

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

Invited paper

Viktor Witkovský *

Institute of Measurement Science, Slovak Academy of Sciences, Bratislava, Slovak Republic

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

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], [55], [62], [63], [64], [69], [70], [71], [72], 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], [57], [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 func-

tions 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

$$y = Xb + Zu + e, \quad (1)$$

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 $Var(u) = G$, and e being the n -vector of random (measurement) errors with $E(e) = 0$ and $Var(e) = R$, 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 $Zu = \sum_{i=1}^s Z_i u_i$, where the $(n \times r_i)$ matrices Z_i and the r_i -dimensional random effects u_i , $i = 1, \dots, s$, 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 $w = \Lambda'(b', u')' = K'b + L'u$ for given (suitable) coefficient matrices Λ , resp. K and L .

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 $K'b$) and the best linear unbiased predictor (BLUP) of u (or any vector $w = K'b + L'u$,

*Corresponding author: witkovsky@savba.sk.

provided $K'b$ 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

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

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

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

we get the MMEs in the following form

$$\begin{pmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{pmatrix} \begin{pmatrix} \tilde{b} \\ \tilde{u} \end{pmatrix} = \begin{pmatrix} X'R^{-1}y \\ Z'R^{-1}y \end{pmatrix}. \quad (4)$$

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

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

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

$$\begin{pmatrix} X'R^{-1}X & X'R^{-1}ZG \\ Z'R^{-1}X & W^{-1} \end{pmatrix} \begin{pmatrix} \tilde{b} \\ \tilde{v} \end{pmatrix} = \begin{pmatrix} X'R^{-1}y \\ Z'R^{-1}y \end{pmatrix}. \quad (6)$$

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

$$\begin{aligned} C &= \begin{pmatrix} C_{11} & C_{12} \\ C_{21} & C_{22} \end{pmatrix} \\ &= \begin{pmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{pmatrix}^- \\ &= \begin{pmatrix} I_p & 0 \\ 0 & G \end{pmatrix} \begin{pmatrix} X'R^{-1}X & X'R^{-1}ZG \\ Z'R^{-1}X & W^{-1} \end{pmatrix}^-, \end{aligned} \quad (7)$$

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 \tilde{b} and \tilde{v} , the solutions from (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 $K'b$, see e.g. [49], is

$$BLUE(K'b) = K'(X'V^{-1}X)^-X'V^{-1}y = K'\tilde{b}, \quad (8)$$

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 $K'b + L'u$, is

$$\begin{aligned} BLUP(K'b + L'u) &= BLUE(K'b) \\ &\quad + L'GZ'V^{-1}(y - BLUE(Xb)), \\ &= K'\tilde{b} + L'\tilde{u}, \end{aligned} \quad (9)$$

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

Important properties of the solutions of the MMEs are summarized bellow, 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. $K'\tilde{b}$ is BLUE of the set of estimable linear functions $K'b$.
3. $E(u|\tilde{u}) = \tilde{u}$.
4. \tilde{u} is unique.
5. $K'\tilde{b} + L'\tilde{u}$ is BLUP of $K'b + L'u$ provided that $K'b$ is estimable.
6. $Var(K'\tilde{b}) = K'C_{11}K$.
7. $Var(K'\tilde{b} + L'\tilde{u}) = K'C_{11}K + L'(G - C_{22})L$.
8. $Var((K'\tilde{b} + L'\tilde{u}) - (K'b + L'u)) = (K', L')C(K', L)'$.
9. $Cov(K'\tilde{b}, \tilde{u}') = 0$.
10. $Cov(K'\tilde{b}, u') = -K'C_{12}$.
11. $Cov(K'\tilde{b}, u' - \tilde{u}') = -K'C_{12}$.
12. $Var(\tilde{u}) = Cov(\tilde{u}, u') = G - C_{22}$.
13. $Var(\tilde{u} - u) = C_{22}$.

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, \dots, u_s and e with $E(u_i) = 0$ for $i = 1, \dots, r$, $E(e) = 0$, $Cov(u_i, u_j) = 0$ for $i \neq j$, and $Cov(u_i, e) = 0$ for all $i = 1, \dots, s$. Further, we shall assume $Var(u_i) = \sigma_i^2 I_{r_i}$, $i = 1, \dots, s$, with $r = \sum_{i=1}^s r_i$, and $Var(e) = \sigma_{s+1}^2 I_n$. Hence,

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

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

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

If the variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2)'$ 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 [34], 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 (lme in the nlme 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 [45], [35], [60], and [40].

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 $\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2$ 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], [19], [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(U,I) (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} , $\hat{u} = (\hat{u}'_1, \dots, \hat{u}'_s)'$, and $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$. Similarly, we shall use the adequate notation \hat{G} , \hat{R} , and \hat{C} for the estimated versions of matrices G , R , 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 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 Λ is $((p+r) \times q)$ -dimensional full-ranked matrix with estimable $K'b$ (i.e. $K = X'A$ for some matrix A).

Let \tilde{b} and \tilde{u} are the solutions of the MMEs (4), so $\tilde{w} = \Lambda'(\tilde{b}', \tilde{u}')' = K'\tilde{b} + L'\tilde{u}$ 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 $K'\tilde{b}$ and the mean squared error (MSE) of \tilde{w} are given by

$$\text{Var}(K'\tilde{b}) = K'C_{11}K, \quad (11)$$

and

$$\begin{aligned} \text{MSE}(\tilde{w}) &= E((\tilde{w} - w)(\tilde{w} - w)') \\ &= \text{Var}(\tilde{w} - w) = \Lambda'CA = M_{\tilde{w}}. \end{aligned} \quad (12)$$

Notice that the MSE matrix of \tilde{w} , $M_{\tilde{w}}$, functionally depends on the variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2)'$.

If the variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2)'$ 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:

$$Q = (K'\tilde{b} - K'b_0)'(K'C_{11}K)^{-1}(K'\tilde{b} - K'b_0) \sim \chi_q^2, \quad (13)$$

and

$$Q = (\tilde{w} - w)'(\Lambda'CA)^{-1}(\tilde{w} - w) \sim \chi_q^2, \quad (14)$$

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

If the variance components are unknown and the estimated values $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$ 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} :

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

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

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

where q is rank of the matrix Λ' .

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

$$t = \frac{k'\hat{b} - k'b_0}{\sqrt{k'\hat{C}_{11}k}}, \quad (17)$$

and/or its generalization

$$t = \frac{\hat{w} - w}{\sqrt{\lambda'\hat{C}\lambda}}, \quad (18)$$

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 ν 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 ν_1 and ν_2 degrees of freedom, where $\nu_1 = q$ and ν_2 , the denominator degrees of freedom (DDF), where ν_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 $\hat{\nu}$ degrees of freedom (DF), where $\hat{\nu}$ is the Satterthwaite's approximation¹ of the (unknown) ν , see [46], [47], i.e.

$$t = \frac{k'\hat{b} - k'b_0}{\sqrt{k'\hat{C}_{11}k}} \sim t_{\hat{\nu}_k}, \quad (19)$$

with

$$\hat{\nu}_k = \frac{2(k'\hat{C}_{11}k)^2}{\widehat{Var}(k'\hat{C}_{11}k)} \equiv \frac{2(k'\hat{C}_{11}k)^2}{\hat{g}'_k \hat{\Sigma} \hat{g}_k}, \quad (20)$$

where $\widehat{Var}(k'\hat{C}_{11}k)$ denotes the estimated value of $Var(k'\hat{C}_{11}k)$.

