Residual analysis for linear mixed models

Julio M Singer

Departamento de Estatística
Universidade de São Paulo

in collaboration with

Juvêncio Santos Nobre, UFC

Example of repeated measures

- Study conducted at the School of Dentistry of the University of São Paulo
- Objective: compare the effect of an experimental toothbrush with that of a conventional one with respect to bacterial plaque reduction
- Design: bacterial plaque index measured on 32 pre-schoolers (16 with conventional and 16 with experimental toothbrush) before and after toothbrushing in 4 sessions spaced by 15 days
- Repeated measures: same characteristic measured on each subject more than once
- Observations on each subject tend to be correlated

The data

Table 1: Bacterial plaque indices

		1st session		...	4th session	
Subject	Toothbrush	Before brushing	After brushing	...	Before brushing	After brushing
1	conventional	1.05	1.00	...	1.13	0.94
2	conventional	1.07	0.62	...	1.15	0.85
3	experimental	0.82	0.62	...	1.78	1.39
⋮	⋮	⋮	...	⋮	⋮	
29	conventional	0.91	0.67	...	1.12	0.37
30	experimental	1.06	0.70	...	1.12	1.00
31	experimental	2.30	2.00	...	2.15	1.90
32	conventional	1.15	1.00	...	1.26	1.00

Approaches for analysis of repeated measures

- Multivariate Analysis
  - Balanced data (all subjects measured at the same occasions)
  - Many covariance parameters
  - Exact inference based on normality assumption
- Generalized Estimating Equations
  - Interest in marginal response
  - Covariance structure based on working covariance matrix
  - Unspecified underlying distribution (except for first two moments)
- Random Effects Models
  - Models for the covariance structure
  - Marginal and subject-specific inference
  - Some flexibility in the form of underlying distributions
- Alencar, Singer and Rocha (2010, submitted) compare different approaches

Linear mixed models

Linear mixed models: popular alternative to analyze repeated measures and, in particular, longitudinal data.

$$\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \mathbf{e}_i, \quad i = 1, ..., m,$$

where

- $\mathbf{y}_i$: $(n_i \times 1)$ vector of response variables measured on subject i
- $\boldsymbol{\beta}$: $(p \times 1)$ vector of parameters (fixed effects)
- $\mathbf{X}_i$ and $\mathbf{Z}_i$: $(n_i \times p)$ and $(n_i \times q)$ known matrices of full rank
- $\mathbf{b}_i$: $(q \times 1)$ random vector, the components of which are called random effects
- $\mathbf{e}_i$: $(n_i \times 1)$ random (within-subject) error term

Linear mixed models

Usually one assumes

- $\mathbf{b}_i \overset{\text{iid}}{\sim} \mathcal{N}_q(\mathbf{0}, \mathbf{G}) \quad i = 1, ..., m$
- $\mathbf{e}_i \overset{\text{ind}}{\sim} \mathcal{N}_{n_i}(\mathbf{0}, \boldsymbol{\Sigma}_i)$
- $\mathbf{b}_i$ and $\mathbf{e}_i$ independent
- $\mathbf{G}$ and $\boldsymbol{\Sigma}_i$ are $(q \times q)$ and $(n_i \times n_i)$ positive definite matrices with elements expressed as functions of a vector of covariance parameters $\boldsymbol{\theta}$ not functionally related to $\boldsymbol{\beta}$
- If $\boldsymbol{\Sigma}_i = \mathbf{I}_{n_i}\sigma^2$: homoskedastic conditional independence model

BLUE and BLUP

Letting

$$\mathbf{y} = (\mathbf{y}_1^\top, \cdots, \mathbf{y}_m^\top)^\top, \quad \mathbf{X} = (\mathbf{X}_1^\top, \cdots, \mathbf{X}_m^\top)^\top, \quad \mathbf{Z} = \oplus_{i=1}^m \mathbf{Z}_i$$

$$\mathbf{b} = (\mathbf{b}_1^\top, \cdots, \mathbf{b}_m^\top)^\top, \quad \mathbf{e} = (\mathbf{e}_1^\top, \cdots, \mathbf{e}_m^\top)^\top$$

$$\boldsymbol{\Gamma} = \mathbf{I}_m \otimes \mathbf{G}, \quad \boldsymbol{\Sigma} = \oplus_{i=1}^m \boldsymbol{\Sigma}_i$$

we can write the model more compactly as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} + \mathbf{e}$$

