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Statistical tools to select for robustness and milk quality

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This work was part of the EU RobustMilk project. In this work package, we have focused on two aspects of robustness, micro- and macro-environmental sensitivity and applied these to somatic cell count (SCC), one aspect of milk quality. We showed that it is possible to combine both categorical and continuous descriptions of the environment in one analysis of genotype by environment interaction. We also developed a method to estimate genetic variation in residual variance and applied it to both simulated and a large field data set of dairy cattle. We showed that it is possible to estimate genetic variation in both micro- and macro-environmental sensitivity in the same data, but that there is a need for good data structure. In a dairy cattle example, this would mean at least 100 bulls with at least 100 daughters each. We also developed methods for improved genetic evaluation of SCC. We estimated genetic variance for some alternative SCC traits, both in an experimental herd data and in field data. Most of them were highly correlated with subclinical mastitis (>0.9) and clinical mastitis (0.7 to 0.8), and were also highly correlated with each other. We studied whether the fact that animals in different herds are differentially exposed to mastitis pathogens could be a reason for the low heritabilities for mastitis, but did not find strong evidence for that. We also created a new model to estimate breeding values not only for the probability of getting mastitis but also for recovering from it. In a progeny-testing situation, this approach resulted in accuracies of 0.75 and 0.4 for these two traits, respectively, which means that it is possible to also select for cows that recover more quickly if they get mastitis.

Keywords: genotype by environment interaction, environmental sensitivity, reaction norm, somatic cell count, mastitis

Introduction

Our perspective on robustness, as applied to cows, is:

- The ability of a cow to function well in the environment she lives in, being resilient to the changes in the 'micro-environment' that she encounters (during her life).
- The ability of a cow to function well over a wide range of (macro)environments, for example, climates, production systems or herds.

We should, however, ask: *do we want cows to be robust*? The answer might seem self-evident, but let us keep that question in mind. In evolutionary genetics, researchers have for a long time struggled with the issues of plasticity (the ability to respond to changes in the environment) in relation to adaptation. Adaptation can be described as a feature that has evolved by natural selection that increases the fitness of the individual. It is important to remember that an adaptation is something that evolves in a population as a result of environmental cues, whereas when an individual 'adapts', this is through plasticity, that is, the ability to change the phenotype in response to a change in the environment. Therefore, genetic variation in plasticity is vital for the adaptation of populations. Environments are to some extent always unpredictable and individuals need to be able to handle smaller or larger changes and still survive and reproduce. Therefore, there is need for both adaptation (of the whole population) and plasticity (of the individual).

So what are the parallels for animal production? We select animals so that the resultant populations (hopefully) become more adapted to the production environments they are used in. This should result in better productivity, health, welfare and profit. In animal husbandry, we try to keep the production environment at a good and constant level; however, there will always be perturbations because of factors that cannot be controlled, or even measured: small differences in feed quality, temperature, rainfall, management, etc. Furthermore, cows from the same population, or even descending from the same sire, may be used in different production environments differing in climate, housing systems, pasture-based or not,

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etc. In these cases, the two aspects of robustness defined above become important. We generally refer to these as micro- and macro-environmental sensitivities and we will come back to these later.

In the RobustMilk project, we have studied both robustness and milk quality. Our chosen aspect of milk quality has been somatic cell count (SCC). SCC is, of course, a generally accepted indicator of clinical (CM) or subclinical mastitis (SCM) but also has negative effects on processing, product quality and shelf life. We have used also SCC (together with milk yield) as an example trait in our studies of robustness.

