

Estimation of Genetic Predisposition

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1 Introduction

This section introduces the basic concepts of estimating genetic predisposition estimation such as:

- basic principle behind estimating genetic predisposition
- accuracy of estimated genetic predisposition
- use of genetic relationships for estimating genetic predisposition
- the connection between genetic parameters and estimated genetic predisposition
- different methods, data sources and experimental designs for estimating genetic predisposition

Breeding value estimation is a fundamental component of breeding programmes, in which the breeding value of each individual is predicted to inform subsequent selection decisions. The breeding value for an individual is the total additive genetic value which is passed on to the offspring. Thus the breeding value is not a measure of how good an individual is in itself, but rather of the effect its genes will have in the population. Breeding values are used for:

- comparing individuals in the breeding population and selecting parents for the next generation
- predicting the consequences of selection decisions
- describing genetic differences over time (result of previous selection)

The true breeding value (TBV) for an individual cannot be observed. It is only possible to measure its phenotypic value, which is influenced both by genotype and environment. Therefore, we need a way to infer the breeding value from the phenotypic value and select individuals based on an estimated breeding value (EBV). This is the objective of breeding value estimation.

2 Basic principles for breeding value estimation

Breeding values are estimated using information on phenotypes and genetic relationships for individuals in a breeding population. As introduced previously the phenotype for a quantitative trait is the sum of both genetic and environmental factors. In general the amount of information provided by the phenotype about the breeding value is determined by the narrow sense heritability (h^2), which measures the proportion of additive genetic variance contained in the total phenotypic variance. Furthermore phenotypes collected from close relatives provide more information about the breeding value of an individual. In this section we will illustrate these principles using phenotypic data and genetic relationships used for estimating genetic predisposition. We will now try to derive a general approach for predicting genetic predisposition for any situation. Even though the procedure is general we will use a simple example to describe it.

2.1 Genetic model

The breeding value is based on an assumption of a specific genetic model. In general the total genetic effect for an individual is the sum of both additive and non-additive effects that affect the trait:

$$y = \mu + a + d + i + \epsilon \quad (1)$$

where μ is the population mean, a is the breeding value (i.e. additive effect), d is the dominance effect, i is the epistasis effect, and e is the environmental deviation (or residual) not explained by the genetic effects in the model. However, only the additive genetic effects are passed on to the offspring and therefore contributes to the breeding value. In contrast non-additive genetic effects (dominance and epistasis) are degraded by recombination and are not inherited, even though they may be important for the individual's phenotype. Therefore we only consider the additive genetic model as the basis for breeding value estimation:

$$y = \mu + a + e$$

The true breeding value for an individual is the sum of all additive genetic effects that affect the quantitative trait:

$$a = \sum_{j=1}^q a_j$$

where a is the total additive genetic effect and a_j is the additive genetic effect for loci j . We therefore assume (based on the central limit theory) that the true breeding values, a , and the residual term, e , are normally distributed which means that the observed phenotype is also normally distributed:

$$\begin{aligned} a &\sim N(0, \sigma_a^2) \\ e &\sim N(0, \sigma_e^2) \\ y &\sim N(\mu, \sigma_a^2 + \sigma_e^2) \end{aligned}$$

2.2 Expected breeding value conditional on observed phenotype

The breeding value cannot be observed but must be estimated from phenotypic data and genetic relationships between individuals from the breeding population. Estimation of an unknown parameter using statistical modelling expresses the estimated quantity as a mathematical function of the observed data. The question is how this function should look like and what properties the estimated genetic predisposition should fulfill. For breeding purposes one objective for the estimated genetic predisposition is that the response to selection is maximized. [Henderson, 1963] found that the improvement of an offspring generation compared to the parent generation can be maximized when parents are selected based on the conditional expected value ($E(a|y)$) of the true breeding value a given the observed phenotypic values y . Under the assumption of multivariate normality for a and y (which are justified under the central limit theorem and the assumptions of many genetic and environmental factors), the expected value of the breeding value conditional on the observed phenotype y can be written as:

