1 Note on Roy's paper

Roy (2009) considers the matter of comparing the agreement of two methods using a linear mixed effects (LME) model. A full discussion of the LME model can be found in Pinheiro and Bates (1994). An LME model used to describe replicate measurements made by two methods on a number of individuals is presented.

$$y_{mir} = \beta_i + \beta_m + b_{mi} + \epsilon_{mir} \tag{1}$$

- Let y_{mir} be the $r-$th response of the ith item (e.g. patient) by the $m-$th method. It is assumed that only two methods to be compared, hence $m = \{1, 2\}$.
- The true value of the measurement of the $i-$th item is a fixed effect, denoted β_i.
- The fixed effect for each method, that gives rise to inter-method bias, is denoted β_m. The inter-method bias is therefore $\beta_1 - \beta_2$.
- The random effect for item i , which is associated with method m, is denoted b_{mi}.
- The residual is denoted ϵ_{mir}.

1.1 Response Vector

Consider the response vector $\boldsymbol{y}_i$ comprises the $2n_i$ observations of the item, as measured by two methods, taking n_i measurements each. (For expository purposes, we will say $n_i = 3$. Hence a 6×1 random vector corresponding to the ith subject.)

Each response on item i is stacked into a response vector.

$$\boldsymbol{y}_i = (y_{1i1}, y_{2i1}, y_{1i2}, \ldots, y_{mir}, \ldots, y_{1in_i}, y_{2in_i})\prime \tag{2}$$

To formulate a model for the response vector $\boldsymbol{y}_i$, the fixed effects for both methods are given as β_1 and β_2 , in addition to the true value effect β_i, respectively, while the random effect terms are given as b_1 and b_2. Two matrices of indicator variables (later

referred to as $\boldsymbol{X}_i$ and $\boldsymbol{Z}_i$) enable the correct effects for each response. Thus, for two methods and each with three replicates, the response vector would be formulated as

$$\boldsymbol{y}_i = \begin{pmatrix} 1 & 1 & 0 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \\ 1 & 1 & 0 \\ 1 & 0 & 1 \end{pmatrix} \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{pmatrix} + \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} + \begin{pmatrix} \epsilon_{1i1} \\ \epsilon_{2i1} \\ \epsilon_{1i2} \\ \epsilon_{2i2} \\ \epsilon_{1i3} \\ \epsilon_{2i3} \end{pmatrix} \tag{3}$$

This model can be conveniently presented in matrix form as follows;

$$\boldsymbol{y_i} = \boldsymbol{X_i}\boldsymbol{\beta} + \boldsymbol{Z_i}\boldsymbol{b_i} + \boldsymbol{\epsilon_i}, \qquad i = 1, \ldots, I \tag{4}$$

It is assumed that $\boldsymbol{b}_i \sim N(0, \boldsymbol{G})$, $\boldsymbol{\epsilon}_i$ is a matrix of random errors distributed as $N(0, \boldsymbol{R}_i)$ and that the random effects and residuals are independent of each other. Assumptions made on the structures of $\boldsymbol{G}$ and $\boldsymbol{R}_i$ will be discussed in due course.

It is important to note the following characteristics of this model.

- Let the number of replicate measurements on each item i for both methods be n_i, hence $2 \times n_i$ responses. However, it is assumed that there may be a different number of replicates made for different items. Let the maximum number of replicates be p. An item will have up to $2p$ measurements, i.e. $Max(n_i) = 2p$.
- $\boldsymbol{y}_i$ is the $2n_i \times 1$ response vector for measurements on the $i-$th item.
- $\boldsymbol{X}_i$ is the $2n_i \times 3$ model matrix for the fixed effects for observations on item i.
- $\boldsymbol{\beta}$ is the 3×1 vector of fixed-effect coefficients, one for the true value for item i, and one effect each for both methods.
- Later on $\boldsymbol{X}_i$ will be reduced to a 2×1 matrix, to allow estimation of terms. This is due to a shortage of rank. The fixed effects vector will have to be modified accordingly.
- $\boldsymbol{Z}_i$ is the $2n_i \times 2$ model matrix for the random effects for measurements on item i.
- $\boldsymbol{b}_i$ is the 2×1 vector of random-effect coefficients on item i, one for each method.
- $\boldsymbol{\epsilon}$ is the $2ni \times 1$ vector of residuals for measurements on item i.
- $\boldsymbol{G}$ is the 2×2 covariance matrix for the random effects.
- $\boldsymbol{R}_i$ is the $2ni \times 2ni$ covariance matrix for the residuals on item i.
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- The expected value is given as $\mathrm{E}(\boldsymbol{y}_i) = \boldsymbol{X}_i\boldsymbol{\beta}$. (Hamlett et al., 2004)
- The variance of the response vector is given by $\mathrm{Var}(\boldsymbol{y}_i) = \boldsymbol{Z}_i\boldsymbol{G}\boldsymbol{Z}_i' + \boldsymbol{R}_i$ (Hamlett et al., 2004).

