Chapter 1

LME models for MCS

1.1 Statement of the LME model

Further to a paper published by Laird and Ware in 1982, a linear mixed effects model is a linear mdoel that combined fixed and random effect terms formulated as follows;

$$Y_i = X_i\beta + Z_i b_i + \epsilon_i$$

- Y_i is the $n \times 1$ response vector
- X_i is the $n \times p$ Model matrix for fixed effects
- β is the $p \times 1$ vector of fixed effects coefficients
- Z_i is the $n \times q$ Model matrix for random effects
- b_i is the $q \times 1$ vector of random effects coefficients, sometimes denoted as u_i
- ϵ is the $n \times 1$ vector of observation errors

1.1.1 Bendix Carstensen's data sets

Carstensen et al. (2008)describes the sampling method when discussing of a motivating example.Diabetes patients attending an outpatient clinic in Denmark have their HbA_{1c} levels routinely measured at every visit.Venous and Capillary blood samples were obtained from all patients appearing at the clinic over two days.

Samples were measured on four consecutive days on each machines, hence there are five analysis days.Carstensen notes that every machine was calibrated every day to the manufacturers guidelines.

1.1.2 Limits of agreement for Carstensen's data

Carstensen et al. (2008) describes the calculation of the limits of agreement (with the inter-method bias implicit) for both data sets, based on his formulation;

$$\hat{\alpha}_1 - \hat{\alpha}_2 \pm 2\sqrt{2\hat{\tau}^2 + \hat{\sigma}_1^2 + \hat{\sigma}_2^2}.$$

For the 'Fat' data set, the inter-method bias is shown to be 0.045. The limits of agreement are $(-0.23, 0.32)$

Carstensen demonstrates the use of the interaction term when computing the limits of agreement for the 'Oximetry' data set. When the interaction term is omitted, the limits of agreement are $(-9.97, 14.81)$. Carstensen advises the inclusion of the interaction term for linked replicates, and hence the limits of agreement are recomputed as $(-12.18, 17.12)$.

1.1.3 Limits of Agreement in LME models

Carstensen et al. (2008) uses LME models to determine the limits of agreement. Between-subject variation for method m is given by d_m^2 and within-subject variation is given by λ_m^2. **?** remarks that for two methods A and B, separate values of d_A^2 and d_B^2 cannot be estimated, only their average. Hence the assumption that $d_x = d_y = d$ is necessary. The between-subject variability $\boldsymbol{D}$ and within-subject variability $\boldsymbol{\Lambda}$ can be presented in matrix form,

$$\boldsymbol{D} = \begin{pmatrix} d_A^2 & 0 \\ 0 & d_B^2 \end{pmatrix} = \begin{pmatrix} d^2 & 0 \\ 0 & d^2 \end{pmatrix}, \qquad \boldsymbol{\Lambda} = \begin{pmatrix} \lambda_A^2 & 0 \\ 0 & \lambda_B^2 \end{pmatrix}.$$

The variance for method m is $d_m^2 + \lambda_m^2$. Limits of agreement are determined using the standard deviation of the case-wise differences between the sets of measurements by two methods A and B, given by

$$\text{var}(y_A - y_B) = 2d^2 + \lambda_A^2 + \lambda_B^2. \tag{1.1}$$

Importantly the covariance terms in both variability matrices are zero, and no covariance component is present.

Roy (2009) has demonstrated a methodology whereby d_A^2 and d_B^2 can be estimated separately. Also covariance terms are present in both $\boldsymbol{D}$ and $\boldsymbol{\Lambda}$. Using Roy's methodology, the variance of the differences is

$$\text{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_A^2 + \lambda_B^2 - 2(d_{AB} + \lambda_{AB}) \tag{1.2}$$

All of these terms are given or determinable in computer output. The limits of agreement can therefore be evaluated using

$$\bar{y_A} - \bar{y_B} \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \tag{1.3}$$

For Carstensen's 'fat' data, the limits of agreement computed using Roy's method are consistent with the estimates given by **?**; $0.044884 \pm 1.96 \times 0.1373979 = (-0.224, 0.314)$.

1.1.4 Repeatability

Barnhart emphasizes the importance of repeatability as part of an overall method comparison study. Before there can be good agreement between two methods, a method must have good agreement with itself. The coefficient of repeatability , as proposed by Bland and Altman (1999) is an important feature of both Carstensen's and Roy's methodologies. The coefficient is calculated from the residual standard deviation (i.e. $1.96 \times \sqrt{2} \times \sigma_m = 2.83\sigma_m$).

1.2 Hamlett and Lam

The methodology proposed by **?** is largely based on Hamlett et al. (2004), which in turn follows on from Lam et al. (1999).

1.2.1 Roy's variability tests

Variability tests proposed by **?** affords the opportunity to expand upon Carstensen's approach.

The first test allows of the comparison the begin-subject variability of two methods. Similarly, the second test assesses the within-subject variability of two methods. A third test is a test that compares the overall variability of the two methods.

The tests are implemented by fitting a specific LME model, and three variations thereof, to the data. These three variant models introduce equality constraints that act null hypothesis cases.

Other important aspects of the method comparison study are consequent. The limits of agreement are computed using the results of the first model.

Bibliography

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