

Chapter 1

Linear Mixed effects Models

1.1 Introduction to Mixed Models

All models are characterized by the mean α and the error terms. In addition to these terms, any model described so far will have either random effects terms or fixed effects terms and accordingly are referred to as random or fixed models. Models that have both fixed effects terms and random effects terms are known as 'mixed effects models'. Once the theory underlying fixed and random effects models has been fully understood, the progression to understanding mixed models is very simple.

Elaborating on the original mice litter example, the six litters by each mouse were fed according to three different dietary treatments (Searle, 1997). Therefore a fixed effect ϕ_j has been added to the model, which is now formulated as follows;

$$y_{ij} = \mu + \delta_i + \phi_j + \gamma_{ij} + \epsilon_{ijk} \quad (1.1)$$

As before, an interaction effect γ_{ij} must also be added to the model. In cases where the interaction term describes the combined effect of fixed and random components, it should be treated as random effect. The variance of the above model is composed of the σ_δ^2 , σ_γ^2 and σ_ϵ^2 .

It may be shown that the interaction factors make no contribution to the outcome, i.e. γ_{ij} is consistently calculated as zero. Considering the skin tumour example, a person's age would bear no relation to their gender and hence there would be plausible interaction between the two factors. Indeed, in keeping with the 'Law of Parsimony', factors should be specified such that each would convey separate information. However, interaction terms are extant when the model specifies repeated observations, as there is necessarily a relationship between observations from the same subject. Importantly, interaction effects, being random effects, are attended by variance component terms and therefore also contribute to the overall variance of the model.

Searle (1997) gives a mixed effects model formulation for the Grubbs artillery study. y_{ij} is the muzzle velocity of the i th shell, as measured by the j th chronometer.

$$y_{ij} = \mu + \alpha_i + \beta_j + \epsilon_{ij} \quad (1.2)$$

In this formulation α_i is the random effect of round i , and the fixed effect component β_j is the bias in chronometer j . (Also, no interaction term is used).

1.2 Linear Mixed effects Models

A linear mixed effects (LME) model is a statistical model containing both fixed effects and random effects (random effects are also known as variance components). LME models are a generalization of the classical linear model, which contain fixed effects only. When the levels of factors are considered to be sampled from a population, and each level is not of particular interest, they are considered random quantities with associated variances. The effects of the levels, as described, are known as random effects. Random effects are represented by unobservable normally distributed random variables. Conversely fixed effects are considered non-random and the levels of each factor are of specific interest.

Fisher (1918) introduced variance components models for use in genetical studies. Whereas an estimate for variance must take a non-negative value, an individual variance component, i.e. a component of the overall variance, may be negative.

The framework has developed since, including contributions from Tippett (1931), who extend the use of variance components into linear models, and Eisenhart (1947), who introduced the ‘mixed model’ terminology and formally distinguished between mixed and random effects models. Henderson (1950) devised a framework for deriving estimates for both the fixed effects and the random effects, using a set of equations that would become known as ‘mixed model equations’ or ‘Henderson’s equations’. LME methodology is further enhanced by Henderson’s later works (Henderson, 1953; Henderson et al., 1959, 1963, 1973, 1984). The key features of Henderson’s work provide the basis for the estimation techniques.

Hartley and Rao (1967) demonstrated that unique estimates of the variance components could be obtained using maximum likelihood methods. However these estimates are known to be biased ‘downwards’ (i.e. underestimated) , because of the assumption that the fixed estimates are known, rather than being estimated from the data. Patterson and Thompson (1971) produced an alternative set of estimates, known as the restricted maximum likelihood (REML) estimates, that do not require the fixed effects to be known. Thusly there is a distinction the REML estimates and the original estimates, now commonly referred to as ML estimates.

1.3 Linear mixed effects models

These models are used when there are both fixed and random effects that need to be incorporated into a model.

