Contents

Chapter 1

Residual Analysis and Influence Diagnostics for Method Comparison

Model validation and model appraisal are vital parts of the modelling process, yet are too often overlooked. Using a small set of simple measures and methods, such as the AIC and R^2 measures, is insufficient to properly assess the usefulness of a fitted model. In classical linear models model diagnostics are now considered a required part of any statistical analysis, and the methods are commonly available in statistical packages and standard textbooks on applied regression. A full and comprehensive analysis that comprises residual analysis and influence analysis for testing model assumptions, should be carried out. However it has been noted by several papers (**??**) that model diagnostics do not often accompany LME model analyses. Furthermore, a suite of dagnostic procedures designed for method comparison should be adopted.

1.1 Influence Diagnostics

Model diagnostic techniques can determine whether or not the distributional assumptions are satisfied, but also to assess the influence of unusual observations. Following model specification and estimation, it is of interest to explore the model-data agreement by raising pertinent questions. **?** provide some insight into how to compute and

interpret model diagnostic plots for LME models. Unfortunately this aspect of LME theory is not as expansive as the corresponding body of work for Linear Models. Their particular observations will be reverted to shortly. Further to the analysis of residuals, **?** recommends the examination of the following questions:

- Does the model-data agreement support the model assumptions?

- Should model components be refined, and if so, which components? For example, should certain explanatory variables be added or removed, and is the covariance of the observations properly specified?

- Are the results sensitive to model and/or data? Are individual data points or groups of cases particularly influential on the analysis?

The last of these three questions, regarding influential points, is of particular interest in the context of Method Comparison. After fitting an LME model, it is important to carry put model diagnostics to check whether distributional assumptions for the residuals as satisfied and whether the fit the model is sensitive to unusual assumptions. The process of carrying out model diagnostic involves several informal and formal techniques, which will mentioned throughout the chapter.

Influential points have a large influence on the fit of the model. Influential points are a set of one or more observations whose removal would cause a different conclusion in the analysis, e.g. substantially changes the estimate of the regression coefficients. **?** remarks that influence diagnostics play an important role in the interpretation of results, because influential data can negatively influence the statistical model and generalizability of the model. **?** remarks that 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 (**?**).

Chapter 2

Residual Analysis and Influence Diagnostics for Method Comparison

In classical linear models model diagnostics are now considered a required part of any statistical analysis, and the methods are commonly available in statistical packages and standard textbooks on applied regression. However it has been noted by several papers (**??**) that model diagnostics do not often accompany LME model analyses. Well established methods are commonly available in statistical packages and standard textbooks on applied regression. However it has been noted by several papers that model diagnostics do not often accompany LME model analyses.

A comprehensive analysis that comprises residual analysis and influence analysis for testing model assumptions, should be carried out.

Following model specification and estimation, it is of interest to explore the model-data agreement by raising pertinent questions. Pinheiro and Bates provide some insight into how to compute and interpret model diagnostic plots for LME models. Unfortunately this aspect of LME theory is not as expansive as the corresponding body of work for linear models. Their particular observations will be reverted to shortly.

? discusses the state of LME diagnostics tools, providing a useful summary of established measures. Further to the analysis of residuals, **?** recommends the examination

of the following questions:

Model diagnostics techniques determine whether or not the distributional assumptions are satisfied, and to assess the influence of unusual observations, and have been become a required part of any statistical analysis. Well established methods are commonly described and implemented available on standard statistics textbooks, and implemented in software packages. However it has been noted by several papers that model diagnostics do not often accompany LME model analyses. **?** discusses the state of LME diagnostics tools, providing a useful summary of established measures.

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2.1 Residual Analysis

As with classical models, there are two key techniques for LME models: a residual plot and the normal probability plot. 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. If the residuals behave randomly, with no discernible trend, the model has fitted the data well. Conversely, if some sort of non-random trend is evident in the model, then the model can be considered to be poorly fitted.

The underlying assumptions for LME models are similar to those of classical linear models. However, for LME models the matter of residuals are more complex, both from a theoretical point of view and from the practicalities of implementing a comprehensive analysis using statistical software. **?** discusses residuals for LME model, providing a useful summary of various techniques. Prominent in literature is the taxonomy of residuals for LME Models, distinguishing between condition residuals, marginal residuals and EBLUPS, including **????**.

