Transfer Report

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2.1 The Linear Mixed Effects Model

The linear mixed effects model is given by

$$Y = X\beta + Zu + \epsilon \tag{2.1}$$

$\mathbf{Y}$ is the vector of n observations, with dimension $n \times 1$. $\mathbf{b}$ is a vector of fixed p effects, and has dimension $p \times 1$. It is composed of coefficients, with the first element being the population mean. $\mathbf{X}$ is known as the design 'matrix', model matrix for fixed effects, and comprises 0s or 1s, depending on whether the relevant fixed effects have any effect on the observation is question. $\mathbf{X}$ has dimension $n \times p$. $\mathbf{e}$ is the vector of residuals with dimension $n \times 1$.

The random effects models can be specified similarly. $\mathbf{Z}$ is known as the 'model matrix for random effects', and also comprises 0s or 1s. It has dimension $n \times q$. $\mathbf{u}$ is a vector of random q effects, and has dimension $q \times 1$.

$\mathbf{V}$, the variance matrix of $\mathbf{Y}$, can be expressed as follows;

$$\mathbf{V} = var(\mathbf{Xb} + \mathbf{Zu} + \mathbf{e}) \tag{2.2}$$

$$\mathbf{V} = var(\mathbf{Xb}) + var(\mathbf{Zu}) + var(\mathbf{e})) \tag{2.3}$$

var($\mathbf{Xb}$) is known to be zero. The variance of the random effects var($\mathbf{Zu}$) can be written as $Z\text{var}(\mathbf{u})Z^T$.

By letting var(u) = G (i.e $\mathbf{u}$ $N(0, \mathbf{G})$), this becomes ZGZ^T. This specifies the covariance due to random effects. The residual covariance matrix $var(e)$ is denoted as R, ($\mathbf{e}$ $N(0, \mathbf{R})$). Residual are uncorrelated, hence $\mathbf{R}$ is equivalent to $\sigma^2\mathbf{I}$, where $\mathbf{I}$ is the identity matrix. The variance matrix $\mathbf{V}$ can therefore be written as;

$$\mathbf{V} = ZGZ^T + \mathbf{R} \tag{2.4}$$

The best linear unbiased predictor (BLUP) is used to estimating random effects, i.e to derive $\mathbf{u}$. The best linear unbiased estimator (BLUE) is used to estimate the fixed effects, $\mathbf{b}$. They were formulated in a paper by **?**, which provides the derivations of both. Inferences about fixed effects have come to be called 'estimates', whereas inferences about random effects have come be called 'predictions'. hence the naming of BLUP is to reinforce distinction between the two , but it is essentially the same principal involved in both cases (**?**). The BLUE of $\mathbf{b}$, and the BLUP of $\mathbf{u}$ can be shown to be;

$$\hat{b} = (X^T V^{-1} X)^{-1} X^T V^{-1} y \tag{2.5}$$

$$\hat{u} = GZ^T V^{-1} (y - X\hat{b}) \tag{2.6}$$

The practical application of both expressions requires that the variance components be known. An estimate for the variance components must be derived to either maximum likelihood (ML) or more commonly restricted maximum likelihood (REML).

Importantly calculations based on the above formulae require the calculation of the inverse of $\mathbf{V}$. In simple examples V^{-1} is a straightforward calculation, but with higher dimensions it becomes a very complex calculation.

2.2 Lai Shiao

? use mixed models to determine the factors that affect the difference of two methods of measurement using the conventional formulation of linear mixed effects models.

If the parameter **b**, and the variance components are not significantly different from zero, the conclusion that there is no inter-method bias can be drawn. If the fixed effects component contains only the intercept, and a simple correlation coefficient is used, then the estimate of the intercept in the model is the inter-method bias. Conversely the estimates for the fixed effects factors can advise the respective influences each factor has on the differences. It is possible to pre-specify different correlation structures of the variance components **G** and **R**.

Oxygen saturation is one of the most frequently measured variables in clinical nursing studies. 'Fractional saturation' (HbO_2) is considered to be the gold standard method of measurement, with 'functional saturation' (SO_2) being an alternative method. The method of examining the causes of differences between these two methods is applied to a clinical study conducted by **?**. This experiment was conducted by 8 lab practitioners on blood samples, with varying levels of haemoglobin, from two donors. The samples have been in storage for varying periods (described by the variable 'Bloodage') and are categorized according to haemoglobin percentages(i.e 0%,20%,40%,60%,80%,100%). There are 625 observations in all.

? fits two models on this data, with the lab technicians and the replicate measurements as the random effects in both models. The first model uses haemoglobin level as a fixed effects component. For the second model, blood age is added as a second fixed factor.

Single fixed effect

The first model fitted by **?** takes the blood level as the sole fixed effect to be analyzed. The following coefficient estimates are estimated by 'Proc Mixed';

$$\text{fixed effects}: 2.5056 - 0.0263\text{Fhbperct}_{ijtl} \tag{2.7}$$

$$(\text{p-values}: \ = 0.0054, < 0.0001, < 0.0001)$$

$$\text{random effects}: u(\sigma^2 = 3.1826) + e_{ijtl}(\sigma_e^2 = 0.1525, \rho = 0.6978)$$

$$(\text{p-values}: \ = 0.8113, < 0.0001, < 0.0001)$$

With the intercept estimate being both non-zero and statistically significant ($p = 0.0054$), this models supports the presence inter-method bias is 2.5% in favour of SO_2. Also, the negative value of the haemoglobin level coefficient indicate that differences will decrease by 0.0263% for every percentage increase in the haemoglobin .

