

## Residual Analysis for Linear Mixed Models

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### Summary

Residuals are frequently used to evaluate the validity of the assumptions of statistical models and may also be employed as tools for model selection. For standard (normal) linear models, for example, residuals are used to verify homoscedasticity, linearity of effects, presence of outliers, normality and independence of the errors. Similar uses may be envisaged for three types of residuals that emerge from the fitting of linear mixed models. We review some of the residual analysis techniques that have been used in this context and propose a standardization of the conditional residual useful to identify outlying observations and clusters. We illustrate the procedures with a practical example.

*Key words:* BLUP; Diagnostic; Longitudinal data; Repeated measures; Residuals.

## 1 Introduction

Linear mixed models constitute a popular alternative to analyze repeated measures and, in particular, longitudinal data. Such models may be expressed as

$$\mathbf{y}_i = \mathbf{X}_i \boldsymbol{\beta} + \mathbf{Z}_i \mathbf{b}_i + \boldsymbol{\varepsilon}_i, \quad i = 1, \dots, m, \quad (1.1)$$

where  $\mathbf{y}_i$  is a  $(n_i \times 1)$  vector of response variables measured on subject  $i$ ,  $\boldsymbol{\beta}$  is a  $(p \times 1)$  vector of parameters (fixed effects),  $\mathbf{X}_i$  and  $\mathbf{Z}_i$  are  $(n_i \times p)$  and  $(n_i \times q)$  known matrices of full rank, respectively,  $\mathbf{b}_i$  is a  $(q \times 1)$  random vector, the components of which are called random effects and  $\boldsymbol{\varepsilon}_i$  is a  $(n_i \times 1)$  random (within-subject) vector of measurement errors. Usually one assumes that

$$\mathbf{b}_1, \dots, \mathbf{b}_m \stackrel{\text{iid}}{\sim} N_q(0, \sigma^2 \mathbf{G}) \quad \text{and} \quad \boldsymbol{\varepsilon}_i \stackrel{\text{ind}}{\sim} N_{n_i}(0, \sigma^2 \mathbf{R}_i), \quad i = 1, \dots, m, \quad (1.2)$$

with  $\mathbf{b}_i$  and  $\boldsymbol{\varepsilon}_i$  independent,  $\mathbf{G}$  and  $\mathbf{R}_i$  being  $(q \times q)$  and  $(n_i \times n_i)$  positive definite matrices respectively, with elements expressed as functions of a vector of covariance parameters,  $\boldsymbol{\theta}$ , not functionally related to  $\boldsymbol{\beta}$ . Letting  $\mathbf{y} = (\mathbf{y}_1^\top, \dots, \mathbf{y}_m^\top)^\top$ ,  $\mathbf{X} = (\mathbf{X}_1^\top, \dots, \mathbf{X}_m^\top)^\top$ ,  $\mathbf{Z} = \bigoplus_{i=1}^m \mathbf{Z}_i$ , where  $\bigoplus$  represents the direct sum (Searle, 1982),  $\mathbf{b} = (\mathbf{b}_1^\top, \dots, \mathbf{b}_m^\top)^\top$  and  $\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1^\top, \dots, \boldsymbol{\varepsilon}_m^\top)^\top$ , we can write model (1.1) more compactly as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} + \boldsymbol{\varepsilon}. \quad (1.3)$$

This implies that

$$\begin{bmatrix} \mathbf{b} \\ \boldsymbol{\varepsilon} \end{bmatrix} \sim N_{qm+n} \left( \begin{bmatrix} \mathbf{0}_{qm} \\ \mathbf{0}_n \end{bmatrix}, \begin{bmatrix} \sigma^2 \mathbf{D} & \mathbf{0}_{qm \times n} \\ \mathbf{0}_{n \times qm} & \sigma^2 \boldsymbol{\Sigma} \end{bmatrix} \right),$$

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where  $n = \sum_{i=1}^m n_i$ ,  $\mathbf{D} = \mathbf{I}_m \otimes \mathbf{G}$  and  $\mathbf{\Sigma} = \bigoplus_{i=1}^m \mathbf{R}_i$ , with  $\otimes$  denoting the Kronecker product (Searle, 1982) and  $\mathbf{I}_m$ , the identity matrix of order  $m$ . Under model (1.3), the covariance matrix of  $\mathbf{y}$  is  $\mathbf{V} = \sigma^2(\mathbf{Z}\mathbf{D}\mathbf{Z}^\top + \mathbf{\Sigma})$ . Conditionally on  $\mathbf{D}$  and  $\mathbf{\Sigma}$ , the best linear unbiased estimator (BLUE) of  $\boldsymbol{\beta}$  and the best linear unbiased predictor (BLUP) of  $\mathbf{b}$  (see Robinson, 1991, for example), are respectively given by

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^\top \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^\top \mathbf{V}^{-1} \mathbf{y} = \mathbf{T}\mathbf{y} \quad (1.4)$$

and

$$\hat{\mathbf{b}} = \mathbf{D}\mathbf{Z}^\top \mathbf{Q}\mathbf{y} \quad (1.5)$$

with  $\mathbf{T} = (\mathbf{X}^\top \mathbf{M}\mathbf{X})^{-1} \mathbf{X}^\top \mathbf{M}$ ,  $\mathbf{Q} = \mathbf{M}(\mathbf{I} - \mathbf{T})$ , where  $\mathbf{M} = \sigma^2 \mathbf{V}^{-1} = (\mathbf{Z}\mathbf{D}\mathbf{Z}^\top + \mathbf{\Sigma})^{-1}$ . The matrix  $\mathbf{T}$  is the oblique projection matrix using the distance induced by the matrix  $\mathbf{M}$ . In practice, replacing  $\mathbf{D}$  and  $\mathbf{V}$  in (1.4) and (1.5) by convenient estimates, generates the so called empirical BLUE (EBLUE) and empirical BLUP (EBLUP). Properties of the EBLUE and the EBLUP are discussed in Jiang (1998, 1999), for example. The most popular estimation methods for the covariance parameters ( $\boldsymbol{\theta}$ ) are based on full and restricted maximum likelihood. Other estimation methods are presented in Searle et al. (1992) and Demidenko (2004), for example. As with standard (normal) linear models, residual analysis may be employed to check the validity of the underlying assumptions. Since mixed models have two sources of variability (within and between-subjects) different types of residuals may be defined and the corresponding analysis is more complex. We summarize the major results in this field and propose a standardization of the conditional residual that is useful for the identification of outlying observations or clusters. In Section 2, we define the three types of residuals generated by fitting model (1.1) and indicate how each of them may be employed to check some of the underlying assumptions; in particular, we detail the proposed standardization of the conditional residuals. In Section 3, we outline the analysis strategy employed to fit linear mixed models to data from a practical example and illustrate how residual analyses may be employed to assess the fit of the chosen model. Our conclusions are discussed in Section 4.