Statistical software environments, such as the `R` programming language, provides a suite of tests and graphical procedures for appraising a fitted LME model, with several of these procedures analysing the model residuals. Texts such as **???** describe what can be implemented for LME residual analyses with statistical software, such as `R` and `SAS`.

In the context of method comparison, a residual analysis would be carried out just as any other LME model would, testing normality. There is little scope for adding additional insights, other than to say that it is possible to create plots specific to each method. The figures on the next page depict the residual analysis for the *Blood* data, which can be used to indicate which methods disagree with the rest, but these would be a confirmation of something detected previously.

Analysis of the residuals could determine if the methods of measurement disagree systematically, or whether or not erroneous measurements associated with a subset of the cases are the cause of disagreement. The figure depicts residual plot for the systolic

blood pressure example used in **?**. Points are labelled by subjects, with cases 67, 68 and 71 being among the prominent cases. Prominent cases warrant further investigation, but an analyst should procede to influence diagnostics beforehand.
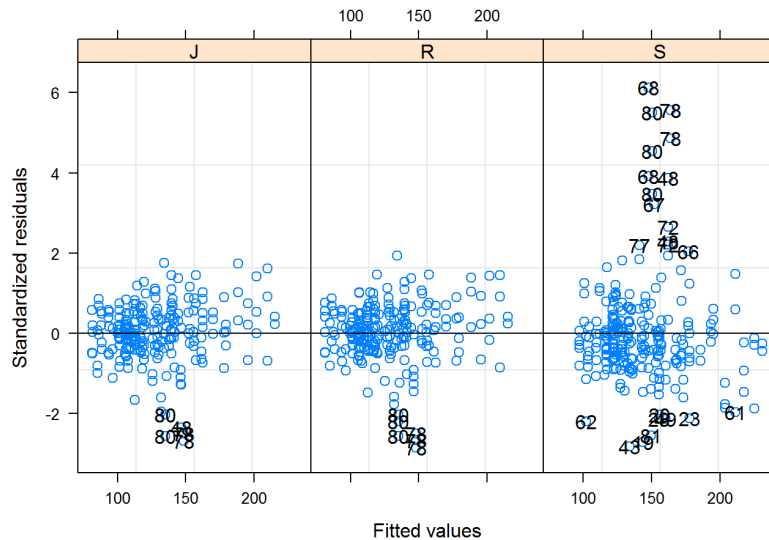
LME Residual Analysis

Figure 2.1.1: LME Residuals by Method (Blood Pressure Data)

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. Residuals are used to examine model assumptions and to detect outliers and potentially influential data point.

As with classical models, there are two key techniques: a residual plot and the normal probability plot. 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.

For classical analyses, 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.

However, for LME models the matter of residual is more complex, both from a theoretical point of view and for implementing a comprehensive analysis using statistical software. As the LME model can be tailored to the needs of the particular research question, the rationale behind the model appraisal must follow accordingly.

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2.1.1 Residual Analysis for MCS

In the context of method comparison, a residual analysis would be carried out just as any other LME model would, testing normality. As such there is little scope for adding additional insights, other than to say that it is possible to create plots specific to each method.

