Contents

Two LME models are fitted to the data, one using the nlme package, one with the lme4 package. These models shall be called “blood.nlme” and “blood.lme4” respectively. In both cases the method is characterized by a fixed effect, while there is a random effect for each subject. This random effect accounts for the replicate measurements associated with each subject. The differences between the estimate provided by the respective models are negligible, due to the simplicity of the model specification.

In the graph above, you can predict non-zero values for the residuals based on the fitted value. For example, a fitted value of 8 has an expected residual that is negative. Conversely, a fitted value of 5 or 11 has an expected residual that is positive.

The non-random pattern in the residuals indicates that the deterministic portion (predictor variables) of the model is not capturing some explanatory information that is leaking into the residuals. The graph could represent several ways in which the model is not explaining all that is possible.

Possibilities include:

- A missing variable
- A missing higher-order term of a variable in the model to explain the curvature
- A missing interction between terms already in the model

Identifying and fixing the problem so that the predictors now explain the information that they missed before should produce a good-looking set of residuals!

In addition to the above, here are two more specific ways that predictive information can sneak into the residuals:

The residuals should not be correlated with another variable. If you can predict the residuals with another variable, that variable should be included in the model. In Minitabs regression, you can plot the residuals by other variables to look for this problem.

Autocorrelation

Adjacent residuals should not be correlated with each other (**autocorrelation**). If you can use one residual to predict the next residual, there is some predictive information present that is not captured by the predictors. Typically, this situation involves time-ordered observations. For example, if a residual is more likely to be followed by another residual that has the same sign, adjacent residuals are positively correlated. You can include a variable that captures the relevant time-related information, or use a time series analysis.

In Minitabs regression, you can perform the ***Durbin-Watson*** test to test for autocorrelation.

0.1 Chapter Overview

0.2 Lin's Reproducibility Index

Lin proposes the use of a reproducibility index, called the Concordance Correlation Coefficent (CCC).While it is not strictly a measure of agreement as such, it can form part of an overall method comparision methodology.

0.3 Outline of Thesis

Thus the study of method comparison is introduced. The intention of this thesis is to progress the study of method comparison studies, using a statistical method known as Linear mixed effects models. Chapter two shall describe linear mixed effects models, and how the use of the linear mixed effects models have so far extended to method comparison studies. Implementations of important existing work shall be presented, using the `R` programming language.

In the first chapter the study of method comparison is introduced, while the second chapter provides a review of current methodologies. The intention of this thesis is to progress the study of method comparison studies, using a statistical method known as Linear mixed effects models.

Chapter three shall describes linear mixed effects models, and how the use of the linear mixed effects models have so far extended to method comparison studies. Implementations of important existing work shall be presented, using the `R` programming language.

Model diagnostics are an integral component of a complete statistical analysis. In chapter three model diagnostics shall be described in depth, with particular emphasis on linear mixed effects models, further to chapter two.

For the fourth chapter, important linear mixed effects model diagnostic methods shall be extended to method comparison studies, and proposed methods shall be demonstrated on data sets that have become well known in literature on method comparison. The purpose is to both calibrate these methods and to demonstrate applications for them. The last chapter shall focus on robust measures of important parameters such as agreement.

0.4 Overview

1. Extending deletion diagnostics to LMEs

2. Christensen et al

3. Haslett hayes

4. Schabenberger

5. Tewomir

1. Residual Diagnostics

   (a) Marginal and Conditional Diagnostics

   (b) Scaled Residuals

2. Influence Diagnostics

   (a) Underlying Concepts

   (b) Managing the Covariance Parameters

   (c) Predicted Values, PRESS Residual and the PRESS Statistic

   (d) Leverage

   (e) Internally and Externally Studentized Residuals

   (f) DFFITs and MDFFITs

   (g) Covariance Ratio and Trace

   (h) Likelihood Distance

(i) Non-iterative Update Procedures

0.5 Residual

A residual (or fitting error), on the other hand, is an observable estimate of the unobservable statistical error. Residual (or error) represents unexplained (or residual) variation after fitting a regression model. It is the difference (or left over) between the observed value of the variable and the value suggested by the regression model. Consider the previous example with men's heights and suppose we have a random sample of n people. The sample mean could serve as a good estimator of the population mean. Then we have:

The difference between the observed value of the dependent variable (y) and the predicted value () is called the residual (e). Each data point has one residual.

$$\text{Residual} = \text{Observed value} - \text{Predicted value}$$

$$e = y - \hat{y}$$

Both the sum and the mean of the residuals are equal to zero. .

The difference between the height of each man in the sample and the unobservable population mean is a statistical error, whereas The difference between the height of each man in the sample and the observable sample mean is a residual. Note that the sum of the residuals within a random sample is necessarily zero, and thus the residuals are necessarily not independent. The statistical errors on the other hand are independent, and their sum within the random sample is almost surely not zero.

Other uses of the word "error" in statistics:

The use of the term "error" as discussed in the sections above is in the sense of a deviation of a value from a hypothetical unobserved value. At least two other uses also occur in statistics, both referring to observable prediction errors:

- Mean square error or mean squared error (abbreviated MSE) and root mean square error (RMSE) refer to the amount by which the values predicted by an estimator differ from the quantities being estimated (typically outside the sample from which the model was estimated).

- Sum of squared errors, typically abbreviated SSE or SSe, refers to the residual sum of squares (the sum of squared residuals) of a regression; this is the sum of the squares of the deviations of the actual values from the predicted values, within the sample used for estimation. Likewise, the sum of absolute errors (SAE) refers to the sum of the absolute values of the residuals, which is minimized in the least absolute deviations approach to regression.

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,

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

0.5.1 Residual Plots

A residual plot is a graph that shows the residuals on the vertical axis and the independent variable on the horizontal axis. If the points in a residual plot are randomly dispersed around the horizontal axis, a linear regression model is appropriate for the data; otherwise, a non-linear model is more appropriate.

Below the table on the left shows inputs and outputs from a simple linear regression analysis, and the chart on the right displays the residual (e) and independent variable (X) as a residual plot.

The residual plot shows a fairly random pattern - the first residual is positive, the next two are negative, the fourth is positive, and the last residual is negative. This random pattern indicates that a linear model provides a decent fit to the data.

Below, the residual plots show three typical patterns. The first plot shows a random pattern, indicating a good fit for a linear model. The other plot patterns are non-random (U-shaped and inverted U), suggesting a better fit for a non-linear model.

In the next lesson, we will work on a problem, where the residual plot shows a non-random pattern. And we will show how to ”transform” the data to use a linear model with nonlinear data.

Chapter 1

Fitting LME Models

Further to previous material, an appraisal of the current state of development for statistical software for fitting for LME models, particularly for `nlme` and `lme4` fitted models.

The **lme4** pacakge is used to fit linear and generalized linear mixed-effects models in the R environment. The **lme4** package is also under active development, under the leadership of Ben Bolker (McMaster Uni., Canada).

Crucially, a review of internet resources indicates that almost all of the progress in this regard has been done for `lme4` fitted models, specifically the *Influence.ME* `R` package. (Nieuwenhuis et al 2014) Conversely there is very little for `nlme` models. One would immediately look at the current development workflow for both packages.

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

With regards to `nlme`, the package is now maintained by the `R` core development team. The most recent major text is by Galecki & Burzykowski, who have published *Linear Mixed Effects Models using* `R`*.* Also, the accompanying `R` package, nlmeU package is under current development, with a version being released $0.70 - 3$.

1.1 Implementation in R

To implement an LME model in R, the nlme package is used. This package is loaded into the R environment using the library command, (i.e. library(nlme)). The lme command is used to fit LME models. The first two arguments to the lme function specify the fixed effect component of the model, and the data set to which the model is to be fitted. The first candidate model ('MCS1') fits an LME model on the data set 'dat'. The variable 'method' is assigned as the fixed effect, with the response variable 'BP' (i.e. blood pressure).

The third argument contain the random effects component of the formulation, describing the random effects, and their grouping structure. The nlme package provides a set of positive-definite matrices , the pdMat class, that can be used to specify a structure for the between-subject variance-covariance matrix for the random effects. For Roy's methodology, we will use the pdSymm and pdCompSymm to specify a symmetric structure and a compound symmetry structure respectively. A full discussion of these structures can be found in Pinheiro and Bates (1994, pg. 158).

Similarly a variety of structures for the with-subject variance-covariance matrix can be implemented using nlme. To implement a particular matrix structure, one must specify both a variance function and correlation structure accordingly. Variance functions are used to model the variance structure of the within-subject errors. varIdent is a variance function object used to allow different variances according to the levels of a classification factor in the data. A compound symmetry structure is implemented using the corCompSymm class, while the symmetric form is specified by corSymm class. Finally, the estimation methods is specified as "ML" or "REML". The first of Roy's candidate model can be implemented using the following code;

```
MCS1 = lme(BP ~ method-1, data = dat,
random =  list(subject=pdSymm(~ method-1)),
weights=varIdent(form=~1|method),
correlation = corSymm(form=~1 | subject/obs), method="ML")
```

For the blood pressure data used in Roy (2009b), all four candidate models are implemented by slight variations of this piece of code, specifying either `pdSymm` or `pdCompSymm` in the second line, and either `corSymm` or `corCompSymm` in the fourth line. For example, the second candidate model 'MCS2' is implemented with the same code as MCS1, except for the term `pdCompSymm` in the second line, rather than `pdSymm`.

```
MCS2 = lme(BP ~ method-1, data = dat,
random = list(subject=pdCompSymm(~ method-1)),
weights = varIdent(form=~1|method),
correlation = corSymm(form=~1 | subject/obs), method="ML")
```

Using this `R` implementation for other data sets requires that the data set is structured appropriately (i.e. each case of observation records the index, response, method and replicate). Once formatted properly, implementation is simply a case of re-writing the first line of code, and computing the four candidate models accordingly.

To perform a likelihood ratio test for two candidate models, simply use the `anova` command with the names of the candidate models as arguments. The following piece of code implement the first of Roy's variability tests.

```
> anova(MCS1,MCS2)
```

```
Model df    AIC    BIC  logLik   Test L.Ratio p-value
MCS1     1  8 4077.5 4111.3 -2030.7
MCS2     2  7 4075.6 4105.3 -2030.8 1 vs 2 0.15291  0.6958
>
```

The fixed effects estimates are the same for all four candidate models. The inter-method bias can be easily determined by inspecting a summary of any model. The summary presents estimates for all of the important parameters, but not the complete variance-covariance matrices (although some simple `R` functions can be written to overcome this). The variance estimates for the random effects for MCS2 is presented below.

```
Random effects:
Formula: ~method - 1 | subject
Structure: Compound Symmetry
StdDev Corr
methodJ  30.765
methodS  30.765 0.829
Residual  6.115
```

Similarly, for computing the limits of agreement the standard deviation of the differences is not explicitly given. Again, A simple `R` function can be written to calculate the limits of agreement directly.

1.2 Studentization

In statistics, a studentized residual is the quotient resulting from the division of a residual by an estimate of its standard deviation. Typically the standard deviations of residuals in a sample vary greatly from one data point to another even when the errors all have the same standard deviation, particularly in regression analysis; thus it does not make sense to compare residuals at different data points without first studentizing. It is a form of a Student's t-statistic, with the estimate of error varying between points.

This is an important technique in the detection of outliers. It is named in honor of William Sealey Gosset, who wrote under the pseudonym Student, and dividing by an estimate of scale is called studentizing, in analogy with standardizing and normalizing: see Studentization.

1.3 Fitting Models with the LME4 R package

Maximum likelihood or restricted maximum likelihood (REML) estimates of the parameters in linear mixed-effects models can be determined using the `lmer` function in the lme4 package for R. As for most model-fitting functions in R, the model is described in an `lmer` call by a formula, in this case including both fixed- and random-effects terms.

The formula and data together determine a numerical representation of the model from which the profiled deviance or the profiled REML criterion can be evaluated as a function of some of the model parameters. The appropriate criterion is optimized, using one of the constrained optimization functions in `R`, to provide the parameter estimates. We describe the structure of the model, the steps in evaluating the profiled deviance or REML criterion, and the structure of classes or types that represents such a model.

Sufficient detail is included to allow specialization of these structures by users who wish to write functions to fit specialized linear mixed models, such as models incorporating pedigrees or smoothing splines, that are not easily expressible in the formula language used by lmer.

`y` : Response variable

`method` : Method of Measurement

`subject` : Subject

`MCSdata`

```
library(lme4)


MCS.lme4 <- lmer(y ~ method-1 + (1|subject) , data=MCSdata)
```

1.3.1 Important Consideration for MCS

The key issue is that `nlme` allows for the particular specification of Roy's Model, specifically direct specification of the VC matrices for within subject and between subject residuals.

The `lme4` package does not allow for Roy's Model, for reasons that will identified shortly. To advance the ideas that eminate from Roys' paper, one is required to use the `nlme` context. However, to take advantage of the infrastructure already provided for `lme4` models, one may change the research question away from that of Roy's paper. To this end, an exploration of what textbfinfluence.ME can accomplished is merited.

1.3.2 Studentized Residuals

Standardization is not possible in practice. Studentized residuals are residuals divided by the estimated standard estimation. [Gregoire,Schabenberger, Barrett (1995)]

$$\boldsymbol{r}_m = \boldsymbol{Y} - \boldsymbol{X}\hat{\boldsymbol{\beta}}$$

$$\boldsymbol{r}_c = \boldsymbol{Y} - \boldsymbol{X}\hat{\boldsymbol{\beta}} - \boldsymbol{Z}\hat{\boldsymbol{\gamma}}$$

For the individual observation the raw studentized and pearson type residuals are computed as follows:

$$r_{mi} = Y_i - X'\hat{\boldsymbol{\beta}}$$

$$r_{ci} = r_{mi} - Y_i - z_i'\hat{\boldsymbol{\gamma}}$$

1.3.3 Residuals in the Blood Data Example

The fitted model used in the Blood data example, `JS.roy1`, was fitted using the `lme()` function from the nlme package, and as such, is stored as an `lme` object. The `residual` functions extracts residuals of a fitted LME model, depending on the type of residual required.

For an lme object, the residuals at level i are obtained by subtracting the fitted levels at that level from the response vector (and dividing by the estimated within-group standard error, if `type="pearson"`). The Pearson residual is the raw residual divided by the square root of the variance function (here, the Within-group standard error for both methods, 6.11 and 9.11 respectively). The fitted values at level i are obtained by adding together the population fitted values (based only on the fixed effects estimates) and the estimated contributions of the random effects to the fitted values at grouping levels less or equal to i.

”`response`” : the raw residuals (*observed - fitted*) are used. This is the default option.

