

Breeding Focus 2018 - Reducing Heat Stress

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Preface

“Breeding Focus 2018 – Reducing Heat Stress” is the third workshop in the series. The Breeding Focus series was developed to provide an opportunity for exchange between industry and research across a number of agricultural industry sectors. With this goal in mind, workshops have included presentations across the livestock and aquaculture industries to take participants outside their area of expertise and encouraged them to think outside the box. This year we increased the scope even further by also inviting presentations from the cropping and horticulture industries. Since the topic of heat stress has recently gained increased attention, we will discuss a wide range of aspects associated with heat stress, such as the physiology of heat stress and phenotypic indicators, genetic approaches and industry impacts.

Heat stress in animals describes a situation where an animal is exposed to high temperatures and unable to dissipate body heat, which causes an increase in body temperature. In the short term, an animal will react to heat stress with behavioural strategies (e.g. seeking shade, panting) to reduce the heat load. With prolonged excessive heat load, feed intake is reduced and production losses occur. Under extreme circumstances, excessive heat load can lead to death. In plants, heat stress can be defined as irreversible damage to plant function and development as a consequence of hot temperatures. Environmental causes of heat stress in plants and animals include high temperatures and high humidity over a long period of time, which is exacerbated by low cloud cover and high solar radiation.

With raising average temperatures, agricultural industries are faced with the challenge to manage potential impacts of heat stress on their crops, their pasture base and welfare and production of their livestock or aquaculture species. Management strategies such as shade and irrigation are effective but costly and, depending on the severity of climatic conditions, may have limited success. Susceptibility of organisms to heat stress can vary due to factors such as age and general health, but also genetic factors, such as breed or variety. Further, as we will hear during the workshop, genetic variation exists within breeds that enables genetic approaches to address heat stress in plants and animals. Selective breeding provides a long term approach that facilitates improvement of the physiology of plants and animals to cope with excessive heat load. The challenge here is to obtain cost-effective phenotypes to describe heat stress.

The chapters of this book discuss where the current climate is trending, and outlines opportunities for the crop, orchard, livestock and aquaculture industries to describe and measure heat stress, all with the focus on genetic improvement.

We would like to thank everyone who has contributed to this event for their time and effort: the authors for their contributions to the book and presentations, the reviewers who all readily agreed to critique the manuscripts. We would like to express a special thanks to Kathy Dobos for her contributions into the organisation of this workshop and the publication. Thank you!

Susanne Hermesch and Sonja Dominik
Armidale, September 2018

Genetic sensitivity of beef cattle to environmental variation

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Abstract

Unravelling genetic sensitivity of beef cattle in relation to environmental variation is important as our current knowledge on this topic is limited, increasing the risk that beef herds move towards losing adaptability and efficiency due to a negative correlated response to selection for increased productivity. Genetic sensitivity to environmental variation can be investigated in different ways in animal breeding programs. Here, two strategies are discussed: i) selection based on a reaction norm (a response curve of each genotype to a range of environmental changes); and ii) selection for reduced environmental variance or increased homogeneity of production. Both strategies can be used to deal with sensitivity to different factors of environmental variation, including heat stress. Possible consequences of selection for reduced environmental sensitivity are considered. Finally, some results are presented of genomic studies focused on unravelling the genetic mechanisms associated with environmental sensitivity.

Introduction

Genotype by environment interaction (GxE) has been shown to be an important source of phenotypic variation in beef cattle production, particularly in tropical environments (Cardoso and Tempelman, 2012; Chiaia *et al.*, 2015; Santana *et al.*, 2015). At least at the extremes (e.g. temperate versus tropical environments) genotypes selected for high production under favourable environments have poor performance in restricted conditions and, conversely, genotypes more adapted to constrained environments do not express the highest productivity with energy dense feed and stress-free environments. However, the latter genotypes may be more robust, i.e. show less sensitivity to environmental variation (Frisch and Vercoe, 1984; Burrow, 2012).

In the presence of GxE, one option is to identify the best genotype for each specific environmental condition. However, this strategy may provide suboptimal results especially in the tropics where animals are predominantly raised on pasture and environmental conditions are highly determined by the extent of the dry season, which can vary substantially among years, even within herds. Furthermore, the environmental conditions experienced by seedstock herds can deviate from those observed in multiplier and commercial herds, and the best genotype for the seedstock conditions will not necessarily have good performance in the other herds. This problem is magnified by climate change, as environmental variation has been more pronounced and more difficult to predict, adversely impacting livestock production (Rojas-Downing *et al.*, 2017).