$$E(a|y) = E(a) + Cov(a, y)[Var(y)]^{-1}(y - E(y)) \quad (2)$$

The breeding value is defined as deviation from the general mean which means that the expected value $E(a)$ of the true breeding value a is $E(a) = 0$. Therefore the expected value of the breeding value is:

$$E(a|y) = Cov(a, y)[Var(y)]^{-1}(y - E(y)) \quad (3)$$

The expression for the estimate of the breeding value consists of two parts; The term $y - E(y)$ shows that the observed phenotypic values are corrected for the fixed effects represented by μ . The term $b_{a|y} = Cov(a, y)[Var(y)]^{-1}$ often referred to as the regression coefficient is a weighting factor with which the corrected phenotypic values are multiplied.

To be able to estimate the breeding value we need to determine the values for the terms $E(a)$, $E(y)$, $Var(y)$, and $Cov(a, y)$ in the expression above. It is possible to derive simple formula's for these terms based on:

- adjusted phenotypic observations for the quantitative trait of related individuals
- heritability of the quantitative trait
- knowledge of inheritance laws and genetic relationships (e.g. parents, grandparents, siblings) for individuals with phenotypic observations of the quantitative trait

We will distinguish between true and estimated breeding value using the following notation:

$$\begin{aligned} a &= \text{additive genetic value} = \text{true breeding value} \\ \hat{a} &= E(a|y) = \text{estimated additive genetic value} = \text{estimated breeding value} \end{aligned}$$

Estimated genetic predisposition are unbiased

Below we show that \hat{a} is an unbiased estimator of a . The expected value ($E(\hat{a})$) of the predicted breeding value \hat{a} can be computed as:

$$\begin{aligned} E(\hat{a}) &= E(Cov(a, y)[Var(y)]^{-1}(y - E(y))) \\ &= Cov(a, y)[Var(y)]^{-1}E((y - E(y))) \\ &= Cov(a, y)[Var(y)]^{-1}(E(y) - E(y)) = 0 \end{aligned}$$

Because we have already specified that $E(\hat{a}) = 0$, it follows that $E(\hat{a}) = E(a) = 0$. This means that \hat{a} is an unbiased estimator of a .

Variance of estimated breeding value (\hat{a})

$$\begin{aligned} Var(\hat{a}) &= Var(Cov(a, y)[Var(y)]^{-1}(y - E(y))) \\ &= Cov(a, y)[Var(y)]^{-1}Var((y - E(y)))[Var(y)]^{-1}Cov(a, y) \\ &= Cov(a, y)[Var(y)]^{-1}Var(y)[Var(y)]^{-1}Cov(a, y) \\ &= Cov(a, y)[Var(y)]^{-1}Cov(a, y) \end{aligned}$$

$$\begin{aligned} Cov(a, \hat{a}) &= Cov(a, Cov(a, y)[Var(y)]^{-1}(y - E(y))) \\ &= Cov(a, y)[Var(y)]^{-1}Cov(a, (y - E(y))) \\ &= Cov(a, y)[Var(y)]^{-1}Cov(a, y) \\ &= Cov(a, y)[Var(y)]^{-1}Cov(a, y) \\ &= Var(\hat{a}) \end{aligned}$$

Conditional density of estimated genetic predisposition (\hat{a})

In some cases, e.g., for specifying confidence intervals of true genetic predisposition, it might be interesting to have a look at the conditional density $f(a|\hat{a})$. This density is a multivariate normal density with expected value $E(a|\hat{a})$ and variance $Var(a|\hat{a})$. These values can be computed based on the theory of conditional multivariate normal densities.

