

Chapter 1

Model Diagnostics

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1.1 Introduction (Page 1)

Linear models for uncorrelated data have well established measures to gauge the influence of one or more observations on the analysis. For such models, closed-form update expressions allow efficient computations without refitting the model.

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.

Moreover, in repeated measures or longitudinal studies, one is often interested in multivariate influence, rather than the impact of isolated points.

1.1.1 Residual

A residual is the difference between an observed quantity and its estimated or predicted value. In LME models, there are two types of residuals, marginal residuals and conditional residuals. A marginal residual is the difference between the observed data and the estimated marginal mean. A conditional residual is the difference between the observed data and the predicted value of the observation. In a model without random effects, both sets of residuals coincide.

1.1.2 Introduction

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?

1.1.3 Model Validation Framework

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

- the informal, graphical examination of estimates of model errors to assess the quality of distributional assumptions: residual analysis
- overall measures of goodness-of-fit
- 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: influence analysis.

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.

1.2 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.

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.

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 technqiues, the choice of methodology is much more restricted for the case of LMEs.

For classical linear models, residual diagnostics are typically implemented as 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.

1.3 Case Deletion Diagnostics

Since the pioneering work of Cook in 1977, deletion measures have been applied to many statistical models for identifying influential observations. Case-deletion diagnostics provide a useful tool for identifying influential observations and outliers.

The key to making deletion diagnostics useable is the development of efficient computational formulas, allowing one to obtain the case deletion diagnostics by making use of basic building blocks, computed only once for the full model.

The computation of case deletion diagnostics in the classical model is made simple by the fact that estimates of β and σ^2 , which exclude the i -th observation, can be computed without re-fitting the model. Such update formulas are available in the mixed model only if you assume that the covariance parameters are not affected by the removal of the observation in question. However, this is rarely a reasonable assumption.

Preisser (1996) describes two type of diagnostics. When the set consists of only one observation, the type is called ‘*observation-diagnostics*’. For multiple observations, Preisser describes the diagnostics as ‘*cluster-deletion*’ diagnostics.

1.3.1 Extension of Diagnostic Methods to LME models

? 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) develops case deletion diagnostics, in particular the equivalent of Cook’s distance, for diagnosing influential observations when estimating the fixed effect parameters and variance components. Deletion diagnostics provide a means of assessing the influence of an observation (or groups of observations) on inference on the estimated parameters of LME models. We shall provide a fuller discussion of Cook’s Distance in due course.

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.

1.3.2 Influence Analysis for LME Models

The linear mixed effects model is a useful methodology for fitting a wide range of models. However, linear mixed effects models are known to be sensitive to outliers. Christensen et al. (1992) advises that identification of outliers is necessary before conclusions may be drawn from the fitted model.

Standard statistical packages concentrate on calculating and testing parameter estimates without considering the diagnostics of the model. The assessment of the effects of perturbations in data, on the outcome of the analysis, is known as statistical influence analysis. Influence analysis examines the robustness of the model. Influence analysis methodologies have been used extensively in classical linear models, and provided the basis for methodologies for use with LME models. Computationally inexpensive diagnostics tools have been developed to examine the issue of influence (Zewotir and Galpin, 2005). Studentized residuals, error contrast matrices and the inverse of the response variance covariance matrix are regular components of these tools.

1.4 Case Deletion Diagnostics for LME models

Data from single individuals, or a small group of subjects may influence non-linear mixed effects model selection. Diagnostics routinely applied in model building may identify such individuals, but these methods are not specifically designed for that purpose and are, therefore, not optimal. We describe two likelihood-based diagnostics for identifying individuals that can influence the choice between two competing models.

Cook's distance

In the study of Linear Model Diagnostics, Cook proposed a measure that combines the information of leverage and residual of the observation, now known simply as the Cook's Distance. ? have adapted this measure for the analysis of LME models.

1.5 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).