The suggested estimator of $\widehat{Var}(k'\hat{C}_{11}k) \equiv \hat{g}'_k \hat{\Sigma} \hat{g}_k$ is based on the estimated version of the Taylor series expansion of the variance of the estimator $k'\hat{b}$ (BLUE), i.e. $Var(k'\hat{b}) =$

¹The Satterthwaite's approximation of the distribution of $k'\hat{C}_{11}k$ is based on assumption that $\nu(k'\hat{C}_{11}k)/\sigma^2 \sim \chi^2_\nu$ for some parameters σ^2 and ν . By comparing the first and the second moments of both random variables we get $E(\nu(k'\hat{C}_{11}k)/\sigma^2) = \nu$ and $Var(\nu(k'\hat{C}_{11}k)/\sigma^2) = 2\nu$. From that we directly get $\sigma^2 = E(k'\hat{C}_{11}k)$ and $\nu = 2(E(k'\hat{C}_{11}k))^2 / Var(k'\hat{C}_{11}k)$. As $E(k'\hat{C}_{11}k)$ and $Var(k'\hat{C}_{11}k)$ depend on unknown parameters they should be estimated. So, we get the natural estimator as $\hat{\nu} = 2(k'\hat{C}_{11}k) / \widehat{Var}(k'\hat{C}_{11}k)$.

$k'\hat{C}_{11}k$, with respect to the variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2)$. Here, $\hat{\Sigma}$ is the estimated (asymptotic) variance-covariance matrix of the estimators (e.g. REML estimators) of the variance components σ^2 , and \hat{g}_k is the estimated version (evaluated at the estimated values of the variance components $\hat{\sigma}^2$) of the gradient g_k of $k'\hat{C}_{11}k$, with respect to the variance components σ^2 , i.e.

$$g_k = \begin{pmatrix} \frac{\partial(k'\hat{C}_{11}k)}{\partial\sigma_1^2} \\ \vdots \\ \frac{\partial(k'\hat{C}_{11}k)}{\partial\sigma_s^2} \\ \frac{\partial(k'\hat{C}_{11}k)}{\partial\sigma_{s+1}^2} \end{pmatrix}. \quad (21)$$

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.

$$t = \frac{\hat{w} - w}{\sqrt{\lambda'\hat{C}\lambda}} \sim t_{\hat{\nu}_\lambda}, \quad (22)$$

with

$$\hat{\nu}_\lambda = \frac{2(\lambda'\hat{C}\lambda)^2}{\widehat{Var}(\lambda'\hat{C}\lambda)} \equiv \frac{2(\lambda'\hat{C}\lambda)^2}{\hat{g}'_\lambda \hat{\Sigma} \hat{g}_\lambda}, \quad (23)$$

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

$$g_\lambda = \begin{pmatrix} \frac{\partial(\lambda'\hat{C}\lambda)}{\partial\sigma_1^2} \\ \vdots \\ \frac{\partial(\lambda'\hat{C}\lambda)}{\partial\sigma_s^2} \\ \frac{\partial(\lambda'\hat{C}\lambda)}{\partial\sigma_{s+1}^2} \end{pmatrix}. \quad (24)$$

For more details on computing gradients of the $MSE(\hat{w})$ see Section 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}_λ 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 $\hat{\lambda} = \hat{C}\lambda$ and let $\hat{\lambda}$ be decomposed into its subvectors such that $\hat{\lambda} = (\hat{\lambda}'_0, \hat{\lambda}'_1, \dots, \hat{\lambda}'_s)'$, where $\hat{\lambda}_0$ is p -dimensional subvector, and $\hat{\lambda}_i$, $i = 1, \dots, s$, are r_i -dimensional subvectors of $\hat{\lambda}$. Then, by using (78) from Section A.3, we get

$$\hat{g}_\lambda = \begin{pmatrix} \frac{1}{(\hat{\sigma}_1^2)^2} \hat{\lambda}'_1 \hat{\lambda}_1 \\ \vdots \\ \frac{1}{(\hat{\sigma}_s^2)^2} \hat{\lambda}'_s \hat{\lambda}_s \\ \frac{1}{(\hat{\sigma}_{s+1}^2)^2} \hat{\lambda}' H_0 \hat{\lambda} \end{pmatrix}, \quad (25)$$

where H_0 is given by

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

Consequently, as $k'b$ is a special case of $\lambda'(b', u')' = k'b + l'u$ with $\lambda = \lambda_{(k)} = (k', 0_r)'$, so we can use (25) also for evaluation of \hat{g}_k by replacing $\hat{\lambda}$ with $\hat{\lambda}_{(k)} = \hat{C}\lambda_{(k)}$.

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 $\nu_1 = q$ and $\nu_2 = \hat{\nu}$, 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 $w = \Lambda'(b', u')' = K'b + L'u$ and its empirical predictor $\hat{w} = K'\hat{b} + L'\hat{u}$, by the Fisher-Snedecor F -distribution with $\nu_1 = q$ and $\nu_2 = \hat{\nu}$ degrees of freedom, where where

$$\hat{\nu} = \frac{2\hat{E}}{\hat{E} - q}, \tag{27}$$

with

$$\hat{E} = \sum_{i=1}^q \frac{\hat{\nu}_i}{\hat{\nu}_i - 2} 1_{\{\hat{\nu}_i > 2\}}. \tag{28}$$

Here, $1_{\{\cdot\}}$ denotes the indicator function and $\hat{\nu}_i$, for $i = 1, \dots, q$, are the degrees of freedom, estimated by the Satterthwaite's method (23), of the t -statistics (18) for $\hat{w}_i = \hat{\lambda}'_i(\hat{b}', \hat{u}')'$, where $\hat{\lambda}_i$, $i = 1, \dots, q$, are the columns of the matrix $\hat{\Lambda}_{FC}$ given by

$$\hat{\Lambda}_{FC} = \Lambda \hat{U}, \tag{29}$$

and \hat{U} denotes the unitary matrix of a spectral decomposition of a matrix $\Lambda' \hat{C} \Lambda$, i.e. such matrix that $\hat{U}' \Lambda' \hat{C} \Lambda \hat{U} = \hat{S}$, 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 [22], usage of the MSE matrix of the BLUP \tilde{w} , say $M_{\tilde{w}}$, (or its estimated version, say $\hat{M}_{\tilde{w}}$), 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 $\hat{M}_{\tilde{w}} = \Lambda' \hat{C} \Lambda$ 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,

$$(\hat{w} - w) = (\tilde{w} - w) + (\hat{w} - \tilde{w}), \tag{30}$$

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

$$M_{\hat{w}} = M_{\tilde{w}} + M_{\delta\hat{w}}, \tag{31}$$

where $M_{\delta\hat{w}} = E((\hat{w} - \tilde{w})(\hat{w} - \tilde{w})') = \text{Var}(\hat{w} - \tilde{w})$, and thus, $M_{\hat{w}} \geq M_{\tilde{w}}$.

The MSE of the first component of the prediction error, $M_{\tilde{w}}$, is given by (12). The MSE of the second component of the prediction error, $M_{\delta\hat{w}}$, 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 $M_{\delta\hat{w}}$ based on first-order Taylor series approximation. In particular, a Taylor series expansion for $\hat{w} - \tilde{w}$ in $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_s^2, \hat{\sigma}_{s+1}^2)'$, as e.g. REML, about $\sigma^2 = (\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2)'$, gives approximation

$$\begin{aligned} (\hat{w} - \tilde{w}) &\approx (\tilde{w} - \tilde{w}) + \sum_{i=1}^{s+1} \frac{\partial \tilde{w}}{\partial \sigma_i^2} (\hat{\sigma}_i^2 - \sigma_i^2) \\ &+ \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \frac{\partial^2 \tilde{w}}{\partial \sigma_i^2 \partial \sigma_j^2} (\hat{\sigma}_i^2 - \sigma_i^2) (\hat{\sigma}_j^2 - \sigma_j^2). \end{aligned} \tag{32}$$

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 $\dot{M}_{\delta\hat{w}}$ of $M_{\delta\hat{w}}$ as

$$\begin{aligned} \dot{M}_{\delta\hat{w}} &= E \left(\frac{\partial \tilde{w}}{\partial \sigma^2} \Sigma \frac{\partial \tilde{w}'}{\partial \sigma^2} \right) \\ &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} E \left(\frac{\partial \tilde{w}}{\partial \sigma_i^2} \frac{\partial \tilde{w}'}{\partial \sigma_j^2} \right) \\ &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} \text{Cov} \left(\frac{\partial (\tilde{w} - w)}{\partial \sigma_i^2}, \frac{\partial (\tilde{w} - w)}{\partial \sigma_j^2} \right), \end{aligned} \tag{33}$$

where Σ_{ij} are elements of the variance-covariance matrix Σ of the estimator $\hat{\sigma}^2$.

