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This chapter is broken into two parts. The first part is a review of diagnostics methods for linear models, intended to acquaint the reader with the subject, and also to provide a basis for material covered in the second part. Particular attention is drawn to graphical methods.

The second part of the chapter looks at diagnostics techniques for LME models, firstly covering the theory, then proceeding to a discussion on implementing these using **R** code. While a substantial body of work has been developed in this area, there are still areas worth exploring. In particular the development of graphical techniques pertinent to LME models should be looked at.

## 0.1 Introduction

### 0.1.1 Robinson's (1991) review

*Robinson's (1991) review of best linear unbiased prediction (BLUP), together with the subsequent discussion, has emphasized the very considerable range of models that may be addressed via the general least squares (GLS) solution to the general linear model  $Y = X\beta + \varepsilon$ , where  $E(\varepsilon) = 0$  and  $\text{var}(\varepsilon) = V$ . These include linear mixed models, geostatistics, time series and multivariate regression.*

*The texts by Christensen (1996, 1991) and the connections to modern topics of image analysis, quality analysis, Bayesian methods, and splines (all in Robinson and discussion) make it an eminently suitable topic for teaching in any course concerning statistical linear models.*

*Nevertheless some of the matrix algebra that results from solving the normal equations for individual specifications of the general linear model will be daunting, and far from intuitive for many students, even those who are at home in linear space. The conventional approach to prediction and estimation from data  $Y$  associated with covariates  $X$  via the general linear model  $Y = X\beta + \varepsilon$  is essentially a two-stage process.*

The first stage is to determine the best, in the GLS sense, estimator  $\hat{\beta}$  of  $\beta$  and subsequently to determine everything else from this.

The estimator is said to be best if it minimizes the generalization of the sum of squares  $\hat{e}^t V^{-1} \hat{e}$ , where  $\hat{e} = Y - X\hat{\beta}$

It is straightforward to show that  $\hat{\beta} = (X^t V^{-1} X)^{-1} X^t V^{-1} Y = B Y$  and at the minimum the sum of squares is  $Y^t (V^{-1} - V^{-1} (X^t V^{-1} X)^{-1} X^t V^{-1}) Y = Y^t Q Y$ .

*The purpose of this note is to give emphasis to one derivation, based on Lagrange multipliers, which leads to a system of equations that is very intuitive and lends itself readily to specialization. This approach is in fact standard in the geostatistical treatment of **kriging** (see Matheron 1962; Journel and Huijbregts 1981; Ripley 1981; Cressie 1993). In the genetics literature it is associated with the name of Henderson (1983); or in the classical statistical literature Hocking (1996, p. 73) is a suitable reference.*

*The approach based on Lagrange multipliers deemphasizes the explicit determination of  $\hat{\beta}$  and leads to a clearer understanding of the complementary (but for some confusing) tasks known as best linear unbiased estimation (BLUE) and best linear unbiased prediction (BLUP). Regrettably, Robinson-despite offering four derivations, and having as his main concern the interplay of BLUP and BLUE-gives it little prominence.*

It has recently been discussed by Searle (1997, p; 278) who said that it makes another approach (Searle, Casella, and McCulloch 1992, p. 271) seem "obtuse and unnecessarily complicated." By contrast, our treatment emphasizes the fact that it leads to a single set of equations whose solution sheds simplifying light on very many issues in general least squares.

The American Statistician's Teacher's Corner (e.g., McLean, Sanders, and Stroup 1991; Puntanen and Styan 1989) has already played host to previous attempts to simplify the explanation of such topics. Various authors (CPJ, Haslett Hayes, Martin) have visited the more specialized area of diagnostics and have developed **down-dating** (leave- $k$ -out) formulas.

The conventional approach here is via tricky identities based on the inverses of partitioned matrices. Here again the Lagrange system of equations leads to a much simplified and-we claim-much more intuitive derivation of these more technical results.

*The essence of the approach is to seek that linear combination of the available data  $Y$  which is best for the estimation of  $Z$  among those linear estimators which are constrained to be unbiased. We adopt therefore a constrained minimization approach, using Lagrange multipliers. By best we mean that combination  $\hat{Z}(Y) = \lambda_z^t Y$  which has least mean square error  $E(Z - \lambda_z^t Y)^2$ , and by unbiased we mean  $E(Z - \lambda_z^t Y) = 0$ . Here  $Z$  denotes that scalar which is to be the objective of the estimation. This estimator is written as  $\hat{Z}(Y)$  to make its dependence on  $Y$  explicit. Note that the term "best" is applied in the context of minimizing the prediction variance  $var(Z - \hat{Z}(Y))$ . We shall see that  $Z$  may be used to denote either a random variable or an unknown parameter, and that it will be sufficient to specify  $Z$  via  $E[Z]$  and  $cov(Z, Y)$ . If  $Z$  is not a random variable then of course the latter is zero and  $E[Z] = Z$ . We establish-very simply, as below-a general solution in terms of  $A$  and  $cov(Z, Y)$  and achieve particular tasks by identification of these. Our presentation is for a scalar  $Z$ , but the notation facilitates generalization to vector  $Z$ .*

## 0.2 Predictors and Estimators

*We note that Robinson (1991) stated "A convention has somehow developed that estimators of random effects are called predictors while estimators of fixed effects are called estimators." We agree that this distinction is confusing and indeed unnecessary.*

We seek  $\hat{Z}(Y) = \lambda_z^t Y$ , where  $\lambda_z^t$  is an  $n \times 1$  vector of estimation coefficients. It is convenient to specify  $E[Z] = A\beta$  for known  $A$ . In this context  $A$  denotes a row vector, but we generalize this in the following. The constraint requiring  $\hat{Z}(Y)$  to be unbiased now reduces to  $(A - \lambda_z^t X) = 0$ . A solution is found by minimizing  $var(Z - \lambda_z^t Y) + \gamma_z^t (X^t \lambda_z - A^t)$ , where  $\gamma_z$  is a  $p \times 1$  vector of Lagrange multipliers, where  $p$  is the length of the parameter vector  $\beta$ . Setting to zero the derivatives with respect to  $\lambda_z$  and  $\gamma_z$  yields the system.

$$\begin{pmatrix} V & X \\ X^t & 0 \end{pmatrix} \begin{pmatrix} \lambda_z \\ \gamma_z \end{pmatrix} = \begin{pmatrix} cov(Y, Z) \\ A^t \end{pmatrix} \quad (1)$$

If the inverse exists we have that

$$\begin{pmatrix} \lambda_z \\ \gamma_z \end{pmatrix} = \begin{pmatrix} V & X \\ X^t & 0 \end{pmatrix}^{-1} \begin{pmatrix} cov(Y, Z) \\ A^t \end{pmatrix} \quad (2)$$

so that

$$\hat{Z}(Y) = \begin{pmatrix} \lambda_z^t & \gamma_z^t \end{pmatrix} \begin{pmatrix} Y \\ 0 \end{pmatrix}$$

In terms of the estimation problem being considered the square matrix on the left-hand side of (1) concerns "what we have," namely, the data plus constraints.