Fixed effects usually correspond to experimental treatments for which one has data

for the entire population of samples corresponding to that treatment.

Random effects, on the other hand, are assigned in the case where we have measurements on a group of samples, and those samples are taken from some larger sample pool, and are presumed to be representative.

As such, linear mixed effects models treat the error for fixed effects differently than the error for random effects.

1.4 Limits of agreement in LME models

Limits of agreement are used extensively for assessing agreement, because they are intuitive and easy to use. Necessarily their prevalence in literature has meant that they are now the best known measurement for agreement, and therefore any newer methodology would benefit by making reference to them.

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 . Carstensen et al. (2008) 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 \mathbf{D} and within-subject variability $\mathbf{\Lambda}$ can be presented in matrix form,

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

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

$$\text{var}(y_A - y_B) = 2d^2 + \lambda_A^2 + \lambda_B^2. \quad (1.3)$$

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

Carstensen et al. (2008) presents a data set ‘fat’, which is a comparison of measurements of subcutaneous fat by two observers at the Steno Diabetes Center, Copenhagen. Measurements are in millimeters (mm). Each person is measured three times by each observer. The observations are considered to be ‘true’ replicates.

A linear mixed effects model is formulated, and implementation through several software packages is demonstrated. All of the necessary terms are presented in the computer output. The limits of agreement are therefore,

$$0.0449 \pm 1.96 \times \sqrt{2 \times 0.0596^2 + 0.0772^2 + 0.0724^2} = (-0.220, 0.309). \quad (1.4)$$

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

$$\text{var}(y_{iA} - y_{iB}) = d_A^2 + \lambda_B^2 + d_A^2 + \lambda_B^2 - 2(d_{AB} + \lambda_{AB}) \quad (1.5)$$

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

$$\bar{y}_A - \bar{y}_B \pm 1.96 \times \sqrt{\sigma_A^2 + \sigma_B^2 - 2(\sigma_{AB})}. \quad (1.6)$$

For Carstensen’s ‘fat’ data, the limits of agreement computed using Roy’s method are consistent with the estimates given by Carstensen et al. (2008); $0.044884 \pm 1.96 \times 0.1373979 = (-0.224, 0.314)$.

1.4.1 Linked replicates

Carstensen et al. (2008) proposes the addition of an random effects term to their model when the replicates are linked. This term is used to describe the ‘item by

replicate’ interaction, which is independent of the methods. This interaction is a source of variability independent of the methods. Therefore failure to account for it will result in variability being wrongly attributed to the methods.

Carstensen et al. (2008) introduces a second data set; the oximetry study. This study done at the Royal Childrens Hospital in Melbourne to assess the agreement between co-oximetry and pulse oximetry in small babies.

In most cases, measurements were taken by both method at three different times. In some cases there are either one or two pairs of measurements, hence the data is unbalanced. Carstensen et al. (2008) describes many of the children as being very sick, and with very low oxygen saturations levels. Therefore it must be assumed that a biological change can occur in interim periods, and measurements are not true replicates.

Carstensen et al. (2008) demonstrate the necessity of accounting for linked replicated by comparing the limits of agreement from the ‘oximetry’ data set using a model with the additional term, and one without. When the interaction is accounted for the limits of agreement are $(-9.62, 14.56)$. When the interaction is not accounted for, the limits of agreement are $(-11.88, 16.83)$. It is shown that the failure to include this additional term results in an over-estimation of the standard deviations of differences.

Limits of agreement are determined using Roy’s methodology, without adding any additional terms, are found to be consistent with the ‘interaction’ model; $(-9.562, 14.504)$. Roy’s methodology assumes that replicates are linked. However, following Carstensen’s example, an addition interaction term is added to the implementation of Roy’s model to assess the effect, the limits of agreement estimates do not change. However there is a conspicuous difference in within-subject matrices of Roy’s model and the modified model (denoted 1 and 2 respectively);

$$\hat{\mathbf{\Lambda}}_1 = \begin{pmatrix} 16.61 & 11.67 \\ 11.67 & 27.65 \end{pmatrix} \quad \hat{\mathbf{\Lambda}}_2 = \begin{pmatrix} 7.55 & 2.60 \\ 2.60 & 18.59 \end{pmatrix}. \quad (1.7)$$

(The variance of the additional random effect in model 2 is 3.01.)

