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BLUP for phenotypic selection in plant breeding and variety testing

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Abstract Best linear unbiased prediction (BLUP) is a standard method for estimating random effects of a mixed model. This method was originally developed in animal breeding for estimation of breeding values and is now widely used in many areas of research. It does not, however, seem to have gained the same popularity in plant breeding and variety testing as it has in animal breeding. In plants, application of mixed models with random genetic effects has up until recently been mainly restricted to the estimation of genetic and non-genetic components of variance, whereas estimation of genotypic values is mostly based on a model with fixed effects. This paper reviews recent developments in the application of BLUP in plant breeding and variety testing. These include the use of pedigree information to model and exploit genetic correlation among relatives and the use of flexible variance–covariance structures for genotype-by-environment interaction. We demonstrate that BLUP has good predictive accuracy compared to other procedures. While pedigree information is often included via the so-called numerator relationship matrix ($\boldsymbol{A}$), we stress that it is frequently straightforward to exploit the same information by a simple mixed model without explicit reference to the $\boldsymbol{A}$-matrix.

Keywords Mixed model · Breeding value · Pedigree · Genetic effect · Genotypic value

This paper is dedicated to Prof. Dr. Wolfgang Köhler (University of Giessen, Germany) on the occasion of his 65th birthday.

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Introduction

Both the development of new cultivars as well as the recommendation of newly released varieties require a selection to be made among a larger set of candidate genotypes, so estimation of genotypic values is at the heart of any breeding effort. Analysis of metric data from plant breeding and variety trials can usually be based on a mixed linear model of the form

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}, \tag{1}$$

where $\boldsymbol{y}$ is the vector of observations, $\boldsymbol{\beta}$ and $\boldsymbol{u}$ are vectors of fixed and random effects, respectively, $\boldsymbol{X}$ and $\boldsymbol{Z}$ are the associated design matrices, and $\boldsymbol{e}$ is a random residual vector. The random effects are assumed to be distributed as $\boldsymbol{u} \sim MVN(\mathbf{0}, \mathbf{G})$ and $\boldsymbol{e} \sim MVN(\mathbf{0}, \mathbf{R})$, where $MVN(\boldsymbol{\mu}, \boldsymbol{V})$ denotes the multivariate normal distribution with mean vector $\boldsymbol{\mu}$ and variance–covariance matrix $\boldsymbol{V}$. The fixed effects can be estimated by Best Linear Unbiased Estimation

(BLUE), while random effects are estimated by Best Linear Unbiased Prediction (BLUP). In practice, BLUE and BLUP need to be replaced by "empirical" BLUE and BLUP, respectively, meaning that variance components in $\boldsymbol{G}$ and $\boldsymbol{R}$ need to be replaced by their estimates, obtained preferably by Restricted Maximum Likelihood (REML) (Patterson and Thompson 1971). Both BLUE and BLUP may be computed by solving the Mixed Model Equations (MME), given by (Henderson 1986; Searle et al. 1992)

$$\begin{bmatrix} \boldsymbol{X}'\boldsymbol{R}^{-1}\boldsymbol{X} & \boldsymbol{X}'\boldsymbol{R}^{-1}\boldsymbol{Z} \\ \boldsymbol{Z}'\boldsymbol{R}^{-1}\boldsymbol{X} & \boldsymbol{Z}'\boldsymbol{R}^{-1}\boldsymbol{Z}+\boldsymbol{G}^{-1} \end{bmatrix} \begin{bmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\boldsymbol{u}} \end{bmatrix} = \begin{bmatrix} \boldsymbol{X}'\boldsymbol{R}^{-1}\boldsymbol{y} \\ \boldsymbol{Z}'\boldsymbol{R}^{-1}\boldsymbol{y} \end{bmatrix}. \tag{2}$$

Often in variety testing and the development of new varieties, genotype effects are considered as fixed and thus become part of $\boldsymbol{\beta}$ in the mixed model. When genotypes can be regarded as random, however, genotypic effects become part of $\boldsymbol{u}$ and thus are estimated by BLUP. The present paper is concerned with applications where $\boldsymbol{u}$ contains the genotypic or genetic effects of interest.

By genetic effects, we refer to a decomposition of the genotypic value into component effects with a genetic interpretation. One such decomposition is into additive and non-additive effects (dominance, epistasis). Alternatively, in a diallel or factorial, the genotypic value of a hybrid may be partitioned into genetic effects for general and specific combining ability. The ultimate objective in breeding applications usually is prediction of the genotypic value of a candidate genotype. Thus, our discussion here is mainly in terms of genotypic values.

One major property of BLUP is shrinkage towards the mean, which anticipates regression of progeny to the mean observed by every breeder (Hill and Rosenberger 1985). Shrinkage is often a desirable statistical property of an estimator, as it increases accuracy, when the bias incurred from shrinkage is more than offset by the reduction in variance, thus leading to a smaller mean squared error (MSE). This is true not only for BLUP, but also for other shrinkage estimators in common usage (Copas 1983; Robinson 1991; Miller 2002). Finally, under certain fairly general assumptions, BLUP maximizes the correlation of true genotypic values and predicted genotypic values (Searle et al. 1992), which is the primary aim of breeders.

There is often considerable debate as to whether it is reasonable to assume that genotypes are a random factor. An argument sometimes put forward against this assumption is that genotypes are not usually a random sample from a defined population as one would obtain, e.g., in survey sampling, because genotypes under test are the result of considerable selection effort. While this is certainly true in most cases, it is often reasonable to regard the genotypes under test as a random sample from some hypothetical population of genotypes that could have arisen as a result of the selection process leading to the genotypes currently available (Piepho and Möhring, 2006). Furthermore, the theory of James and Stein (1961) justifies the use of BLUP even if we think of the parameters as fixed, provided the number of parameters is large (Lee et al. 2006, pp. 151–152). James and Stein (1961) showed that BLUE can be beaten by shrinkage estimation, when the effect in question has more than two levels. Note, also, that in a Bayesian framework, the distinction between fixed and random effects vanishes. To a Bayesian, all effects are random, because all parameters of a model have a prior density, reflecting the uncertainty about parameter values (Gianola and Fernando 1986). It is also useful to realize that BLUE can be regarded as a limiting case of BLUP, when $\boldsymbol{G}^{-1}$ in the mixed model equations tends to zero, so that the MME reduce to ordinary least squares equations. To a Bayesian this simply means that prior knowledge about $\boldsymbol{u}$ is ignored (Gianola and Fernando 1986; Sorensen and Gianola 2002). The most critical practical issue is whether good estimates of $\boldsymbol{G}$ can be obtained (Smith et al. 2005). Whether or not this is the case, depends foremost on sample size and on the availability of complete data back to a base population, to which genetic variance components refer (Thompson 1973, 1979; Van der Werf and de Boer 1990; Piepho and Möhring 2006). Only when the data does not permit accurate estimation of genetic variance components or when the main emphasis of analysis is on the comparison of genotypes by a statistical test, does it seem reasonable to take genotypes as fixed.

BLUP does not appear to have gained the same popularity as in animal breeding, where it is the standard procedure. There are some applications in

forestry and perennial crops (White and Hodge 1989; Durel et al. 1998; Dutkowski et al. 2002; Xiang and Li 2003), but publications using BLUP with annual crops are less abundant. One reason may be that plant breeding programmes usually yield a relatively large amount of phenotypic data per genotype from series of experiments, so BLUE and BLUP often do not provide grossly different results. This may lead to the false impression that the choice of estimator is not important. Also, in animal breeding, BLUP or similar procedures are usually a necessity due to lack of direct observations, such as in the case of breeding values of sires for milk yield in dairy, while this type of problem occurs less frequently in plant breeding (one example in kind is general combining ability, which cannot be directly observed). In addition, animal breeding programmes typically comprise a very large number of genotypes, so genetic variance component estimates are very accurate. By contrast, genetic variance estimates in plant breeding applications are often relatively inaccurate due to more limited numbers of genotypes and more complex genetic covariance structures.