## 2 Types of Residuals in Linear Mixed Models

Cox and Snell (1968) present a general definition of residuals for models with a single source of variability. Authors like Hilden-Minton (1995), Verbeke and Lesaffre (1996a) or Pinheiro and Bates (2000), for example, extended such ideas to define three types of residuals that accommodate the extra source of variability present in linear mixed models, namely

- (i) Marginal residuals,  $\hat{\boldsymbol{\xi}} = \mathbf{y} - \mathbf{X}\hat{\boldsymbol{\beta}} = \mathbf{M}^{-1}\mathbf{Q}\mathbf{y}$ , that predict the marginal errors,  $\boldsymbol{\xi} = \mathbf{y} - \mathbb{E}[\mathbf{y}] = \mathbf{y} - \mathbf{X}\boldsymbol{\beta} = \mathbf{Z}\mathbf{b} + \boldsymbol{\varepsilon}$ ;
- (ii) Conditional residuals,  $\hat{\boldsymbol{\varepsilon}} = \mathbf{y} - \mathbf{X}\hat{\boldsymbol{\beta}} - \mathbf{Z}\hat{\mathbf{b}} = \mathbf{\Sigma}\mathbf{Q}\mathbf{y}$ , that predict the conditional errors  $\boldsymbol{\varepsilon} = \mathbf{y} - \mathbb{E}[\mathbf{y} | \mathbf{b}] = \mathbf{y} - \mathbf{X}\boldsymbol{\beta} - \mathbf{Z}\mathbf{b}$ ;
- (iii) The BLUP,  $\mathbf{Z}\hat{\mathbf{b}}$ , that predict the random effects,  $\mathbf{Z}\mathbf{b} = \mathbb{E}[\mathbf{y} | \mathbf{b}] - \mathbb{E}[\mathbf{y}]$ .

Each type of residual is useful to evaluate some assumption of model (1.1).

According to Hilden-Minton (1995), a residual is considered *pure* for a specific type of error if it depends only on the fixed components and on the error that it is supposed to predict. Residuals that depend on other types of errors are called *confounded* residuals. Given that, under (1.3)–(1.5), we have

$$\hat{\boldsymbol{\xi}} = [\mathbf{I} - \mathbf{X}(\mathbf{X}^\top \mathbf{M}\mathbf{X})^{-1} \mathbf{X}^\top \mathbf{M}] \boldsymbol{\xi}, \quad (2.1)$$

$$\hat{\boldsymbol{\varepsilon}} = \mathbf{\Sigma}\mathbf{Q}\boldsymbol{\varepsilon} + \mathbf{\Sigma}\mathbf{Q}\mathbf{Z}\mathbf{b}, \quad (2.2)$$

$$\mathbf{Z}\hat{\mathbf{b}} = \mathbf{Z}\mathbf{D}\mathbf{Z}^\top \mathbf{Q}\mathbf{Z}\mathbf{b} + \mathbf{Z}\mathbf{D}\mathbf{Z}^\top \mathbf{Q}\boldsymbol{\varepsilon}, \quad (2.3)$$

the residuals  $\hat{\boldsymbol{\varepsilon}}$  and  $\mathbf{Z}\hat{\boldsymbol{b}}$  are confounded with  $\boldsymbol{b}$  and  $\boldsymbol{\varepsilon}$ , respectively. This implies, for example, that  $\hat{\boldsymbol{\varepsilon}}$  may not be adequate to check for the normality of  $\boldsymbol{\varepsilon}$  since when  $\boldsymbol{b}$  is grossly non-normal,  $\hat{\boldsymbol{\varepsilon}}$  may not present a normal behaviour even when  $\boldsymbol{\varepsilon}$  is normal.

### 2.1 Marginal residuals

Given that marginally  $\boldsymbol{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\xi}$ , plots of the elements of the vector of marginal residuals  $\hat{\boldsymbol{\xi}} = (\hat{\boldsymbol{\xi}}_1^\top, \dots, \hat{\boldsymbol{\xi}}_m^\top)^\top$  versus the explanatory variables in  $\mathbf{X}$  may be employed to check the linearity of  $\boldsymbol{y}$  with respect to such variables with the same spirit as the usual residuals in standard (normal) linear models. A random behavior around zero is expected when the linear relationship holds.

They may also be used to check the validity of the within-subjects covariance structure, i.e.,  $\mathbf{V}_i = \sigma^2(\mathbf{Z}_i\mathbf{D}\mathbf{Z}_i^\top + \mathbf{R}_i)$ . In this direction, Lesaffre and Verbeke (1998) consider  $\|\mathbf{I}_{n_i} - \mathcal{R}_i\mathcal{R}_i^\top\|^2$  where  $\mathcal{R}_i = \hat{\mathbf{V}}_i^{-1/2}\hat{\boldsymbol{\xi}}_i$  and  $\|\mathbf{A}\|$  denotes the Frobenius norm of the matrix  $\mathbf{A}$  as the appropriate residuals for the within-subjects covariance matrix. Given that  $\text{Var}[\boldsymbol{y}_i]$  can be estimated by  $\hat{\boldsymbol{\xi}}_i\hat{\boldsymbol{\xi}}_i^\top$  when the vector of means for the  $i$ -th subject is correctly modeled by  $\mathbf{X}_i\boldsymbol{\beta}$ ,  $\|\mathbf{I}_{n_i} - \mathcal{R}_i\mathcal{R}_i^\top\|^2$  is expected to lie near zero and a plot of such values versus the subject indices may help to detect cases for which the assumed covariance structure does not fit well.

### 2.2 Conditional residuals

Pinheiro and Bates (2000, p. 115) consider plots of the elements of  $\hat{\boldsymbol{\varepsilon}}/\hat{\sigma}$ , where  $\hat{\sigma}$  is an estimate of  $\sigma$ , versus those of  $\hat{\boldsymbol{y}} = \mathbf{X}\hat{\boldsymbol{\beta}} + \mathbf{X}\hat{\boldsymbol{b}}$  and Q-Q plots of  $\hat{\boldsymbol{\varepsilon}}/\hat{\sigma}$  for checking homoscedasticity and normality of the conditional error  $\boldsymbol{\varepsilon}$ . Similar proposals to check for homoscedasticity using conditional residuals are given in Weiss and Lazaro (1992) and Oman (1995).