Akaike (1974) introduces the Akaike information criterion (AIC), a model selection tool based on the likelihood function. Given a data set, candidate models are ranked according to their AIC values, with the model having the lowest AIC being considered the best fit. Two candidate models can be said to be equally good if there is a difference of less than 2 in their AIC values.

The Akaike information criterion (AIC) for both models are $AIC_1 = 2304.226$ and $AIC_2 = 2306.226$, indicating little difference in models. The AIC values for the Carstensen ‘unlinked’ and ‘linked’ models are 1994.66 and 1955.48 respectively, indicating an improvement by adding the interaction term.

The $\hat{\mathbf{A}}$ matrices are informative as to the difference between Carstensen’s unlinked and linked models. For the oximetry data, the covariance terms (given above as 11.67 and 2.6 respectively) are of similar magnitudes to the variance terms. Conversely for the ‘fat’ data the covariance term (-0.00032) is negligible. When the interaction term is added to the model, the covariance term remains negligible. (For the ‘fat’ data, the difference in AIC values is also approximately 2).

To conclude, Carstensen’s models provided a rigorous way to determine limits of agreement, but don’t provide for the computation of $\hat{\mathbf{D}}$ and $\hat{\mathbf{A}}$. Therefore the test’s proposed by Roy (2009a) can not be implemented. Conversely, accurate limits of agreement as determined by Carstensen’s model may also be found using Roy’s method. Addition of the interaction term erodes the capability of Roy’s methodology to compare candidate models, and therefore shall not be adopted.

Finally, to complement the blood pressure (i.e. ‘J vs S’) method comparison from the previous section (i.e. ‘J vs S’), the limits of agreement are $15.62 \pm 1.96 \times 20.33 = (-24.22, 55.46)$.

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Laird and Ware (1982) provides a form of notation for notation for LME models that has since become the standard form, or the basis for more complex formulations. Due to computation complexity, linear mixed effects models have not seen widespread use until many well known statistical software applications began facilitating them. SAS Institute added PROC MIXED to its software suite in 1992 (Singer, 1998). Pinheiro and Bates (1994) described how to compute LME models in the **S-plus** environment.

Using Laird-Ware form, the LME model is commonly described in matrix form,

$$y = X\beta + Zb + \epsilon \tag{1.8}$$

where y is a vector of N observable random variables, β is a vector of p fixed effects, X and Z are $N \times p$ and $N \times q$ known matrices, and b and ϵ are vectors of q and N , respectively, random effects such that $E(b) = 0$, $E(\epsilon) = 0$ and where D and Σ are positive definite matrices parameterized by an unknown variance component parameter vector θ . The variance-covariance matrix for the vector of observations y is given by $V = ZDZ' + \Sigma$. This implies $y \sim (X\beta, V) = (X\beta, ZDZ' + \Sigma)$. It is worth noting that V is an $n \times n$ matrix, as the dimensionality becomes relevant later on. The notation provided here is generic, and will be adapted to accord with complex formulations that will be encountered in due course.

1.5.1 Formulation of the response vector

Information of individual i is recorded in a response vector \mathbf{y}_i . The response vector is constructed by stacking the response of the 2 responses at the first instance, then the 2 responses at the second instance, and so on. Therefore the response vector is a $2n_i \times 1$ column vector. The covariance matrix of \mathbf{y}_i is a $2n_i \times 2n_i$ positive definite matrix $\mathbf{\Omega}_i$.