$$\begin{aligned} E(a|\hat{a}) &= E(a) + Cov(a, \hat{a})[Var(\hat{a})]^{-1}(\hat{a} - E(\hat{a})) \\ &= 0 + Var(\hat{a})[Var(\hat{a})]^{-1}(\hat{a} - 0) \\ &= \hat{a} \\ Var(a|\hat{a}) &= Var(a) - Cov(a, \hat{a})[Var(\hat{a})]^{-1}Cov(a, \hat{a}) \\ Var(a|\hat{a}) &= Var(a)(1 - Cov(a, \hat{a})^2 Var(a)^{-1} Var(\hat{a})^{-1}) \\ Var(a|\hat{a}) &= Var(a)(1 - r_{a,\hat{a}}^2) \end{aligned}$$

2.3 Accuracy of breeding value estimates

Estimates of genetic predisposition (\hat{a}) are estimates of the true genetic predisposition (a), which cannot be observed directly. It is important to determine how well we have estimated the breeding value in relation to the true breeding value. This can be done using accuracy or reliability.

Accuracy is the correlation between the estimated and the true breeding value:

$$r_{a,\hat{a}} = \frac{Cov(a, \hat{a})}{\sqrt{Var(a) Var(\hat{a})}} \quad (4)$$

A high correlation means that the estimated breeding value is very accurate.

Reliability is the squared correlation, $r_{a,\hat{a}}^2$, between the estimated breeding value and the true breeding value. To be able to compute the accuracy or reliability of the estimated breeding value we need to determine the values for the terms, $Cov(a, \hat{a})$, $Var(\hat{a})$, and $Var(a)$ in the expression above. It can be shown that the variance of the estimated breeding value is the same as the covariance between the true and estimated breeding value (i.e. $Cov(a, \hat{a}) = Var(\hat{a})$). Therefore the reliability can be expressed as:

$$r_{a,\hat{a}}^2 = \frac{\text{Var}(\hat{a})}{\text{Var}(a)} \quad (5)$$

Therefore reliability ($r_{a,\hat{a}}^2$) can be interpreted as the part of the genetic variation that is explained by the estimated genetic predisposition whereas the remainder ($1 - r_{a,\hat{a}}^2$) is the uncertainty. Reliability of the breeding value ($r_{a,\hat{a}}^2$) is important because it determines how well we can predict an individual's genetic value. It can be used to control the risk of a breeding plan: for example, low $r_{a,\hat{a}}^2$ leads to greater “risk” for both lower and higher true breeding value and we might consider more phenotypic records, in order to make better-informed selection decisions. Lastly reliability is one of the crucial factors that determines the genetic progress (e.g., breeders equation which will be introduced later in the course).

The variance of the estimated breeding value (\hat{a}) can be computed as:

$$\sigma_{\hat{a}}^2 = r_{a,\hat{a}}^2 \sigma_a^2$$

and from this expression it is clear that when the reliability increases, the variation in \hat{a} increases (breeding value estimates are more variable over values of y), and the estimation becomes more precise (the residual variability of y , the part left unexplained, has decreased). If the reliability is 0, then we know nothing and the variance of \hat{a} is 0. If the reliability is 1, then we know everything and the variance of \hat{a} is $\sigma_{\hat{a}}^2 = \sigma_a^2$ and the error variance (uncertainty) is 0.

2.4 Prediction error variance (PEV) of estimated genetic predisposition

Because every prediction is associated with an error, the same is true for the estimated genetic predisposition \hat{a} . The variability of the error for the predicted genetic predisposition are quantified by the prediction error variance (PEV). This is computed as:

$$\text{Var}(a - \hat{a}) = \text{Var}(a)(1 - r_{a,\hat{a}}^2) \quad (6)$$

$$\begin{aligned} \text{Var}(a - \hat{a}) &= \text{Var}(a) - 2\text{Cov}(a, \hat{a}) + \text{Var}(\hat{a}) = \text{Var}(a - \hat{a}) \\ &= \text{Var}(a)(1 - \text{Var}(\hat{a})\text{Var}(a)^{-1}) \\ &= \text{Var}(a)(1 - r_{a,\hat{a}}^2) \end{aligned}$$