Since  $\text{Var}[\hat{\boldsymbol{\varepsilon}}] = \sigma^2\boldsymbol{\Sigma}\boldsymbol{Q}\boldsymbol{\Sigma}$  (see Appendix for details), the elements of  $\hat{\boldsymbol{\varepsilon}}$  may have different variances, depending on both  $\sigma^2$  and  $p_{kk}$ , with  $p_{kk}$  representing the  $k$ -th principal diagonal element of  $\boldsymbol{\Sigma}\boldsymbol{Q}\boldsymbol{\Sigma}$ ,  $k = 1, \dots, n$ . For many diagnostic procedures, it is useful to define a studentized version of the residuals that does not depend on the scale and allows a comparison among them, as advocated by Cook and Weisberg (1982, p. 18) in a different setup. We suggest to standardize the conditional residuals by taking

$$\hat{\boldsymbol{\varepsilon}}_k^* = \frac{\hat{\boldsymbol{\varepsilon}}_k}{\hat{\sigma}\sqrt{\hat{p}_{kk}}}, \tag{2.4}$$

where  $\hat{p}_{kk}$  is an estimate of  $p_{kk}$ . The elements  $\hat{p}_{kk}$  are functions of the joint leverage of the fixed and random effects (Nobre and Singer, 2006), indicating that the residuals (2.4) constitute a generalization of the usual studentized residuals. When  $\boldsymbol{\Sigma} = \mathbf{I}_n$  (i.e., under an independence and conditional homoscedasticity assumption), the standardized conditional residuals (2.4) are reduced to  $\hat{\boldsymbol{\varepsilon}}_k^* = \hat{\boldsymbol{\varepsilon}}_k / (\hat{\sigma}\sqrt{\hat{q}_{kk}})$ , with  $\hat{q}_{kk}$  denoting an estimate of the  $k$ -th principal diagonal element of  $\boldsymbol{Q}$ .

To motivate the use of (2.4) for the identification of outliers, consider an unbiased estimator of  $\sigma^2$  obtained when we delete a group  $K = \{k_1, k_2, \dots, k_v\}$  of observations from the sample, given by  $\hat{\sigma}_{(K)}^2 = [\boldsymbol{y}^\top(\boldsymbol{Q} - \boldsymbol{Q}\boldsymbol{U}_K(\boldsymbol{U}_K^\top\boldsymbol{Q}\boldsymbol{U}_K)^{-1}\boldsymbol{U}_K^\top\boldsymbol{Q})\boldsymbol{y}] / (n - p - v)$  where  $\boldsymbol{U}_K = (\boldsymbol{u}_{ij})_{n \times v} = (\boldsymbol{U}_{k_1}, \boldsymbol{U}_{k_2}, \dots, \boldsymbol{U}_{k_v})$  with  $\boldsymbol{U}_k$  denoting the  $k$ -th column of  $\mathbf{I}_n$ . Details are presented in the Appendix. When we eliminate only the  $k$ -th observation, it is possible to show that  $\hat{\boldsymbol{\varepsilon}}_k^2 / q_{kk} = \boldsymbol{y}^\top\boldsymbol{Q}\boldsymbol{U}_k(\boldsymbol{U}_k^\top\boldsymbol{Q}\boldsymbol{U}_k)^{-1}\boldsymbol{U}_k^\top\boldsymbol{Q}\boldsymbol{y}$ ; therefore

$$\frac{(n - p)\hat{\sigma}^2}{\sigma^2} = \frac{(n - p - 1)\hat{\sigma}_{(k)}^2}{\sigma^2} + \frac{\hat{\boldsymbol{\varepsilon}}_k^2}{\sigma^2 q_{kk}},$$

implying that

$$\frac{\hat{\sigma}_{(k)}^2}{\hat{\sigma}^2} = \left( \frac{n - p - \hat{\boldsymbol{\varepsilon}}_k^2 / q_{kk}}{n - p - 1} \right), \tag{2.5}$$

which is a monotone decreasing function of  $|\hat{\varepsilon}_k^*|$ . Consequently, the standardized conditional residuals (2.4) are useful to identify observations with high influence on the estimate of  $\sigma^2$ . In standard (normal) linear models, this residual can be used to test if the  $k$ -th observation is an outlier. For longitudinal data, the relevant groups correspond to the observations carried on the  $i$ -th subject. In such a case, when we eliminate the set  $I$  of all the  $n_i$  observations of the  $i$ th subject, it follows that

$$\frac{\hat{\sigma}_{(I)}^2}{\hat{\sigma}^2} = \left( \frac{n-p-M_I}{n-p-n_i} \right), \quad (2.6)$$

with  $M_I = \mathbf{y}^\top \mathbf{Q} \mathbf{U}_I (\mathbf{U}_I^\top \mathbf{Q} \mathbf{U}_I)^{-1} \mathbf{U}_I^\top \mathbf{Q} \mathbf{y}$ . As in the previous case, large values of  $M_I$  suggest the existence of at least one outlying observation for subject  $i$ . We can use this approach to verify the influence of subjects on the estimation of  $\sigma^2$ . This is a generalization of the *multiple cases* approach in the standard (normal) linear context (Cook and Weisberg, 1982, p. 28).

To check for homoscedasticity of the conditional errors (when  $\boldsymbol{\Sigma} = \mathbf{I}_n$ ), we suggest to plot the standardized conditional residuals defined in (2.4) versus the fitted values. To check for normality, we should keep in mind the *confounding* present in  $\varepsilon$ . Hilden-Minton (1995) comments that the ability to check for normality of  $\varepsilon$ , using  $\varepsilon$ , decreases as  $\text{Var}[\boldsymbol{\Sigma} \mathbf{Q} \mathbf{Z}^\top \mathbf{b}] = \sigma^2 \boldsymbol{\Sigma} \mathbf{Q} \mathbf{Z} \mathbf{D} \mathbf{Z}^\top \mathbf{Q} \boldsymbol{\Sigma}$  increases in relation to  $\text{Var}[\boldsymbol{\Sigma} \mathbf{Q} \varepsilon] = \sigma^2 \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma}$ ; this motivates the definition of the *fraction of confounding* for the  $k$ -th conditional residual  $\varepsilon_k$  as

$$0 \leq F_k = \frac{\mathbf{U}_k^\top \boldsymbol{\Sigma} \mathbf{Q} \mathbf{Z} \mathbf{D} \mathbf{Z}^\top \mathbf{Q} \boldsymbol{\Sigma} \mathbf{U}_k}{\mathbf{U}_k^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{U}_k} = 1 - \frac{\mathbf{U}_k^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{U}_k}{\mathbf{U}_k^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{U}_k} \leq 1. \quad (2.7)$$

It represents the proportion of the variability of  $\hat{\varepsilon}_k$  attributed to the confounding with the BLUP. Hilden-Minton's proposal is to consider a linear transformation,  $\mathbf{L}^\top \hat{\varepsilon}$ , such that  $\mathbf{L}^\top \hat{\varepsilon}$  has minimal confounding. For example, denoting the rows of  $\mathbf{L}$  by  $\mathbf{l}_i$ ,  $\mathbf{l}_i^\top \hat{\varepsilon}$  is said to be least confounded if

$$\lambda_i = \frac{\mathbf{l}_i^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{l}_i}{\mathbf{l}_i^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{l}_i} \quad (2.8)$$

is at a maximum, subject to the restriction that  $\text{Var}[\mathbf{l}_i^\top \hat{\varepsilon}] \propto \mathbf{l}_i^\top \boldsymbol{\Sigma} \mathbf{Q} \boldsymbol{\Sigma} \mathbf{l}_i > 0$ . Thus, the *least confounded residual* is obtained by maximizing (2.8), generating a sequence of homoscedastic uncorrelated errors with variance  $\sigma^2$  and with minimum fraction of confounding. Details are presented in the Appendix. Checking the assumption of normality of the conditional errors may be carried out via normal quantile plots with simulated envelopes (Atkinson, 1985) for the standardized least confounded residuals. To illustrate this, a simulation study is outlined in Section 4.

