

# Using LME Models for Method Comparison Studies

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# Intro

- Commonly encountered issue in medical statistics
- “Do two methods of measurement agree statistically?”.
- “Can the two methods be used interchangeably?”
- Sources of disagreement can arise from differing population means (i.e. inter-method bias), differing between-subject and with-in subject variances [1].

# The Bland-Altman Plot

- The Bland-Altman plot [2, 3] is a very simple graphical method to compare two measurements techniques.
- In this approach the case-wise differences between the two methods are plotted against the corresponding case-wise averages of the two methods.
- A horizontal lines is drawn at the mean difference(the inter-method bias) , and at the limits of agreement, which are defined as the inter-method bias plus and minus 2 times the standard deviation of the differences.

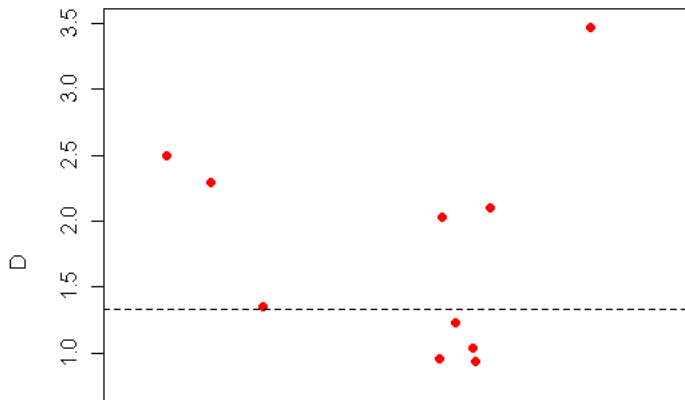
# Bland-Altman Plot

```
>X = rnorm(14,6,1);Y = rnorm(14,5.3,1.1)
>
>A=(X+Y)/2 #case-wise averages
>D=X-Y #case-wise differences
>
>Dbar=mean(D) #inter-method bias
>SdD=sd(D) #standard deviation of the differences
>
>plot(A,D,pch=16,col="red", ylim=c(-3,3))
>
>abline(h=Dbar,lty=2)
>abline(h=(Dbar-2*SdD),lty=2)
>abline(h=(Dbar+2*SdD),lty=2)
```

# Simple Bland-Altman Plot

Inter-method Bias : 0.45

Limits of Agreement: [-1.32, 2.23]



# The Bland-Altman Plot: Prevalence

- Limits of Agreement are used extensively in medical literature for assessing agreement between two methods.
- According to Google Scholar, Bland and Altman's 1986 paper has 22,456 citations.  
("The Pricing of Options and Corporate Liabilities" by Black and Scholes has 19,019 citations.)

# Replicate Measurements

- Bland and Altman's approach originally devised for a single measurement on each item by each of the methods.
- Their 1999 paper [3] extended their approach to replicate measurements:  
*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.*
- Emphasis put on "repeatability".

# Three Conditions

For two methods of measurement to be considered interchangeable, the following conditions must apply [1]:

- 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 (repeatability)



# 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.

# 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

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

- $\beta_1$  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.

# 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  $i$ )

## 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 Structures

$$\begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}$$

- Symmetric structure specifies that  $\sigma_1^2$  may differ from  $\sigma_2^2$ .
- Compound symmetric structure specifies that  $\sigma_1^2 = \sigma_2^2$ .
- In both cases,  $\sigma_{12}$  may take value other than 0.

# 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)

# 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.

## 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 methodJ  
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

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

# 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).

# 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.



## 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.

# References

-  A Roy (2009): *An application of linear mixed effects model to assess the agreement between two methods with replicated observations* Journal of Biopharmaceutical Statistics
-  Bland JM, Altman DG (1986) *Statistical method for assessing agreement between two methods of clinical measurement.*
-  Bland JM, Altman DG (1999) *Measuring agreement in method comparison studies.* Statistical Methods in Medical Research
-  Pinheiro JC, Bates DM (2000): *Mixed-effects models in S and S-PLUS*, Springer.

# Thanks

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