Robustness

Macro-environmental sensitivity or genotype by environment interaction (G × E)

Cows may respond differently to differences in the macro-environmental system. For example, SCC of one cow may be low across production systems, whereas another cow may tend to have a high SCC in one production system but low in another. If this different response to a change in environment has a genetic basis, this is called genotype by environment interaction (G × E). G × E can be analysed by using a multi-trait model in which a trait measured in different environments is considered as separate traits. This method is used when the environment is naturally classified into discrete categories (e.g. production systems, climatic zones). When the environmental descriptor is of continuous nature (e.g. temperature, herd size), one can either categorize it and use the multi-trait method, or analyse it using a reaction norm model, in which the trait is considered to be a function of the environmental descriptor. Each of these methods has been used in several studies before, but we combined them in a study of SCC in Irish dairy cattle (Windig *et al.*, 2011). We had production system as a categorical environmental descriptor (either spring calving or year-round calving) and herd average milk production as a continuous environmental descriptor and analysed SCC across environments with a bivariate linear reaction norm model. In this model, the genetic correlation between systems was around 0.83, which was lower than if the reaction norm on milk production was not included (0.91). However, within the same production system, there was practically no G × E between herds with low or high milk production.

Micro-environmental sensitivity or genetic heterogeneity of residual variance

Micro-environmental sensitivity or genetic heterogeneity of residual variance has been much less studied than macro-environmental sensitivity. In a review, Hill and Mulder (2010) showed that several studies, mainly in body weight traits or litter size, have detected genetic variation in residual variance. Most recent studies have used a Bayesian approach with Markov Chain Monte Carlo sampling algorithms for estimation of variance components (e.g. Sorensen and Waagepetersen, 2003; Ibanez-Escriche *et al.*, 2008a and 2008b). However, this method has computational limitations, and for larger data sets the computation time becomes a severe restriction.

Therefore, a new method for estimating genetic variance in residual variance was developed using double hierarchical generalized linear models (DHGLM; Rönnegård *et al.*, 2010). This approach is based on iterating between two sets of mixed model equations, one on the level of the observations and the other on the level of residual variances. This approach was validated both using simulated data and by application on the data set on litter size of pigs, previously analysed by Sorensen and Waagepetersen (2003).

One particular problem that needed to be addressed was the estimation of the (genetic) correlation between the breeding value (BV) for the level of the trait (the ordinary BV) and the BV for the residual variance. The way to estimate this correlation had not been derived earlier by the founders of the DHGLM framework (Lee and Nelder, 2006). The DHGLM theory was therefore extended and approximated by a bivariate linear mixed model (Felleki *et al.*, 2012).

The approach developed makes it possible to estimate genetic variation in residual variance also in large data sets. We applied it to a relatively large dairy cattle data with 180 000 Holstein cows having about 1.6 million test-day records (Rönnegård *et al.*, 2012). Estimation of variance components took less than a week on a normal Linux server. We found genetic variation in residual variance in both milk yield and SCC: a change of one genetic standard deviation of the BVs for residual variance would result in a change in the residual variance of about 20%, for both traits.

Genetic variation in residual variance was also found in a population of Swedish Red dairy cattle. Estimated variance components were very similar to those estimated by Rönnegård *et al.* (2012) in the Swedish Holstein population. BVs for residual variance were subsequently used for a genome-wide association study (GWAS) and signals on several chromosome were found (Fikse *et al.*, 2012).

The same approach was also applied to milk yield, somatic cell score, saturated fatty acid (SFA), unsaturated fatty acids (UFA) and C18:1 *cis*-9 contents in milk in Walloonian Holstein cows (Vandenplas *et al.*, 2012). For milk and SCC, the genetic variance in residual variance was a bit smaller than in Swedish Holsteins (Rönnegård *et al.*, 2012) with genetic standard deviations of 17% and 16%, respectively. For SFA, UFA and C18:1 *cis*-9 genetic standard deviations were 12%.

Simultaneous estimation of micro- and macro-environmental sensitivity

In one part of our project, we tested, on simulated data, whether it was possible to estimate genetic variance in both micro- and macro-environmental sensitivity in the same analysis. The DHGLM method developed by Rönnegård *et al.* (2010) was extended with a linear reaction norm to account for micro- and macro-environmental sensitivity (Mulder *et al.*, 2011 and 2012). A data set with true genetic variation in micro-environmental, or macro-environmental sensitivity or both was analysed with models including either or both of these components, and the models were compared