### 2.3 EBLUP

In model (1.1),  $\mathbf{Z}_i \hat{\mathbf{b}}_i$  reflects the difference between the predicted responses for the  $i$ -th subject and the population average; therefore it can also be used to find outlying subjects, as suggested in Waternaux et al. (1989), Verbeke and Lesaffre (1996a), Pinheiro and Bates (2000) and Longford (2001), for example. Pinheiro and Bates (2000), for instance, recommend a plot of the elements of  $\hat{\mathbf{b}}_i$ , versus the subject indices. Such a plot is useful to identify subjects that are outliers with respect to the  $j$ -th element of the respective BLUP. Given that the  $\hat{\mathbf{b}}_i$  ( $i = 1, \dots, m$ ) are comparable only when the covariates in  $\mathbf{Z}_i$  are the same for all subjects (Verbeke and Lesaffre, 1996a), we can use a plot of the elements of  $\mathbf{Z}_i \hat{\mathbf{b}}_i$ , or of Mahalanobis's distance,  $\hat{\xi}_i = \hat{\mathbf{b}}_i^\top \widehat{\text{Var}}[\hat{\mathbf{b}}_i - \mathbf{b}_i] \hat{\mathbf{b}}_i$  versus the subject indices as proposed by Waternaux et al. (1989) to identify outlying subjects.

To assess which subjects are sensitive to the homogeneity of the covariance matrices of the random effects, Pinheiro and Bates (2000, p. 187) use the scatter plot matrix of the predicted random effects. Another alternative, proposed by Nobre (2004), consists in perturbing the covariance matrix of the  $i$ -th random effect by letting  $\text{Var}[\mathbf{b}_i] = w_i \sigma^2 \mathbf{D}$  with the  $w_i$  representing weights and identifying subjects

**Table 1** Uses of residuals for diagnostic purposes.

Diagnostic for	Type of residual	Plot
Linearity of effects ( $E[y] = X\beta$ )	Marginal	$\hat{\xi}_k$ vs. explanatory variables
Within-subjects covariance matrix ( $V_i$ )	Marginal	$\ I_{n_i} - R_i R_i^T\ ^2$ vs. subject indices
Presence of outlying observations	Conditional	$\hat{\xi}_k^*$ vs. observation indices
Homoscedasticity of conditional errors ( $\varepsilon_i$ )	Conditional	$\hat{\xi}_k^*$ vs. fitted values
Normality of conditional errors ( $\varepsilon_i$ )	Conditional	QQ for least confounded residuals
Presence of outlying subjects	EBLUP	$\zeta_i$ vs. subject indices
Random effects covariance structure ( $G$ )	EBLUP	$ d_{\max} $ vs. subject indices
Normality of the random effects ( $b_i$ )	EBLUP	Weighted QQ for $b_i$

which are sensitive to this assumption via local influence methods (Cook, 1986). In this direction, a plot of the normalized eigenvector ( $|d_{\max}|$ ) associated with the direction of largest normal curvature of the influence graph under a perturbation of the covariance matrix of the random effects versus the subject indices is useful to identify the influential subjects.

The EBLUP can also be used to check for normality of the vector of random effects  $b$ . Lange and Ryan (1989) suggest the use of weighted normal quantile plots of standardized linear combinations of the random effects for such purposes. Jiang (2001) proposes a test to check the assumption that the distributions of  $b$  and  $\varepsilon$  are as specified. Both papers rely on asymptotic arguments. On the other hand, considering that the mean vector and the covariance matrix of  $y$  are correctly specified, Butler and Louis (1992) showed through a simulation study, that the BLUE is not affected by an incorrect specification of the distribution of  $b$ . Such a result was theoretically confirmed by Verbeke and Lesaffre (1996b, 1997) who showed that the estimates of the parameters of model (1.1) obtained under normality assumptions are asymptotically consistent even when the distribution of  $b$  is not normal but has third finite absolute moment, and only requires a correction in the covariance matrix of the fixed effects estimators.

The use of each type of residual is summarized in Table 1.

### 3 Example

To illustrate the above procedures, we analyze data from a study conducted at the School of Dentistry of the University of São Paulo, Brazil, designed to compare a low cost toothbrush (monoblock) with a conventional toothbrush with respect to the maintenance of the capacity to remove bacterial plaque under daily use. The data in Table 2 correspond to bacterial plaque indices obtained from 32 children aged 4 to 6 before and after toothbrushing in four evaluation sessions. A trellis display for the pretreatment ( $x$ ) and posttreatment ( $y$ ) bacterial plaque indices is presented in Figure 1.

Following Singer et al. (2004) who analyze a different data set from the same study, we considered fitting models of the form

$$\ln y_{ijd} = \alpha_{jd} + \beta_{jd} \ln x_{ijd} + b_i + \varepsilon_{ijd}, \quad (3.1)$$

where  $y_{ijd}(x_{ijd})$  is the posttreatment (pretreatment) bacterial plaque index for the  $i$ -th subject evaluated in the  $d$ -th session with the  $j$ -th type of toothbrush ( $j = 0$  for the conventional toothbrush and  $j = 1$  for the monoblock toothbrush),  $\alpha_{jd}$  is a (fixed) effect associated to the  $j$ -th toothbrush type in the  $d$ -th session,  $\beta_{jd}$  is a coefficient of uniformity of the expected bacterial plaque index reduction rate associated to the  $j$ -th toothbrush type in the  $d$ th session,  $b_i \sim N(0; \tau^2)$  and  $\varepsilon_{ijkl} \sim N(0; \sigma^2)$  are independent random variables, respectively corresponding to the random effects of subjects and the random measurement errors.