A desirable feature of BLUP is its ability to borrow strength from relatives by exploiting genetic correlation arising from the pedigree. The closer the genetic correlation with relatives, the more information can be extracted from phenotypic information on relatives. The most common approach to exploiting pedigree information involves use of the so-called numerator relationship matrix (Mrode 1996), computed from the coefficient of coancestry. As is emphasised in this paper, one may also consider mixed models, which incorporate pedigree information in simple pedigrees without explicitly using the numerator relationship matrix.

The purpose of this paper is to review applications of BLUP in plant breeding and variety testing and to underline the potential advantages of BLUP, which have been demonstrated in a considerable number of publications. The paper is organized as follows. The next section deals with applications of BLUP that do not exploit pedigree information. Sections 3 and 4 consider the use of pedigree information. Section 3 reviews applications that exploit the coefficient of coancestry, while section 4 deals with pedigree-based BLUP when the coefficient of coancestry is not utilized. Some examples are given in Section 5. Much of the theoretical work on pedigree-based BLUP using the coefficient of coancestry was done in an animal breeding context, where this methodology originated. We give a cursory account of some of the theoretical underpinnings and statistical assumptions as relevant in a plant breeding context. The main focus is on BLUP of genotypic values for selection in annual crops.

BLUP without pedigree information

The simplest case of BLUP occurs when a single genotypic effect in a linear model is taken as independent random variable without any correlation imposed by the pedigree. Thus, genotypes are considered as independent, and pedigree information is not exploited. Gain in accuracy compared to BLUE therefore stems mainly from the shrinkage property, while genetic covariance between related genotypes plays no role. In multi-environment trials, genetic correlation among performances of the same genotype in different environments may be exploited.

Single trials

Cullis et al. (1989) and Stroup and Mulitze (1991) showed that BLUP of genotypic values in single trials can be enhanced by a spatial model for local field trends. Cullis et al. (1989) focused on trials, where a large number of new entries are tested without replication. A particular class of designs for such settings are the augmented designs, where some replicated design for checks is augmented by unreplicated entries. Federer (1998) proposed to analyse such designs (and other incomplete block designs) assuming random genotypic values. Santos et al. (2002) showed by simulation that BLUP in augmented designs may be hampered by poor estimates of genetic variance components. With known variance components, BLUP was always superior to BLUE. Cullis et al. (2006) suggested a strategy to find optimal designs for early-generation variety testing, when analysis is to be based on a spatial model and genotype effects are to be estimated by BLUP. The objective criterion is based on an approximation to the expected genetic gain from selection.

Multi-environment trials

Hill and Rosenberger (1985) considered BLUP of genotype main effects in genotype-by-environment data and found BLUP to outperform BLUE. Yan et al. (2002) compared on-farm strip trials versus replicated performance trials with wheat (*Triticum aestivum*) based on BLUP of genotype effects. Yan and Rajcan (2003) used BLUP in soybean (*Glycine max*) based on a three-way model (genotype-by-location-by-year).

Gauch (1988) popularized the Additive Main Effect Multiplicative Interaction (AMMI) model for genotype-environment data and pointed out that retention of a small number of multiplicative terms leads to shrinkage of estimated interaction effects compared to ordinary least squares estimates based on the usual two-way ANOVA model. The AMMI model suggested by Gauch (1988) is a fixed effects model. He showed by cross validation that the resulting estimates of genotype-by-environment means were more accurate than ordinary least squares estimates. Essentially, the AMMI model improves accuracy of genotypic mean estimates for an environment by borrowing strength from other environments via multiplicative interaction terms. The shrinkage property of AMMI led Piepho (1994) to conduct a comparison with BLUP based on a two-way ANOVA model. This study provided evidence that BLUP was more accurate than the fixed effects AMMI model. Further improvement is possible by a mixed-model version of the AMMI model, also known as the factor-analytic model (Piepho 1997), as demonstrated in a cross-validation study by Piepho (1998). The factor-analytic model gleans information from correlated environments via (factor-analytic) correlation of genotype-by-environment effects. A parallel literature has developed various alternative shrinkage factors for the AMMI model (Cornelius et al. 1996; Cornelius and Crossa 1999; Moreno-Gonzalez et al. 2003, 2004), including a Bayesian approach (Viele and Srinivasan 2000), but these do not strictly fall in the mixed model framework.

Combination of single trial information based on spatial models with flexible variance–covariance structures for genotype-by-environment effects, e.g. heteroscedastic and factor-analytic, has been suggested, e.g., by Frensham et al. (1997), Cullis et al. (1998) and Smith et al. (2001b). BLUP of variety effects based on such models is now routinely used in the analysis of crop variety evaluation data in Australia (Smith et al. 2001a, 2005).

Curnow (1988) demonstrated that use of correlated information on treatment effects is beneficial when selecting the best treatment. This idea was taken up by Atlin (2000), who investigated the response to selection in a subdivided target region. Piepho and Möhring (2005) put this approach in a BLUP framework and showed that fitting a genetic correlation structure across sub-regions can improve predictions for target regions by exploiting information from adjacent sub-regions.

Plant breeding data from multiple environments are notoriously unbalanced, as poor performers are discarded every year, while new entries are added to the system. Piepho and Möhring (2006) have shown based on the theory of Rubin (1976) and Little and Rubin (1987, 2002) as well as by simulation that selection is ignorable so long as all data that have been used in selection decisions are included in the analysis. This is in agreement with accounts dealing with pedigree-based BLUP in animal breeding (Thompson 1973; Henderson 1975) (see sect. 3), though most of the publications in that area do not mention Rubin (1976) or Little and Rubin (1987). One notable exception is Im et al. (1989).

Pedigree-based BLUP using the coefficient of coancestry

Exploitation of pedigree information in animal breeding is mostly based on the numerator relationship matrix, usually denoted as $\boldsymbol{A}$, which is computed from the coefficient of coancestry (kinship, consanguinity) θ_{xy} (Falconer and Mackay 1996, p.153) between genotypes x and y as $\boldsymbol{A} = \{2\theta_{xy}\}$, assuming relatives are not inbred. Breeding values are considered as random effects with variance–covariance matrix $\boldsymbol{A}\sigma_A^2$, where σ_A^2 is the additive genetic variance component. Non-additive genetic effects, such as dominance and epistasis, can be modelled in a similar way. For example, under the same assumption as for $\boldsymbol{A}$, dominance relationships may be modelled by a matrix $\boldsymbol{D}$, computed from the probability that both alleles at a locus are identical by descent, which is also a function of the coefficient of coancestry (Henderson 1985; Falconer and Mackay 1996): The

dominance relationship between a genotype with parents a and b and another genotype with parents c and d is $\boldsymbol{D} = \{\theta_{ac}\theta_{bd} + \theta_{ad}\theta_{bc}\}$, where θ_{ac} is the coefficient of coancestry between parents a and c (Falconer and Mackay 1996, p. 153). BLUP of genetic effects exploits genetic correlation among relatives. The higher the genetic correlation of a genotype of interest with related genotypes, the more information can be gained from records of relatives.

It should be stressed that BLUP based on the coefficient of coancestry aims primarily to estimate genetic effects (breeding values etc.) rather than genotypic values. When only a single genetic effect prevails such as the breeding value, estimating genetic effects rather the genotypic value may yield better estimates of genotypic performance. When several genetic effect estimates are involved, these may be combined to yield improved estimates of genotypic values. Whether genotypic values versus genetic effects should be predicted also depends on the purpose of the analysis. If the candidates being evaluated will be used as varieties themselves (e.g., clones or single crosses between inbreds), then their genotypic values should be predicted. But if the candidates will be used as parents for developing new inbreds, then their breeding values (equivalent to additive genetic effects) should be predicted.