The matrix does not depend on  $Z$  and consequently need only be constructed once before application to a range of problems. The right-hand side contains the term  $cov(Z, Y)$  and can be specified for whatever  $Z$  is being considered.

It is this feature of system (1) that makes a generic approach to estimation possible.  
Model Diagnostics

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## Abstract

This chapter is broken into two parts. The first part is a review of diagnostics methods for linear models, intended to acquaint the reader with the subject, and also to provide a basis for material covered in the second part. Particular attention is drawn to graphical methods.

# 1 Framework for Model Validation using Residual Diagnostics

In statistical modelling, the process of model validation is a critical step, but also a step that is too often overlooked. A very simple procedure is to examine commonly encountered metrics, such as the  $R^2$  value. However, using a small handful of simple measures and methods is insufficient to properly assess the quality of a fitted model. To do so properly, a full and comprehensive analysis that tests of all of the assumptions, as far as possible, must be carried out. A statistical model, whether of the fixed-effects or mixed-effects variety, represents how you think your data were generated. Following model specification and estimation, it is of interest to explore the model-data agreement by raising questions such as

- Does the model-data agreement support the model assumptions?
- Should model components be refined, and if so, which components? For example, should regressors be added or removed, and is the covariation of the observations modeled properly?
- Are the results sensitive to model and/or data? Are individual data points or groups of cases particularly influential on the analysis?

## 1.1 Residual Analysis

A residual is the difference between an observed quantity and its estimated or predicted value. Residual analysis is a widely used model validation technique. A residual is simply the difference between an observed value and the corresponding fitted value, as predicted by the model. The rationale is that, if the model is properly fitted to the model, then the residuals would approximate the random errors that one should expect. that is to say, if the residuals behave randomly, with no discernible trend, the model has fitted the data well. If some sort of non-random trend is evident in the model, then the model can be considered to be poorly fitted. Statistical software environments, such as the R Programming language, provides a suite of tests and graphical procedure sfor appraising a fitted linear model, with several of these procedures analysing the model residuals.

In classical linear models, an examination of model-data agreement has traditionally revolved around

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While a substantial body of work has been developed in this area, there is still areas worth exploring. In particular the development of graphical techniques pertinent to LME models should be looked at.



## 2 Model Validation Framework

In statistical modelling, the process of model validation is a critical step of model fitting process, but also a step that is too often overlooked. A very simple procedure is to examine commonly-used metrics, such as the  $R^2$  value. However, using a small handful of simple measures and methods is insufficient to properly assess the quality of a fitted model. To do so properly, a full and comprehensive analysis that tests of all of the assumptions, as far as possible, must be carried out.

Schabenberger (2005) describes the model validation framework as comprised of the following tasks [origin/master](#)

- overall measures of goodness-of-fit
- the informal, graphical examination of estimates of model errors to assess the quality of distributional assumptions: residual analysis
- the quantitative assessment of the inter-relationship of model components; for example, collinearity diagnostics
- the qualitative and quantitative assessment of influence of cases on the analysis, i.e. influence analysis.

**HEAD** The sensitivity of a model is studied through measures that express its stability under perturbations. You are not interested in a model that is either overly stable or overly sensitive. Changes in the data or model components should produce commensurate changes in the model output. The difficulty is to determine when the changes are substantive enough to warrant further investigation, possibly leading to a reformulation of the model or changes in the data (such as dropping outliers). This paper is primarily concerned with stability of linear mixed models to perturbations of the data; that is, with influence analysis. =====

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Statistical software environments, such as the R Programming language, provides a suite of tests and graphical procedure sfor appraising a fitted linear model, with several of these procedures analysing the model residuals.

### 2.1 Outliers and Leverage

The question of whether or not a point should be considered an outlier must also be addressed. An outlier is an observation whose true value is unusual given its value

on the predictor variables. The leverage of an observation is a further consideration. Leverage describes an observation with an extreme value on a predictor variable is a point with high leverage. High leverage points can have a great amount of effect on the estimate of regression coefficients.

Influence can be thought of as the product of leverage and outlierness. An observation is said to be influential if removing the observation substantially changes the estimate of the regression coefficients. The R programming language has a variety of methods used to study each of the aspects for a linear model. While linear models and GLMS can be studied with a wide range of well-established diagnostic techniques, the choice of methodology is much more restricted for the case of LMEs.

For classical linear models, residual diagnostics are typically conducted using a plot of the observed residuals and the predicted values. A visual inspection for the presence of trends inform the analyst on the validity of distributional assumptions, and to detect outliers and influential observations.

## 2.2 Matrix Notation for Case Deletion

For notational simplicity,  $\mathbf{A}(i)$  denotes an  $n \times m$  matrix  $\mathbf{A}$  with the  $i$ -th row removed,  $a_i$  denotes the  $i$ -th row of  $\mathbf{A}$ , and  $a_{ij}$  denotes the  $(i, j)$ -th element of  $\mathbf{A}$ .

## 2.3 Extension of Diagnostic Methods to LME models

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When similar notions of statistical influence are applied to mixed models, things are more complicated. Removing data points affects fixed effects and covariance parameter estimates. Update formulas for *leave-one-out* estimates typically fail to account for changes in covariance parameters.

? noted the case deletion diagnostics techniques have not been applied to linear mixed effects models and seeks to develop methodologies in that respect. ? develops these techniques in the context of REML. ===== Christensen et al. (1992) noted the case deletion diagnostics techniques had not been applied to linear mixed effects models and seeks to develop methodologies in that respect. Christensen et al. (1992) develops these techniques in the context of REML. llllllll origin/master

Demidenko (2004) extends several regression diagnostic techniques commonly used in linear regression, such as leverage, infinitesimal influence, case deletion diagnostics, Cook's distance, and local influence to the linear mixed-effects model. In each case, the proposed new measure has a direct interpretation in terms of the effects on a parameter of interest, and reduces to the familiar linear regression measure when there are no random effects.

