

LME models

- In a linear mixed-effects model, responses from a subject are due to both fixed and random effects. A random effect is an effect associated with a sampling procedure.
- Replicate measurements would require use of random effect terms in model.
- Can have differing number of replicate measurements for different subjects.

The nlme Package

- LME models can be implemented in R using the `nlme` package, one of the core packages.
- Authors: Jose Pinheiro, Douglas Bates (up to 2007), Saikat DebRoy (up to 2002), Deepayan Sarkar (up to 2005), the R Core team
(source: `nlme` package manual)
- "Mixed-Effects Models in S and S-PLUS" by JC Pinheiro and DM Bates (Springer, 2000)

Method Comparison Studies with R

- The absence of inter-method bias by itself is not sufficient to establish whether two measurement methods agree.
- The two methods must also have equivalent levels of precision.
- Should one method yield results considerably more variable than that of the other, they can not be considered to be in agreement.
- With this in mind a methodology is required that allows an analyst to estimate the inter-method bias, and to compare the precision of both methods of measurement.

Roy's method

- Roy 2009 [6] formulates a very powerful method of assessing whether two methods of measurement, with replicate measurements, also using LME models.
- Roy's approach is based on the construction of variance-covariance matrices.
- Importantly, Roy's approach does not address the issue of limits of agreement (though another related analysis, the coefficient of repeatability, is mentioned).

- Roy proposes a novel method using the LME model with Kronecker product covariance structure in a doubly multivariate set-up to assess the agreement between a new method and an established method with unbalanced data and with unequal replications for different subjects (alertRoy).
- Using Roy's method, four candidate models are constructed, each differing by constraints applied to the variance covariance matrices.
- In addition to computing the inter-method bias, three significance tests are carried out on the respective formulations to make a judgement on whether or not two methods are in agreement.

- Roy's model uses fixed effects $\beta_0 + \beta_1$ and $\beta_0 + \beta_1$ to specify the mean of all observations by methods 1 and 2 respectively.

Roy's Approach

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

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

- 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.

Roy's LME model

- Let \mathbf{y}_i be the set of responses for subject i (in matrix form).
- $\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i$
- $\mathbf{b}_i \sim N_m(0, \mathbf{D})$ (m : number of methods)
- $\boldsymbol{\epsilon}_i \sim N_{n_i}(0, \mathbf{R})$ (n_i : number of measurements on subject i)

Roy (2009) - Model terms

It is important to note the following characteristics of this model.

- Let the number of replicate measurements on each item i for both methods be n_i , hence $2 \times n_i$ responses. However, it is assumed that there may be a different number of replicates made for different items. Let the maximum number of replicates be p . An item will have up to $2p$ measurements, i.e. $\max(n_i) = 2p$.
- Later on \mathbf{X}_i will be reduced to a 2×1 matrix, to allow estimation of terms. This is due to a shortage of rank. The fixed effects vector can be modified accordingly.
- \mathbf{Z}_i is the $2n_i \times 2$ model matrix for the random effects for measurement methods on item i .
- \mathbf{b}_i is the 2×1 vector of random-effect coefficients on item i , one for each method.

Roy(2009) - Model terms

- ϵ is the $2n_i \times 1$ vector of residuals for measurements on item i .
- \mathbf{G} is the 2×2 covariance matrix for the random effects.
- \mathbf{R}_i is the $2n_i \times 2n_i$ covariance matrix for the residuals on item i .
- The expected value is given as $E(\mathbf{y}_i) = \mathbf{X}_i\beta$.
- The variance of the response vector is given by $\text{Var}(\mathbf{y}_i) = \mathbf{Z}_i\mathbf{G}\mathbf{Z}_i' + \mathbf{R}_i$.

