1 Basic Models Fits

Further to Pinheiro and Bates (1994), several simple LME models are constructed for the blood pressure data. This data set is the subject of a method comparison study in Bland and Altman (1999).

1.1 Implementing the Mixed Models Fits

They are implemented using the following R code, utilising the 'nlme' package. An analysis of variance is used to compare the model fits.

The R script:

```
fit1 = lme( BP ~ method, data = dat, random = ~1 | subject )
fit2 = update(fit1, random = ~1 | subject/method )
fit3 = update(fit1, random = ~method - 1 | subject )
#analysis of variance
anova(fit1,fit2,fit3)
```

1. Simplest workable model, allows differences between methods and incorporates a random intercept for each subject. For subject 1 we have

$$
\boldsymbol{X}_i = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 1 & 1 \\ 1 & 1 \\ 1 & 1 \end{pmatrix}, \quad \boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \end{pmatrix}, \quad \boldsymbol{Z}_i = \begin{pmatrix} 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \end{pmatrix}, \quad \boldsymbol{b}_i = b
$$

   where $\mathrm{E}(b) = 0$ and $\mathrm{var}(b) = \psi$.

2.

$$
\boldsymbol{Z}_i = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} \quad \boldsymbol{b}_i = \begin{pmatrix} b_1 & 0 \\ 0 & b_2 \end{pmatrix}
$$

   where $\mathrm{E}(b_i) = 0$ and $\mathrm{var}(\boldsymbol{b}) = \boldsymbol{\Psi}$.

   The variance of error terms is a 6×6 matrix.

1.2 Model Fit 1

This is a simple model with no interactions. There is a fixed effect for each method and a random effect for each subject.

$$y_{ijk} = \beta_j + b_i + \epsilon_{ijk}, \qquad i = 1, \ldots, 2, j = 1, \ldots, 85, k = 1, \ldots, 3$$

$$b_i \sim \mathcal{N}(0, \sigma_b^2), \qquad \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2155.853
Fixed: BP ~ method
(Intercept)      methodS
127.40784     15.61961


Random effects:
Formula: ~1 | subject
(Intercept) Residual
StdDev:    29.39085 12.44454


Number of Observations: 510
Number of Groups: 85
```

1.3 Model Fit 2

This is a simple model, this time with an interaction effect. There is a fixed effect for each method. This model has random effects at two levels b_i for the subject, and another, b_{ij}, for the respective method within each subject.

$$y_{ijk} = \beta_j + b_i + b_{ij} + \epsilon_{ijk}, \qquad i = 1, \ldots, 2, j = 1, \ldots, 85, k = 1, \ldots, 3$$

$$b_i \sim \mathcal{N}(0, \sigma_1^2), \qquad b_{ij} \sim \mathcal{N}(0, \sigma_2^2), \qquad \epsilon_i \sim \mathcal{N}(0, \sigma^2)$$

In this model, the random interaction terms all have the same variance σ_2^2. These terms are assumed to be independent of each other, even within the same subject.

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2047.714
Fixed: BP ~ method
(Intercept)      methodS
```

```
127.40784      15.61961


Random effects:
Formula: ~1 | subject
(Intercept)
StdDev:     28.28452


Formula: ~1 | method %in% subject
(Intercept) Residual
StdDev:     12.61562 7.763666


Number of Observations: 510
Number of Groups:
subject method %in% subject
85                    170
```

1.4   Model Fit 3

This model is a more general model, compared to 'model fit 2'. This model treats the random interactions for each subject as a vector and allows the variance-covariance matrix for that vector to be estimated from the set of all positive-definite matrices. $\boldsymbol{y_i}$ is the entire response vector for the ith subject. $\boldsymbol{X_i}$ and $\boldsymbol{Z_i}$ are the fixed- and random-effects design matrices respectively.

$$\boldsymbol{y_i} = \boldsymbol{X_i\beta} + \boldsymbol{Z_i b_i} + \boldsymbol{\epsilon_i}, \qquad i = 1, \ldots, 85$$

$$\boldsymbol{Z_i} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\Psi}), \qquad \boldsymbol{\epsilon_i} \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{\sigma^2 \Lambda})$$

For the first subject the response vector, $\boldsymbol{y_1}$, is:

observation	BP	subject	method	replicate
1	100.00	1	J	1
86	106.00	1	J	2
171	107.00	1	J	3
511	122.00	1	S	1
596	128.00	1	S	2
681	124.00	1	S	3

The fixed effects design matrix $\boldsymbol{X_i}$ is given by:

(Intercept)	method S
1	0
1	0
1	0
1	1
1	1
1	1

The random effects design matrix $\boldsymbol{Z_i}$ is given by:

method J	method S
1	0
1	0
1	0
0	1
0	1
0	1

The following output was obtained.

```
Linear mixed-effects model fit by REML
Data: dat
Log-restricted-likelihood: -2047.582
Fixed: BP ~ method
(Intercept)     methodS
127.40784    15.61961


Random effects:
Formula: ~method - 1 | subject
Structure: General positive-definite, Log-Cholesky parametrization
StdDev    Corr
methodJ  30.455093 methdJ
methodS  31.477237 0.835
Residual  7.763666


Number of Observations: 510
Number of Groups: 85
```

1.5   Extended LME model

The extended single level LME model relaxes the independence assumption, allowing heteroscedastic and correlated within group errors.

$$\epsilon_i = \mathcal{N}(0, \sigma^2 \Lambda_i) \tag{1}$$

Λ_i are positive definite matrices. σ^2 is factored out of the matrix for computational reasons.

2   Variance functions

Variance functions are applied to LME models through the 'weights' argument. R supports several variance functions.

'varIdent' cosntructs a model with different variances per stratum.

2.1   Diagnostic plots

Diagnostic plots for identifying within-group heteroscedascity and assessing the adequacy of a variance function can also be used with 'nlme' objects.

References

Bland, J. and D. Altman (1999). Measuring agreement in method comparison studies. *Statistical Methods in Medical Research 8*(2), 135–160.

Pinheiro, J. and D. Bates (1994). *Mixed Effects Models in S and S plus* (2nd ed.). Reading, Massachusetts: Springer.