In the random effects estimates, the variance due to the practitioners is 3.1826, indicating that there is a significant variation due to technicians ($p = 0.0311$) affecting the differences. The variance for the estimates is given as 0.1525, ($p < 0.0001$).

Two fixed effects

Blood age is added as a second fixed factor to the model, whereupon new estimates are calculated;

$$\text{fixed effects}: \ -0.2866 + 0.1072\text{Bloodage}_{ijtl} - 0.0264\text{Fhbperct}_{ijtl}$$

$$(\text{p-values}: \ = 0.8113, < 0.0001, < 0.0001)$$

$$\text{random effects}: u(\sigma^2 = 10.2346) + e_{ijtl}(\sigma_e^2 = 0.0920, \rho = 0.5577)$$

$$(\text{p-values}: \ = 0.0446, < 0.0001, < 0.0001) \tag{2.8}$$

With this extra fixed effect added to the model, the intercept term is no longer statistically significant. Therefore, with the presence of the second fixed factor, the model is no longer supporting the presence of inter-method bias. Furthermore, the second coefficient indicates that the blood age of the observation has a significant bearing on the size of the difference between both methods ($p < 0.0001$). Longer storage times for blood will lead to higher levels of particular blood factors such as MetHb and HbCO (due to the breakdown and oxidisation of the haemoglobin). Increased levels of MetHb and HbCO are concluded to be the cause of the differences. The coefficient for the haemoglobin level doesn't differ greatly from the single fixed factor model, and has a much smaller effect on the differences. The random effects estimates also indicate significant variation for the various technicians; 10.2346 with $p = 0.0446$.

? demonstrates how that linear mixed effects models can be used to provide greater insight into the cause of the differences. Naturally the addition of further factors to the model provides for more insight into the behavior of the data.

2.3 Carstensen's Mixed Models

? proposes linear mixed effects models for deriving conversion calculations similar to Deming's regression, and for estimating variance components for measurements by different methods. The following model (in the authors own notation) is formulated as follows, where y_{mir} is the rth replicate measurement on subject i with method m.

$$y_{mir} = \alpha_m + \beta_m \mu_i + c_{mi} + e_{mir} \qquad (e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)) \tag{2.9}$$

The intercept term α and the $\beta_m \mu_i$ term follow from **?**, expressing constant and proportional bias respectively , in the presence of a real value μ_i. c_{mi} is a interaction term to account for replicate, and e_{mir} is the residual associated with each observation. Since variances are specific to each method, this model can be fitted separately for each method.

The above formulation doesn't require the data set to be balanced. However, it does require a sufficient large number of replicates and measurements to overcome the problem of identifiability. The import of which is that more than two methods of measurement may be required to carry out the analysis. There is also the assumptions that observations of measurements by particular methods are exchangeable within subjects. (Exchangeability means that future samples from a population behaves like earlier samples).

? uses the above formula to predict observations for a specific individual i by method m;

$$BLUP_{mir} = \hat{\alpha_m} + \hat{\beta}_m \mu_i + c_{mi} \tag{2.10}$$

. Under the assumption that the μs are the true item values, this would be sufficient to estimate parameters. When that assumption doesn't hold, regression techniques

(known as updating techniques) can be used additionally to determine the estimates. The assumption of exchangeability can be unrealistic in certain situations. **?** provides an amended formulation which includes an extra interaction term ($d_{mr} \sim N(0, \omega_m^2)$to account for this.

? sets out a methodology of computing the limits of agreement based upon variance component estimates derived using linear mixed effects models. Measures of repeatability, a characteristic of individual methods of measurements, are also derived using this method.

? also advocates the use of linear mixed models in the study of method comparisons. The model is constructed to describe the relationship between a value of measurement and its real value. The non-replicate case is considered first, as it is the context of the Bland-Altman plots. This model assumes that inter-method bias is the only difference between the two methods. A measurement y_{mi} by method m on individual i is formulated as follows;

$$y_{mi} = \alpha_m + \mu_i + e_{mi} \qquad (e_{mi} \sim N(0, \sigma_m^2)) \tag{2.11}$$

The differences are expressed as $d_i = y_{1i} - y_{2i}$ For the replicate case, an interaction term c is added to the model, with an associated variance component. All the random effects are assumed independent, and that all replicate measurements are assumed to be exchangeable within each method.

$$y_{mir} = \alpha_m + \mu_i + c_{mi} + e_{mir} \qquad (e_{mi} \sim N(0, \sigma_m^2), c_{mi} \sim N(0, \tau_m^2)) \tag{2.12}$$

? proposes a methodology to calculate prediction intervals in the presence of replicate measurements, overcoming problems associated with Bland-Altman methodology in this regard. It is not possible to estimate the interaction variance components τ_1^2 and τ_2^2 separately. Therefore it must be assumed that they are equal. The variance of the difference can be estimated as follows:

$$var(y_{1j} - y_{2j}) \tag{2.13}$$

Bibliography