Estimation, Testing, and Prediction Regions of the Fixed and Random Effects by Solving the Henderson’s Mixed Model Equations

Viktor Witkovský∗

∗Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovakia

Abstract

We present a brief overview of the methods for making statistical inference (testing statistical hypotheses, construction of confidence and/or prediction intervals and regions) about linear functions of the fixed effects and/or about the fixed and random effects simultaneously, in conventional simple linear mixed model. The presented approach is based on solutions from the Henderson’s mixed model equations.

Keywords: Linear mixed model, mixed model equations, fixed effects; random effects, REML, BLUP, EBLUP, MSE, Satterthwaite approximation, Fai-Cornelius approximation, Harville-Jeske and Prasad-Rao approximation, Kenward-Roger approximation.

2000 MSC: 62J07, 62J10, 62F10.

1. Introduction

The applications of data analysis based on the statistical linear mixed model, as a natural generalization of the analysis of variance methods and the ANOVA models, (see e.g. [44], [15], [36]), are widespread. Such applications with analytical methods based on linear mixed models include different fields of the biomedical and technical research, (see [56] and/or [11]). For illustration, here we shall mention just few of them: e.g. genetics with its microarray experiments, [7], [8], [9], [74], the plant and animal breeding in agricultural, [5], statistical meta-analysis in medical research, [18], neurophysiology, [51], as well as different technical applications, like e.g. calibration of devices, derivation of the tolerance intervals for industrial applications, interlaboratory comparisons in metrology, and methods for expression the uncertainties in measurements, see e.g. [6], [14], [24], [31], [48], [53], [62], [63], [64], [69], [70], [71], [73], and [73].

Although the linear mixed models and the methods for statistical inference based on such models have been recognized and used for long time by the researchers in different fields, it seems that some sort of misunderstanding of the principles and/or the technical details (of the used methods for statistical inference based on such linear mixed models) may lead to improper usage of the implemented methods and algorithms. Moreover, there are still some further open theoretical problems (like e.g. methods for testing and constructing confidence intervals/regions about the variance components, see e.g. [2], [3], [4], [52], [53], [58], [59], [61], [65], [66], [67]).

So, the main goal of the paper is to present a brief overview of the standard (conventionally used) methods for making statistical inference (in particular the methods for testing statistical hypotheses and the methods for construction of the confidence and/or prediction intervals/regions) about linear functions of the fixed effects and/or about the fixed and random effects simultaneously, in conventional simple linear mixed model, (with pointing to potential problems which may appear based on usage of these methods), and to present some of the recently developed improvements, as well as some generalizations, together with relatively detailed technical description of the model and the methods. The presented approach is based on the elements of the solution of the Henderson’s mixed model equations.

2. Henderson’s mixed model equations

We consider the linear mixed model (LMM) in the following form

\[ y = Xb + Zu + e, \]

with \( y \) being an \( n \)-dimensional vector of observations, \( b \) being the \( p \)-vector of fixed effects, \( u \) being the \( r \)-vector of random effects with \( E(u) = 0 \) and \( \text{Var}(u) = G \), and \( e \) being the \( n \)-vector of random (measurement) errors with \( E(e) = 0 \) and \( \text{Var}(e) = R \), where \( R \) is assumed to be strictly positive definite variance-covariance matrix of \( e \). The \((n \times p)\)-matrix \( X \) and the \((n \times r)\)-matrix \( Z \) are the known design matrices. Typically, we can write \( Zu = \sum_{i=1}^{r} Z_i u_i \), where the \((n \times r_i)\) matrices \( Z_i \) and the \( r_i \)-dimensional random effects \( u_i \), \( i = 1, \ldots, s \), could be specified from the structure of the model.

The main goal of this paper is to present an overview of the methods for making statistical inference about linear functions of the fixed effects \( b \) and the random effects \( u \), i.e. about \( K'b \) and/or about \( w = N(b', u)\)' = \( K'b + L'u \) for given (suitable) coefficient matrices \( A \), resp. \( K \) and \( L \).

Preprint submitted to Measurement Science Review, Vol. 12, No. 6, 2012, 234–248.

May 6, 2014
Henderson in [23] developed a set of equations, termed as the mixed model equations (MMEs), that simultaneously yield the best linear unbiased estimator (BLUE) of $Xb$ (or any vector of estimable linear functions $Kb$) and the best linear unbiased predictor (BLUP) of $u$ (or any vector $w = Kb + Lu$, provided $Kb$ is estimable), under the assumption that the covariance structure is known.

The MMEs were derived based on the normality assumptions, i.e. $u \sim N(0,G), \ e \sim N(0,R)$, with $Cov(u,e) = 0$, for known variance-covariance matrices $G$ and $R$. Thus, the joint probability density function (pdf) of the random vector $(y',u')'$ is given as

$$f(y,u) = \frac{1}{(2\pi)^{n/2}|R|^{1/2}} \exp \left\{ -\frac{1}{2} (y - Xb - Zu)'R^{-1}(y - Xb - Zu) \right\} \times \frac{1}{(2\pi)^{q/2}|G|^{1/2}} \exp \left\{ -\frac{1}{2} u'G^{-1}u \right\}. \tag{2}$$

By solving the ML equations for $b$ and $u$, i.e.

$$\frac{\partial f(y,u)}{\partial b} = 0, \quad \frac{\partial f(y,u)}{\partial u} = 0 \tag{3}$$

we get the MMEs in the following form

$$\left( X'R^{-1}X \quad X'R^{-1}Z \right) \left( \begin{array}{c} \tilde{b} \\ \tilde{u} \end{array} \right) = \left( X'R^{-1}y \quad Z'R^{-1}y \right). \tag{4}$$

The left-hand side matrix of (4) will be termed as the Henderson’s MME’s matrix, here denoted by $H$, i.e.

$$H = (X,Z)'R^{-1}(X,Z) + (0,1)'G^{-1}(0,1), \tag{5}$$

where by $0$ we denote a zero matrix with suitable dimensions, here $(r \times p)$.

Alternatively,

$$\left( X'R^{-1}X \quad X'R^{-1}ZG \right) \left( \begin{array}{c} \tilde{b} \\ \tilde{v} \end{array} \right) = \left( X'R^{-1}y \quad Z'R^{-1}y \right), \tag{6}$$

where $W = (I + Z'R^{-1}ZG)^{-1}$. Notice, that based on (6), there is no need to restrict the variance-covariance matrix $G$ to be strictly positive definite. This version of MMEs is preferred for numerical evaluations, if $G$ can be a bad conditioned matrix.

Given the variance-covariance matrices $G$ and $R$, let us denote as $C$ the following matrix of coefficients

$$C = \left( \begin{array}{cc} C_{11} & C_{12} \\ C_{21} & C_{22} \end{array} \right) = \left( \begin{array}{cc} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{array} \right), \tag{7}$$

where by $A^-$ we denote any $g$-inverse of the matrix $A$.

Let $\tilde{b}$ and $\tilde{u}$ be any solution to the MMEs (4). Notice that based on (6), we can reconstruct $\tilde{u}$ by $\tilde{u} = G\tilde{v}$. Then the BLUE of the vector of linear estimable functions of the fixed effects $Kb$, see e.g. [49], is

$$\text{BLUE}(Kb) = Kb'X'V^{-1}Kb', \tag{8}$$

where $K'$ is a $(q \times p)$-matrix of coefficients of the estimable linear function $K'b$, i.e. $K = X'A$ for some matrix $A$, and $V = Z'GZ + R$. The BLUP of the vector of linear functions of the fixed and random effects, say $K'b + Lu$, is

$$\text{BLUE}(K'b + Lu) = \text{BLUE}(K'b) + L'GZV^{-1}(y - \text{BLUE}(Xb)), \quad Kb + Lu, \tag{9}$$

where $L'$ is an arbitrary $(q \times r)$-matrix of coefficients, and $\text{BLUE}(Xb) = Xb$.

Important properties of the solutions of the MMEs are summarized below, for more details see e.g. [38]:

1. In the class of linear unbiased predictors, BLUP maximizes the correlation between $u$ and $\tilde{u}$.
2. $K'b$ is BLUE of the set of estimable linear functions $K'b$.
3. $E(u|\tilde{u}) = \tilde{u}$.
4. $\tilde{u}$ is unique.
5. $K'b + Lu$ is BLUE of $K'b + Lu$ provided that $K'b$ is estimable.
6. $\text{Var}(K'b) = K'C_11K$.
7. $\text{Var}(K'b + Lu) = K'C_11K + L'(G - C_{22})L$.
8. $\text{Var}(K'b + Lu) - (K'b + Lu) = (K',L')(C(K',L')'$. 
9. $\text{Cov}(K'b,\tilde{u}) = 0$.
10. $\text{Cov}(K'b,\tilde{u}' - \tilde{u}) = -K'C_{12}$.
11. $\text{Cov}(K'b,\tilde{u}' - \tilde{u}) = -K'C_{12}$.
12. $\text{Var}(\tilde{u}) = \text{Cov}(\tilde{u},\tilde{u}) = G - C_{22}$.
13. $\text{Var}(\tilde{u} - u) = C_{22}$.

In this paper we shall consider only a special form of the model (1) — a conventional simple LMM with normally distributed errors and random effects. That is, we shall assume mutually uncorrelated (independent) normally distributed random effects $u_1, \ldots, u_s$ and $e$ with $E(u_i) = 0$ for $i = 1, \ldots, r$, $E(e) = 0$, $\text{Cov}(u_i, u_j) = 0$ for $i \neq j$, and $\text{Cov}(u_i, e) = 0$ for all $i = 1, \ldots, s$.

Further, we shall assume $\text{Var}(u_i) = \sigma_i^2 I_s$, $i = 1, \ldots, s$, with $r = \sum_{i=1}^s r_i$, and $\text{Var}(e) = \sigma_{ss}^2 I_s$. Hence,

$$E(y) = Xb, \quad \text{and} \quad \text{Var}(y) = \sum_{i=1}^s \sigma_i^2 Z_i'Z_i + \sigma_{ss}^2 I_s. \tag{10}$$

with $\sigma^2 = (\sigma_1^2, \ldots, \sigma_s^2, \sigma_{ss}^2)$ being the vector of variance components with the parameter space specified by $\sigma_i^2 \geq 0$ for $i = 1, \ldots, s$, and $\sigma_{ss}^2 > 0$. However, in order to avoid possible technical and numerical problems, it is reasonable to assume that the true parameter $\sigma^2 = (\sigma_1^2, \ldots, \sigma_s^2, \sigma_{ss}^2)$ is in the interior of this parameter space. So, here we shall assume that $\sigma_i^2 > 0$ for $i = 1, \ldots, s + 1$.

In other words, we shall assume $y \sim N(Xb, V)$, with $V = \text{Var}(y) = ZGZ' + R$, where $G$ is $(r \times r)$ diagonal matrix, $G = \text{Var}(u) = \text{diag}(\sigma_i^2 I_s)$, and $R$ is $(n \times n)$ diagonal matrix, $R = \text{Var}(e) = \sigma_{ss}^2 I_s$, with $\sigma_{ss}^2 > 0$ for $i = 1, \ldots, s + 1$.