Given $\boldsymbol{\Gamma}$ and $\boldsymbol{\Sigma}$

- Best Linear Unbiased Estimator (BLUE) of $\boldsymbol{\beta}$: $\quad \widehat{\boldsymbol{\beta}} = \mathbf{T}\mathbf{y}$
- Best Linear Unbiased Predictor (BLUP) of $\mathbf{b}$: $\quad \widehat{\mathbf{b}} = \boldsymbol{\Gamma}\mathbf{Z}^\top\mathbf{Q}\mathbf{y}$

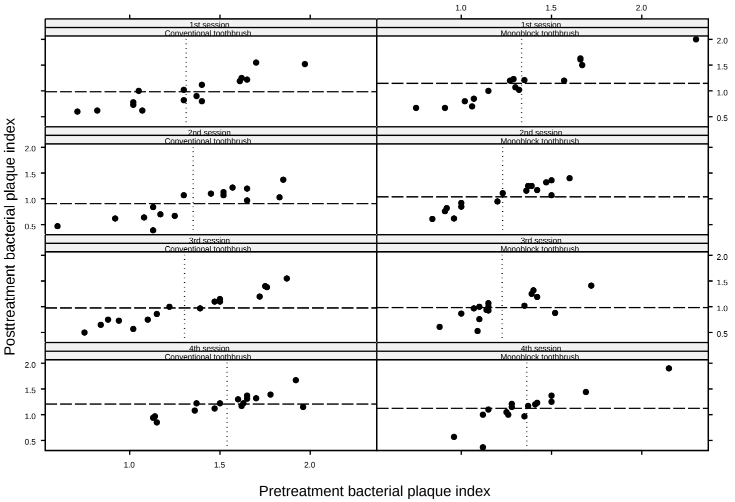
with

- $\mathbf{T} = \left(\mathbf{X}^\top\mathbf{M}\mathbf{X}\right)^{-1}\mathbf{X}^\top\mathbf{M}$
- $\mathbf{Q} = \mathbf{M}(\mathbf{I} - \mathbf{X}\mathbf{T})$
- $\mathbf{M} = \mathbf{V}^{-1} = (\mathbf{Z}\boldsymbol{\Gamma}\mathbf{Z}^\top + \boldsymbol{\Sigma})^{-1}$

Estimation of covariance parameters

- Most popular methods for estimation of covariance parameters in $\boldsymbol{\theta}$ and consequently in $\boldsymbol{\Gamma}$ and $\boldsymbol{\Sigma}$
    - maximum likelihood
    - restricted maximum likelihood (REML)
- Replacing $\boldsymbol{\Gamma}$ and $\boldsymbol{\Sigma}$ in the expressions for $\widehat{\boldsymbol{\beta}}$ and $\widehat{\mathbf{b}}$ with convenient estimates leads to the so called empirical BLUE (EBLUE) and empirical BLUP (EBLUP)
- Other estimation methods for the parameters of linear mixed models discussed in Searle et al. (1992, Wiley) and Demidenko (2004, Wiley)

Trellis display for the example data



Linear mixed model for the example

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

$$\ln y_{ijd} = \alpha_{jd} + \beta_{jd} \ln x_{ijd} + b_i + e_{ijd}, \tag{1}$$

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 ($j = 0$: conventional)
- α_{jd} is a effect associated to the j-th toothbrush type in the d-th session
- β_{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
- $b_i \sim \mathcal{N}(0, \tau^2)$ and $e_{ijd} \sim \mathcal{N}(0, \sigma^2)$ are independent

Analysis strategy

i) Test whether uniformity coefficients are homogeneous for the two types of toothbrush across the four sessions, *i.e.*, whether $\beta_{jd} = \beta$, $j = 0, 1$, $d = 1, ..., 4$

ii) Test whether main effect of type of toothbrush and interaction between type of toothbrush and evaluation session regarding the coefficients of residual bacterial plaque index are null, *i.e.*,