**Table 2** Bacterial plaque indices.

Subject	Toothbrush	1st session		2nd session		3rd session		4th session	
		Before	After	Before	After	Before	After	Before	After
1	Conventional	1.05	1.00	1.13	0.84	1.15	0.86	1.13	0.94
2	Conventional	1.07	0.62	0.92	0.62	1.02	0.57	1.15	0.85
3	Conventional	0.82	0.62	1.52	1.07	1.39	0.97	1.78	1.39
4	Conventional	1.37	0.90	1.65	1.20	1.75	1.40	1.92	1.67
5	Conventional	1.97	1.52	1.30	1.07	1.50	1.15	1.65	1.37
6	Conventional	1.30	0.82	1.17	0.70	0.75	0.50	1.47	1.12
7	Conventional	1.61	1.19	1.52	1.13	1.22	1.00	1.63	1.22
8	Conventional	1.02	0.73	1.08	0.64	0.94	0.73	1.14	0.97
9	Conventional	1.62	1.25	1.45	1.10	1.10	0.75	1.70	1.32
10	Conventional	1.65	1.22	1.57	1.22	1.47	1.10	1.62	1.17
11	Conventional	1.02	0.78	0.60	0.47	0.88	0.75	1.36	1.08
12	Conventional	0.71	0.60	1.13	0.39	0.84	0.65	1.65	1.31
13	Conventional	1.70	1.55	1.85	1.37	1.87	1.55	1.60	1.30
14	Conventional	1.30	1.02	1.65	0.97	1.72	1.20	1.37	1.22
15	Conventional	1.40	0.80	1.83	1.03	1.76	1.38	1.96	1.15
16	Conventional	1.40	1.12	1.25	0.67	1.50	1.10	1.50	1.22
17	Monoblock	1.66	1.63	1.36	1.16	1.52	0.88	1.41	1.20
18	Monoblock	1.02	0.80	0.92	0.82	1.10	0.76	1.28	1.15
19	Monoblock	0.75	0.67	1.00	0.92	1.00	0.87	1.15	1.10
20	Monoblock	1.29	1.23	0.91	0.76	1.14	0.94	1.35	0.97
21	Monoblock	1.27	1.20	1.20	0.95	1.10	1.00	1.37	1.17
22	Monoblock	1.07	0.85	1.39	1.25	1.39	1.25	1.28	1.21
23	Monoblock	1.35	1.21	1.42	1.17	1.42	1.19	1.42	1.23
24	Monoblock	1.32	1.02	1.60	1.40	1.35	1.02	1.50	1.25
25	Monoblock	1.66	1.61	1.50	1.36	1.72	1.41	1.69	1.44
26	Monoblock	1.30	1.07	0.84	0.61	0.88	0.61	0.96	0.57
27	Monoblock	1.57	1.20	1.50	1.07	1.15	1.00	1.25	1.05
28	Monoblock	1.67	1.50	1.47	1.32	1.07	0.97	1.50	1.37
29	Monoblock	0.91	0.67	0.96	0.62	1.09	0.53	1.12	0.37
30	Monoblock	1.06	0.70	1.00	0.85	1.15	0.93	1.12	1.00
31	Monoblock	2.30	2.00	1.37	1.25	1.40	1.32	2.15	1.90
32	Monoblock	1.15	1.00	1.23	1.11	1.15	1.07	1.26	1.00

The analysis strategy used to simplify the saturated model (14) consisted of

- (i) Testing whether the uniformity coefficients for the two types of toothbrush are homogeneous across the four sessions, i.e., whether  $(\beta_{jd} = \beta, j = 0, 1, d = 1, \dots, 4)$  or, in other words, whether the model (3.1) could be reduced to

$$\ln y_{ijd} = \alpha_{jd} + \beta \ln x_{ijd} + b_i + \varepsilon_{ijd}. \quad (3.2)$$

- (ii) Testing whether the main effect of type of toothbrush and the interaction between type of toothbrush and evaluation session regarding the coefficients of residual bacterial plaque index are null or, in other words, whether

$$\alpha_{01} - \alpha_{11} = \alpha_{02} - \alpha_{12} = \alpha_{03} - \alpha_{13} = \alpha_{04} - \alpha_{14}$$

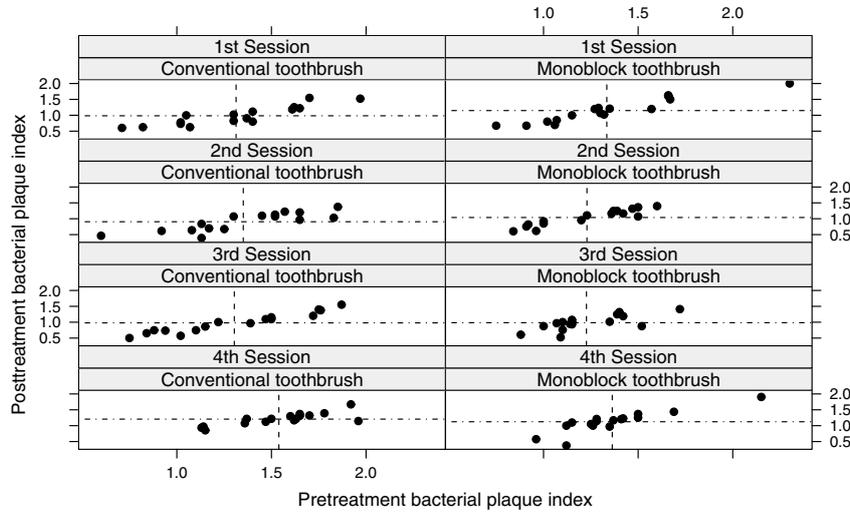


Figure 1 Trellis display for the data in Table 2.

and

$$\alpha_{jd} = \alpha_j, \quad d = 1, 2, 3, 4, \quad j = 0, 1.$$

(iii) Fitting the model that incorporates the conclusions in (i) and (ii), i.e., reducing model (3.2) to

$$\ln y_{ijd} = \alpha_j + \beta \ln x_{ijd} + b_i + \varepsilon_{ijd}.$$

The model reduction procedure was based on likelihood ratio tests (LRT) and on the Akaike and Bayesian information criteria (AIC and BIC, respectively). The LRT  $p$ -values corresponding to the reduction of (3.1) to (3.2) and of (3.2) to (3.3) were, respectively 0.3420 and 0.1623. The AIC (BIC) for models (3.1), (3.2) and (3.3) were respectively  $-95.0$  ( $-68.6$ ),  $-102.8$  ( $-86.7$ ) and  $-105.6$  ( $-92.1$ ). Based on these results, we adopted (3.3) to illustrate the use of the proposed diagnostic procedures.

To check for the linearity of effects, we plot the marginal residuals versus the logarithms of the pretreatment bacterial plaque index in Figure 2(a). In Figure 2(b) we plot the residuals for the structure of the covariance matrix versus subject indices. The former supports the regression model for the transformed response (log of the bacterial plaque index) and the latter suggests the fitted covariance matrix is not adequate for subjects #12 and #29.