Estimating genetic effects via the coefficient of coancestry requires embedding genetic correlation structures derived from quantitative genetic theory. There is a large body of quantitative-genetic literature studying the resemblence of genotypes in populations, which can potentially be used to derive genetic variance–covariance structures in a number of settings (Cockerham 1954; Schnell 1965; Stuber and Cockerham 1966; Falconer and Mackay 1996), including diallels and other crossing schemes. It is important to realize, however, that the underlying quantitative-genetic theory often makes a number of strong assumptions, which usually are not, and cannot be, fully met in practice (Nyquist 1991, p. 264 and p. 270; also see Holland et al. 2003). The most important assumptions in many cases are that (i) genotypes under consideration can be traced back to the same idealized base population, (ii) in the base population all genotypes are unrelated, and (iii) the base population is in gametic-phase equilibrium or even in Hardy–Weinberg equilibrium. In particular, this requires that genotypes in the base population are unselected. By contrast, breeding populations of plants and animals typically have undergone strong selection, so these assumptions will not usually hold in current populations. There has been a considerable amount of research, mostly in animal breeding, studying the effect of selection on the validity of mixed model procedures exploiting pedigree information. Both theory and simulation results suggest that REML analysis may proceed as if no selection had occurred, provided that all data that were the basis for selection decisions, starting from an ideal base population, are included in the analysis (Henderson 1975; Im et al. 1989). If complete records back to the base populations are not included, biases will result for variance component estimates and BLUP (Sorensen and Kennedy 1984; Van der Werf and de Boer 1990; Schenkel et al. 2002). Also, selection and the associated gametic-phase disequilibrium induce a correlation among dominance and additive effects (Chevalet and Gillois 1977; Cockerham and Weir 1984; De Boer and Hoeschele 1993). Even if dominance and epistasis are assumed absent, tying all records back to the base population remains essential. As Henderson (1986) points out, "REML does have the important property of estimating the base population parameters even though only data arising from selection are available. [...] these are the parameters that should be used in mixed model equations with data from selected animals. [...] $\boldsymbol{A}^{-1}$ can be used effectively to control bias in breeding value predictions that can be caused by selection. If evaluation of non-additive effects is desired, the computing strategy for estimating variances and for solving mixed model equations of Henderson (1985) can be used to remarkably reduce computational labor. These methods apply only to non-inbred progeny and use the results of Cockerham (1954)". In the same volume, Goddard (1986) remarked that "for BLUP prediction of breeding values, the usual mixed model equations must include the whole selection history of the population (via the $\boldsymbol{A}$ matrix) back to an unselected base population, and estimates of $\boldsymbol{G}$ and $\boldsymbol{R}$ on the base population are required. Unbiased estimates of $\boldsymbol{G}$ and $\boldsymbol{R}$ can be obtained by REML, again provided that the data used includes the base population and the $\boldsymbol{A}$ matrix. However, commercial populations are constantly undergoing selection and so records on an unselected base population may not be available. Fortunately, in dairy cattle,

little effective selection was practiced in the early years of artificial insemination so these populations may include a suitable base". It is doubtful whether such favourable conditions hold for current breeding populations in plants (Durel et al. 1998), and, in fact, for most other animal populations. Thus, using pedigree-based BLUP based on the $\boldsymbol{A}$ matrix must often be seen as a method that operates under somewhat unrealistic assumptions.

Why, then, is it that despite these imperfections, use of the $\boldsymbol{A}$ matrix has proven so successful in the past, mostly in animal breeding? Lynch and Walsh (1998, p. 793) argue that "even though imperfect, likelihood methods always at least partially account for biases introduced by selection, in part because the additive genetic relationship matrix $\boldsymbol{A}$ corrects for the patterns of flow of genetic information from generation to generation." In plant breeding, perhaps the most ideal case for BLUP occurs, when a pedigree derived from a single cross of two genotypes of a self-fertilized crop is considered, as the F_2-population can be regarded as a random mating population in equilibrium, when linkage is ignored (Wricke and Weber 1986). Similar reasoning applies to single crosses in cross-fertilized crops. Providing complete data is recorded back to the F_2 base population, BLUP should have nearly optimal properties.

In what follows, we will review a few recent publications that applied pedigree-based BLUP in plant breeding. BLUP for multivariate data is a generalization of the selection index, in that the latter assumes known fixed effects and balanced data (White and Hodge 1989), while the former includes fixed estimates in the estimation procedure and allows for unbalanced data. Literature on the application of selection index theory in plant breeding is ample and will not be dwelt on here (see, e.g., Wricke and Weber 1986; Falconer and Mackay 1996, Chapter 13). Instead, our account will be restricted to publications that explicitly consider BLUP. The review distinguishes self-fertilized and cross-fertilized crops.

Self-fertilized crops

Panter and Allan (1995a, b) determined the $\boldsymbol{A}$ matrix for soybean (*Glycine max*) parental genotypes based on historical records and predicted cross performance based on the simple average of BLUPs of two parents. These predictions were found to be more closely correlated with actual cross performance than the mid-parent value. Pattee et al. (2001, 2002) used a similar approach in peanuts (*Arachis hypogaea*), and Souza et al. (2000) in peaches (*Prunus persica*). It should be stressed that setting up the $\boldsymbol{A}$ matrix based on historical records implies reference to some base population, starting from which selection has been exercised. Data available for estimating the additive genetic variance are not complete because not all records used in selection decisions, starting from the base population, were available. Thus, some bias is expected. Nevertheless, BLUP performed better here than the commonly used alternatives such as BLUE. Bauer (2006) and Bauer et al. (2006) used similar methods in barley (*Hordeum vulgare*) and found BLUP to outperform genotype means in simulations. These authors accounted for inbreeding in the base population. They also considered estimation of $\boldsymbol{A}$ for parental genotypes by genetic markers and in simulations observed good performance relative to BLUE. Eagles and Moody (2004) reported that a REML analysis for gene effects in breeding populations of barley based on data from multiple stages of selection minimized bias due to selection. They compared BLUP with and without the $\boldsymbol{A}$ matrix and found no substantial benefit from the use of pedigree information. Xu and Virmani (2000) used the approach of Bernardo (1994; see Sect. 3.2) to predict hybrid performance in rice (*Oryza sativa*) and indicated that BLUP was superior to other approaches. Oakey at al. (2006) considered single wheat yield trials. They fitted mixed models without the inclusion of pedigree information and pedigree-based BLUP using the coefficient of coancestry. It was shown how $\boldsymbol{A}$ can be efficiently computed accounting for repeated selfing of parental lines. In addition to the $\boldsymbol{A}$ matrix, the authors included a residual independent genetic effect, so that pedigree-based and pedigree-free models were nested. Likelihood-ratio tests indicated that inclusion of pedigree information was worthwhile.

Cross-fertilized crops

There is a series of publications (Bernardo 1993–1995, 1996a–c, 1999; Parisseaux and Bernardo 2004; also see Charcosset et al. 1998) on the prediction of hybrid performance in crosses of inbred lines from

two different heterotic pools in maize (*Zea mays*) using the coefficient of coancestry to model general combining ability (GCA) and specific combining ability (SCA) effects. Cross-validation studies showed that BLUP provides good predictions. Estimation of the coefficient of coancestry may be enhanced by using marker data. In fact, markers are potentially superior to pedigree data in estimating the actual genomic contribution of a parent because they reflect the sampling process through selection and genetic drift. Also, epistasis may be included (Bernardo 1995), but this does not necessarily lead to better predictions. The approach is based on the assumptions of gametic phase equilibrium in both populations (heterotic pools), absence of linkage, as well as no selection and drift (Schnell 1965; Stuber and Cockerham 1966; Melchinger 1988). Descent measures such as the coefficient of coancestry are defined with respect to a base population in each heterotic pool. The theory of Melchinger (1988) assumes that in each heterotic pool a set of inbred lines are inter-crossed at random to develop the base population for selection of improved inbred lines to be used as parents in hybrid development. Coancestry is defined in terms of this base population. Analysis proposed by Bernardo is purely based on cross performance data, so in practice it is impossible to account for selection by including all data back to the base population. Also, the assumptions about the base population are idealized. For example, inbred lines are seldom if ever inter-crossed fully at random.