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

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

iii) Fit model that incorporates the conclusions in (i) and (ii), *i.e.*,

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

Results

i) Model $\ln y_{ijd} = \alpha_j + \beta \ln x_{ijd} + b_i + e_{ijd}$ has a good fit when compared with saturated model

ii) Maximum likelihood estimates and standard errors are

$$\hat{\alpha_0} = -0.32 \pm 0.03, \quad \hat{\alpha_1} = -0.21 \pm 0.03, \quad \hat{\beta} = 1.06 \pm 0.06$$

$$\hat{\tau}^2 = 0.006 \pm 0.0028, \quad \hat{\sigma}^2 = 0.021 \pm 0.002$$

Essentially, the results indicate that

a) The expected reduction in the bacterial plaque index lies around 27% for the conventional toothbrush compared to 19% for the experimental one

b) There is no reduction in efficiency for either toothbrush within the investigation period

Residual Analysis

Residuals frequently used to

- evaluate validity of assumptions of statistical models
- help in model selection

For standard (normal) linear models, residuals are used to verify

- homoskedasticity
- linearity of effects
- presence of outliers
- normality and independence of the errors

Type of residuals in linear mixed models

- Cox and Snell (1968, JRSS-B): general definition of residuals for models with single source of variability
- Hilden-Minton (1995, PhD thesis UCLA), Verbeke and Lesaffre (1997, CSDA) or Pinheiro and Bates (2000, Springer): extension to define three types of residuals that accommodate the extra source of variability present in linear mixed models, namely:
  i) Marginal residuals, $\widehat{\boldsymbol{\xi}} = \mathbf{y} - \mathbf{X}\widehat{\boldsymbol{\beta}} = \widehat{\mathbf{M}}^{-1}\widehat{\mathbf{Q}}\mathbf{y}$, predictors of marginal errors, $\boldsymbol{\xi} = \mathbf{y} - \mathbb{E}[\mathbf{y}] = \mathbf{y} - \mathbf{X}\boldsymbol{\beta} = \mathbf{Zb} + \mathbf{e}$
  ii) Conditional residuals, $\widehat{\mathbf{e}} = \mathbf{y} - \mathbf{X}\widehat{\boldsymbol{\beta}} - \mathbf{Z}\widehat{\mathbf{b}} = \widehat{\boldsymbol{\Sigma}}\widehat{\mathbf{Q}}\mathbf{y}$, predictors of conditional errors $\mathbf{e} = \mathbf{y} - \mathbb{E}[\mathbf{y}|\mathbf{b}] = \mathbf{y} - \mathbf{X}\boldsymbol{\beta} - \mathbf{Zb}$
  iii) BLUP, $\mathbf{Z}\widehat{\mathbf{b}}$, predictors of random effects, $\mathbf{Zb} = \mathbb{E}[\mathbf{y}|\mathbf{b}] - \mathbb{E}[\mathbf{y}]$

Confounded Residuals

- Hilden-Minton (1995, PhD thesis, UCLA): residual is 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

$$
\begin{aligned}
\widehat{\boldsymbol{\xi}} &= [\mathbf{I} - \mathbf{X}(\mathbf{X}^\top \widehat{\mathbf{M}} \mathbf{X})^{-1} \mathbf{X}^\top \widehat{\mathbf{M}}] \boldsymbol{\xi}, \\
\widehat{\mathbf{e}} &= \widehat{\boldsymbol{\Sigma}} \widehat{\mathbf{Q}} \mathbf{e} + \widehat{\boldsymbol{\Sigma}} \widehat{\mathbf{Q}} \mathbf{Z} \mathbf{b}, \\
\mathbf{Z} \widehat{\mathbf{b}} &= \mathbf{Z} \widehat{\boldsymbol{\Gamma}} \mathbf{Z}^\top \widehat{\mathbf{Q}} \mathbf{Z} \mathbf{b} + \mathbf{Z} \widehat{\boldsymbol{\Gamma}} \mathbf{Z}^\top \widehat{\mathbf{Q}} \mathbf{e},
\end{aligned}
$$

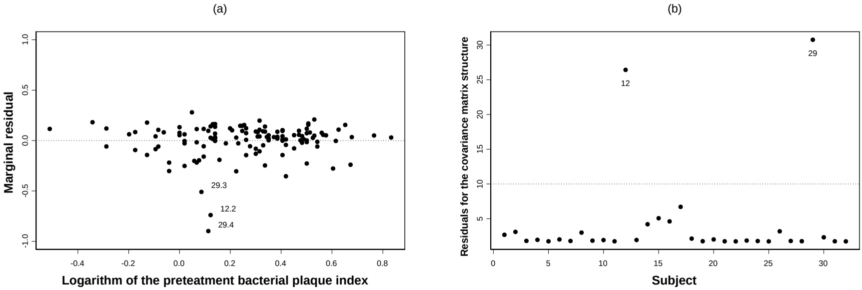
  we have
- $\widehat{\mathbf{e}}$ is confounded with $\mathbf{b}$
- $\mathbf{Z}\widehat{\mathbf{b}}$ is confounded with $\mathbf{e}$