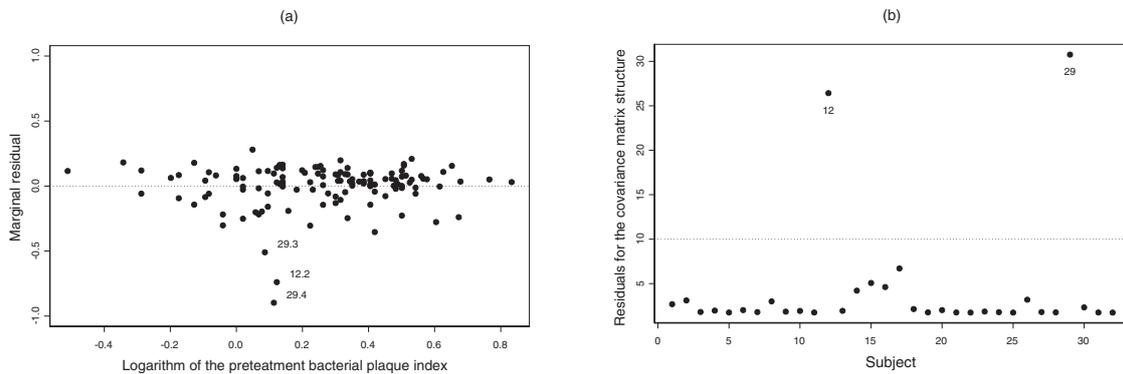
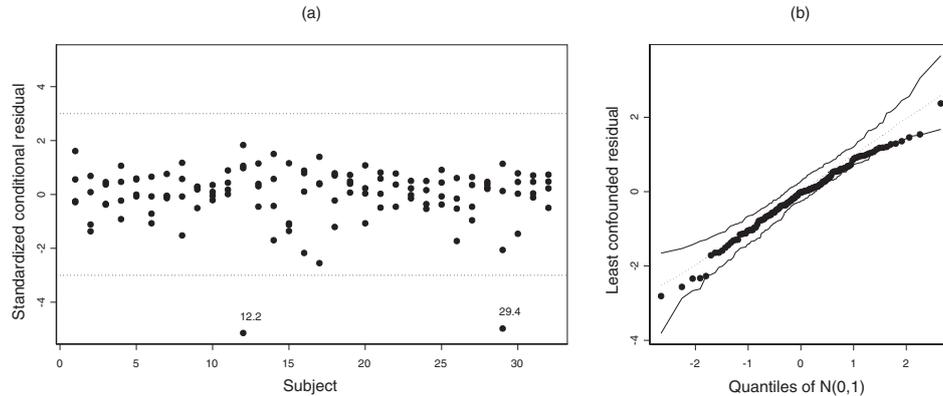


Figure 2 Marginal residual (a) and residuals for the within-subjects covariance matrix structure (b) for model (3.3).

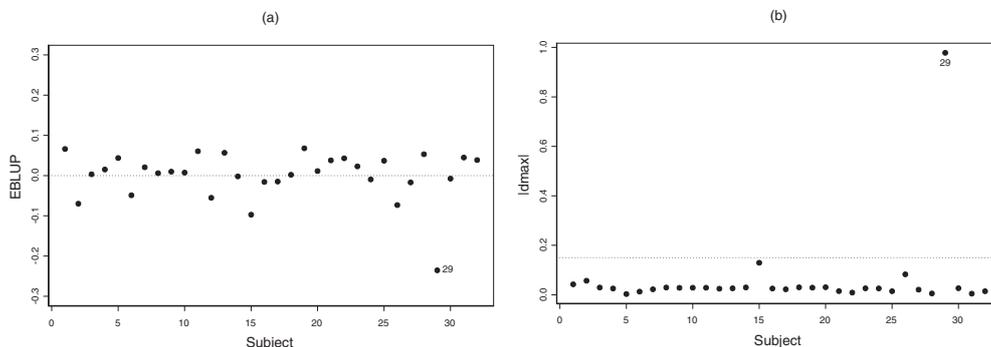


**Figure 3** Standardized conditional residuals (a) and simulated 95% confidence envelope for the standardized least confounded residuals (b) for model (3.3).

In Figure 3(a) we plot the standardized conditional residuals versus subject indices and in Figure 3(b) the simulated 95% confidence envelopes for the standardized least confounded residuals to verify the presence of outlying observations and homoscedasticity and normality of conditional errors  $\varepsilon_i$ , respectively. Observations #12.2 (second observation for subject 12) and #29.4 (fourth observation for subject 29) are highlighted in Figure 3(a) as being atypical with respect to the remaining standardized conditional residuals, suggesting that they may be possible outliers. We do not identify observations outside the simulated envelope and do not observe any trends in Figure 3(b), suggesting the plausibility of the normality assumption for the conditional error.

In Figure 4(a) we plot the EBLUP versus the subject indices, to identify outlying subjects. Also, in Figure 4(b) we plot Cook's (1986)  $|d_{\max}|$  computed under a perturbation of the variance of the random effects versus the subject indices to identify subjects that are sensitive to the homogeneity of the variances of the random effects. The plot in Figure 4(a) suggests that subject #29 is an outlier; similarly, the plot in Figure 4(b) suggests that subject #29 does not support the assumption of homogeneity of the variance of the random effects,  $\tau^2$ .

As we mentioned in Section 2, weighted normal quantile plot (that disregarding the possible *confounding*) for checking the normality of the random effects are difficult to implement; however, this assumption is not crucial for the analysis in view of the robustness of the BLUE with respect to an incorrect specification of the distribution of the random effects.



**Figure 4** EBLUP (a) and Cook's  $|d_{\max}|$  for the perturbed variance of random effects (b) for model (3.3).

**Table 3** Estimates ( $\pm$  estimated standard errors) and relative changes of the parameters of model (16) with and without subjects #12 and #29.

Parameters	$\alpha_0$	$\alpha_1$	$\beta$	$\tau^2$	$\sigma^2$
Complete data	$-0.32 \pm 0.03$	$-0.21 \pm 0.03$	$1.06 \pm 0.06$	$0.00634 \pm 0.0028$	$0.021 \pm 0.02$
Subject #12 removed	$-0.32 \pm 0.03$	$-0.22 \pm 0.03$	$1.06 \pm 0.06$	$0.00691 \pm 0.0027$	$0.015 \pm 0.02$
	(0.0%)	(-4.8%)	(0.0%)	(-9.0%)	(28.6%)
Subject #29 removed	$-0.33 \pm 0.03$	$-0.19 \pm 0.03$	$1.07 \pm 0.05$	$0.00148 \pm 0.0013$	$0.017 \pm 0.02$
	(0.0%)	(9.5%)	(0.9%)	(76.7%)	(-19.1%)
Subjects #12 and #29 removed	$-0.32 \pm 0.03$	$-0.19 \pm 0.03$	$1.07 \pm 0.05$	$0.00299 \pm 0.0014$	$0.012 \pm 0.01$
	(0.0%)	(9.5%)	(0.9%)	(52.8%)	(42.9%)

In Table 3 we present estimates of the parameters (and their relative changes within parentheses) when subjects #12 and #29 are not considered in the analysis along with corresponding estimates obtained with complete data. The relative change is defined as  $[(\hat{\theta}_{(I)} - \hat{\theta})/\hat{\theta}] \times 100\%$ , where  $\hat{\theta}_{(I)}$  denotes the parameter estimate obtained without the observations belonging to the index set  $I$ , i.e., without the observations for subject #12, subject #29 or both (the covariance parameters were estimated by restricted maximum likelihood).