Despite these theoretical imperfections, the approach suggested by Bernardo (1993) has been demonstrated by simulation and cross-validation to be very successful in practice. Recently, the proposed methods have been investigated by a number of authors. Bromley et al. (2000) showed for inbred lines of maize that ignoring pedigree relationships resulted in a reduction in estimates of genetic variance. Reis et al. (2005) demonstrated both by simulation and by cross-validation with maize data that BLUP of hybrid performance had better accuracy than BLUE. Purba et al. (2001) applied Bernardo's approach to predict performance of oilpalm (*Elaeis guineensis*) hybrids. Davik and Honne (2005) modeled GCA effects in a diallel experiment with strawberry (*Fragaria* spp.) using the $\boldsymbol{A}$ matrix "under the usual assumptions of a large random mating parental population", while SCA effects were assumed to be uncorrelated. Field plot heterogeneity was modelled using spatial covariance structures. Resende et al. (2004) used a model with both additive and dominance effects to predict breeding values in families of tetraploid progenies of *Panicum maximum*.

Further issues

A matrix

The $\boldsymbol{A}$ matrix, as computed from pedigree data or estimated from marker data, may turn out to be non-positive definite. Some mixed model packages that handle pedigree data, such as PROC MIXED of the SAS System, require $\boldsymbol{A}$ to be positive-definite, or at least non-negative definite. If a given $\boldsymbol{A}$ matrix does not meet that requirement, one may set the negative eigenvalues of a spectral decomposition equal to zero, thus yielding a non-negative definite matrix that approximates $\boldsymbol{A}$ (Colvin and Dykstra 1991; Calinski et al. 2005). Provided the negative eigenvalues of the original $\boldsymbol{A}$ matrix are small in absolute value, this should constitute a reasonable approximation. The proposed approach is feasible provided the $\boldsymbol{A}$ matrix is not very large ($<10^4$ rows, say). Other packages, such as ASReml, require provision of the inverse of $\boldsymbol{A}$. This can be computed directly from the pedigree using the method of Henderson (1976) and Meuwissen and Luo (1992), provided $\boldsymbol{A}$ is positive-definite. Alternatively, if an $\boldsymbol{A}$ matrix is given, but is not positive-definite, non-positive eigenvalues of the spectral decomposition can be replaced by tiny, but positive values (10^{-8}, say), and an inverse computed using standard procedures. A further option is to use a modification of the mixed model equation for singular $\boldsymbol{A}$ that employs the Cholesky decomposition of $\boldsymbol{A}$, as proposed by Henderson (1984).

Multivariate BLUP

Selection is usually exercised on several traits. Thus, in order to avoid bias due to selection, it is common in animal breeding to perform a multivariate mixed model analysis (Henderson and Quaas 1976; Mrode 1996, pp. 77–78). Multi-trait BLUP is most advantageous when traits are highly correlated, but a disadvantage is that it can make the Mixed Model Equations very large. A multivariate approach has

been employed in forestry breeding (Silva et al. 2000; Aleta et al. 2004; Persson and Andersson 2004) and with perennial crops (Durel et al. 1998; Purba et al. 2001; Da Costa et al. 2002), but as yet its use appears to be rare in annual crops. Simeao et al. (2002) use multivariate BLUP considering environments as different traits in Paraguay Tea (*Ilex paraguariensis*).

Experimental design

Optimal experimental design for pedigree-based BLUP of random effects is an area where little work has been done so far. Bueno and Gilmour (2003) investigated the merits of some simple incomplete block designs, when the $\boldsymbol{A}$ matrix was used for prediction. In general, the same types of search algorithms as used for designs having a fixed effects analysis in mind can be used (John and Williams 1995; Cullis et al. 2006). A difficulty in practice is that, as opposed to fixed effects models, variance components must be known in advance. Further research along the lines of Bueno and Gilmour (2003) is certainly warranted.

Modelling genotype-by-environment interaction

The $\boldsymbol{A}$ matrix and similar matrices for other terms may be used to model genotype-by-environment effects (Smith et al. 2001a). For example, one may use a model of the form $\mathrm{var}(\boldsymbol{u}) = \boldsymbol{A} \otimes \Sigma$, where Σ is some variance–covariance structure corresponding to environments-specific effects, e.g., factor-analytic or heteroscedastic, and $\otimes$ denotes the Kronecker or direct product. Analogous structures may be built using the $\boldsymbol{D}$ matrix and matrices for higher-order terms (Henderson 1985). Also, Σ could be further partitioned, e.g., into year and location effects. Flachenecker et al. (2005) used the $\boldsymbol{A}$ and $\boldsymbol{D}$ matrices with a compound symmetry structure for Σ to predict genotypic and genotype-by-environment effects in a recurrent selection programme with maize. Crossa et al. (2006) considered factor-analytic structures for Σ in order to predict breeding values of wheat genotypes. Burgueno et al. (2007) extended this approach to cover epistasis. With multivariate data, the general structure could be extended as $\mathrm{var}(\boldsymbol{u}) = \boldsymbol{A} \otimes \Sigma \otimes \Omega$, where Ω is a matrix pertaining to a multivariate observation vector per genotype-environment combination.

Genotype-by-environment data are often quite large, so that incorporation of the $\boldsymbol{A}$ matrix in a single-stage analysis can pose major computational obstacles. Many authors, therefore, have chosen a two-stage approach, by which genotype means across enviroments are computed in the first stage, while the $\boldsymbol{A}$ matrix is fitted to genetic main effects in the second stage (Bernardo 1994). A shortcoming of this approach is that genetic main effects and interactions cannot be fully dissected. A more satisfactory approach that allows modelling not only the genetic main effects, but also the genotype-by-environment interaction via the $\boldsymbol{A}$ matrix, is to compute genotype-by-environment means in the first stage and then to fit a mixed model to the genotype-by-environment data.

QTL mapping

This review mainly focusses on BLUP of genotypic values based on mixed models with random genetic effects. Such models are also useful for mapping QTL by linkage methods and association mapping methods, where it is necessary to account for genetic correlations induced by the pedigree (Jannink et al. 2001; Piepho and Pillen 2004; Yu et al. 2006; Jannink 2007). The effects of QTL are commonly modelled as fixed. Much can be gained from modeling QTL effects as random and estimating QTL effects by BLUP. This is a common approach in animal breeding, and it is beginning to gain popularity in plant breeding (Wang et al. 1999; Zhang et al. 2005). A detailed discussion of this use of BLUP is beyond the scope of this paper.

Pedigree-based BLUP not using the coefficient of coancestry

Use of the coefficient of coancestry is based on a number of strong assumptions related to the underlying quantitative-genetic theory. The necessary assumptions can be relaxed somewhat, when the pedigree structure is simple back to a common set of parents, such that simple mixed models can be formulated with nested and crossed effects and the coefficient of coancestry is not involved in the derivation. Apart from the weaker assumptions, this approach has the virtue of simplicity. A disadvantage is the limitation to simple pedigrees

and that it is not possible to dissect additive and non-additive genetic effects (Gallais 1980). Also, it must still be assumed that full data are available back to some common base such as the initial cross or set of crosses. Gallais (1980) discusses the idea of modelling covariance directly in terms of genotypic values rather than in terms of genetic effects. His approach still requires probabilities of different identity by descent states, and it assumes absence of epistasis. By contrast, the approaches considered in this section do not make such assumptions. Instead, a suitable mixed model is derived from first principles by nesting and crossing of random effects to represent simple pedigree structures.