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using Akaike Information Criterion (AIC) or likelihood ratio test. In 95% to 100% or 97% to 100% of the cases, the correct statistical model (corresponding to the true) was chosen for AIC and likelihood ratio test, respectively. We also found that it was necessary to have at least 100 bulls with at least 100 daughters each to estimate all genetic parameters with sufficient precision. The estimate of the genetic variance in micro-environmental sensitivity had lower precision than the genetic variance of macro-environmental sensitivity. Furthermore, the genetic correlations between micro-environmental sensitivity with macro-environmental sensitivity, or with the intercept of the reaction norm, were estimated with low precision (s.d. across replicates >0.15), even with designs with 100 bulls each with 100 daughters. In designs with only 20 daughters per bull, a majority of the replicates failed to converge to positive definite variance–covariance matrices.

Milk quality – SCC

To lower the SCC in milk, it is necessary to decrease the incidence of both CM and SCM. This can be done both by using observations on actual mastitis cases and by using SCC, being an indicator of both SCM and CM. Apart from the studies above on genetic variation in residual variance in SCC, which could be used to select for lower SCC (lower variation is also associated with lower average levels), we have studied how to decrease SCC in various ways.

Definition of alternative SCC traits

One option is to try to improve the actual trait used in the genetic evaluation. In our case, we want a trait on the basis of SCC that is more closely related to CM. Currently, most commonly an average of the (log of) SCC over a certain period in the lactation is used (e.g. first 50 or 150 days) or a test-day model is used, and the EBV for the average level (or maybe a sum of SCC over a certain period based on the EBVs) is used for selection purposes. We first studied some alternative SCC traits that could be defined using test-day SCC from weekly observations in an experimental herd and then tested whether these would also be useful with only monthly observations (Urioste *et al.*, 2010). Standard deviation of SCC within the lactation and a discrete indicator of at least 1 test day with SCC above 500 000 cells/ml (TD $>$ 500) were those most strongly associated with CM in both the weekly and monthly data sets. In the weekly data set, also the number of days of the widest SCC peak was selected, and in the monthly data set the number of SCC peaks (NPeak) and average number of days per SCC peak (AveDays) were chosen. Heritabilities were in general between 10% and 16% (except for AveDays: 5%). Heritabilities were at least high in the monthly data set, which indicated that these traits would be potentially useful also in a field data set.

To test this, these traits were also studied in a large field data set consisting of about 178 000, 116 000 and 64 000 lactation records in the first three lactations, respectively (Urioste *et al.*, 2012). Heritability was estimated at 0.12 to 0.17 for SCCSD, TD $>$ 500 and AveDays, but lower, 0.06 to 0.10, for NPeak and TD41-80 (an indicator of at least 1 test day with SCC between 41 000 and 80 000 cells/ml). All traits, except TD41-80, were highly positively genetically correlated with CM (0.67 to 0.82) and even more so with SCM (0.94 to 0.99) in all three lactations. TD41-80 showed a negative (as expected) correlation from -0.22 to -0.50 with CM and from -0.48 to -0.85 with SCM. All alternative traits, except TD41-80, were strongly correlated with each other within lactation; however, TD41-80 had a negative correlation of around 0.4 to 0.5 with other traits in first lactation.

Epidemiological reaction norms

One problem with selecting for better udder health is that the traits of interest have rather low heritabilities, especially for CM. One possible reason for the low heritabilities is that not all animals have been exposed to the pathogens causing the disease. Consequently, in a typical study analysing the genetics of (sub)clinical mastitis using national recording schemes, healthy animals are a mixture of non-resistant animals that have been exposed and resistant animals that may or may not have been in contact with pathogens. Bishop and Woolliams (2010) showed that incomplete exposure of animals to pathogens can reduce estimated heritabilities considerably. One way to account for this is to quantify the exposure probability and estimate heritabilities in environments differing in exposure probability. We did this using a reaction norm model, where the environmental descriptor was a measure of prevalence on the basis of what percentage of cows in a herd had either CM or elevated SCC, and the trait was CM or SCM. We found that including information on herd prevalence in the model explained more variation in CM and SCM. We also found a somewhat curvilinear concave relation between heritability and prevalence, but no strong evidence for the hypothesis by Bishop and Woolliams (2010) of decreasing heritability with decreasing prevalence and exposure.

