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ESTIMATION PROCEDURES IN LINEAR MIXED EFFECTS MODELS FOR REPEATED-MEASURES DATA

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ABSTRACT

The purpose of this paper is to derive estimation procedures; namely Miximum Likelihood (ML), Residual Maximum Likelihood (RML) and Minimum Norm Quadratic Unbiased estimates (MINQUE), for estimating the parameters and variance components in linear models with repeated measurements data. In these models individual's regression coefficients are subject to both fixed and random effects over different individuals. An iterative procedure is proposed for solving the ML and RML equations and the MINQUE estimates are also obtained. A closed form solutions for these methods are derived for growth curve models when the design matrices are the same for each individual.

I. INTRODUCTION

Many longtudinal studies are designed to investigate changes over time in some characteristics which are measured repeatedly for each experimental unit. Multiple measurements are obtained for each individual, at different times and possibly under changing experimental conditions. Often, we cannot fully control circumstances under which the measurements are taken and there may be considerable variation among individuals in the number and timing of observations.

In this paper, the model that characterized the common structure of repeated measures, growth curve or serial measurements

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data is considered. The analysis and estimation of this model were considered by several authors such as Reinsel (1982) and Laird et al (1987). In section 3, we have considered several methods of estimating variance components and fixed effects in the model. These methods are the ML, RML and MINQUE approaches. We derived the equations required for each estimation procedure and proposed iterative procedure for solving them. For certain class of multivariate growth curve mixed models, we have derived closed form solutions for ML, RML and MINQUE estimates. Laird et al (1987) derived closed form solutions for a special case of our class of models and for the ML and RML approaches only. These results are shown in section 4. Section 5 was designed to illustrate the estimation procedures given above by an example.

II. THE MODEL

The general model that we use to characterize the common structure of repeated measures, growth curve or serial measurements data is that described by Laird and Ware (1982). Specifically; let y_i denote $n_i x1$ vector of n_i measurements observed on the i-th experimental unit. We assume that the model has the form

$$y_i = X_i\alpha + Z_i b_i + e_i, \qquad i=1,\dots,m \qquad (2.1)$$

where α denote the px1 vector of unknown population parameters and X_i is a known $n_i xp$, design matrix linking to y_i, b_i denote a qx1 vector of individual effects which are assumed to be random variables distributed as N(0,D) independent of e_i and Z_i is a known $n_i xq$ design matrix linking b_i to y_i, e_i represents the error term which is assumed to be independent random variable distributed as $N(0,\sigma^2)$, D is a positive semidefinite qxq matrix of unknown parameters to be estimated.

Thus $E(y_i) = X_i\alpha$, $V(y_i) = V_i = \sigma^2 I + Z_i D Z_i'$

and $Cov(y_i,y_j) = 0$ for i=j

Also, if we let $y = \begin{vmatrix} y_1 \\ y_2 \\ . \\ . \\ . \\ y_m \end{vmatrix}$ and $X = \begin{vmatrix} X_1 \\ X_2 \\ . \\ . \\ . \\ X_m \end{vmatrix}$,

then, $E(y) = X\alpha$ and $V(y) = \text{diag}\ (V_1, V_2, \ldots V_m) = V$ (2.2)

However, when the number of observations on each unit is not large, one may prefer to assume that $V(y_i)$ is unstructured. This may be achieved by taking $\sigma^2 = 0$ and $Z_i = I$ if a unit is measured at all n occasions, or the identity matrix after deleting rows corresponding to the missing measurements when $n_i < n$.

If D is diagonal and each Z_i consists of zeros and ones, pur model reduces to a special case of the general ANOVA mixed model.

Model (2.1) can be reparameterized to characterize growth curve models which have the form:

$$y_i = x_i\ \beta_i + e_i,\ i=1,2,\ldots,m \qquad (2.3),$$

where the coeficients β_i's are composed of both fixed effects that incorporate concomitant information and individual random effects. That is

$$\beta_i = Ba_i + b_i. \qquad (2.4)$$

where $A = (a_1,\ldots,a_m)$ is an rxm "across individual" design matrix of known elements, whose i-th column a_i represents the values of "background" regressor variables associated with the i-th individual and B is a sxr matrix of unknown parameters. In this case $\beta_i = (a_i' \otimes I_s)\alpha$, $X_i = a_i \otimes x_i$, where $rs = p$ and $\otimes$ denotes kronecker product.

