Intro to MCS
ooooooo

Roy's LME Model
oooo

Implementation
oooooo

Example
ooooooooo

References
oo

UNIVERSITY *of* LIMERICK

O L L S C O I L   L U I M N I G H

Using LME Models for Method Comparison Studies

Kevin O'Brien (University of Limerick)

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.
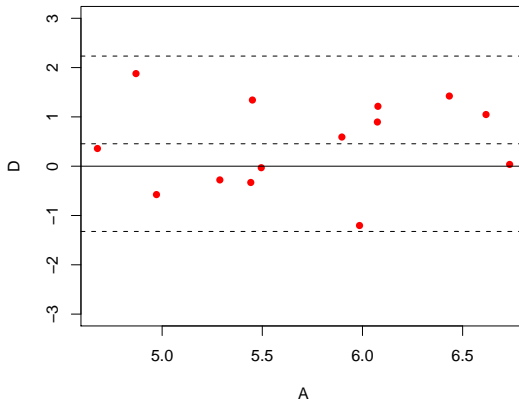
Bland-Altman Plot

```
>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 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.

Roy's LME model

- Let $\boldsymbol{y}_i$ be the set of responses for subject i (in matrix form).

- $\boldsymbol{y}_i = \boldsymbol{X}_i \beta + \boldsymbol{Z}_i \boldsymbol{b}_i + \epsilon_i$

- $\boldsymbol{b}_i \sim N_m(0, \boldsymbol{D})$ (m: number of methods)

- $\epsilon_i \sim N_{n_i}(0, \boldsymbol{R})$ (n_i: number of measurements on subject i)

Variance-covariance matrix

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

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

- can be re-expressed as follows:

$$\boldsymbol{Z}_i \left[\begin{array}{cc} d_1^2 & d_{12} \\ d_{12} & d_2^2 \end{array} \right] \boldsymbol{Z}_i' + \left(V \otimes \left[\begin{array}{cc} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{array} \right] \right)$$

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

$$\text{Block } \boldsymbol{\Omega}_i = \left[\begin{array}{cc} d_1^2 & d_{12} \\ d_{12} & d_2^2 \end{array} \right] + \left[\begin{array}{cc} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{array} \right].$$

Variance-Covariance Structures

$$\left(\begin{array}{cc} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{array} \right)$$

- Symmetric structure specifies that σ_1^2 may differ from σ_2^2.
- Compound symmetric structure specifies that $\sigma_1^2 = \sigma_2^2$.
- In both cases, σ_{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 methdJ
methodS  31.165565 0.829
Residual  6.116251
..
```

$$\hat{\boldsymbol{D}} = \left(\begin{array}{cc} 923.97 & 785.34 \\ 785.34 & 971.29 \end{array} \right)$$

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
```

$$\hat{\Sigma} = \left(\begin{array}{cc} 37.40 & 16.06 \\ 16.06 & 83.14 \end{array} \right)$$

Overall variance covariance matrix

- Overall variance

$$\text{Block } \hat{\boldsymbol{\Omega}} = \hat{\boldsymbol{D}} + \hat{\boldsymbol{\Sigma}} = \left(\begin{array}{cc} 961.38 & 801.40 \\ 801.40 & 1054.43 \end{array} \right)$$

- 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 symmetry 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

- Dr Kevin Hayes, University of Limerick
- Mr Kevin Burke, university of Limerick