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LME Residual Analysis

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For classical analysese, 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. Diagnostics plots for the systolic blood pressure are featured in figure 2.1.2
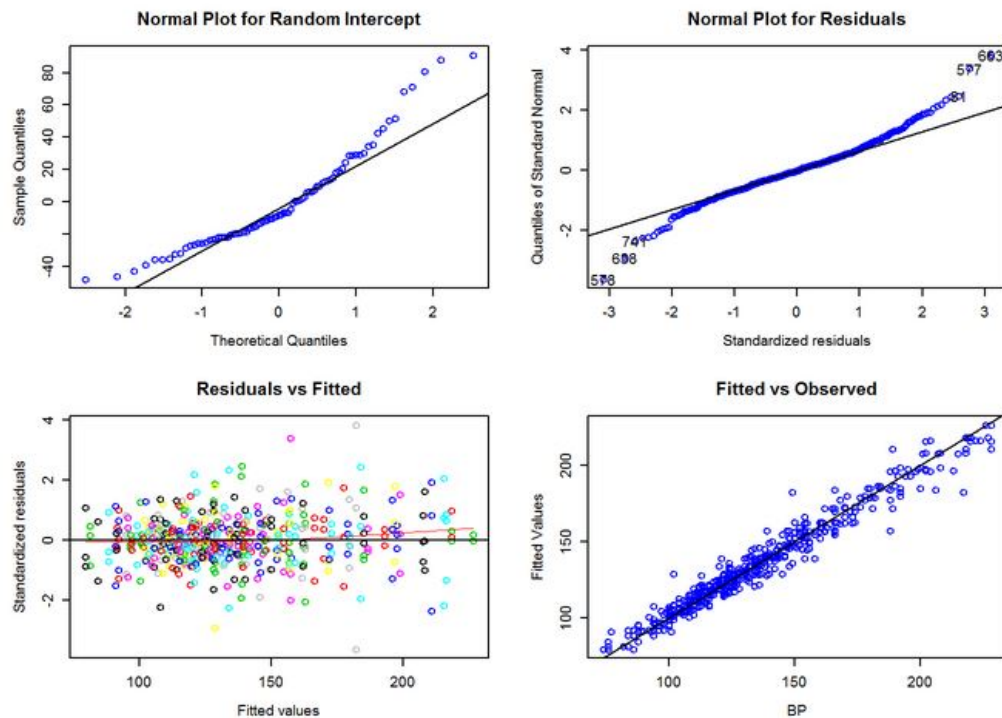

Figure 2.1.2:

As the LME model can be tailored to the needs of the particular research question, the rationale behind the model appraisal must follow accordingly. For method comparison studies, one can create plots specific to each method, useful in determining which methods disagree with the rest.

The next figure depicts residual plot for the Systolic Blood Pressure example, panelled by the various measurement methods. It serves to confirm agreement between methods J and R, with lack of agreement between those two methods and method S. However, little insight can be gained as to what actually causes lack of agreement here.
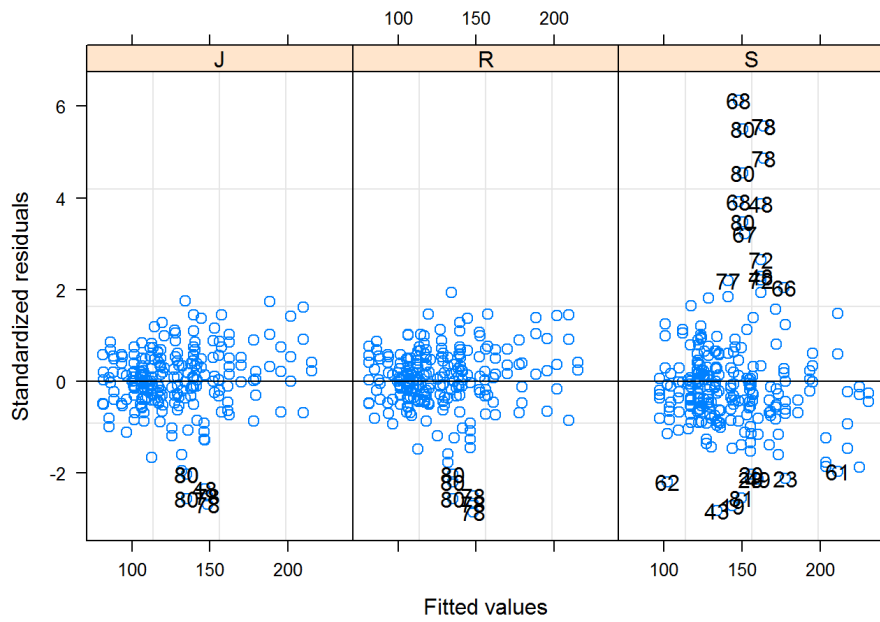

Figure 2.1.3: LME Residuals by Method (Blood Pressure Data)

The underlying assumptions for LME models are similar to those of classical linear mdoels. There are two key techniques: a residual plot and the normal probability plot. Using the nlme package it is possible to create plots specific to each method. This is useful in determine which methods disagree with the rest.

Analysis of the residuals would determine if the methods of measurement disagree systematically, or whether or not erroneous measurements associated with a subset of the cases are the cause of disagreement. Erroneous measurements are incorrect measurements that indicate disagreement between methods that would otherwise be in agreement. Once the residuals are computed, they can be used to make an assessment about the model fit. For LME models, we can plot the residuals against the fitted values, to assess the assumption of constant variance.