Using the identity vec(ABC) = (c' x A) vec (B), it follows that $\text{vec}(Ba_k) = (a_i' \otimes I)$ vec B. Hence Vec $(B) = \alpha$.

Model (2.4) may have more general form; $\beta_i = Ba_i + w_i b_i$, for some known matrix w_i of order sxq. Therefore Z_i of (2.1) is $x_i w_i$, that is Z_i lies in the column space of x_i.

An important special case of (2.3) that we consider in detail occurs when the individual design matrix x_i is equal to an nxs matrix x. Hence $X = A' \otimes x$ and $Z_i = xw$.

III. ESTIMATION PROCEDURES FOR ESTIMATING α, D AND σ^2

There has been two main approaches for estimating unknown parameters in linear models. One is to estimate variance components by quadratic functions of the vector of observations using ANOVA techniques and then estimate the fixed parameters using generalized least squares (GLS) procedure. Another approach is to estimate the unknown parameters by maximizing the likelihood function of the vector of observations or the vector of all error contrasts assuming normality. Rao (1971) introduced the MINQUE theory for estimating variance components in mixed linear models when the random effects are independent. This approach is considered a distribution free approach, Abdel-Wahed (1989) derived the MINQUE of variance components when the random effects are correlated with dispersion matrix of unknown elements.

(3.1) The ML Approach

The log-likelihood function corresponding to the marginal density of y for α, σ^2 and θ (the vector θ contains the unique elements of D), is given by:

$$L = \text{const} - \tfrac{1}{2}\log|V| - \tfrac{1}{2}(y - X\alpha)'\,V^{-1}(y - X\alpha). \qquad (3.1)$$

Let $\frac{\partial V_i}{\partial \theta_j} = C_{ij}$, where θ_j is the j-th element of θ.

The derivations of the log-likelihood function with respect to α, θ, σ^2 are:

$$\frac{\partial L}{\partial \alpha} = \sum_{i=1}^{m} X_i'\,V_i^{-1}\,X_i \quad - \sum_i X_i'\,V_i^{-1}\,y_i,$$

$$\frac{\partial L}{\partial \sigma^2} = \tfrac{1}{2}\sum_i \operatorname{tr} V_i^{-1} - \tfrac{1}{2}\sum_i h_i'\,V_i^{-1}\,h_i,$$

and

$$\frac{\partial L}{\partial \theta_j} = \tfrac{1}{2}\sum_i V_i^{-1}\,C_{ij} - \tfrac{1}{2}\sum_i h_i'\,V_i^{-1}\,C_{ij}\,V_i^{-1}\,h_i,$$

where $h_i = y_i - X\alpha$.

Equating these derivatives to zero, we have the following set of equations:

$$\hat{\alpha}_{ML} = \left(\sum_i X_i'\,V_i^{-1}\,X_i\right)^{-1}\sum_i X_i'\,V_i^{-1}\,y_i, \qquad (3.2)$$

$$\sum_i \operatorname{tr} V_i^{-1} = \sum_i h_i'\,V_i^{-1}\,h_i, \qquad (3.3)$$

and

$$\sum_i \operatorname{tr} V_i^{-1}\,C_{ij} = \sum_i h_i'\,V_i^{-1}\,C_{ij}\,V_i^{-1}\,h_i. \qquad (3.4)$$

(3.3) and (3.4) can not be solved analytically except for some special cases. Lindstrom and Bates (1988) described Newton Raphson and EM Algorithms for solving them. We propose to use Anderson's Iterative Algrithm for solving (3.3) and (3.4) as $V_i = I\sigma^2 + \sum_k C_{ik}\theta_k$. Therefore, (3.3) and (3.4) may be written as

$$\sum_i \operatorname{tr} V_i^{-2}\sigma^2 + \sum_k \sum_i \operatorname{tr} V_i^{-2} C_{ik}\theta_k = \sum_i r_i' V_i^{-1} h_i \qquad (3.5)$$

and

$$\sum_i \operatorname{tr} V_i^{-1} C_{ij} V_i^{-1} \sigma^2 + \sum_k \sum_i \operatorname{tr} V_i^{-1} C_{ij} V_i^{-1} C_{ik}\theta_k =$$

$$\sum_i h_i' V_i^{-1} C_{ij} V_i^{-1} h_i. \qquad (3.6)$$

Note that $V_i^{-1} = [I - Z_i(D^{-1}\sigma^2 + Z_i' Z_i)^{-1} Z_i'] / \sigma^2$.