Another strategy to deal with GxE is to select animals not only based on their productivity but also on their robustness or sensitivity to environmental variation, since this has been shown to be heritable (Kirkpatrick *et al.*, 1990). More robust genotypes not only have phenotypic performance less affected by environmental variation but also tend to be more adapted to challenging conditions (Strandberg, 2009). Moreover, the strategy of breeding for robustness is aligned with an increasing necessity of adopting more sustainable and low-cost production systems in the tropics, i.e. systems that focus on efficiency (and perhaps profitability) rather than total productivity (O'Neill *et al.*, 2010).

Genetic sensitivity to environmental variation can be addressed in different ways in animal breeding programs. One alternative is to use crossbreeding among breeds that complement each other regarding their adaptability and performance as, for example, crosses between indicine (*Bos indicus*) and taurine (*Bos taurus*) breeds. The drawback of this strategy is that crossbred animals may have considerable variation in adaptation or sensitivity to environmental variation. Another option to address sensitivity is to select directly for traits related to robustness or adaptation as, for example, tick resistance or heat tolerance. This, however, requires reliable recording of data that are sometimes not easily or routinely measured. Two other strategies to select for reduced sensitivity include: i) selection based on a reaction norm (a response curve of each genotype to environmental variation); and ii) selection for reduced environmental variance or increased homogeneity of production. As further discussed in the next two sections, both strategies seem to be effective selection tools to improve robustness or resilience to environmental variation, including selection for heat tolerance. There are few publications on these approaches in beef cattle. Therefore, some results from other species are also provided to illustrate the approaches and how they might be applied in breeding programs.

Environmental variation is influenced through a number of factors. Temperature is one of the important factors because it influences not only feed availability but also has direct physiological consequences if, for example, temperature exceeds comfort level causing heat stress. Among different problems, heat stress causes production and reproduction losses, increases health problems and mortality rates and is, consequently, also important for animal welfare (Rolf, 2015). The selection strategies discussed here can be used to deal with sensitivity to different factors of environmental variation, including heat stress.

Changing sensitivity by selection based on reaction norm

Genetic sensitivity to environmental variation can be assessed, for example, by reaction norm models (Falconer, 1990; Fiske *et al.*, 2003). In this framework, the response of each individual or genotype to environmental variation is modelled as a unique curve that has its trajectory determined by a continuous environmental descriptor. For instance, if a linear regression is considered, individuals with a flatter reaction norm (slope) are supposedly more robust to environmental variation (Strandberg, 2009). In this case, a non-zero genetic variation of the slope would indicate the presence of GxE, and offer the possibility of using the individual random slopes as a selection criterion for robustness.

An important aspect of modelling GxE through reaction norm models is the characterization of the environmental descriptor. Nguyen *et al.* (2016), for example, used a temperature humidity index as an indicator (continuous descriptor) of heat load to study tolerance to heat stress in dairy cattle. Heat tolerance was defined as the rate of decline (random slope) in milk production of each cow as a function of the temperature humidity index. Bradford *et al.* (2016) adopted a similar indicator of heat load to assess the impact of heat stress on weaning (WW) and yearling weight (YW) in Angus cattle, using data from the Upper South region of the United States. Their results indicated little effect of heat stress on YW and an important effect on WW.

In the absence of proper environmental descriptor information to model the reaction norms, descriptors derived from phenotypic data are commonly used, such as herd-year-season mean performance or contemporary group effect estimates (Calus *et al.*, 2002; Cardoso and Tempelman, 2012). However, such implementation may result in biased GxE estimates if genetic differences that may exist among environmental gradient levels are not properly taken in to account (Calus *et al.*, 2004). Hierarchical statistical models have been recommended to avoid biased estimates of the reaction norms, when the environmental descriptor needs to be derived from phenotypic data (Su *et al.*, 2006; Cardoso and Tempelman, 2012).

The choice of the curve to model the reaction norm is of primary importance when assessing the sensitivity of each animal. In practice, a linear regression is usually adopted since higher order polynomial coefficients may be difficult to estimate and interpret. However, if the true reaction norms are not linear, the random slope of a linear regression may not be a good indicator of the animal's sensitivity. Therefore, testing higher-order polynomial regression models is recommended (Schaeffer, 2004).

A further aspect to be considered is the genetic correlation among the parameters of a reaction norm curve. For instance, if a linear regression is used, a high genetic correlation between the intercept and the slope indicates that selection for increased production performance in 'good' (less restrictive) environments would result in increased sensitivity (Falconer, 1990). It also indicates that it would be difficult to jointly select for increased performance and reduced sensitivity. On the other hand, a low or null genetic correlation between the intercept and the slope would suggest more opportunity to select for increased performance and reduced

sensitivity. The response to selection also depends on the genetic variability (heritability) of the parameters of the curve.