The new measures that are proposed by Demidenko (2004) are explicitly defined functions and do not require re-estimation of the model, especially for cluster deletion diagnostics. The basis for both the cluster deletion diagnostics and Cook's distance

is a generalization of Miller's simple update formula for case deletion for linear models. Furthermore Demidenko (2004) shows how Pregibon's infinitesimal case deletion diagnostics is adapted to the linear mixed-effects model.

Demidenko (2004) proposes two likelihood-based diagnostics for identifying individuals that can influence the choice between two competing models.

## 3 Analysis of Influence

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### 3.1 Further Assumptions of Linear Models

As with fitted models, the assumption of normality of residuals and homogeneity of variance is applicable to LMEs also.

Homoscedascity is the technical term to describe the variance of the residuals being constant across the range of predicted values. Heteroscedascity is the converse scenario : the variance differs along the range of values.

In recent years, mixed models have become invaluable tools in the analysis of experimental and observational data. In these models, more than one term can be subject to random variation. Mixed model technology enables you to analyze complex experimental data with hierarchical random processes, temporal, longitudinal, and spatial data, to name just a few important applications.

### 3.2 Stating the LME Model

The general linear mixed model is

$$Y = X\beta + Zu + \varepsilon$$

where  $Y$  is a  $(n \times 1)$  vector of observed data,  $X$  is an  $(n \times p)$  fixed-effects design or regressor matrix of rank  $k$ ,  $Z$  is a  $(n \times g)$  random-effects design or regressor matrix,  $u$  is a  $(g \times 1)$  vector of random effects, and  $\varepsilon$  is an  $(n \times 1)$  vector of model errors (also random effects). The distributional assumptions made by the MIXED procedure are as follows:  $u$  is normal with mean 0 and variance  $G$ ;  $\varepsilon$  is normal with mean 0 and variance  $R$ ; the random components  $u$  and  $\varepsilon$  are independent. Parameters of this model are the fixed-effects  $\beta$  and all unknowns in the variance matrices  $G$  and  $R$ . The unknown variance elements are referred to as the covariance parameters and collected in the vector *theta*.

The concept of critiquing the model-data agreement applies in mixed models in the same way as in linear fixed-effects models. In fact, because of the more complex model structure, you can argue that model and data diagnostics are even more important. For example, you are not only concerned with capturing the important variables in the model. You are also concerned with distributing them correctly between the fixed and random components of the model. The mixed model structure presents unique and interesting challenges that prompt us to reexamine the traditional ideas of influence and residual analysis. This paper presents the extension of traditional tools and statistical measures for influence and residual analysis to the linear mixed model and demonstrates their implementation in the MIXED procedure (experimental features in SAS 9.1). The remainder of this paper is organized as follows. The Background section briefly

discusses some mixed model estimation theory and the challenges to model diagnosis that result from it.

### **3.3 Summary of Schabenberger's Paper**

=====

On occasion, quantification is not possible. Assume, for example, that a data point is removed and the new estimate of the  $G$  matrix is not positive definite. This may occur if a variance component estimate now falls on the boundary of the parameter space. Thus, it may not be possible to compute certain influence statistics comparing the full-data and reduced-data parameter estimates. However, knowing that a new singularity was encountered is important qualitative information about the data points influence on the analysis.

The basic procedure for quantifying influence is simple:

1. Fit the model to the data and obtain estimates of all parameters.
2. Remove one or more data points from the analysis and compute updated estimates of model parameters.
3. Based on full- and reduced-data estimates, contrast quantities of interest to determine how the absence of the observations changes the analysis.

We use the subscript (U) to denote quantities obtained without the observations in the set U. For example, (U) denotes the fixed-effects *leave-U-out* estimates. Note that the set U can contain multiple observations.

If the global measure suggests that the points in U are influential, you should next determine the nature of that influence. In particular, the points can affect

- the estimates of fixed effects
- the estimates of the precision of the fixed effects
- the estimates of the covariance parameters
- the estimates of the precision of the covariance parameters
- fitted and predicted values

It is important to further decompose the initial finding to determine whether data points are actually troublesome. Simply because they are influential somehow, should not trigger their removal from the analysis or a change in the model. For example, if points primarily affect the precision of the covariance parameters without exerting much influence on the fixed effects, then their presence in the data may not distort hypothesis tests or confidence intervals about  $\beta$ .