We may use initial values for σ^2, D; $\sigma^2_{(o)}$ and $D_{(o)}$. These initial values can be calculated from OLS estimates as suggested by Laird et al (1987). Evaluate V_i^{-1} and solve (3.2) and (3.6) to give new estimates; $\sigma^2_{(1)}$ and $D_{(1)}$. These procedures may be repeated untill the differences of two successive iteration do not exceed a certain value (10^{-6}, say).

(3.2) The RML Approach:-

A criticism of ML estimates for the variance components is that they take no account of the loss of degrees of freedom resulting from the estimation of α. To overcome this problem, Patterson and Thompson (1971) and (1974) suggested to maximize the likelihood function of all error contrasts (transformations of the vector of observations with zero expectations). The resulting estimates are the residual maximum likelihood (RML) estimators. The log likelihood of all error contrasts is given by

$$L_1 = \text{const} - \tfrac{1}{2}\log|SVS| - \tfrac{1}{2}\, y'(SVS)^{-}y\,, \qquad (3.7)$$

where $S=I - X(X'X)^{-1}X'$ and A^{-} is the g-inverse of A.

The RML equations are given by:

$$\operatorname{tr}(svs)^{-} = y'(SVS)^{-}y - \sum_i h_i V_i^{-1} \qquad (3.8)$$

and

$$\operatorname{tr}(SVS)^{-}C_j = y'(SVS)^{-}C_j.(SVS)^{-}y$$
$$= \sum_i h_i' V_i^{-1} c_{ij} V_i^{-1} h_i \qquad (3.9)$$

where $C_j = \operatorname{diag}(c_{1j}, c_{2j}, \ldots c_{mj})$.

Note that $(SVS)^{-} = V^{-1} - V^{-1}X(X'V^{-1}X)^{-1}X'V^{-1} = R$

The block diagonal matrices of order $n_i \times n_i$ in $(SVS)^{-}$ are given by $V_i^{-1} - V_i^{-1}X_i(\sum_i X_i' V_i^{-1} X_i)^{-1} X_i' V_i^{-1} = R_{ii}$, and the $n_i \times n_s$ block off diagonal matrices are given by

$$- V_i^{-1} X_i (\sum_i X_i' V_i^{-1} X_i)^{-1} X_s' V_s^{-1} = R_{is},$$

Equations (3.8) and (3.9) have no analytic solution in general and they may be solved using Anderson's iterative procedure. Its set of equations are given by:

$$\sum_i \operatorname{tr} V_i^{-1}\sigma^2 + \sum_k \sum_i R_{ii} V_i^{-1} C_{ik}\theta_k = \sum_i h_i' V_i^{-1} h_i, \qquad (3.10)$$

and $\sum_i \operatorname{tr} R_{ii} C_{ij} V_i^{-1}\sigma^2 + \sum_k \sum_i R_{ii} C_{ij} V_i^{-1} C_{ik}\theta_k$

$$= \sum_i h_i' V_i^{-1} C_{ij} V_i^{-1} h_i,$$

for all j. (3.11)

Setting initial values for $\hat{\sigma}$, D; $\hat{\sigma}^2_{(o)}$ and D(o), say . Evaluate V_i^{-1} and Solve (3.10) and (3.11) to get new estimates $\hat{\sigma}^2_{(1)}$, $D_{(1)}$. These procedures are stopped when convergence is reached.

(3.3) The MINQUE Estimators

Abdel-Wahed (1989) derived minimum norm quadratic unbiased estimates for variance components in linear models when the random effects are correlated with dispersion matrix Σ such that, the variance covariance matrix of y can be written as $\sum_{r,s} v_{rs} \sigma_{rs} = \sum_j U_j \theta_j$, where θ_j's are the different σ_{rs}'s in Σ. He derived the MINQUE estimate of tr $N\Sigma$, for any matrix N, in the form y'Ay such that the resulting estimates are invariant to a translation of α, unbiased and has minimum norm. The fundamental equations are

$$F\theta = L, \qquad (3.12)$$

where the rs-th element of F is tr $RU_r RU_s$ and the r-th element of L is $y'RU_rRy$ and θ is the vector of variance components θ_j's.