Transition probability model

The SCC in milk associated with mastitis could be decreased both by having cows that do not get mastitis and by having cows that recover quickly from mastitis. Previously, genetic evaluation and selection has aimed at decreasing the first factor, but in one part of our project we have aimed at including both aspects in our genetic evaluation (Franzén *et al.*, 2012). In this approach, we estimated breeding values (EBVs) for the probability of transition from a healthy to a diseased state as well as for the reverse probability. The approach takes into account the recovery process and repeated cases. In a scenario with about 16% of lactations having at least one mastitis case, and with 150 daughters per bull, the accuracy of EBVs (correlation between true and EBVs) was about 0.75 for the transition from healthy to diseased, and about 0.4 in the opposite direction. The lower accuracy for the EBV from diseased to healthy is expected because it is based on severely reduced data consisting only

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of daughters that have had mastitis. However, we managed to deliver as accurate EBVs of mastitis liability as some previously used methods using data of confirmed cases of mastitis, even though we estimated mastitis based on SCC only. In addition, the approach generated valuable information about the recovery process that could be included in the genetic evaluation of mastitis.

Discussion

We have studied two types of robustness or environmental sensitivity, related either to a wider spectrum of macro-environments or to smaller changes in the micro-environment. Traditionally, the macro-environmental sensitivity (G × E) has been studied quite extensively, and given large environmental differences, there is no doubt that it exists. It is more a matter of when it becomes important enough for us to take it into account.

An obvious consequence of G × E is that if individuals are selected to become parents on the basis of information from one environment but their offspring are used in another environment, at least partly the wrong animals may have been selected. The equally obvious solution is to include information from the production environment into the genetic evaluation. Mulder and Bijma (2005) showed that the loss in genetic gain (compared with a situation with no G × E) was lowest when progenies of males were tested in the production environment and that this system was better than testing of sibs in that environment, and both systems were superior to testing only in the selection environment.

Another question is whether two breeding programmes should cooperate even if their breeding goals differ to a certain extent, resulting in G × E. This could apply to two countries or to different production systems, for example, organic and conventional production. Mulder and Bijma (2006) showed that long-term cooperation was beneficial if the correlations between breeding goals were higher than 0.8 to 0.9. However, initial cooperation was beneficial even when the correlation was as low as 0.4 to 0.6; however, after some generations the two populations had diverged so much that selection was practiced only within population. Furthermore, small breeding programmes also benefited from long-term cooperation at values of genetic correlation below 0.8 (Mulder and Bijma, 2006). It was also shown that for dairy cattle breeding programmes the genetic correlation had to be lower than 0.6 before it was beneficial to run two separate breeding programmes rather than progeny-testing bulls in both environments. If the selection intensity was high, the genetic correlation increased from 0.7 to 0.8, below which separate programmes were optimal. Again, for a small population (e.g. organic or niche production), the genetic correlation had to be even lower before two programmes were optimal (Mulder *et al.*, 2006).

Therefore, in summary, it seems that even if there is G × E, it is beneficial to cooperate and use information from other environments, unless the G × E is extremely large. This is not the same as ignoring the existence of G × E; rather it is to acknowledge its existence as something natural, and then adapting to that reality.

The discussion of genetic variation in micro-environmental sensitivity in animal breeding is more recent and has not yet been incorporated into breeding programmes in any systematic way. Apart from being related to robustness, selection for decreased heterogeneity is in general of interest for traits where large variation is undesirable. This might be true for, for example, carcass traits where uniformity is favourable for the slaughtering process, but in general for traits with an intermediate optimum. When the mean performance is close to the optimum, more of the selection pressure will move towards reducing the residual variance (Mulder *et al.*, 2008).

For the two example traits that we have mainly studied, milk production and SCC, selection for decreased heterogeneity would seem to be of most benefit for SCC. It is unclear whether the economic value of milk production is non-linear. There might be some value in having less variation in production level among cows in a herd, making it easier to formulate the feed rations. It might also be beneficial to have less variation in milk components from the dairy plant point of view; however, this must then be translated into an adequate pricing system. An added complication is that the genetic correlation between milk production level and residual variation is positive, meaning that lowering the residual variation is antagonistic to increasing the average level (Rönnegård *et al.*, 2012).