In general, reaction norm models have had limited adoption in beef cattle breeding programs mainly because they cannot be used to evaluate young sires as progeny are required in different environments to derive accurate sire breeding values for robustness. Genotypic information from high-density single-nucleotide polymorphism (SNP) panels may allow this problem to be overcome. Accurate genomic breeding values of the individual reaction norms can be obtained, even for young animals, given that a good prediction equation is developed (Meuwissen *et al.*, 2001).

Reducing sensitivity by reducing environmental variance

Selection for reduced environmental variance (V_e) or increased homogeneity of production has also been indicated as a strategy to reduce sensitivity (Blasco *et al.*, 2017). There is a strong evidence in the literature suggesting that V_e is under some degree of genetic control (Morgante *et al.*, 2015; Ørsted *et al.*, 2018), meaning that variation in V_e among individuals or genotypes is heritable and subject to selection and other evolutionary forces (Hill and Mulder, 2010). In a breeding context, selection to reduce V_e is attractive since it can lead to more stable or uniform performance without depleting genetic variance and, consequently, genetic progress at the mean phenotypic level of the trait (Mulder *et al.*, 2008).

Environmental variance may be estimated with repeated measures of the same trait within individuals as, for example, litter size per dam in multiparous species (e.g. pigs), with some dams with consistent (homogeneous) number of progeny per parity and others having heterogeneous litter size among parities. Environmental variance can also be estimated within families as, for example, body weight of progeny, with some sires having progeny with more uniform (less variable) body weight at a specific age compared to other sires. An application in beef cattle, for example, would be to assess uniformity of body weight of half sib (bull) families.

Furthermore, variation in V_e can be assessed within environment, being in this case a measure of the extent to which individuals with the same genotype can produce consistent phenotype within an environmental condition. This is most commonly studied under an evolutionary perspective and is usually referred as within-environment variation (Ørsted *et al.*, 2018) or micro-environmental plasticity (Morgante *et al.*, 2015). In animal breeding, however, variation in V_e is typically assessed by within-family performance or repeated measures of an individual being expressed in different environmental conditions, and the heritable component of such variation is commonly referred as genetic heterogeneity of residual variance (Mulder *et al.*, 2008).

Although the genetic mechanisms related to heterogeneity of residual variance are poorly understood, individuals with lower V_e for a specific trait may be assumed to be more 'robust' or less sensitive to changes in environmental conditions, especially for traits related to fitness.

Blasco *et al.* (2017), for instance, hypothesized that rabbit females (does) showing low variability in litter size could have higher resilience or would be more able to cope with differences in environmental conditions than females with ‘less adaptable’ genotypes which, in turn, would be more sensitive to diseases and to stress and show a higher degree of variability in litter size. The authors performed a ten-generation divergent selection experiment, selecting one line of rabbits for litter size homogeneity and one line for litter size heterogeneity by measuring intra-doe (pre-corrected) phenotypic variance of litter size among parities. A substantial selection response was observed, indicating that V_e of litter size is genetically affected (Blasco *et al.*, 2017). Results of a subsequent study, using data from the same divergent selection experiment, supported the hypothesis that reduced litter size V_e is associated to higher resilience (lower ‘sensitivity’) to external pathogens and stressful conditions (Blasco *et al.*, 2018).

Ørsted *et al.* (2018), studying cold tolerance in *Drosophila melanogaster*, also found evidence that selection for reduced V_e could be used as a strategy to reduce sensitivity to environmental variation (cold stress, in their case). No publication was found in beef cattle suggesting to use the heritable component of V_e as a strategy to improve robustness or resilience to environmental stressors (e.g. heat stress). Nonetheless, the previously mentioned studies in rabbits (Blasco *et al.*, 2018) and *Drosophila* (Ørsted *et al.*, 2018) highlight its feasibility.

Although they may be seen as related or complementary strategies, trying to reduce sensitivity by decreasing V_e is different from changing sensitivity by selection based on reaction norm, since the former is focussed on the environmental variance (dispersion) and the latter on the mean (location) level of a trait (Ørsted *et al.*, 2018). Also, the genetic mechanisms underlying differences in V_e are not necessarily the same as those associated with differences in sensitivity, being in both cases poorly understood.