If the variance components $\sigma^2 = (\sigma_1^2, \ldots, \sigma_s^2, \sigma_{ss}^2)$ are unknown, they can be (and in general must be) estimated from the observed data by any reasonably effective and computationally efficient method, like e.g. by the methods based on moments (the minimum variance (norm) quadratic estimation) or the methods based on likelihood function (ML or REML).
There are several efficient implementations for estimation of the variance components in general LMMs. One method used to fit such LMMs is the expectation-maximization (EM) algorithm, see [1, 4], where the variance components are treated as unobserved nuisance parameters in the joint likelihood. Currently, such methods are implemented in the major statistical software packages SAS (Proc MIXED) and R (in the nleme library). In particular, Proc MIXED uses a ridge-stabilized Newton-Raphson algorithm to optimize either a full (ML) or residual (REML) likelihood function, see also [35], [36], [49], and [41].

However, here we present a relatively simple method, based on repeated iterative solving of the MMEs, suggested by Searle, Casella and McCulloch in [49]. The elements of MMEs are used for setting up iterative procedures for simultaneous estimation of the variance components $\sigma^2_1, \ldots, \sigma^2_q, \sigma^2_{q+1}$ and the empirical versions of the BLUE of $b$ and the BLUP of $u$, in the simple LMM (10).

The algorithm provides solution to the maximum likelihood (ML) or the restricted maximum likelihood (REML) equations for estimating variance components, see e.g. [17], [39], [49], [32], and [49]. The algorithm can be also used for estimation of the related Fisher information matrices for ML and/or REML estimators of the variance components (i.e. the inverse of the asymptotic variance-covariance matrix of the ML/REML estimators). Moreover, it can be also used for computing the minimum norm quadratic estimates MINQE(i) (realizations of the invariant minimum norm quadratic estimators) or the MINQE(UJ) (invariant and unbiased minimum norm quadratic estimators) of the variance components, for more details see e.g. [33], [42], and [43].

The final solutions of such iterative procedure will be denoted by $\hat{b}, \hat{u} = (\hat{u}_1', \ldots, \hat{u}_q')$, and $\hat{\sigma}^2 = (\hat{\sigma}^2_1, \ldots, \hat{\sigma}^2_{q+1})'$. Similarly, we shall use the adequate notation $\hat{G}, \hat{R}$, and $\hat{C}$ for the estimated versions of matrices $G, R, \text{ and } C$. The solutions $\hat{b}$ and $\hat{u}$ satisfy the MMEs (4) if the unknown matrices $G$ and $R$ are replaced by the estimated versions $\hat{G}$ and $\hat{R}$. Finally, based on $\hat{\sigma}^2$, the important output of the algorithm is the estimated Fisher information matrix, say $I_{ML}(\hat{\sigma}^2)$ or $I_{REML}(\hat{\sigma}^2)$, respectively. Consequently, it provides the estimated asymptotic variance-covariance matrix of the estimated variance components $\hat{\sigma}^2$, say $\hat{\Sigma} = (I_{ML}(\hat{\sigma}^2))^{-1}$ or $\hat{\Sigma} = (I_{REML}(\hat{\sigma}^2))^{-1}$, provided that the inverses do exist. For detailed description of the algorithm see Section Appendix B.

3. Standard methods for statistical inference on fixed and random effects

Here we consider the problem of making statistical inference about $q$ linear functions of the fixed effects $b$ and the random effects $u$, i.e. about $\Lambda' (b', u')' = K' b + L' u$ where $\Lambda$ is $((p+r) \times q)$-dimensional full-ranked matrix with estimable $K' b$ (i.e. $K = \Lambda A$ for some matrix $A$).

Let $\hat{b}$ and $\hat{u}$ be the solutions of the MMEs (4), so $\hat{w} = \Lambda' (\hat{b}', \hat{u}')' = K' \hat{b} + L' \hat{u}$ is the best linear unbiased predictor (BLUP) of $w = K' b + L' u$. Then, according to the properties 6 and 8 of Section 2, the variance of $K' \hat{b}$ and the mean squared error (MSE) of $\hat{w}$ are given by

$$Var(K' \hat{b}) = K' C_{11} K,$$  \hspace{1cm} (11)

and

$$MSE(\hat{w}) = E ((\hat{w} - w)(\hat{w} - w)',$$

$$Var(\hat{w} - w) = \Lambda' C \Lambda = M_\theta.$$  \hspace{1cm} (12)

Notice that the MSE matrix of $\hat{w}$, $M_\theta$, functionally depends on the variance components $\sigma^2 = (\sigma^2_1, \ldots, \sigma^2_q, \sigma^2_{q+1})'$. If the variance components $\sigma^2 = (\sigma^2_1, \ldots, \sigma^2_q, \sigma^2_{q+1})'$ are known, based on the model assumptions and from (11) and (12), we trivially get the pivot, Wald-type statistic, useful for making statistical inference about $K' b$ (e.g. testing a null hypothesis $H_0 : K' b = K' b_0$ for some $b_0$) and/or about the variable $w = K' b + L' u$ with their exact (null) distribution:

$$Q = (K' \hat{b} - K' b_0)' (K' C_{11} K)^{-1} (K' \hat{b} - K' b_0) \sim \chi^2_q, \hspace{1cm} (13)$$

and

$$Q = (\hat{w} - w)' (\Lambda' C \Lambda)^{-1} (\hat{w} - w) \sim \chi^2_q, \hspace{1cm} (14)$$

where $\chi^2_q$ denotes the chi-squared distribution with $q = \text{rank}(\Lambda')$ degrees of freedom.

If the variance components are unknown and the estimated values $\hat{\sigma}^2 = (\hat{\sigma}^2_1, \ldots, \hat{\sigma}^2_{q+1})'$ are available together with $\hat{C}$, a commonly used test statistic for fixed effects hypothesis $H_0 : K' b = K' b_0$ is based on $K' \hat{b}$ and $\hat{C}_{11}$:

$$F = \frac{1}{q} (K' \hat{b} - K' b_0)' (K' \hat{C}_{11} K)^{-1} (K' \hat{b} - K' b_0), \hspace{1cm} (15)$$

where $K' \hat{b}$ denotes the empirical version of the best linear unbiased estimator $K' \hat{b}$ of $K' b$ (i.e. version with the estimated variance-covariance components). Notice that $C_{11} = (X' V^{-1} X)^{-1}$, see e.g. [49] (Eqn. (55) p. 276), and consequently $\hat{C}_{11} = (X' \hat{V}^{-1} X)^{-1}$, where $\hat{V} = Z \hat{G} Z' + \hat{R}$.

As a generalization, for making simultaneous statistical inference on the fixed as well as the random effects, i.e. on $w = \Lambda' (b', u)' = K' b + L' u$ (e.g. construction of the prediction region) based on the empirical BLUP (EBLUP), i.e. the predictor $\hat{w} = \Lambda' (\hat{b}', \hat{u}')$ (where $\hat{b}$ and $\hat{u}$ are solutions of the MMEs with estimated $\hat{R}$ and $\hat{G}$), it is natural to consider the following statistic

$$F = \frac{1}{q} (\hat{w} - w)' (\Lambda' \hat{C} \Lambda)^{-1} (\hat{w} - w), \hspace{1cm} (16)$$

where $q$ is rank of the matrix $\Lambda$.

As a special case, if $w$ is a one-dimensional function given by $w = \Lambda' (b', u)' = K' b + L' u$, in analogy with (15) and (16), it is natural to consider the pivot statistic

$$t = \frac{K' \hat{b} - K' b_0}{\sqrt{K' \hat{C}_{11} K}} \hspace{1cm} (17)$$

and/or its generalization

$$t = \frac{\hat{w} - w}{\sqrt{\Lambda' \hat{C} \Lambda}}. \hspace{1cm} (18)$$
where $\hat{w} = \lambda'(\hat{b}, \hat{u}')$ is the EBLUP of $w$.

The (null) distribution of the statistics (17) and (18) is commonly approximated by the Student’s $t$-distribution with $v$ degrees of freedom (DF), estimated by applying the Satterthwaite’s approximation. The (null) distribution of the statistics (15) and (16) is commonly approximated by the Fisher-Snedecor’s $F$-distribution with $v_1$ and $v_2$ degrees of freedom, where $v_1 = q$ and $v_2$, the denominator degrees of freedom (DDF), where $v_2$ is typically estimated by a generalization of the Satterthwaite’s method, as suggested e.g. by Fai and Cornelius in [13], or alternatively, by applying moment based approximation for the $F$-distribution. The explicit expressions for DF and DDF estimators of (17), (18), (15) and (16) are given in Sections 3.1 and 3.2.

### 3.1. DF estimated by the Satterthwaite’s method

Giesbrecht and Burns in [16], (see also [37], [12], and [50]), suggested to approximate the null distribution of the pivotal quantity (17) by the Student’s $t$-distribution with $\hat{v}$ degrees of freedom (DF), where $\hat{v}$ is the Satterthwaite’s approximation of the (unknown) $v$, see [48], [47], i.e.

$$ t = \frac{k^2\hat{b} - k^2b_0}{\sqrt{k^2C_{11}k}} - \nu_0, \quad (19) $$

with

$$ \hat{v}_k = \frac{2(\lambda Ck)^2}{\text{Var}(\lambda Ck)} \equiv \frac{2(\lambda Ck)^2}{\hat{g}_1^T \hat{g}_k}, \quad (20) $$

where $\text{Var}(\lambda Ck)$ denotes the estimated value of $\text{Var}(\lambda Ck)$. The suggested estimator of $\text{Var}(\lambda Ck)$ is based on the estimated version of the Taylor series expansion of the variance of the estimator $k^2b$ (BLUE), i.e. $\text{Var}(k^2b) = k^2C_{11}k$, with respect to the variance components $\sigma^2 = (\sigma^2_1, \ldots, \sigma^2_{r+1})$. Here, $\hat{S}$ is the estimated (asymptotic) variance-covariance matrix of the estimators (e.g. REML estimators) of the variance components $\sigma^2$, and $\hat{g}_k$ is the estimated version (evaluated at the estimated values of the variance components $\sigma^2$) of the gradient $g_k$ of $k^2C_{11}k$, with respect to the variance components $\sigma^2$, i.e.

$$ g_k = \frac{\partial(c_k)}{\partial \sigma^2_1} \cdots \frac{\partial(c_k)}{\partial \sigma^2_{r+1}}. \quad (21) $$

As a generalization of the approach by Giesbrecht and Burns, it is natural to consider similar approximation for the distribution of the pivotal quantity (18), i.e.

$$ t = \frac{\hat{w} - w}{\sqrt{\lambda'\hat{C}\lambda}} - \nu_1, \quad (22) $$

with

$$ \hat{v}_\lambda = \frac{2(\lambda C\lambda)^2}{\text{Var}(\lambda C\lambda)} = \frac{2(\lambda C\lambda)^2}{\hat{g}_1^T \hat{g}_\lambda}, \quad (23) $$

where $\hat{g}_\lambda$ is the estimated version of the gradient $g_\lambda$ of $\text{MSE}(\hat{w}) = \lambda'\hat{C}\lambda$ with respect to the variance components $\sigma^2$, defined by

$$ g_\lambda = \begin{pmatrix} \frac{\partial(\lambda C\lambda)}{\partial \sigma^2_1} \\ \vdots \\ \frac{\partial(\lambda C\lambda)}{\partial \sigma^2_{r+1}} \end{pmatrix}. \quad (24) $$

For more details on computing gradients of the MSE$(\hat{w})$ see Section Appendix A.

