

# 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` package 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 pack-

age is under current development, with a version being released 0.70 – 3.

## 1.1 Relevance of Roy's Methodology

The relevance of Roy's methodology is that estimates for the between-item variances for both methods  $\hat{d}_m^2$  are computed. Also the VC matrices are constructed with covariance terms and, so the difference variance must be formulated accordingly.

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm \sqrt{\hat{d}_1^2 + \hat{d}_2^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2 - 2\hat{d}_{12} - 2\hat{\sigma}_1\hat{\sigma}_2}$$

## Roy Test

Roy's Tests (Roy 2009) Roy 2009 devised an LME based Testing approach to the MCS problem, based on earlier work by Hamlett et al. Roy 2009 presents a series of three formal hypothesis tests for assessing agreement between two methods of measurement. Roy also alludes to some of the current shortcomings of the approach.

Comparing different model specifications with LRT tests

- Roy 2007 - Roy 2009 - Hamlett et al. - Roy Leiva 2011

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. These 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 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 is 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 Vari
> testW    = anova(Ref.Fit,NMW.fit)                # Within-Subject Variabil
> testO    = anova(Ref.Fit,NMO.fit)                # Overall Variabilities
```

## 1.2 Interaction Terms in Model

*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.*

Further to ?, if the measurements by a method on an item are not necessarily true replications, e.g., repeated measures over time, then additional terms may be needed for  $e_{mir}$ . ? also addresses this issue by the addition of an interaction term (i.e. a random effect)  $u_{mi}$ , yielding

$$y_{mir} = \alpha_{mi} + u_{mi} + e_{mi}.$$

The additional interaction term is characterized as  $u_{mi} \sim \mathcal{N}(0, \tau_m^2)$  (?). This extra interaction term provides a source of extra variability, but this variance is not relevant to computing the case-wise differences.

## 1.3 Difference Variance further to Carstensen

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  $\alpha$  can not be estimated, only their difference can be estimated as  $\bar{D}$

We assume that that the variance of the measurements is different for both methods, but it does not mean that the separate variances can be estimated with the data available.

## 1.4 Why use LMEs for Method Comparison?

The LME model approach has seen increased use as a framework for method comparison studies in recent years (Lai & Shaio, Carstensen and Choudhary as examples). In part this is due to the increased profile of LME models, and furthermore the availability of capable software. Additionally LME based approaches may utilise the diagnostic and influence analysis techniques that have been developed in recent times.

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

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

- $\beta_1$  and  $\beta_2$  are fixed effects corresponding to both methods. ( $\beta_0$  is the intercept.)
- $b_{1i}$  and  $b_{2i}$  are random effects corresponding to both methods.

Overall variability between the two methods ( $\Omega$ ) is sum of between-subject ( $D$ ) and within-subject variability ( $\Sigma$ ),

$$\text{Block } \mathbf{\Omega}_i = \begin{bmatrix} d_1^2 & d_{12} \\ d_{12} & d_2^2 \end{bmatrix} + \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix}.$$

The well-known “Limits of Agreement”, as developed by Bland and Altman (1986) are easily computable using the LME framework, proposed by Roy. While we will not be considering this analysis, a demonstration will be provided in the example.

Further to this, Roy(2009) demonstrates a suite of tests that can be used to determine how well two methods of measurement, in the presence of repeated measures, agree with each other.

- No Significant inter-method bias
- No difference in the between-subject variabilities of the two methods

- No difference in the within-subject variabilities of the two methods

## 1.5 Definition of Replicate measurements

Further to ?, a formal definition is required of what exactly replicate measurements are

*By replicates we mean two or more measurements on the same individual taken in identical conditions. In general this requirement means that the measurements are taken in quick succession.*

? also remark that an important feature of replicate observations is that they should be independent of each other. This issue is addressed by ?, in terms of exchangeability and linkage. Carstenen advises that repeated measurements come in two *substantially different* forms, depending on the circumstances of their measurement: exchangeable and linked.

### 1.5.1 Exchangeable measurements

Repeated measurements are said to be exchangeable if no relationship exists between successive measurements across measurements. If the condition of exchangeability exists, a group of measurement of the same item determined by the same method can be re-arranged in any permutation without prejudice to proper analysis. There is no reason to believe that the true value of the underlying variable has changed over the course of the measurements.

For the purposes of method comparison studies the following remarks can be made. The  $r$ -th measurement made by method 1 has no special correspondence to the  $r$ -th measurement made by method 2, and consequently any pairing of repeated measurements are as good as each other.

Exchangeable repeated measurements can be treated as true replicates.

### **1.5.2 Linked measurements**

Repeated measurements are said to be linked if a direct correspondence exists between successive measurements across measurements, i.e. pairing. Such measurements are commonly made with a time interval between them, but simultaneously for both methods. Paired measurements are exchangeable, but individual measurements are not.

If the paired measurements are taken in a short period of time so that no real systemic changes can take place on each item, they can be considered true replicates. Should enough time elapse for systemic changes, linked repeated measurements can not be treated as true replicates.