A further relevant aspect to be considered is that, like sensitivity in the mean, variation in V_e seems also to be trait-specific, i.e. reduced V_e for a trait is not necessarily associated with reduced V_e for other traits. For example, Bodin *et al.* (2018) observed low positive genetic correlation between the dispersion components (V_e) of birth weight and litter size, in an experimental population of mice divergently selected for (within-litter) birth weight V_e . This suggested that the least sensitive animals (lower V_e) for one trait tended to be slightly less sensitive for the expression of the other trait. The divergent selection was highly successful and led to a large difference in birth weight variability between the lines but, in accordance with the genetic correlation estimate, the indirect response on litter size variability was low (Bodin *et al.*, 2018).

Is lower genetic sensitivity to environmental variation desired?

An animal may show lower sensitivity to environmental variation (a flatter reaction norm) by having reasonably good production performance in challenging environments or by not having a steep response on performance in good environments. The former is essential for beef cattle production in the tropics where animals are frequently exposed to challenging conditions. However, if good production in unfavourable environments results in decreased

reproduction performance, for example, then less sensitivity to environmental variation may be undesirable. This highlights the necessity of having a holistic view about the animals, the traits, the production systems and their interplay before deciding to select for reduced sensitivity to environmental variation.

It is important to emphasize that good production performance in poor environments does not necessarily compromise reproduction in cattle. For instance, a (robust) cow may show reasonably good production performance in challenging environments without having her reproduction compromised, by having low maintenance requirements and good temperament. Additionally, despite possible antagonism between robustness and production, a joint positive genetic response for both can be achieved if they are properly accounted for in the breeding goal and as selection criteria (Knap and Wang, 2006).

Considering the subject under an evolutionary perspective is important to reflect on the possible consequences of selection for reduced sensitivity. In an evolutionary genetic context, sensitivity of genotypes to environmental variation is termed as phenotypic plasticity and is usually considered as an alternative for organisms to adapt to changes in environmental conditions (Bradshaw, 2006). From that perspective, plasticity (increased sensitivity) can be seen as beneficial. However, in nature, plasticity for fitness must be selected against, since individuals with high and stable fitness in multiple environmental conditions have higher chance of reproducing and procreating.

Another important discussion under an evolutionary perspective is related to the (hypothetical) limits and costs associated with phenotypic plasticity, given that in nature no organism is 'infinitely' or perfectly plastic (Murren *et al.*, 2015). Connected to that topic is whether, or under which circumstances, nature favours generalists ('one size fits all') or specialists. Reflecting on that and speculating about its implications for animal breeding, Strandberg (2009) made the following reasonable considerations:

“What then can we learn from studies of plasticity and adaptation in evolutionary genetics? First of all, the concept of ‘one size fits all’ is not a reasonable one. If you have too large an environmental range in nature, specialists evolve. If we look at animal breeding from a truly global perspective, I think that we need to come to the same conclusion. For instance, there are too many diseases in the world for all cows to be especially resistant to all of them, and even if it were possible it would be extremely costly to achieve such a resistance (e.g. to diseases that cows in a certain region never encounter). Specialisation is also expected to give rise to higher genetic diversity as a between population component. Having said that, within a smaller range of environments, animals should be robust.”

Although Strandberg (2009) referred to robustness in a disease resistance context, his considerations could also be applied to heat tolerance and other types of resilience to environmental variation.

Unravelling genetic sensitivity to environmental variation

As previously discussed, genetic markers (e.g. SNP) can be used to help attain more accurate predictions of sensitivity to environmental variation. Genotypic data has also been used to map genome regions associated with sensitivity through, for example, genome-wide association studies (GWAS). Unravelling the genetic mechanisms affecting sensitivity can be beneficial in different aspects, such as using this knowledge to attain more accurate genomic breeding values (Pérez-Enciso *et al.*, 2015; MacLeod *et al.*, 2016). Also, if markers linked to major effects are identified, genomic tests can be developed to better drive selection and mating decisions (VanRaden *et al.*, 2011).

A full understanding of the genetic basis of sensitivity to environmental variation remains elusive but important studies have been performed to address this topic (e.g. Lillehammer *et al.*, 2009; Hayes *et al.*, 2009; Streit *et al.*, 2013a; Silva *et al.*, 2014; Macciotta *et al.*, 2017; Lafuente *et al.*, 2018). A common conclusion from these studies is that environmental sensitivity is a typical quantitative ‘trait’, genetically controlled by many genes with small effects and few genes with moderate to large effect. Unfortunately, agreement about other aspects, such as the existence or not of overlapping regions affecting sensitivity of different traits or affecting the same trait under different environmental descriptors (Hayes *et al.*, 2009; Streit *et al.*, 2013a,b), is not so evident. Although it has been shown that sensitivity for a specific trait is not necessarily associated with sensitivity for other traits (Santana *et al.*, 2015), Streit *et al.* (2013b) and Carreira *et al.* (2013) identified some candidate genes having a pleiotropic effect on environmental sensitivity of milk production traits in dairy cattle and plasticity of morphological traits in *Drosophila melanogaster*, respectively.