Consider the case where three measurements are taken by both methods A and B , \mathbf{y}_i is a 6×1 random vector describing the i th subject.

$$\mathbf{y}_i = (y_i^{A1}, y_i^{B1}, y_i^{A2}, y_i^{B2}, y_i^{A3}, y_i^{B3})'$$

The response vector \mathbf{y}_i can be formulated as an LME model according to Laird-Ware form.

$$\mathbf{y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\epsilon}_i$$

$$\mathbf{b}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{D})$$

$$\boldsymbol{\epsilon}_i \sim \mathcal{N}(\mathbf{0}, \mathbf{R}_i)$$

Information on the fixed effects are contained in a three dimensional vector $\boldsymbol{\beta} = (\beta_0, \beta_1, \beta_2)'$. For computational purposes β_2 is conventionally set to zero. Consequently $\boldsymbol{\beta}$ is the solutions of the means of the two methods, i.e. $E(\mathbf{y}_i) = \mathbf{X}_i\boldsymbol{\beta}$. The variance covariance matrix \mathbf{D} is a general 2×2 matrix, while \mathbf{R}_i is a $2n_i \times 2n_i$ matrix.

1.5.2 Decomposition of the response covariance matrix

The variance covariance structure can be re-expressed in the following form,

$$\text{Cov}(\mathbf{y}_i) = \mathbf{\Omega}_i = \mathbf{Z}_i\mathbf{D}\mathbf{Z}_i' + \mathbf{R}_i.$$

\mathbf{R}_i can be shown to be the Kronecker product of a correlation matrix \mathbf{V} and $\mathbf{\Lambda}$. The correlation matrix \mathbf{V} of the repeated measures on a given response variable is

assumed to be the same for all response variables. Both Hamlett et al. (2004) and Lam et al. (1999) use the identity matrix, with dimensions $n_i \times n_i$ as the formulation for \mathbf{V} . Roy (2009b) remarks that, with repeated measures, the response for each subject is correlated for each variable, and that such correlation must be taken into account in order to produce a valid inference on correlation estimates. ? proposes various correlation structures may be assumed for repeated measure correlations, such as the compound symmetry and autoregressive structures, as alternative to the identity matrix.

However, for the purposes of method comparison studies, the necessary estimates are currently only determinable when the identity matrix is specified, and the results in Roy (2009b) indicate its use.

For the response vector described, Hamlett et al. (2004) presents a detailed covariance matrix. A brief summary shall be presented here only. The overall variance matrix is a 6×6 matrix composed of two types of 2×2 blocks. Each block represents one separate time of measurement.

$$\mathbf{\Omega}_i = \begin{pmatrix} \mathbf{\Sigma} & \mathbf{D} & \mathbf{D} \\ \mathbf{D} & \mathbf{\Sigma} & \mathbf{D} \\ \mathbf{D} & \mathbf{D} & \mathbf{\Sigma} \end{pmatrix}$$

The diagonal blocks are $\mathbf{\Sigma}$, as described previously. The 2×2 block diagonal matrix in $\mathbf{\Omega}$ gives $\mathbf{\Sigma}$. $\mathbf{\Sigma}$ is the sum of the between-subject variability \mathbf{D} and the within subject variability $\mathbf{\Lambda}$.

$\mathbf{\Omega}_i$ can be expressed as

$$\mathbf{\Omega}_i = \mathbf{Z}_i \mathbf{D} \mathbf{Z}_i' + (\mathbf{I}_{n_i} \otimes \mathbf{\Lambda}).$$

The notation dim_{n_i} means an $n_i \times n_i$ diagonal block.

1.6 Repeated measurements in LME models

In many statistical analyzes, the need to determine parameter estimates where multiple measurements are available on each of a set of variables often arises. Further to Lam et al. (1999), Hamlett et al. (2004) performs an analysis of the correlation of replicate measurements, for two variables of interest, using LME models.