For SCC, however, this correlation is favourable, and therefore lowering residual variation goes hand in hand with lowering the average SCC. As there is some concern about lowering the SCC to too low levels, and there is a price penalty for too high levels, one might think of an optimal range of SCC with two boundaries. This means that there is also an economic value for lowering not only the average level but also the variation itself (because a certain proportion of animals (or herd averages) will fall outside the range).

We want to lower the average level of SCC for several other reasons as well. High SCC in the milk is connected to decreased processing efficiency, product quality and shelf life. Furthermore, it is an indication of CM or SCM and as such an indication of a welfare problem. Having cows that are healthy is another important aspect of robustness. In this project, we have used SCC in several ways, with the aim to improve the genetic evaluation of both CM and SCM. The alternative traits used in our project were all strongly genetically correlated with CM and SCM; however, they were also strongly correlated with each other and with the more conventional average of (log) SCC in the first 150 days of lactation. The only exception was TD41-80, which was less strongly correlated to other SCC-based traits, but still strongly correlated with, especially, SCM in later lactations.

The new approach of estimating BVs also for the ability to recover from a mastitis case is promising and could improve the selection for robust cows and improve milk quality (Franzén *et al.*, 2012). Naturally, there are several limitations to the method. It relies on good data quality, the more

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frequent sampling of SCC the better. A combination of knowledge of CM, SCC and milk yield could be used to better describe the disease and recovery process. Management procedures (e.g. drying off one quarter) could influence the inference (e.g. making the cow seem to recover quickly) and that information might need to be collected or inferred from the milk yield drop.

There are also several developments of the model that need further research. One natural extension would be to add another state: SCM. One could also fine-tune the classification by going from the current fixed thresholds to a mixture model approach. It would also be of scientific interest to use the EBVs for both mastitis liability and the ability to recover, in GWAS or genomic selection. It is not unlikely that partly different genes are responsible for the defence mechanisms for these two aspects.

In general, all the methods developed and used in this project could also be applied using molecular genetic data (Rönnegård and Valdar, 2011). However, it is important to remember that to have reliable estimates of quantitative trait loci (QTL) affecting the traits, it is vital to have a good data structure when estimating the EBVs that are the basis for GWAS or QTL detection. Both the estimation of EBVs for residual variance and the estimation of BVs for the ability to recover from mastitis put higher demands on the data structure than does the more ordinary estimation of BVs.

Thus, do we want cows to be robust? If we look at animal breeding from a truly global perspective, we think that we need to come to the conclusion that it is not reasonable to expect that a cow will function well in *all* environments; we do need specialists. For instance, there are too many diseases in the world for all cows to be 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). Specialization 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, that is, achieve a high value of total merit, regardless of differences in the environment. This could apply both to changes within the cow's own herd, across herds within the country or across countries with relatively similar environmental conditions. It is also important that we relate robustness to the total merit index (TMI) and not only to a single trait. TMI should be broad and include both production and functional traits. Otherwise it will be in too much conflict with the natural fitness; diseases and fertility will become severely limiting, and thus the breeding programme will not be sustainable in the long term. Furthermore, we might achieve 'robustness' in one trait (say, milk production) over a range of environments, but at the expense of a large change in, say, fertility. Therefore, it might be important to breed animals that are robust in terms of TMI, meaning small variation in TMI over a range of environments.

The predictor of the TMI is used to select animals for breeding and the genetic change in any trait is proportional to the covariance between that trait and the predictor of TMI. Therefore, it is important to ensure that the structure of the breeding programme allows for good prediction of all traits, otherwise the genetic response pattern will be very different from that indicated by the TMI.

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For more information, please visit the website www.robustmilk.eu, read the other papers in these proceedings or contact the project coordinator: Roel F. Veerkamp (E-mail: Roel.Veerkamp@wur.nl).

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