Variance-covariance matrix

- Overall variance covariance matrix for response vector \mathbf{y}_i

$$\text{Cov}(\mathbf{y}_i) = \mathbf{Z}_i \mathbf{D} \mathbf{Z}_i' + \mathbf{R}_i$$

- can be re-expressed as follows:

$$\mathbf{Z}_i \begin{bmatrix} d_1^2 & d_{12} \\ d_{12} & d_2^2 \end{bmatrix} \mathbf{Z}_i' + \left(V \otimes \begin{bmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{bmatrix} \right)$$

- Overall variability between the two methods is sum of between-subject and within-subject variability,

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

Variance Covariance Matrices

- Under Roy's model, random effects are defined using a bivariate normal distribution.
- Consequently, the variance-covariance structures can be described using 2×2 matrices.
- A discussion of the various structures a variance-covariance matrix can be specified under is required before progressing.
- The following structures are relevant:
 - 1 the identity structure,
 - 2 the compound symmetric structure
 - 3 the symmetric structure.

Variance Covariance Matrices

- The **identity** structure is simply an abstraction of the identity matrix.
- The **compound symmetric** structure and **symmetric** structure can be described with reference to the following matrix (here in the context of the overall covariance Block- Ω_i , but equally applicable to the component variabilities \mathbf{G} and $\mathbf{\Sigma}$);

$$\begin{pmatrix} \omega_1^2 & \omega_{12} \\ \omega_{12} & \omega_2^2 \end{pmatrix}$$

Variance-covariance matrix

$$\begin{pmatrix} \omega_1^2 & \omega_{12} \\ \omega_{12} & \omega_2^2 \end{pmatrix}$$

- Symmetric structure requires the equality of all the diagonal terms, hence $\omega_1^2 = \omega_2^2$.
- Conversely compound symmetry make no such constraint on the diagonal elements.
- Under the identity structure, $\omega_{12} = 0$.
- A comparison of a model fitted using symmetric structure with that of a model fitted using the compound symmetric structure is equivalent to a test of the equality of variance.

The Reference Model

```
REF = lme(y ~ meth,  
  data = dat,  
  random = list(item=pdSymm(~ meth-1)),  
  weights=varIdent(form=~1|meth),  
  correlation = corSymm(form=~1 | item/repl),  
  method="ML")
```

- LME model that specifies a symmetric matrix structure for both between-subject and within-subject variances.

The Nested Model 1

```
NMB = lme(y ~ meth,  
  data = dat,  
  random = list(item=pdCompSymm(~ meth-1)),  
  weights=varIdent(form=~1|meth),  
  correlation = corSymm(form=~1 | item/repl),  
  method="ML")
```

- LME model that specifies a compound symmetric matrix structure for between-subject and symmetric structure within-subject variances.

The Nested Model 2

```
NMW = lme(y ~ meth,
  data = dat,
  random = list(item=pdSymm(~ meth-1)),
  #weights=varIdent(form=~1|meth),
  correlation = corCompSymm(form=~1 | item/repl),
  method="ML")
```

- LME model that specifies a symmetric matrix structure for between-subject and compound symmetric structure within-subject variances.

The Nested Model 3

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

- LME model that specifies a compound symmetric matrix structure for both between-subject and within-subject variances.

Likelihood Ratio Tests

- The relationship between the respective models presented by Roy is known as “nesting”. A model A to be nested in the reference model, model B, if Model A is a special case of Model B, or with some specific constraint applied.
- A general method for comparing models with a nesting relationship is the **likelihood ratio test (LRTs)**.
- LRTs are a family of tests used to compare the value of likelihood functions for two models, whose respective formulations define a hypothesis to be tested (i.e. the nested and reference model).
- The significance of the likelihood ratio test can be found by comparing the likelihood ratio to the χ^2 distribution, with the appropriate degrees of freedom.

Some useful R commands

- `intervals` :

This command obtains the estimate and confidence intervals on the parameters associated with the model. This is particularly useful in writing some code to extract estimates for inter-method bias and variances, and hence estimates for the limits of agreement.

- `anova` :

When a reference model and nested model are specified as arguments, this command performs a likelihood ratio test.