The standard error of prediction (SEP) can be a useful quantity. SEP corresponds just to the square root of PEV. Hence

$$\begin{aligned} \text{SEP}(\hat{a}) &= \sqrt{\text{Var}(a - \hat{a})} \\ &= \sqrt{\text{Var}(a)(1 - r_{a,\hat{a}}^2)} \\ &= \sigma_a \sqrt{(1 - r_{a,\hat{a}}^2)} \end{aligned}$$

3 Phenotypic data and genetic relationships are used to estimate genetic predisposition

We will illustrate the basic principles of breeding value estimation using some simple examples where the trait has been measured on the individuals themselves or close relatives.

3.1 Estimation of breeding value and accuracy based on own phenotype:

An estimate of the breeding value (a) based on own phenotype (y) can be calculated as:

$$\begin{aligned} E(a|y) &= E(a) + Cov(a, y)[Var(y)]^{-1}(y - E(y)) \\ E(a|y) &= 0 + \sigma_a^2[\sigma_a^2 + \sigma_e^2]^{-1}(y - \mu) \\ E(a|y) &= h^2(y - \mu) \end{aligned}$$

Thus the estimated breeding value using own phenotypic record can be computed based on an estimate of the trait heritability (h^2) and the observed phenotype deviation ($y - \mu$). Use of records on the candidate itself is called performance testing. For performance testing to be efficient, the heritability should be at least moderately high (as suggested by equation: $E(a|y) = h^2(y - \mu)$).

The expression for expected value terms ($E(a)$ and $E(y)$) in the equation above are based on rules for expected value of a sum of (normally distributed) random variables:

$$\begin{aligned} E(a) &= 0 \\ E(e) &= 0 \\ E(y) &= E(\mu + a + e) \\ &= E(\mu) + E(a) + E(e) \\ &= \mu + 0 + 0 \\ &= \mu \end{aligned}$$

The expression for (co)variance terms ($Var(y)$, and $Cov(a, y)$) in the equation above are based on rules for the variance of a sum of (normally distributed) random variables:

$$\begin{aligned} Var(y) &= Var(a) + Var(e) + 2Cov(a, e) \\ Var(a) &= \sigma_a^2 \\ Var(e) &= \sigma_e^2 \\ Cov(a, e) &= 0 \\ Var(y) &= \sigma_a^2 + \sigma_e^2 \\ Cov(a, y) &= Cov(a, a + e) \\ &= Cov(a, a) + Cov(a, e) \\ &= \sigma_a^2 + 0 \\ &= \sigma_a^2 \end{aligned}$$

The accuracy for the breeding value based on own phenotype (y) can be calculated as:

$$\begin{aligned} r_{a,\hat{a}} &= \frac{Cov(a, \hat{a})}{\sqrt{Var(a)}\sqrt{Var(\hat{a})}} \\ r_{a,\hat{a}} &= \frac{(h^2)^2\sigma_y^2}{\sqrt{h^2\sigma_y^2}\sqrt{(h^2)^2\sigma_y^2}} \\ r_{a,\hat{a}} &= \sqrt{h^2} \end{aligned}$$

The variance of the estimated breeding value, $Var(\hat{a})$, can be expressed as:

$$\begin{aligned} Var(\hat{a}) &= Var(h^2(y - \mu)) \\ Var(\hat{a}) &= (h^2)^2 Var(y - \mu) = (h^2)^2 Var(y) = (h^2)^2 \sigma_y^2 \end{aligned}$$

The variance of the true breeding value, $Var(a)$, can be expressed by the heritability and phenotypic variance:

$$\sigma_a^2 = (\sigma_a^2)/(\sigma_y^2)\sigma_y^2 = h^2\sigma_y^2$$

Estimation of breeding value based on own phenotype is only possible when the trait in question can be measured (directly or indirectly) on the breeding individual, i.e., the candidate to be evaluated for selection. Sometimes this is not possible, e.g., traits that are sex-limited (milk production, female fertility, etc.) cannot be measured in male individuals. Traits like carcass composition and meat quality cannot be measured on live animals, unless an indirect method can be used (e.g. ultra-sonic measurement of carcass composition). In this situation it might be possible to use phenotypic information on relatives.