1.6 Effects on fitted and predicted values

$$\hat{e}_{i(U)} = y_i - x\hat{\beta}_{(U)} \quad (1.1)$$

$$\delta_{(U)} = \hat{\beta} - \hat{\beta}_{(U)} \quad (1.2)$$

1.7 Exention of Cook's Distance methodology to LME 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.

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

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.

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

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

1.7.1 Cook's Distance

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

1.7.2 Cook's Distance for LMEs

For linear mixed effects models, Cook's distance can be extended to model influence diagnostics by defining.

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

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

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

Cook's Distance is a well known diagnostic technique used in classical linear models, 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 β or θ .

1.8 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.

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

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.

Random Effects

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

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 β or θ .

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For random effect estimates, the Cook's distance is

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

1.9.1 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.

1.9.2 Overall Influence

An overall influence statistic measures the change in the objective function being minimized. For example, in OLS regression, the residual sums of squares serves that purpose. In linear mixed models fit by maximum likelihood (ML) or restricted maximum likelihood (REML), an overall influence measure is the likelihood distance [Cook and Weisberg].

1.9.3 Influence Diagnostics: Basic Idea and Statistics

The general idea of quantifying the influence of one or more observations relies on computing parameter estimates based on all data points, removing the cases in question from the data, refitting the model, and computing statistics based on the change between full-data and reduced-data estimation.

1.9.4 Cook's 1986 paper on Local Influence

Cook 1986 introduced methods for local influence assessment. These methods provide a powerful tool for examining perturbations in the assumption of a model, particularly the effects of local perturbations of parameters of observations.

The local-influence approach to influence assessment is quite different from the case deletion approach, comparisons are of interest.

1.10 Measures of Influence

The impact of an observation on a regression fitting can be determined by the difference between the estimated regression coefficient of a model with all observations and the estimated coefficient when the particular observation is deleted. The measure DFBETA is the studentized value of this difference.

1.10.1 DFFITS

DFFITS is a statistical measure designed to show how influential an observation is in a statistical model. It is closely related to the studentized residual.

$$DFFITS = \frac{\hat{y}_i - \widehat{y}_{i(k)}}{s_{(k)}\sqrt{h_{ii}}}$$

1.10.2 PRESS

The prediction residual sum of squares (PRESS) is an value associated with this calculation. When fitting linear models, PRESS can be used as a criterion for model selection, with smaller values indicating better model fits.

$$PRESS = \sum (y - y^{(k)})^2 \quad (1.3)$$

- $e_{-Q} = y_Q - x_Q \hat{\beta}^{-Q}$
- $PRESS_{(U)} = y_i - x_i \hat{\beta}_{(U)}$

DFBETA

$$DFBETA_a = \hat{\beta} - \hat{\beta}_{(a)} \quad (1.4)$$

$$= B(Y - Y_{\bar{a}}) \quad (1.5)$$

1.11 Influence in LME Models

Model diagnostic techniques, well established for classical models, have since been adapted for use with linear mixed effects models. Diagnostic techniques for LME models are inevitably more difficult to implement, due to the increased complexity.

1.11.1 Influence Statistics for LME models

Influence statistics can be coarsely grouped by the aspect of estimation that is their primary target:

- overall measures compare changes in objective functions: (restricted) likelihood distance (Cook and Weisberg 1982, Ch. 5.2)
- influence on parameter estimates: Cook's (Cook 1977, 1979), MDFFITS (Belsley, Kuh, and Welsch 1980, p. 32)

- influence on precision of estimates: CovRatio and CovTrace
- influence on fitted and predicted values: PRESS residual, PRESS statistic (Allen 1974), DFFITS (Belsley, Kuh, and Welsch 1980, p. 15)
- outlier properties: internally and externally studentized residuals, leverage

Beckman, Nachtsheim and Cook (1987) Beckman et al. (1987) applied the local influence method of Cook (1986) to the analysis of the linear mixed model.

While the concept of influence analysis is straightforward, implementation in mixed models is more complex. Update formulae for fixed effects models are available only when the covariance parameters are assumed to be known.