Simple crossed models: diallels and factorials

Henderson (1952, 1977) proposed a mixed model for analysis of a diallel experiment with reciprocal crosses and showed how to obtain BLUP of genetic effects. The model does not make use of coefficients of coancestry through the $\boldsymbol{A}$ matrix. Zhu and Weir (1994a, b, 1996a, 1996b) extended this type of model for seed traits to include cytoplasmatic effects. They used Minimum Variance Quadratic Unbiased Estimation (MIVQUE) instead of REML to estimate variance components. Curnow (1980) suggested that use of a selection index, which is essentially BLUP, based on a diallel model is unlikely to be advantageous compared to alternative selection methods for identifying promising crosses, largely due to uncertainties in the estimation of variance components in small samples. Xiang and Li (2001) showed how to fit a mixed model for diallels that includes random effects for GCA and SCA that are unrelated by pedigree. Tancred et al. (1995) used BLUP to estimate GCA and SCA effects for date of ripening in apples (*Malus domestica*). Factorial experiments, where crosses are made among genotypes from two different heterotic pools, can be analysed similarly as diallels, without taking recourse to the coefficient of conancestry. Essentially this amounts to replacing the $\boldsymbol{A}$ and $\boldsymbol{D}$ matrices in the approach of Bernardo (1993) by identity matrices. As opposed to Bernardo (1993), this approach allows computation of BLUPs of SCA effects only for crosses in the trials, but not for untested crosses.

Simple nested models

Cervantes-Martinez et al. (2001, 2002) used BLUP based on a hierarchical mixed model to predict genotypic values in sets of lines of oats (*Avena sativa*). Piepho and Williams (2006) considered a hierarchical mixed model for simple pedigrees with genotypes nested within families and showed by simulation that BLUP gave better estimates than BLUE. They also found that in terms of accuracy of BLUPs, α-designs perform well compared to split-plot designs, in which families are randomised as a main-plot factor.

Examples

In this section, we give three examples of the use of BLUP in plant breeding. Two of the examples stress the option to derive a mixed model that reflects simple pedigree structures without using the coefficient of coancestry.

Prediction of hybrid performance in maize

This example concerns a set of eleven mostly complete factorial crosses among inbred lines from the flint and dent heterotic pools in maize (data kindly provided by Tobias Schrag, University of Hohenheim, Germany). A total of 61 trials were performed in 6 years. The trials were laid out in resolvable incomplete blocks with three replicates. There were 417 crosses among 38 dent lines and 55 flint lines. In addition to crosses, parents were tested to assess per se performance. The trials for crosses comprised a number of check genotypes. The genotypic effects of parents and crosses were modelled as random, while check effects were fixed. Separation of fixed genotypic effects and random genetic effects was done as described in Piepho and Williams (2006). The variance–covariance structure of crosses was modelled by GCA and SCA effects, as proposed by Bernardo (1993), using $\boldsymbol{A}$ matrices corresponding to the GCA effects pertaining to the two pools and a $\boldsymbol{D}$ matrix associated with the SCA effects. The minimum, median and maximum of the off-diagonal entries of the $\boldsymbol{A}$ matrix were (0, 0.12, 1.98) for the dent pool and (0, 0.23, 1.75) for the flint pool. For the $\boldsymbol{D}$ matrix the corresponding values were (0, 0.0047, 0.98). Per se effects of parents were assumed to be

correlated with GCA effects, thus exploiting per se data for predicting GCA effects. The models were fitted by ASReml, which requires inverses of $\boldsymbol{A}$ and $\boldsymbol{D}$ to be supplied. We computed these in SAS/IML (Most statistical packages have facilities to compute inverses). Examples of how to fit models with known $\boldsymbol{A}$ and $\boldsymbol{D}$ matrixes in ASReml can be found in the manual (Gilmour et al. 2005). Details of the analysis will be presented elsewhere. Here, we only report the fits of the model just described and a simplified model, in which $\boldsymbol{A}$ and $\boldsymbol{D}$ matrices were replaced by identity matrices, implying independence among GCA effects and among SCA effects (Henderson 1977) (Table 3). The log-likelihood for the independent model was considerably higher than for the correlated model. This may be a result of the fact that the quantitative theory underlying the model of Bernardo (1993) makes a number of strong assumptions, which may not be fully met here. Also, higher order epistatic terms have been assumed to be absent, which is likely to be an unrealistic assumption. The example illustrates that it is important to critically check model assumptions and to compare fits of alternative models by suitable, preferably likelihood-based procedures (Oakey et al. 2006).

DH development in a heterotic pool

In hybrid breeding, the development of hybrid parents frequently yields treatment structures that have a two-stage nested form with additional structure at the group level. For example, inbred lines from a heterotic pool may be intercrossed according to a diallel. Each cross is used to generate doubled haploid (DH) lines, of which a sample of about five to ten DH lines is propagated. The DHs are then crossed to a single tester from the opposing heterotic pool in order to assess GCA effects. The test crosses clearly have a nested treatment structure with the originating diallel crosses corresponding to groups and test crosses corresponding to entries within groups. Thus, the simple nested treatment model **cross/DH** could be contemplated for analysis, where **cross** codes the particular cross and the DH nested within a cross is coded by **DH**. Nesting is symbolized by the slash, following a notation common in statistical packages such as GenStat (McCullagh and Nelder 1989). This notation provides a convenient tool for developing complex mixed models, and we will use it in the subsequent development. For a review of the notation and its syntax rules see Piepho et al. (2003). In the case at hand, the nested structure **cross/DH** resolves as **cross + cross·DH**, where the dot indicates a crossed effect.

The model **cross/DH** can be further refined, as the group effect has a two-way structure imposed by the diallel. Specifically, the group effect may be decomposed into GCA and SCA effects, implying a genetic correlation among group effects. The model then has the form

$$(\mathbf{parent1} \times \mathbf{parent2})/\mathbf{DH} = \mathbf{parent1} + \mathbf{parent2} + \mathbf{parent1} \cdot \mathbf{parent2} + \mathbf{parent1} \cdot \mathbf{parent2} \cdot \mathbf{DH}$$

where **parent1** and **parent2** denote the two parents of a cross, and the associated main effects model GCA. Similarly, the SCA effect is modelled by **parent1 · parent2**, while the nested effect of DHs within a cross is represented by **parent1 · parent2 · DH**. In the above notation, the symbol " × " indicates a full factorial model involving the factors before and after the cross, while the dot indicates a crossed effect (Piepho et al. 2003). When implementing this model using a mixed model package, some care must be exercised because the same genotype may appear as **parent1** in some crosses and as **parent2** in the other crosses, thus inducing a perfect correlation among a level of **parent1** and the same level of **parent2**. In SAS PROC MIXED, this can be implemented using a Toeplitz covariance structure (Xiang and Li 2001). It is also possible to account for maternal effects.

Deriving a mixed model for BLUP in a simple pedigree without using coancestry

This example concerns a simple pedigree derived from a single cross. It is shown how a suitable model not relying on the coefficient of coancestry can be developed from first principles. The present subsection will be somewhat more detailed than the rest of the paper, because it uses a notation that may not be well known to all readers and because to our knowledge the proposed model is somewhat complex and has not been discussed in this form elsewhere in the literature.

Assume that a single cross between two inbred lines is performed. The F2 plants are selfed in subsequent generations and propagated by single-seed descent. This gives rise to a hierarchical pedigree, which can be depicted as in Fig. 1. It is

assumed here for simplicity that in each generation, selection is exercised among individual plants, but extension to the case of selection among families/groups of plants is straightforward. If BLUP is to be used for selection in each generation, the question arises as to how the genetic part of the mixed model should be formulated. The F2 population can be regarded as a base population. Thus, we would like to use all phenotypic data, starting from the F2, so that the analysis meets the missing-at-random (MAR) assumption under selection and we actually estimate genetic variance components related to the base population (Piepho and Möhring 2006). If the coefficient of coancestry is to be used, the model may be obtained by straightforward application of the method described in Henderson (1985) and Mrode (1996). It is then necessary, however, to truncate higher order terms, e.g. for epistasis, and to assume absence of linkage, so the model will always constitute an approximation based on strong assumptions. Thus, it is useful to consider an alternative mixed model that truthfully represents the pedigree, but does not rely on the coefficient of coancestry and strong assumptions regarding the quantitative genetics. Such a model is useful in its own right for prediction of genotypic values in each generation. In addition, it may provide a baseline model (full model) against which to compare alternative, simpler models (reduced models) such as those based on Henderson (1985), e.g., by likelihood ratio tests (lack-of-fit tests) or model selection criteria (e.g., Akaike's Information Criterion; Wolfinger 1996).

