable use of phenotypic and genotypic data across families to estimate marker scores but accuracies may be slightly lower than for direct markers due to incomplete marker–QTL LD and a greater number of effects that must be estimated. Accuracy of estimates of molecular scores based on data from 1,000 individuals was 0.66 and 0.79 for haplotypes of 4 and 11 markers. Increasing the number of markers from 4 to 11 increased accuracy, but to a greater degree if more progeny were evaluated. Final considerations regarding the use of LE versus LD versus direct markers involve opportunities for marketing and protection (Dekkers, 2004).

Calculating the benefit requires focus on three main aspects: where returns are realized, because this determines the value of a unit of improvement and the genetic parameters to be applied; where the technology is applied, because this determines the rate of gain and the flow of genes to the sector in which the return is gained and the direct costs of implementing the technology and; the source of returns, i.e., whether the technology affects genetic structure of the population, the estimation of genetic value, and/ or the accuracy of the estimated genetic value. This needs to be assessed in order to predict the volume of improvement that will arise from application of the technology. The impact of a genetic

technology can be calculated relevant to the breeding objective for the production/ market system in which the return is realized. This is because the value of one unit change in a trait in the breeding objective is not constant across different enterprises. Associations between marker haplotypes and QTL alleles may predict performance traits, like milk quality, without the requirement for large-scale measurement of phenotypes. The benefit of application of a genetic improvement technology can be assessed by defining the net value of the improvement on an individual breeding female scale, an enterprise scale, and an industry scale. These predicted annual improvements can then be compared with the annual costs of implementing the technology and analyzed with a conventional economic analysis to determine the overall net present value and the benefit:cost or internal rate of return when the technology is applied to an industry (Davis and DeNise, 1998).

MAS divert selection emphasis away from polygenes and traits without marked QTL, and the ultimate success of MAS is determined by its impact on total genetic merit. It has also been shown that the impact of MAS on other loci and traits differs between the three selection strategies, and is greatest for tandem selection, followed by index selection, and preselection. Commercial application of MAS requires careful consideration of economic aspects and business risks. Economic analysis of MAS requires a comprehensive approach that aims to evaluate the economic feasibility and optimal implementation of MAS. Generally, implementation of MAS will have a greater impact on market share than on genetic gain. Nevertheless, it is important that economic analysis is conducted in relation to business and market realities and goals (Dekkers, 2004).

If seed stock decision makers routinely replace animals with non-conforming genes with those having conforming genes, then both the gains and level of biodiversity will diminish over time. Livestock breeding contains many public good attributes, and it is important for policy makers to properly understand these attributes before determining whether policy intervention is warranted ((Akhimienmhonan and Vercammen, 2007). One way of evaluating the success of genetic improvement is to calculate genetic trends in a population over time (Leitóna et al., 2008). Genetic selection on production traits is reducing reproductive efficiency of dairy cattle (Castillo-Juarez et al., 2000), and increasing susceptibility to some diseases which, consequently, increases the risk of culling. Functional traits, and possibly also fertility traits, should, therefore, be included as part of the breeding goal (Dal Zotto et al., 2005).

8.2. Molecular analysis of genetic diversity

The use of microsatellites in genetic distancing of breeds is gaining momentum in characterizing and better understanding of animal genetic variation. The increasing knowledge of mammalian genetic structure and the development of convenient ways of measuring that structure have opened up a range of new possibilities in the areas of animal and product identification and tracing. Parentage verification by livestock breed and registry associations has now being based on microsatellite characterization and other genetic markers rather than blood typing. The advantages of the new system are substantial.

Better precision in identification should be possible, because the number of independent loci typed can be increased at will. The value of any particular locus depends on the number and relative frequencies of the alleles present or marker identity in the population, as well as on the ease with which it can be amplified and read in the laboratory (Naqvi, 2007).