From Table 3, we conclude that subjects #12 and #29 are influential with respect to the covariance parameters; in particular, subject #12 is influential with respect to  $\sigma^2$  and subject #29 with respect to  $\tau^2$ . Such results are compatible with the residual analyses (see Figures 2, 3 and 4). A description of the characteristics of the influential subjects follows:

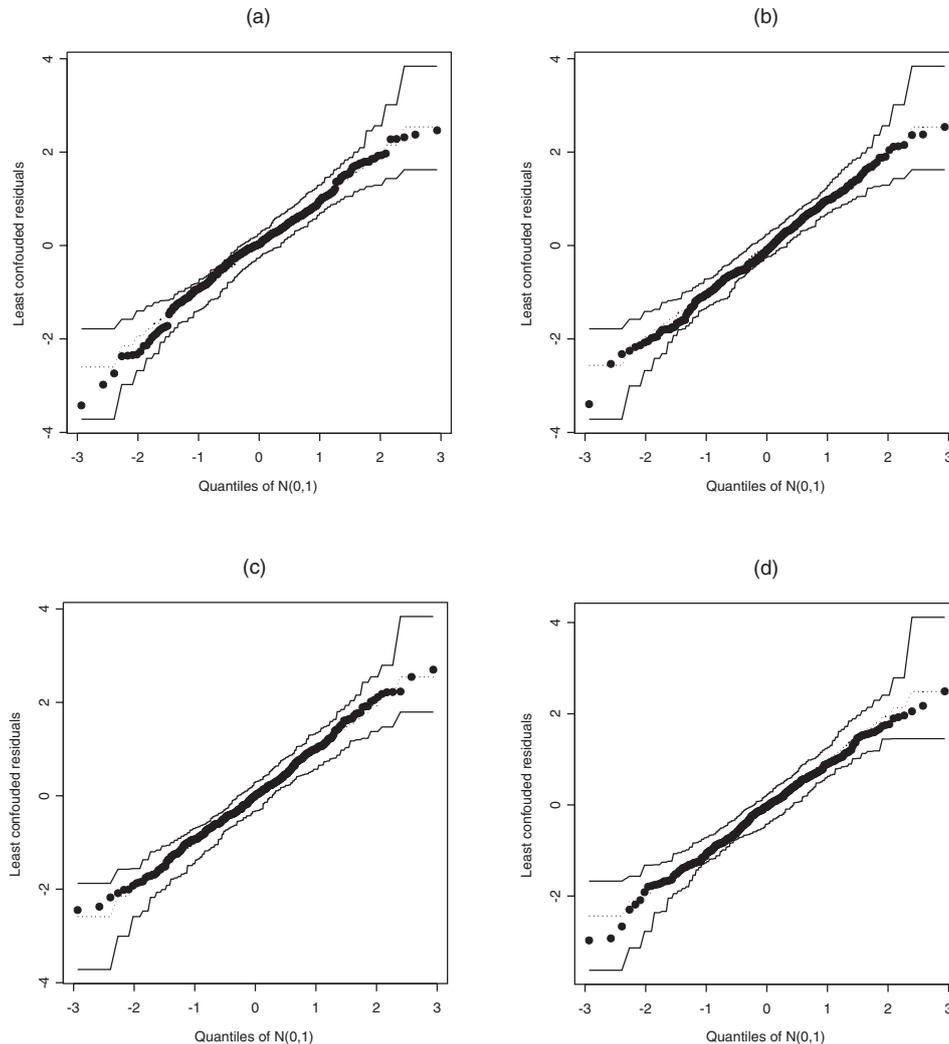
- **# 12:** this subject used the conventional toothbrush; he/she presented the second smallest pretreatment plaque index (0.71) and the smallest posttreatment plaque index (0.39), both on the second session; he/she also presents a high posttreatment plaque index (in the fourth quartile) contradicting the results based on the fitted model, that predicts larger posttreatment plaque indices for subjects that use the monoblock toothbrush. He/she presents the largest variability among the four within-subjects posttreatment plaque indices and the second smallest reduction of the bacterial plaque index ( $y/x$ );
- **# 29:** this subject used the monoblock toothbrush and presents all posttreatment plaque indices in the first quartile, with the smallest (0.37) occurring in the fourth session. This contradicts the expected results under the proposed model, that predicts smaller indices for subjects using the conventional toothbrush; he/she also presented two among the three smallest, including the smallest, indices of reduction of bacterial plaque ( $y/x$ ).

## 4 Discussion

We present a brief review of residual analysis techniques for linear mixed models of the form (1.1). In an implicit way, we assume that the covariance parameters are known and discuss the properties of the different types of residuals. Fei and Pan (2003) showed through a practical example, that incorrect identification of influential subjects may occur when the covariance structure is misspecified. Consequently, it is important to know whether  $\mathbf{D}$  and  $\mathbf{\Sigma}$  are correctly specified before performing the proposed residual analysis. The reader is referred to Wolfinger (1993), Rutter and Elashoff (1994) or Grady and Helms (1995), among others, for methods of selection of the within-subjects covariance structure in mixed models.