To illustrate formulation of a mixed model, we use the syntax described in Piepho et al. (2003, 2004), which is akin to syntax used in mixed model packages. We assume that data only up to the F4 are available, but note that extension to more generations is straightforward. The following variables are used for defining a model:

ID2: ID for F2 plants

ID3: ID for F3 plants/families

ID4: ID for F4 plants/families

GTN: ID of the generation, e.g. with levels F2, F3, and F4

Generation-specific models

If data from only a single generation is used, e.g. the F3, the appropriate mixed model is a simple hierarchical model given by

$$\mathbf{ID2/ID3 = ID2 + ID2 \cdot ID3.}$$

Similarly, the hierarchical model for the F4-generation is

$$\mathbf{ID2/(ID3/ID4) = ID2 + ID2 \cdot ID3 + ID2 \cdot ID3 \cdot ID4.}$$

If in addition data from the F2 were available, the model for that generation would be represented simply by **ID2**.

Model for combined analysis across generations

A great potential of BLUP that to our knowledge so far has rarely if ever been exploited is to combine information from several generations in the same pedigree. This is expected to improve genotypic value estimates for the current generation. Analysis

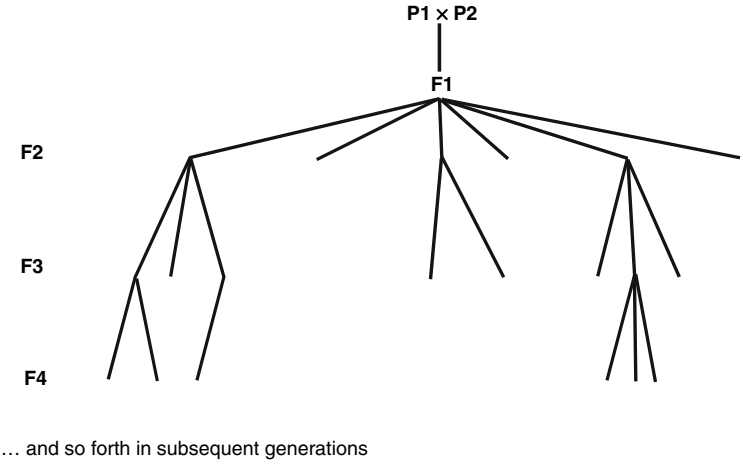

Fig. 1 Schematic representation of a simple pedigree resulting from a single cross (P1 × P2)

of data from multiple generations requires a joint model that includes the generation (**GNT**) as a factor.

In all three generation-specific models, there is a term **ID2**. Also, generation-specific models for F3 and F4 have the term **ID2** · **ID3** in common. Despite this notational identity, the effects in question cannot be exactly the same over generations, as genotypes in different generations are distinct due to meiotic events. In order to formulate a single model over generations, it is therefore necessary to introduce the factor **GTN** coding different generations. Thus, the model could be written **GTN** · **ID2** + **GTN** · **ID2** · **ID3** + **GTN** · **ID2**· **ID3** · **ID4** There are two details that need to be incorporated yet. Firstly, the effects **GTN** · **ID2** · **ID3** and **GTN** · **ID2** · **ID3** · **ID4** do not appear in all generations. Secondly, the effects are correlated across generations. For example, **GTN** · **ID2** represents the effect of an F2-plant as operating in the F2 as well as in the subsequent generations F3 and F4. The effects in different generations corresponding to the same F2-plant, while not identical, will be positively correlated. This can be accommodated by regarding **GTN** as a repeated factor and **ID2** as the subject effect in repeated measures terminology. In the notation of Piepho et al. (2004) this is highlighted by writing the model as

$$\mathbf{GTN}\cdot\boldsymbol{ID2} + \mathbf{GTN}\cdot\boldsymbol{ID2}\cdot\boldsymbol{ID3} + \mathbf{GTN}\cdot\boldsymbol{ID2}\cdot\boldsymbol{ID3}\cdot\boldsymbol{ID4}, \tag{3}$$

where italizised terms are subject effects and non-italizised effects are repeated effects (the model is still not quite complete yet, as detailed below). Thus, if u_2, u_3 and u_4 represent the effect of an F2-plant as operating in generations F2, F3 and F4, respectively, modelled by **GTN** · **ID2**, we fit the model

$$var\begin{pmatrix} u_2 \\ u_3 \\ u_4 \end{pmatrix} = \Sigma_{F2}. \tag{4}$$

Similarly, if v_3 and v_4 represent the effect of an F3-plant or family in generations F3 and F4, respectively, modelled by **GTN** · ***ID2*** · ***ID3***, we fit

$$var\begin{pmatrix} v_3 \\ v_4 \end{pmatrix} = \Sigma_{F3}. \tag{5}$$

Finally, for consistency, the variance of an effect w_4 for the F4-families/individuals in the F4 generation, modelled by **GTN** · ***ID2*** · ***ID3*** · ***ID4***, is denoted as

$$var(w_4) = \Sigma_{F4}. \tag{6}$$

Model (3) does not yet correctly represent this structure, because the factor **GTN**, appearing in all three effects, has three levels, implying a 3-dimensional covariance structure for each effect. This is in contrast to structures (5) and (6), which have only two and one dimension, respectively. Thus, **GTN** needs to be replaced by terms specific to the different effects. Depending on the mixed model package being used, there are different ways of doing this. For example, with SAS PROC MIXED it is convenient to define the factors given in Table 1.

In Table 1, levels of a factor given in brackets correspond to unobserved levels. They need to be set equal to one of the observed levels (which one is arbitrary!) so that the model can be fitted. Unobserved levels will then be blocked out using dummy variables as suggested in Piepho et al. (2006). The dummies are defined in Table 2. With the definitions in Tables 1 and 2, model (3) is modified as follows:

$$\mathbf{Z2}\cdot\mathbf{GTN2}\cdot\boldsymbol{ID2} + \mathbf{Z3}\cdot\mathbf{GTN3}\cdot\boldsymbol{ID2}\cdot\boldsymbol{ID3} + \mathbf{Z4}\cdot\mathbf{GTN4}\cdot\boldsymbol{ID2}\cdot\boldsymbol{ID3}\cdot\boldsymbol{ID4}. \tag{7}$$

Note that the dummy **Z2** would not be strictly needed, as its level is the same for all generations. It

Table 1 Definition of generation factors for repeated mixed models representing a simple pedigree with phenotypic data from several generations (Eq. 1)

Factor	Levels			Description
	F2	F3	F4	
GNT	2	3	4	Generation factor for F2 effects
GNT	(3)	3	4	Generation factor for F3 effects
GNT	(4)	(4)	4	Generation factor for F4 effects

Table 2 Definition of dummy variables for repeated mixed models representing a simple pedigree with phenotypic data from several generations (model 1)

Dummy variable	Levels			Description
	F2	F3	F4	
Z2	1	1	1	Selector for F2 effects
Z3	0	1	1	Selector for F3 effects
Z4	0	0	1	Selector for F4 effects

Table 3 Fits of two mixed models for factorial crosses of maize (flint x dent) (Data kindly provided by T. Schrag, University of Hohenheim, Germany)

	REML estimates		
	Covariance parameter	With $\boldsymbol{A}$ & $\boldsymbol{D}$	Without $\boldsymbol{A}$ & $\boldsymbol{D}$
Dent	Var(per se)	17.36	33.12
	Var(GCA)	18.18	22.03
	Cov(GCA, per se)	8.48	9.14
Flint	Var(per se)	62.29	39.16
	Var(GCA)	30.92	18.12
	Cov(GCA, per se)	7.67	2.76
Dent × Flint	Var(SCA)	1.39	5.24
Log-likelihood (REML):		−21721.4	−21656.6

is introduced simply for consistency with the other effects, thus clarifying the model structure.