3.2 Estimation of breeding value and accuracy based on phenotypes of close relatives:

In practice we often use phenotypic records from close relatives, such as progenies, half-sibs, full-sibs, parents and grandparents. Phenotypes collected on close relatives (as compared to distant relatives) provide more information about the breeding value of an individual (as close relatives share more DNA in common). In the following we will provide a general formula for estimating genetic predisposition and their accuracies using phenotypic information on different types of relatives.

General formula for estimating genetic predisposition using different sources of information:

$$\hat{a} = b_{a|y}(y - \mu) \quad (7)$$

where the regression coefficient quantifies the weight (or importances) of the phenotypic information:

$$b_{a|y} = \frac{a'nh^2}{(1 + (n-1)r)} \quad (8)$$

where a' is the genetic relationship between the breeding individual and individuals with phenotypes, n is the number of phenotypic records, h^2 is the trait heritability, and r is correlation between individuals with observations ($r = a''h^2 + c^2$, where a'' = genetic relationship between individuals with records and target, c^2 = common environmental component).

Thus the importance given to a specific source of information depends on the additive genetic relationship (a') with the breeding candidate, the heritability of the trait (h^2), and the amount of information (n), i.e. the number of progenies or sibs, etc.

General formula for reliability of estimated breeding value using different sources of information:

$$r_{a,\hat{a}}^2 = \frac{(a')^2nh^2}{1 + (n-1)r} \quad (9)$$

Thus reliability depends on the same factors as the estimated breeding value except for the phenotypic value. Although the reliability depends on the number of records it does not depend on the numerical value of phenotypes. From this formula is it clear that higher reliability (and accuracy) can be achieved when:

- genetic relationship to individuals with information (a') is high
- there are many records (n)
- heritability (h^2) is high
- correlation between individuals with observations ($r = a''h^2 + c^2$) is low

3.3 Genetic relationship used for estimating breeding value

Related individuals share genes and thus resemble each other (have correlated phenotypes, to an extent that depends on additive genetic relationships). Consider a simple parent-offspring example. The offspring get half of the genes from each parent and therefore the breeding value for the offspring is the average of the parents' genetic predisposition plus the Mendelian deviation (the part of the breeding value that is due to random segregation of the genes from each parent):

$$a_{\text{offspring}} = \frac{1}{2}a_{\text{father}} + \frac{1}{2}a_{\text{mother}} + a_{\text{mendelian}}$$

(a = additive genetic value = breeding value)

The term $a_{\text{mendelian}}$ is necessary, because two fullsibs i and j both having parents *father* and *mother* receive different random samples of parental alleles. Hence the genetic predisposition a_i and a_j of fullsibs i and j are not going to be the same. The Mendelian deviation reflects that random contribution of (Mendelian) segregation to genetic predisposition of individuals.

In this equation the $\frac{1}{2}$ refers to the additive genetic relationship which in this example indicates that the offspring receives half of its genes from its parent. In general the weight given to a specific source of information depends on the additive genetic relationship with the candidate. Examples of different types of additive genetic relationships (A_{ij}) between the various sources (j) and the individual itself, i.e. the candidate to be evaluated (i), can be seen in the table below.