Example: Blood Data

- Used in Bland and Altman's 1999 paper [3]. Data was supplied by Dr E O'Brien.
- Simultaneous measurements of systolic blood pressure each made by two experienced observers, J and R, using a sphygmometer.
- Measurements also made by a semi-automatic blood pressure monitor, denoted S.
- On 85 patients, 3 measurement made in quick succession by each of the three observers (765 measurements in total)

Example: Blood Data

Inter-method Bias between J and S: 15.62 mmHg

```
>summary(REF)
```

```
.....
```

```
Fixed effects: y ~ meth
```

	Value	Std.Error	DF	t-value	p-value
(Intercept)	127.41	3.3257	424	38.310	0
methS	15.62	2.0456	424	7.636	0

```
.....
```

Between-subject variance covariance matrix

```

..
Random effects:
  Formula: ~method - 1 | subject
  Structure: General positive-definite
             StdDev      Corr
methodJ    30.396975 methdJ
methodS    31.165565 0.829
Residual   6.116251
..

```

$$\hat{\mathbf{D}} = \begin{pmatrix} 923.97 & 785.34 \\ 785.34 & 971.29 \end{pmatrix}$$

Within-subject variance covariance matrix

Correlation Structure: General

Formula: ~1 | subject/obs

Parameter estimate(s):

Correlation:

1

2 0.288

Variance function:

Structure: Different standard deviations per stratum

Formula: ~1 | method

Parameter estimates:

J

S

1.000000 1.490806

$$\hat{\Sigma} = \begin{pmatrix} 37.40 & 16.06 \\ 16.06 & 83.14 \end{pmatrix}$$

- The limits of agreement computed by Roy's method are derived from the variance covariance matrix for overall variability.
- This matrix is the sum of the between subject VC matrix and the within-subject VC matrix.
- The standard deviation of the differences of methods x and y is computed using values from the overall VC matrix.

$$\text{var}(x - y) = \text{var}(x) + \text{var}(y) - 2\text{cov}(x, y)$$

Overall variance covariance matrix

- Overall variance

$$\text{Block } \hat{\Omega} = \hat{D} + \hat{\Sigma} = \begin{pmatrix} 961.38 & 801.40 \\ 801.40 & 1054.43 \end{pmatrix}$$

- Standard deviation of the differences can be computed accordingly : 20.32 mmHg.
- Furthermore, limits of agreement can be computed:
[15.62 \pm (2 \times 20.32)] (mmHg).

Formal Tests: Between-subject Variances

- Test the hypothesis that both methods have equal between-subject variances.
- Constructed an alternative model “Nested Model B” using ***compound symmetric*** form for between-subject variance (hence specifying equality of between-subject variances).
- Use a likelihood ratio test to compare models.

...

```
> anova(REF, NMB)
```

	Model	df	...	logLik	Test	L.Ratio	p-value
REF	1	8	...	-2030.736			
NMB	2	7	...	-2030.812	1 vs 2	0.1529142	0.6958

...

- Fail to reject hypothesis of equality.

Formal Tests: Within-subject Variances

- Test the hypothesis that both methods have equal within-subject variances.
- Constructed an alternative model “Nested Model W” using compound symmetric form for within-subject variance (hence specifying equality of within-subject variances).
- Again, use a likelihood ratio test to compare models.

...

```
> anova (REF, NMW)
```

	Model	df	...	logLik	Test	L.Ratio	p-value
REF	1	8	...	-2030.736			
NMW	2	7	...	-2045.044	1 vs 2	28.61679	<.0001

- Reject hypothesis of equality.

Formal Tests : Outcomes

- Inter-method bias: Significant difference in mean values detected.
- Between-subject variance: No significant difference in between-subject variances between the two methods detected.
- Within-subject variance: A significant difference in within-subject variances is detected.
- Can not recommend switching between the two methods.

Remarks

- Can perform a test for equality of overall variances.
- This can be done by specifying a compound symmetry structure for both between-subject and within-subject variances when constructing a nested model.
- Roy controls the family-wise error rate in paper, using Bonferroni correction procedure.