If the global measure suggests that the points in U are influential, the nature of that influence should be determined. In particular, the points in U can affect the following

- 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.

1.12 Influence analysis for LME Models

Likelihood based estimation methods, such as ML and REML, are sensitive to unusual observations. Influence diagnostics are formal techniques that assess the influence of observations on parameter estimates for β and θ . A common technique is to refit the model with an observation or group of observations omitted.

West et al. (2007) examines a group of methods that examine various aspects of influence diagnostics for LME models. For overall influence, the most common approaches are the ‘likelihood distance’ and the ‘restricted likelihood distance’.

1.12.1 Influence Analysis for LME Models

The linear mixed effects model is a useful methodology for fitting a wide range of models. However, linear mixed effects models are known to be sensitive to outliers. Christensen et al. (1992) advises that identification of outliers is necessary before conclusions may be drawn from the fitted model.

Standard statistical packages concentrate on calculating and testing parameter estimates without considering the diagnostics of the model. The assessment of the effects of perturbations in data, on the outcome of the analysis, is known as statistical influence analysis. Influence analysis examines the robustness of the model. Influence analysis methodologies have been used extensively in classical linear models, and provided the basis for methodologies for use with LME models. Computationally inexpensive diagnostics tools have been developed to examine the issue of influence (Zewotir and Galpin, 2005). Studentized residuals, error contrast matrices and the inverse of the response variance covariance matrix are regular components of these tools.

Influence arises at two stages of the LME model. Firstly when V is estimated by \hat{V} , and subsequent estimations of the fixed and random regression coefficients β and u , given \hat{V} .

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1.12.4 What is Influence

Broadly defined, influence is understood as the ability of a single or multiple data points, through their presence or absence in the data, to alter important aspects of the analysis, yield qualitatively different inferences, or violate assumptions of the statistical model. The goal of influence analysis is not primarily to mark data points for deletion so that a better model fit can be achieved for the reduced data, although this might be a result of influence analysis (Schabenberger, 2004).

1.12.5 Quantifying Influence

The basic procedure for quantifying influence is simple as follows:

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

Cook (1986) introduces powerful tools for local-influence assessment and examining perturbations in the assumptions of a model. In particular the effect of local perturbations of parameters or observations are examined.

1.13 Extension of techniques to LME Models

Model diagnostic techniques, well established for classical models, have since been adapted for use with linear mixed effects models. Diagnostic techniques for LME models are inevitably more difficult to implement, due to the increased complexity.

Beckman, Nachtsheim and Cook (1987) Beckman et al. (1987) applied the local influence method of Cook (1986) to the analysis of the linear mixed model.

While the concept of influence analysis is straightforward, implementation in mixed models is more complex. Update formulae for fixed effects models are available only when the covariance parameters are assumed to be known.

If the global measure suggests that the points in U are influential, the nature of that influence should be determined. In particular, the points in U can affect the following

- 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.

1.14 Likelihood Distance

The likelihood distance is a global summary measure that expresses the joint influence of the subsets of observations, U , on all parameters in ϕ that were subject to updating. Schabenberger (2005) points out the likelihood distance gives the amount by which the log-likelihood of the model fitted from the full data changes if one were to estimate the model from a reduced-data estimates. Importantly $LD(\psi_U)$ is not the log-likelihood obtained by fitting the model to the reduced data set. It is obtained by evaluating

the likelihood function based on the full data set (containing all n observations) at the reduced-data estimates.

$$LD((\mathbf{U})) = 2[l(\hat{\phi}) - l\hat{\phi}_{\omega}]$$

$$RLD((\mathbf{U})) = 2[l_R(\hat{\phi}) - l_R(\hat{\phi})_{\omega}]$$

1.15 Analyzing Influence in LME models

1.16 Zewotir Measures of Influence in LME Models

Zewotir and Galpin (2005) describes a number of approaches to model diagnostics, investigating each of the following;

- Variance components
- Fixed effects parameters
- Prediction of the response variable and of random effects
- likelihood function

Zewotir and Galpin (2005) lists several established methods of analyzing influence in LME models. These methods include

- Cook's distance for LME models,
- likelihood distance,
- the variance (information) ration,
- the Cook-Weisberg statistic,
- the Andrews-Prebigon statistic.