Provided that the estimated matrix $\hat{C}$ is available, e.g. as an output of the algorithm for estimating the variance components, the estimators $\hat{g}_k$ and $\hat{g}_\lambda$ of the gradients (21) and (24) could be evaluated, by using the elements of the estimated matrix $\hat{C}$ (instead of $C$).

For that, let us define $\lambda = \hat{C} \lambda$, and let $\lambda$ be decomposed into its subvectors such that $\lambda = (\lambda_0', \lambda_1', \ldots, \lambda_{r'}')$, where $\lambda_0$ is $p$-dimensional subvector, and $\lambda_i, i = 1, \ldots, s$, are $r_i$-dimensional subvectors of $\lambda$. Then, by using (A.31) from Section Appendix A we get

$$ \hat{g}_\lambda = \begin{pmatrix} \frac{\partial(\lambda_1 C_1)}{\partial \sigma^2_1} \\ \vdots \\ \frac{\partial(\lambda_{r'} C_{r'})}{\partial \sigma^2_{r+1}} \end{pmatrix} \lambda H_0 \lambda, \quad (25) $$

where $H_0$ is given by

$$ H_0 = (X, X)(X, Z) = \begin{pmatrix} X'X & X'Z \\ Z'X & Z'Z \end{pmatrix}. \quad (26) $$

Consequently, as $k'b$ is a special case of $\lambda'(b', u)' = k'b + \lambda u$ with $\lambda = \lambda_{h_{1:}}(k, \lambda_0)'$, so we can use (25) also for evaluation of $\hat{g}_k$ by replacing $\lambda$ with $\lambda_{h_{1:}} = \hat{C} \lambda_{h_{1:}}$.

### 3.2. DDF estimated by the Fai-Cornelius method

Fai and Cornelius in [13] proposed a generalization of the Satterthwaite’s method for multivariate linear functions of the fixed and random effects to approximate the (null) distribution of the statistic (15) by the Fisher-Snedecor F-distribution with $v_1 = q$ and $v_2 = \hat{v}$, i.e. with the estimated denominator degrees of freedom (DDF).

As a straightforward generalization of the Fai-Cornelius approach, it is natural to approximate the distribution of the $F$-statistic (16), based on the multivariate function $w = \lambda'(b', u)' = \lambda'\lambda$.
\( K^*b + Lu \) and its empirical predictor \( \hat{w} = K^*\hat{b} + Lu \), by the Fisher-Snedecor F-distribution with \( v_1 = q \) and \( v_2 = \nu \) degrees of freedom, where where
\[
\hat{\nu} = \frac{2\hat{E}}{\hat{E} - q},
\]
(27)
with
\[
\hat{E} = \sum_{i=1}^{q} \frac{\hat{v}_i}{\hat{v}_i - 2} 1_{\{\hat{v}_i > 2\}}.
\]
(28)
Here, \( 1_{\{\cdot\}} \) denotes the indicator function and \( \hat{v}_i \), for \( i = 1, \ldots, q \), are the degrees of freedom, estimated by the Satterthwaite’s method (22), of the \( t \)-statistics (18) for \( \hat{v}_i = \lambda_i (\hat{b}, \hat{u}) \), where \( \lambda_i, i = 1, \ldots, q \), are the columns of the matrix \( \hat{\Lambda}_{FC} \) given by
\[
\hat{\Lambda}_{FC} = \Lambda \hat{U},
\]
(29)
and \( \hat{U} \) denotes the unitary matrix of a spectral decomposition of a matrix \( \Lambda^* \hat{C} \Lambda \), i.e. such matrix that \( U^* \Lambda^* \hat{C} \Lambda \hat{U} = \hat{S} \), where \( \hat{S} \) is a diagonal matrix.

4. Statistical inference on fixed and random effects based on adjusted estimator of the MSE matrix of the EBLUP

As argued by Harville in (23), usage of the MSE matrix of the EBLUP \( \hat{w} \), say \( M_\hat{w} \), (or its estimated version, say \( \hat{M}_\hat{w} \)), instead of the correct MSE matrix of the EBLUP \( \hat{w} \), say \( M_\hat{w} \), (or its estimated version, say \( \hat{M}_\hat{w} \)), is inadequate, as the estimator \( \hat{M}_\hat{w} = \Lambda^* \hat{C} \Lambda \) can severely underestimate the true MSE of the EBLUP \( \hat{w} \). As will be explained bellow, there are two main sources of such bias. For a comprehensive discussion on the problem and proposed solutions see also (27), (28), (20), (25), (41), (21), (26), (50), (53), (54), (10), (29), (30), and (1).

4.1. Decomposition of the EBLUP prediction error and its MSE

The first source of the bias can be observed if we decompose the prediction error of the EBLUP \( \hat{w} \). In particular,
\[
(\hat{w} - \hat{w}) = (\hat{w} - w) + (w - \hat{w}),
\]
(30)
and consequently, based on unbiasedness of EBLUP and its independence on BLUP, see (27), (28), (20), and (21), we get the MSE matrix of \( \hat{w} \) in the form
\[
M_\hat{w} = M_\hat{w} + M_{\hat{w}},
\]
(31)
where \( M_{\hat{w}} = \text{Var}(\hat{w} - \hat{w}) \), and thus, \( M_\hat{w} \geq M_{\hat{w}} \).

The MSE of the first component of the prediction error, \( M_{\hat{w}} \), is given by (12). The MSE of the second component of the prediction error, \( M_{\hat{w}} \), is not expressible in closed form, except for very simple special cases. Kackar and Harville in (28), see also (29) and (30), suggested approximation of \( M_{\hat{w}} \) based on first-order Taylor series approximation. In particular, a Taylor series expansion for \( \hat{w} - \hat{w} \) in \( \sigma^2 = (\sigma_1^2, \ldots, \sigma_r^2, \sigma_{r+1}^2) \), as e.g. REML, about \( \sigma^2 = (\sigma_1^2, \ldots, \sigma_r^2, \sigma_{r+1}^2) \), gives approximation
\[
(\hat{w} - \hat{w}) \approx (\hat{w} - w) + \sum_{i=1}^{r+1} \frac{\partial^2 \hat{w}}{\partial \sigma_i^2} (\hat{\sigma}_i^2 - \sigma_i^2),
\]
\[
\frac{1}{2} \sum_{i=1}^{r+1} \sum_{j=1}^{r+1} \frac{\partial^2 \hat{w}}{\partial \sigma_i^2} (\hat{\sigma}_i^2 - \sigma_i^2)(\hat{\sigma}_j^2 - \sigma_j^2)
\]
Then taking expectation of the square of the first-order term, and using the results in (28) and (21), we get the first-order approximation \( M_{\hat{w}} \) of \( M_{\hat{w}} \) as
\[
M_{\hat{w}} = \frac{\partial^2 \hat{w}}{\partial \sigma_i^2} \frac{\partial^2 \hat{w}}{\partial \sigma_j^2} (\hat{\sigma}_i^2 - \sigma_i^2)(\hat{\sigma}_j^2 - \sigma_j^2)
\]
(32)
where \( \Sigma_{ij} \) are elements of the variance-covariance matrix \( \Sigma \) of the estimator \( \hat{\sigma}^2 \).

For derivation of the approximation of \( M_{\hat{w}} \) see Section Appendix A.3.

The second component of the EBLUP’s MSE matrix \( M_{\hat{w}} \) in the simple LMM (10) can be approximated by
\[
M_{\hat{w}} = \sum_{i=1}^{r+1} \sum_{j=1}^{r+1} \Sigma_{ij} C_{ij},
\]
(34)
where \( C_{ij}, i = 1, \ldots, s + 1 \), are given by (A.40), or alternatively by
\[
M_{\hat{w}} = -\frac{1}{2} \sum_{i=1}^{r+1} \sum_{j=1}^{r+1} \Sigma_{ij} M_{\hat{w}}^{ij},
\]
(35)
where the matrices \( M_{\hat{w}}^{ij} \) are given by (A.32), (A.33), (A.34), and (A.35).

Consequently, we get the approximation \( M_\hat{w} \) of the EBLUP’s MSE matrix \( M_\hat{w} \) in the form
\[
M_\hat{w} \approx M_\hat{w} + M_{\hat{w}} \equiv M_\hat{w} + \frac{1}{2} \sum_{i=1}^{r+1} \sum_{j=1}^{r+1} \Sigma_{ij} M_{\hat{w}}^{ij},
\]
(36)
where \( \Sigma_{ij} \) are elements of the variance-covariance matrix of the REML estimator \( \hat{\sigma}^2 \), and \( M_{\hat{w}}^{ij} \) represent the second partial derivatives of the BLUP’s MSE matrix \( M_\hat{w} \) with respect to the variance components \( \sigma_i^2 \) and \( \sigma_j^2 \), \( i, j = 1, \ldots, s+1 \), in simple LMM (10).

4.2. Bias-corrected estimator of the EBLUP’s MSE matrix \( M_\hat{w} \)

As the EBLUP’s MSE matrix \( M_\hat{w} \), as well as its approximation \( M_\hat{w} \) (which is a function of \( \Sigma \)), depend on the unknown variance components \( \sigma^2 = (\sigma_1^2, \ldots, \sigma_r^2) \), for further applications it is necessary to use its estimator, say \( \hat{M}_\hat{w} \). A natural option for such estimator would be
\[
\hat{M}_\hat{w} = \hat{M}_\hat{w} + \hat{M}_{\hat{w}}.
\]
(37)
i.e. by using (36), where the true (unknown) vector of variance components is replaced by its estimator . Notice that the true variance-covariance matrix of the REML estimator also depends on . So, the estimator functionally depends on the elements of estimated variance-covariance matrix .

Based on similar arguments as given by Alnosaier in [1] for the special case of empirical BLUE of the fixed effects, we can assume that is approximately unbiased estimator of , for another formal justification see also [41] and [10].