In our model, the vector $\theta = (\sigma^2, \theta_1, \dots)$ and $U_k = C_j$. That is $\Sigma = I\sigma^2 + \sum_j C_j \theta_j$. As tr $R\, U_k\, RU_s$ = tr $R\, U_k V^{-1} U_s$, and $y'R_k U\, Ry = \sum_i r_i' V_i^{-1} C_{ik} V_i^{-1} r_i$; the first equation in (3.12) is given by

$$\sum_i \text{tr } R_{ii} V_i^{-1} \sigma^2 + \sum_k \sum_i R_{ii} V_i^{-1} C_{ik} \theta_k = \sum_i h_i' V_i^{-1} h_i, \qquad (3.13)$$

and the other equations in (3.12) are given by

$$\sum_i \text{tr } R_{ii} V_i^{-1} C_{ij} \sigma^2 + \sum_k \sum_i R_{ii} C_{ij} V_i^{-1} C_{ik} \theta_k = \sum_i h_i' V_i^{-1} C_{ij} V_i^{-1} h_i \quad \text{for all } j \qquad (3.14)$$

* This is one of the contribution in this paper, I have derived these closed forms.

Note that the elements of R_{ii} and V_i involve the elements of D and σ^2 that are to be estimated. Rao (1971) argued to use priori values of them if they are available or we may solve the previous equations iteratively, but the property of unbiasedness is usually lost. Note that equations (3.13) and (3.14) are identical to (3.10) and (3.11) therefore, a similar procedure for solving them may be suggested, however, MINQUE estimates may be derived without any assumption concerning the distribution of random effects.

IV. CLOSED FORMS FOR THE ESTIMATION OF α , σ^2 AND D.

In this section, we prove that, for the growth curve model (2.3) when, $n_i=n$ for all i, all x_i's and w_i's are equal to x and w respectively, there exists closed forms for ML, RML and MINQUE estimates for both fixed and variance components parameters. When $x_i=x$ and $w_i=w$, for all i thus,

$X = A' \otimes x$, and $z_i=z = xw$ and $V_i = v$

$V(y) = V = I_n \otimes v$ and let $Y = (y_1,y_2,\ldots,y_m)$ i.e vec (Y)=y.

Then $X'V^{-1} = A \otimes x'v^{-1}$, $X'V^{-1}X = AA' \otimes x'v^{-1}x$

But $v^{-1} = (I - z(\sigma^2 D^{-1} + z'z)^{-1} z') / \sigma^2$

$$= [I - x(\sigma^2(wDw')^{-1} + x'x)^{-1} x'] / \sigma^2$$

$$x'v^{-1} = (wDw')^{-1} [\sigma^2(wDw')^{-1} + x'x]^{-1} x'$$

and

$$x'v^{-1}x = (wDw')^{-1} [\ ^2(wDw')^{-1} + x'x]^{-1}, \qquad (4.1)$$

$$(x'v^{-1}x)^{-1} = (x'x)^{-1} [\sigma^2(wDw')^{-1} + x'x] (wDw')$$

All the previous methods of estimation use GLS to estimate α.

Hence; $\hat{\alpha} = \text{vec}(\hat{\beta}) = (X'V^{-1}X)^{-1} X'V^{-1}y$

$$= [(AA')^{-1} A \otimes (x'x)^{-1} x'] y$$

Therefore, the closed form of B is given by

$$\hat{B} = (x'x)^{-1} \; x' \; Y \; A'(AA')^{-1}. \tag{4.2}$$

Equation (4.2) is the ordinary least squares estimate of B . Evaluating the estimates of D and σ^2, we use the following identities:-

Let $M_A = I_m - A'(AA')^{-1}A$, $M_x = I_n - x(x'x)^{-1}x'$

$= I - C_A$ $\qquad\qquad = 1 - C_x$

and

$$M_z = I_n - z(z'z)^{-1} \; z' = I - C_z.$$

Hence

$$M_x v^{-1} = M_x \text{ and } M_x \; x = 0.$$

$$\begin{aligned} R &= I \otimes v^{-1} - (A' \otimes v^{-1}x)[(AA')^{-1} \; A' \otimes (x'x)^{-1}x'] \\ &= I \otimes v^{-1} - C_A \otimes v^{-1} \; C_x \\ &= I \otimes M_x \; / \sigma^2 + M_A \otimes v^{-1} \; C_x, \end{aligned} \tag{4.3}$$