1.17 Matrix Notation for Case Deletion

1.17.1 Case deletion notation

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} .

Chapter 2

Model Diagnostics

2.0.2 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.

2.0.3 Residuals diagnostics in LME Models

The marginal and conditional means in the linear mixed model are $E[\mathbf{Y}] = \mathbf{X}\boldsymbol{\beta}$ and $E[\mathbf{Y}|\mathbf{u}] = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}$, respectively.

A residual is the difference between an observed quantity and its estimated or predicted value. In the mixed model you can distinguish marginal residuals r_m and conditional residuals r_c . Schabenberger (2004) provides a useful summary.

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A residual is the difference between an observed quantity and its estimated or predicted value. In the mixed model you can distinguish marginal residuals r_m and conditional

residuals r_c .

A residual is the difference between an observed quantity and its estimated or predicted value. In LME models, there are two types of residuals, marginal residuals and conditional residuals. A marginal residual is the difference between the observed data and the estimated marginal mean. A conditional residual is the difference between the observed data and the predicted value of the observation. In a model without random effects, both sets of residuals coincide.

- A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x'_0 \hat{b}$
- A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x'_i \hat{b} - z'_i \hat{\gamma}$

The marginal and conditional means in the linear mixed model are $E[\mathbf{Y}] = \mathbf{X}\boldsymbol{\beta}$ and $E[\mathbf{Y}|\mathbf{u}] = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}$, respectively.

In linear mixed effects models, diagnostic techniques may consider ‘conditional’ residuals. A conditional residual is the difference between an observed value y_i and the conditional predicted value \hat{y}_i .

$$\epsilon_{\hat{\epsilon}}_i = y_i - \hat{y}_i = y_i - (X_i \hat{\beta} + Z_i \hat{b}_i)$$

However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

2.0.5 Marginal and Conditional Residuals

A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x'_0 \hat{b}$ A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x'_i \hat{b} - z'_i \hat{\gamma}$

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$$\epsilon_{i|} = y_i - \hat{y}_i = y_i - (X_i\hat{\beta} + Z_i\hat{b}_i)$$

However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

$$r_{mi} = x_i^T \hat{\beta} \tag{2.1}$$

2.0.6 Marginal Residuals

$$\begin{aligned} \hat{\beta} &= (X^T R^{-1} X)^{-1} X^T R^{-1} Y \\ &= BY \end{aligned}$$

2.0.7 Marginal and Conditional Residuals

A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x_0' \hat{b}$ A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x_i' \hat{b} - z_i' \hat{\gamma}$

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However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

$$r_{mi} = x_i^T \hat{\beta} \quad (2.2)$$

2.0.8 Marginal Residuals

$$\begin{aligned} \hat{\beta} &= (X^T R^{-1} X)^{-1} X^T R^{-1} Y \\ &= BY \end{aligned}$$

2.0.9 Marginal and Conditional Residuals

A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x_0' \hat{b}$. A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x_i' \hat{b} - z_i' \hat{\gamma}$.

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However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

Residuals

Residuals are used to examine model assumptions and to detect outliers and potentially influential data point. The raw residuals r_{mi} and r_{ci} are usually not well suited for these purposes.