”`pearson`” : the standardized residuals (raw residuals divided by the corresponding standard errors) are used;

”`normalized`” : the normalized residuals (standardized residuals pre-multiplied by the inverse square-root factor of the estimated error correlation matrix) are used.

```
data.frame( response = resid(JS.roy1, type = "response"),
pearson  = resid(JS.roy1, type = "pearson"),
normalized = resid(JS.roy1, type = "normalized") )
```

```
response      pearson    normalized
1    -4.65805902 -0.761587227 -0.7615872269
2    -0.88701342 -0.145025661  0.0776238081
3    -5.16580898 -0.844603753 -0.8446037530
4     2.29041830  0.374480726  0.6450898404
5     7.87508366  1.287567009  1.2875670086
```

```
6    -6.57048659 -1.074266908 -1.5090772378
...........................................
```

For the J observations, the variance is 6.116252 whereas for the S observations, the denominator is 9.118144. (with the expected ratio of 1.490806)

```
> pearson %>%
+   as.numeric %>%
+   matrix(nrow=85) %>%
+   round(4)
[,1]    [,2]    [,3]    [,4]    [,5]    [,6]
[1,] -0.7616  0.2194  0.3829 -0.2983  0.3597 -0.0790
[2,] -0.1450  0.1820 -0.1450 -0.5014  0.1567  0.2663
[3,] -0.8446  0.4634  0.1364 -0.1630 -0.2727  0.1660
[4,]  0.3745 -0.2795 -0.2795 -0.2658 -0.2658  0.6115
[5,]  1.2876 -0.6744 -0.6744  0.8935 -0.0935 -0.8612
[6,] -1.0743  1.8687 -0.7473 -0.0383  0.2908 -0.3673
...........................................
```

We can plot the residuals against the fitted values, to assess the assumption of constant variance.

```
# standardized residuals versus fitted values
plot(JS.roy1, resid(., type = "pearson") ~ fitted(.) ,
abline = 0, id = 0.05)
```

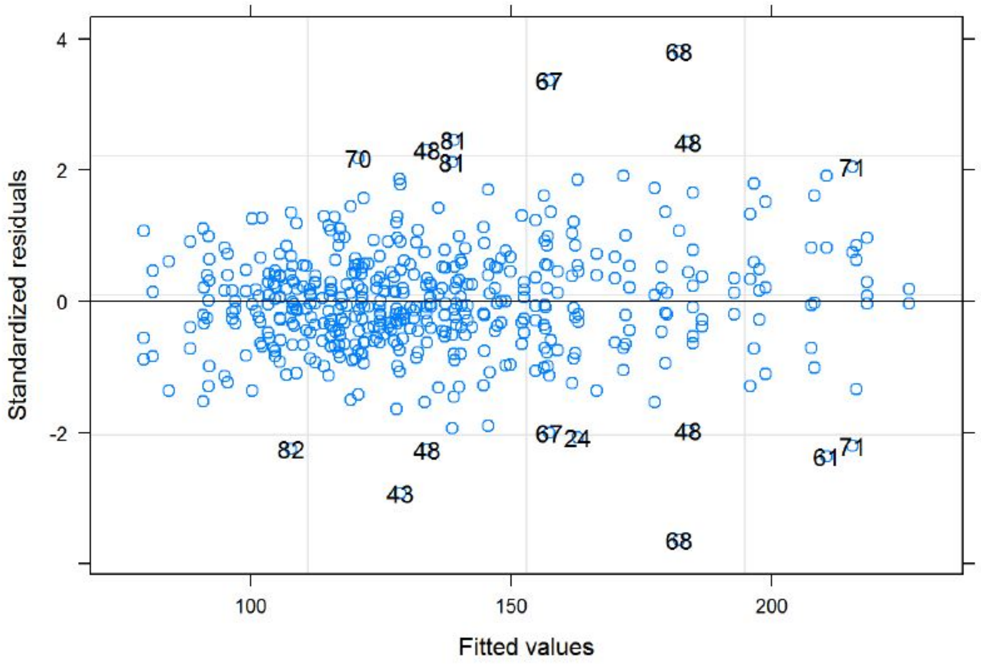


Figure 1.3.1:

1.3.4 Residual Plots

A residual plot is a graph that shows the residuals on the vertical axis and the independent variable on the horizontal axis. If the points in a residual plot are randomly dispersed around the horizontal axis, a linear regression model is appropriate for the data; otherwise, a non-linear model is more appropriate.

```
par(mfrow=c(1,2))
qqnorm((resid(JS.roy1)[1:255]),
pch="*",col="red",
ylim=c(-40,40),
main="Method J")
qqline(resid(JS.roy1)[1:255],col="blue")
qqnorm((resid(JS.roy1)[256:510]),
pch="*",col="red",
ylim=c(-40,40),
main="Method S")
qqline(resid(JS.roy1)[256:510],col="blue")
par(mfrow=c(1,1))
```

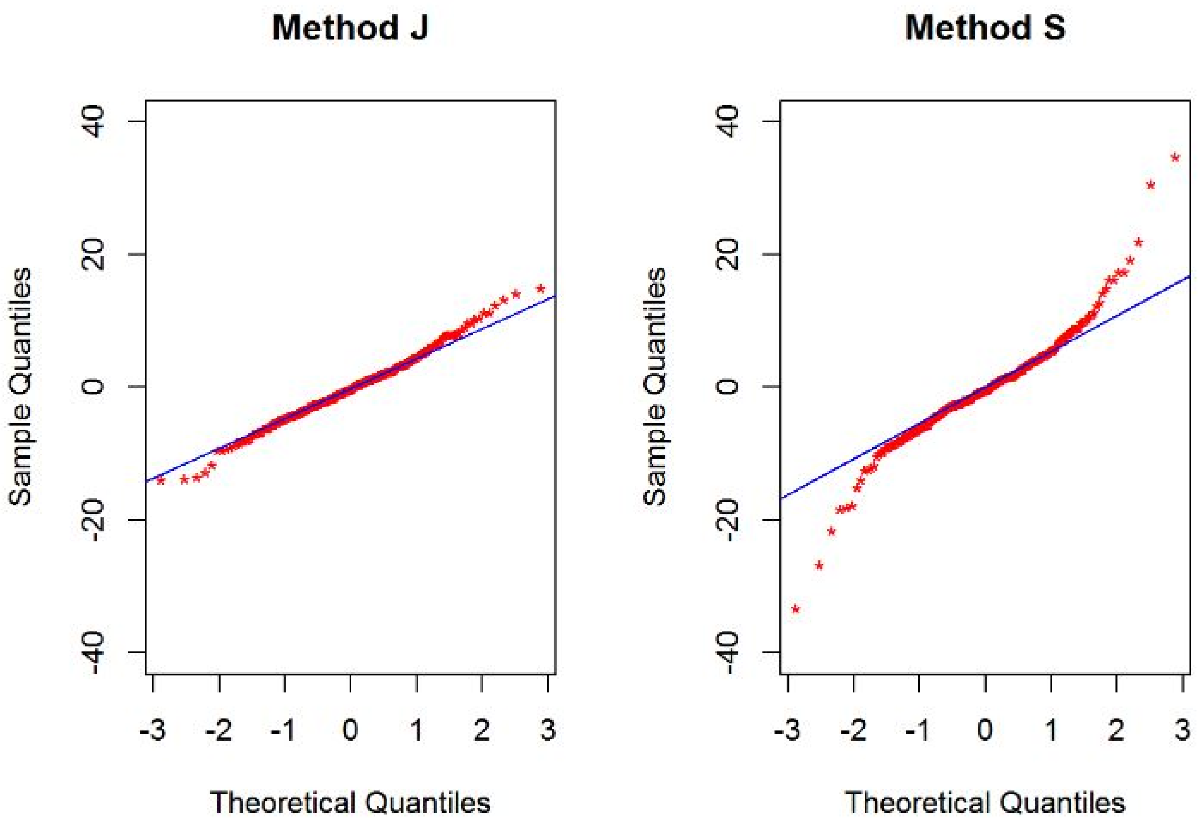
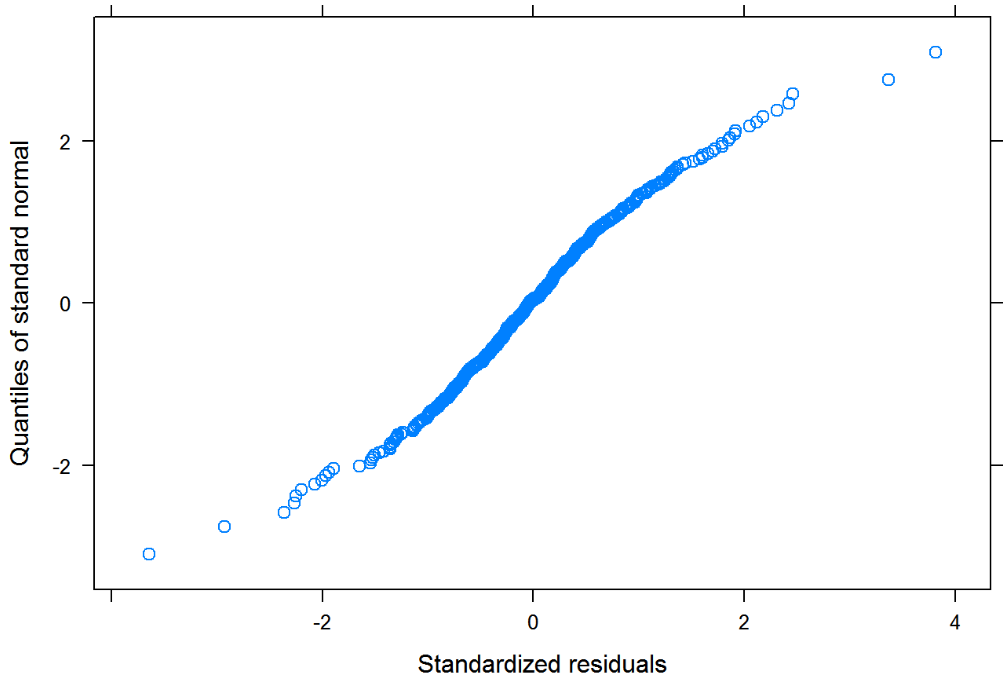


Figure 1.3.2:

This code will allow you to make QQ plots 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. Depending on the model, you can vary the level from 0, 1, 2 and so on



```
qqnorm(JS.roy1, ~ranef(.))


#  qqnorm(JS.roy1, ~ranef(.,levels=1)
```

1.4 Residual Diagnostics

Consider a residual vector of the form $\hat{e} = \boldsymbol{PY}$, where $\boldsymbol{P}$ is a projection matrix, possibly an oblique projector. External studentization uses an estimate of Var that does not involve the ith observation. Externally studentized residuals are often preferred over studentized residuals because they have well known distributional properties in the standard linear models for independent data. Residuals that are scaled by the estimated

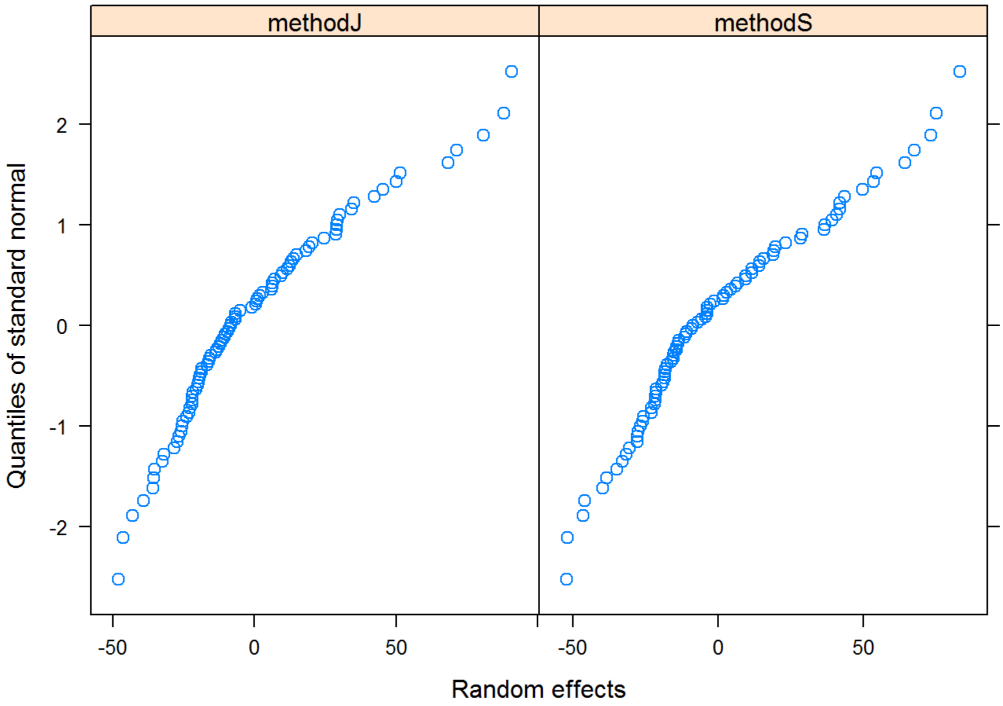


Figure 1.3.3:

variances of the responses are referred to as Pearson-type residuals. Standardization:

$$\frac{\hat{e}_i}{\sqrt{v_i}}$$

Studentization

$$\frac{\hat{e}_i}{\sqrt{\hat{v}_i}}$$

1.5 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***

Chapter 2

Appendices

2.1 Haslett Hayes

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

A general theory is presented for residuals from the general linear model with correlated errors. It is demonstrated that there are two fundamental types of residual associated with this model, referred to here as the marginal and the conditional residual. These measure respectively the distance to the global aspects of the model as represented by the expected value and the local aspects as represented by the conditional expected value. These residuals may be multivariate.

In contrast to classical linear models, diagnostics for LME are difficult to perform and interpret, because of the increased complexity of the model

2.2 RSquared for LME models

As a complement to this, one can also consider how to properly employ the R^2 measure, in the context of Methoc Comparison Studies, further to the work by Edwards et al, namely "An R^2 statistic for fixed effects in the linear mixed model".

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

The value and familiarity of the R2 statistic in the linear univariate model naturally creates great interest in extending it to the linear mixed model. We define and describe how to compute a model R2 statistic for the linear mixed model by using only a single model.

The proposed R2 statistic measures multivariate association between the repeated outcomes and the fixed effects in the linear mixed model. The R2 statistic arises as a 11 function of an appropriate F statistic for testing all fixed effects (except typically the intercept) in a full model.

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

Furthermore, the R2 statistic leads immediately to a natural definition of a partial R2 statistic. A mixed model in which ethnicity gives a very small p-value as a longitudinal predictor of blood pressure (BP) compellingly illustrates the value of the statistic.