For derivation of the approximation of $\dot{M}_{\delta\hat{w}}$ see Section A.4. The second component of the EBLUP's MSE matrix $M_{\delta\hat{w}}$ in the simple LMM (10) can be approximated by

$$\dot{M}_{\delta\hat{w}} = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} \mathbb{C}_{ij}. \tag{34}$$

where \mathbb{C}_{ij} , $i, j = 1, \dots, s+1$, are given by (87), or alternatively by

$$\dot{M}_{\delta\hat{w}} = -\frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} M_{\tilde{w}}^{(i,j)}, \tag{35}$$

where the matrices $M_{\tilde{w}}^{(i,j)}$ are given by (79), (80), (81), and (82).

Consequently, we get the approximation $\dot{M}_{\hat{w}}$ of the EBLUP's MSE matrix $M_{\hat{w}}$ in the form

$$\dot{M}_{\hat{w}} = M_{\tilde{w}} + \dot{M}_{\delta\hat{w}}$$

$$\begin{aligned}
 &= M_{\hat{w}} + \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} C_{ij} \\
 &\equiv M_{\hat{w}} - \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} M_{\hat{w}}^{(i,j)}, \quad (36)
 \end{aligned}$$

where Σ_{ij} are elements of the variance-covariance matrix of the REML estimator $\hat{\sigma}^2$, and $M_{\hat{w}}^{(i,j)}$ represent the second partial derivatives of the BLUP's MSE matrix $M_{\hat{w}}$ with respect to the variance components σ_i^2 and σ_j^2 , $i, j = 1, \dots, s+1$, 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 $\hat{M}_{\hat{w}}$ (which is a function of Σ), depend on the unknown variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_{s+1}^2)'$, for further applications it is necessary to use its estimator, say $\hat{M}_{\hat{w}}$. A natural option for such estimator would be

$$\hat{M}_{\hat{w}} = \hat{M}_{\hat{w}} + \hat{M}_{\delta\hat{w}}, \quad (37)$$

i.e. by using (36), where the true (unknown) vector of variance components σ^2 is replaced by its estimator $\hat{\sigma}^2$. Notice that Σ , the true variance-covariance matrix of the REML estimator $\hat{\sigma}^2$ also depends on σ^2 . So, the estimator (37) functionally depends on $\hat{\Sigma}_{ij}$, the elements of estimated variance-covariance matrix $\hat{\Sigma}$.

Based on similar arguments as given by Alnoaiser in [1] for the special case of empirical BLUE of the fixed effects, we can assume that $\hat{M}_{\delta\hat{w}}$ is approximately unbiased estimator of $M_{\delta\hat{w}}$, 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 $\hat{M}_{\hat{w}}$ is used as an estimators of the MSE matrix $M_{\hat{w}}$ in (37). In order to show that, let us expand $\hat{M}_{\hat{w}}$ in $\hat{\sigma}^2$ about σ^2 , and then take expectation of this approximation, so

$$\begin{aligned}
 E(\hat{M}_{\hat{w}}) &\approx M_{\hat{w}} + \sum_{i=1}^{s+1} E(\hat{\sigma}_i^2 - \sigma_i^2) \frac{\partial M_{\hat{w}}}{\partial \sigma_i^2} \\
 &\quad + \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} E((\hat{\sigma}_i^2 - \sigma_i^2)(\hat{\sigma}_j^2 - \sigma_j^2)) \frac{\partial^2 M_{\hat{w}}}{\partial \sigma_i^2 \partial \sigma_j^2} \\
 &\approx M_{\hat{w}} + \frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} M_{\hat{w}}^{(i,j)} \\
 &= M_{\hat{w}} - \hat{M}_{\delta\hat{w}}, \quad (38)
 \end{aligned}$$

where we have assumed that the first-order term could be ignored, and $\hat{M}_{\delta\hat{w}}$ is given by (35). This could be informally justified by the assumption that $\hat{\sigma}_i^2$ is approximately an unbiased estimator of σ_i^2 , as was suggested in [29]. However, formal justification was provided by Alnoaiser in [1] and by

Kenward and Roger in [30]. Kenward and Roger derived Taylor series approximation for the bias of REML estimator, i.e. $E(\hat{\sigma}_i^2 - \sigma_i^2)$, and proved that in linear mixed models with linear parametrization of the variance-covariance matrix $V = Z'GZ + R$, like 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 $M_{\hat{w}}$, given by

$$\hat{M}_{\hat{w},A} = \hat{M}_{\hat{w}} + 2\hat{M}_{\delta\hat{w}}. \quad (39)$$

The explicit form of the estimator (39) in simple LMM (10) is given by (92) in Section 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

$$F = \frac{1}{q} (\hat{w} - w)' \left(\hat{M}_{\hat{w},A} \right)^{-1} (\hat{w} - w), \quad (40)$$

where $\hat{M}_{\hat{w},A}$ is given by (39), or (in its explicit form) by (92) from Section A.5, respectively.

In accordance with [29] and [1], we suggest to approximate the (null) distribution of the scaled Wald-type F -statistic (40) by the Fisher-Snedecor F -distribution with q and ν degrees of freedom. In particular,

$$\kappa F \stackrel{approx.}{\sim} F_{q,\nu}, \quad (41)$$

where the unknown parameters κ and ν should be estimated from the data.

In analogy with derivation of the estimators presented by Alnoaiser in [1] for the fixed effects problem, here we suggest the following estimators of the scale κ and the denominator degrees of freedom ν :

$$\begin{aligned}
 \hat{\kappa} &= \frac{\hat{\nu}}{\hat{E}(\hat{\nu} - 2)}, \\
 \hat{\nu} &= 4 + \frac{2+q}{q\hat{Q} - 1}, \quad (42)
 \end{aligned}$$

where

$$\hat{Q} = \frac{\hat{\nu}}{2\hat{E}^2},$$

$$\begin{aligned}\hat{E} &= 1 + \frac{\hat{A}_2}{q}, \\ \hat{V} &= \frac{2}{q}(1 + \hat{B}), \\ \hat{B} &= \frac{1}{2q}(\hat{A}_1 + 6\hat{A}_2),\end{aligned}\quad (43)$$

and

$$\begin{aligned}\hat{A}_1 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \operatorname{tr}(\hat{M}_{\hat{w}}^{-1} \hat{M}_{\hat{w}}^{(i)}) \operatorname{tr}(\hat{M}_{\hat{w}}^{-1} \hat{M}_{\hat{w}}^{(j)}), \\ \hat{A}_2 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \operatorname{tr}(\hat{M}_{\hat{w}}^{-1} \hat{M}_{\hat{w}}^{(i)} \hat{M}_{\hat{w}}^{-1} \hat{M}_{\hat{w}}^{(j)}).\end{aligned}\quad (44)$$

By $\operatorname{tr}(A)$ we denote the trace of a matrix A , i.e. $\operatorname{tr}(A) = \sum_i \sum_j A_{ij}$, $\hat{M}_{\hat{w}} = \Lambda' \hat{C} \Lambda$ denotes the estimated version of $M_{\hat{w}}$, and $\hat{M}_{\hat{w}}^{(i)}$, $i = 1, \dots, s+1$, denote the estimated versions of the first partial derivatives of $M_{\hat{w}}$, defined by (78). For more details and explicit forms of the estimators \hat{A}_1 and \hat{A}_2 see Section A.6, (107) and (108).