- Conditional Residuals r_{ci}
- Marginal Residuals r_{mi}

-

Conditional Residuals

Marginal Residuals

Distinction From Linear Models

- The differences between perturbation and residual analysis in the linear model and the linear mixed model are connected to the important facts that b and b depend on the estimates of the covariance parameters, that b has the form of an (estimated) generalized least squares (GLS) estimator, and that b is a random vector.
- In a mixed model, you can consider the data in a conditional and an unconditional sense. If you imagine a particular realization of the random effects, then you are considering the conditional distribution $Y|b$ —
- If you are interested in quantities averaged over all possible values of the random effects, then you are interested in Y ; this is called the marginal formulation. In a clinical trial, for example, you may be interested in drug efficacy for a particular patient. If random effects vary by patient, that is a conditional problem. If you are interested in the drug efficacy in the population of all patients, you are using a marginal formulation. Correspondingly, there will be conditional and marginal residuals, for example.
- The estimates of the fixed effects depend on the estimates of the covariance parameters. If you are interested in determining the influence of an observation on the analysis, you must determine whether this is influence on the fixed effects for a given value of the covariance parameters, influence on the covariance parameters, or influence on both.
- Mixed models are often used to analyze repeated measures and longitudinal data. The natural experimental or sampling unit in those studies is the entity that is repeatedly observed, rather than each individual repeated observation. For example, you may be analyzing monthly purchase records by customer.

- An influential data point is then not necessarily a single purchase. You are probably more interested in determining the influential customer. This requires that you can measure the influence of sets of observations on the analysis, not just influence of individual observations.
- The computation of case deletion diagnostics in the classical model is made simple by the fact that model. Such update formulas are available in the mixed model only if you assume that the covariance parameters are not affected by the removal of the observation in question. This is rarely a reasonable assumption.
- The application of well-known concepts in model-data diagnostics to the mixed model can produce results that are at first counter-intuitive, since our understanding is steeped in the ordinary least squares (OLS) framework. As a consequence, we need to revisit these important concepts, ask whether they are portable to the mixed model, and gain new appreciation for their changed properties. An important example is the ostensibly simple concept of leverage.
- The definition of leverage adopted by the MIXED procedure can, in some instances, produce negative values, which are mathematically impossible in OLS. Other measures that have been proposed may be non-negative, but trade other advantages. Another example are properties of residuals. While OLS residuals necessarily sum to zero in any model (with intercept), this not true of the residuals in many mixed models.

2.1 Residual diagnostics

For classical linear models, residual diagnostics are typically implemented as 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.

2.1.1 Residuals diagnostics in mixed models

The marginal and conditional means in the linear mixed model are $E[\mathbf{Y}] = \mathbf{X}\boldsymbol{\beta}$ and $E[\mathbf{Y}|\mathbf{u}] = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}$, respectively.

A residual is the difference between an observed quantity and its estimated or predicted value. In the mixed model you can distinguish marginal residuals r_m and conditional residuals r_c .

2.1.2 Marginal and Conditional Residuals

A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x_0'\hat{b}$. A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x_i'\hat{b} - z_i'\hat{\gamma}$.

In linear mixed effects models, diagnostic techniques may consider ‘conditional’ residuals. A conditional residual is the difference between an observed value y_i and the conditional predicted value \hat{y}_i .

$$\epsilon_{i|} = y_i - \hat{y}_i = y_i - (X_i\hat{\beta} + Z_i\hat{\gamma})$$

However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

$$r_{mi} = x_i^T \hat{\beta} \tag{2.3}$$

2.1.3 Marginal Residuals

$$\begin{aligned}\hat{\beta} &= (X^T R^{-1} X)^{-1} X^T R^{-1} Y \\ &= BY\end{aligned}$$

2.2 Conditional and Marginal Residuals

Conditional residuals include contributions from both fixed and random effects, whereas marginal residuals include contribution from only fixed effects.

Suppose the linear mixed-effects model `lme` has an $n \times p$ fixed-effects design matrix \mathbf{X} and an $n \times q$ random-effects design matrix \mathbf{Z} .

Also, suppose the p -by-1 estimated fixed-effects vector is $\hat{\beta}$, and the q -by-1 estimated best linear unbiased predictor (BLUP) vector of random effects is \hat{b} . The fitted conditional response is

$$\hat{y}_{Cond} = X\hat{\beta} + Z\hat{b}$$

and the fitted marginal response is

$$\hat{y}_{Mar} = X\hat{\beta}$$

residuals can return three types of residuals:

- raw,
- Pearson, and
- standardized.