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

2.3 Remarks on the Multivariate Normal Distribution

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

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

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

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

with k-dimensional mean vector

$$\mu = [\mathrm{E}[X_1], \mathrm{E}[X_2], \ldots, \mathrm{E}[X_k]]$$

and $k \times k$ covariance matrix

$$\Sigma = [\mathrm{Cov}[X_i, X_j]], \ i = 1, 2, \ldots, k; \ j = 1, 2, \ldots, k$$

1. Univariate Normal Distribution

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

2. Bivariate Normal Distribution

   (a)

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

(b)

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

2.4 Alternative agreement indices

As an alternative to limits of agreement, Lin et al. (2002) proposes the use of the mean square deviation is assessing agreement. The mean square deviation is defined as the expectation of the squared differences of two readings . The MSD is usually used for the case of two measurement methods X and Y , each making one measurement for the same subject, and is given by

$$MSDxy = E[(x-y)^2] = (\mu_x - \mu_y)^2 + (\sigma_x - \sigma_y)^2 + 2\sigma_x\sigma_y(1 - \rho_{xy}).$$

Barnhart et al. (2007) advises the use of a predetermined upper limit for the MSD value, MSD_{ul}, to define satisfactory agreement. However, a satisfactory upper limit may not be properly determinable, thus creating a drawback to this methodology.

Barnhart et al. (2007) proposes both the use of the square root of the MSD or the expected absolute difference (EAD) as an alternative agreement indices. Both of these indices can be interpreted intuitively, being denominated in the same units of measurements as the original measurements. Also they can be compare to the maximum acceptable absolute difference between two methods of measurement d_0.

$$EAD = E(|x-y|) = \frac{\sum |x_i - y_i|}{n}$$

The EAD can be used to supplement the inter-method bias in an initial comparison study, as the EAD is informative as a measure of dispersion, is easy to calculate and requires no distributional assumptions.

Barnhart et al. (2007) remarks that a comparison of EAD and MSD , using simulation studies, would be interesting, while further adding that ‘It will be of interest to investigate the benefits of these possible new unscaled agreement indices’. For the

Grubbs' 'F vs C' and 'F vs T' comparisons, the inter-method bias, difference variances, limits of agreement and EADs are shown in Table 1.5. The corresponding Bland-Altman plots for 'F vs C' and 'F vs T' comparisons were depicted previously on Figure 1.3. While the inter-method bias for the 'F vs T' comparison is smaller, the EAD penalizes the comparison for having a greater variance of differences. Hence the EAD values for both comparisons are much closer.

	F vs C	F vs T
Inter-method bias	-0.61	0.12 3
Difference variances	0.06	0.22
Limits of agreement	(-1.08, -0.13)	(-0.81,1.04)
EAD	0.61	0.35

Table 2.4.1: Agreement indices for Grubbs' data comparisons.

2.5 Coverage Probability

Further to Lin (2000) and Lin et al. (2002), individual agreement between two measurement methods may be assessed using the the coverage probability (CP) criteria or the total deviation index (TDI). If d_0 is predetermined as the maximum acceptable absolute difference between two methods of measurement, the probability that the absolute difference of two measures being less than d_0 can be computed. This is known as the coverage probability (CP).

$$CP = P(|x_i - y_i| \leq d_0) \tag{2.1}$$

If π_0 is set as the predetermined coverage probability, the boundary under which the proportion of absolute differences is π_0 may be determined. This boundary is known as the 'total deviation index' (TDI). Hence the TDI is the $100\pi_0$ percentile of the absolute difference of paired observations.

2.6 Basic Models Fits

Further to Pinheiro and Bates (1994), several simple LME models are constructed for the blood pressure data. This data set is the subject of a method comparison study in Bland and Altman (1999).

2.6.1 Implementing the Mixed Models Fits

They are implemented using the following `R` code, utilising the 'nlme' package. An analysis of variance is used to compare the model fits.

The `R` script:

```
fit1 = lme( BP ~ method, data = dat, random = ~1 | subject )
fit2 = update(fit1, random = ~1 | subject/method )
fit3 = update(fit1, random = ~method - 1 | subject )
#analysis of variance
anova(fit1,fit2,fit3)
```

1. Simplest workable model, allows differences between methods and incorporates a random intercept for each subject. For subject 1 we have

$$\boldsymbol{X}_i = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 1 & 1 \\ 1 & 1 \\ 1 & 1 \end{pmatrix}, \quad \boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}, \quad \boldsymbol{Z}_i = \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}, \quad \boldsymbol{b}_i = b$$

   where $\mathrm{E}(b) = 0$ and $\mathrm{var}(b) = \psi$.

2.

$$\boldsymbol{Z}_i = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} \qquad \boldsymbol{b}_i = \begin{pmatrix} b_1 & 0 \\ 0 & b_2 \end{pmatrix}$$

where $\mathrm{E}(b_i) = 0$ and $\mathrm{var}(\boldsymbol{b}) = \boldsymbol{\Psi}$.

The variance of error terms is a 6 × 6 matrix.

2.6.2 Model Fit 1

This is a simple model with no interactions. There is a fixed effect for each method and a random effect for each subject.

$$y_{ijk} = \beta_j + b_i + \epsilon_{ijk}, \qquad i = 1, \ldots, 2, j = 1, \ldots, 85, k = 1, \ldots, 3$$

$$b_i \sim \mathcal{N}(0, \sigma_b^2), \qquad \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2155.853
Fixed: BP ~ method
(Intercept)     methodS
127.40784    15.61961

Random effects:
Formula: ~1 | subject
(Intercept) Residual
```

```
StdDev:    29.39085 12.44454


Number of Observations: 510

Number of Groups: 85
```

The following output was obtained.

```
Linear mixed-effects model fit by REML

Data: dat

Log-restricted-likelihood: -2047.582

Fixed: BP ~ method

(Intercept)     methodS

127.40784    15.61961


Random effects:

Formula: ~method - 1 | subject

Structure: General positive-definite, Log-Cholesky parametrization

StdDev    Corr

methodJ  30.455093 methdJ

methodS  31.477237 0.835

Residual  7.763666


Number of Observations: 510

Number of Groups: 85
```

2.6.3 Model Fit 1

This is a simple model with no interactions. There is a fixed effect for each method and a random effect for each subject.

$$y_{ijk} = \beta_j + b_i + \epsilon_{ijk}, \qquad i = 1, \ldots, 2, j = 1, \ldots, 85, k = 1, \ldots, 3$$

$$b_i \sim \mathcal{N}(0, \sigma_b^2), \qquad \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2155.853
Fixed: BP ~ method
(Intercept)     methodS
127.40784    15.61961

Random effects:
Formula: ~1 | subject
(Intercept) Residual
StdDev:    29.39085 12.44454

Number of Observations: 510
Number of Groups: 85
```

The following output was obtained.

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2047.582
Fixed: BP ~ method
(Intercept)     methodS
```

```
127.40784    15.61961

Random effects:
Formula: ~method - 1 | subject
Structure: General positive-definite, Log-Cholesky parametrization
StdDev    Corr
methodJ  30.455093 methdJ
methodS  31.477237 0.835
Residual  7.763666

Number of Observations: 510
Number of Groups: 85
```

2.6.4 Model Fit 2

This is a simple model, this time with an interaction effect. There is a fixed effect for each method. This model has random effects at two levels b_i for the subject, and another, b_{ij}, for the respective method within each subject.

$$y_{ijk} = \beta_j + b_i + b_{ij} + \epsilon_{ijk}, \qquad i = 1, \dots, 2, j = 1, \dots, 85, k = 1, \dots, 3$$

$$b_i \sim \mathcal{N}(0, \sigma_1^2), \qquad b_{ij} \sim \mathcal{N}(0, \sigma_2^2), \qquad \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

In this model, the random interaction terms all have the same variance σ_2^2. These terms are assumed to be independent of each other, even within the same subject.

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2047.714
Fixed: BP ~ method
(Intercept)     methodS
127.40784    15.61961

Random effects:
Formula: ~1 | subject
(Intercept)
StdDev:    28.28452

Formula: ~1 | method %in% subject
(Intercept) Residual
StdDev:    12.61562 7.763666

Number of Observations: 510
Number of Groups:
```

```
subject method %in% subject
85                 170
```

2.6.5 Model Fit 3

This model is a more general model, compared to 'model fit 2'. This model treats the random interactions for each subject as a vector and allows the variance-covariance matrix for that vector to be estimated from the set of all positive-definite matrices. $\boldsymbol{y_i}$ is the entire response vector for the ith subject. $\boldsymbol{X_i}$ and $\boldsymbol{Z_i}$ are the fixed- and random-effects design matrices respectively.

$$\boldsymbol{y_i} = \boldsymbol{X_i}\boldsymbol{\beta} + \boldsymbol{Z_i}\boldsymbol{b_i} + \boldsymbol{\epsilon_i}, \qquad i = 1, \ldots, 85$$

$$\boldsymbol{Z_i} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Psi}), \qquad \boldsymbol{\epsilon_i} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\sigma^2}\boldsymbol{\Lambda})$$

For the first subject the response vector, $\boldsymbol{y_1}$, is:

observation	BP	subject	method	replicate
1	100.00	1	J	1
86	106.00	1	J	2
171	107.00	1	J	3
511	122.00	1	S	1
596	128.00	1	S	2
681	124.00	1	S	3

The fixed effects design matrix $\boldsymbol{X_i}$ is given by:

(Intercept)	method S
1	0
1	0
1	0
1	1
1	1
1	1

The random effects design matrix $\boldsymbol{Z_i}$ is given by:

method J	method S
1	0
1	0
1	0
0	1
0	1
0	1

2.6.6 Using LME models to create Prediction Intervals

Carstensen (2004) also advocates the use of linear mixed models in the study of method comparisons. The model is constructed to describe the relationship between a value of measurement and its real value. The non-replicate case is considered first, as it is the context of the Bland Altman plots. This model assumes that inter-method bias is the only difference between the two methods. A measurement y_{mi} by method m on individual i is formulated as follows;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \qquad (e_{mi} \sim N(0, \sigma^2_m)) \tag{2.2}$$

The differences are expressed as $d_i = y_{1i} - y_{2i}$ For the replicate case, an interaction term c is added to the model, with an associated variance component. All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \qquad (e_{mi} \sim N(0, \sigma^2_m), c_{mi} \sim N(0, \tau^2_m)) \tag{2.3}$$

Carstensen et al. (2008) proposes a methodology to calculate prediction intervals in the presence of replicate measurements, overcoming problems associated with Bland-Altman methodology in this regard. It is not possible to estimate the interaction variance components τ^2_1 and τ^2_2 separately. Therefore it must be assumed that they are equal. The variance of the difference can be estimated as follows:

$$var(y_{1j} - y_{2j}) \tag{2.4}$$

2.6.7 Computation

Modern software packages can be used to fit models accordingly. The best linear unbiased predictor (BLUP) for a specific subject i measured with method m has the form $BLUP_{mir} = \hat{\alpha_m} + \hat{\beta_m}\mu_i + c_{mi}$, under the assumption that the μs are the true item values.

2.7 Demonstration of Roy's testing

Roy provides three case studies, using data sets well known in method comparison studies, to demonstrate how the methodology should be used. The first two examples used are from the 'blood pressure' data set introduced by Bland and Altman (1999). The data set is a tabulation of simultaneous measurements of systolic blood pressure were made by each of two experienced observers (denoted 'J' and 'R') using a sphygmomanometer and by a semi-automatic blood pressure monitor (denoted 'S'). Three sets of readings were made in quick succession. Roy compares the 'J' and 'S' methods in the first of her examples.

The inter-method bias between the two method is found to be 15.62 , with a $t-$value of -7.64, with a $p-$value of less than 0.0001. Consequently there is a significant inter-method bias present between methods J and S, and the first of the Roy's three agreement criteria is unfulfilled.

Next, the first variability test is carried out, yielding maximum likelihood estimates of the between-subject variance covariance matrix, for both the null model, in compound symmetry (CS) form, and the alternative model in symmetric (symm) form. These matrices are determined to be as follows;

$$\hat{\boldsymbol{D}}_{CS} = \begin{pmatrix} 946.50 & 784.32 \\ 784.32 & 946.50 \end{pmatrix}, \qquad \hat{\boldsymbol{D}}_{Symm} = \begin{pmatrix} 923.98 & 785.24 \\ 785.24 & 971.30 \end{pmatrix}.$$

A likelihood ratio test is perform to compare both candidate models. The log-likelihood of the null model is -2030.7, and for the alternative model -2030.8. The test statistic, presented with greater precision than the log-likelihoods, is 0.1592. The $p-$value is 0.6958. Consequently we fail to reject the null model, and by extension, conclude that the hypothesis that methods J and S have the same between-subject variability. Thus the second of the criteria is fulfilled.

The second variability test determines maximum likelihood estimates of the within-subject variance covariance matrix, for both the null model, in CS form, and the alternative model in symmetric form.

$$\hat{\boldsymbol{\Lambda}}_{\boldsymbol{CS}} = \begin{pmatrix} 60.27 & 16.06 \\ 16.06 & 60.27 \end{pmatrix}, \qquad \hat{\boldsymbol{\Lambda}}_{Symm} = \begin{pmatrix} 37.40 & 16.06 \\ 16.06 & 83.14 \end{pmatrix}.$$

Again, A likelihood ratio test is perform to compare both candidate models. The log-likelihood of the alternative model model is -2045.0. As before, the null model has a log-likelihood of -2030.7. The test statistic is computed as 28.617, again presented with greater precision. The $p-$value is less than 0.0001. In this case we reject the null hypothesis of equal within-subject variability. Consequently the third of Roy's criteria is unfulfilled. The coefficient of repeatability for methods J and S are found to be 16.95 mmHg and 25.28 mmHg respectively.

The last of the three variability tests is carried out to compare the overall variabilities of both methods. With the null model the MLE of the within-subject variance covariance matrix is given below. The overall variabilities for the null and alternative models, respectively, are determined to be as follows;

$$\hat{\boldsymbol{\Sigma}}_{CS} = \begin{pmatrix} 1007.92 & 801.65 \\ 801.65 & 1007.92 \end{pmatrix}, \qquad \hat{\boldsymbol{\Sigma}}_{Symm} = \begin{pmatrix} 961.38 & 801.40 \\ 801.40 & 1054.43 \end{pmatrix},$$

The log-likelihood of the alternative model model is -2045.2, and again, the null model has a log-likelihood of -2030.7. The test statistic is 28.884, and the $p-$value is less than 0.0001. The null hypothesis, that both methods have equal overall variability, is rejected. Further to the second variability test, it is known that this difference is specifically due to the difference of within-subject variabilities.