In order to match the exact values for the scale κ and the denominator degrees of freedom ν 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 $\hat{\nu}^*$, which can be analogically generalized and used to approximate the (null) distribution of the scaled Wald-type F -statistic (40)

$$\begin{aligned}\hat{\kappa}^* &= \frac{\hat{\nu}^*}{\hat{E}^* (\hat{\nu}^* - 2)}, \\ \hat{\nu}^* &= 4 + \frac{2 + q}{q \hat{\varrho}^* - 1},\end{aligned}\quad (45)$$

where

$$\begin{aligned}\hat{\varrho}^* &= \frac{\hat{V}^*}{2\hat{E}^{*2}}, \\ \hat{E}^* &= \left(1 - \frac{\hat{A}_2}{q}\right)^{-1}, \\ \hat{V}^* &= \frac{2}{q} \left(\frac{1 + c_1 \hat{B}}{(1 - c_2 \hat{B})^2 (1 - c_3 \hat{B})} \right),\end{aligned}\quad (46)$$

and

$$\begin{aligned}c_1 &= \frac{g}{3q + 2(1 - g)}, \\ c_2 &= \frac{q - g}{3q + 2(1 - g)}, \\ c_3 &= \frac{q - g + 2}{3q + 2(1 - g)}, \\ g &= \frac{(q + 1)\hat{A}_1 - (q + 4)\hat{A}_2}{(q + 2)\hat{A}_2},\end{aligned}\quad (47)$$

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 Henderson'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 Alnosaier 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 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.

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APPENDIX

A. DERIVATIVES OF THE MSE MATRIX WITH RESPECT TO THE VARIANCE COMPONENTS

Here we shall assume that G^{-1} , the inverse of $G = \operatorname{Var}(u)$, does exist, and thus we can use the MMEs as defined by

(4). 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: $G = \text{Var}(u) = \text{diag}\{\sigma_i^2 I_{r_i}\}$, $i = 1, \dots, s$, and $R = \text{Var}(e) = \sigma_{s+1}^2 I_n$, so $V = \text{Var}(y) = ZGZ' + R = \sum_{i=1}^s \sigma_i^2 Z_i Z_i' + \sigma_{s+1}^2 I_n$.

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 (4)) does exist, in particular we shall assume that the inverse of $X'R^{-1}X$ does exist. Recall that

$$H = (X, Z)'R^{-1}(X, Z) + (0, I_r)'G^{-1}(0, I_r), \quad (48)$$

and so,

$$C = H^{-1} \quad \text{or} \quad H = C^{-1}, \quad (49)$$

Further, we shall denote

$$\Delta_0 = (0, I_r)'(0, I_r), \quad (50)$$

$$\begin{aligned} \Delta_i &= \left(0, \left(0, \dots, I_{r_i}, \dots, 0\right)\right)' \left(0, \left(0, \dots, I_{r_i}, \dots, 0\right)\right) \\ &= \begin{pmatrix} 0 & 0 \\ 0 & \text{diag}_i\{I_{r_i}\} \end{pmatrix}, \end{aligned} \quad (51)$$

$$\Delta_{s+1} = (X, Z)'(X, Z) = H_0, \quad (52)$$

for $i = 1, \dots, s$, where $\text{diag}_i\{I_{r_i}\}$ 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 $\theta = (\theta_1, \dots, \theta_{s+1})'$ as

$$A^{(i)} = \frac{\partial A}{\partial \theta_i}, \quad A^{(i,j)} = \frac{\partial^2 A}{\partial \theta_i \partial \theta_j}, \quad A^{(i,j,k)} = \frac{\partial^3 A}{\partial \theta_i \partial \theta_j \partial \theta_k}, \quad (53)$$

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

Here we shall 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 $G^{(i)}$, $G^{(i,j)}$, $G^{(i,j,k)}$, 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 θ , is given by

$$\frac{\partial}{\partial \theta} A^{-1} = -A^{-1} \frac{\partial A}{\partial \theta} A^{-1}, \quad (54)$$

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

$$\frac{\partial}{\partial \theta} ABA = AB \frac{\partial A}{\partial \theta} + \frac{\partial A}{\partial \theta} BA + A \frac{\partial B}{\partial \theta} A. \quad (55)$$

Let A be an inverse of a symmetric matrix B , i.e. $A = B^{-1}$. Then, based on (54) and (55), we define the following matrix operators:

$$\mathcal{D}^{(i)}(A, B) = -AB^{(i)}A, \quad (56)$$

$$\mathcal{D}^{(i,j)}(A, B) = A \left(B^{(i)}AB^{(j)} + B^{(j)}AB^{(i)} - B^{(i,j)} \right) A, \quad (57)$$

$$\begin{aligned} \mathcal{D}^{(i,j,k)}(A, B) &= -A \left(B^{(i)}AB^{(j)} + B^{(j)}AB^{(i)} - B^{(i,j)} \right) AB^{(k)}A \\ &\quad - AB^{(k)}A \left(B^{(i)}AB^{(j)} + B^{(j)}AB^{(i)} - B^{(i,j)} \right) A \\ &\quad + A \left(B^{(i)}AB^{(j,k)} + B^{(i,k)}AB^{(j)} + B^{(j)}AB^{(i,k)} + B^{(j,k)}AB^{(i)} - \right. \\ &\quad \left. - B^{(i)}AB^{(k)}AB^{(j)} - B^{(j)}AB^{(k)}AB^{(i)} + B^{(i,j,k)} \right) A. \end{aligned} \quad (58)$$

From that we directly get

$$\begin{aligned} C^{(i)} &= \mathcal{D}^{(i)}(C, H) \\ &= -CH^{(i)}C, \end{aligned} \quad (59)$$

$$\begin{aligned} C^{(i,j)} &= \mathcal{D}^{(i,j)}(C, H) \\ &= C \left(H^{(i)}CH^{(j)} + H^{(j)}CH^{(i)} - H^{(i,j)} \right) C, \end{aligned} \quad (60)$$

$$C^{(i,j,k)} = \mathcal{D}^{(i,j,k)}(C, H), \quad (61)$$

for $i, j, k = 1, \dots, s+1$,

Further, based on (48), we directly get the derivatives of the matrix H . For $i, j, k = 1, \dots, s$

$$H^{(i)} = (0, I_r)'G^{-1(i)}(0, I_r), \quad (62)$$

$$H^{(s+1)} = (X, Z)'R^{-1(s+1)}(X, Z), \quad (63)$$

$$H^{(i,j)} = (0, I_r)'G^{-1(i,j)}(0, I_r), \quad (64)$$

$$H^{(s+1,s+1)} = (X, Z)'R^{-1(s+1,s+1)}(X, Z), \quad (65)$$

$$H^{(i,j,k)} = (0, I_r)'G^{-1(i,j,k)}(0, I_r), \quad (66)$$

$$H^{(s+1,s+1,s+1)} = (X, Z)'R^{-1(s+1,s+1,s+1)}(X, Z), \quad (67)$$

where

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

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

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

$$R^{-1(s+1)} = \mathcal{D}^{(s+1)}(R^{-1}, R)$$

$$R^{-1(s+1,s+1)} = \mathcal{D}^{(s+1,s+1)}(R^{-1}, R)$$

$$R^{-1(s+1,s+1,s+1)} = \mathcal{D}^{(s+1,s+1,s+1)}(R^{-1}, R). \quad (68)$$

Notice that

$$H^{(i,s+1)} = H^{(s+1,j)} = 0, \quad i, j \neq s+1 \quad (69)$$

$$H^{(i,j,k)} = 0, \quad (70)$$

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

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

In the simple LMM (10), we get

$$H^{(i)} = -\frac{1}{(\sigma_i^2)^2} \Delta_i, \quad (71)$$

$$H^{(i,i)} = \frac{2}{(\sigma_i^2)^3} \Delta_i, \quad (72)$$

$$H^{(i,i,i)} = -\frac{6}{(\sigma_i^2)^4} \Delta_i, \quad (73)$$

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

$$H^{(i,j)} = 0, \quad \text{and} \quad H^{(i,j,k)} = 0, \quad (74)$$

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

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

By combining (59), (60), (71), (72), and (74), in simple LMM (10), we directly get

$$C^{(i)} = \frac{1}{(\sigma_i^2)^2} C \Delta_i C, \quad (75)$$

$$C^{(i,i)} = \frac{2}{(\sigma_i^2)^4} C (\Delta_i C \Delta_i - \sigma_i^2 \Delta_i) C, \quad (76)$$

$$C^{(i,j)} = \frac{1}{(\sigma_i^2 \sigma_j^2)^2} C (\Delta_i C \Delta_j + \Delta_j C \Delta_i) C, \quad i \neq j, \quad (77)$$

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

The explicit expression for $C^{(i,j,k)}$, i.e. the third partial derivative of C for $i, j, k = 1, \dots, s+1$, is not presented here, however, it can be similarly evaluated based on (61), (71), (72), (73), and (74).