However, as pointed out by Harville and Jeske in [21], Prasad and Rao in [41], and in special case of fixed effects estimator by Kenward and Roger in [29] and [30], additional bias will appear if the estimator is used as an estimators of the MSE matrix . In order to show that, let us expand in about , and then take expectation of this approximation, so

\[ E(\hat{M}_b) = M_b + \sum_{i=1}^{s+1} E(\hat{\sigma}^2_i - \sigma^2_i) \frac{\partial M_b}{\partial \sigma^2_i} + \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} E(\hat{\sigma}^2_i - \sigma^2_i)(\hat{\sigma}^2_j - \sigma^2_j) \frac{\partial^2 M_b}{\partial \sigma^2_i \partial \sigma^2_j} \]

\[ \approx M_b + \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \sum_{i,j} \Sigma_i \Sigma_j \hat{M}_b(i,j) \]

\[ = M_b - M_{\hat{b}b}. \quad (38) \]

where we have assumed that the first-order term could be ignored, and is given by (35). This could be informally justified by the assumption that is approximately an unbiased estimator of , as was suggested in [29]. However, formal justification was provided by Alnosaier in [1] and by Kenward and Roger in [30]. Kenward and Roger derived Taylor series approximation for the bias of REML estimator, i.e. \( E(\hat{\sigma}^2_i - \sigma^2_i) \), and proved that in linear mixed models with linear parametrization of the variance-covariance matrix where e.g. in simple LMM [10], its first-order approximation is equal to zero.

Hence, by combining (37) and (38), we get the adjusted, bias-corrected estimator of the EBLUP’s MSE matrix , given by

\[ \hat{M}_{b, A} = \hat{M}_b + 2\hat{M}_{\hat{b}b}. \quad (39) \]

The explicit form of the estimator in simple LMM is given by (A.45) in Section Appendix A.5.

4.3. Generalization of the Kenward-Roger method for statistical inference on fixed and random effects based on adjusted estimator of the MSE matrix of the EBLUP

For statistical inference about the vector of linear functions of fixed effects \( K'b \) based on its empirical BLUE. Kenward and Roger suggested in [29] to use the Wald-type statistic as a pivot, with adjusted covariance matrix of the empirical BLUE of the function \( K'b \).

Here we suggest to consider a generalization of the Kenward-Roger method for the inference about the vector of functions of fixed and random effects \( w = \Lambda'(b, u') \) (which is useful for testing hypotheses about the fixed effects and for constructing the prediction regions for functions of the fixed and the random effects simultaneously), based on its EBLUP and the adjusted MSE matrix. For that we shall consider the Wald-type pivot \( F \)-statistic

\[ F = \frac{1}{q} (\hat{w} - w)' (\hat{M}_{b, A})^{-1} (\hat{w} - w), \quad (40) \]

where \( \hat{M}_{b, A} \) is given by (39), or (in its explicit form) by (A.45) from Section Appendix A.5 respectively.

In accordance with [29] and [1], we suggest to approximate the (null) distribution of the scaled Wald-type \( F \)-statistic by the Fisher-Snedecor \( F \)-distribution with \( q \) and \( v \) degrees of freedom. In particular,

\[ \kappa F \approx F_{q,v}. \quad (41) \]

where the unknown parameters \( \kappa \) and \( v \) should be estimated from the data.

In analogy with derivation of the estimators presented by Alnosaier in [1] for the fixed effects problem, here we suggest the following estimators of the scale \( \kappa \) and the denominator degrees of freedom \( v \):

\[ \hat{\kappa} = E(\hat{\nu} - 2), \quad (42) \]

where

\[ \hat{\nu} = \frac{\hat{V}}{2E(\hat{\nu})}, \quad \hat{E} = 1 + \frac{\hat{A}_2}{q}, \quad \hat{V} = \frac{2}{q} (1 + \hat{B}), \quad \hat{B} = \frac{1}{2q} (\hat{A}_1 + 6\hat{A}_2), \quad (43) \]

and

\[ \hat{A}_1 = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{E}_{ij} \text{tr} (\hat{M}_w^{-1} \hat{M}_w^{(0)}) \text{tr} (\hat{M}_w^{-1} \hat{M}_w^{(0)}) \]

\[ \hat{A}_2 = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{E}_{ij} \text{tr} (\hat{M}_w^{-1} \hat{M}_w^{(0)}) \text{tr} (\hat{M}_w^{-1} \hat{M}_w^{(0)}). \quad (44) \]

By \( \text{tr}(A) \) we denote the trace of a matrix , i.e. \( \text{tr}(A) = \sum_i A_{ii} \), \( \hat{M}_b = \Lambda' \hat{C} \Lambda \) denotes the estimated version of , and \( \hat{M}_w^{(0)} \), \( i = 1, \ldots, s + 1 \), denote the estimated versions of the first partial derivatives of , defined by (A.31). For more details and explicit forms of the estimators \( \hat{A}_1 \) and \( \hat{A}_2 \) see Section Appendix A.6 (A.60) and (A.61).

In order to match the exact values for the scale \( \kappa \) and the denominator degrees of freedom \( v \) for testing hypothesis on fixed effects in two special cases, in particular in the balanced one-way ANOVA and the Hotelling \( T^2 \) models, Kenward and Roger in [29] suggested the modified estimators \( \hat{\kappa}^* \) and \( \hat{v}^* \), which can
be analogically generalized and used to approximate the (null) distribution of the scaled Wald-type $F$-statistic \((40)\)

\[
\begin{align*}
\hat{k}^* &= \frac{\hat{\nu}^2}{E^*(\hat{\nu}^2 - 2)}, \\
\hat{\nu}^* &= 4 + \frac{2 + q}{q\hat{\nu}^2 - 1},
\end{align*}
\]

(45)

where

\[
\begin{align*}
\hat{\nu}^* &= \frac{\hat{\nu}^2}{2E^2}, \\
\hat{E}^* &= \left(1 - \frac{\hat{A}_1}{q}\right)^{-1}, \\
\hat{\nu}^* &= \frac{2}{q}\left(\frac{1 + c_1\hat{B}}{(1 - c_3\hat{B})^2(1 - c_2\hat{B})}\right),
\end{align*}
\]

(46)

and

\[
\begin{align*}
c_1 &= \frac{g}{3q + 2(1 - g)}, \\
c_2 &= \frac{g}{3q + 2(1 - g)}, \\
c_3 &= \frac{g}{3q + 2(1 - g)}, \\
g &= \frac{q + 1}{q - g + 2}A_2.
\end{align*}
\]

(47)

with $\hat{B},\hat{A}_1,\hat{A}_2$ given by \((43)\) and \((44)\). For more details see Section 4 in \([1]\).

5. Conclusions

Here we have presented a brief overview of the conventionally used methods for making statistical inference about linear functions of the fixed effects and/or about the fixed and random effects simultaneously, in conventional simple linear mixed model, by using the elements of the solution of the Hensderson’s mixed model equations. Further, we have also presented some improvements, based on the adjusted MSE matrix of the EBLUP, as well as a generalization of the standard Kenward-Roger method (suggested for making statistical inference about the fixed effects) for derivation of the approximate distribution of the Wald-type pivot statistic, suggested for making statistical inference about the fixed and random effects simultaneously. Notice that this method for derivation of the approximate distribution of the Wald-type pivot statistic is not unique. As pointed out by Almosaier in \([1]\), there are several other alternative solutions available, however, such modifications have not been considered here.

The presented (explicit) expressions are valid in the simple LMM defined by \((10)\). They are rather simple, and can be readily implemented in practically any (statistical) software environment. Based on the results presented in Section \(\text{Appendix A}\) it is straightforward to get explicit expressions also for the more general LMM with linear parametrization of the variance-covariance matrices $G$ and $R$, provided that the REML of variance components and its estimated variance-covariance matrix is available. The situation with nonlinear parametrization of the matrices $G$ and $R$ requires more specific approach.

6. Acknowledgements

The work was supported by the Slovak Research and Development Agency, grant APVV-0096-10, and by the Scientific Grant Agency of the Ministry of Education of the Slovak Republic and the Slovak Academy of Sciences, grants VEGA 2/0038/12, 2/0019/10.

Valuable discussion and feedback from Barbora Arendacká, Francisco Carvalho, Augustyn Markiewicz, João T. Mexia, Roman Zmyślony, Tadeusz Caliński and Paweł Krajewski, during the research group meeting on \textit{Sufficient and Optimal Statistical Procedures in Mixed Linear Model}, sponsored by the Stefan Banach International Mathematical Center, Będlewo, Poland, November 11–17, 2012, is gratefully acknowledged, as well as discussion on implementation of the Microsoft Excel version of the algorithm which is under development by Mohammad Ovais of Xepa Soul Pattinson (Malaysia).

\textbf{APPENDIX}

\textbf{Appendix A. Derivatives of the MSE matrix with respect to the variance components}

Here we shall assume that $G^{-1}$, the inverse of $G = \text{Var}(u)$, does exist, and thus we can use the MMEs as defined by \((9)\). Although the subsequent derivation of the derivatives of the matrix $C$ is general, finally we shall consider only a special case, based on the covariance structure of the simple linear mixed model \((10)\), with the variance-covariance matrices of the following form: $G = \text{Var}(u) = \text{diag}(\sigma_r^2 I_r), i = 1,\ldots,s$, and $R = \text{Var}(e) = \sigma_{v+1}^2 I_n$, so $V = \text{Var}(y) = ZGZ' + R = \sum_{i=1}^s \sigma_r^2 Z_r Z_r' + \sigma_{v+1}^2 I_n$.

Moreover, as we consider methods for statistical inference for estimable linear functions $w = \Lambda'(b',u')' = K'b + L'u$, i.e. such that $K = X'A$ for some matrix $A$, further we shall assume, without loss of generality, that the inverse of the MME matrix $H$ (the matrix on the left-hand side of the equation \((3)\)) does exist, in particular we shall assume that the inverse of $X'R^{-1}X$ does exist. Recall that

\[
H = (X, Z)'R^{-1}(X, Z) + (0, I_r)'G^{-1}(0, I_r),
\]

(A.1)

and so,

\[
C = H^{-1} \quad \text{or} \quad H = C^{-1},
\]

(A.2)

Further, we shall denote

\[
\begin{align*}
\Delta_0 &= (0, I_r)'(0, I_r), \\
\Delta_i &= (0, (0,\ldots,I_r,\ldots,0))'((0,\ldots,0,\ldots)) = \\
&= \left(\begin{array}{cccc}
0 & 0 \\
0 & \text{diag}(I_{r_i})
\end{array}\right), \\
\Delta_{s+1} &= (X, Z)'(X, Z) = H_0,
\end{align*}
\]

(A.3)

(A.4)

(A.5)

for $i = 1,\ldots,s$, where $\text{diag}(I_{r_i})$ is $(r \times r)$-matrix with its $i$-th diagonal block equal to $I_{r_i}$, otherwise with zero elements.

Further, for arbitrary matrix $A$ we shall denote its partial derivatives with respect to the components of a vector parameter $\theta = (\theta_1,\ldots,\theta_{s+1})'$ as

\[
\frac{\partial^k A}{\partial \theta_1}\frac{\partial^j A}{\partial \theta_2} = \frac{\partial^k A}{\partial \theta_1}\frac{\partial^j A}{\partial \theta_2} = \frac{\partial^k A}{\partial \theta_1}\frac{\partial^j A}{\partial \theta_2},
\]

(A.6)
for $i, j, k = 1, \ldots, s + 1$.

Here we derive explicit expressions for derivatives of the matrix $C$, i.e. $C^{(i)}$, $C^{(i,j)}$, and $C^{(i,j,k)}$, which depend on the derivatives of the matrices $G$ and $R$, i.e. on $G^{(i)}$, $G^{(i,j)}$, and $R^{(i)}$, $R^{(i,j)}$, and $R^{(i,j,k)}$.

