Linear Mixed Effects Models

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Intro

- “Do two methods of measurement agree statistically?".
- Sources of disagreement can arise from differing population means, differing between-subject and with-in subject variances

Intro

- What is Agreement
- An application of Linear mixed effects models to assess agreement between two methods with replicated observations (Anuradha Roy, University of Texas)

Intro

- The Bland-Altman plot (Bland & Altman, 1986 and 1999), or difference plot, is a graphical method to compare two measurements techniques. In this graphical method the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques.
- Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences.
- Limits of Agreement are used extensively in medical literature for assessing agreement between two methods.

Bland-Altman Plot

What is a Bland-Altman plot?

- Graphical plot of case-wise means against case-wise differences.
- Very simple to implement.
- Can detect constant variance across range of measurement.
- `nlme` package (Pinheiro Bates)

Roy's Three Conditions

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

- 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

LME Models

- “Do two methods of measurement agree statistically?".

LME models

- In a linear mixed-effects model, responses from a subject are thought to be the sum (linear) of so-called fixed and random effects.
- If an effect, such as a medical treatment, affects the population mean, it is fixed. If an effect is associated with a sampling procedure (e.g., subject effect), it is random.
- In a mixed-effects model, random effects contribute only to the covariance structure of the data.

Roy's Approach

- unequal number of replications for different subjects
- LME model with Kroneckor product covariance structure in a doubly multivariate setup
- replicated observations are linked over time

The Reference Model

```
fit1 = lme(y ~ meth-1,
    data = dat,
    random = list(item=pdSymm(~ meth-1)),
    weights=varIdent(form=~1|meth),
    correlation = corSymm(form=~1 | /repl),
    method="ML")
```

The Nested Model 1

```
fit2 = lme(y ~ meth-1,
    data = dat,
    random = list(item=pdCompSymm(~ meth-1)),
    weights=varIdent(form=~1|meth),
    correlation = corSymm(form=~1 | /repl),
    method="ML")
```

The Nested Model 2

```
fit2 = lme(y ~ meth-1,
    data = dat,
    random = list(item=pdSymm(~ meth-1)),
    weights=varIdent(form=~1|meth),
    correlation = corCompSymm(form=~1 | /repl),
    method="ML")
```

The Nested Model 3

```
fit4 = lme(y ~ meth-1,
    data = dat,
    random = list(item=pdCompSymm(~ meth-1)),
    weights=varIdent(form=~1|meth),
    correlation = corCompSymm(form=~1 | /repl),
    method="ML")
```

Intro

```
>fit2 = lme(y ~ meth-1, data = dat,random = list(item=
  correlation = corSymm(form=~1 | item/repl), method="
>
>fit3 = lme(y ~ meth-1, data = dat,random = list(item=
  weights=varIdent(form=~1|meth),
  correlation = corCompSymm(form=~1 | item/repl), meth
>
>fit4 = lme(y ~ meth-1, data = dat,random = list(item=
 correlation = corCompSymm(form=~1 | item/repl), metho
```

Outline

- Bland Altman
- Method Comparison Studies
- Limits of Agreement (Bland Altman 1986)
- Likelihood Ratio Tests
- Linear Mixed Effects Models

LME Models

- Linear Mixed Effects Models
- modelled by both Random Effects and Fixed Effects
-
- Linear models can be seen as a special case of the LME model

Sub Sec 1

- Stuff

Sub Sec 1

- $b_i \sim N(0, D)$
- $\epsilon_i \sim N(0, R)$

Sub Sec 1

- Symmetric
- Compound Symmetry

Inter-Method Bias

A formal test for inter-method bias can be done by re-specifying the reference model, this time allowing an intercept term.

```
fit1 = lme(y ~ meth,
    data = dat,
    ...
```

```
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
```

Likelihood Ratio Test

- Limits of Agreement
- `anova`
- Roy's three conditions.
- Variability
- Matrices

Likelihood Ratio Test

- Limits of Agreement
- `anova`
- Inter-Method Bias
- Sigma and Delta
- Kroneckor Product

Likelihood Ratio Tests

```
> anova(Ref,NM1)
    Mdl df  .....  logLik  Test L.Ratio p-value
Ref  1  8   ..... -2029.8
NM1  2  6   ..... -2044.0  1 vs 2  28.364  <.0001
```

Between Subject Variability

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

$K_\sigma : \sigma_1^1 = \sigma_1^2$
$H_\sigma : \sigma_1^1 \neq \sigma_1^2$

Between Subject Variability

$$\begin{matrix} d_1^2 & d_{12} \\ d_{12} & d_2^2 \end{matrix}$$

$$K_d : d_1^2 = d_1^2$$
$$H_d : d_1^1 \neq d_1^2$$

References

McCullagh, P. and Nelder, J. (1989): *Generalized Linear Models*, Chapman and Hall/CRC.