Marginal Residuals

- Since $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\xi}$, plots of the marginal residuals $(\widehat{\boldsymbol{\xi}})$ versus explanatory variables may be employed to check linearity of $\mathbf{y}$ with respect to such variables
- Lesaffre and Verbeke (1998, Biometrics): $\mathcal{R}_i = \widehat{\mathbf{V}}_i^{-1/2}\widehat{\boldsymbol{\xi}}_i$ are residuals to check appropriateness of the within-subjects covariance matrix
- When $||\mathbf{I}_{n_i} - \mathcal{R}_i\mathcal{R}_i^\top||^2$ is small, within-subjects covariance matrix is acceptable

Marginal Residuals: example

Marginal residuals (a) and residuals for the within-subjects covariance matrix structure (b)



Some indications that linearity and/or within-subjects covariance structure might not be appropriate for subjects 12 and 29

Conditional Residuals

- Identification of outlying observations/subjects
  - Conditional standardized residuals (Nobre and Singer, 2007, Biometrical Journal)

$$\widehat{\mathbf{e}}_k^* = \frac{\widehat{\mathbf{e}}_k}{\widehat{\sigma}\sqrt{\widehat{p}_{kk}}}$$

  - p_{kk}: k-th element of the main diagonal of $\mathbf{\Sigma Q \Sigma}$, $k = 1, \ldots, n$
  - $\widehat{p}_{kk}$: functions of the joint leverage of the fixed and random effects (Nobre and Singer, 2010, Journal of Applied Statistics)
  - $\widehat{\mathbf{e}}_k^*$: generalization of usual studentized residuals

Conditional Residuals

- Check homoskedasticity of conditional errors ($\boldsymbol{\Sigma} = \sigma^2 \mathbf{I}_n$): plot standardized conditional residuals versus fitted values
- Check normality of conditional errors
  - Keep in mind the confounding present in $\widehat{\mathbf{e}}$
  - Hilden-Minton (1995, PhD thesis, UCLA): ability to check for normality of $\mathbf{e}$, using $\hat{\mathbf{e}}$, decreases as $\mathbb{V}[\boldsymbol{\Sigma}\mathbf{Q}\mathbf{Z}^\top \mathbf{b}] = \boldsymbol{\Sigma}\mathbf{Q}\mathbf{Z}\boldsymbol{\Gamma}\mathbf{Z}^\top\mathbf{Q}\boldsymbol{\Sigma}$ increases in relation to $\mathbb{V}[\boldsymbol{\Sigma}\mathbf{Q}\mathbf{e}] = \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}$
  - Fraction of confounding for the k-th conditional residual $\widehat{\mathbf{e}}_k$

$$0 \leq F_k = \frac{\mathbf{u}_k^\top \boldsymbol{\Sigma}\mathbf{Q}\mathbf{Z}\boldsymbol{\Gamma}\mathbf{Z}^\top\mathbf{Q}\boldsymbol{\Sigma}\mathbf{u}_k}{\mathbf{u}_k^\top \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{u}_k} = 1 - \frac{\mathbf{u}_k^\top \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{u}_k}{\mathbf{u}_k^\top \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{u}_k} \leq 1$$

  - Least confounded residual linear transformation $\mathbf{t}^\top \widehat{\mathbf{e}}$ such that

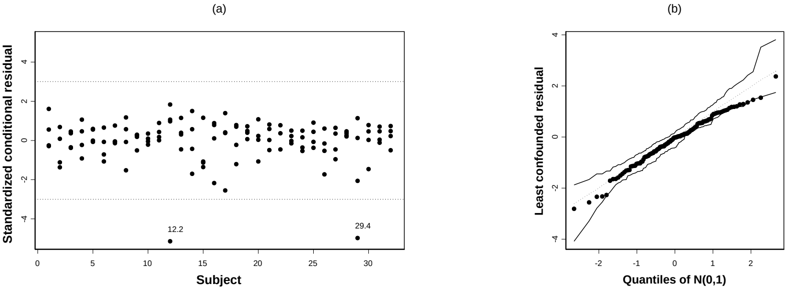
$$\lambda_i = \frac{\mathbf{t}_i^\top \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{t}_i}{\mathbf{t}_i^\top \boldsymbol{\Sigma}\mathbf{Q}\boldsymbol{\Sigma}\mathbf{t}_i}$$

  is maximum

Least Confounded Residuals: example

- Least confounded residuals: homoskedastic and uncorrelated with variance σ^2
- Check normality of the conditional errors via normal quantile plots with simulated envelopes

