

# Chapter 1

## Appendix C

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.

### 1.1 Roy's Candidate Models

For the blood pressure data used in Roy (2009), 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.

### 1.2 Test 1

The first of Roy's candidate model can be implemented using the following code;

```
> 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")
```

### 1.2.1 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
```

The following output was obtained.

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

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.

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.

### 1.2.2 Nested Model (Between-Item Variability)

For example, the first test model ‘test1.nlme’ is implemented with the same code as `ref.nlme`, except for the term `pdCompSymm` in the second line, rather than `pdSymm`.

#### 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")
```

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.

### 1.2.3 Roy's Reference Model

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

### 1.2.4 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")
```

### 1.2.5 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")
```

### 1.2.6 Variability test 1

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

$$H_0 : d_A = d_B \quad (1.1)$$

$$H_A : d_A \neq d_B \quad (1.2)$$

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  $\hat{\Sigma}$  has a symmetric form for both models, and will be the same for both.

### 1.2.7 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.

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

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

# Bibliography

Roy, A. (2009). An application of the linear mixed effects model to ass the agreement between two methods with replicated observations. *Journal of Biopharmaceutical Statistics* 19, 150–173.