Normal probability plots can be rendered for each level of the random effects. LME models assume that not only the within-cluster residuals are normally distributed, but that each level of the random effects are as well. LME models assume that the residuals of the model are normally distributed. The residuals can be divided according to groups according to the method of measurement. In the following examples, we seperately assess normality the J method residuals (the first 255 residuals) and S method residuals (the remaining 255). Importantly the residuals from the J method are normally distributed, but there is non-normality of the residuals according to the S method.

Taxonomy of LME Residuals

Standard residual and influence diagnostics for linear models can be extended to linear mixed models. The dependence of fixed-effects solutions on the covariance parameter estimates has important ramifications in perturbation analysis. To gauge the full impact of a set of observations on the analysis, covariance parameters need to be updated, which requires refitting of the model.

? describes three types of residual that describe the variabilities present in LME models

1. marginal residuals, $\hat{\xi}$, which predict marginal errors,

2. conditional residuals, $\hat{\epsilon}$, which predict conditional errors,

3. the BLUP, $\boldsymbol{Z}\hat{\boldsymbol{b}}$, that predicts random effects.

Each type of residual is useful to evaluates some assumption of the model.

? describes three types of residual that describe the variabilities present in LME models, marginal residuals, $\hat{\xi}$, which predict marginal errors, conditional residuals, $\hat{\epsilon}$, which predict conditional errors, and the BLUP, $\boldsymbol{Z}\hat{\boldsymbol{b}}$, that predicts random effects. Each type of residual is useful to evaluates some assumption of the model.

The definitions of both marginal residuals (r_m) and conditional residuals (r_c) follow from the definitions of marginal and conditional means in the LME model $E[Y] = X\beta$ and $E[Y|u] = X\beta + Zu$, respectively.

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.

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.

The raw residuals r_{mi} and r_{ci} are usually not well suited for these purposes.

According to Hilton & Minton (1995), a residual is considered pure for a specfic type fo 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 error are known as 'confounded errors'.

The marginal raw residual is

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

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

Marginal residuals are good for checking fixed effects.

Conditional residuals include contributions from both fixed and random effects, whereas marginal residuals include contribution from only fixed effects. Marginal residuals should have mean of zero, but may show grouping structure. Also they may not be homoscedastic.

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 residual 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 (**?**).

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.

2.2   Influence Diagnostics

Influential points have a large influence on the fit of the model. Influential points are a set of one or more observations whose removal would cause a different conclusion in the analysis, e.g. substantially changes the estimate of the regression coefficients. **?** remarks that influence diagnostics play an important role in the interpretation of results, because influential data can negatively influence the statistical model and generalizability of the model. Influence diagnostics are formal techniques that allow the identification observation that heavily influence estimates of parameters.

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Influence can be thought of as consequence of leverage and outlierness. 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. They can point to a model breakdown and lead to development of a better model.

LME model are a useful framework for fitting a wide range of models. However, they are known to be sensitive to outliers. Specifically likelihood based estimation techniques, such as ML and REML, are sensitive to outliers. **?** advises that identification of outliers is necessary before conclusions may be drawn from the fitted model. The leverage of an observation is a further consideration.

2.2.1 Analyzing 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.

Influence diagnostics are formal techniques allowing for the identification of observations that exert substantial influence on the estimates of fixed effects and variance covariance parameters. 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. However influence diagnostics for LME Models is an area of active research. Research on diagnostic analyses for LME models are presented in **?, ?, ?, ?, ?, ?, ?, ?** and **??**.

? states that 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.

2.2.2 Cook's Distance

Cooks Distance (D_i) is a diagnostic technique used in classical linear models, that functions as an overall measure of the influence of an observation that is a measure of aggregate impact of each observation on the group of regression coefficients, as well as the group of fitted values. Cook's Distance as a measure of the influence of observations in subset U on a vector of parameter estimates is given below (**?**)

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

Observations, or sets of observations, that have high Cook's distance usually have high residuals, although this is not necessarily the case.

If the predictions are the same with or without the observation in question, then the observation has no influence on the regression model. If the predictions differ greatly when the observation is not included in the analysis, then the observation is influential.

Large values for Cook's distance indicate observations for special attention. Cook's distance can be used in several ways: to indicate data points that are particularly worth checking for validity; to indicate regions of the design space where it would be good to be able to obtain more data points.