### 3.4 Summary of Paper

~~~~~ origin/master Standard residual and influence diagnostics for linear models can be extended to LME models. The dependence of the fixed effects solutions on the covariance parameters has important ramifications on the perturbation analysis. Calculating the studentized residuals-And influence statistics whereas each software

procedure can calculate both conditional and marginal raw residuals, only SAS Proc Mixed is currently the only program that provides studentized residuals. Which are preferred for model diagnostics. The conditional raw residuals are not well suited to detecting outliers as are the studentized conditional residuals. (Schabenberger)

LME are flexible tools for the analysis of clustered and repeated measurement data. LME extend the capabilities of standard linear models by allowing unbalanced and missing data, as long as the missing data are MAR. Structured covariance matrices for both the random effects  $G$  and the residuals  $R$ , missing at random.

A conditional residual is the difference between the observed value and the predicted value of a dependent variable. Influence diagnostics are formal techniques that allow the identification of observations that heavily influence estimates of parameters. To alleviate the problems with the interpretation of conditional residuals that may have unequal variances, we consider scaling. Residuals obtained in this manner are called studentized residuals.

- Standard residual and influence diagnostics for linear models can be extended to linear mixed models. The dependence of fixed-effects solutions on the covariance parameter estimates has important ramifications in perturbation analysis.
- To gauge the full impact of a set of observations on the analysis, covariance parameters need to be updated, which requires refitting of the model.
- The conditional (subject-specific) and marginal (population-averaged) formulations in the linear mixed model enable you to consider conditional residuals that use the estimated BLUPs of the random effects, and marginal residuals which are deviations from the overall mean.
- Residuals using the BLUPs are useful to diagnose whether the random effects components in the model are specified correctly, marginal residuals are useful to diagnose the fixed-effects components.
- Both types of residuals are available in SAS 9.1 as an experimental option of the MODEL statement in the MIXED procedure.
- It is important to note that influence analyses are performed under the assumption that the chosen model is correct. Changing the model structure can alter the conclusions. Many other variance models have been fit to the data presented in the repeated measures example. You need to see the conclusions about which model component is affected in light of the model being fit.

## 4 Case Deletion Diagnostics for LME models

Haslett & Dillane (19XX) remark that linear mixed effects models didn't experience a corresponding growth in the use of deletion diagnostics, adding that McCullough and Searle (2001) makes no mention of diagnostics whatsoever.

Christensen (19XX) describes three propositions that are required for efficient case-deletion in LME models. The first proposition describes how to efficiently update  $V$  when the  $i$ th element is deleted.

$$V_{[i]}^{-1} = \Lambda_{[i]} - \frac{\lambda\lambda'}{\nu ii} \quad (3)$$

The second of Christensen's propositions is the following set of equations, which are variants of the Sherman Woodbury updating formula.

$$X'_{[i]} V_{[i]}^{-1} X_{[i]} = X' V^{-1} X - \frac{\hat{x}_i \hat{x}_i'}{s_i} \quad (4)$$

$$(X'_{[i]} V_{[i]}^{-1} X_{[i]})^{-1} = (X' V^{-1} X)^{-1} + \frac{(X' V^{-1} X)^{-1} \hat{x}_i \hat{x}_i' (X' V^{-1} X)^{-1}}{s_i - \bar{h}_i} \quad (5)$$

$$X'_{[i]} V_{[i]}^{-1} Y_{[i]} = X' V^{-1} Y - \frac{\hat{x}_i \hat{y}_i'}{s_i} \quad (6)$$

In LME models, fitted by either ML or REML, an important overall influence measure is the likelihood distance (?). The procedure requires the calculation of the full data estimates  $\hat{\psi}$  and estimates based on the reduced data set  $\hat{\psi}_{(U)}$ . The likelihood distance is given by determining

$$LD_{(U)} = 2\{l(\hat{\psi}) - l(\hat{\psi}_{(U)})\} \quad (7)$$

$$RLD_{(U)} = 2\{l_R(\hat{\psi}) - l_R(\hat{\psi}_{(U)})\} \quad (8)$$

Haslett & Dillane (199X) offers an procedure to assess the influences for the variance components within the linear model, complementing the existing methods for the fixed components.

The essential problem is that there is no useful updating procedures for  $\hat{V}$ , or for  $\hat{V}^{-1}$ . Haslett & Dillane (199X) propose an alternative, and computationally inexpensive approach, making use of the 'delete=replace' identity.

Haslett (1999) considers the effect of 'leave k out' calculations on the parameters  $\beta$  and  $\sigma^2$ , using several key results from Haslett and Hayes (1998) on partitioned matrices.



## 5 Haslett's Analysis

For fixed effect linear models with correlated error structure Haslett (1999) showed that the effects on the fixed effects estimate of deleting each observation in turn could be cheaply computed from the fixed effects model predicted residuals.

## 6 Haslett's Analysis

For fixed effect linear models with correlated error structure Haslett (1999) showed that the effects on the fixed effects estimate of deleting each observation in turn could be cheaply computed from the fixed effects model predicted residuals.

A general theory is presented for residuals from the general linear model with correlated errors. It is demonstrated that there are two fundamental types of residual associated with this model, referred to here as the marginal and the conditional residual.

These measure respectively the distance to the global aspects of the model as represented by the expected value and the local aspects as represented by the conditional expected value.

These residuals may be multivariate.

Haslett and Hayes (1998) developes some important dualities which have simple implications for diagnostics.

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## Haslett and Hayes - Residuals

Haslett and Hayes (1998) and Haslett (1999) considered the case of an LME model with correlated covariance structure.

### 7.1 Residual Diagnostics in LME models

- A **residual** is the difference between the observed quantity and the predicted value. In LME models a distinction is made between marginal residuals and conditional residuals.
- A **Marginal residual** is the difference between the observed data and the estimated marginal mean (Schabenberger pg3) The computation of case deletion diagnostics in the classical model is made simple by the fact that important estimates can be computed without refitting the model.
- Such update formulae are available in the mixed model only if you assume that the covariance parameters are not affect by the removal of the observation in question. Schabenberger remarks that this is not a reasonable assumption.

Basic procedure for quantifying influence is simple

1. Fit the model to the data
2. Remove one or more data points from the analysis and compute updated estimates of model parameters

3. Based on the full and reduced data estimates, contrast quantities of interest to determine how the absence of the observations changed the analysis.

The likelihood distance is a global summary measure expressing the joint influence of the observations in the set  $U$  on all parameters in  $\Psi$  that were subject to updating.

## 8 Case Deletion Diagnostics for LME models

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$$(X'_{[i]} V_{[i]}^{-1} X_{[i]})^{-1} = (X'V^{-1}X)^{-1} + \frac{(X'V^{-1}X)^{-1}\hat{x}_i\hat{x}_i'(X'V^{-1}X)^{-1}}{s_i - \bar{h}_i} \quad (11)$$

$$X'_{[i]} V_{[i]}^{-1} Y_{[i]} = X'V^{-1}Y - \frac{\hat{x}_i\hat{y}_i'}{s_i} \quad (12)$$

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$$RLD_{(U)} = 2\{l_R(\hat{\psi}) - l_R(\hat{\psi}_{(U)})\} \quad (14)$$

Let  $y_{mir}$  be the  $r$ th replicate measurement on the  $i$ th item by the  $m$ th method, where  $m = 1, 2$ ,  $i = 1, \dots, N$ , and  $r = 1, \dots, n_i$ . When the design is balanced and there is no ambiguity we can set  $n_i = n$ . The LME model underpinning Roy's approach can be written

$$y_{mir} = \beta_0 + \beta_m + b_{mi} + \epsilon_{mir}. \quad (15)$$