2 Variance Matrices

$\boldsymbol{G}$ is the variance covariance matrix for the random effects. i.e. between-item sources of variation. The between-item variance covariance matrix $\boldsymbol{G}$ is constructed as follows:

$$\boldsymbol{G} = \begin{pmatrix} g_1^2 & g_{12} \\ g_{12} & g_2^2 \end{pmatrix}$$

It is important to note that no special assumptions about the structure of $\boldsymbol{G}$ are made. An example of such an assumption would be that $\boldsymbol{G}$ is the product of a scalar value and the identity matrix.

$\boldsymbol{R}_i$ is the variance covariance matrix for the residuals, i.e. the within-item sources of variation between both methods. Computational analysis of linear mixed effects models allow for the explicit analysis of each.

Hamlett et al. (2004) shows that $\boldsymbol{R}_i$ can be expressed as $\boldsymbol{R}_i = \boldsymbol{I}_{n_i} \otimes \boldsymbol{\Sigma}$. The partial within-subject variancecovariance matrix of two methods at any replicate is denoted $\boldsymbol{\Sigma}$, where σ_1^2 and σ_2^2 are the within-subject variances of the respective methods, and σ_{12} is the within-subject covariance between the two methods. It is assumed that the within-subject variancecovariance matrix $\boldsymbol{\Sigma}$ is the same for all replications. Again it is important to note that no special assumptions are made about the structure of the matrix.

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix} \tag{5}$$

3 overall variability

The overall variability between the two methods is the sum of between-item variability $\boldsymbol{G}$ and within-item variability $\boldsymbol{\Sigma}$. Roy (2009) denotes the overall variability as Block - $\boldsymbol{\Omega}_i$. The overall variation for methods 1 and 2 are given by

$$\begin{pmatrix} \omega_1^2 & \omega_{12} \\ \omega_{12} & \omega_2^2 \end{pmatrix} = \begin{pmatrix} g_1^2 & g_{12} \\ g_{12} & g_2^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & \sigma_{12} \\ \sigma_{12} & \sigma_2^2 \end{pmatrix}$$

The computation of the limits of agreement require that the variance of the difference of measurements. This variance is easily computable from the estimate of the Block - $\mathbf{\Omega}_i$ matrix. Lack of agreement can arise if there is a disagreement in overall variabilities. This may be due to due to the disagreement in either between-item variabilities or within-item variabilities, or both. Roy (2009) allows for a formal test of each.

4 Carstensen's Limits of agreement

Carstensen et al. (2008) presents a methodology to compute the limits of agreement based on LME models. Carstensens underlying model can be considered as a special case of the model presented above, when assumptions are applied, specifically that the off-diagonal elements are zero. Also, implementation requires that the between-item variances are estimated as the same value: $g_1^2 = g_2^2 = g^2$.

$$\begin{pmatrix} \omega_2^1 & 0 \\ 0 & \omega_2^2 \end{pmatrix} = \begin{pmatrix} g^2 & 0 \\ 0 & g^2 \end{pmatrix} + \begin{pmatrix} \sigma_1^2 & 0 \\ 0 & \sigma_2^2 \end{pmatrix}$$

In cases where the off-diagonal terms in the overall variability matrix are close to zero, the limits of agreement due to Carstensen are very similar to the limits of agreement that follow from the general model. Necessarily Carstensen's method does not allow for a formal test of the between-item variability.

References

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