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References

Using LME Models for Method Comparison Studies

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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,

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

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".

Linked and Unlinked Replicates

- Roy approach the assessment of the agreement between two methods with replicates by using the maximum likelihood estimation where the replicated observations are linked over time.

- However, her approach can easily extend the method to situations where the replicated observations are not linked, using the approaches set out by Hamlett et al.

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
```

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

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.

Relative Precision

- Dunn remarks that the question of whether or not two methods have the same level of precision is not as important as knowing which of the two methods is more precise.

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Enabling One Tailed Testing

- A useful approach is to compute the confidence intervals for the ratio of within-item standard deviations (equivalent to the ratio of repeatability coefficients), which can be interpreted in the usual manner (or alternatively, the ratio of the variances).

- In fact, the ratio of within-item standard deviations, with the attendant confidence interval, can be determined using a single R command: *intervals()*.

Enabling One Tailed Testing

- Pinheiro and Bates (pg 93-95) give a description of how confidence intervals for the variance components are computed.
- Furthermore a complete set of confidence intervals can be computed to complement the variance component estimates.
- However , to facilitate one tailed testing; what is required is the computation of the variance ratios of within-item and between-item standard deviations.

One Tailed Testing

- To implement a one tailed test, we will compute the ratio of the variance estimates for D and G respectively
- The variance ratios are:

$$\frac{d_1^2}{d_2^2}, \frac{g_1^2}{g_2^2}$$

- Necessarily we need to compute the confidence intervals associated with these variance ratio estimates.

Skewed Distributions

"The omission of standard errors on variance components is intentional. The distribution of an estimator of a variance component is highly skewed and obtaining an estimate of the standard deviation of a skewed distribution is not very useful. A much better approach is based on profiling the objective function." (Douglas Bates May 2012)

Profile Likelihood

- Normal-based confidence intervals for a parameter of interest are inaccurate when the sampling distribution of the estimate is skewed.
- The technique known as profile likelihood can produce confidence intervals with better coverage.
- It may be used when the model includes only the variable of interest or several other variables in addition.
- Profile-likelihood confidence intervals are particularly useful in nonlinear models.
- Profile likelihood confidence intervals are based on the log-likelihood function.

Implementation of PL Confidence Intervals

- The suitable calculation of confidence limits for this variance ratio are to be computed using the profile likelihood approach.
- The R package *profilelikelihood* will be assessed for feasibility, particularly the command *profilelikelihood.lme()*

profilelike.lme

- The *profilelike.lme()* function provides values for a profile likelihood and a normalized profile likelihood for a parameter of interest in a linear mixed-effects model.

References

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Bland JM, Altman DG (1986) *Statistical method for assessing agreement between two methods of clinical measurement*.

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