Recall that the derivative of $A^{-1}$, the inverse of a symmetric matrix $A$, with respect to some scalar parameter $\theta$, is given by

$$
\frac{\partial}{\partial \theta} A^{-1} = -A^{-1} \frac{\partial A}{\partial \theta} A^{-1},
$$

and the rule for computing the derivative of a symmetric matrix $ABA$ with respect to some parameter $\theta$ is

$$
\frac{\partial}{\partial \theta} ABA = AB \frac{\partial A}{\partial \theta} + \frac{\partial A}{\partial \theta} BA + A \frac{\partial B}{\partial \theta} A.
$$

Let $A$ be an inverse of a symmetric matrix $B$, i.e. $A = B^{-1}$. Then, based on $(A.7)$ and $(A.8)$, we define the following matrix operators:

$$
\mathcal{D}^{(i)} (A, B) = -AB^{(i)} A,
$$

$$
\mathcal{D}^{(i,j)} (A, B) = A \left( B^{(i)} AB^{(j)} + B^{(j)} AB^{(i)} - B^{(i,j)} \right) A,
$$

$$
\mathcal{D}^{(i,j,k)} (A, B) = -A \left( B^{(i)} AB^{(j)} + B^{(j)} AB^{(i)} - B^{(i,j)} \right) AB^{(k)} A
+ \left( B^{(i)} AB^{(j,k)} + B^{(j,k)} AB^{(i)} + B^{(i,j)} AB^{(k)} + B^{(j,k)} AB^{(i)} - B^{(i,j,k)} \right) A.
$$

From that we directly get

$$
C^{(i)} = \mathcal{D}^{(i)} (C, H),
$$

$$
C^{(i,j)} = \mathcal{D}^{(i,j)} (C, H),
$$

$$
C^{(i,j,k)} = \mathcal{D}^{(i,j,k)} (C, H),
$$

for $i, j, k = 1, \ldots, s + 1$.

Further, based on $(A.1)$, we directly get the derivatives of the matrix $H$. For $i, j, k = 1, \ldots, s$

$$
H^{(i)} = (0, I, G^{-1}(0, I))\),
$$

$$
H^{(i+1)} = (X, Z)\, R^{-1(i+1)}(X, Z),
$$

$$
H^{(i,j)} = (0, I, G^{-1}(0, I))\),
$$

$$
H^{(i+1,j)} = (X, Z)\, R^{-1(i+1)}(X, Z),
$$

$$
H^{(i,j,k)} = (0, I, G^{-1(i,j,k)}(0, I))\),
$$

$$
H^{(i+1,j,k)} = (X, Z)\, R^{-1(i+1,j+1)}(X, Z),
$$

where

$$
G^{-1(i)} = \mathcal{D}^{(i)} \left( G^{-1} \right),
$$

$$
G^{-1(i,j)} = \mathcal{D}^{(i,j)} \left( G^{-1} \right),
$$

$$
G^{-1(i,j,k)} = \mathcal{D}^{(i,j,k)} \left( G^{-1} \right),
$$

$$
R^{-1(i+1)} = \mathcal{D}^{(i+1)} \left( R^{-1} \right),
$$

$$
R^{-1(i+1,j+1)} = \mathcal{D}^{(i+1,j+1)} \left( R^{-1} \right).
$$

Notice that

$$
H^{(i+1)} = H^{(i+1,j)},
$$

$$
H^{(i,j+k)} = 0,
$$

whenever one index is equal to $s + 1$ and some of the other indices is different from for $s + 1$, for $i, j, k = 1, \ldots, s + 1$.

Appendix A.1. Derivatives of the MME matrix $H$ in simple LMM

In the simple LMM $(A)$, we get

$$
H^{(i)} = -\frac{1}{(\sigma^2_i)^2} \Delta_i,
$$

$$
H^{(i,j)} = \frac{2}{(\sigma^2_i)^2} \Delta_i,
$$

$$
H^{(i,j,k)} = -\frac{6}{(\sigma^2_i)^2} \Delta_i,
$$

for $i = 1, \ldots, s + 1$. Notice that

$$
H^{(i,j)} = 0, \quad \text{and} \quad H^{(i,j,k)} = 0,
$$

for any combination of unequal indices $i, j, k = 1, \ldots, s + 1$.

Appendix A.2. Derivatives of the MME matrix $C$ in simple LMM

By combining $(A.12)$, $(A.13)$, $(A.24)$, $(A.25)$, and $(A.27)$, in simple LMM $(A)$, we directly get

$$
C^{(i)} = \frac{1}{(\sigma^2_i)^2} C \Delta_i C,
$$

$$
C^{(i,j)} = \frac{2}{(\sigma^2_i)^2} C \left( \Delta_i C \Delta_j - \sigma^2_i \Delta_j \right) C,
$$

$$
C^{(i,j)} = \frac{1}{(\sigma^2_i)^2} C \left( \Delta_i C \Delta_j + \Delta_j C \Delta_i \right) C, \quad i \neq j,
$$

for $i, j = 1, \ldots, s + 1$.

The explicit expression for $C^{(i,j,k)}$, i.e. the third partial derivative of $C$ for $i, j, k = 1, \ldots, s + 1$, is not presented here, however, it can be similarly evaluated based on $(A.14)$, $(A.24)$, $(A.25)$, $(A.26)$, and $(A.27)$.

Appendix A.3. Derivatives of the MSE matrix $M$ in simple LMM

Recall that $M_{\theta}$, the MSE matrix of the best linear unbiased predictor of $w$, is given by $M_{\theta} = \Lambda' C \Lambda$, where $\Lambda$ is $(p + r) \times q$-block-matrix of given coefficients.

Let $\Lambda$ be a solution of a system of linear equations $H \Lambda = \Lambda$, i.e. $\Lambda = C \Lambda$, and let $\Lambda$ be decomposed into block-matrices such that $\Lambda = (\Lambda_0', \Lambda_1', \ldots, \Lambda_s')$, where $\Lambda_i$ is $(p \times q)$-dimensional block-matrix, and $\Lambda_i, \: i = 1, \ldots, s$, are $(r \times q)$-dimensional block-matrices of $\Lambda$. Similarly, let $(C)_{ij}$ denote the $(i, j)$-th
block\(^3\) of the matrix \(C\), and let \(\{C_i\}\) denote the \(i\)-th row-block and \(\{C\}_i\), the \(i\)-th column-block of the matrix \(C\).

Then, based on the derivatives of the matrix \(C\), we directly get the first partial derivatives of the MSE matrix \(M_\theta\) with respect to the variance components \(\sigma_1^2, \ldots, \sigma_s^2, \sigma_{s+1}^2\) as

\[
M_\theta^{(i)} = \frac{1}{(\sigma_i^2)^2} \tilde{\lambda}_i' \tilde{\lambda}_i, \quad \text{for } i = 1, \ldots, s,
\]

\[
M_\theta^{(s+1)} = \frac{1}{(\sigma_{s+1}^2)^2} \tilde{\lambda}_{i+1}^2 \tilde{\lambda}_{i+1}, \quad \text{for } i = 1, \ldots, s.
\]

where the matrices \(\tilde{\lambda}_i\) are defined by (A.4) and (A.5). The second partial derivatives of \(M_\theta\) are given by:

\[
M_\theta^{(ij)} = \frac{2}{(\sigma_i^2)^2} \tilde{\lambda}_i' (\Delta C \Delta_i - \sigma_i^2 \Delta_i) \tilde{\lambda}_i = \frac{2}{\sigma_i^2 \sigma_j^2} (\tilde{\lambda}_i' C_{ij} \tilde{\lambda}_i + \tilde{\lambda}_j' C_{ji} \tilde{\lambda}_j), \quad \text{for } i \neq j, i, j = 1, \ldots, s.
\]

Further,

\[
M_\theta^{(i,i)} = \frac{1}{(\sigma_i^2)^2} \tilde{\lambda}_i' (\Delta C \Delta_i + \Delta_i C \Delta_i) \tilde{\lambda}_i = \frac{1}{\sigma_i^2 \sigma_j^2} (\tilde{\lambda}_i' C_{ii} \Delta_i \tilde{\lambda}_i + \tilde{\lambda}_j' C_{jj} \Delta_j \tilde{\lambda}_j), \quad \text{for } i = 1, \ldots, s.
\]

where \(C_{ij}\) denote the elements of the variance-covariance matrix \(\Sigma\) of \(\tilde{\theta}\). Then, by using

\[
\tilde{w} - w = \lambda' C(X, Z)' R^{-1} (y - Xb) - \lambda'(0, I)' u, \quad \text{(A.37)}
\]

we get

\[
\frac{\partial (\tilde{w} - w)}{\partial \sigma_i^2} = -\lambda' C(X, Z)' R^{-1} (y - Xb)
\]

and then, by taking the covariances of the vectors with \(i, j = 1, \ldots, s + 1\), we get,

\[
\mathcal{C}_{ij} = \lambda' C(X, Z)' R^{-1} V R^{-1} (X, Z) C H^j + H(X, Z)' R^{-1} V R^{-1} (X, Z) C H^j + C(X, Z)' R^{-1} R^{-1} R^{-1} (X, Z) C A,
\]

where \(V = ZGZ' + R\).

Notice that in the simple LMM (10) we have \(R^{(i)} = R^{(j)} = 0\), for \(i, j = 1, \ldots, s\), and \(R^{(s+1)} = I_s\). From that we get \(R^{-1} R^{(i+1)} = R^{(i+1)} R^{-1} = R^{-1} = \frac{1}{\sigma_i^2} I_n\), and

\[
\mathcal{C}_{ij} = \frac{1}{(\sigma_i^2 \sigma_j^2)} \lambda' C(X, Z)' R^{-1} V R^{-1} (X, Z) C H^j + H(X, Z)' R^{-1} V R^{-1} (X, Z) C H^j + C(X, Z)' R^{-1} R^{-1} R^{-1} (X, Z) C A,
\]

where \(V = ZGZ' + R\).

Hence, the approximation of the second component of the EBLUP’s MSE matrix, i.e. \(M_{\delta\theta}\), in simple LMM is

\[
M_{\delta\theta} = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \mathcal{C}_{ij} C_{ij}.
\]

Appendix A.4. Approximation of the second component of the EBLUP’s MSE matrix in simple LMM

According to (33), let us define \(M_{\delta\theta}\) by

\[
\hat{M}_{\delta\theta} = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} C_{ij} \left( \frac{\partial (\tilde{w} - w)}{\partial \sigma_i^2}, \frac{\partial (\tilde{w} - w)}{\partial \sigma_j^2} \right),
\]

\[
\hat{M}_{\delta\theta} = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} C_{ij} (A.36)
\]

\(^2\)Notice that for \(i, j = 1, \ldots, s\) the block \(\{C_{ij}\}\) = \(\{C_{ij}\}\), i.e. it is the \((i, j)\)-th block of the matrix \(C_{ij}\), which can be, based on (7), efficiently computed as \(C_{22} = \sigma_{s+1}^2 G (\sigma_{s+1}^2 I_s + MG)^{-1}\), where \(M = Z'Z - Z'X(X'X)^{-1} X'Z\).
Appendix A.6. Generalized Kenward-Roger method for statistical inference on fixed and random effects based on adjusted estimator of the MSE matrix of the EBLUP in simple LMM

Here we shall consider the scaled Wald-type \( F \)-statistic defined by \((40)\), in particular

\[
\kappa F_* = \frac{\kappa}{q} \left( \hat{w} - w \right)' \left( \hat{M}_{\hat{w},A} \right)^{-1} \left( \hat{w} - w \right) \approx F_{q,v},
\]

where \( \hat{M}_{\hat{w},A} \) is given by \((45)\).