To complete the model, we also need to include a fixed main effect for generations (**GNT**). As generation and year effects are confounded, this effect will capture both year effects as well as true generation effects due to inbreeding depression etc. For example, with the definition of factors used here, assuming a completely randomized design and homogeneity of error variance for simplicity, specification of the model in PROC MIXED of the SAS System is as shown in Fig. 2. The corresponding code for ASReml is given in Fig. 3. To illustrate the effect of shrinkage,

```
Proc mixed data=all_generations lognote;
class gtn gtn2 gtn3 gtn4 ID2 ID3 ID4;
model y=gtn/outp=BLUP;
random Z2*gtn2/sub=ID2          type=unr;
random Z3*gtn3/sub=ID2*ID3      type=unr;
random Z4*gtn4/sub=ID2*ID3*ID4 type=unr;
```

Fig. 2 SAS code for model (3)

a small pedigree was simulated with 100 F2 plants, 5 F3 plants per F2 plant, and 4 F4 plants per F3 plant. The simulation programme is available from the first author upon request. Figure 4 shows a plot of simulated BLUP, simulated BLUE and true genotypic values versus true values. The shrinkage of BLUP compared to BLUE is clearly visible. The plot also shows that BLUP is slightly biased downwards for high true values, while it is biased upwards for low true values. This bias, which is typical of BLUP, is more than compensated for by the reduction in variance. Consequently, the rank correlation of simulated BLUP with true values (0.75) is higher than that of simulated BLUE with true values (0.59). It is perhaps useful here to point out that the meaning of unbiasedness is different for BLUE and BLUP (Searle et al. 1992). Unbiasedness for BLUE means that $E\left(\hat{\boldsymbol{\beta}}\right) = \boldsymbol{\beta}$, while for BLUP unbiasedness relates

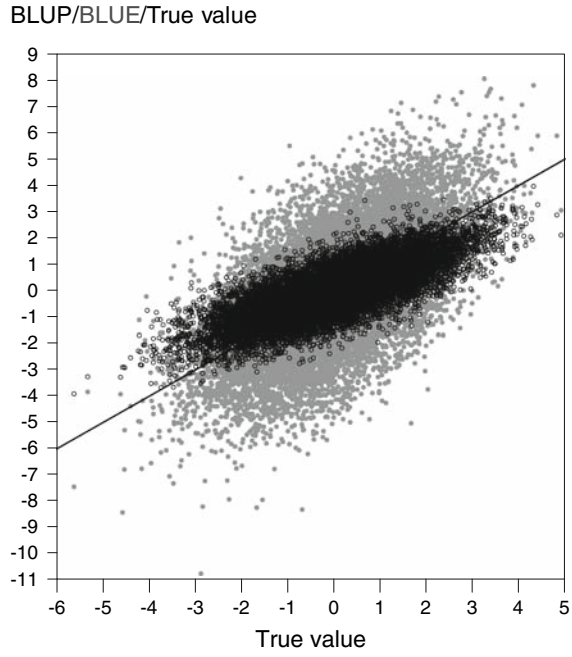

Fig. 4 Plot of simulated BLUP (black circles), BLUE (grey dots), and true genetic values (solid line) versus true values

```
y ~ mu gtn !r gtn2.id2.z2 gtn3.id2.id3.z3 gtn4.id4.id3.id2.z4 !f mv
0 0 2
gtn2.id2.z2 2
gtn2.z2 gtn2.z2 us 0.1 0.01 0.1 0.01 0.01 0.1
id2 id2 id
gtn3.id2.id3.z3 2
gtn3 gtn3 us 0.1 0.01 0.1
id2.id3.z3 id2.id3.z3 id
```

Fig. 3 ASREML code for model (3).

to the fact that $\boldsymbol{u}$ and its BLUP have the same expected values over the population, i.e., $E(\hat{\boldsymbol{u}}) = E(\boldsymbol{u}) = 0$. Note in particular that for BLUP $E(\hat{\boldsymbol{u}}) \neq \boldsymbol{u}$, which is commensurate with the type of bias seen in Fig. 4.

It should be stressed that generation-specific and genotype-by-environment effects are confounded. There seems little one can do to dissect these effects, unless several generations are planted in the same trials, which is often impossible. If year main effects are to be dissected from genotypic generation effects, one needs to include standards, which would be modelled as fixed effects. This can be done as described in Piepho et al. (2006).

It may happen occasionally that the $\boldsymbol{G}$ matrix fitted by REML is not positive-definite, particularly in smaller datasets. In these cases, the mixed model equations may be modified as suggested by Henderson (1984), and this option is implemented in PROC MIXED. Also, the unstructured models for Σ_{F2} and Σ_{F3} may be replaced by more parsimonious models such as the factor-analytic model (Piepho 1997, 1998) or autoregressive models.

Discussion

This paper has reviewed the application of BLUP in plant breeding both with and without pedigree information. The use of pedigree information requires defining a base population. There is no absolute truth, however, concerning where we place that base, though some choices are usually more reasonable than others depending on the assumptions involved regarding the base population (linkage phase equilibrium, Hardy–Weinberg equilibrium, etc.) and the availability of complete pedigree information. Assuming that current genotypes are entirely uncorrelated might be taken as the extreme choice, where we equate the base population to the current set of genotypes. Alternatively, when pedigree information is exploited, the base is placed backwards in time to a point up to which all ancestral relationships are known. To give an example, consider a maize hybrid testing program involving two heterotic pools. If we fit a model with independent GCA and SCA effects, the base refers to the current set of parental inbred lines, which are then assumed unrelated. Alternatively, pedigree information may be available back to the controlled crosses between the most promising elite inbreds used to develop the current parental inbred lines. In this case, correlated GCA and SCA effects may be modelled using the approach of Bernardo (1994). The base would then correspond to the population of initial founder inbreds, from which current parental inbreds were derived. The fact that variance component estimates differ whether or not pedigree information is exploited does not necessarily imply a bias. Differences must be expected because variance components have different meaning, as they refer to different base populations. Also, it should perhaps be stressed that the assumption of uncorrelated effects does not imply that we deny the fact that the genotypes will always be related by pedigree relative to some base population further back in time.

In this paper we have contrasted BLUP based on pedigree information derived from the coefficient of coancestry and BLUP not using the coefficient of coancestry. When the coefficient of coancestry is used, it is possible to dissect different genetic effects (additive, dominance, epistasis). This may be useful, when only some of the genetic effects are easily exploitable, as is the case in pedigree breeding with self-pollinators, where mainly the additive genetic effects are involved in response to selection. By contrast, pedigree-based BLUP not using the coefficient of coancestry cannot discern additive and non-additive genetic effect. It can, however, dissect effects such as specific and general combining ability (assuming these are not correlated by pedigree) as well as within and between-family effects. Often the main focus is merely on the estimation of the whole genotypic value rather than on component genetic effects comprising the genotype, so BLUP not using the coefficient of coancestry is perfectly reasonable.

It is our belief that most of the time it is difficult to give a strong justification for use of the coefficient of coancestry based on quantitative-genetic theory, because the full set of underlying statistical assumptions is difficult to fully meet or verify. In large animal breeding programmes, where pedigree structures are extensive and complex, estimation of genetic effects based on the coefficient of coancestry making some strong simplifying assumptions often is the only practical option. By contrast, many plant breeding experiments give rise to fairly simple

hierarchical or crossed pedigree structures, for which suitable mixed models can be derived from first principles without taking recourse to a set of strong assumptions based on quantitative-genetic theory such as gametic-phase equilibrium, absence of epistasis or selection, etc. The main assumption required, when the coefficient of coancestry is not used, is that genotypes in a reference generation, e.g. inbred parents of a diallel or factorial experiment, can be regarded as a random sample from some hypothetical parent population. By ignoring the coefficient of coancestry, we simply assume that all genotypes in the reference generation are stochastically independent. By contrast, when exploiting the coefficient of coancestry, we go further back in time, tracing all genotypes to a more distant base population were all genotypes were unrelated. Thus, genotypes in the current reference population become correlated by pedigree. As a result, pedigree information is exploited via genetic correlation. If we ignore the pedigree, that information remains unutilized. Not using the pedigree information relative to a hypothetical, distant base population may be quite a reasonable thing to do, however, when use of that information would require unrealistic assumptions, which one is not prepared to make.