A.3. Derivatives of the MSE matrix $M_{\tilde{w}}$ in simple LMM

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

Let $\tilde{\Lambda}$ be a solution of a system of linear equations $H\tilde{\Lambda} = \Lambda$, i.e. $\tilde{\Lambda} = C\Lambda$, and let $\tilde{\Lambda}$ be decomposed into block-matrices such that $\tilde{\Lambda} = (\tilde{\Lambda}'_0, \tilde{\Lambda}'_1, \dots, \tilde{\Lambda}'_s)'$, where $\tilde{\Lambda}_0$ is $(p \times q)$ -dimensional block-matrix, and $\tilde{\Lambda}_i$, $i = 1, \dots, s$, are $(r_i \times q)$ -dimensional block-matrices of $\tilde{\Lambda}$. Similarly, let $\{C\}_{ij}$ denote the (i, j) -th block² of the matrix C , and let $\{C\}_i$ denote the i -th row-block and $\{C\}_{\cdot i}$ 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 $M_{\tilde{w}}$ with respect to the variance components $\sigma_1^2, \dots, \sigma_s^2, \sigma_{s+1}^2$ as

$$\begin{aligned} M_{\tilde{w}}^{(i)} &= \frac{1}{(\sigma_i^2)^2} \tilde{\Lambda}' \Delta_i \tilde{\Lambda} = \frac{1}{(\sigma_i^2)^2} \tilde{\Lambda}'_i \tilde{\Lambda}_i, \quad i = 1, \dots, s, \\ M_{\tilde{w}}^{(s+1)} &= \frac{1}{(\sigma_{s+1}^2)^2} \tilde{\Lambda}' \Delta_{s+1} \tilde{\Lambda}, \end{aligned} \quad (78)$$

where the matrices Δ_i are defined by (51) and (52). The second partial derivatives of $M_{\tilde{w}}$ are given by:

$$M_{\tilde{w}}^{(i,i)} = \frac{2}{(\sigma_i^2)^4} \tilde{\Lambda}' (\Delta_i C \Delta_i - \sigma_i^2 \Delta_i) \tilde{\Lambda}$$

²Notice that for $i, j = 1, \dots, s$ the block $\{C\}_{ij} = \{C_{22}\}_{ij}$, i.e. it is the (i, j) -th block of the matrix C_{22} , which can be, based on (7), efficiently computed as $C_{22} = \sigma_{s+1}^2 G (\sigma_{s+1}^2 I_r + MG)^{-1}$, where $M = Z'Z - Z'X(X'X)^{-1}X'Z$.

$$= \frac{2}{(\sigma_i^2)^4} (\tilde{\Lambda}'_i \{C\}_{ii} \tilde{\Lambda}_i - \sigma_i^2 \tilde{\Lambda}'_i \tilde{\Lambda}_i), \quad (79)$$

for $i = 1, \dots, s$, and in for $i = s+1$ we get

$$M_{\tilde{w}}^{(s+1,s+1)} = \frac{2}{(\sigma_{s+1}^2)^4} \tilde{\Lambda}' (\Delta_{s+1} C \Delta_{s+1} - \sigma_{s+1}^2 \Delta_{s+1}) \tilde{\Lambda}, \quad (80)$$

Further,

$$\begin{aligned} M_{\tilde{w}}^{(i,j)} &= M_{\tilde{w}}^{(j,i)} \\ &= \frac{1}{(\sigma_i^2 \sigma_j^2)^2} \tilde{\Lambda}' (\Delta_i C \Delta_j + \Delta_j C \Delta_i) \tilde{\Lambda} \\ &= \frac{1}{(\sigma_i^2 \sigma_j^2)^2} (\tilde{\Lambda}'_i \{C\}_{ij} \tilde{\Lambda}_j + \tilde{\Lambda}'_j \{C\}_{ji} \tilde{\Lambda}_i), \end{aligned} \quad (81)$$

for $i \neq j$, $i, j = 1, \dots, s$, and

$$\begin{aligned} M_{\tilde{w}}^{(i,s+1)} &= M_{\tilde{w}}^{(s+1,i)} \\ &= \frac{1}{(\sigma_i^2 \sigma_{s+1}^2)^2} \tilde{\Lambda}' (\Delta_i C \Delta_{s+1} + \Delta_{s+1} C \Delta_i) \tilde{\Lambda}, \\ &= \frac{1}{(\sigma_i^2 \sigma_{s+1}^2)^2} (\tilde{\Lambda}'_i \{C\}_{i, \cdot} \Delta_{s+1} \tilde{\Lambda} \\ &\quad + \tilde{\Lambda}' \Delta_{s+1} \{C\}_{\cdot i} \tilde{\Lambda}_i), \end{aligned} \quad (82)$$

for $i = 1, \dots, s$.

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

According to (33), let us define $\dot{M}_{\delta\tilde{w}}$ by

$$\begin{aligned} \dot{M}_{\delta\tilde{w}} &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} \text{Cov} \left(\frac{\partial(\tilde{w} - w)}{\partial \sigma_i^2}, \frac{\partial(\tilde{w} - w)}{\partial \sigma_j^2} \right), \\ &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} C_{ij} \end{aligned} \quad (83)$$

where Σ_{ij} denote the elements of the variance-covariance matrix Σ of $\hat{\sigma}^2$. Then, by using

$$\tilde{w} - w = \Lambda' C (X, Z)' R^{-1} (y - Xb) - \Lambda' (0, I_r)' u, \quad (84)$$

we get

$$\begin{aligned} \frac{\partial(\tilde{w} - w)}{\partial \sigma_i^2} &= -\Lambda' C H^{(i)} C (X, Z)' R^{-1} (y - Xb) \\ &\quad - \Lambda' C (X, Z)' R^{-1} R^{(i)} R^{-1} (y - Xb). \end{aligned} \quad (85)$$

and then, by taking the covariances of the vectors with $i, j = 1, \dots, s+1$, we get,

$$\begin{aligned} C_{ij} &= \Lambda' C \left(H^{(i)} C (X, Z)' R^{-1} V R^{-1} (X, Z) C H^{(j)} \right. \\ &\quad + H^{(i)} C (X, Z)' R^{-1} V R^{-1} R^{(j)} R^{-1} (X, Z) \\ &\quad \left. + (X, Z)' R^{-1} R^{(i)} R^{-1} V R^{-1} (X, Z) C H^{(j)} \right) \end{aligned}$$

$$+ C(X, Z)' R^{-1} R^{(i)} R^{-1} V R^{-1} R^{(j)} R^{-1} (X, Z) \Big) C \Lambda, \quad (86)$$

where $V = ZGZ' + R$.

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

$$\begin{aligned} \mathbb{C}_{i,j} = & \frac{1}{(\sigma_i^2 \sigma_j^2)^2} \Lambda' C (\Delta_i C H_V C \Delta_j \\ & - 1_{\{i=s+1\}} \sigma_{s+1}^2 H_V C \Delta_j - 1_{\{j=s+1\}} \sigma_{s+1}^2 \Delta_i C H_V \\ & + 1_{\{i=j=s+1\}} (\sigma_{s+1}^2)^2 H_V) C \Lambda, \end{aligned} \quad (87)$$

for $i, j = 1, \dots, s+1$, where $1_{\{i=s+1\}}$, $1_{\{j=s+1\}}$, $1_{\{i=j=s+1\}}$ are the indicator functions, and $H_V = (X, Z)' R^{-1} V R^{-1} (X, Z)$ fulfills the property

$$C H_V C = \begin{pmatrix} C_{11} & 0 \\ 0 & G - C_{22} \end{pmatrix}. \quad (88)$$

Hence, the approximation of the second component of the EBLUP's MSE matrix, i.e. $\dot{M}_{\delta\hat{w}}$, in simple LMM is

$$\dot{M}_{\delta\hat{w}} = \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} \mathbb{C}_{ij}. \quad (89)$$

with \mathbb{C}_{ij} , $i, j = 1, \dots, s+1$, given by (87).