Studies have also been made to assess if environmental sensitivity is affected by specific loci determining sensitivity responses or by the same pleiotropic loci controlling the expression of the trait (Nicoglou, 2015). Results from different studies support the existence of both types of loci (e.g. Lillehammer *et al.*, 2009; Streit *et al.*, 2013a). In a breeding context, understanding the relationship among the genetic mechanisms underpinning environmental sensitivity and the expression of the trait at a given environment is relevant since it directly affects the response to selection that can be achievable. Lillehammer *et al.* (2009) argued that there are more opportunities to select for ‘robustness’ if sensitivity is mainly affected by alleles with a positive effect on the trait and a negative correlation between production and environmental sensitivity. In this case, improved robustness would not need to come at the expense of reduced productivity. However, it seems that markers within this category are not so common, at least for milk production traits in dairy cattle (Streit *et al.*, 2013a,b).

Effects of different genetic markers (loci) on genetic sensitivity to environmental variation can also be viewed as allele by environment interaction and reaction norm models can be extended to the individual locus level (Lillehammer *et al.*, 2009; Hayes *et al.*, 2009). In this framework, the reaction norm of each locus can reveal the size and direction of its effect on the trait along the environmental gradient. This strategy has been adopted in plant breeding to identify gene by environmental patterns, allowing prediction of performance of different genotypes in multiple

environments (even those not observed in the field) to optimize the breeding schemes (Li *et al.*, 2018). An interesting extension of this approach would be to consider nonlinear reaction norms and investigate the possible existence of markers expressing environment-dependent sensitivity, i.e. markers more sensitive to improvements in the environment and less sensitive to its deterioration (and vice versa).

GWAS have also been used to identify candidate regions and genes associated with reduced V_e of different traits in various species such as chicken (Wolc *et al.*, 2012), pigs (Sell-Kubiak *et al.*, 2015; Wang *et al.*, 2016; Wang *et al.*, 2017), cattle (Mulder *et al.*, 2013; Lung *et al.*, 2018), among others (e.g. Morgante *et al.*, 2015). Lung *et al.* (2018) studied genomic regions associated with within-family residual variance of yearling weight (YW) in Nelore cattle from Brazil. Their results suggest that the mean and uniformity of YW are partially under different genetic control, although some common candidate genes associated with both mean and uniformity were identified. Similarly, Wolc *et al.* (2012) observed both common and independent regions affecting mean and uniformity of egg weight in layer chickens. Lung *et al.* (2018) also observed that the common candidate genes for mean and uniformity of YW were mainly involved in metabolism, whereas the candidate genes associated only with uniformity were involved in a greater variety of processes such as metabolism, stress, inflammatory and immune responses, mineralization, neuronal activity and bone formation. These results suggest that, compared to the mean, uniformity may have a genetic architecture even more complex and may be controlled by several processes and mechanisms in order to reach homeostasis (stability) under different environmental conditions.

Interestingly, members of the heat shock protein family have been considered candidate genes for either V_e (Morgante *et al.*, 2015; Sell-Kubiak *et al.*, 2015; Lung *et al.*, 2018) or sensitivity/plasticity (Queitsch *et al.*, 2002; Sangster *et al.*, 2008; Macciotta *et al.*, 2017). These findings suggest that the genetic mechanisms underlying differences in V_e may be partially the same as those associated with differences in sensitivity on the mean level of a trait. Moreover, they support the hypothesis that genetic heterogeneity of residual variance can be used to drive selection not only towards a more uniform production but also for ‘robustness’ (lower sensitivity).

Concluding remarks

Beef cattle breeding programs should focus not only on increasing productivity but also on reducing sensitivity to environmental variation, especially in the tropics where animals are frequently exposed to challenging conditions and there is limited control of the environment. Breeding for reduced sensitivity (‘robustness’) is desired when it does not compromise substantially productivity. Understanding the genetic mechanisms underlying sensitivity is of ultimate importance to help attaining joint positive genetic responses for both productivity and reduced sensitivity. Genomic information should help animal breeders to unravel these mechanisms and produce more accurate genetic and performance predictions when applied together with appropriate methods, such as reaction norm models. Selection for increased

uniformity or homogeneity of production may also help to produce animals that are more resilient and more able to cope with environmental variations. If animals are exposed to heat stress, selection based on reaction norms and selection for increased homogeneity of production may be used as tools to improve heat tolerance.

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