8.3. Molecular conservation

The first step in considering sustainable management or conservation of a particular population of animals is genetic characterization. How unique is it in genetic terms? How different is it from other populations? How wide or narrow and, therefore, how endangered, are its internal genetic resources? The development of efficient methods of reading the molecular structure of populations has added a totally new range of instruments that can be used for the development of rational and balanced genetic management strategies. The most widely used of these techniques is the characterization of a population at a range of microsatellite loci. The compelling need for conserving domestic species is to prevent the loss of the many differentiated populations that, because of geographic or reproductive isolation, have evolved distinct characteristics and now occupy different environmental niches. Three basic approaches can be identified for preserving genetic diversity: maintaining living herds or flocks, cryo- preserving gametes or embryos and establishing genomic libraries (Naqvi, 2007).

9. Cloning adult dairy animals

Cloning an animal is the production of a genetically identical individual, by transferring the nucleus of differentiated adult cells into an oocyte from which the nucleus has been removed. This is known as “nuclear transfer” and is how the Dolly sheep was produced. In the case of Dolly, mammary gland cells in culture from a 6-year old donor ewe where subjected to a reduction in the concentration of serum and, consequently, obliged to enter in a quiescent state of the cell cycle (G0). Nuclear transfers to enucleated oocytes, was followed by electrical pulses for fusion of the donor cell nucleus and oocyte membranes and to activate division (Wilmut et al., 1997). Use of cloning in animal genetic improvement for milk production may increase the rates of selection progress in certain cases, particularly in situations where artificial insemination is not possible, like in pastoral systems with ruminants. Cloning is another technique that raises concerns both from the ethical and practical point of view. In animals, besides the very low success rates, some abnormalities should suggest that more information is required on the consequences of such practices in humans but also in animals, before its routine use (Montaldo, 2006).

10. Transgenic dairy animals

The production of transgenic farm animals that contain exogenous DNA stably incorporated into their genome so that the 'transgene' is transmitted to the offspring in a Mendelian fashion has several applications. Besides the obvious scientific interest for the study of genes

and their regulation, transgenic animal technologies have been proposed as a method to accelerate livestock improvement, by means of introducing new genes or modifying the expression of endogenous genes that regulate traits of economic importance (Wheeler, 2003) like milk production traits.

The ability to insert genes into livestock embryos, the incorporation of those genes and their stable transmission into the genome of the resultant offspring will enable major genetic advances to be realized in animal agriculture. Some of the other methods that have been used to produce transgenic animals include: (i) DNA transfer by retroviruses; (ii) microinjection of genes into pronuclei of fertilized ova; (iii) injection of embryonic stem (ES) cells and/ or embryonic germ (EG) cells, previously exposed to foreign DNA, into the cavity of blastocysts; (iv) sperm mediated exogenous DNA transfer during *in vitro* fertilization; (v) liposome-mediated DNA transfer into cells and embryos; (vi) electroporation of DNA into sperm, ova or embryos; (vii) biolistics; and (viii) nuclear transfer with somatic or embryonic cells (Wheeler, 2003). The use of the bovine α lactalbumin gene promoter and regulatory regions has great potential for studying the basic biology of milk secretion as well as for many additional applications in agriculture and biomedicine (Wheeler, 2003).

Because so many separate steps are involved in the transgenic technology, the success rates are often low usually one or two per cent. Normally about half express the transgene. In those, which do show expression, the gene may be activated in unintended tissues or at abnormal times in the animal's development. This unpredictability of gene expression is to a greater extent contributed by lack of control either of the site of integration in the host genome, or the number of copies integrated. Furthermore, transgene transmission to the next generation is sometimes abnormal. One consequence of variable expression has been to produce unacceptable side effects on the health and welfare of animals. Consumer concern from lack of convincing information on transgenics and antipathy to transgenesis is very strong in many countries, and both producers and consumers would reject a technology which had negative effects on animal welfare. Genes promoting productivity (milk yield) or reducing costs (disease resistance) are most likely to be found within the species concerned. If a gene is sufficiently well characterized to permit its use in transgenesis, then it will also be possible to genetically characterize individuals carrying the gene and to make direct selection and propagation highly efficient. In dairy animals, most consideration has been given to genes that modify fat or protein synthesis in the mammary gland (Naqvi, 2007).