Here  $\beta_0$  and  $\beta_m$  are fixed-effect terms representing, respectively, a model intercept and an overall effect for method  $m$ . The  $\beta$  terms can be gathered together into (fixed effect) intercept terms  $\alpha_m = \beta_0 + \beta_m$ . The  $b_{1i}$  and  $b_{2i}$  terms are correlated random

effect parameters having  $E(b_{mi}) = 0$  with  $\text{Var}(b_{mi}) = g_m^2$  and  $\text{Cov}(b_{mi}, b_{m'i}) = g_{12}$ . The random error term for each response is denoted  $\epsilon_{mir}$  having  $E(\epsilon_{mir}) = 0$ ,  $\text{Var}(\epsilon_{mir}) = \sigma_m^2$ ,  $\text{Cov}(b_{mir}, b_{m'ir}) = \sigma_{12}$ ,  $\text{Cov}(\epsilon_{mir}, \epsilon_{m'ir'}) = 0$  and  $\text{Cov}(\epsilon_{mir}, \epsilon_{m'ir'}) = 0$ . Two methods of measurement are in complete agreement if the null hypotheses  $H_1: \beta_1 = \beta_2$  and  $H_2: \sigma_1^2 = \sigma_2^2$  and  $H_3: g_1^2 = g_2^2$  hold simultaneously. Roy (2009) proposes a Bonferroni correction to control the familywise error rate for tests of  $\{H_1, H_2, H_3\}$  and account for difficulties arising due to multiple testing. Let  $\omega_m^2 = \sigma_m^2 + g_m^2$  represent the overall variability of method  $m$ . Roy also integrates  $H_2$  and  $H_3$  into a single testable hypothesis  $H_4: \omega_1^2 = \omega_2^2$ . CONCERNS?

? demonstrates how to implement a method comparison study further to model (1) using the SAS proc mixed package. Carstensen et al. (2008) demonstrates how to construct limits of agreement using SAS, STATA and R. In the case of SAS, the PROC MIXED procedure is used. Implementation in R is performed using the nlme package (?).

Carstensen et al. (2008) remarks that the implementation using R is quite “arcane”.

As R is freely available, this paper demonstrates an implementation of Roy’s model using R.

The R statistical software package is freely available.

The LME model is very easy to implement using PROC MIXED of SAS and the results are also easy to interpret. The SAS proc mixed procedure has very simple syntax.

As the required code to fit the models is complex, R code necessary to fit the models is provided.

A demonstration is provided on how to use the output to perform the tests, and to compute limits of agreement.

We assume the data are formatted as a dataset with four columns named:

meth, method of measurement, the number of methods being M, item, items (persons, samples) measured by each method, of which there are I, repl, replicate indicating repeated measurement of the same item by the same method, and y, the measurement.

## 9 Regression Of Differences On Averages

Further to Carstensen, we can formulate the two measurements  $y_1$  and  $y_2$  as follows:

$$y_1 = \alpha + \beta\mu + \epsilon_1$$

$$y_2 = \alpha + \beta\mu + \epsilon_2$$

## 9.1 Remarks on the Multivariate Normal Distribution

Diligence is required when considering the models. Carstensen specifies his models in terms of the univariate normal distribution. Roy's model is specified using the bivariate normal distribution. This gives rise to a key difference between the two models, in that a bivariate model accounts for covariance between the variables of interest. The multivariate normal distribution of a  $k$ -dimensional random vector  $X = [X_1, X_2, \dots, X_k]$  can be written in the following notation:

$$X \sim \mathcal{N}(\mu, \Sigma),$$

or to make it explicitly known that  $X$  is  $k$ -dimensional,

$$X \sim \mathcal{N}_k(\mu, \Sigma).$$

with  $k$ -dimensional mean vector

$$\mu = [E[X_1], E[X_2], \dots, E[X_k]]$$

and  $k \times k$  covariance matrix

$$\Sigma = [\text{Cov}[X_i, X_j]], \quad i = 1, 2, \dots, k; \quad j = 1, 2, \dots, k$$

### 1. Univariate Normal Distribution

$$X \sim \mathcal{N}(\mu, \sigma^2),$$

### 2. Bivariate Normal Distribution

(a)

$$X \sim \mathcal{N}_2(\mu, \Sigma),$$

(b)

$$\mu = \begin{pmatrix} \mu_x \\ \mu_y \end{pmatrix}, \quad \Sigma = \begin{pmatrix} \sigma_x^2 & \rho\sigma_x\sigma_y \\ \rho\sigma_x\sigma_y & \sigma_y^2 \end{pmatrix}.$$

## 9.2 Note 1: Coefficient of Repeatability

The coefficient of repeatability is a measure of how well a measurement method agrees with itself over replicate measurements (Bland and Altman, 1999). Once the within-item variability is known, the computation of the coefficients of repeatability for both methods is straightforward.

## 9.3 Note 2: Carstensen model in the single measurement case

Carstensen (2004) presents a model to describe the relationship between a value of measurement and its real value. The non-replicate case is considered first, as it is the context of the Bland-Altman plots. This model assumes that inter-method bias is the only difference between the two methods.

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \quad e_{mi} \sim \mathcal{N}(0, \sigma_m^2) \quad (16)$$

The differences are expressed as  $d_i = y_{1i} - y_{2i}$ .

For the replicate case, an interaction term  $c$  is added to the model, with an associated variance component.

## 9.4 Note 3: Model terms

It is important to note the following characteristics of this model.

- Let the number of replicate measurements on each item  $i$  for both methods be  $n_i$ , hence  $2 \times n_i$  responses. However, it is assumed that there may be a different number of replicates made for different items. Let the maximum number of replicates be  $p$ . An item will have up to  $2p$  measurements, i.e.  $\max(n_i) = 2p$ .
- Later on  $\mathbf{X}_i$  will be reduced to a  $2 \times 1$  matrix, to allow estimation of terms. This is due to a shortage of rank. The fixed effects vector can be modified accordingly.
- $\mathbf{Z}_i$  is the  $2n_i \times 2$  model matrix for the random effects for measurement methods on item  $i$ .
- $\mathbf{b}_i$  is the  $2 \times 1$  vector of random-effect coefficients on item  $i$ , one for each method.
- $\boldsymbol{\epsilon}$  is the  $2n_i \times 1$  vector of residuals for measurements on item  $i$ .
- $\mathbf{G}$  is the  $2 \times 2$  covariance matrix for the random effects.
- $\mathbf{R}_i$  is the  $2n_i \times 2n_i$  covariance matrix for the residuals on item  $i$ .
- The expected value is given as  $E(\mathbf{y}_i) = \mathbf{X}_i\boldsymbol{\beta}$ . (Hamlett et al., 2004)
- The variance of the response vector is given by  $\text{Var}(\mathbf{y}_i) = \mathbf{Z}_i\mathbf{G}\mathbf{Z}_i' + \mathbf{R}_i$  (Hamlett et al., 2004).



Roy uses and LME model approach to provide a set of formal tests for method comparison studies.

Four candidates models are fitted to the data.

These models are similar to one another, but for the imposition of equality constraints.

These tests are the pairwise comparison of candidate models, one formulated without constraints, the other with a constraint.

Roy's model uses fixed effects  $\beta_0 + \beta_1$  and  $\beta_0 + \beta_1$  to specify the mean of all observations by methods 1 and 2 respectively.

Roy adheres to Random Effect ideas in ANOVA

Roy treats items as a sample from a population.

Allocation of fixed effects and random effects are very different in each model

Carstensen's interest lies in the difference between the population from which they were drawn.

Carstensen's model is a mixed effects ANOVA.

$$Y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir}, \quad c_{mi} \sim \tau_{\Downarrow}^{\epsilon}, \quad e_{mir} \sim \sigma_{\Downarrow}^{\epsilon},$$

This model includes a method by item interaction term.

Carstensen presents two models. One for the case where the replicates, and a second for when they are linked.

Carstensen's model does not take into account either between-item or within-item covariance between methods.

In the presented example, it is shown that Roy's LoAs are lower than those of Carstensen. Carstensen makes some interesting remarks in this regard.

The only slightly non-standard (meaning "not often used") feature is the differing residual variances between methods.

## 10 Cook's Distance

Cook (1977) greatly expanded the study of residuals and influence measures. Cook's Distance, denoted as  $D_{(i)}$ , is a well known diagnostic technique used in classical linear models, used as an overall measure of the combined impact of the  $i$ th case of all estimated regression coefficients. Cook's key observation was the effects of deleting each observation in turn could be calculated with little additional computation. That is to say,  $D_{(i)}$  can be calculated without fitting a new regression coefficient each time an observation is deleted. Consequently deletion diagnostics have become an integral part of assessing linear models.