### **1.5.3 Replicate measurements in ARoy2009's paper**

? takes its definition of replicate measurement: two or more measurements on the same item taken under identical conditions. ARoy2009 also assumes linked measurements, but it can be used for the non-linked case.



### 1.5.4 Random effects

Further to ?, if the measurements by a method on an item are not necessarily true replications, e.g., repeated measures over time, then additional terms may be needed for  $e_{mir}$ . ? also addresses this issue by the addition of an interaction term (i.e. a random effect)  $u_{mi}$ , yielding

$$y_{mir} = \alpha_{mi} + u_{mi} + e_{mi}.$$

The additional interaction term is characterized as  $u_{mi} \sim \mathcal{N}(0, \tau_m^2)$  (?).

This extra interaction term provides a source of extra variability, but this variance is not relevant to computing the case-wise differences.

? advises that the formulation of the model should take the exchangeability (in other words, whether or not the measurements are ‘true replicates’) into account. If there is a linkage between measurements (therefore not ‘true’ replicates), the ‘item by replicate’ should be included in the model. If there is no linkage, and the replicates are indeed true replicates, the interaction term should be omitted.

? demonstrates how to compute the limits of agreement for two methods in the case of linked measurements. As a surplus source of variability is excluded from the computation, the limits of agreement are not unduly wide, which would have been the case if the measurements were treated as true replicates.

? also assigns a random effect  $u_{mi}$  for each response  $y_{mir}$ . Importantly ARoy2009’s model assumes linkage.

## 1.6 Model for replicate measurements

We generalize the single measurement model for the replicate measurement case, by additionally specifying replicate values. Let  $y_{mir}$  be the  $r$ –th replicate measurement

for subject “i” made by method “m”. Further to ? fixed effect can be expressed with a single term  $\alpha_{mi}$ , which incorporate the true value  $\mu_i$ .

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

Combining fixed effects (?), we write,

$$y_{mir} = \alpha_{mi} + e_{mir}.$$

The following assumptions are required

- $e_{mir}$  is independent of the fixed effects with mean  $E(e_{mir}) = 0$ .
- Further to ? between-item and within-item variances  $\text{Var}(\alpha_{mi}) = \sigma_{Bm}^2$  and  $\text{Var}(e_{mir}) = \sigma_{Wm}^2$
- In keeping with ?, these variance shall be considered as part of the between-item variance covariance matrix  $\mathbf{D}$  and the within-item variance covariance matrix  $\mathbf{\Sigma}$  respectively, and will be denoted accordingly ( i.e.  $d_m^2$  and  $\sigma_m^2$ ).
- Additionally, the total variability of method ”m”, denoted  $\omega_m^2$  is the sum of the within-item and between-item variabilities.

$$\omega_m^2 = d_m^2 + \sigma_m^2$$

## 1.7 Off-Diagonal Components in Roy's Model

The Within-item variability is specified as follows, where  $x$  and  $y$  are the methods of measurement in question.

$$\begin{pmatrix} \sigma_x^2 & \sigma_{xy} \\ \sigma_{xy} & \sigma_y^2 \end{pmatrix}$$

$\sigma_x^2$  and  $\sigma_y^2$  describe the level of measurement error associated with each of the measurement methods for a given item. Attention must be given to the off-diagonal elements of the matrix.

It is intuitive to consider the measurement error of the two methods as independent of each other.

## 1.8 Formal Testing

A formal test can be performed to test the hypothesis that the off-diagonal terms are zero.

$$\begin{pmatrix} \sigma_x^2 & \sigma_{xy} \\ \sigma_{xy} & \sigma_y^2 \end{pmatrix} vs \begin{pmatrix} \sigma_x^2 & 0 \\ 0 & \sigma_y^2 \end{pmatrix}$$

## 1.9 Basic Models Fits

Further to ?, several simple LME models are constructed for the blood pressure data. This data set is the subject of a method comparison study in ?.

### 1.9.1 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

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

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

- 2.

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

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

The variance of error terms is a  $6 \times 6$  matrix.

### 1.9.2 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.

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

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

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

### 1.9.3 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.

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

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

In this model, the random interaction terms all have the same variance  $\sigma_2^2$ . 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

### 1.9.4 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.  $\mathbf{y}_i$  is the entire response vector for the  $i$ th subject.  $\mathbf{X}_i$  and  $\mathbf{Z}_i$  are the fixed- and random-effects design matrices respectively.

$$\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i, \quad i = 1, \dots, 85$$

$$\mathbf{Z}_i \sim \mathcal{N}(\mathbf{0}, \boldsymbol{\Psi}), \quad \boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \sigma^2 \boldsymbol{\Lambda})$$

For the first subject the response vector,  $\mathbf{y}_1$ , is: The fixed effects design matrix  $\mathbf{X}_i$

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

is given by:

The random effects design matrix  $\mathbf{Z}_i$  is given by: The following output was obtained.

Linear mixed-effects model fit by REML

Data: dat

Log-restricted-likelihood: -2047.582

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

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

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

### 1.9.5 Extended LME model

The extended single level LME model relaxes the independence assumption, allowing heteroscedastic and correlated within group errors.

$$\epsilon_i = \mathcal{N}(0, \sigma^2 \Lambda_i) \quad (1.1)$$

$\Lambda_i$  are positive definite matrices.  $\sigma^2$  is factored out of the matrix for computational reasons.

## 1.10 Variance functions

Variance functions are applied to LME models through the ‘weights’ argument. *R* supports several variance functions.

‘varIdent’ constructs a model with different variances per stratum.

### 1.10.1 Diagnostic plots

Diagnostic plots for identifying within-group heteroscedascity and assessing the adequacy of a variance function can also be used with ‘nlme’ objects.