Lastly, Roy considers the overall correlation coefficient. The diagonal blocks $\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii}$ of the correlation matrix indicate an overall coefficient of 0.7959. This is less than the threshold of 0.82 that Roy recommends.

$$\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii} = \begin{pmatrix} 1 & 0.7959 \\ 0.7959 & 1 \end{pmatrix}$$

The off-diagonal blocks of the overall correlation matrix $\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii'}$ present the correlation coefficients further to Hamlett et al. (2004).

$$\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii'} = \begin{pmatrix} 0.9611 & 0.7799 \\ 0.7799 & 0.9212 \end{pmatrix}.$$

The overall conclusion of the procedure is that method J and S are not in agreement, specifically due to the within-subject variability, and the inter-method bias. The repeatability coefficients are substantially different, with the coefficient for method S being 49% larger than for method J. Additionally the overall correlation coefficient did not exceed the recommended threshold of 0.82.

2.8 Demonstration of Roy's testing

Roy provides three case studies, using data sets well known in method comparison studies, to demonstrate how the methodology should be used. The first two examples used are from the 'blood pressure' data set introduced by Bland and Altman (1999). The data set is a tabulation of simultaneous measurements of systolic blood pressure were made by each of two experienced observers (denoted 'J' and 'R') using a sphygmomanometer and by a semi-automatic blood pressure monitor (denoted 'S'). Three sets of readings were made in quick succession. Roy compares the 'J' and 'S' methods in his first example, and the 'R' and 'S' methods in his second.

2.8.1 Matrix structures

Before discussing the tests, it is useful to point out the difference between symmetric form and compound symmetry form. Consider a generic matrix A,

$$\boldsymbol{A} = \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix}. \tag{2.5}$$

A symmetric matrix allows the diagonal terms a_{11} and a_{22} to differ. The compound symmetry structure requires that both of these terms be equal, i.e $a_{11} = a_{22}$.

2.8.2 Variability test 1

This is a test on whether both methods A and B have the same between-subject variability or not.

$$H_0: \ d_A = d_B \tag{2.6}$$

$$H_A: \ d_A \neq d_B \tag{2.7}$$

When implemented using `R`, this test is facilitated by constructing a model specifying a symmetric form for D (i.e. the alternative model) and comparing it with a model that has compound symmetric form for D (i.e. the null model). For this test $\hat{\mathbf{\Lambda}}$ has a symmetric form for both models, and will be the same for both.

Bland-Altman's blood data

With the alternative model, the MLE of the between-subject variance covariance matrix is given by

$$\hat{\boldsymbol{D}}_{\boldsymbol{Symm}} = \begin{pmatrix} 923.98 & 785.24 \\ 785.24 & 971.30 \end{pmatrix} \tag{2.8}$$

With the null model the MLE is as follows:

$$\hat{\boldsymbol{D}}_{\boldsymbol{CS}} = \begin{pmatrix} 946.50 & 784.32 \\ 784.32 & 946.50 \end{pmatrix} \tag{2.9}$$

A likelihood ratio test is perform to determine which model is more suitable. The outcome of this test is presented in the following `R` code.

```
> anova(MCS1,MCS2)
>
>
Model df     AIC    BIC  logLik   Test L.Ratio p-value
MCS1      1  8 4077.5 4111.3 -2030.7
MCS2      2  7 4075.6 4105.3 -2030.8 1 vs 2 0.15291  0.6958
```

The test statistic is the difference of the -2 log likelihoods; 0.15291. The $p-$value is 0.6958. Therefore we fail to reject the hypothesis that both have the same between-subject variabilities.

2.8.3 Variability test 2

This is a test on whether both methods A and B have the same within-subject variability or not.

$$H_0: \ \lambda_A = \lambda_B \tag{2.10}$$

$$H_A: \ \lambda_A = \lambda_B \tag{2.11}$$

This model is performed in the same manner as the first test, only reversing the roles of $\hat{\boldsymbol{D}}$ and $\hat{\boldsymbol{\Lambda}}$. The null model is constructed a symmetric form for $\hat{\boldsymbol{\Lambda}}$ while the alternative model uses a compound symmetry form. This time $\hat{\boldsymbol{D}}$ has a symmetric form for both models, and will be the same for both.

Bland-Altman's blood data

For the null model the MLE of the within-subject variance covariance matrix is given below.

$$\hat{\boldsymbol{\Lambda}}_{\boldsymbol{Symm}} = \begin{pmatrix} 37.40 & 16.06 \\ 16.06 & 83.14 \end{pmatrix} \tag{2.12}$$

With the alternative model the MLE is as follows:

$$\hat{\boldsymbol{\Lambda}}_{\boldsymbol{CS}} = \begin{pmatrix} 60.27 & 16.06 \\ 16.06 & 60.27 \end{pmatrix} \tag{2.13}$$

A likelihood ratio test is perform to determine which model is more suitable. The outcome of this test is that it can be assumed that they have equal The test statistic is the difference of the -2 log likelihoods; 28.617. The $p-$value is less than 0.0001. In this case we reject the null hypothesis that both models have the same within-subject variabilities.

2.8.4 Variability test 3

This is a test on whether both methods A and B have the same overall variability or not.

$$H_0: \ \sigma_A = \sigma_B \tag{2.14}$$

$$H_A: \ \sigma_A = \sigma_B \tag{2.15}$$

The null model is constructed a symmetric form for both $\hat{\boldsymbol{D}}$ and $\hat{\boldsymbol{\Lambda}}$ while the alternative model uses a compound symmetry form for both.

Bland-Altman's blood data

With the null model the MLE of the within-subject variance covariance matrix is given below.

$$\hat{\boldsymbol{\Sigma}}_{\boldsymbol{Symm}} = \begin{pmatrix} 961.38 & 801.40 \\ 801.40 & 1054.43 \end{pmatrix} \tag{2.16}$$

With the alternative model the MLE is as follows:

$$\hat{\boldsymbol{\Sigma}}_{\boldsymbol{CS}} = \begin{pmatrix} 1007.92 & 801.65 \\ 801.65 & 1007.92 \end{pmatrix} \tag{2.17}$$

Again a likelihood ratio test is used to determine the most suitable of the two candidate models. The test statistic is the difference of the -2 log likelihoods; 28.884. The $p-$value is less than 0.0001. We again reject the null hypothesis. Each model has a different overall variability, a foregone conclusion from the second variability test.

2.8.5 Test for inter-method bias

The inter-method bias between the two method is found to be 15.62 , with a $p-$value of

2.8.6 Correlation Test

$$\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii} = \begin{pmatrix} 1 & 0.7959 \\ 0.7959 & 1 \end{pmatrix} \tag{2.18}$$

The diagonal blocks $\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii}$ of the correlation matrix indicate an overall coefficient of 0.7959. This is less than the threshold of 0.82 that Roy recommends.

The off diagonal blocks of the overall correlation matrix $\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii'}$ are

$$\hat{\boldsymbol{r}}_{\boldsymbol{\Omega}ii'} = \begin{pmatrix} 0.9611 & 0.7799 \\ 0.7799 & 0.9212 \end{pmatrix}. \tag{2.19}$$

2.8.7 Conclusion of procedure

The overall conclusion of the procedure is that the two methods are not in agreement, specifically due to the within-subject variability, and the inter-method bias. The repeatability coefficients are substantially different, one being 49% larger than the other. Additionally the overall correlation coefficient did not exceed the recommended threshold of 0.82.

Using Roy's Test to Identify cause of Lack of agreement

Barnhart specifies three conditions for method of measurement that are required for two methods of measurement to be considered in agreement.

(i) No Significant Inter-method bias

(ii) No significant Difference in Within-Subject Variance

(iii) No significant Difference in Within-Subject Variance

Roy(2009) demonstrates a LME model specification, and a series of tests that look at each of these agreement criteria individually. If two methods of measuement lack agreement, the specific reason or reasons for this lack of agreement can be identified.

Roy proposes an LME model with Kronecker product covariance structure in a doubly multivariate setup. Response for ith subject can be written as

$$y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + b_{1i} z_{i1} + b_{2i} z_{i2} + \epsilon_i$$

- β_1 and β_2 are fixed effects corresponding to both methods. (β_0 is the intercept.)
- b_{1i} and b_{2i} are random effects corresponding to both methods.

Overall variability between the two methods (Ω) is sum of between-subject (D) and within-subject variability (Σ),

$$\text{Block } \boldsymbol{\Omega}_i = \left[\begin{array}{cc} d^2_1 & d_{12} \\ d_{12} & d^2_2 \end{array} \right] + \left[\begin{array}{cc} \sigma^2_1 & \sigma_{12} \\ \sigma_{12} & \sigma^2_2 \end{array} \right].$$

Using Roy's Model to Compute LoAs and CR

In this short section, a demonstration of how Roy's technique can be used to compute two common MCS metrics: Limits of Agreement and the Coefficient of Repeatabilty.

While Limits of Agreement are not used in the analysis proposed here, they are ubiquituous in literature, and a demonstration on how to compute them with the Roy Model would assist the adoption of this proposed method.

The coefficient of repeatability is encountered in Gage R & R analysis. *(A future exploration of how LME models can be used in that field would be of interest. This is something to include in the Conclusions Section).*

2.9 Worked Eamples : LikelihoodRatio Tests

Conventionally LME models can be tested using Likelihood Ratio Tests, wherein a reference model is compared to a nested model.

```
> Ref.Fit = lme(y ~ meth-1, data = dat,   #Symm , Symm#
+     random = list(item=pdSymm(~ meth-1)),
+     weights=varIdent(form=~1|meth),
+     correlation = corSymm(form=~1 | item/repl),
+     method="ML")
```

Roy(2009) presents two nested models that specify the condition of equality as required, with a third nested model for an additional test. There three formulations share the same structure, and can be specified by making slight alterations of the code for the Reference Model. Nested Model (Between-Item Variability)

```
> NMB.fit  = lme(y ~ meth-1, data = dat,   #CS , Symm#
+     random = list(item=pdCompSymm(~ meth-1)),
+     correlation = corSymm(form=~1 | item/repl),
+     method="ML")
```

```
Nested Model (Within ?item Variability)
> NMW.fit = lme(y ~ meth-1, data = dat,   #Symm , CS#
+     random = list(item=pdSymm(~ meth-1)),
+     weights=varIdent(form=~1|meth),
+     correlation = corCompSymm(form=~1 | item/repl),
+     method="ML")
```

Nested Model (Overall Variability) Additionally there is a third nested model, that can be used to test overall variability, substantively a a joint test for between-item and within-item variability. The motivation for including such a test in the suite is not clear, although it does circumvent the need for multiple comparison procedures in certain circumstances, hence providing a simplified procedure for non-statisticians.

```
> NMO.fit = lme(y ~ meth-1, data = dat,   #CS , CS#
+     random = list(item=pdCompSymm(~ meth-1)),
+     correlation = corCompSymm(form=~1 | item/repl),
+     method="ML")
```

ANOVAs for Original Fits The likelihood Ratio test is very simple to implement in R. All that is required it to specify the reference model and the relevant nested mode as arguments to the command anova(). The figure below displays the three tests described by Roy (2009).

```
> testB    = anova(Ref.Fit,NMB.fit)                          # Between-Subject Var
> testW   = anova(Ref.Fit,NMW.fit)                        # Within-Subject Variabi
> testO     = anova(Ref.Fit,NMO.fit)                        # Overall Variabilitie
> anova(MCS1,MCS2)
>
>
Model df     AIC    BIC  logLik   Test L.Ratio p-value
MCS1     1  8 4077.5 4111.3 -2030.7
MCS2     2  7 4075.6 4105.3 -2030.8 1 vs 2 0.15291  0.6958
```

2.9.1 Roy's Reference Model

Conventionally LME models can be tested using Likelihood Ratio Tests, wherein a reference model is compared to a nested model.

```
> Ref.Fit = lme(y ˜ meth-1, data = dat,   #Symm , Symm#
+     random = list(item=pdSymm(˜ meth-1)),
+     weights=varIdent(form=˜1|meth),
+     correlation = corSymm(form=˜1 | item/repl),
+     method="ML")
```

Roy(2009) presents two nested models that specify the condition of equality as required, with a third nested model for an additional test. There three formulations share the same structure, and can be specified by making slight alterations of the code for the Reference Model.

2.9.2 Nested Model (Between-Item Variability)

```
> NMB.fit  = lme(y ˜ meth-1, data = dat,   #CS , Symm#
+     random = list(item=pdCompSymm(˜ meth-1)),
+     correlation = corSymm(form=˜1 | item/repl),
+       method="ML")
```

2.10 Fat Data Examples: LoAs for Carstensen's data

Carstensen et al. (2008) presents a data set 'fat', which is a comparison of measurements of subcutaneous fat by two observers at the Steno Diabetes Center, Copenhagen. Measurements are in millimeters (mm). Each person is measured three times by each observer. The observations are considered to be 'true' replicates.

A linear mixed effects model is formulated, and implementation through several software packages is demonstrated. All of the necessary terms are presented in the computer output. The limits of agreement are therefore,

$$0.0449 \pm 1.96 \times \sqrt{2 \times 0.0596^2 + 0.0772^2 + 0.0724^2} = (-0.220, 0.309). \tag{2.20}$$

Carstensen et al. (2008) describes the calculation of the limits of agreement (with the inter-method bias implicit) for both data sets, based on his formulation;

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm 2\sqrt{2\hat{\tau}^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2}.$$

For the 'Fat' data set, the inter-method bias is shown to be 0.045. The limits of agreement are $(-0.23, 0.32)$

For Carstensen's 'fat' data, the limits of agreement computed using Roy's method are consistent with the estimates given by Carstensen et al. (2008); $0.044884 \pm 1.96 \times 0.1373979 = (-0.224, 0.314)$.

2.11 HBA1C Diabetes Example

Carstensen et al. (2008) describes the sampling method when discussing of a motivating example

Diabetes patients attending an outpatient clinic in Denmark have their HbA_{1c} levels routinely measured at every visit. Venous and Capillary blood samples were obtained from all patients appearing at the clinic over two days. Samples were measured on four consecutive days on each machines, hence there are five analysis days.

Carstensen et al. (2008) notes that every machine was calibrated every day to the manufacturers guidelines. Measurements are classified by method, individual and replicate. In this case the replicates are clearly not exchangeable, neither within patients nor simulataneously for all patients.

2.12 Oximetry Data

Carstensen et al. (2008) introduces a second data set; the oximetry study. This study done at the Royal Childrens Hospital in Melbourne to assess the agreement between co-oximetry and pulse oximetry in small babies.

In most cases, measurements were taken by both method at three different times. In some cases there are either one or two pairs of measurements, hence the data is unbalanced. Carstensen et al. (2008) describes many of the children as being very sick, and with very low oxygen saturations levels. Therefore it must be assumed that a biological change can occur in interim periods, and measurements are not true replicates.