Let y_{Aij} and y_{Bij} be the j th repeated observations of the variables of interest A and B taken on the i th subject. The number of repeated measurements for each variable may differ for each individual. Both variables are measured on each time points. Let n_i be the number of observations for each variable, hence $2 \times n_i$ observations in total.

It is assumed that the pair y_{Aij} and y_{Bij} follow a bivariate normal distribution.

$$\begin{pmatrix} y_{Aij} \\ y_{Bij} \end{pmatrix} \sim \mathcal{N}(\boldsymbol{\mu}, \boldsymbol{\Sigma}) \text{ where } \boldsymbol{\mu} = \begin{pmatrix} \mu_A \\ \mu_B \end{pmatrix}$$

The matrix $\boldsymbol{\Sigma}$ represents the variance component matrix between response variables at a given time point j .

$$\boldsymbol{\Sigma} = \begin{pmatrix} \sigma_A^2 & \sigma_{AB} \\ \sigma_{AB} & \sigma_B^2 \end{pmatrix}$$

σ_A^2 is the variance of variable A , σ_B^2 is the variance of variable B and σ_{AB} is the covariance of the two variable. It is assumed that $\boldsymbol{\Sigma}$ does not depend on a particular time point, and is the same over all time points.

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various correlation structures may be assumed for repeated measure correlations, such as the compound symmetry and autoregressive structures, as alternative to the identity matrix.

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For the response vector described, Hamlett et al. (2004) presents a detailed covariance matrix. A brief summary shall be presented here only. The overall variance matrix is a 6×6 matrix composed of two types of 2×2 blocks. Each block represents one separate time of measurement.

$$\mathbf{\Omega}_i = \begin{pmatrix} \mathbf{\Sigma} & \mathbf{D} & \mathbf{D} \\ \mathbf{D} & \mathbf{\Sigma} & \mathbf{D} \\ \mathbf{D} & \mathbf{D} & \mathbf{\Sigma} \end{pmatrix}$$

The diagonal blocks are $\mathbf{\Sigma}$, as described previously. The 2×2 block diagonal matrix in $\mathbf{\Omega}$ gives $\mathbf{\Sigma}$. $\mathbf{\Sigma}$ is the sum of the between-subject variability \mathbf{D} and the within subject variability $\mathbf{\Lambda}$.

$\mathbf{\Omega}_i$ can be expressed as

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The notation dim_{n_i} means an $n_i \times n_i$ diagonal block.

1.6.3 Correlation terms

Hamlett et al. (2004) demonstrated how the between-subject and within subject variabilities can be expressed in terms of correlation terms.

$$\mathbf{D} = \begin{pmatrix} \sigma_A^2 \rho_A & \sigma_A \sigma_B \rho_{AB} \delta \\ \sigma_A \sigma_B \rho_{AB} \delta & \sigma_B^2 \rho_B \end{pmatrix}$$

$$\mathbf{\Lambda} = \begin{pmatrix} \sigma_A^2 (1 - \rho_A) & \sigma_{AB} (1 - \delta) \\ \sigma_{AB} (1 - \delta) & \sigma_B^2 (1 - \rho_B) \end{pmatrix}.$$

ρ_A describe the correlations of measurements made by the method A at different times. Similarly ρ_B describe the correlation of measurements made by the method B at different times. Correlations among repeated measures within the same method are known as intra-class correlation coefficients. ρ_{AB} describes the correlation of measurements taken at the same same time by both methods. The coefficient δ is added for when the measurements are taken at different times, and is a constant of less than 1 for linked replicates. This is based on the assumption that linked replicates measurements taken at the same time would have greater correlation than those taken at different times. For unlinked replicates δ is simply 1. Hamlett et al. (2004) provides a useful graphical depiction of the role of each correlation coefficients.

1.7 Extended LME model

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

$$\epsilon_i = \mathcal{N}(0, \sigma^2 \Lambda_i) \tag{1.9}$$

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

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