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



EBLUP

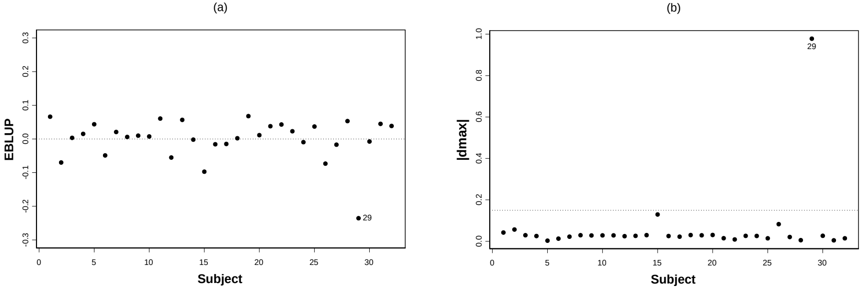
- EBLUP: reflects the difference between the predicted responses for the i-th subject and the population average
- Useful to detect outlying subjects: plot $\widehat{\zeta}_i = \widehat{\mathbf{b}}_i^\top \{\widehat{\mathbb{V}}[\widehat{\mathbf{b}}_i - \mathbf{b}_i]\}^{-1} \widehat{\mathbf{b}}_i$ versus subject indices
- Useful to assess which subjects are sensitive to homogeneity of the covariance matrices of the random effects
  - Pinheiro and Bates (2000, Springer): scatter plot matrix of the predicted random effects
  - Nobre (2004, MSc dissertation, USP): perturbation of the covariance matrix of the i-th random effect by letting $\mathbb{V}[\mathbf{b}_i] = w_i \mathbf{G}$ and identifying subjects which are sensitive to this perturbation via local influence methods

EBLUP

- Useful to check normality of random effects
  - Lange and Ryan (1989, Annals of Statistics): weighted normal quantile plots of standardized linear combinations of the random effects
  - Jiang (2001, Annals of Statistics): test to check the assumption that the distributions of $\mathbf{b}$ and $\mathbf{e}$ are as specified
  - Both papers rely on asymptotic arguments
- Butler and Louis (1992, Statistics in Medicine): BLUE is not affected by incorrect specification of distribution of $\mathbf{b}$ (simulation study)
- Result confirmed theoretically by Verbeke and Lesaffre (1997, CSDA) when distribution of $\mathbf{b}$ has finite third absolute moment, and only requires a correction in the covariance matrix of the fixed effects estimators

EBLUP: example

Figure 4: EBLUP (a) and Cook's $|\mathrm{d}_{\max}|$ for the perturbed variance of random effects (b)



Diagnostic results

- Figure 2(b): Fitted covariance matrix may not be adequate for subjects #12 and #29
- Figure 3(a): Observations #12.2 and #29.4 are highlighted as atypical with respect to the remaining standardized conditional residuals: possible outliers
- Figure 3(b): No observations outside the simulated envelope and do not show trends: plausibility of the normality assumption for the conditional error
- Figure 4(a): subject #29 may be an outlier
- Figure 4(b): data for subject # 29 not compatible with assumption of homogeneity of variance of the random effects

Summary

Table 2: Uses of residuals for diagnostic purposes

Diagnostic for	Residual	Plot
Linearity of effects ($\mathbb{E}[\mathbf{y}] = \mathbf{X}\boldsymbol{\beta}$)	Marginal	$\widehat{\xi}_k$ vs explanatory variables
Within-subjects covariance matrix ($\mathbf{V}_i$)	Marginal	$\|\|\mathbf{I}_{n_i} - \mathcal{R}_i\mathcal{R}_i^\top\|\|^2$ vs subjects
Presence of outlying observations	Conditional	$\widehat{\mathbf{e}}_k^*$ vs. observations
Homoskedasticity of conditional errors ($\mathbf{e}_i$)	Conditional	$\widehat{\mathbf{e}}_k^*$ vs. fitted values
Normality of conditional errors ($\mathbf{e}_i$)	Conditional	QQ least confounded resid
Presence of outlying subjects	EBLUP	$\hat{\zeta}_i$ (or $\widehat{\mathbf{b}}_i$) vs subjects
Random effects covariance structure ($\mathbf{G}$)	EBLUP	$\|\mathrm{d}_{\max}\|$ vs. subjects
Normality of the random effects ($\mathbf{b}_i$)	EBLUP	Weighted QQ for $\widehat{\mathbf{b}}_i$