The moment based estimators of the parameters \( \kappa \) and \( \nu \) are based on comparing the first and the second moments of the scaled \( F \)-statistic \((46)\) with the moments of the \( F \)-distribution with \( q \) and \( \nu \) degrees of freedom, i.e. by solving the system of equations

\[
E(\kappa F_* ) = \kappa E_*, \quad \text{Var}(\kappa F_* ) = \kappa^2 V_*,
\]

where \( E_* = E(F_*) \) and \( V_* = \text{Var}(F_*) \). Based on the properties of the \( F \)-distribution we get

\[
E_* = \frac{v}{v-2}, \quad V_* = 2v^2 (v+q-2) q (v-4) \frac{2E^2}{v-4}, \quad \text{provided that } v > 4.
\]

By denoting

\[
\hat{q} = \frac{V}{2E^2}, \quad \text{we get}
\]

\[
v = 4 + \frac{q+2}{\hat{q}^2 - 1},
\]

and consequently, the moment estimators of \( \nu \) and \( \kappa \) are given as

\[
\hat{\kappa} = \frac{\hat{\nu}}{E_* (\hat{\nu} - 2)}, \quad \hat{\nu} = 4 + \frac{q+2}{\hat{q}^2 - 1}.
\]

where

\[
\hat{\nu} = \frac{V_*}{2E^2}.
\]

The expectation and the variance of the statistic \( F_* \) defined by \((46)\) can be estimated by using

\[
E_* = E(F_*) = E_{\nu} \left( E_{\nu} \left( F_* | \sigma^2 \right) \right), \quad V_* = \text{Var}(F_*) = \text{Var}_{\nu} \left( \text{Var}_{\nu} \left( F_* | \sigma^2 \right) \right) + \text{Var}_{\nu^2} \left( E_{\nu} \left( F_* | \sigma^2 \right) \right).
\]

Ahnosaer in [11] derived approximations for \( E_* \) and \( V_* \) in the special case, when the \( F \)-statistic \((46)\) is restricted on fixed effects only. The derivation of the approximations \( E_* \) and \( V_* \) in the general case, i.e. for the \( F \)-statistic defined by \((46)\), is not presented here. However, in analogy with the derivation of the approximations presented in [1], we suggest \( E_* \) and \( V_* \), as the approximations of \( E_* \) and \( V_* \), in the following form

\[
E_* = 1 + \frac{A_2}{q}, \quad V_* = 2 \frac{1}{q} (1 + B),
\]

where

\[
B = \frac{1}{2q} \left( A_1 + 6A_2 \right), \quad A_1 = \sum_{i=1}^{s} \sum_{j=1}^{r} \Sigma_{ij} \text{tr} \left( M_{\nu}^{-1} M_{\nu}^{(0)} \right) \text{tr} \left( M_{\nu}^{-1} M_{\nu}^{(0)} \right), \quad A_2 = \sum_{i=1}^{s} \sum_{j=1}^{r} \Sigma_{ij} \text{tr} \left( M_{\nu}^{-1} M_{\nu}^{(0)} M_{\nu}^{(0)} \right). \]

10
The suggested approximations depend on the unknown variance components \( \sigma^2 = (\sigma_1^2, \ldots, \sigma_{s+1}^2) \). Consequently, the suggested estimators of the parameters \( \kappa \) and \( \nu \), based on the estimated versions of \( \hat{A}_i \) and \( \hat{V}_i \), are

\[
\hat{\kappa} = \frac{\hat{\nu}}{\hat{E}_s(\hat{\kappa} - 2)},
\]

\[
\hat{\nu} = 4 + \frac{q}{q^2 - 1},
\]

(A.56)

where

\[
\hat{\nu} = \frac{\hat{V}_s}{2\hat{E}_s},
\]

(A.57)

and

\[
\hat{E}_s = 1 + \frac{\hat{A}_1}{q},
\]

\[
\hat{V}_s = \frac{2}{q} (1 + \hat{B}),
\]

(A.58)

with

\[
\hat{B} = \frac{1}{2q} (\hat{A}_1 + 6\hat{A}_2),
\]

\[
\hat{A}_1 = \sum_{i=1}^s \sum_{j=1}^s \hat{\Sigma}_{ij} \text{tr} (\hat{M}_i^{-1}\hat{M}_j^{-1}) \text{tr} (\hat{M}_i^{-1}\hat{M}_j^{-1}),
\]

\[
\hat{A}_2 = \sum_{i=1}^s \sum_{j=1}^s \hat{\Sigma}_{ij} \text{tr} (\hat{M}_i^{-1}\hat{M}_j^{-1}) \text{tr} (\hat{M}_i^{-1}\hat{M}_j^{-1}),
\]

(A.59)

In particular, by using \( \hat{M}_i = A^i C A = A^i \hat{A} \) and \( \Lambda \), we finally get

\[
\hat{\tilde{A}}_1 = \sum_{i=1}^s \frac{\hat{\tilde{\Sigma}}_i}{(\hat{\sigma}_i^2 + \hat{\sigma}_i^2)} \text{tr} (\hat{\Lambda}^i \hat{A}_i^i \hat{\Lambda}^i)^2
\]

\[
+ \sum_{i=1}^s \sum_{j=1}^s \frac{2\hat{\Sigma}_{ij}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)} \text{tr} (\hat{\Lambda}^i \hat{A}_i^i \hat{\Lambda}^i \hat{A}_j^j) \text{tr} (\hat{\Lambda}^i \hat{A}_i^i \hat{\Lambda}^i \hat{\Lambda}_j^j)
\]

\[
+ \sum_{i=1}^s \frac{2\hat{\Sigma}_{ii + 1}}{(\hat{\sigma}_i^2 \hat{\sigma}_i^2)} \text{tr} (\hat{\Lambda}^i \hat{A}_i^i \hat{\Lambda}^i \hat{H}_0 \hat{A})
\]

\[
+ \frac{\hat{\Sigma}_{s+1,i + 1}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)} \text{tr} (\hat{\Lambda}^i \hat{A}_i^i \hat{\Lambda}^i \hat{H}_0 \hat{A})^2,
\]

(A.60)

\[
\hat{\tilde{A}}_2 = \sum_{i=1}^s \frac{\hat{\tilde{\Sigma}}_i}{(\hat{\sigma}_i^2)} \text{tr} (\hat{\Lambda}^i \hat{\tilde{\Lambda}}_i \hat{\Lambda}^i)^2
\]

\[
+ \sum_{i=1}^s \sum_{j=1}^s \frac{2\hat{\Sigma}_{ij}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)} \text{tr} (\hat{\Lambda}^i \hat{\tilde{\Lambda}}_i \hat{\Lambda}^i \hat{\tilde{\Lambda}}_j) \text{tr} (\hat{\Lambda}^i \hat{\tilde{\Lambda}}_i \hat{\Lambda}^i \hat{\tilde{\Lambda}}_j)
\]

\[
+ \sum_{i=1}^s \frac{2\hat{\Sigma}_{ii + 1}}{(\hat{\sigma}_i^2 \hat{\sigma}_i^2)} \text{tr} (\hat{\Lambda}^i \hat{\tilde{\Lambda}}_i \hat{\Lambda}^i \hat{H}_0 \hat{A})
\]

\[
+ \frac{\hat{\Sigma}_{s+1,i + 1}}{(\hat{\sigma}_i^2 \hat{\sigma}_i^2)} \text{tr} (\hat{\Lambda}^i \hat{\tilde{\Lambda}}_i \hat{\Lambda}^i \hat{H}_0 \hat{A})^2,
\]

(A.61)

as before, \( \hat{\Lambda} = \hat{\tilde{\Lambda}} \Lambda, H_0 = \Delta_{s+1} = (X, Z)'(X, Z), \) and \( \hat{\tilde{\Sigma}} \) (with elements \( \hat{\tilde{\Sigma}}_{ij}, i, j = 1, \ldots, s + 1 \), is the estimated variance-covariance matrix of the REML estimator \( \hat{\sigma}^2 = (\hat{\sigma}_1^2, \ldots, \hat{\sigma}_{s+1}^2)' \).

\( \hat{\Lambda} = (\hat{\Lambda}_1, \hat{\Lambda}_2, \ldots, \hat{\Lambda}_s)' \) is decomposed into block-matrices such that \( \hat{\Lambda}_0 \) is \( (p \times q) \)-dimensional block-matrix, and \( \hat{\Lambda}_i, i = 1, \ldots, s \), are \( (r_i \times q) \)-dimensional block-matrices of \( \Lambda \). Similarly, \( \hat{\tilde{\Sigma}} \) denote the \((i, j)\)-th \((r_i \times r_j)\)-dimensional block of the matrix \( \tilde{\Sigma} \), and \( \hat{\Lambda} \), denote the \((i, j)\) \((r_i \times (p + r))\)-dimensional row-block and \( \hat{\Lambda} \), denote the \((i, q)\) \((p + r) \times r_j)\)-dimensional column-block of the matrix \( \hat{\Lambda} \).

Appendix B. Estimation of the variance components by solving the MMEs

The presented iterative procedure for estimation of the variance components by solving the Henderson’s mixed model equations has been suggested by Searle, Casella and McCulloch in [49], see pp. 275–286. The MATLAB version of the algorithm has been implemented by Witkovský in [68].

Here we use the same notation as in [49]. In each step of the suggested iterative procedure, we shall denote \( V^{(i)} = \sigma_r^{2(s)} I_r + Z' Z)^{G^{(i)}}, G^{(i)} = \text{diag} (\sigma_{r+1}^{2(s)}, \ldots, \sigma_{s+1}^{2(s)}) \) and setting \( i = 0 \). In the \( i \)-th step of the procedure the algorithm solves the system of mixed model equations:

\[
\begin{pmatrix}
X'X & X'Z \Sigma^{G^{(i)}} \\
Z'X & Y^{G^{(i)}}
\end{pmatrix}
\begin{pmatrix}
\hat{b}^{(i)} \\
\hat{y}^{(i)}
\end{pmatrix}
= \begin{pmatrix}
X'y \\
Z'y
\end{pmatrix},
\]

(B.1)

and \( \hat{u}^{(i)} = G^{(i)} \hat{y}^{(i)} \).