$$\begin{aligned} (R)(I \otimes z) &= (I \otimes M_x \; / \sigma^2 + M_A \otimes \; v^{-1}C_x) \; (I \otimes z) \\ &= M_A \otimes v^{-1}z \end{aligned} \tag{4.4}$$

and

$$(I \otimes z') \; R(I \otimes z) = M_A \otimes z'v^{-1}z, \tag{4.5}$$

where

$$v^{-1}z = (z - z(\sigma^2 D^{-1} + z'z)^{-1} \; z'z) \; / \sigma^2 = z(\sigma^2 I + Dz'z)^{-1}$$

and (4.6)

$$z'v^{-1}z = z'z \; (\sigma^2 I + Dz'z)^{-1}. \tag{4.7}$$

(4.1) The ML Estimates

The ML Equations for estimating D and σ^2 are given by Equations (3.3) and (3.4).

As $\dfrac{\partial zDz'}{\partial d_{ij}} = z_i z_j'$, where z_i is the i-th column of z, the ML equations are

$$m \operatorname{tr} v^{-1} = y' R^2 y, \tag{4.8}$$

and

$$m \operatorname{tr} v^{-1} z_i z_j' = y' R (I \otimes z_i z_j') Ry \quad \text{for all } j. \tag{4.9}$$

$$= (I \otimes z_j') Ryy' R (I \otimes z_i)$$

The set of equations (4.8) may be written in matrix form as

$$m\, z' v^{-1} z = (M_A \otimes z' v^{-1})\, yy'\, (M_A \otimes v^{-1} z)$$

$$= z' v^{-1} Y M_A Y' v^{-1} z \; . \tag{4.10}$$

Using (4.5) and (4.6), Equation (4.10) becomes

$$m\, z'z(\sigma^2 I + Dz'z)^{-1}) = (\sigma^2 I + D'z'z)^{-1} z' Y M_A Y' z (\sigma^2 I + Dz'z)^{-1}.$$

Hence

$$m\, z'z(\sigma^2 I + Dz'z) = z' Y M_A T' z. \tag{4.11}$$

This is

$$\hat{D}_{ML} = \frac{1}{m} (z'z)^{-1} z' Y M_A Y' z (z'z)^{-1} - \sigma^2_{ML} (z'z)^{-1} \tag{4.12}$$

The right hand side of (4.8) is given by

$$\frac{n}{\sigma^2} \operatorname{tr}(I - z(\sigma^2 D^{-1} + z'z)^{-1} z') = \{ mn - m \operatorname{tr}[z \Gamma z'] \} / \sigma^2 \tag{4.13}$$

$$\text{where } \Gamma = (\sigma^2 D^{-1} + z'z)^{-1},$$

while the left hand side of (4.8) is given by

$$y' R^2 y = \operatorname{tr}(M_x YY' M_x) / \sigma^4 + \operatorname{tr}(C_x v^{-1} Y M_A Y' v^{-1} C_x)$$

But $v^{-1} C_x = C_x / \sigma^2 - z \Gamma z' / \sigma^2$, and $C_x z = z$

Thus $\quad y' R^2 y = \operatorname{tr}(M_x YY' M_x)/\sigma^4 + \operatorname{tr}(C_x Y M_A Y' C_x) / \sigma^4$

$$- \frac{2}{\sigma^4} tr(C_x \; YM_A \; Y'z \Gamma z') + \frac{1}{\sigma^4} \; tr(z \Gamma z' \; YM_A Y' z \Gamma z') \qquad (4.14)$$

From (4.11), equation (4.14) becomes

$$y'R^2 y = tr(M_x \; Y'YM_x) / \sigma^4 + tr(C_x \; YM_A \; Y'C_x) / \sigma^4$$

$$- \frac{2m}{\sigma^4} tr(zDz') + \frac{m}{\sigma^4} [tr(zDz') - \sigma^2 \; tr \; z \Gamma z'].$$

As $\quad m tr(z\hat{D}_{ML} z') = C_z YM_A Y'C_z - \hat{\sigma}^2_{ML} C_z,$

therefore (4.8) is

$$\frac{mn}{\sigma^2} = tr(M_x YY'M_x) / \sigma^4 + tr(C_x YM_A Y'C_x) / \sigma^4$$

$$- \frac{m}{\sigma^4} \; tr(zDz') \qquad (4.15)$$

substituting $\hat{D}$ of (4.12) in (4.15) results

$$m(n-q) \hat{\sigma}^2_{ML} = tr(M_x YY'M_x) + tr(C_x YM_A Y'C_x) - Tr(C_z \; YM_A YC_z) \qquad (4.16)$$

Equations (4.12) and (4.16) are the closed form estimates of D and σ^2.