The focus of this analysis is related to the estimation of point estimates (i.e. regression coefficients). It must be pointed out that the effect on the precision of estimates is separate from the effect on the point estimates. Data points that have a small Cook's distance, for example, can still greatly affect hypothesis tests and confidence intervals, if their influence on the precision of the estimates is large.

As well as individual observations, Cook's distance can be used to analyse the influence of observations in subset  $U$  on a vector of parameter estimates (Cook, 1977).

$$\hat{e}_{i(U)} = y_i - x\hat{\beta}_{(U)} \quad (17)$$

$$\delta_{(U)} = \hat{\beta} - \hat{\beta}_{(U)} \quad (18)$$

- *The previous Section (Section 4) is a literary review of residual diagnostics and influence procedures for Linear Mixed Effects Models, drawing heavily on Schabenberger and Zewotir.*
- *Section 4 begins with an introduction to key topics in residual diagnostics, such as influence, leverage, outliers and Cook's distance. Other concepts such as DF-FITS and DFBETAs will be introduced briefly, mostly to explain why they are not particularly useful for the Method Comparison context, and therefore are not elaborated upon.*
- *In brief, Variable Selection is not applicable to Method Comparison Studies, in the commonly used context. Testing a rather simplistic specified model against one with more random effects terms is tractable, but this research question is of secondary importance.*

## Appendix to Section 4

As an appendix to section 4, an appraisal of the current state of development (or lack thereof) for current implemenations for LME models, particularly for `nlme` and `lme4` fitted models.

Crucially, a review of internet resources indicates that almost all of the progress in this regard has been done for `lme4` fitted models, specifically the *Influence.ME* R package. (Nieuwenhuis et 2012)

Conversely there is very little for `nlme` models. To delve into this mor, one would immediately investigate the current development workflow for both packages.

As an aside, Douglas Bates was arguably the most prominent R developer working in the LME area. However Bates has now prioritised the development of LME models in another computing environment , i.e Julia.

### The `nlme` package

With regards to `nlme`, the torch has been passed to Galecki Galecki & Burzykowski (UMich. and Hasselt respectely). Galecki & Burzykowski published *Linear Mixed Effects Models using R*. Also, the accompanying R package, `nlmeU` package is under current development, with a version being released XXXX.

### The `lme4` package

The `lme4` package is also under active development, under the leadership of Ben Bolker (McMaster University). According to CRAN, the LME4 package, fits linear and generalized linear mixed-effects models

The models and their components are represented using S4 classes and methods. The core computational algorithms are implemented using the Eigen C++ library for numerical linear algebra and RcppEigen "glue".  
(CRAN)

The key issue is that `nlme` allows for the particular specification of Roy's Model, speciifiically direct spefication of the VC matrices for within subject and between subject residuals. The `lme4` package does not allow for this. To advance the ideas that emanate from Roys' paper, one is required to use the `nlme` context. However, to take advantage of the infrastructure already provided for `lme4` models, one may change the research question away from that of Roy's paper. To this end, an exploration of what textitinfluence.ME can accomplished is merited. As a complement to this, one can also consider how to properly employ the  $R^2$  measure, in the context of Methoc Comparison Studies, further to the work by Edwards et al, namely "An  $R^2$  statistic for fixed effects in the linear mixed model".

**Abstract for “An  $R^2$  statistic for fixed effects in the linear mixed model”** Statisticians most often use the linear mixed model to analyze Gaussian longitudinal data.

The value and familiarity of the  $R^2$  statistic in the linear univariate model naturally creates great interest in extending it to the linear mixed model. We define and describe how to compute a model  $R^2$  statistic for the linear mixed model by using only a single model.

The proposed  $R^2$  statistic measures multivariate association between the repeated outcomes and the fixed effects in the linear mixed model. The  $R^2$  statistic arises as a 11 function of an appropriate  $F$  statistic for testing all fixed effects (except typically the intercept) in a full model.

The statistic compares the full model with a null model with all fixed effects deleted (except typically the intercept) while retaining exactly the same covariance structure.

Furthermore, the  $R^2$  statistic leads immediately to a natural definition of a partial  $R^2$  statistic. A mixed model in which ethnicity gives a very small p-value as a longitudinal predictor of blood pressure (BP) compellingly illustrates the value of the statistic.

In sharp contrast to the extreme p-value, a very small  $R^2$ , a measure of statistical and scientific importance, indicates that ethnicity has an almost negligible association with the repeated BP outcomes for the study.

## Leave-One-Out Diagnostics with `lmeU`

Galecki et al discuss the matter of LME influence diagnostics in their book, although not into great detail.

The command `lmeU` fits a model with a particular subject removed. The identifier of the subject to be removed is passed as the only argument

A plot of the per-observation diagnostics individual subject log-likelihood contributions can be rendered.

## Likelihood Displacement

## Missing Data in Method Comparison Studies

The matter of missing data has not been commonly encountered in either Method Comparison Studies or Linear Mixed Effects Modelling. However Roy (2009) deals with the relevant assumptions regarding missing data.

Galecki & Burzykowski (2013) tackles the subject of missing data in LME Modelling.

Furthermore the nlmeU package includes the `patMiss` function, which “allows to compactly present pattern of missing data in a given vector/matrix/data frame or combination of thereof”.

## 11 Exention of Cook's Distance methodology to LME models

Cook's Distance is extended to LME models. For LME models, two formulations exist; a Cook's distance that examines the change in fixed fixed parameter estimates, and another that examines the change in random effects parameter estimates. The outcome of either Cook's distance is a scaled change in either  $\beta$  or  $\theta$ .

Diagnostic methods for variance components are based on 'one-step' methods. Cook (1986) gives a completely general method for assessing the influence of local departures from assumptions in statistical models. For fixed effects parameter estimates in LME models, the Cook's distance can be extended to measure influence on these fixed effects.

$$CD_i(\beta) = \frac{(c_{ii} - r_{ii}) \times t_i^2}{r_{ii} \times p}$$

For random effect estimates, the Cook's distance is

$$CD_i(b) = g'_{(i)}(I_r + \text{var}(\hat{b})D)^{-2}\text{var}(\hat{b})g_{(i)}.$$

Large values for Cook's distance indicate observations for special attention.

Cook's Distance was extended from classical linear models to LME models. For linear mixed effects models, Cook's distance can be extended to model influence diagnostics by definining.

$$CD_{\beta i} = \frac{(\hat{\beta} - \hat{\beta}_{[i]})^T (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})(\hat{\beta} - \hat{\beta}_{[i]})}{p}$$

It is also desirable to measure the influence of the case deletions on the covariance matrix of  $\hat{\beta}$ .

### 11.1 Cook's Distance

- For variance components  $\gamma$ :  $CD(\gamma)_i$ ,
- For fixed effect parameters  $\beta$ :  $CD(\beta)_i$ ,
- For random effect parameters  $\mathbf{u}$ :  $CD(u)_i$ ,
- For linear functions of  $\hat{\beta}$ :  $CD(\psi)_i$

It is also desirable to measure the influence of the case deletions on the covariance matrix of  $\hat{\beta}$ .



## 12 Cook's Distance for LMEs

Diagnostic methods for fixed effects are generally analogues of methods used in classical linear models. Diagnostic methods for variance components are based on ‘one-step’ methods. Cook (1986) gives a completely general method for assessing the influence of local departures from assumptions in statistical models.