Among the different applications of milk modification in transgenic animals are the following (Montaldo, 2006): (i) to modify bovine milk to make it more appropriate to the consumption of infants. Human milk lacks β-lactoglobulin, has a higher relationship of serum proteins to caseins, and has a higher content in lactoferrin and lysozyme when compared to bovine milk; (ii) to reduce the content of lactose in the milk to allow their consumption to people with intolerance to lactose; (iii) to alter the content of caseins of the milk to increase their nutritive value, cheese yield and processing properties. Research has intended to increase the number of copies of the gene of the κ- casein, to reduce the size of the micelles and modifying the κ-casein to make it more susceptible to the digestion with

chymosin; and (iv) to express antibacterial substances in the milk, such as proteases to increase mastitis resistance.

10.1. Ethical issues on applications of transgenic technology

Arguments opposing animal biotechnology can be divided into two categories; (i) concerns of technological ethics that might be raised with regard to the general unintended consequences of technical change; and (ii) concerns that relate specifically to biotechnology by virtue of new techniques for moving genetic materials from one organism to another. Among arguments that relate to biotechnology in a way that does not apply generally to technical change, concerns about patenting can be treated as a special case. The ethics of biotechnology include arguments for the development of transgenic animals, as well as objections and limitations. Research on ethical issues in biotechnology can improve the evaluation and implementation of transgenics farm animals by analyzing arguments of ethical concern and by presenting logically rigorous arguments for alternative perspectives. This element of ethical concern can be interpreted as an expression of anxiety or uncertainty about the definition of the moral community and the identification of borders or limits for ethical concern. Transgenic animals reinforce a challenge to implicitly accepted borders that define the scope of the moral community in terms of the human species (Thompson, 1993).

There are two very different and unresolved conceptions of animal welfare. One conception assumes that animal welfare is optimal only when the animal is allowed to realize its "natural" potentials and live accordingly in environments that closely resemble those of the animal in a wild setting. That implies, e.g., that animals would be free roaming and competing for the feed to the extent that aggression may occur and only the strongest would receive sufficient nourishment. According to this view, if the animal is seen to be suffering for causes that are natural, then welfare is not necessarily compromised. There is debate among different nations, and also among different experts, about the need to label food that is derived from genetically modified products. The mere application of gene-technology would not on that basis alone justify the need of labelling. The foregoing points represent a summary and rough overview of the most salient ethical issues surrounding the use of transgenic dairy production. One of the important points made in this connection was that more specific assessments need to be made on a case-by-case and step-by-step basis (Kaiser, 2003).

11. Conclusions

In livestock, knowledge of effects of specific genes and gene combinations on important traits could lead to their enhanced control to create new, more useful populations. The use of specific gene information could help to increase rates of genetic improvement, and open opportunities for using additive and non-additive genetic effects of domestic species, provided wise improvement goals are used and this new technology is optimally used together with the so called 'traditional' or 'conventional' methods based on phenotypic and genealogical information (Montaldo, 2006). Success of commercial application of MAS is

unclear and undocumented, and will depend on the ability to integrate marker information in selection and breeding programmes. Opportunities for the application of MAS exist, in particular for GAS and linkage disequilibrium MAS and, to a lesser degree, for linkage equilibrium MAS because of greater implementation requirements. Regardless of the strategy, successful application of MAS requires a comprehensive integrated approach with continued emphasis on phenotypic recording programmes to enable quantitative trait loci detection, estimation and confirmation of effects, and use of estimates in selection (Dekkers, 2004).

Donors and governments should fund research that examines the usefulness of gene marker technology for dairy cattle producers, find ways to educate producers about this new technology, and report to producers all third-party analysis of specific test claims. Finally, policy makers should promote the efficient commercialization of this emerging technology (Akhimienmhonan and Vercammen, 2007). A rational use of the molecular methodologies in milk production genetic improvement requires the simultaneous optimization of selection on all the genes affecting important traits in the population. The maximum benefit can be obtained when these techniques are used in conjunction with reproductive technologies like artificial insemination, and collection and production *in vitro* of embryos to accelerate genetic change (Bishop et al., 1995).

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