For any type, you can compute the conditional or the marginal residuals. For example, the conditional raw residual is

$$r_{Cond} = y - X\hat{\beta} - Z\hat{b}$$

and the marginal raw residual is

$$r_{Mar} = y - X\hat{\beta}$$

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,
predictors of marginal errors,
- ii) Conditional residuals,

$$be = yX\hat{\beta}Zbb = \hat{\sigma}Q\hat{y}$$

, predictors of conditional errors

$$e = yE[y|b] = yX\beta Zb$$

- iii) BLUP, Zbb , predictors of random effects,

$$Zb = E[y|b]E[y]$$

Marginal residuals

$$y - X\beta = Z\eta + \epsilon$$

- Should be mean 0, but may show grouping structure
- May not be homoskedastic.
- Good for checking fixed effects, just like linear regr.

Conditional residuals

$$y - X\beta - Z\eta = \epsilon$$

- Should be mean zero with no grouping structure
- Should be homoscedastic.
- Good for checking normality of outliers

Random effects

$$y - X\beta - \epsilon = Z\eta$$

- Should be mean zero with no grouping structure
- May not be be homoscedastic.

2.3 Residual diagnostics

For classical linear models, residual diagnostics are typically implemented as 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.

2.3.1 Residuals diagnostics in mixed models

The marginal and conditional means in the linear mixed model are $E[\mathbf{Y}] = \mathbf{X}\boldsymbol{\beta}$ and $E[\mathbf{Y}|\mathbf{u}] = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u}$, respectively.

A residual is the difference between an observed quantity and its estimated or predicted value. In the mixed model you can distinguish marginal residuals r_m and conditional residuals r_c .

2.3.2 Marginal and Conditional Residuals

A marginal residual is the difference between the observed data and the estimated (marginal) mean, $r_{mi} = y_i - x'_0\hat{b}$. A conditional residual is the difference between the observed data and the predicted value of the observation, $r_{ci} = y_i - x'_i\hat{b} - z'_i\hat{\gamma}$.

In linear mixed effects models, diagnostic techniques may consider ‘conditional’ residuals. A conditional residual is the difference between an observed value y_i and the conditional predicted value \hat{y}_i .

$$\epsilon_{i} = y_i - \hat{y}_i = y_i - (X_i\hat{\beta} + Z_i\hat{\gamma})$$

However, using conditional residuals for diagnostics presents difficulties, as they tend to be correlated and their variances may be different for different subgroups, which can lead to erroneous conclusions.

$$r_{mi} = x_i^T \hat{\beta} \tag{2.4}$$

2.3.3 Marginal Residuals

$$\begin{aligned} \hat{\beta} &= (X^T R^{-1} X)^{-1} X^T R^{-1} Y \\ &= BY \end{aligned}$$

2.3.4 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*.

2.4 Iterative and non-iterative influence analysis

Schabenberger (2004) highlights some of the issue regarding implementing mixed model diagnostics.

2.4.1 Iterative Influence Analysis

For linear models, the implementation of influence analysis is straightforward. However, for LME models, the process is more complex. Update formulas for the fixed effects are available only when the covariance parameters are assumed to be known. A measure of total influence requires updates of all model parameters. This can only be achieved in general is by omitting observations, then refitting the model.

Schabenberger (2004) describes the choice between iterative influence analysis and non-iterative influence analysis.

2.5 Iterative and non-iterative influence analysis

Schabenberger (2004) highlights some of the issue regarding implementing mixed model diagnostics. A measure of total influence requires updates of all model parameters.

however, this doesn't increase the procedures execution time by the same degree.

2.5.1 Iterative Influence Analysis

For linear models, the implementation of influence analysis is straightforward. However, for LME models, the process is more complex. Update formulas for the fixed effects are available only when the covariance parameters are assumed to be known. A measure of total influence requires updates of all model parameters. This can only be achieved in general is by omitting observations, then refitting the model.