To evaluate the efficiency of the least confounded residuals with respect to the detection of violation of the normality assumption for the conditional errors, we generated observations from the model

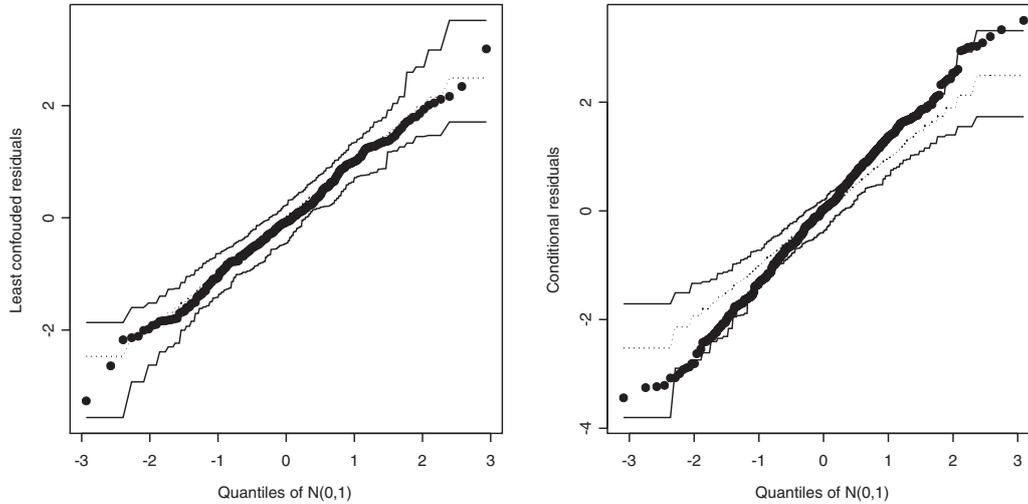
$$y_{ij} = 1 + 2x_{ij} + b_i z_{ij} + e_{ij}, \quad i = 1, \dots, 100, \quad j = 1, \dots, 5 \quad (4.1)$$



**Figure 5** Simulated 95% confidence envelope for the standardized least confounded residuals for different distributions of the random effects.

where  $e_{ij}$  and  $b_i$  are independent random variables such that  $e_{ij} \sim N(0,1)$  and  $b_i \sim F$ , where  $F$  is either (a)  $N(0,1)$ , (b) Student  $t$  distribution with 3 degrees of freedom, (c) chi-squared with 3 degrees of freedom and (d) Poisson with mean 3. We also generated  $x_{ij}$  and  $z_{ij}$  from a Uniform (0,2) distribution. In Figure 5, we plot simulated envelopes for the standardized least confounded residuals under cases (a)–(d) described above.

In all four situations, we do not identify observations outside the simulated envelope and no type of trend is observed; this suggests that standardized least confounded residuals may be employed to evaluate the plausibility of the normality assumption for the conditional error even when the random effects are not normal. To show that confounding present in  $\varepsilon$  must be taken into account, we generated observations according to (4.1), with  $b_i$  obtained from a Student  $t$  distribution with 3 degrees of freedom multiplied by 10 and  $z_{ij}$  from a Uniform (0,10) distribution. In Figure 6, we plot the simulated 95% confidence envelope for the standardized least confounded residuals and for the standardized conditional residuals.



**Figure 6** Simulated 95% confidence envelope for the standardized least confounded and standardized conditional residuals.

As we may see, the standardized conditional residuals do not present a normal behaviour, even when the conditional error is normally distributed.

Some of the procedures discussed in Section 2 are already implemented in the S-plus (nlme3) and R (nlme and lme4) packages as indicated in Pinheiro and Bates (2000, chapter 4), though some modifications are needed to take confounding and the correct standardization of the conditional residuals in consideration. The codes employed for the analysis of the example and the simulation were developed in R and can be obtained directly from the authors.

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### Appendix

Here, we sketch some proofs of the results considered in Section 2.

Firstly, note that since  $\hat{\epsilon} = \Sigma Q y$  and  $\text{Var}[y] = \sigma^2 M^{-1}$ , it follows that  $Q M^{-1} Q = Q$  and consequently, that  $\text{Var}[\hat{\epsilon}] = \sigma^2 \Sigma Q \Sigma$ .

Secondly, we show that  $\hat{\sigma}_{(K)}^2 = [y^\top (Q - Q U_K (U_K^\top Q U_K)^{-1} U_K^\top Q) y] / (n - p - v)$  is unbiased for  $\sigma^2$ . Under the assumptions of model (1.3), we have  $y \sim N(X\beta, \sigma^2 V)$ , and using  $Q X = 0$  and  $\text{tr}(Q M^{-1}) = \text{tr}(I_n - M X (X^\top M X)^{-1} X^\top) = (n - p)$ , we obtain  $\mathbb{E}[y^\top Q y] = \sigma^2 (n - p)$ . Furthermore, since  $\text{tr}(Q U_K (U_K^\top Q U_K)^{-1} U_K^\top Q M^{-1}) = v$ , we obtain  $\mathbb{E}[y^\top Q U_K (U_K^\top Q U_K)^{-1} U_K^\top Q y] = \sigma^2 v$ , implying that  $\hat{\sigma}_{(K)}^2$  is unbiased for  $\sigma^2$ .

Finally, we note that Hilden-Minton's (1995) suggestion to obtain the least confounded residuals is to maximize

$$\lambda_i = \frac{l_i^\top \Sigma Q \Sigma Q \Sigma l_i}{l_i^\top \Sigma Q \Sigma l_i} \tag{18}$$

subject to the restriction  $\text{Var}[l_i^\top \hat{\epsilon}] \propto l_i^\top \Sigma Q \Sigma l_i > 0$ . Since  $\Sigma$  is a positive definite matrix, we only need to be concerned with the non-null space of  $Q$ . Given that  $Q$  has rank  $n - p$ , we may consider the

singular value decomposition

$$\Sigma^{1/2} Q \Sigma^{1/2} = K \Lambda K^T$$

where

$$K^T K = I_{(n-p)}$$

with  $K$  denoting a  $n \times (n-p)$  matrix and  $\Lambda$  a  $(n-p) \times (n-p)$  diagonal matrix. Now, consider  $l_i = \Sigma^{-1/2} K \Lambda^{-1/2} v_i$  for any  $(n-p)$ -vector  $v_i$  and note that (4.2) can be written by

$$\lambda_i = \frac{v_i^T \Lambda v_i}{v_i^T v_i}.$$

Taking  $v_i$  as the  $i$ th column of  $I_{(n-p)}$ , it is possible to show that the maximum of (2.8) is obtained when

$$l_i = \pi_i^{-1/2} \Sigma^{-1/2} K_i^{-1/2}, \quad (i = 1, \dots, n-p)$$

with  $K_i$  representing the  $i$ th column of  $K$  and  $\pi_{n-p} \leq \dots \leq \pi_1 \leq 1$  denoting the ordered elements of  $\Lambda$ . Then,  $l_i^T \varepsilon = \pi_i^{1/2} K_i^T \Sigma y$  and it is not difficult to show that  $l_1^T \varepsilon, \dots, l_{n-p}^T \varepsilon$  constitutes a sequence of homoscedastic uncorrelated errors with variance  $\sigma^2$ .

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## Correction

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## Residual Analysis for Linear Models

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Unfortunately, in this article, the equation on page 7 is incorrect and its numbering is missing. We apologize for these errors. For the correct equation and numeration see below.

(iii) Fitting the model that incorporates the conclusions in (i) and (ii), i.e., reducing model (3.2) to

$$\ln y_{ijd} = \alpha_{jd} + \beta \ln x_{ijd} + b_i + \varepsilon_{ijd}; \quad (3.3)$$