Relative	A_{ij}
Self	1.0
Unrelated	0
Mother	0.5
Father	0.5
Grandparent	0.25
Half-sib	0.25
Full-sib	0.5
Cousin	0.0625
Progeny	0.5
Twin(MZ/DZ)	1/0.5

3.4 Estimation of genetic predisposition using phenotypic information from multiple sources

Several factors influence which sources of information to use when estimating genetic predisposition for a trait: what information is available, the heritability of the trait, and how and on what individuals the trait can be measured. Therefore in practice it is common to combine information from several sources. As already mentioned, all information available is usually utilized when an animal's breeding value is predicted. The weight given to a specific source of information depends on the additive genetic relationship with the candidate, the heritability and the amount of information, i.e. the number of progenies or sibs, etc.

- Phenotypic records on progenies are generally the most accurate source of information for genetic evaluation (high genetic relationship a' and high n). The average phenotypic value of a progeny group gives the best indication of the additive genetic value (i.e. the breeding value) of the candidate. The reliability (and accuracy) of breeding value estimates increases with the size of the progeny group. Progeny testing is useful also when the heritability is low. For example, it can be much more accurate than evaluation on own phenotype when the heritability is low (say, 0.1) and the progeny is large (~100-150). The disadvantage is that it takes resources (time and money) before results on progenies

are available. In animal breeding, progeny testing is often used for male animals as they usually get many more progenies than females, especially when artificial insemination is practiced.

- Phenotypic records on the candidate’s sibs, half-sibs and full-sibs, are often used in addition to other information, or to give supplementary information, for example on traits that cannot be measured on the candidate itself. The accuracy of sib testing depends on the number of sibs that have records. Common-environment effects (e.g. full- sibs raised in the same herd) may bias the estimation of genetic predisposition, unless we are able to adjust for them (e.g., by additional fixed effects in linear models).
- Parental information at different generations (parents, grandparents, etc.) is generally available even before the candidate is born, and can provide information very early. However, the genes from each locus of the parents are transmitted at random, so information based on pedigree alone is not very accurate, but can be valuable as additional information. Moreover, the additive genetic relationship, and thus the proportion of common genes between the candidate and the pedigree, is halved for every generation backwards (at least 0.5 for a parent, 0.25 for a grandparent, etc.). Finally, there is redundancy in the information provided by different generations of parents. For example, if there is an accurate estimate of the parent’s genetic predisposition, then there is little to gain in using information on grandparents (actually, if the parents true genetic predisposition are known, there would be no additional gain of information from grandparents).

As already mentioned, all information available is usually utilized when an individual’s breeding value is predicted. The weight given to a specific source of information depends on the additive genetic relationship with the candidate, the heritability and the amount of information, i.e. the number of relatives (progenies, sibs, parents, etc.). In the following sections we will show how genetic predisposition can be calculated when different types of phenotypic information (from different types of relatives) are available.

4 BLUP a general approach for estimation of breeding values

Breeding value estimation in animal and plant breeding programmes are nowadays based on the BLUP (Best Linear Unbiased Prediction) method. BLUP allows for estimation of breeding values using phenotypic information for individuals from a general pedigree (with arbitrary relationships among them). BLUP is based on linear mixed model methodology, and estimates of breeding values can be obtained by solving the mixed model equations. The BLUP method also requires a genetic relationship matrix and estimates of variance components (e.g., σ_a^2 and σ_e^2).

The estimation of breeding values based on multiple sources of information must correct for the redundancy between them (e.g., the redundant information provided by parents and grandparents). Moreover, they need to be adjusted for average effects in the populations, “fixed effects”. So far we have referred to that fixed effect as the population mean and we have assumed this adjustment μ to be known. Indeed, we defined the true breeding value a and the non-identifiable environmental effects e as deviations from a common mean, the average effect of all fixed genetic and environmental factors captured by the population mean μ . But this is only true in a single idealized population where all selection candidates are kept in the same environment in which they deliver their performances at the same time. In practice the phenotypic records often need to be adjusted for systematic (fixed) environmental effects, such as age, parity, litter size, days open, sex, herd, year, season, management, etc. Several of those effects fluctuate very little over time, so accurate estimates of their effect may be obtained from previous (“historical”) sets of data. Effects of factors like herd, year, season, and management fluctuate more and are therefore best estimated directly from the data to be used in the genetic evaluations.