By recognizing that in simple LMM (10) we have $M_{\hat{w}}^{(i,i)} = -2\mathbb{C}_{i,i}$ and $M_{\hat{w}}^{(i,j)} = -(\mathbb{C}_{i,j} + \mathbb{C}_{j,i})$, $i, j = 1, \dots, s+1$, see also [22] eq. (4.6), we get the alternative expression for the approximation of the second component of the EBLUP's MSE matrix in simple LMM, given by

$$\dot{M}_{\delta\hat{w}} = -\frac{1}{2} \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \Sigma_{ij} M_{\hat{w}}^{(i,j)}, \quad (90)$$

where the matrices $M_{\hat{w}}^{(i,j)}$ are given by (79), (80), (81), and (82).

A.5. Bias-corrected estimator of the MSE matrix of EBLUP in simple LMM

In simple LMM (10), the bias-corrected estimator of the MSE matrix of the empirical BLUP of $w = \Lambda'(b', u')'$, i.e. $M_{\hat{w}}$, is given (based on (39) and (90)), as

$$\begin{aligned} \widehat{M}_{\hat{w},A} &= \widehat{M}_{\hat{w}} + 2\widehat{M}_{\delta\hat{w}} \\ &= \widehat{M}_{\hat{w}} - \left(\sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \widehat{\Sigma}_{ij} \widehat{M}_{\hat{w}}^{(i,j)} \right), \end{aligned} \quad (91)$$

and in particular, by using $\widehat{M}_{\hat{w}} = \Lambda' \hat{C} \Lambda$ and (79), (80), (81), and (82), we get

$$\widehat{M}_{\hat{w},A} = \Lambda' \hat{\Lambda} + \frac{4\widehat{\Sigma}_{s+1,s+1}}{(\hat{\sigma}_{s+1}^2)^4} \hat{\Lambda}' (\hat{\sigma}_{s+1}^2 H_0 - H_0 \hat{C} H_0) \hat{\Lambda}$$

$$\begin{aligned} &+ \sum_{i=1}^s \frac{4\widehat{\Sigma}_{ii}}{(\hat{\sigma}_i^2)^4} (\hat{\sigma}_i^2 \hat{\Lambda}'_i \hat{\Lambda}_i - \hat{\Lambda}'_i \{\hat{C}\}_{ii} \hat{\Lambda}_i) \\ &- \sum_{i=1}^s \frac{4\widehat{\Sigma}_{i,s+1}}{(\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2)^2} (\hat{\Lambda}'_i \{\hat{C}\}_{i,} H_0 \hat{\Lambda} + \hat{\Lambda}' H_0 \{\hat{C}\}_{,i} \hat{\Lambda}_i) \\ &- \sum_{i<j}^s \sum_{i<j}^s \frac{4\widehat{\Sigma}_{ij}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)^2} (\hat{\Lambda}'_i \{\hat{C}\}_{ij} \hat{\Lambda}_j + \hat{\Lambda}'_j \{\hat{C}\}_{ji} \hat{\Lambda}_i), \end{aligned} \quad (92)$$

where $\hat{\Lambda} = \hat{C} \Lambda$, $H_0 = \Delta_{s+1} = (X, Z)' (X, Z)$, and $\widehat{\Sigma}$, (with elements $\widehat{\Sigma}_{ij}$, $i, j = 1, \dots, s+1$), is the estimated variance-covariance matrix of the REML estimator $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$. Here, $\hat{\Lambda} = (\hat{\Lambda}'_0, \hat{\Lambda}'_1, \dots, \hat{\Lambda}'_s)'$ is decomposed into block-matrices such that $\hat{\Lambda}_0$ is $(p \times q)$ -dimensional block-matrix, and $\hat{\Lambda}_i$, $i = 1, \dots, s$, are $(r_i \times q)$ -dimensional block-matrices of $\hat{\Lambda}$. Similarly, $\{\hat{C}\}_{ij}$ denote the (i, j) -th $(r_i \times r_j)$ -dimensional block of the matrix \hat{C} , and $\{\hat{C}\}_{i,}$ denote the i -th $(r_i \times (p+r))$ -dimensional row-block and $\{\hat{C}\}_{,i}$ the i -th $((p+r) \times r_i)$ -dimensional column-block of the matrix \hat{C} .

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

$$\kappa F_* = \frac{\kappa}{q} (\hat{w} - w)' \left(\widehat{M}_{\hat{w},A} \right)^{-1} (\hat{w} - w) \stackrel{approx.}{\sim} F_{q,\nu}, \quad (93)$$

where $\widehat{M}_{\hat{w},A}$ is given by (92).

The moment based estimators of the parameters κ and ν are based on comparing the first and the second moments of the scaled F -statistic (93) with the moments of the F -distribution with q and ν degrees of freedom, i.e. by solving the system of equations

$$\begin{aligned} E(\kappa F_*) &= \kappa E_* \cong E = E(F_{q,\nu}), \\ \text{Var}(\kappa F_*) &= \kappa^2 V_* \cong V = \text{Var}(F_{q,\nu}), \end{aligned} \quad (94)$$

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

$$\begin{aligned} E &= \frac{\nu}{\nu-2}, \\ V &= \frac{2\nu^2(\nu+q-2)}{q(\nu-2)^2(\nu-4)} \\ &= \frac{2E^2 \nu + q - 2}{q \nu - 4}, \end{aligned} \quad (95)$$

provided that $\nu > 4$. By denoting

$$\varrho = \frac{V}{2E^2} \quad (96)$$

we get

$$\nu = 4 + \frac{q+2}{q\varrho-1}, \quad (97)$$

and consequently, the moment estimators of κ and ν are given as

$$\begin{aligned}\tilde{\kappa} &= \frac{\tilde{\nu}}{E_*(\tilde{\nu}-2)} \\ \tilde{\nu} &= 4 + \frac{q+2}{q\tilde{\varrho}-1},\end{aligned}\quad (98)$$

where

$$\tilde{\varrho} = \frac{V_*}{2E_*^2}.\quad (99)$$

The expectation and the variance of the statistic F_* defined by (93) can be estimated by using

$$\begin{aligned}E_* &= E(F_*) = E_{\hat{\sigma}^2}(E_{\hat{w}}(F_*|\hat{\sigma}^2)) \\ V_* &= \text{Var}(F_*) = E_{\hat{\sigma}^2}(\text{Var}_{\hat{w}}(F_*|\hat{\sigma}^2)) \\ &\quad + \text{Var}_{\hat{\sigma}^2}(E_{\hat{w}}(F_*|\hat{\sigma}^2)).\end{aligned}\quad (100)$$

Alnoaiser in [1] derived approximations for E_* and V_* in the special case, when the F -statistic (93) 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 (93)), is not presented here. However, in analogy with the derivation of the approximations presented in [1], we suggest \hat{E}_* and \hat{V}_* , as the approximations of E_* and V_* , in the following form

$$\begin{aligned}\hat{E}_* &= 1 + \frac{A_2}{q}, \\ \hat{V}_* &= \frac{2}{q}(1+B),\end{aligned}\quad (101)$$

where

$$\begin{aligned}B &= \frac{1}{2q}(A_1 + 6A_2), \\ A_1 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \text{tr}(M_w^{-1} M_w^{(i)}) \text{tr}(M_w^{-1} M_w^{(j)}), \\ A_2 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \text{tr}(M_w^{-1} M_w^{(i)} M_w^{-1} M_w^{(j)}).\end{aligned}\quad (102)$$