Schabenberger (2004) describes the choice between iterative influence analysis and non-iterative influence analysis.

2.5.2 Iterative vs Non-Iterative Influence Analysis

While the basic idea of influence analysis is straightforward, the implementation in mixed models can be tricky. For example, update formulas for the fixed effects are available only when the covariance parameters are assumed to be known. At most the profiled residual variance can be updated without refitting the model.

A measure of total influence requires updates of all model parameters, and the only way that this can be achieved in general is by removing the observations in question and refitting the model.

Because this **bruteforce** method involves iterative reestimation of the covariance parameters, it is termed *iterative influence analysis*. Reliance on closed-form update formulas for the fixed effects without updating the (un-profiled) covariance parameters is termed a noniterative influence analysis.

An iterative analysis seems like a costly, computationally intensive enterprise. If you compute iterative influence diagnostics for all n observations, then a total of $n + 1$

mixed models are fit iteratively. This does not imply, of course, that the procedures execution time increases n -fold. Keep in mind that

- iterative reestimation always starts at the converged full-data estimates. If a data point is not influential, then its removal will have little effect on the objective function and parameter estimates. Within one or two iterations, the process should arrive at the reduced-data estimates.
- if complete reestimation does require many iterations, then this is important information in itself. The likelihood surface has probably changed drastically, and the reduced-data estimates are moving away

from the full-data estimates.

2.5.3 Influence

Schabenberger (2005) examines the use and implementation of influence measures in LME models.

Influence is understood to be the ability of a single or multiple data points, through their presences or absence in the data, to alter important aspects of the analysis, yield qualitatively different inferences, or violate assumptions of the statistical model (*schabenberger*).

Outliers are the most noteworthy data points in an analysis, and an objective of influence analysis is how influential they are, and the manner in which they are influential.

Schabenberger (2005) describes a simple procedure for quantifying influence. Firstly a model should be fitted to the data, and estimates of the parameters should be obtained. The second step is that either single or multiple data points, specifically outliers, should be omitted from the analysis, with the original parameter estimates being updated.

This is known as ‘*leave one out*’ *leave k out*’ analysis. The final step of the procedure

is comparing the sets of estimates computed from the entire and reduced data sets to determine whether the absence of observations changed the analysis.

schabenberger notes that it is not always possible to derive influence statistics necessary for comparing full- and reduced-data parameter estimates.

2.5.4 Influence

Broadly defined, *influence* is understood as the ability of a single or multiple data points, through their presence or absence in the data, to alter important aspects of the analysis, yield qualitatively different inferences, or violate assumptions of the statistical model.

The goal of influence analysis is not primarily to mark data points for deletion so that a better model fit can be achieved for the reduced data, although this might be a result of influence analysis. The goal is rather to determine which cases are influential and the manner in which they are important to the analysis. Outliers, for example, may be the most noteworthy data points in an analysis. They can point to a model breakdown and lead to development of a better model.

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.

2.5.5 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 ε 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 ; ε is normal with mean 0 and variance R ; the random components u and ε are independent. Parameters of this model are the fixed-effects 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.

2.5.6 INFLUENCE DIAGNOSTICS IN THE MIXED PROCEDURE

Key to the implementations of influence diagnostics in the MIXED procedure is the attempt to quantify influence, where possible, by drawing on the basic definitions of the various statistics in the classical linear model.

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 β .

2.5.7 Summary of Paper

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 provide studentized residuals Which ave preferred for model diagnostics. The conditional Raw residuals ave not well suited to detecting outliers as are the studentized conditional residuals. (schabenbege r)

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 observation 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.

2.6 Schabenberger: Summary and Conclusions

- 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 experimental INFLUENCE option of the MODEL statement in the MIXED procedure (SAS 9.1) enables you to perform iterative and noniterative influence analysis for individual observations and sets of observations.
- 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.

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