Compared to the idealized cases described in the previous section, a practical breeding scenario poses two problems: accounting for heterogeneous sources of genetic information (different types of relatives); and adjusting for fixed effects in the breeding population(s) (fixed environmental or genetic effects).

The BLUP solution to these problems was presented by Charles R. Henderson in several publications (e.g. Henderson1973a and Henderson1975). The key idea behind the solution is to estimate the identifiable

environmental factors as fixed effects and to predict the breeding values as random effects simultaneously in a linear mixed model. Here, mixed refers to the presence of two types of effects: fixed effects (identifiable effects from environmental or genetic factors) and random effects (non-identifiable effects from segregating genetic factors and fluctuating environmental conditions). The methodology developed by Henderson is called **BLUP** and the properties of this methodology are directly incorporated into its name:

- **B** stands for **best** which means that the correlation between the true (a) and the predicted breeding value (\hat{a}) is maximal or the prediction error variance ($Var(a - \hat{a})$) is minimal.
- **L** stands for **linear** which means the predicted breeding values are linear functions of the observations (y)
- **U** stands for **unbiased** which means that the expected values of the predicted breeding values are equal to the true breeding values
- **P** stands for **prediction**

BLUP approaches are widely used in genetic evaluations, for both traditional predictions of breeding values and also for predicting genomic breeding values. The popularity of BLUP is not only due to the theoretical foundations behind BLUP, but also the efficient algorithms developed by Henderson for computing predicted breeding values, even in very large breeding populations. The theoretical foundations, and the development of efficient algorithms, together with the availability of large computational resources at a very low price, have made BLUP the de-facto standard for breeding value estimation.

4.1 Linear Mixed Model

The linear mixed model contains the observation vector for the trait(s) of interest (y), the **fixed effects** that explain systematic differences in y , and the **random genetic effects** a and **random residual effects** e .

A matrix formulation of a general model equation is:

$$y = Xb + a + e$$

where

y : is the vector of observed values of the trait,

b : is a vector of fixed effects,

a : is a vector of random genetic effects,

e : is a vector of random residual effects,

X : is a known design matrix that relates the elements of b to their corresponding element in y .

In the statistical model (specified above) the random effects (a and e) and the phenotypes (y) are considered to be random variables which follow a multivariate normal (MVN) distribution. In general terms the expectations of these random variables are:

$$\begin{aligned} a &\sim MVN(0, G) \\ e &\sim MVN(0, R) \\ y &\sim MVN(Xb, V) \end{aligned} \tag{10}$$

where $G = A\sigma_a^2$, and $R = I\sigma_e^2$ are square matrices of genetic and residual (co)variances among the individuals, respectively, and $V = A\sigma_a^2 + I\sigma_e^2$ is the overall phenotypic covariance matrix.

4.2 Estimating fixed and random effects in the linear mixed model

The goal of the BLUP analysis is the estimate the fixed effect b , and random genetic effects, a , in the linear mixed model specified above. This can be done using the BLUE and BLUP equations shown below.

The best linear unbiased estimator (BLUE) of \hat{b} is:

$$\hat{b} = (X'V^{-1}X)^{-1}X'V^{-1}y \quad (11)$$

The matrix $(X'V^{-1}X)^{-1}$ denotes the inverse of the matrix $(X'V^{-1}X)$.