That being said, we should also stress that, imperfections notwithstanding, use of the coefficient of coancestry often does provide valuable information, even when the usual quantitative-genetic assumptions do not fully hold (Lynch and Walsh 1998, p. 793). We believe that often the use of the coefficient of coancestry can be motivated and justified heuristically without taking recourse to strong assumptions about the population genetic structure. For example, the coefficient of coancestry may be regarded as a measure of similarity, from which distances can be derived. Thus, there is some analogy between BLUP based on the $\boldsymbol{A}$ matrix, which makes predictions of genetic effects based on genetic correlation with relatives, and geostatistical methods such as Kriging, where local predictions are made exploiting information from neighboring observations based on spatial correlation (Schabenberger and Gotway 2005). In fact, use of the $\boldsymbol{A}$ and $\boldsymbol{D}$ matrix in case idealized assumptions of quantitative-genetic theory do not hold may be justified to some degree by this analogy. Spatial methods mainly require that spatial observations can be regarded as a realization of a multivariate random variable with covariance depending on spatial distance. By analogy, one could assume that observed genotypes constitute a realization of a multivariate random variable with covariance depending on genetic distance. This assumption does not require reference to a specific base population with idealized properties. All that is assumed is that genetic covariance depends on genetic distance, while the specific form of this dependence needs to be identified during the model-building phase. For example, using principal coordinate analysis (Digby and Kempton 1987), one might consider finding a representation of genotypes in Euclidean space, such that the implied distances are as close as possible to those implied by the $\boldsymbol{A}$ matrix. Then, a spatial model might be fitted to the principal coordinates associated with the largest eigenvalues. Use of the $\boldsymbol{A}$ matrix corresponds to the assumption that genetic covariance shows a linear decay with genetic distance. Alternatively, there are a large number of non-linear models that might be explored, including the exponential, power, and spherical models. For these models there is no need of justification by quantitative genetic theory, such as reference to an idealized base population, except, perhaps, that use of the coefficient of coancestry to define distance must be justified. In addition, genetic distances may be assessed based on marker data and distances can be used in conjunction with geostatistical models in the same way as the $\boldsymbol{A}$ matrix. Non-linear genetic covariance structures may be further justified by the fact that higher-order variance–covariance components (dominance, additive $\times$ dominance, etc.) need to be ignored and the coefficient of coancestry enters these components in a non-linear way.

When marker data are used to infer genetic relationships, such information may not be available for all genotypes to be included in an analysis, while complete pedigree data is available. In order to make full use of the marker data, one might consider using a compromise between the $\boldsymbol{A}$ matrix, as inferred from the pedigree, and genetic similarity information as assessed, e.g., by a similarity matrix $\boldsymbol{S}$. Assume that $\boldsymbol{A}$ is partitioned as

$$\boldsymbol{A} = \begin{pmatrix} \boldsymbol{A_{11}} & \boldsymbol{A_{12}} \\ \boldsymbol{A_{21}} & \boldsymbol{A_{22}} \end{pmatrix}, \tag{8}$$

such that $\boldsymbol{A}_{11}$ is the numerator relationship matrix for the genotypes with marker information, while $\boldsymbol{A}_{22}$ is

the partition of $\boldsymbol{A}$ corresponding to genotypes without marker information. The genetic variance–covariance structure may then be modelled as

$$\boldsymbol{V} = \begin{pmatrix} 0 & \boldsymbol{A_{12}} \\ \boldsymbol{A_{21}} & \boldsymbol{A_{22}} \end{pmatrix} \boldsymbol{\sigma}^2_{A1} + \begin{pmatrix} \boldsymbol{A_{11}} & 0 \\ 0 & 0 \end{pmatrix} \boldsymbol{\sigma}^2_{A2} + \begin{pmatrix} \boldsymbol{S} & 0 \\ 0 & 0 \end{pmatrix} \boldsymbol{\sigma}^2_{S}. \tag{9}$$

This structure allows finding the optimal compromise among relationships from pedigree information ($\boldsymbol{A}_{11}$) and marker information ($\boldsymbol{S}$) for those genotypes with information from both sources. The same idea can be used when pedigree data is lacking for some genotypes. When marker data is available for all genotypes in addition to pedigree, one may consider combining both sources in a similar fashion according to $\boldsymbol{V} = A\boldsymbol{\sigma}^2_A + S\boldsymbol{\sigma}^2_S$. In all of these cases, likelihood ratio tests (Oakay et al. 2006) or other model selection criteria (Wolfinger 1996) may be used to check which of the components of the genetic variance–covariance structure is needed.

There is little literature on the robustness of BLUP as used in plant breeding applications against departure from assumptions. Bernardo (1996c) found in a simulation study that BLUP is robust when inbred relationships are erroneously specified. Results from the animal breeding literature indicate, however, that biases may be substantial when information back to the base population is not complete (Sorensen and Kennedy 1984; Van der Werf & de Boer 1990; Dietl et al. 1998; Schenkel et al. 2002; Jamrozik et al. 2007), and this was also found by Piepho and Möhring (2006) in a plant breeding context. A thorough investigation of robustness to mis-specified pedigrees in diverse plant breeding settings is as yet lacking. A further issue is robustness to non-normality. Departure from normality in the random effects is rather difficult to detect (Verbeke and Lesaffre 1996; Houseman et al. 2006). The fact that REML is equivalent to iterated Minimum Norm Quadratic Unbiased Estimation (I-MINQUE), which does not require normality (Searle et al. 1992, p. 399), would suggests that REML is robust to departures from normality. Theoretical results show, however, that inferences can be quite sensitive to departures from normality, in particular in the presence of outliers (Copt and Victoria-Feser 2006). Again, comprehensive simulations with a focus on the plant breeding context are as yet lacking.

The performance of BLUP depends crucially on the availability of good variance estimates. In animal breeding programmes there is often a very large database for estimation of genetic variance components. By contrast, plant breeding designs typically yield a more limited number of genotypes. Also, there may be heterogeneity of variance among crosses, requiring cross-specific variance estimates based on a small number of genotypes (White and Hodge 1989, p. 295). In such cases, BLUP may perform poorly when the genetic variance components are not accurately estimated. An advantage of the use of the coefficient of coancestry is that only a single variance component needs to be estimated, while all correlation is modelled via the $\boldsymbol{A}$ matrix. By contrast, when the coefficient of coancestry is not used, it is usually necessary to estimate several variance components.

Heterogeneity of genetic variance components among crosses could be tackled by a Bayesian approach, by which estimation of the genetic variance for a particular cross combines data from that cross and from other crosses. In a plant breeding context, this idea has been employed for estimating heterogeneous genotype-by-environment variance components for assessing stability (Edwards and Jannink 2006). Generally, Bayesian methods are very commonly used in animal breeding (Gianola and Fernando 1986), while applications in plant breeding so far are relatively rare (see, e.g., Theobald et al. 2002).

When phenotypic data at the plot level are available, it is preferable to perform a single-stage analysis that accounts for all sources of variation. For computational reasons, however, it may be necessary to perform a two-stage analysis, where in the first step, individual trials are analysed to compute treatment means, which are then subjected to a mixed model analysis over trials in the second stage. A critical question in two-stage analyses is how to optimally weight treatment means in the second stage, based on the variance–covariance matrix of trial-specific treatment means from stage one. That matrix may be set equal to the residual variance–covariance matrix $\boldsymbol{R}$ in the mixed model equations (Eq. 1), when a model is formulated for means. Smith et al. (2001a) propose to compute weights from the diagonal elements of the inverse of $\boldsymbol{R}$, arguing that this inverse needs to be approximated in the mixed model equations. Alternative weighting schemes are

possible, and a comparison of different options is currently under way (Piepho and Möhring 2007).

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