Appendix B.1. ML estimates of the variance components

The ML estimates of the variance components are calculated iteratively as

\[
\sigma_r^{2(s+1)} = \frac{\hat{\mu}^{(s)}_i \hat{y}^{(s)}_i}{r_i - \text{tr} (W^{(s)}_i)}, \quad i = 1, \ldots, s,
\]

\[
\sigma_{s+1}^{2(s+1)} = \frac{\lambda' (y - \hat{X} \hat{b}^{(s)} - Z \hat{u}^{(s)})}{n},
\]

(B.2)

where \( \hat{u}^{(s)}_i \) is the \( i \)-th \( r_i \)-dimensional subvector of \( \hat{u}^{(s)} \) and \( W^{(s)}_i \) is the \( i \)-th diagonal block of the matrix \( W^{(s)} \), where

\[
W^{(s)} = \sigma_{r+1}^{2(s+1)} I_{r+1} + Z' Z^{G^{(s)}}. \]

(B.3)

The iterative procedure should be stopped after the \( i \)-th step if \( \| \sigma_r^{2(s)} - \sigma_r^{2(s-1)} \| < \varepsilon \), for the chosen precision limit \( \varepsilon \), and where \( \sigma_r^{2(s)} = (\sigma_1^{2(s)}, \ldots, \sigma_{s+1}^{2(s)}) \).

The final solutions of the iterative procedure are denoted by \( \hat{b}, \hat{u} = (\hat{u}_1', \ldots, \hat{u}_s') \), and \( \sigma^2 = (\sigma_1^2, \ldots, \sigma_{s+1}^2)' \). Similarly, we
denote $\hat{W}$ and use the adequate notation $\hat{G}$, $\hat{R}$, and $\hat{C}$ for the estimated versions of matrices $G$, $R$, and $C$. The log-likelihood function for ML estimation evaluated at the ML estimates $\hat{b}$ and $\hat{\sigma}^2$, say $\loglik_{ML}$, is
\[
\loglik_{ML} = \frac{1}{2} n \log(2\pi) - \frac{1}{2} \log \left( |\hat{W}| \right ) + \frac{1}{2} \left( y - X\hat{b} \right) \hat{W}^{-1} \left( y - X\hat{b} \right) + \frac{1}{2} n \log \left( 2\pi \hat{\sigma}^2 \right).
\]
where $\hat{W} = Z\hat{G} + \hat{\sigma}^2 I_n$ and $\hat{W} = (I_r + Z'Z\hat{G}/\hat{\sigma}^2)_{s+1}^{-1}$.

The Fisher information matrix of the REML estimators of $\hat{\sigma}^2$, can be evaluated at the ML estimates $\hat{\sigma}^2$ as
\[
I_{REML}(\hat{\sigma}^2) = \frac{1}{2} n \left( \begin{array}{c} r_i - \text{tr}(\hat{T}_i^{(0)}) \\ \text{col}(\hat{\delta}_i^{(0)}, \hat{\theta}_i^{(0)}) \end{array} \right) \left( \begin{array}{c} r_i - \text{tr}(\hat{T}_i^{(0)}) \\ \text{col}(\hat{\delta}_i^{(0)}, \hat{\theta}_i^{(0)}) \end{array} \right)^T, \quad (B.5)
\]
where $\delta_i = 1$ if $i = j$, otherwise $\delta_{ij} = 0$, and $\hat{W}_{ij}$ is the $(r_i \times r_j)$ block of the matrix $\hat{W}$.

**Appendix B.2. REML estimates of the variance components**

Similarly, the REML estimates of the variance components are calculated iteratively as
\[
\hat{\sigma}^{2(0)}_i = \frac{\hat{\mu}^{(0)}_i}{r_i - \text{tr}(\hat{T}_i^{(0)})}, \quad i = 1, \ldots, s,
\]
\[
\hat{\sigma}^{2(0)}_{i+1} = \frac{y'y - X\hat{b}^{(0)} - Z\hat{\theta}^{(0)}}{n - r_X}, \quad (B.6)
\]
where by $r_X$ we denote the rank of the matrix $X$, $\hat{b}^{(0)}_i$ is the $i$-th $r_i$-dimensional subvector of $\hat{b}^{(0)}$ and $\hat{T}_i^{(0)}$ is the $i$-th diagonal block of the matrix $T^{(0)}$, where
\[
T^{(0)} = \sigma^{2(0)}_{s+1} I_r + MG^{(0)}_{s+1}^{-1}, \quad (B.7)
\]
where $M = Z'Z - Z'X(X'X)^{-1}X'Z$.

The log-likelihood function for REML estimation evaluated at the REML estimates $\hat{\sigma}^2$, say $\loglik_{REML}$, is
\[
\loglik_{REML} = -\frac{1}{2} (n - r_X) \log(2\pi) - \frac{1}{2} \log \left( |B'\hat{V}B| \right ) + \frac{1}{2} \left( y' B (B'^{-1} B')^{-1} B'y \right) \right.
\]
\[+ \frac{1}{2} \left( \frac{1}{2} (n - r_X) \log(2\pi) - \frac{1}{2} \left( y' B (B'^{-1} B')^{-1} B'y \right) \right) - \frac{1}{2} \left( \frac{1}{2} (n - r_X) \log(2\pi) - \frac{1}{2} \left( y' B (B'^{-1} B')^{-1} B'y \right) \right), \quad (B.8)
\]

where $B$ is an $nX(n-r_X)$ matrix, such that $BB' = I_n - X'X^{-1}X$ and $B'R = I_{r \times r_X}$. Further, $\hat{T} = (I_r + MG\hat{\sigma}^{2(0)}_{s+1})^{-1}$.

The Fisher information matrix of the REML information matrix of the variance components, $I_{REML}(\hat{\sigma}^2)$, can be evaluated at the REML estimates $\hat{\sigma}^2$ as
\[
I_{REML}(\hat{\sigma}^2) = \frac{1}{2} \left( \begin{array}{c} \sigma^{2(0)}_i \delta_i^{(0)} \delta_i^{(0)} \sigma^{2(0)}_{i+1} \\ \text{col}(\sigma^{2(0)}_i \delta_i^{(0)} \delta_i^{(0)} \sigma^{2(0)}_{i+1}) \end{array} \right) I_{i-1} \left( \begin{array}{c} \sigma^{2(0)}_i \delta_i^{(0)} \delta_i^{(0)} \sigma^{2(0)}_{i+1} \\ \text{col}(\sigma^{2(0)}_i \delta_i^{(0)} \delta_i^{(0)} \sigma^{2(0)}_{i+1}) \end{array} \right)^T, \quad (B.9)
\]
where $\delta_i = 1$ if $i = j$, otherwise $\delta_{ij} = 0$, and $\hat{T}_{ij}$ is the $(r_i \times r_j)$ block of the matrix $\hat{T}$.

Similarly, the final solutions of the procedure are denoted by $\hat{b}$, $\hat{u} = (\hat{u}_1, \ldots, \hat{u}_s)'$, and $\hat{\sigma}^2 = (\hat{\sigma}^2_1, \ldots, \hat{\sigma}^2_{s+1})'$. Further, we denote $\hat{T}$, and use the adequate notation $\hat{G}$, $\hat{R}$, and $\hat{C}$ for the estimated versions of matrices $G$, $R$, and $C$.

For more details on ML and REML estimators see the Chapter 6 in Searle et al. (1992).

**Appendix B.3. MINQE’s of the variance components**

For completeness, here we present procedures to calculate the MINQE(I) and the MINQE(U,1) estimators of the variance components at (given) prior values of the variance components $\sigma^{2(0)} = (\sigma^{2(0)}_1, \ldots, \sigma^{2(0)}_{s+1})'$. Here we assume that $\sigma^{2(0)}_i > 0$ for all $i = 1, \ldots, s + 1$. For more details on minimum norm quadratic estimation of the variance components see e.g. [33], [42], and [43].

The $\text{MINQE}(I)$ of $\sigma^2$, say $\hat{\sigma}^2$, at the prior value $\sigma^{2(0)}$ is defined as the solution of the following system of equations
\[
H_I\hat{\sigma}^2 = q, \quad (B.10)
\]
where $H_I$ we denote the $(s+1 \times s+1)$-dimensional MINQE(I)-matrix and $q = (q_1, \ldots, q_{s+1})'$ denotes the vector of MINQE quadratic forms. The matrix $H_I$ is defined by its elements as
\[
H_I_{ij} = \text{tr} \left( (V^{(0)})^{-1} V_i (V^{(0)})^{-1} V_j \right), \quad (B.11)
\]
for $i, j = 1, \ldots, s + 1$, where $V_i = Z_{ii}'$, for $i = 1, \ldots, s$, $V_{s+1} = I_n$, and $V^{(0)} = (ZG^{(0)})'Z + \sigma^{2(0)}_{s+1} I_n = \sum_{i=1}^{s+1} \sigma^{2(0)}_i V_i$. The matrix $H_I$ can be easily evaluated by using $\text{MINQE}$, namely
\[
H_I = 2I_{ML}(\sigma^{2(0)}). \quad (B.12)
\]
Furthermore, the vector $q$ of MINQE quadratic forms, defined by its elements as
\[
q_i = \left( M_X V^{(0)} M_X \right) V_i \left( M_X V^{(0)} M_X \right)' y, \quad (B.13)
\]
for $i = 1, \ldots, s + 1$, with $M_X = I_n - X(X'X)^{-1}X$, could be easily evaluated by using
\[
q_i = \left( \hat{u}_i \hat{b}^{(0)} - \hat{\theta}_i^{(0)} \right), \quad i = 1, \ldots, s,
\]
\[
q_{s+1} = \left( y' - X\hat{b}^{(0)} - Z\hat{\theta}^{(0)} \right)' \left( y' - X\hat{b}^{(0)} - Z\hat{\theta}^{(0)} \right) (\sigma^{2(0)}_{s+1})^2, \quad (B.14)
\]
where $\hat{u}^{(0)}_i$ is the $i$-th $r_i$-dimensional subvector of $\hat{u}^{(0)}$.

Similarly, the MINQE(U,1) of $\sigma^2$, say $\hat{\sigma}^2$, at the prior value $\sigma^{2(0)}$ is defined as the solution of the following system of equations
\[
H_{(U,1)}\hat{\sigma}^2 = q, \quad (B.15)
\]
where $H_{UI}$ denotes the $(s+1 \times s+1)$-dimensional MINQE(U,I) matrix, defined by its elements
\[
[H_{UI}]_{ij} = \text{tr}\left((M_X V^0 M_X)^T V_i (M_X V^0 M_X)^T V_j\right), \quad (B.16)
\]
i, j = 1, \ldots, s + 1, and by using (B.9) we get
\[
H_{UI} = 2I_{REML} \sigma^2(0). \quad (B.17)
\]

Note that the MINQE $\hat{\sigma}^2$, defined by (B.10) or by (B.15), is not given uniquely unless the MINQE matrix is of full rank. In fact, one version of the solution to the MINQE equations is $\hat{\sigma}^2 = H g$, where $H$ denote the Moore-Penrose g-inverse of the appropriate MINQE matrix.

The MINQE of unbiasedly estimable vector $F \hat{\sigma}^2$, where $F$ is such matrix that $F' = HA$ for some matrix $A$, is $\hat{\sigma}^2$, and is unique.