The best linear unbiased prediction (BLUP) of \hat{a} is:

$$\hat{a} = GV^{-1}(y - X\hat{b}) \quad (12)$$

which is similar to the expression shown earlier for the expected value of the breeding value conditional on the observed phenotype y :

$$E(a|y) = Cov(a, y)[Var(y)]^{-1}(y - E(y)) \quad (13)$$

The BLUP equation for the estimate of the breeding value consists of three parts; The term, $y - X\hat{b}$, shows that the observed phenotypic values are corrected for the fixed effects represented by $X\hat{b}$. The covariance between the true breeding values (a) and phenotypes (y) is $Cov(a, y) = G$. The inverse of the phenotypic covariance matrix is $[Var(y)]^{-1} = V^{-1}$.

4.3 Mixed Model Equations

The solutions shown in (12) for \hat{a} and in (11) for \hat{b} are not suitable for practical purposes. Both solutions contain the inverse V^{-1} of matrix V . The matrix V corresponds to the variance-covariance matrix of all observations y . The inverse matrix V^{-1} is not easy to compute. Furthermore, procedures to invert general matrices are computationally expensive and are prone to rounding errors. In one of his many papers, Henderson has shown that the results for \hat{a} and \hat{b} are the same when solving the following system of equations simultaneously:

$$\begin{bmatrix} X^T R^{-1} X & X^T R^{-1} Z \\ Z^T R^{-1} X & Z^T R^{-1} Z + G^{-1} \end{bmatrix} \begin{bmatrix} \hat{b} \\ \hat{a} \end{bmatrix} = \begin{bmatrix} X^T R^{-1} y \\ Z^T R^{-1} y \end{bmatrix} \quad (14)$$

The above shown equations are called **mixed model equations** (MME). They no longer contain the inverse V^{-1} and hence these MME are much simpler to solve. Instead, the MME contain the inverses R^{-1} and G^{-1} , which are easier to invert: $R = I\sigma_e^2$ is often a very simple matrix, and $G = A\sigma_a^2$ is usually smaller than (or the same size as) V . As a consequence, whenever we have to estimate breeding values using BLUP we will usually use the mixed model equations shown in (14).

In order to solve the mixed model equations (or BLUP equations), the additive genetic relationship matrix A and estimates of the variance components (i.e. σ_a^2 and σ_e^2) are required. The additive genetic relationship matrix A can be computed using a recursive method from a pedigree of the individuals in the breeding population. The variance components can be estimated using the REML method based on phenotypes and genetic relationships for individuals in the breeding population.

4.4 BLUP breeding values are useful for ranking and selection

BLUP estimates of breeding values (EBVs), especially from the linear mixed model including all relationships, are useful tools in selection. Selection on BLUP breeding values maximizes the probability for correct ranking of breeding individuals and selection on them maximizes genetic gain from one generation to another. There are many factors that contribute to this:

- The linear mixed model which makes full use of information from all relatives increases accuracy (precision)
- The breeding values are adjusted for systematic environmental effects in an optimal way. This means that individuals can also be compared across herds, age classes, plots etc, assuming the data is connected
- Non-random mating can be accounted for
- Several traits can be analyzed simultaneously
- Bias due to culling within generation (e.g., between the 1st and 2nd lactations in dairy cattle) and selection (over generations) is accounted for, assuming that also non-selected individuals' data are included in the analysis.

It should, however, be noted that the genetic evaluation is based on phenotypic observations, and that regardless of how great the BLUP procedure may be, it cannot compensate for bad data. So a good recording system is necessary for a reliable genetic evaluation and subsequent genetic gain. It should also not be forgotten that BLUP assumes that the genetic parameters used are the true ones. In practice that means that EBVs will only be accurate if the estimated genetic parameters are close enough to their true value.

It should be noted that there is a potential risk for increased inbreeding when selection is based on information from all relatives. The probability that several family members are selected jointly is increased, which may result in increased inbreeding. To avoid this, and to optimize longterm selection response, selection on BLUP breeding values might be combined with some restriction on average relationship of the selected individuals. A useful side effect of genetic evaluation by BLUP estimates is that it gives estimates of the realized genetic trend. This trend can be observed by comparing BLUP breeding values of individuals from different years.