For fixed effects parameter estimates in LME models, the Cook's distance can be extended to measure influence on these fixed effects.

$$\text{CD}_i(\beta) = \frac{(c_{ii} - r_{ii}) \times t_i^2}{r_{ii} \times p}$$

For random effect estimates, the Cook's distance is

$$\text{CD}_i(b) = g'_{(i)}(I_r + \text{var}(\hat{b})D)^{-2}\text{var}(\hat{b})g_{(i)}.$$

Large values for Cook's distance indicate observations for special attention.

### 12.0.1 Random Effects

A large value for  $CD(u)_i$  indicates that the  $i$ -th observation is influential in predicting random effects.

### 12.0.2 linear functions

$CD(\psi)_i$  does not have to be calculated unless  $CD(\beta)_i$  is large.

For LME models, two formulations exist; a Cook's distance that examines the change in fixed fixed parameter estimates, and another that examines the change in random effects parameter estimates. The outcome of either Cook's distance is a scaled change in either  $\beta$  or  $\theta$ .

## 12.1 Change in the precision of estimates

The effect on the precision of estimates is separate from the effect on the point estimates. Data points that have a small Cook's distance, for example, can still greatly affect hypothesis tests and confidence intervals, if their influence on the precision of the estimates is large.

## 12.2 Introduction

### 12.2.1 Robinson's (1991) review

*Robinson's (1991) review of best linear unbiased prediction (BLUP), together with the subsequent discussion, has emphasized the very considerable range of models that may be addressed via the general least squares (GLS) solution to the general linear model  $Y = X\beta + \varepsilon$ , where  $E(\varepsilon) = 0$  and  $\text{var}(\varepsilon) = V$ . These include linear mixed models, geostatistics, time series and multivariate regression.*

*The texts by Christensen (1996, 1991) and the connections to modern topics of image analysis, quality analysis, Bayesian methods, and splines (all in Robinson and discussion) make it an eminently suitable topic for teaching in any course concerning statistical linear models.*

*Nevertheless some of the matrix algebra that results from solving the normal equations for individual specifications of the general linear model will be daunting, and far from intuitive for many students, even those who are at home in linear space. The conventional approach to prediction and estimation from data  $Y$  associated with covariates  $X$  via the general linear model  $Y = X\beta + \varepsilon$  is essentially a two-stage process.*

The first stage is to determine the best, in the GLS sense, estimator  $\hat{\beta}$  of  $\beta$  and subsequently to determine everything else from this.

The estimator is said to be best if it minimizes the generalization of the sum of squares  $\hat{e}^t V^{-1} \hat{e}$ , where  $\hat{e} = Y - X\hat{\beta}$

It is straightforward to show that  $\hat{\beta} = (X^t V^{-l} X)^{-l} X^t V^{-l} Y = BY$  and at the minimum the sum of squares is  $Y^t (V^{-l} - V^{-l} (X^t V^{-l} X)^{-l} X^t V^{-l}) Y = Y^t QY$ .

*The purpose of this note is to give emphasis to one derivation, based on Lagrange multipliers, which leads to a system of equations that is very intuitive and lends itself readily to specialization. This approach is in fact standard in the geostatistical treatment of **kriging** (see Matheron 1962; Journel and Huijbregts 1981; Ripley 1981; Cressie 1993). In the genetics literature it is associated with the name of Henderson (1983); or in the classical statistical literature Hocking (1996, p. 73) is a suitable reference.*

*The approach based on Lagrange multipliers deemphasizes the explicit determination of  $\hat{\beta}$  and leads to a clearer understanding of the complementary (but for some confusing) tasks known as best linear unbiased estimation (BLUE) and best linear unbiased prediction (BLUP). Regrettably, Robinson-despite offering four derivations, and having as his main concern the interplay of BLUP and BLUE-gives it little prominence.*

It has recently been discussed by Searle (1997, p; 278) who said that it makes another approach (Searle, Casella, and McCulloch 1992, p. 271) seem "obtuse and unnecessarily complicated." By contrast, our treatment emphasizes the fact that it leads to a single set of equations whose solution sheds simplifying light on very many issues in general least squares.

The American Statistician's Teacher's Corner (e.g., McLean, Sanders, and Stroup 1991; Puntanen and Styan 1989) has already played host to previous attempts to simplify the explanation of such topics. Various authors (CPJ, Haslett Hayes, Martin) have visited the more specialized area of diagnostics and have developed **down-dating** (leave- $k$ -out) formulas.

The conventional approach here is via tricky identities based on the inverses of partitioned matrices. Here again the Lagrange system of equations leads to a much simplified and-we claim-much more intuitive derivation of these more technical results.

*The essence of the approach is to seek that linear combination of the available data  $Y$  which is best for the estimation of  $Z$  among those linear estimators which are constrained to be unbiased. We adopt therefore a constrained minimization approach, using Lagrange multipliers. By best we mean that combination  $\hat{Z}(Y) = \lambda_z^t Y$  which has least mean square error  $E(Z - \lambda_z^t Y)^2$ , and by unbiased we mean  $E(Z - \lambda_z^t Y) = 0$ . Here  $Z$  denotes that scalar which is to be the objective of the estimation. This estimator is written as  $\hat{Z}(Y)$  to make its dependence on  $Y$  explicit. Note that the term "best" is applied in the context of minimizing the prediction variance  $var(Z - Z(Y))$ . We shall see that  $Z$  may be used to denote either a random variable or an unknown parameter, and that it will be sufficient to specify  $Z$  via  $E[Z]$  and  $cov(Z, Y)$ . If  $Z$  is not a random variable then of course the latter is zero and  $E[Z] = Z$ . We establish-very simply, as below-a general solution in terms of  $A$  and  $cov(Z, Y)$  and achieve particular tasks by identification of these. Our presentation is for a scalar  $Z$ , but the notation facilitates generalization to vector  $Z$ .*

### 12.3 Predictors and Estimators

*We note that Robinson (1991) stated "A convention has somehow developed that estimators of random effects are called predictors while estimators of fixed effects are called estimators." We agree that this distinction is confusing and indeed unnecessary.*

We seek  $\hat{Z}(Y) = \lambda_z^t Y$ , where  $\lambda_z^t$  is an  $n \times 1$  vector of estimation coefficients. It is convenient to specify  $E[Z] = A\beta$  for known  $A$ . In this context  $A$  denotes a row vector, but we generalize this in the following. The constraint requiring  $\hat{Z}(Y)$  to be unbiased now reduces to  $(A - \lambda_z^t X) = 0$ . A solution is found by minimizing  $var(Z - \lambda_z^t Y) + \gamma_z^t (X^t \lambda_z - A^t)$ , where  $\gamma_z$  is a  $p \times 1$  vector of Lagrange multipliers, where  $p$  is the length of the parameter vector  $\beta$ . Setting to zero the derivatives with respect to  $\lambda_z$  and  $\gamma_z$  yields the system.

$$\begin{pmatrix} V & X \\ X^t & 0 \end{pmatrix} \begin{pmatrix} \lambda_z \\ \gamma_z \end{pmatrix} = \begin{pmatrix} cov(Y, Z) \\ A^t \end{pmatrix} \quad (19)$$

If the inverse exists we have that

$$\begin{pmatrix} \lambda_z \\ \gamma_z \end{pmatrix} = \begin{pmatrix} V & X \\ X^t & 0 \end{pmatrix}^{-1} \begin{pmatrix} cov(Y, Z) \\ A^t \end{pmatrix} \quad (20)$$

so that

$$\hat{Z}(Y) = (\lambda_z^t \quad \gamma_z^t) = \begin{pmatrix} Y \\ 0 \end{pmatrix}$$

In terms of the estimation problem being considered the square matrix on the left-hand side of (1) concerns "what we have," namely, the data plus constraints.

The matrix does not depend on  $Z$  and consequently need only be constructed once before application to a range of problems. The right-hand side contains the term  $cov(Z, Y)$  and can be specified for whatever  $Z$  is being considered.

It is this feature of system (1) that makes a generic approach to estimation possible.

### 12.3.1 The extended likelihood

The desire to have an entirely likelihood-based justification for estimates of random