The suggested approximations depend on the unknown variance components $\sigma^2 = (\sigma_1^2, \dots, \sigma_{s+1}^2)'$. Consequently, the suggested estimators of the parameters κ and ν , based on the estimated versions of (98), are

$$\begin{aligned}\hat{\kappa} &= \frac{\hat{\nu}}{\hat{E}_*(\hat{\nu}-2)} \\ \hat{\nu} &= 4 + \frac{q+2}{q\hat{\varrho}-1},\end{aligned}\quad (103)$$

where

$$\hat{\varrho} = \frac{\hat{V}_*}{2\hat{E}_*^2},\quad (104)$$

and

$$\hat{E}_* = 1 + \frac{\hat{A}_2}{q},$$

$$\hat{V}_* = \frac{2}{q}(1+\hat{B}),\quad (105)$$

with

$$\begin{aligned}\hat{B} &= \frac{1}{2q}(\hat{A}_1 + 6\hat{A}_2), \\ \hat{A}_1 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \text{tr}(\hat{M}_w^{-1} \hat{M}_w^{(i)}) \text{tr}(\hat{M}_w^{-1} \hat{M}_w^{(j)}), \\ \hat{A}_2 &= \sum_{i=1}^{s+1} \sum_{j=1}^{s+1} \hat{\Sigma}_{ij} \text{tr}(\hat{M}_w^{-1} \hat{M}_w^{(i)} \hat{M}_w^{-1} \hat{M}_w^{(j)}).\end{aligned}\quad (106)$$

In particular, by using $\hat{M}_w = \Lambda' \hat{C} \Lambda = \Lambda' \hat{\Lambda}$ and (78), we finally get

$$\begin{aligned}\hat{A}_1 &= \sum_{i=1}^s \frac{\hat{\Sigma}_{ii}}{(\hat{\sigma}_i^2)^4} \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i)^2 \\ &\quad + \sum_{i < j}^s \sum_{j=1}^s \frac{2\hat{\Sigma}_{ij}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)^2} \\ &\quad \times \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i) \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_j' \hat{\Lambda}_j) \\ &\quad + \sum_{i=1}^s \frac{2\hat{\Sigma}_{i,s+1}}{(\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2)^2} \\ &\quad \times \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i) \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}' H_0 \hat{\Lambda}) \\ &\quad + \frac{\hat{\Sigma}_{s+1,s+1}}{(\hat{\sigma}_{s+1}^2)^4} \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}' H_0 \hat{\Lambda})^2,\end{aligned}\quad (107)$$

$$\begin{aligned}\hat{A}_2 &= \sum_{i=1}^s \frac{\hat{\Sigma}_{ii}}{(\hat{\sigma}_i^2)^4} \text{tr}(((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i)^2) \\ &\quad + \sum_{i < j}^s \sum_{j=1}^s \frac{2\hat{\Sigma}_{ij}}{(\hat{\sigma}_i^2 \hat{\sigma}_j^2)^2} \\ &\quad \times \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i (\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_j' \hat{\Lambda}_j) \\ &\quad + \sum_{i=1}^s \frac{2\hat{\Sigma}_{i,s+1}}{(\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2)^2} \\ &\quad \times \text{tr}((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}_i' \hat{\Lambda}_i (\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}' H_0 \hat{\Lambda}) \\ &\quad + \frac{\hat{\Sigma}_{s+1,s+1}}{(\hat{\sigma}_{s+1}^2)^4} \text{tr}(((\Lambda' \hat{\Lambda})^{-1} \hat{\Lambda}' H_0 \hat{\Lambda})^2),\end{aligned}\quad (108)$$

as before, $\hat{\Lambda} = \hat{C} \Lambda$, $H_0 = \Delta_{s+1} = (X, Z)'(X, Z)$, and $\hat{\Sigma}$, (with elements $\hat{\Sigma}_{ij}$, $i, j = 1, \dots, s+1$), is the estimated variance-covariance matrix of the REML estimator $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$. $\hat{\Lambda} = (\hat{\Lambda}_0', \hat{\Lambda}_1', \dots, \hat{\Lambda}_s')'$ is decomposed into block-matrices such that $\hat{\Lambda}_0$ is $(p \times q)$ -dimensional block-matrix, and $\hat{\Lambda}_i$, $i = 1, \dots, s$, are $(r_i \times q)$ -dimensional block-matrices of $\hat{\Lambda}$. Similarly, $\{\hat{C}\}_{ij}$ denote the (i, j) -th $(r_i \times r_j)$ -dimensional block of the matrix \hat{C} , and $\{\hat{C}\}_{i \cdot}$ denote the i -th $(r_i \times (p+r))$ -dimensional row-block and $\{\hat{C}\}_{\cdot i}$ the i -th $((p+r) \times r_i)$ -dimensional column-block of the matrix \hat{C} .

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 $V^{(t)} = \sigma_{s+1}^{2(t)} I_r + Z'ZG^{(t)}$, $G^{(t)} = \text{diag}(\sigma_i^{2(t)} I_{r_i})$. The algorithm starts with the choice of the starting values for variance components $\sigma^{2(0)} = (\sigma_1^{2(0)}, \dots, \sigma_{s+1}^{2(0)})'$ and setting $t = 0$. In the t -th step of the procedure the algorithm solves the system of mixed model equations:

$$\begin{pmatrix} X'X & X'ZG^{(t)} \\ Z'X & V^{(t)} \end{pmatrix} \begin{pmatrix} \tilde{b}^{(t)} \\ \tilde{v}^{(t)} \end{pmatrix} = \begin{pmatrix} X'y \\ Z'y \end{pmatrix}, \quad (109)$$

and $\tilde{u}^{(t)} = G^{(t)}\tilde{v}^{(t)}$.

B.1. ML estimates of the variance components

The ML estimates of the variance components are calculated iteratively as

$$\begin{aligned} \sigma_i^{2(t+1)} &= \frac{\tilde{u}_i^{(t)'} \tilde{u}_i^{(t)}}{r_i - \text{tr}(W_{ii}^{(t)}), \quad i = 1, \dots, s, \\ \sigma_{s+1}^{2(t+1)} &= \frac{y'(y - X\tilde{b}^{(t)} - Z\tilde{u}^{(t)})}{n}, \end{aligned} \quad (110)$$

where $\tilde{u}_i^{(t)}$ is the i -th r_i -dimensional subvector of $\tilde{u}^{(t)}$ and $W_{ii}^{(t)}$ is the i -th diagonal block of the matrix $W^{(t)}$, where

$$W^{(t)} = \sigma_{s+1}^{2(t)} V^{(t)-1} = \sigma_{s+1}^{2(t)} (\sigma_{s+1}^{2(t)} I_r + Z'ZG^{(t)})^{-1}. \quad (111)$$

The iterative procedure should be stopped after the t -th step if $\|\sigma^{2(t)} - \sigma^{2(t-1)}\| < \varepsilon$, for the chosen precision limit ε , and where $\sigma^{2(t)} = (\sigma_1^{2(t)}, \dots, \sigma_{s+1}^{2(t)})'$.

The final solutions of the iterative procedure are denoted by \hat{b} , $\hat{u} = (\hat{u}'_1, \dots, \hat{u}'_s)'$, and $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$. 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

$$\begin{aligned} \text{loglik}_{ML} &= -\frac{1}{2} n \log(2\pi) - \frac{1}{2} \log(|\hat{V}|) \\ &\quad - \frac{1}{2} (y - X\hat{b})' \hat{V}^{-1} (y - X\hat{b}), \\ &= -\frac{1}{2} (n \log(2\pi \hat{\sigma}_{s+1}^2) - \log(|\hat{W}|) + n), \end{aligned} \quad (112)$$

where $\hat{V} = Z\hat{G}Z' + \hat{\sigma}_{s+1}^2 I_n$ and $\hat{W} = (I_r + Z'Z\hat{G}/\hat{\sigma}_{s+1}^2)^{-1}$.

The Fisher information matrix (which is in fact the inverse of the asymptotic variance-covariance matrix) of the ML estimators of the variance components, say $I_{ML}(\hat{\sigma}^2)$, can be evaluated at the ML estimates $\hat{\sigma}^2$ as

$$I_{ML}(\hat{\sigma}^2) = \frac{1}{2} \times \begin{pmatrix} \left\{ \frac{\delta_{ij}[r_i - 2\text{tr}(\hat{W}_{ii}) + \text{tr}(\hat{W}_{ij}\hat{W}_{ji})]}{\hat{\sigma}_i^2 \hat{\sigma}_j^2} \right\}_{i,j=1}^s & \left\{ \frac{\text{tr}(\hat{W}_{ii}) - \sum_j^s \text{tr}(\hat{W}_{ij}\hat{W}_{ji})}{\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2} \right\}_{i=1}^s \\ \left\{ \frac{\text{tr}(\hat{W}_{ii}) - \sum_j^s \text{tr}(\hat{W}_{ij}\hat{W}_{ji})}{\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2} \right\}_{i=1}^s & \frac{n - m + \text{tr}(\hat{W}^2)}{\hat{\sigma}_{s+1}^4} \end{pmatrix}, \quad (113)$$

where $\delta_{ij} = 1$ if $i = j$, otherwise $\delta_{ij} = 0$, and \hat{W}_{ij} is the $(r_i \times r_j)$ block of the matrix \hat{W} .