In particular, under given assumptions, the MINQE(U,I) $F \hat{\sigma}^2$, with $F$ such that $F' = H_{UI} A$ for some matrix $A$, is the $\sigma^2(0)$-locally minimum variance unbiased invariant estimator of $F \hat{\sigma}^2$ with
\[
E(F \hat{\sigma}^2) = F \sigma^2, \\
\text{Var}(F \hat{\sigma}^2 | \sigma^2(0)) = 2F H_{UI} F', \\
\text{Var}(F \hat{\sigma}^2) = 2A'H_{UI} A. \quad (B.18)
\]
On the other hand, the MINQE(I) $F \hat{\sigma}^2$ is a biased estimator of $F \sigma^2$ with
\[
E(F \hat{\sigma}^2) = F H_{UI} \hat{\sigma}^2, \\
\text{Var}(F \hat{\sigma}^2 | \sigma^2(0)) = 2F H_{UI} F'. \quad (B.19)
\]

References

[1] Ahnosaier, W.S. (2007). Kenward-Roger Approximate F Test for Fixed Effects in Mixed Linear Models. Dissertation Thesis submitted to Oregon State University, April 25, 2007.

[2] Arendacká, B. (2007). Fiducial generalized pivots for a variance component vs. an approximate confidence Interval. Measurement Science Review 7 (6), 55 – 63.

[3] Arendacká, B. (2012). Approximate interval for the between-group variance under heteroscedasticity. Journal of Statistical Computation & Simulation 82 (2), 209 – 218.

[4] Arendacká, B. (2012). A note on fiducial generalized pivots for $\sigma^2$ in one-way heteroscedastic ANOVA with random effects. Statistics 46 (4), 489 – 504.

[5] Caliński, T., Kageyama, S. (2008). On the analysis of experiments in affine resolvable designs. Journal of Statistical Planning and Inference 138, 3330 – 3356.

[6] Chvosteková, M., Witkovský, V. (2009). Exact likelihood ratio test for the parameters of the linear regression model with normal errors. Measurement Science Review 9 (1), 1 – 8.

[7] Cui, X., Churchill, G.A. (2003). How many mice and how many arrays? Replication of cDNA microarray experiments. In Lin, S.M, and Allred, E.T. (eds). Methods of Microarray Data Analysis III, New York: Kluwer.

[8] Cui, X., Hwang, J.T.G, Qu, J., Blades, N.J., Churchill, G.A. (2005). Improved statistical tests for differential gene expression by shrinking variance components estimates. Biostatistics 6 (1), 59 – 75.

[9] Cui, X., Alfaroiti, J., Shockley, K.R., Woo, Y., Churchill, G.A. (2006). Inheritance patterns of transcript levels in F1 hybrid mice. Genetics 174, 627 – 637.

[10] Das, K., Jiang, J., Rao, J.N.K. (2004). Mean squared error of empirical predictor. Annals of Statistics 32, 818 – 840.

[11] Domotor, Z. (2012). Algebraic frameworks for measurement in the natural sciences. Measurement Science Review 12 (6), 213 – 233.

[12] Elston, D.A. (1998). Estimation of denominator degrees of freedom of F-distributions for assessing Wald statistics for fixed-effect factors in unbalanced mixed models. Biometrics 54 (3), 1085 – 1096.

[13] Fai, A.H.T., Cornelius, P.L. (1996). Approximate F-tests of multiple degree of freedom hypotheses in generalized least squares analyses of unbalanced split-plot experiments. Journal of Statistical Computing and Simulation 54, 363 – 378.

[14] Fonseca, M., Mathew, T., Metia, J.T., Zmyślony, R. (2007). Tolerance intervals in a two-way nested model with mixed or random effects. Statistics 41 (4), 289 – 300.

[15] Gelman, A. (2005). Analysis of variance: Why it is more important than ever. The Annals of Statistics 33 (1), 1 – 31.

[16] Giesbrecht, F.G., Burns, J.C. (1985). Two-stage analysis based on a mixed model: Large sample asymptotic theory and small-sample simulation results. Biometrics 41, 477 – 486.

[17] Hartley, H.O., Rao, J.N.K. (1967). Maximum-likelihood estimation for the mixed analysis of variance model. Biometrika 54, 93 – 108.

[18] Hartung, J., Knapp, G., Sinha, B.K. (2008). Statistical Meta-Analysis with Applications, New York: Wiley.

[19] Harville, D.A. (1977). Maximum likelihood approaches to variance component estimation and to related problems. Journal of the American Statistical Association 72, 320 – 38.

[20] Harville, D.A. (1985). Decomposition of prediction error. Journal of the American Statistical Association 80, 132 – 138.

[21] Harville, D.A., Jeske, D.R. (1992). Mean squared error of estimation or prediction under a general linear model. Journal of the American Statistical Association 87, 724 – 731.

[22] Harville, D.A. (2008). Accounting for the estimation of variances and covariances in prediction under general linear model: An overview. Tatra Mountains Mathematical Publications 39, 1 – 15.

[23] Henderson, C.R. (1953). Mixed estimation in linear models. Biometrics 9 (2), 226 – 252.

[24] Herdahl, M. (2008). Linear mixed model for compressor head and flow data with an application. Department of Mathematical Sciences, Norwegian University of Science and Technology (NTNU), Norway, June 2008.

http://ntnu.diva-portal.org

[25] Jeske, D.R., Harville, D.A., (1988). Prediction-interval procedures and components Biometrics 9 (2), 226 – 252.

[26] Jiang, J. (1999). On unbiasedness of the empirical BLUE and BLUP. Statistical and Probability Letters 41 (1999), 19 – 24.

[27] Kackar, R.N., Harville, D.A. (1981). Unbiasedness of two-stage estimation and prediction procedures for mixed linear models. Communications in Statistics - Theory and Methods 17, 1053 – 1087.

[28] Kackar, R.N., Harville, D.A. (1984). Approximations for standard errors of estimators of fixed and random effects in mixed linear models. Journal of the American Statistical Association 79, 853 – 862.

[29] Kenward, M.G., Roger, J.H. (1997). Small sample inference for fixed effects from restricted maximum likelihood, Biometrics 53, 983 – 997.

[30] Kenward, M.G., Roger, J.H. (2009). An improved approximation to the precision of fixed effects from restricted maximum likelihood. Computational Statistics and Data Analysis 53, 2583 – 2595.

[31] Krishnamoorthi, K., Mathew, T. (2009). Statistical Tolerance Regions: Theory, Applications, and Computation, New York: Wiley.

[32] Laird, N.M., Lange, N., Stram, D. (1987). Maximum likelihood computations with repeated measures: Application of the EM algorithm. Journal of the American Statistical Association 82, 97 – 105.

[33] LaMotte, L.R. (1973). Quadratic estimation of variance components. Bioometrics 29, 311 – 330.

[34] Lindstrom, M.J., Bates, D.M. (1988). Newton-Raphson and EM algorithms for linear mixed-effects models for repeated-measures data. Journal of the American Statistical Association 83, 1014 – 1022.

[35] Littell, R.C., Milliken, G.A., Stroup, W.W., Wolfinger, R.D., Schabenberger, O. (2006). SAS for Mixed Models, Second Edition, Cary, NC: SAS Institute Inc.

[36] McCulloch, C.E., Searle, S.R. (2001). Generalized, Linear, and Mixed Models, New York: Wiley.
McLean, R.A., Sanders, W.L. (1988). Approximating degrees of freedom for standard errors in mixed linear models. In: Proceedings of the Statistical Computing Section, Alexandria, VA: American Statistical Association, 50–59.

McLean, R.A., Sanders, W.L., Stroup, W.W. (1991). A unified approach to mixed linear models. The American Statistician 45, 54–64.

Patterson, H.D., Thompson, R. (1971). Recovery of inter-block information when block sizes are unequal. Biometrika 58, 545–554.

Pinheiro, J.C., Bates, D.M. (2000). Mixed-Effects Models in S and S-PLUS. Springer-Verlag, New York.

Prasad, N.G.N., Rao, J.N.K. (1990). The estimation of the mean squared error of small area estimators. Journal of the American Statistical Association 85, 163–171.

Rao, C.R. (1972). Estimation of variance and covariance components in linear models. Journal of the American Statistical Association 67, 112–115.

Rao, C.R., Kleffe, J. (1988). Estimation of Variance Components and Applications. North-Holland Publishing Company, Amsterdam.

Robinson, G.K. (1991). That BLUP is a good thing: The estimation of random effects. Statistical Science 6, 15–51.

Rao, C.R., Kleffe, J. (1988). Estimation of Variance Components and Applications. North-Holland Publishing Company, Amsterdam.

SAS Institute, Inc. (2012), SAS®/STAT 9.2 Users Guide The MIXED Procedure. Online Help, Cary, NC: SAS Institute.

Satterthwaite, F.E. (1941). Synthesis of variance. Psychometrika 6, 309–316.

Satterthwaite, F.E. (1946). An approximate distribution of estimates of variance components. Biometrics Bulletin 2 (6), 110–114.

Savin, A., Wimmer, G., Witkovský, V. (2003). On Kenward-Roger confidence intervals for common mean in interlaboratory trials. Measurement Science Review 3, 53–56.

Searle, S.R., Casella, G., McCulloch, C.E. (1992). Variance Components. John Wiley & Sons, New York.

Schulz, E., Tiemann, L., Witkovský, V., Schmidt, P., Ploner, M. (2012). Estimated results and extensions of professor Kubáček’s research. Acta Universitatis Palackianae Olomucensis, Facultas Rerum Naturalium, Mathematica 50 (2), 123–130.

Witkovský, V. (1998). Estimation of variance components with constraints. Journal of Statistical Planning and Inference 69 (1), 81–87.

Witkovský, V. (1998). Modified minimax quadratic estimation of variance components. Kybernetika 34 (5), 535–543.

Witkovský, V. (2002). MATLAB algorithm mixed.m for solving Henderson’s mixed model equations. Technical Report, Institute of Measurement Science, Slovak Academy of Sciences, Bratislava. 2002. http://www.mathworks.com/matlabcentral/fileexchange/200-mixed

Witkovský, V. (2005). Comparison of some exact and approximate interval estimators for common mean. Measurement Science Review 5 (1), 19–22.

Witkovský, Savin, A., Wimmer, G. (2003). On small sample inference for common mean in heteroscedastic one-way model. Discussiones Mathematicae Probability and Statistics 23 (2), 123–145.

Witkovský, V., Wimmer, G. (2001). On statistical models for consensus values. Measurement Science Review 1 (1), 33–36.

Witkovský, V., Wimmer, G. (2003). Consensus mean and interval estimators for the common mean. Tatra Mountains Mathematical Publications 26 (1), 183–194.

Witkovský, V., Wimmer, G. (2007). Confidence interval for common mean in interlaboratory comparisons with systematic laboratory biases. Measurement Science Review 7 (6), 64–73.

Wu, H., Yang, H., Churchill, G.A. (2012). RMAANOVA: An extensive R environment for the analysis of microarray experiments. http://www.bioconductor.org