Carstensen et al. (2008) proposes the addition of an random effects term to their model when the replicates are linked. This term is used to describe the 'item by replicate' interaction, which is independent of the methods. This interaction is a source of variability independent of the methods. Therefore failure to account for it will result in variability being wrongly attributed to the methods.

Limits of agreement are determined using Roy's methodology, without adding any additional terms, are found to be consistent with the 'interaction' model; $(-9.562, 14.504)$. Roy's methodology assumes that replicates are linked. However, following Carstensen's example, an addition interaction term is added to the implementation of Roy's model to assess the effect, the limits of agreement estimates do not change. However there is a conspicuous difference in within-subject matrices of Roy's model and the modified model (denoted 1 and 2 respectively);

Carstensen demonstrates the use of the interaction term when computing the limits of agreement for the 'Oximetry' data set. When the interaction term is omitted, the limits of agreement are $(-9.97, 14.81)$. Carstensen advises the inclusion of the interaction term for linked replicates, and hence the limits of agreement are recomputed as $(-12.18, 17.12)$.

Limits of agreement are determined using Roy's methodology, without adding any additional terms, are found to be consistent with the 'interaction' model; $(-9.562, 14.504)$. Roy's methodology assumes that replicates are linked. However, following Carstensen's example, an addition interaction term is added to the implementation of Roy's model to assess the effect, the limits of agreement estimates do not change. However there is a conspicuous difference in within-subject matrices of Roy's model and the modified model (denoted 1 and 2 respectively);
(The variance of the additional random effect in model 2 is 3.01.)

Akaike (1974) introduces the Akaike information criterion (AIC), a model selection tool based on the likelihood function. Given a data set, candidate models are ranked according to their AIC values, with the model having the lowest AIC being considered the best fit.Two candidate models can said to be equally good if there is a difference of less than 2 in their AIC values.

The Akaike information criterion (AIC) for both models are $AIC_1 = 2304.226$ and $AIC_2 = 2306.226$, indicating little difference in models. The AIC values for the Carstensen 'unlinked' and 'linked' models are 1994.66 and 1955.48 respectively, indicating an improvement by adding the interaction term.

The $\hat{\boldsymbol{\Lambda}}$ matrices are informative as to the difference between Carstensen's unlinked and linked models. For the oximetry data, the covariance terms (given above as 11.67 and 2.6 respectively) are of similar magnitudes to the variance terms. Conversely for the 'fat' data the covariance term (-0.00032) is negligible. When the interaction term is added to the model, the covariance term remains negligible. (For the 'fat' data, the difference in AIC values is also approximately 2).

To conclude, Carstensen's models provided a rigorous way to determine limits of agreement, but don't provide for the computation of $\hat{\boldsymbol{D}}$ and $\hat{\boldsymbol{\Lambda}}$. Therefore the test's proposed by Roy (2009b) can not be implemented. Conversely, accurate limits of agreement as determined by Carstensen's model may also be found using Roy's method. Addition of the interaction term erodes the capability of Roy's methodology to compare candidate models, and therefore shall not be adopted.

Finally, to complement the blood pressure (i.e.'J vs S') method comparison from the previous section (i.e.'J vs S'), the limits of agreement are $15.62 \pm 1.96 \times 20.33 = (-24.22, 55.46)$.)

2.13 Linked replicates

Carstensen et al. (2008) proposes the addition of an random effects term to their model when the replicates are linked. This term is used to describe the 'item by replicate' interaction, which is independent of the methods. This interaction is a source of variability independent of the methods. Therefore failure to account for it will result in variability being wrongly attributed to the methods.

Carstensen et al. (2008) introduces a second data set; the oximetry study. This study done at the Royal Childrens Hospital in Melbourne to assess the agreement between co-oximetry and pulse oximetry in small babies.

In most cases, measurements were taken by both method at three different times. In some cases there are either one or two pairs of measurements, hence the data is unbalanced. Carstensen et al. (2008) describes many of the children as being very sick, and with very low oxygen saturations levels. Therefore it must be assumed that a biological change can occur in interim periods, and measurements are not true replicates.

Limits of agreement are determined using Roy's methodology, without adding any additional terms, are found to be consistent with the 'interaction' model; $(-9.562, 14.504)$. Roy's methodology assumes that replicates are linked. However, following Carstensen's example, an addition interaction term is added to the implementation of Roy's model to assess the effect, the limits of agreement estimates do not change. However there is a conspicuous difference in within-subject matrices of Roy's model and the modified model (denoted 1 and 2 respectively);

$$\hat{\boldsymbol{\Lambda}}_1 = \begin{pmatrix} 16.61 & 11.67 \\ 11.67 & 27.65 \end{pmatrix} \qquad \hat{\boldsymbol{\Lambda}}_2 = \begin{pmatrix} 7.55 & 2.60 \\ 2.60 & 18.59 \end{pmatrix}. \tag{2.21}$$

(The variance of the additional random effect in model 2 is 3.01.)

Akaike (1974) introduces the Akaike information criterion (AIC), a model selection tool based on the likelihood function. Given a data set, candidate models are ranked according to their AIC values, with the model having the lowest AIC being considered the best fit.Two candidate models can said to be equally good if there is a difference of less than 2 in their AIC values.

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To conclude, Carstensen's models provided a rigorous way to determine limits of agreement, but don't provide for the computation of $\hat{\boldsymbol{D}}$ and $\hat{\boldsymbol{\Lambda}}$. Therefore the test's proposed by Roy (2009a) can not be implemented. Conversely, accurate limits of agreement as determined by Carstensen's model may also be found using Roy's method. Addition of the interaction term erodes the capability of Roy's methodology to compare candidate models, and therefore shall not be adopted.

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2.14 Limits of agreement for Carstensen's data

Carstensen et al. (2008) describes the calculation of the limits of agreement (with the inter-method bias implicit) for both data sets, based on his formulation;

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm 2\sqrt{2\hat{\tau}^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2}.$$

For the 'Fat' data set, the inter-method bias is shown to be 0.045. The limits of agreement are $(-0.23, 0.32)$

Carstensen et al. (2008) demonstrate the necessity of accounting for linked replicated by comparing the limits of agreement from the 'oximetry' data set using a model with the additional term, and one without. When the interaction is accounted for the limits of agreement are (-9.62,14.56). When the interaction is not accounted for, the limits of agreement are (-11.88,16.83). It is shown that the failure to include this additional term results in an over-estimation of the standard deviations of differences.

Carstensen et al. (2008) demonstrates the use of the interaction term when computing the limits of agreement for the 'Oximetry' data set. When the interaction term is omitted, the limits of agreement are $(-9.97, 14.81)$. Carstensen advises the inclusion of the interaction term for linked replicates, and hence the limits of agreement are recomputed as $(-12.18, 17.12)$.

2.14.1 RV-IV

For the the RV-IC comparison, $\hat{D}$ is given by

$$\hat{D} = \begin{bmatrix} 1.6323 & 1.1427 \\ 1.1427 & 1.4498 \end{bmatrix} \tag{2.22}$$

The estimate for the within-subject variance covariance matrix is given by

$$\hat{\Sigma} = \begin{bmatrix} 0.1072 & 0.0372 \\ 0.0372 & 0.1379 \end{bmatrix} \tag{2.23}$$

The estimated overall variance covariance matrix for the the 'RV vs IC' comparison is given by

$$Block\Omega_i = \begin{bmatrix} 1.7396 & 1.1799 \\ 1.1799 & 1.5877 \end{bmatrix}. \tag{2.24}$$

The power of the likelihood ratio test may depends on specific sample size and the specific number of replications, and the author proposes simulation studies to examine this further.

2.15 Zewotir: Computation and Notation

with $\boldsymbol{V}$ unknown, a standard practice for estimating $\boldsymbol{X\beta}$ is the estime the variance components σ_j^2, compute an estimate for $\boldsymbol{V}$ and then compute the projector matrix A, $\boldsymbol{X}\hat{\boldsymbol{\beta}} = \boldsymbol{AY}$.

Zewotir remarks that $\boldsymbol{D}$ is a block diagonal with the $i-$th block being $u\boldsymbol{I}$

2.16 LME - Pankaj Choudhury

Consistent with the conventions of mixed models, (?) formulates the measurement $y_{ij}$from method i on individual j as follows;

$$y_{ij} = P_{ij}\theta + W_{ij}v_i + X_{ij}b_j + Z_{ij}u_j + \epsilon_{ij}, (j = 1, 2, i = 1, 2....n) \qquad (2.25)$$

The design matrix P_{ij} , with its associated column vector θ, specifies the fixed effects common to both methods. The fixed effect specific to the jth method is articulated by the design matrix W_{ij} and its column vector v_i. The random effects common to both methods is specified in the design matrix X_{ij}, with vector b_j whereas the random effects specific to the ith subject by the jth method is expressed by Z_{ij}, and vector u_j. Noticeably this notation is not consistent with that described previously. The design matrices are specified so as to includes a fixed intercept for each method, and a random intercept for each individual. Additional assumptions must also be specified;

$$v_{ij} \sim N(0, \Sigma), \qquad (2.26)$$

These vectors are assumed to be independent for different is, and are also mutually independent. All Covariance matrices are positive definite. In the above model effects can be classed as those common to both methods, and those that vary with method. When considering differences, the effects common to both effectively cancel each other out. The differences of each pair of measurements can be specified as following;

$$d_{ij} = X_{ij}b_j + Z_{ij}u_j + \epsilon_{ij}, (j = 1, 2, i = 1, 2....n) \qquad (2.27)$$

This formulation has seperate distributional assumption from the model stated previously.

This agreement covariate x is the key step in how this methodology assesses agreement.

2.17 LME diagnostic measures

2.17.1 Andrews-Pregibon statistic

- For fixed effect parameters β.

The Andrews-Pregibon statistic AP_i is a measure of influence based on the volume of the confidence ellipsoid. The larger this statistic is for observation i, the stronger the influence that observation will have on the model fit.

2.17.2 Cook's Distance

- For variance components γ

Diagnostic tool for variance components

$$C_{\theta i} = (\hat{(\theta)}_{[i]} - \hat{(\theta)})^T \mathrm{cov}(\hat{(\theta)})^{-1}(\hat{(\theta)}_{[i]} - \hat{(\theta)})$$

2.17.3 Variance Ratio

- For fixed effect parameters β.

2.17.4 Cook-Weisberg statistic

- For fixed effect parameters β.

2.17.5 Andrews-Pregibon statistic

- For fixed effect parameters β.

The Andrews-Pregibon statistic AP_i is a measure of influence based on the volume of the confidence ellipsoid. The larger this statistic is for observation i, the stronger the influence that observation will have on the model fit.

2.18 Computing DFBETAs with R

- This function computes the DFBETAS based on the information returned by the estex() function.

- The dfbeta refers to how much a parameter estimate changes if the observation or case in question is dropped from the data set.

- Cook's distance is presumably more important to you if you are doing predictive modeling, whereas dfbeta is more important in explanatory modeling.

- The DFBETAS statistics are the scaled measures of the change in each parameter estimate and are calculated by deleting the th observation:

  Missing Formula

  where is the th element of . In general, large values of DFBETAS indicate observations that are influential in estimating a given parameter.

- **Belsley, Kuh, and Welsch (1980)** recommend 2 as a general cutoff value to indicate influential observations and as a size-adjusted cutoff.

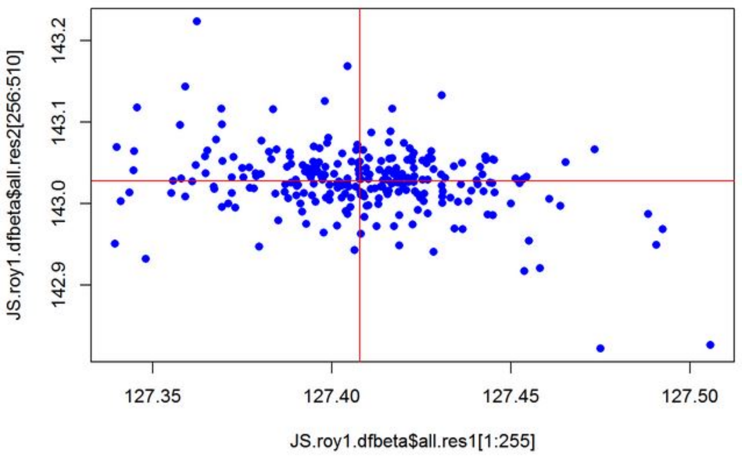

Figure 2.19.1:

2.19 DFbetas for Blood Data

```
plot(JS.roy1.dfbeta$all.res1[1:255],JS.roy1.dfbeta$all.res2[256:510],
pch=16,col="blue")
abline(v=JS.roy1.dfbeta$all.res1[256],col="red")
abline(h=JS.roy1.dfbeta$all.res2[1],col="red")
```

2.20 Cooks's Distance - Implementation with R

Cook's Distance is a measure indicating to what extent model parameters are influenced by (a set of) influential data on which the model is based. This function computes the Cook's distance based on the information returned by the `estex()` function.

2.21 residuals.lme nlme- Extract lme Residuals

The residuals at level i are obtained by subtracting the fitted levels at that level from the response vector (and dividing by the estimated within-group standard error, if type="pearson").

The fitted values at level i are obtained by adding together the population fitted values (based only on the fixed effects estimates) and the estimated contributions of the random effects to the fitted values at grouping levels less or equal to i.

```
fm1 <- lme(distance ~ age + Sex,
data = Orthodont, random = ~ 1)
head(residuals(fm1, level = 0:1))
summary(residuals(fm1) /
residuals(fm1, type = "p"))

# constant scaling factor 1.432
```

Chapter 3

Lesaffre's paper.

3.1 Lesaffre's paper.

Lesaffre considers the case-weight perturbation approach.

Cook's 86 describes a local approach wherein each case is given a weight w_i and the effect on the parameter estimation is measured by perturbing these weights. Choosing weights close to zero or one corresponds to the global case-deletion approach.

Lesaffre describes the displacement in log-likelihood as a useful metric to evaluate local influence

Lesaffre describes a framework to detect outlying observations that matter in an LME model. Detection should be carried out by evaluating diagnostics C_i , $C_i(\alpha)$ and $C_i(D, \sigma^2)$.

Lesaffre defines the total local influence of individual i as

$$C_i = 2|\triangle\prime_i L^{-1} \triangle_i|. \tag{3.1}$$

The influence function of the MLEs evaluated at the ith point IF_i, given by

$$IF_i = -L^{-1} \triangle_i \tag{3.2}$$

can indicate how $th\hat{e}ta$ changes as the weight of the ith subject changes.

The manner by which influential observations distort the estimation process can be determined by inspecting the interpretable components in the decomposition of the above measures of local influence.