Relative changes of estimates without outliers

Table 3: Estimates ($\pm$ estimated standard errors) of parameters and relative change with and without subjects #12 and #29

Parameters	α_0	α_1	β	τ^2	σ^2
Complete data	-0.32±0.03	-0.21±0.03	1.06±0.06	0.0063±0.0028	0.021±0.02
- Sub.#12	-0.32±0.03 (0.0%)	-0.22±0.03 (-4.8%)	1.06±0.06 (0.0%)	0.0069±0.0027 (-9.0%)	0.015±0.02 (**28.6%**)
- Sub #29	-0.33±0.03 (0.0%)	-0.19±0.03 (9.5%)	1.07±0.05 (0.9%)	0.0015±0.0013 (**76.7%**)	0.017±0.02 (-19.1%)
- Both	-0.32±0.03 (0.0%)	-0.19±0.03 (9.5%)	1.07±0.05 (0.9%)	0.0030±0.0014 (**52.8%**)	0.012±0.01 (**42.9%**)

- Details for influential subjects given in Nobre and Singer (2007, Biometrical Journal)

Discussion

- Incorrect identification of influential subjects may occur when the covariance structure is misspecified (Fei and Pan, 2003, 18-th International Workshop on Statistical Modelling)
- Wolfinger (1993, Communications in Statistics), Rutter and Elashoff (1994, Statistics in Medicine), Grady and Helms (1995, Statistics in Medicine) or Rocha and Singer (2010, in preparation): methods of selection of the covariance structure in mixed models

Efficiency of Least Confounded Residuals

- Objective: evaluate robustness of the least confounded conditional residuals
- Generated observations from the model

$$y_{ij} = 1 + 2x_{ij} + b_i z_{ij} + e_{ij},\ i = 1, ..., 100,\ j = 1, ..., 5$$

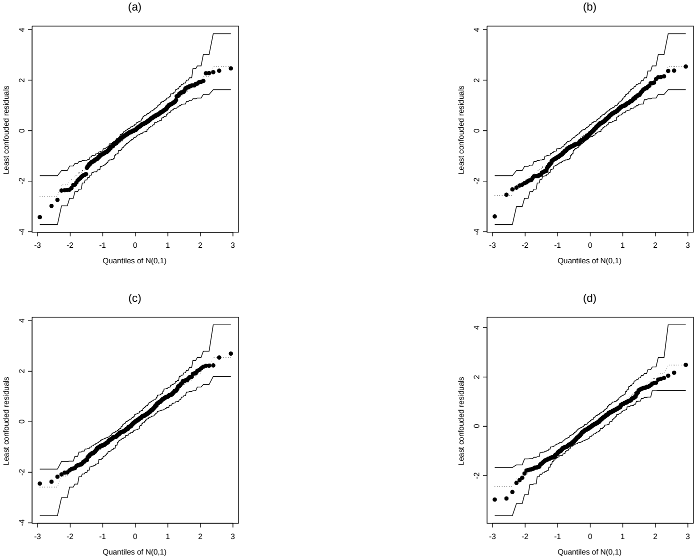
where $e_{ij} \sim \mathcal{N}(0, 1)$ and $b_i \sim F$ are independent random variables and F is either:

a) $\mathcal{N}(0, 1)$
b) t_3
c) χ^2_3
d) Poisson with mean 3

- x_{ij} and z_{ij} generated from a Uniform(0,2) distribution

Efficiency of Least Confounded Residuals

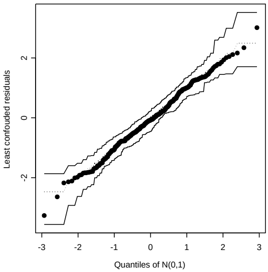
Figure 5: Simulated 95% confidence envelope for the least confounded residuals