Use of threshold values for Cook's Distance is discouraged (**?**). However, informal heuristics do exist for OLS models, with an informal threshold of $4/n$ or $4/(n-k-1)$, where n is the number of observations and k the number of explanatory variables.

? advises the use of diagnostic plotting and to examine in closer details the points with *"values of D that are substantially larger than the rest"*, and that thresholds should feature only to enhance graphical displays.

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.

? 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, adapting the Cook's Distance measure for the analysis of 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. **?** gives a detailed discussion of the various formulation for Cook's distances for LME Models.

Consideration of how leave-U-out diagnostics would work in the context of Method Comparison problems is required. There are several scenarios. **?** 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. Suppose we have two methods of measurement X and Y, each with three measurements for a specific case: $(x_1, x_2, x_3, y_1, y_2, y_3)$

- Leave One Out - one observation is omitted (e.g. x_1)

- Leave Pair Out - one pair of observation is omitted (e.g. x_1 and y_1)

- Leave Case (or Item or Subject) Out - All observations associated with a particular case or subject are omitted. (e.g. $\{x_1, x_2, x_3, y_1, y_2, y_3\}$)

The natural sampling unit is the item or subject, similar to the example provided by **?**. Hence, the third option, henceforth, referred to as "Leave subject Out" will be the option used.

2.3   Model Diagnostics for Roy's Models

Further to previous work, this section revisits case-deletion and residual diagnostics, and explores how approaches devised by **?** can be used to appraise Roy's model. These authors specifically look at Cook's Distances and Likelihood Distances.
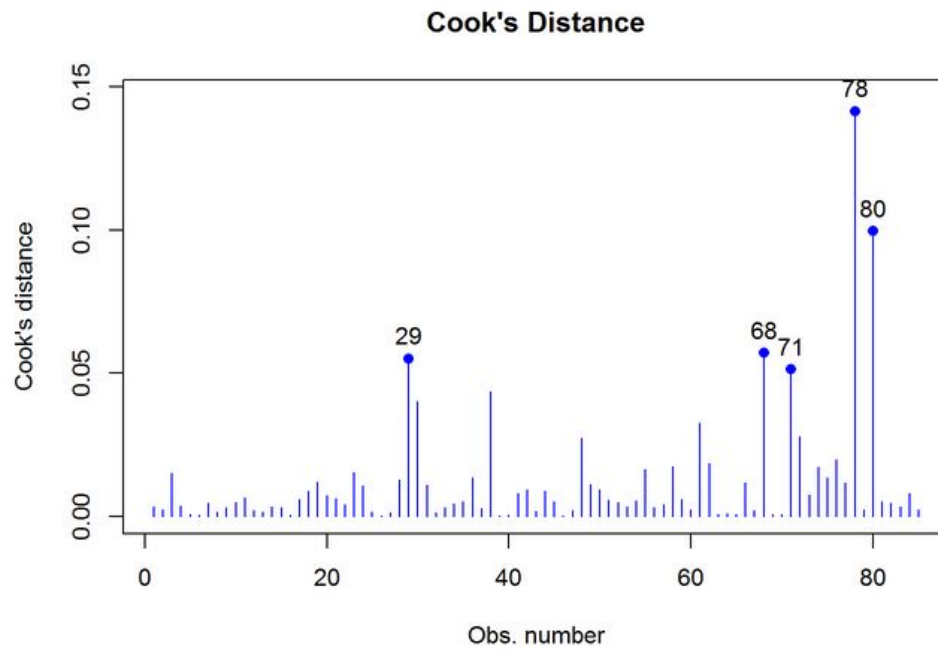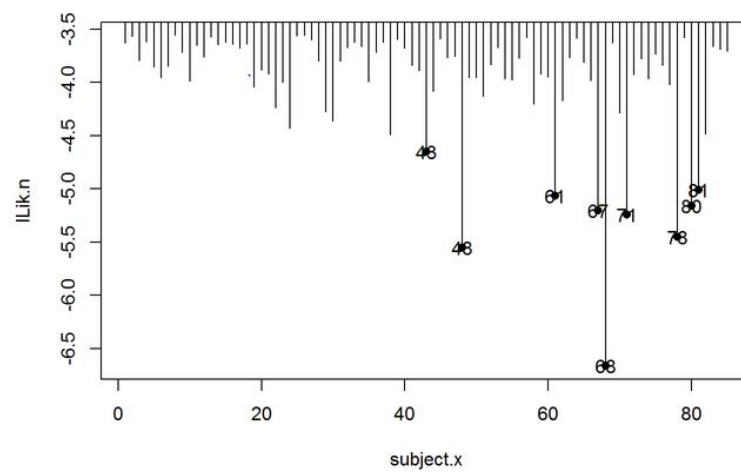
Figure 2.2.4:

Figure 2.3.5:

2.3.1   Deletion Diagnostics

Deletion diagnostics provide a means of assessing the influence of an observation (or groups of observations) on parameters inferences for a fitted model. For classical linear

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models, **?** greatly expands the study of residuals and influence measures. 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. Cook's key observation was the effects of deleting each observation in turn could be calculated with little additional computation. Cook proposed a measure that combines the information of leverage and residual of the observation, now known simply as the Cook's Distance, $D_{(i)}$, which 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.

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.

? notes the case deletion diagnostics techniques have not been applied to linear mixed effects models and seeks to develop methodologies in that respect. **?** developed their global influences for the deletion of single observations in two steps: a one-step estimate for the REML (or ML) estimate of the variance components, and an ordinary case-deletion diagnostic for a weighted resgression problem (conditional on the estimated covariance matrix) for fixed effects.

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 ith 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. This is rarely a reasonable assumption, and undermines the use of many proposed procedures for method comparison.

Case Deletion Diagnostics for Variance Ratios

Taking the core principals of his methods, and applying them to the method comparison problem, case deletion diagnostics are used on the variance components of the Roy's model, specifically the ratio of between subject variances and the within subject covariances respecitvely.

$$\text{BSVR} = \frac{\sigma_1^2}{\sigma_2^2} \qquad\qquad \text{WSVR} = \frac{g_1^2}{g_2^2}$$

These variance ratios are re-computed for each case removed, and may be analysed seperately or jointly for outliers.

The Grubbs' Test for Outliers is a commonly used technique for assessing outlier in a univariate data set, of which there are several variants. As there may be several outliers present, the Grubbs test is not practical. However an indication that a point being beyond the fences according to Tukey's specification for boxplots will suffice.

The WSVR values are plotted against the corresponding BSVR values, with commonly used bivariate methods may be applied jointly to the both sets of data sets, e.g Mahalanobis distances. Confidence ellipses can be superimposed over the plot with minimal effort. Two ellipses are generated by this technique, a 50 % and 97.5% confidence ellipse respectively. Outlying cases are idenified by the plot. Subject 68 is the most prominent case.

The subjects were ranked by Mahalanobis distance, with the top 10 being presented in the following table. Both sets of ratio are addtionally expressed as a ratio of the full model variance ratios.

Subject (u)	MD	WSVR$_{(u)}$	WSVR (%)	BSVR$_{(u)}$	BSVR (%)
68	44.7284	1.3615	0.9132	1.0353	0.9849
30	16.7228	1.5045	1.0092	1.1024	1.0487
71	11.5887	1.5210	1.0202	1.0932	1.0400
80	11.0326	1.4796	0.9925	1.0114	0.9621
38	10.3671	1.5011	1.0069	1.0917	1.0385
67	10.1940	1.4308	0.9598	1.0514	1.0002
43	7.6932	1.4385	0.9649	1.0511	0.9999
72	4.7350	1.4900	0.9995	1.0262	0.9762
48	4.4321	1.4950	1.0028	1.0280	0.9779
29	4.3005	1.4910	1.0001	1.0769	1.0244