Lesaffre comments that there is no clear way of interpreting the information contained in the angles, but that this doesn't mean the information should be ignored.

3.2 Lesaffre's paper.

Lesaffre considers the case-weight perturbation approach.

(Cook, 1986) Cook's 86 describes a local approach wherein each case is given a weight w_i and the effect on the parameter estimation is measured by perturbing these weights. Choosing weights close to zero or one corresponds to the global case-deletion approach.

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Lesaffre comments that there is no clear way of interpreting the information contained in the angles, but that this doesn't mean the information should be ignored.

3.3 influence.ME

influence.ME allows you to compute measures of influential data for mixed effects models generated by lme4.

influence.ME provides a collection of tools for detecting influential cases in generalized mixed effects models. It analyses models that were estimated using lme4. The basic rationale behind identifying influential data is that when iteratively single units are omitted from the data, models based on these data should not produce substantially different estimates.

To standardize the assessment of how influential a (single group of) observation(s) is, several measures of influence are common practice, such as DFBETAS and Cook's Distance. In addition, we provide a measure of percentage change of the fixed point estimates and a simple procedure to detect changing levels of significance.

3.3.1 Influence() command

`influence()` is the workhorse function of the influence.ME package. Based on a priorly estimated mixed effects regression model (estimated using lme4), the `influence()` function iteratively modifies the mixed effects model to neutralize the effect a grouped set of data has on the parameters, and which returns returns the fixed parameters of these iteratively modified models. These are used to compute measures of influential data.

3.3.2 Classical Model

The classical model is based on measurements y_{mi} by method $m = 1, 2$ on item $i = 1, 2 \ldots$

$$y_{mi} + \alpha_m + \mu_i + e_{mi}$$

$$e_{mi} \sim \backslash(0, \sigma^2_m)$$

Even though the separate variances can not be identified, their sum can be estimated by the empirical variance of the differences.

Like wise the separate α can not be estimated, only theiir difference can be estimated as $\bar{D}$

3.4 Lai Shiao

Lai and Shiao (2005) advocates the use of LME models to study method comparison problems. The authors analyse a data set typical of method comparison studies using SAS software, with particular use of the *'Proc Mixed'* package. The stated goal of this study is to determine which factor from a specified group of factors is the key contributor to the difference in the two methods.

The study relates to oxygen saturation, the most investigated variable in clinical nursing studies (Lai and Shiao, 2005). The two method compared are functional saturation (SO2, percent functional oxy-hemoglobin) and fractional saturation (HbO2, percent fractional oxy-hemoglobin), which is considered to be the 'gold standard' method of measurement.

Lai and Shiao (2005) establishes an LME model for analysing the differences D_{ijtl}, where D_{ijtl} is the differences of the measurements (i.e = $SO2_{ijtl}$ - $HbO2_{ijtl}$) for the ith donor at the jth level of foetal haemoglobin percent (Fhbperct) and the tth repeated measurement by the lth practitioner of the experiment.

(Carstensen (2004) also advocates the use of LME models in comparing methods, but with a different emphasis.) Lai and Shiao (2005) use mixed models to determine the factors that affect the difference of two methods of measurement using the conventional formulation of linear mixed effects models.

If the parameter **b**, and the variance components are not significantly different from zero, the conclusion that there is no inter-method bias can be drawn. If the fixed effects component contains only the intercept, and a simple correlation coefficient is used, then the estimate of the intercept in the model is the inter-method bias. Conversely the estimates for the fixed effects factors can advise the respective influences each factor has on the differences. It is possible to pre-specify different correlation structures of the variance components $\mathbf{G}$ and $\mathbf{R}$.

Oxygen saturation is one of the most frequently measured variables in clinical nursing studies. 'Fractional saturation' (HbO_2) is considered to be the gold standard method of measurement, with 'functional saturation' (SO_2) being an alternative method. The method of examining the causes of differences between these two methods is applied to a clinical study conducted by **?**. This experiment was conducted by 8 lab practitioners on blood samples, with varying levels of haemoglobin, from two donors. The samples have been in storage for varying periods (described by the variable 'Bloodage') and are categorized according to haemoglobin percentages(i.e 0%,20%,40%,60%,80%,100%). There are 625 observations in all.

Lai and Shiao (2005) fits two models on this data, with the lab technicians and the replicate measurements as the random effects in both models. The first model uses haemoglobin level as a fixed effects component. For the second model, blood age is added as a second fixed factor.

Single fixed effect

The first model fitted by Lai and Shiao (2005) takes the blood level as the sole fixed effect to be analyzed. The following coefficient estimates are estimated by 'Proc Mixed';

$$\begin{aligned} \text{fixed effects :}\ & 2.5056 - 0.0263\text{Fhbperct}_{ijtl} \qquad (3.5)\\ (\text{p-values :}\ & = 0.0054, < 0.0001, < 0.0001) \end{aligned}$$

$$\begin{aligned} \text{random effects :}\ & u(\sigma^2 = 3.1826) + e_{ijtl}(\sigma^2_e = 0.1525, \rho = 0.6978)\\ (\text{p-values :}\ & = 0.8113, < 0.0001, < 0.0001) \end{aligned}$$

With the intercept estimate being both non-zero and statistically significant ($p =$

0.0054), this models supports the presence inter-method bias is 2.5% in favour of SO_2. Also, the negative value of the haemoglobin level coefficient indicate that differences will decrease by 0.0263% for every percentage increase in the haemoglobin .

In the random effects estimates, the variance due to the practitioners is 3.1826, indicating that there is a significant variation due to technicians ($p = 0.0311$) affecting the differences. The variance for the estimates is given as 0.1525, ($p < 0.0001$).

Two fixed effects

Blood age is added as a second fixed factor to the model, whereupon new estimates are calculated;

$$\begin{aligned}
\text{fixed effects :} \quad & -0.2866 + 0.1072\text{Bloodage}_{ijtl} - 0.0264\text{Fhbperct}_{ijtl} \\
& \text{(p-values : } = 0.8113, < 0.0001, < 0.0001) \\
\\
\text{random effects :} \quad & u(\sigma^2 = 10.2346) + e_{ijtl}(\sigma^2_e = 0.0920, \rho = 0.5577) \\
& \text{(p-values : } = 0.0446, < 0.0001, < 0.0001) \qquad (3.6)
\end{aligned}$$

With this extra fixed effect added to the model, the intercept term is no longer statistically significant. Therefore, with the presence of the second fixed factor, the model is no longer supporting the presence of inter-method bias. Furthermore, the second coefficient indicates that the blood age of the observation has a significant bearing on the size of the difference between both methods ($p < 0.0001$). Longer storage times for blood will lead to higher levels of particular blood factors such as MetHb and HbCO (due to the breakdown and oxidisation of the haemoglobin). Increased levels of MetHb and HbCO are concluded to be the cause of the differences. The coefficient for the haemoglobin level doesn't differ greatly from the single fixed factor model, and has a much smaller effect on the differences. The random effects estimates also indicate significant variation for the various technicians; 10.2346 with $p = 0.0446$.

Lai and Shiao (2005) demonstrates how that linear mixed effects models can be used to provide greater insight into the cause of the differences. Naturally the addition of further factors to the model provides for more insight into the behavior of the data.

Chapter 4

Updating Techniques and Cross Validation

4.1 The Hat Matrix

The hat matrix, also known as the projection matrix, is well known in classical linear models. The diagonal elements h_{ii} are known as 'leverages'. The properties of $\boldsymbol{H}$,such as symmetry and idempotency, are well known.

$$\boldsymbol{H} = \boldsymbol{X}(\boldsymbol{X'X})^{-1}\boldsymbol{X'}$$

$$\boldsymbol{H} = \begin{bmatrix} h_{ii} & \boldsymbol{h}_i' \\ \boldsymbol{h}_i & \boldsymbol{H}_{(i)} \end{bmatrix}$$

$\boldsymbol{H}_{(i)}$ is an $(n-1) \times (n-1)$ matrix. It's inversion for each i is computationally expensive.

$$\boldsymbol{C} = \boldsymbol{H}^{-1} = \begin{bmatrix} c_{ii} & \boldsymbol{h}_c' \\ \boldsymbol{c}_i & \boldsymbol{C}_{(i)} \end{bmatrix}$$

4.1.1 The Hat Matrix

The projection matrix H (also known as the hat matrix), is a well known identity that maps the fitted values $\hat{Y}$ to the observed values Y, i.e. $\hat{Y} = HY$.

$$H = \quad X(X^TX)^{-1}X^T \tag{4.1}$$

H describes the influence each observed value has on each fitted value. The diagonal elements of the H are the 'leverages', which describe the influence each observed value has on the fitted value for that same observation. The residuals (R) are related to the observed values by the following formula:

$$R = (I - H)Y \tag{4.2}$$

The variances of Y and R can be expressed as:

$$\begin{aligned} \text{var}(Y) &= H\sigma^2 \\ \text{var}(R) &= (I - H)\sigma^2 \end{aligned} \tag{4.3}$$

Updating techniques allow an economic approach to recalculating the projection matrix, H, by removing the necessity to refit the model each time it is updated. However this approach is known for numerical instability in the case of down-dating.

4.2 Efficient updating theorem

It is convenient to write partitioned matrices in which the i-th case is isolated. The partitioned matrix is written as $i = 1$, but the results apply in general.

If $\boldsymbol{C'}_i = [c_{ii}, \boldsymbol{c'}_i]$, such that $\boldsymbol{C}_i$ is the i-th column of $\boldsymbol{H}^{-1}$ then

- $m_i = \frac{1}{c_{ii}}$
- $\breve{x}_i = \frac{1}{c_{ii}} \boldsymbol{X'C}_i$
- $\breve{\boldsymbol{z}}_{ji} = \frac{1}{c_{ii}} \boldsymbol{Z'}_j \boldsymbol{C}_i$
- $\breve{y}_i = \frac{1}{c_{ii}} \boldsymbol{y'C}_i$

Once $\boldsymbol{H}^{-1}$ is determined, an efficient updating formula can be applied.

$$\boldsymbol{H}^{-1} = \boldsymbol{I} - \boldsymbol{Z}(\boldsymbol{D}^{-1} + \boldsymbol{ZZ})^{-1}\boldsymbol{Z'} \tag{4.4}$$

4.2.1 Updating Regression Estimates

Let the observation j be omitted from the data set. The estimates for the variance identities can be updating using minor adjustments to the full sample estimates. Where (j) denotes that the jth has been omitted, these identities are

$$Sxx^{(j)} = \frac{\sum_{i=1}^{n}(x_i^2) - (x_j)^2 - \frac{((\sum_{i=1}^{n} x_i)-x_j)^2}{n-1}}{n-2} \tag{4.5}$$

$$Syy^{(j)} = \frac{\sum_{i=1}^{n}(y_i^2) - (y_j)^2 - \frac{((\sum_{i=1}^{n} y_i)-y_j)^2}{n-1}}{n-2} \tag{4.6}$$

$$Sxy^{(j)} = \frac{\sum_{i=1}^{n}(x_i y_i) - (y_j x_j) - \frac{((\sum_{i=1}^{n} x_i)-x_j)(\sum_{i=1}^{n} y_i)-y_k)}{n-1}}{n-2} \tag{4.7}$$

The updated estimate for the slope is therefore

$$\hat{\beta}_1^{(j)} = \frac{Sxy^{(j)}}{Sxx^{(j)}} \tag{4.8}$$

It is necessary to determine the mean for x and y of the remaining $n-1$ terms

$$\bar{x}^{(j)} = \frac{(\sum_{i=1}^{n} x_i) - (x_j)}{n-1}, \tag{4.9}$$

$$\bar{y}^{(j)} = \frac{(\sum_{i=1}^{n} y_i) - (y_j)}{n-1}. \tag{4.10}$$

The updated intercept estimate is therefore

$$\hat{\beta}_0^{(j)} = \bar{y}^{(j)} - \hat{\beta}_1^{(j)} \bar{x}^{(j)}. \tag{4.11}$$

4.2.2 Updating of Regression Estimates

Updating techniques are used in regression analysis to add or delete rows from a model, allowing the analyst the effect of the observation associated with that row. In time series problems, there will be scientific interest in the changing relationship between variables. In cases where there a single row is to be added or deleted, the procedure used is equivalent to a geometric rotation of a plane.

Updating techniques are used in regression analysis to add or delete rows from a model, allowing the analyst the effect of the observation associated with that row.

Consider a $p \times p$ matrix X, from which a row x_i^T is to be added or deleted. **?** sets $A = X^T X$, $a = -x_i^T$ and $b = x_i^T$, and writes the above equation as

$$(X^T X \pm x_i x_i^T)^{-1} = \quad (X^T X)^{-1} \mp \frac{(X^T X)^{-1}(x_i x_i^T (X^T X)^{-1}}{1 - x_i^T (X^T X)^{-1} x_i} \tag{4.12}$$

This approach allows an economic approach to recalculating the projection matrix, V, by removing the necessity to refit the model each time it is updated.

This approach is known for numerical instability in the case of downdating.

4.2.3 Updating Standard deviation

A simple, but useful, example of updating is the updating of the standard deviation when an observation is omitted, as practised in statistical process control analyzes. From first principles, the variance of a data set can be calculated using the following formula.

$$S^2 = \frac{\sum_{i=1}^n (x_i^2) - \frac{(\sum_{i=1}^n x_i)^2}{n}}{n-1} \tag{4.13}$$

While using bivariate data, the notation Sxx and Syy shall apply hither to the variance of x and of y respectively. The covariance term Sxy is given by

$$Sxy = \frac{\sum_{i=1}^n (x_i y_i) - \frac{(\sum_{i=1}^n x_i)(\sum_{i=1}^n y_i)}{n}}{n-1}. \tag{4.14}$$

4.2.4 Inference on intercept and slope

$$\hat{\beta}_1 \pm t_{(\alpha,n-2)}\sqrt{\frac{S^2}{(n-1)S_x^2}} \tag{4.15}$$

$$\frac{\hat{\beta}_0 - \beta_0}{SE(\hat{\beta}_0)} \tag{4.16}$$

$$\frac{\hat{\beta}_1 - \beta_1}{SE(\hat{\beta}_0)} \tag{4.17}$$

4.2.5 Inference on correlation coefficient

This test of the slope is coincidentally the equivalent of a test of the correlation of the n observations of X and Y.

$$\begin{aligned} H_0 &: \rho_{XY} = 0 \\ H_A &: \rho_{XY} \neq 0 \end{aligned} \tag{4.18}$$

4.2.6 Sherman Morrison Woodbury Formula

The 'Sherman Morrison Woodbury' Formula is a well known result in linear algebra;

$$(A + a^T B)^{-1} \quad = \quad A^{-1} - A^{-1}a^T(I - bA^{-1}a^T)^{-1}bA^{-1} \tag{4.19}$$

This result is highly useful for analyzing regression diagnostics, and for matrices inverses in general. Consider a $p \times p$ matrix X, from which a row x_i^T is to be added or deleted. **?** sets $A = X^T X$, $a = -x_i^T$ and $b = x_i^T$, and writes the above equation as

$$(X^T X \pm x_i x_i^T)^{-1} = \quad (X^T X)^{-1} \mp \quad \frac{(X^T X)^{-1}(x_i x_i^T(X^T X)^{-1}}{1 - x_i^T(X^T X)^{-1}x_i} \tag{4.20}$$

The projection matrix H (also known as the hat matrix), is a well known identity that maps the fitted values $\hat{Y}$ to the observed values Y, i.e. $\hat{Y} = HY$.

$$H = \quad X(X^T X)^{-1}X^T \tag{4.21}$$

H describes the influence each observed value has on each fitted value. The diagonal elements of the H are the ‘leverages’, which describe the influence each observed value has on the fitted value for that same observation. The residuals (R) are related to the observed values by the following formula:

$$R = (I - H)Y \tag{4.22}$$

The variances of Y and R can be expressed as:

$$\begin{aligned} \mathrm{var}(Y) &= H\sigma^2 \\ \mathrm{var}(R) &= (I - H)\sigma^2 \end{aligned} \tag{4.23}$$

Updating techniques allow an economic approach to recalculating the projection matrix, H, by removing the necessity to refit the model each time it is updated. However this approach is known for numerical instability in the case of down-dating.