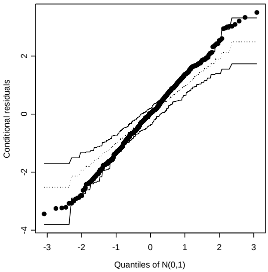


Efficiency of Least Confounded Residuals

- Objective: show that confounding present in $\widehat{\mathbf{e}}$ must be taken into account
- Generated observations according to model adopted previously, with b_i obtained from a t_3 multiplied by 4 and z_{ij} from a Uniform(3,5) distribution

Figure 6: simulated 95% confidence envelope for the standardized least confounded residuals and for the standardized conditional residuals





Conclusions and computational aspects

- 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
- Some diagnostic tools implemented in S-plus (NLME) and R (NLME and lme4) packages
- Modifications needed to take confounding and correct standardization of the conditional residuals in consideration
- Codes employed for the analysis of the example and the simulation developed in R (function lmmresdidual) and can be obtained directly from the authors

References

- Butler, S.M. and Louis, T.A. (1992). Random effects models with non-parametric priors. *Statistics in Medicine* **11**, 1981–2000.
- Cox, D.R. and Snell, E.J. (1968) A general definition of residuals (with discussion). *Journal Royal Statistical Society B* **30**, 248–275.
- Demidenko, E. (2004). *Mixed models: theory and applications*. New York: John Wiley & Sons.
- Fei, Y. & Pan, J. (2003). Influence assessments for longitudinal data in linear mixed models. In *18-th International Workshop on Statistical Modelling*. Eds. G. Verbeke, G. Molenberghs, M. Aerts and S. Fieuws. Leuven: Belgium, 143–148.
- Grady, J.J. and Helms, R.W. (1995).Model selection techniques for the covariance matrix for incomplete longitudinal data. *Statistics in Medicine* **14**, 1397–1416.
- Hilden-Minton, J.A. (1995). *Multilevel diagnostics for mixed and hierarchical linear models*. PhD Thesis, UCLA, Los Angeles.
- Jiang, J. (2001). Goodness-of-fit tests for mixed model diagnostics. *The Annals of Statistics* **29**, 1137–1164.

References

- Lange, N. and Ryan, L. (1989). Assessing normality in random effects models. *The Annals of Statistics* **17**, 624–642.
- Lesaffre, E. and Verbeke, G. (1998). Local influence in linear mixed models. *Biometrics* **54**, 570–582.
- Nobre, J.S. (2004). *Métodos de diagnóstico para modelos lineares mistos.* São Paulo: Instituto de Matemática e Estatística, Universidade de São Paulo. M.Sc. dissertation (in Portuguese).
- Nobre, J.S. and Singer, J.M. (2007). Residual analysis for linear mixed models. *Biometrical Journal*, **49**, 863–875.
- Nobre, J.S. and Singer, J.M. (2011). Leverage analysis for linear mixed models. *Journal of Applied Statistics*, **38**, 1063–1072.
- Pinheiro, J.C. and Bates, D.M. (2000). *Mixed-effects in S and S-PLUS*. Springer, New York.
- Searle, S.R., Casella, G. and McCullogh, C.E. (1992). *Variance components*. New York: Jonh Wiley & Sons.

References

- Singer, J.M., Nobre, J.S. and Sef, H.C. (2004). Regression models for pretest/posttest data in blocks. *Statistical Modelling* **4**, 324–338.
- Rocha, F.M.M. and Singer, J.M. (2009). Selection of fixed and random effects in linear mixed models. *Submitted*
- Rutter, C.M. and Elashoff, R.M. (1994). Analysis of longitudinal data: random coefficient regression modelling. *Statistics in Medicine* **13**, 1211–1231.
- Verbeke, G. and Lesaffre, E. (1996b). Large samples properties of the maximum likelihood estimators in linear mixed models with misspecified random-effects distributions. Technical report, Biostatistical Centre for Clinical Trials, Catholic University of Leuven, Belgium.
- Verbeke, G. and Lesaffre, E. (1997). The effect of misspecifying the random-effects distributions in linear mixed models for longitudinal data. *Computational Statistics & Data Analysis* **23**, 541–556.
- Wolfinger, R. (1993). Covariance structure selection in general mixed models. *Communications in Statistics-Simulation* **22**, 1079–1106.