B.2. REML estimates of the variance components

Similarly, the REML estimates of the variance components are calculated iteratively as

$$\begin{aligned} \sigma_i^{2(t+1)} &= \frac{\tilde{u}_i^{(t)'} \tilde{u}_i^{(t)}}{r_i - \text{tr}(T_{ii}^{(t)}), \quad i = 1, \dots, s, \\ \sigma_{s+1}^{2(t+1)} &= \frac{y'(y - X\tilde{b}^{(t)} - Z\tilde{u}^{(t)})}{n - r_X}, \end{aligned} \quad (114)$$

where by r_X we denote the rank of the matrix X , $\tilde{u}_i^{(t)}$ is the i -th r_i -dimensional subvector of $\tilde{u}^{(t)}$ and $T_{ii}^{(t)}$ is the i -th diagonal block of the matrix $T^{(t)}$, where

$$T^{(t)} = \sigma_{s+1}^{2(t)} (\sigma_{s+1}^{2(t)} I_r + MG^{(t)})^{-1}, \quad (115)$$

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

$$\begin{aligned} \text{loglik}_{REML} &= -\frac{1}{2} (n - r_X) \log(2\pi) - \frac{1}{2} \log(|B' \hat{V} B|) \\ &\quad - \frac{1}{2} y' B (B' \hat{V} B)^{-1} B' y, \\ &= -\frac{1}{2} (n - r_X) \log(2\pi \hat{\sigma}_{s+1}^2) \\ &\quad - \frac{1}{2} (-\log(|\hat{T}|) + (n - r_X)), \end{aligned} \quad (116)$$

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

The Fisher information matrix of the REML estimators of the variance components, $I_{REML}(\hat{\sigma}^2)$, can be evaluated at the REML estimates $\hat{\sigma}^2$ as

$$I_{REML}(\hat{\sigma}^2) = \frac{1}{2} \times \begin{pmatrix} \left\{ \frac{\delta_{ij}[r_i - 2\text{tr}(\hat{T}_{ii}) + \text{tr}(\hat{T}_{ij}\hat{T}_{ji})]}{\hat{\sigma}_i^2 \hat{\sigma}_j^2} \right\}_{i,j=1}^s & \left\{ \frac{\text{tr}(\hat{T}_{ii}) - \sum_j^s \text{tr}(\hat{T}_{ij}\hat{T}_{ji})}{\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2} \right\}_{i=1}^s \\ \left\{ \frac{\text{tr}(\hat{T}_{ii}) - \sum_j^s \text{tr}(\hat{T}_{ij}\hat{T}_{ji})}{\hat{\sigma}_i^2 \hat{\sigma}_{s+1}^2} \right\}_{i=1}^s & \frac{n - r_X - r + \text{tr}(\hat{T}^2)}{\hat{\sigma}_{s+1}^4} \end{pmatrix}, \quad (117)$$

where $\delta_{ij} = 1$ 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} , $\hat{u} = (\hat{u}'_1, \dots, \hat{u}'_s)'$, and $\hat{\sigma}^2 = (\hat{\sigma}_1^2, \dots, \hat{\sigma}_{s+1}^2)'$. 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).

B.3. MINQE's of the variance components

For completeness, here we present procedures to calculate the MINQE(I) and the MINQE(U,I) estimators of the variance components at given (prior) values of the variance components $\sigma^{2(0)} = (\sigma_1^{2(0)}, \dots, \sigma_{s+1}^{2(0)})'$. Here we assume that $\sigma_i^{2(0)} > 0$ for all $i = 1, \dots, s + 1$. For more details on minimum norm quadratic estimation of the variance components see e.g. [33], [42], and [43].

The MINQE(I) of σ^2 , say $\hat{\sigma}^2$, at the prior value $\sigma^{2(0)}$ is defined as the solution of the following system of equations

$$H_{(I)}\hat{\sigma}^2 = q, \tag{118}$$

where by $H_{(I)}$ we denote the $(s + 1 \times s + 1)$ -dimensional MINQE(I)-matrix and $q = (q_1, \dots, q_{s+1})'$ denotes the vector of MINQE quadratic forms. The matrix $H_{(I)}$ is defined by its elements as

$$\{H_{(I)}\}_{ij} = \text{tr}\left(V^{(0)-1} V_i V^{(0)-1} V_j\right), \tag{119}$$

$i, j = 1, \dots, s + 1$, where $V_i = Z_i Z_i'$, for $i = 1, \dots, s$, $V_{s+1} = I_n$, and $V^{(0)} = ZG^{(0)}Z' + \sigma_{s+1}^{2(0)}I_n = \sum_{i=1}^{s+1} \sigma_i^{2(0)}V_i$. The matrix $H_{(I)}$ can be easily evaluated by using (113), namely

$$H_{(I)} = 2I_{ML}(\sigma^{2(0)}). \tag{120}$$

Further, the vector q of MINQE quadratic forms, defined by its elements as

$$q_i = y' (M_X V^{(0)} M_X)^+ V_i (M_X V^{(0)} M_X)^+ y, \tag{121}$$

$i = 1, \dots, s + 1$, with $M_X = I_n - X(X'X)^-X$, could be easily evaluated by using

$$\begin{aligned} q_i &= \frac{\tilde{u}_i^{(0)'} \tilde{u}_i^{(0)}}{(\sigma_i^{2(0)})^2}, \quad i = 1, \dots, s, \\ q_{s+1} &= \frac{(y - X\tilde{b}^{(0)} - Z\tilde{u}^{(0)})' (y - X\tilde{b}^{(0)} - Z\tilde{u}^{(0)})}{(\sigma_{s+1}^{2(0)})^2}, \end{aligned} \tag{122}$$

where $\tilde{u}_i^{(0)}$ is the i -th r_i -dimensional subvector of $\tilde{u}^{(0)}$.

Similarly, the MINQE(U,I) of σ^2 , say $\hat{\sigma}^2$, at the prior value $\sigma^{2(0)}$ is defined as the solution of the following system of equations

$$H_{(UI)}\hat{\sigma}^2 = q, \tag{123}$$

where $H_{(UI)}$ denotes the $(s + 1 \times s + 1)$ -dimensional MINQE(U,I) matrix, defined by its elements

$$\{H_{(UI)}\}_{ij} = \text{tr}\left((M_X V^{(0)} M_X)^+ V_i (M_X V^{(0)} M_X)^+ V_j\right), \tag{124}$$

$i, j = 1, \dots, s + 1$, and by using (117) we get

$$H_{(UI)} = 2I_{REML}(\sigma^{2(0)}). \tag{125}$$

Note that the MINQE $\hat{\sigma}^2$, defined by (118) or by (123), is not given uniquely unless the MINQE matrix is of full rank. In fact, one version of the solution to the MINQE equations is $\hat{\sigma}^2 = H^+ q$, where H^+ denote the Moore-Penrose g -inverse of the appropriate MINQE matrix.

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

$$\begin{aligned} E(F\hat{\sigma}^2) &= F\sigma^2, \\ \text{Var}(F\hat{\sigma}^2 | \sigma^{2(0)}) &= 2FH_{(UI)}F' \\ &= 2A'H_{(UI)}A. \end{aligned} \tag{126}$$

On the other hand, the MINQE(I) $F\hat{\sigma}^2$ is a biased estimator of $F\sigma^2$ with

$$\begin{aligned} E(F\hat{\sigma}^2) &= FH_{(I)}^- H_{(UI)}\sigma^2, \\ \text{Var}(F\hat{\sigma}^2 | \sigma^{2(0)}) &= 2FH_{(I)}^- H_{(UI)}H_{(I)}^- F'. \end{aligned} \tag{127}$$

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