Chapter 5

Appendices 1

5.1 Model Terms (Roy 2009)

- Let y_{mir} be the response of method m on the ith subject at the $r-$th replicate.

- Let $\boldsymbol{y}_{ir}$ be the 2×1 vector of measurements corresponding to the $i-$th subject at the $r-$th replicate.

- Let $\boldsymbol{y}_{i}$ be the $R_i \times 1$ vector of measurements corresponding to the $i-$th subject, where R_i is number of replicate measurements taken on item i.

- Let $\alpha_m i$ be the fixed effect parameter for method for subject i.

- Formally Roy uses a separate fixed effect parameter to describe the true value μ_i, but later combines it with the other fixed effects when implementing the model.

- Let u_{1i} and u_{2i} be the random effects corresponding to methods for item i.

- $\boldsymbol{\epsilon}_i$ is a n_i-dimensional vector comprised of residual components. For the blood pressure data $n_i = 85$.

- $\boldsymbol{\beta}$ is the solutions of the means of the two methods. In the LME output, the bias ad corresponding t-value and p-values are presented. This is relevant to Roy's first test.

5.2 Application to MCS

Let $\hat{\beta}$ denote the least square estimate of β based upon the full set of observations, and let $\hat{\beta}^{(k)}$ denoted the estimate with the k^{th} case excluded.

5.3 Grubbs' Data

For the Grubbs data the $\hat{\beta}$ estimated are $\hat{\beta}_0$ and $\hat{\beta}_1$ respectively. Leaving the fourth case out, i.e. $k = 4$ the corresponding estimates are $\hat{\beta}_0^{-4}$ and $\hat{\beta}_1^{-4}$

$$Y^{-Q} = \hat{\beta}^{-Q} X^{-Q} \tag{5.1}$$

When considering the regression of case-wise differences and averages, we write $D^{-Q} = \hat{\beta}^{-Q} A^{-Q}$

	F	C	D	A
1	793.80	794.60	-0.80	794.20
2	793.10	793.90	-0.80	793.50
3	792.40	793.20	-0.80	792.80
4	794.00	794.00	0.00	794.00
5	791.40	792.20	-0.80	791.80
6	792.40	793.10	-0.70	792.75
7	791.70	792.40	-0.70	792.05
8	792.30	792.80	-0.50	792.55
9	789.60	790.20	-0.60	789.90
10	794.40	795.00	-0.60	794.70
11	790.90	791.60	-0.70	791.25
12	793.50	793.80	-0.30	793.65

$$Y^{(k)} = \hat{\beta}^{(k)} X^{(k)} \tag{5.2}$$

Consider two sets of measurements , in this case F and C , with the vectors of case-wise averages A and case-wise differences D respectively. A regression model of differences on averages can be fitted with the view to exploring some characteristics of the data.

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Consider two sets of measurements , in this case F and C , with the vectors of case-wise averages A and case-wise differences D respectively. A regression model of differences on averages can be fitted with the view to exploring some characteristics of the data.

```
Call: lm(formula = D ~ A)


Coefficients: (Intercept)            A
-37.51896      0.04656
```

When considering the regression of case-wise differences and averages, we write

$$D^{-Q} = \hat{\beta}^{-Q} A^{-Q} \tag{5.5}$$

5.4 Grubbs' data

Let $\hat{\beta}$ denote the least square estimate of β based upon the full set of observations, and let $\hat{\beta}^{(k)}$ denoted the estimate with the k^{th} case excluded.

For the Grubbs data the $\hat{\beta}$ estimated are $\hat{\beta}_0$ and $\hat{\beta}_1$ respectively. Leaving the fourth case out, i.e. $k = 4$ the corresponding estimates are $\hat{\beta}_0^{-4}$ and $\hat{\beta}_1^{-4}$

$$Y^{(k)} = \hat{\beta}^{(k)} X^{(k)} \tag{5.6}$$

Consider two sets of measurements , in this case F and C , with the vectors of case-wise averages A and case-wise differences D respectively. A regression model of differences on averages can be fitted with the view to exploring some characteristics of the data.

```
Call: lm(formula = D ~ A)

Coefficients: (Intercept)          A
-37.51896      0.04656
```

	F	C	D	A
1	793.80	794.60	-0.80	794.20
2	793.10	793.90	-0.80	793.50
3	792.40	793.20	-0.80	792.80
4	794.00	794.00	0.00	794.00
5	791.40	792.20	-0.80	791.80
6	792.40	793.10	-0.70	792.75
7	791.70	792.40	-0.70	792.05
8	792.30	792.80	-0.50	792.55
9	789.60	790.20	-0.60	789.90
10	794.40	795.00	-0.60	794.70
11	790.90	791.60	-0.70	791.25
12	793.50	793.80	-0.30	793.65

When considering the regression of case-wise differences and averages, we write

$$D^{-Q} = \hat{\beta}^{-Q} A^{-Q} \tag{5.7}$$

5.5 Grubb's example

For the Grubbs data the $\hat{\beta}$ estimated are $\hat{\beta}_0$ and $\hat{\beta}_1$ respectively. Leaving the fourth case out, i.e. $Q = 4$ the corresponding estimates are $\hat{\beta}_0^{-4}$ and $\hat{\beta}_1^{-4}$

$$Y^{-Q} = \hat{\beta}^{-Q} X^{-Q} \tag{5.8}$$

5.6 Influence measures using R

R provides the following influence measures of each observation.

	dfb.1_	dfb.A	dffit	cov.r	cook.d	hat
1	0.42	-0.42	-0.56	1.13	0.15	0.18
2	0.17	-0.17	-0.34	1.14	0.06	0.11
3	0.01	-0.01	-0.24	1.17	0.03	0.08
4	-1.08	1.08	1.57	0.24	0.56	0.16
5	-0.14	0.14	-0.24	1.30	0.03	0.13
6	-0.00	0.00	-0.11	1.31	0.01	0.08
7	-0.04	0.04	-0.08	1.37	0.00	0.11
8	0.02	-0.02	0.15	1.28	0.01	0.09
9	0.69	-0.68	0.75	2.08	0.29	0.48
10	0.18	-0.18	-0.22	1.63	0.03	0.27
11	-0.03	0.03	-0.04	1.53	0.00	0.19
12	-0.25	0.25	0.44	1.05	0.09	0.12

5.7 Sherman Morrison Woodbury Formula

The ‘Sherman Morrison Woodbury’ Formula is a well known result in linear algebra;

$$(A + a^T B)^{-1} \quad = \quad A^{-1} - A^{-1}a^T(I - bA^{-1}a^T)^{-1}bA^{-1} \tag{5.9}$$

This result is highly useful for analyzing regression diagnostics, and for matrices inverses in general. Consider a $p \times p$ matrix X, from which a row x_i^T is to be added or deleted. ? sets $A = X^TX$, $a = -x_i^T$ and $b = x_i^T$, and writes the above equation as

$$(X^TX \pm x_ix_i^T)^{-1} = \quad (X^TX)^{-1} \mp \quad \frac{(X^TX)^{-1}(x_ix_i^T(X^TX)^{-1}}{1-x_i^T(X^TX)^{-1}x_i} \tag{5.10}$$

The projection matrix H (also known as the hat matrix), is a well known identity that maps the fitted values $\hat{Y}$ to the observed values Y, i.e. $\hat{Y} = HY$.

$$H = \quad X(X^TX)^{-1}X^T \tag{5.11}$$

H describes the influence each observed value has on each fitted value. The diagonal elements of the H are the 'leverages', which describe the influence each observed value has on the fitted value for that same observation. The residuals (R) are related to the observed values by the following formula:

$$R = (I - H)Y \tag{5.12}$$

The variances of Y and R can be expressed as:

$$\begin{aligned} \text{var}(Y) &= H\sigma^2 \\ \text{var}(R) &= (I - H)\sigma^2 \end{aligned} \tag{5.13}$$

Updating techniques allow an economic approach to recalculating the projection matrix, H, by removing the necessity to refit the model each time it is updated. However this approach is known for numerical instability in the case of down-dating.

5.8 Hat Values for MCS regression

With A as the averages and D as the casewise differences.

```
fit = lm(D~A)
```

$$H = A\left(A^{\top}A\right)^{-1}A^{\top},$$

Chapter 6

Augmented GLMs

Generalized linear models are a generalization of classical linear models.

6.1 Augmented GLMs

With the use of h-likihood, a random effected model of the form can be viewed as an 'augmented GLM' with the response varaibkes $(y^t, \phi_m^t)^t$, (with $\mu = E(y)$,$u = E(\phi)$, $var(y) = \theta V(\mu)$. The augmented linear predictor is

$$\eta_{ma} = (\eta^t, \eta_m^t)^t) = T\omega.$$

.

The subscript M is a label referring to the mean model.

$$\begin{pmatrix} Y \\ \psi_M \end{pmatrix} = \begin{pmatrix} X & Z \\ 0 & I \end{pmatrix} \begin{pmatrix} \beta \\ \nu \end{pmatrix} + e^* \tag{6.1}$$

The error term e^* is normal with mean zero. The variance matrix of the error term is given by

$$\Sigma_a = \begin{pmatrix} \Sigma & 0 \\ 0 & D \end{pmatrix}. \tag{6.2}$$

$y_a = T\delta + e^*$

Weighted least squares equation

6.1.1 The Augmented Model Matrix

$$X = \begin{pmatrix} T & Z \\ 0 & I \end{pmatrix} \delta = \begin{pmatrix} \beta \\ \nu \end{pmatrix} \tag{6.3}$$

6.2 Algorithms : ML v REML

Maximum likelihood estimation is a method of obtaining estimates of unknown parameters by optimizing a likelihood function. The ML parameter estimates are the values of the argument that maximise the likelihood function, i.e. the estimates that make the observed values of the dependent variable most likely, given the distributional assumptions

The most common iterative algorithms used for the optimization problem in the context of LMEs are the EM algoritm, fisher scoring algorithm and NR algorithm, which [cite:West] commends as the preferred method.

A mixed model is an extension of the general linear models that can specify additional random effects terms.

Parameter of the mixed model can be estimated using either ML or REML, while the AIC and the BIC can be used as measures of "goodness of fit" for particular models, where smaller values are considered preferable.

(***Wikipedia***)The restricted (or residual, or reduced) maximum likelihood (REML) approach is a particular form of maximum likelihood estimation which does not base estimates on a maximum likelihood fit of all the information, but instead uses a likelihood function calculated from a transformed set of data, so that nuisance parameters have no effect.

In contrast to the earlier maximum likelihood estimation, REML can produce unbiased estimates of variance and covariance parameters.

ML procedures for LME

The maximum likelihood procedure of Hartley and Rao yields simultaneous estimates for both the fixed effects and the random effect, by maximising the likelihood of $\boldsymbol{y}$ with respect to each element of $\boldsymbol{\beta}$ and $\boldsymbol{b}$.

6.3 Estimation of random effects

Estimation of random effects for LME models in the NLME package is accomplished through use of both EM (Expectation-Maximization) algorithms and Newton-Raphson algorithms.

- EM iterations bring estimates of the parameters into the region of the optimum very quickly, but convergence to the optimum is slow when near the optimum.
- Newton-Raphson iterations are computationally intensive and can be unstable when far from the optimum. However, close to the optimum they converge quickly.
- The LME function implements a hybrid approach, using 25 EM iterations to quickly get near the optimum, then switching to Newton-Raphson iterations to quickly converge to the optimum.
- If convergence problems occur, the "controlargument in LME can be used to change the way the model arrives at the optimum.

6.4 Covariance Parameters

The unknown variance elements are referred to as the covariance parameters and collected in the vector θ.

6.4.1 Methods and 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.

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.

6.5 Haslett's Analysis

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

6.6 Computation and Notation

with $\boldsymbol{V}$ unknown, a standard practice for estimating $\boldsymbol{X\beta}$ is the estime the variance components σ_j^2, compute an estimate for $\boldsymbol{V}$ and then compute the projector matrix A, $\boldsymbol{X}\hat{\boldsymbol{\beta}} = \boldsymbol{AY}$.

Zewotir and Galpin (2005) remarks that $\boldsymbol{D}$ is a block diagonal with the $i-$th block being $u\boldsymbol{I}$

Chapter 7

Generalized linear models

7.1 Generalized Linear model

In statistics, the generalized linear model (GzLM) is a flexible generalization of ordinary least squares regression. The GzLM generalizes linear regression by allowing the linear model to be related to the response variable via a link function and by allowing the magnitude of the variance of each measurement to be a function of its predicted value.

Mixed Effects Models offer a flexible framework by which to model the sources of variation and correlation that arise from grouped data. This grouping can arise when data collection is undertaken in a hierarchical manner, when a number of observations are taken on the same observational unit over time, or when observational units are in some other way related, violating assumptions of independence.

7.2 Generalized Model(GzLM)

Nelder and Wedderburn (1972) integrated the previously disparate and separate approaches to models for non-normal cases in a framework called ”generalized linear models.” The key elements of their approach is to describe any given model in terms of it’s link function and it’s variance function.

7.2.1 What is a GzLM

$$\mathrm{E}(\mathbf{Y}) = \boldsymbol{\mu} = g^{-1}(\mathbf{X}\boldsymbol{\beta}) \tag{7.1}$$

where $E(Y)$ is the expected value of Y, $X\beta$ is the linear predictor, a linear combination of unknown parameters,β and g is the link function.