From this table one may conclude that subjects 72, 48 and 29 are not particularly influential. Interestingly Subject 78, which was noticeable in the case deletion diagnostics for fixed effects, does not feature in this table.
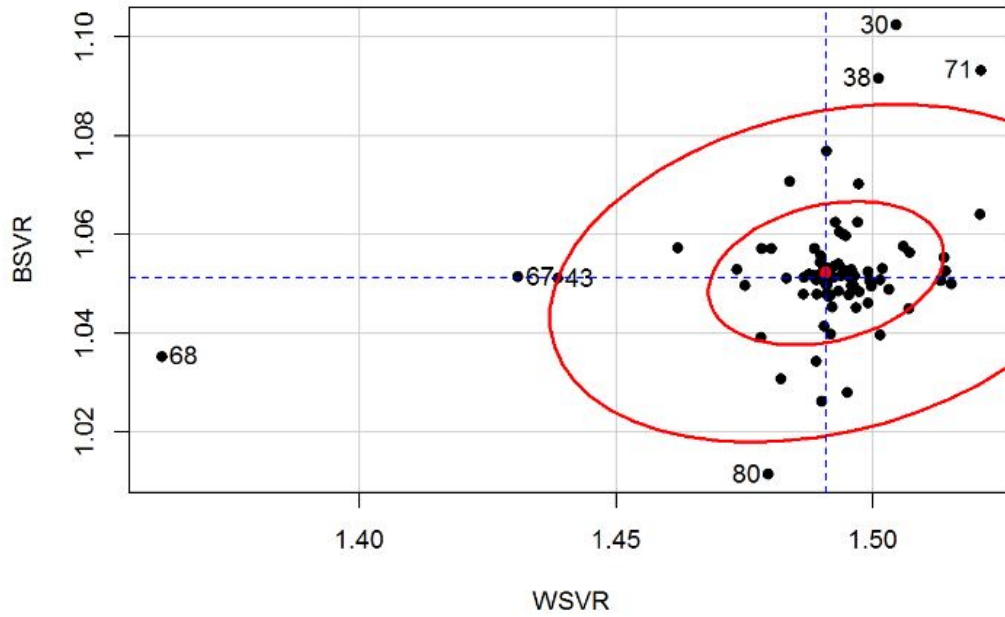

Figure 2.3.6:

Confidence Intervals for Variance Ratios

Variance Ratios

? establishes the equivalence of repeatability and within-item variability, and hence precision. The method with the smaller within-item variability can be deemed to be the more precise.

A useful approach is to compute the confidence intervals for the ratio of within-item standard deviations, which is interpreted in the usual manner. Pinheiro and Bates (pg 93-95) give a description of how confidence intervals for the variance components are computed. Furthermore a complete set of confidence intervals can be computed to complement the variance component estimates.

What is required is the computation of the variance ratios of within-item and between-item standard deviations.

A naive approach would be to compute the variance ratios by relevant F distribution quantiles. However, the question arises as to the appropriate degrees of freedom. Bootstrap methods for computing confidence intervals may be considered. **?**, pg 93-95 give a description of how confidence intervals for the variance components are computed. Furthermore a complete set of confidence intervals can be computed to complement the variance component estimates.

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2.4 Agreement Criteria for Replicate Measurements

Varying degrees of importances should be attached to each the three agreement criteria listed by **?**. Between-item variance g_i^2 is fundamentally a measure of the variability of the item-wise means, as measured by method i, but it does contain limited information on the precision of that method.

For conventional method comparison problems, both methods measures the same set of items using the same unit of measurement. Convergence to equality of between-item variance is inevitable as the number of items n increases. Significantly different estimates for g_1^2 and g_2^2 should not be expected for any practical problem.

Therefore a violation of third criterium (i.e. different between-item variances) criterium is contingent upon, and a possible consequence of, the violation of the other two agreement criteria. However, a violation of the third criterium will not occur in isolation. As noted elsewhere, the matter of inter-method bias can be easily accounted for, once detected. Both between-items and within-items variances must be calculated such that sources of variances are properly assigned, and to compute limits of agreement. However, testing the within-item criterium is the most informative analysis and therefore requires the most attention.

2.5 Using DFBETAs from LME Models to Assess Agreement

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. DFBETA and DFFITS are well known measures of influence. Emphasis shall be placed on DFBETA, but a brief discussion of DFFITS is merited as it potentially provides for useful techniques in method comparison. **?** provides a mathematical desciption of both.

DFBETAS is a standardized measure of the absolute difference between the esti-

mate with a particular case included and the estimate without that particular case,, thus measuring the impact each observation has on a particular predictor (**?**). For LME models, the DFBETA is a measure that standardizes the absolute difference in parameter estimates between an LME model based on a full set of data, and a model from reduced data.

In general, large values of DFBETAS indicate observations that are influential in estimating a given parameter. There is no agreement as to the critical threshold for DFBETAs. **?** recommend 2 as a general cutoff value to indicate influential observations and as a size-adjusted cutoff. The cut-off value for DFBETAs is $\frac{2}{\sqrt{n}}$, where n is the number of observations.

Bibliography