```
\begin{eqnarray*}
\ell_h(\beta, \theta, b|y)
&= \displaystyle -\frac{1}{2} \left\{ \log|\Sigma| + (y - X\beta - Zb)' \Sigma^{-1} \right. \\
&\quad \left. + \log|D| + b' D^{-1} b \right\}.
\end{eqnarray*}
```

Given  $\theta$ , differentiating with respect to  $\beta$  and  $b$  returns Henderson's

```
\subsubsection{The LME model as a general linear model}
Henderson's equations in (\ref{Henderson:Equations}) can be rewritten  $(T'W$ 
\[
\delta = \begin{pmatrix} \beta \\ b \end{pmatrix},
y_a = \begin{pmatrix}
y \\ \psi
\end{pmatrix},
T = \begin{pmatrix}
X & Z \\ 0 & I
\end{pmatrix},
\text{and } W = \begin{pmatrix}
\Sigma & 0 \\ 0 & D
\end{pmatrix},
\]
```

where \cite{Lee:Neld:Pawi:2006} describe  $\psi = 0$  as quasi-data with mean  $\mathbf{0}$

## 13 Repeated measurements in LME models

In many statistical analyses, the need to determine parameter estimates where multiple measurements are available on each of a set of variables often arises. Further to Lam et al. (1999), Hamlett et al. (2004) performs an analysis of the correlation of replicate measurements, for two variables of interest, using LME models.

Let  $y_{Aij}$  and  $y_{Bij}$  be the  $j$ th repeated observations of the variables of interest  $A$  and  $B$  taken on the  $i$ th subject. The number of repeated measurements for each variable may differ for each individual. Both variables are measured on each time points. Let  $n_i$  be the number of observations for each variable, hence  $2 \times n_i$  observations in total.

It is assumed that the pair  $y_{Aij}$  and  $y_{Bij}$  follow a bivariate normal distribution.

$$\begin{pmatrix} y_{Aij} \\ y_{Bij} \end{pmatrix} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \text{ where } \boldsymbol{\mu} = \begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}$$

The matrix  $\Sigma$  represents the variance component matrix between response variables at a given time point  $j$ .

$$\Sigma = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}$$

$\sigma_A^2$  is the variance of variable  $A$ ,  $\sigma_B^2$  is the variance of variable  $B$  and  $\sigma_{AB}$  is the covariance of the two variable. It is assumed that  $\Sigma$  does not depend on a particular time point, and is the same over all time points.

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