$\mathrm{Var}(\mathbf{Y}) = \mathrm{V}(\boldsymbol{\mu}) = \mathrm{V}(g^{-1}(\mathbf{X}\boldsymbol{\beta}))$

7.2.2 GzLM Structure

The GzLM consists of three elements.

1. A probability distribution from the exponential family.
2. A linear predictor $\eta = X\beta$.
3. A link function g such that $E(Y) = \mu = g^{-1}(eta)$.

7.2.3 Link Function

Definition 1 : The link function provides the relationship between the linear predictor and the mean of the distribution function. There are many commonly used link functions, and their choice can be somewhat arbitrary. It can be convenient to match the domain of the link function to the range of the distribution function's mean.

Definition 2 : A link function is the function that links the linear model specified in the design matrix, where columns represent the beta parameters and rows the real parameters.

7.2.4 Canonical parameter

θ, called the dispersion parameter,

7.2.5 Dispersion parameter

τ, called the dispersion parameter, typically is known and is usually related to the variance of the distribution.

7.2.6 Iteratively weighted least square

IWLS is used to find the maximum likelihood estimates of a generalized linear model. Definition: An iterative algorithm for fitting a linear model in the case where the data may contain outliers that would distort the parameter estimates if other estimation procedures were used. The procedure uses weighted least squares, the influence of an outlier being reduced by giving that observation a small weight. The weights chosen in one iteration are related to the magnitudes of the residuals in the previous iteration with a large residual earning a small weight.

7.2.7 Residual Components

In GzLMS the deviance is the sum of the deviance components

$$D = \sum d_i \tag{7.2}$$

In GzLMS the deviance is the sum of the deviance components

7.3 Generalized linear mixed models

[pawitan section 17.8]

The Generalized linear mixed model (GLMM) extend classical mixed models to non-normal outcome data.

In statistics, a generalized linear mixed model (GLMM) is a particular type of mixed model. It is an extension to the generalized linear model in which the linear predictor contains random effects in addition to the usual fixed effects. These random effects are usually assumed to have a normal distribution.

Fitting such models by maximum likelihood involves integrating over these random effects.

Chapter 8

LME Likelihood

8.1 One Way ANOVA

8.1.1 Page 448

Computing the variance of $\hat{\beta}$

$$\text{var}(\hat{\beta}) = (X'V^{-1}X)^{-}1 \tag{8.1}$$

It is not necessary to compute V^{-1} explicitly.

$$\begin{aligned} V^{-1}X &= \Sigma^{1}X - Z()Z'\Sigma^{-1}X & (8.2)\\ &= \Sigma^{-1}(X - Zb_x) & (8.3)\end{aligned}$$

The estimate b_x is the same term obtained from the random effects model; $X = Zb_x + e$, using X as an outcome variable. This formula is convenient in applications where b_x can be easily computed. Since X is a matrix of p columns, b_x can simple be computed column by column. according to the columns of X.

8.1.2 Page 448- simple example

Consider a simple model of the form;

$$y_{ij} = \mu + \beta_i + \epsilon_{ij}.$$

The iterative procedure is as follows Evaluate the individual group mean $\bar{y}_i$ and variance $\hat{Sigma}^2{}_i$. Then use the variance of the group means as an estimate of the σ^2_b. The average of the the variances of the groups is the initial estimate of the σ^2_e.

Iterative procedure

The iterative procedure comprises two steps, with 0 as the first approximation of b_i.

The first step is to compute λ, the ratio of variabilities,

$$\lambda = \frac{\sigma^2_b}{\sigma^2_e}$$

$$\mu = \frac{1}{N} \sum_{ij} (y_{ij} - b_i)$$

$$b_i = \frac{n(\bar{y}_i - \mu)}{n + \lambda}$$

The second step is to updat $sigma^2_e$

$$\sigma^2_e = \frac{e'e}{N - df} \tag{8.4}$$

where e is the vector of $e_{ij} = y_{ij} - \mu - b_i$ and $df = qn/n + \lambda$ and

$$\sigma^2_b = \frac{1}{q} \sum_{i=1}^{q} b^2_1 + (\frac{n}{\sigma^2_e} + \frac{1}{\sigma^2_b})^{-1} \tag{8.5}$$

Worked Example

Further to [pawitan 17.1] the initial estimates for variability are $\sigma^2_b = 1.7698$ and $\sigma^2_e = 0.3254$. At convergence the following results are obtained.
n=16, q=5

$$\begin{aligned} \hat{\mu} = \bar{y} &= 14.175 \\ \hat{\sigma}^2 &= 0.325 \\ \hat{\sigma}^2_b &= 1.395 \\ \sigma &= 0.986 \end{aligned}$$

At convergene the following estimates are obtained,

$$\begin{aligned} \hat{\mu} &= 14.1751 \\ \hat{b} = (-0.6211, 0.2683, 1.4389, -1.914, 0.8279) \\ \hat{\sigma}^2_b &= 1.3955 \\ \hat{\sigma}^2_e &= 0.3254 \end{aligned}$$

8.1.3 Extention to several random effects

[pawitan section 17.7]

8.2 Classical model for single measurements

The classical model is based on measurements y_{mi} by method $m = 1, 2$ on item $i = 1, 2 \ldots$

$$y_{mi} + \alpha_m + \mu_i + e_{mi}$$

$$e_{mi} \sim \backslash(0, \sigma^2_m)$$

Even though the separate variances can not be identified, their sum can be estimated by the empirical variance of the differences.

Like wise the separate α can not be estimated, only theiir difference can be estimated as $\bar{D}$

In the first instance, we require a simple model to describe a measurement by method m. We use the term *item* to denote an individual, subject or sample, to be measured, being randomly sampled from a population. Let y_{mi} be the measurement for item i made by method m.

$$y_{mi} = \alpha_m + \mu_i + e_{mi}$$

- α_m is the fixed effect associated with method m,
- μ_i is the true value for subject i (fixed effect),
- e_{mi} is a random effect term for errors with $e_{mi} \sim \mathcal{N}(0, \sigma^2_m)$.

.

This model implies that the difference between the paired measurements can be expressed as

$$d_i = y_{1i} - y_{2i} \sim \mathcal{N}(\alpha_1 - \alpha_2, \sigma^2_1 - \sigma^2_2).$$

Importantly, this is independent of the item levels μ_i. As the case-wise differences are of interest, the parameters of interest are the fixed effects for methods α_m.

$$y_{mi} = \alpha_m + \mu_i + e_{mi}$$

Importantly these variance covariance structures are central to Roy methodology.

? proposes a series of hypothesis tests based on these matrices as part of her methodology. These tests shall be reverted to in due course.

The standard deviation of the differences of variables a and b is computed as

$$\text{var}(a - b) = \text{var}(a) + \text{var}(b) - 2\text{cov}(a, b)$$

Hence the variance of the difference of two methods, that allows for the calculation of the limits of agreement, can be calculated as

$$\text{var}(d) = \omega_1^2 + \omega_2^2 - 2 \times \omega_1 2$$

8.3 Sampling

One important feature of replicate observations is that they should be independent of each other. In essence, this is achieved by ensuring that the observer makes each measurement independent of knowledge of the previous value(s). This may be difficult to achieve in practice. (Check who said this)

8.4 Limits of agreement in LME models

Limits of agreement are used extensively for assessing agreement, due to they're being intuitive and easy to use. Necessarily their prevalence in literature has meant that they are now the best known measurement for agreement, and that any newer methodology would benefit by making reference to them.

Carstensen et al. (2008) uses LME models to determine the limits of agreement. Between-subject variation for method m is given by d^2_m and within-subject variation is given by λ^2_m. Carstensen et al. (2008) remarks that for two methods A and B, separate values of d^2_A and d^2_B cannot be estimated, only their average. Hence the assumption that $d_x = d_y = d$ is necessary. The between-subject variability $\boldsymbol{D}$ and within-subject variability $\boldsymbol{\Lambda}$ can be presented in matrix form,

$$\boldsymbol{D} = \begin{pmatrix} d_A^2 & 0 \\ 0 & d_B^2 \end{pmatrix} = \begin{pmatrix} d^2 & 0 \\ 0 & d^2 \end{pmatrix}, \qquad \boldsymbol{\Lambda} = \begin{pmatrix} \lambda_A^2 & 0 \\ 0 & \lambda_B^2 \end{pmatrix}. \tag{8.6}$$

The variance for method m is $d_m^2 + \lambda_m^2$. Limits of agreement are determined using the standard deviation of the case-wise differences between the sets of measurements by two methods A and B, given by

$$\mathrm{var}(y_A - y_B) = 2d^2 + \lambda_A^2 + \lambda_B^2. \tag{8.7}$$

Importantly the covariance terms in both variability matrices are zero, and no covariance component is present.

Carstensen et al. (2008) presents a data set ‘fat’, which is a comparison of measurements of subcutaneous fat by two observers at the Steno Diabetes Center, Copenhagen. Measurements are in millimeters (mm). Each person is measured three times by each observer. The observations are considered to be ‘true’ replicates.

A linear mixed effects model is formulated, and implementation through several software packages is demonstrated. All of the necessary terms are presented in the computer output. The limits of agreement are therefore,

$$0.0449 \pm 1.96 \times \sqrt{2 \times 0.0596^2 + 0.0772^2 + 0.0724^2} = (-0.220, 0.309). \tag{8.8}$$

Roy (2009a) has demonstrated a methodology whereby d_A^2 and d_B^2 can be estimated separately. Also covariance terms are present in both $\boldsymbol{D}$ and $\boldsymbol{\Lambda}$. Using Roy’s methodology, the variance of the differences is

$$\mathrm{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_A^2 + \lambda_B^2 - 2(d_{AB} + \lambda_{AB}) \tag{8.9}$$

All of these terms are given or determinable in computer output. The limits of agreement can therefore be evaluated using

$$\bar{y_A} - \bar{y_B} \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \tag{8.10}$$

For Carstensen’s ‘fat’ data, the limits of agreement computed using Roy’s method are consistent with the estimates given by Carstensen et al. (2008); $0.044884 \pm 1.96 \times 0.1373979 = (-0.224, 0.314)$.

8.4.1 Linked replicates

Carstensen et al. (2008) proposes the addition of an random effects term to their model when the replicates are linked. This term is used to describe the 'item by replicate' interaction, which is independent of the methods. This interaction is a source of variability independent of the methods. Therefore failure to account for it will result in variability being wrongly attributed to the methods.

Carstensen et al. (2008) introduces a second data set; the oximetry study. This study done at the Royal Children?s Hospital in Melbourne to assess the agreement between co-oximetry and pulse oximetry in small babies.

In most cases, measurements were taken by both method at three different times. In some cases there are either one or two pairs of measurements, hence the data is unbalanced. Carstensen et al. (2008) describes many of the children as being very sick, and with very low oxygen saturations levels. Therefore it must be assumed that a biological change can occur in interim periods, and measurements are not true replicates.

Carstensen et al. (2008) demonstrate the necessity of accounting for linked replicated by comparing the limits of agreement from the 'oximetry' data set using a model with the additional term, and one without. When the interaction is accounted for the limits of agreement are (-9.62,14.56). When the interaction is not accounted for, the limits of agreement are (-11.88,16.83). It is shown that the failure to include this additional term results in an over-estimation of the standard deviations of differences.

Limits of agreement are determined using Roy's methodology, without adding any additional terms, are are found to be consistent with the 'interaction' model; $(-9.562, 14.504)$. Roy's methodology assumes that replicates are linked. However, following Carstensen's example, an addition interaction term is added to the implementation of Roy's model to assess the effect, the limits of agreement estimates do not change. However there is a conspicuous difference in within-subject matrices of both models (denoted 1 and 2 respectively);

```
\begin{equation}
```

```
\hat{\boldsymbol{\Lambda}}_{1}= \pmatrix{
16.61 & 11.67\cr
11.67 & 27.65 }\qquad
\boldsymbol{\hat{\Lambda}}_{2}= \pmatrix{
7.55 & 2.60 \cr
2.60 & 18.59}
\end{equation}
```

The variance of the additional random effect in model 2 is 3.01.

The Akaike information criterion (AIC) for both of models are $AIC_1 = 2304.226$ and $AIC_2 = 2306.226$. Having a difference of AIC values of 2 is equivalent to both models being equally as good as the other. The AIC values for the Carstensen 'unlinked' and 'linked' models are 1994.66 and 1955.48 respectively.

The $\hat{\boldsymbol{\Lambda}}$ matrices are informative as to the difference between Carstensen's unlinked and linked models. For the oximetry data, the covariance terms (given above as 11.67 and 2.6 respectively) are of similar magnitudes to the variance terms. Conversely for the 'fat' data the covariance term (-0.00032) is negligible. When the interaction term is added to the model, the covariance term remains negligible. (For the 'fat' data, the difference in AIC values is also 2).

To conclude, Carstensen's models provided a rigorous way to determine limits of agreement, but don't provide for the computation of $\hat{\boldsymbol{D}}$ and $\hat{\boldsymbol{\Lambda}}$. Therefore the test's proposed by Roy (2009a) can not be implemented. Conversely, accurate limits of agreement can be found using Roy's method.

Addition of the interaction term erodes the capability of Roy's methodology to compare candidate models, and therefore shall not be adopted.

(N.B. To complement the blood pressure 'J vs S' analysis, the limits of agreement are $15.62 \pm 1.96 \times 20.33 = (-24.22, 55.46)$.)

8.5 Conclusion

Carstensen et al. (2008) and Roy (2009a) highlight the need for method comparison methodologies suitable for use in the presence of replicate measurements. Roy (2009a) presents a comprehensive methodology for assessing the agreement of two methods, for replicate measurements. This methodology has the added benefit of overcoming the problems of unbalanced data and unequal numbers of replicates. Implementation of the methodology, and interpretation of the results, is relatively easy for practitioners who have only basic statistical training. Furthermore, it can be shown that widely used existing methodologies, such as the limits of agreement, can be incorporated into Roy's methodology.

9. Permutation Test, Power Tests and Missing Data

This section explores topics such as dependent variable simulation and power analysis, introduced by Galecki & Burzykowski (2013), and implementable with their ***nlmeU*** `R` package. Using the ***predictmeans*** `R` package, it is possible to perform permutation t-tests for coefficients of (fixed) effects and permutation F-tests.

The matter of missing data has not been commonly encountered in either Method Comparison Studies or Linear Mixed Effects Modelling. However Roy (2009) deals with the relevant assumptions regrading missing data. Galecki & Burzykowski (2013) approaches the subject of missing data in LME Modelling. The ***nlmeU*** package includes the `patMiss` function, which "*allows to compactly present pattern of missing data in a given vector/matrix/data frame or combination of thereof*".

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