(4.2) <u>The RML Estimates</u>

The right hand side of RML equations are equivelant to (4.8) and (4.9) while the left hand sides are tr R and tr $R(I \otimes z_i z_j)$ respectively. That is, the set of equations (3.11) may be put in matrix form as

$$(m-r) \; z'v^{-1}z = z'Y'M_A Yz \; . \qquad (4.17)$$

Hence $\hat{D}_{RML} = \frac{1}{m-r} \; (z'z)^{-1} z'YM_A Y'z \; (z'z)^{-1} - \hat{\sigma}^2_{RML} (z'z)^{-1} \qquad (4.18)$

and $\quad tr \; R = \frac{1}{\sigma^2} \; tr \; (I \otimes M_x + M_A \otimes C_x - M_A \otimes z \Gamma \; z')$

$$= \frac{1}{\sigma^2} \; (m(n-s) + (m-r)s - (m-r) \; tr(z \Gamma z')$$

Thus equation (3.10) is

$$\frac{1}{\sigma^2}\,[m(n-s) + (m-r)s - (m-r)\ tr(z\ \Gamma\ z')]$$

$$= \frac{1}{\sigma^4}\ \{[tr\ M_x\ YY'M_x] + tr[C_x\ YM_AY'C_x]$$

$$- 2(m-r)\ tr(zDz') + (m-r)\ tr(zDz')$$

$$- (m-r)\ tr(zDz') + (m-r)\ tr(zDz')$$

$$- (m-r)\ tr(z\Gamma z')\sigma^2\} \qquad (4.19)$$

Therefore equation (4.19) becomes

$$[m(n-s)+(m-r)(s-1)]\ \hat{\sigma}^2_{RML} = tr(M_xYY'M_x)+tr(C_x\,YM_AY'C_x) - tr(C_z\ YM_AY'C_z) \qquad (4.20)$$

Since $(m-r)\ tr(z\hat{D}z')_{RML} = C_zYM_AY'C_z - \hat{\sigma}^2_{RML}\ C_z$.

Equations (4.18) and (4.20) are the closed form estimates of D and $\hat{\sigma}^2$. It should be noted that Laird et al (1987) derived a similar formula for ML but for special case where $X = z \otimes A'$, that is when $w = \underline{1}$.

(4.3) The MINQUE Estimates

The fundamental equations for MINQUE estimates may be written in the form

$$tr\ R = y'R^2y$$

and

$$tr\ R(I \otimes z_iz_j) = tr\ y'R(I \otimes z_iz_j)\ Ry \qquad \text{for all } i \ \& \ j$$

as $V^{-1}\ \sigma^2 I + \sum_{i,j} V^{-1}\ (I \otimes z_iz_j')\ d_{ij} = I.$

These are the same equations as the RML. Therefore, the MINQUE estimates are given by

$$\hat{D}_{MIN} = \frac{1}{m-r} (z'z)^{-1} z'YM_A Y'z(z'z)^{-1} - \hat{\sigma}^2_{MIN}(z'z)^{-1},$$

$$\hat{\sigma}^2_{MIN} = \frac{1}{(m-r)(s-q)+m(n-s)} [tr(M_x YY'M_x) + tr(C_x YM_AY'C_x) - tr(C_z YM_AY'(C_z)]$$

and $\hat{B} = (x'x)^{-1} x' YA'(AA')^{-1}$.

Note that MINQUE estimates may be derived whatever the distribution of the random effects is while ML and RML are based on the assumption of normally distributed random effects.

5. ILLUSTRATION

To illustrate the estimation procedures discussed in the previous sections, a numerical example using bioassay data from Volund (1980) is considered, following Reinsel (1985), these data consists of blood-suger concentrations measured on each 36 experimental subject at t=1,2,3,4 and 5 hours after adminstration of an insulin does , together with an initial blood sugar measurement at time t=o. The experimental subjects were assigned in a 2^2 factorial design with two insulin treatments (standard and test) and two dose levels (low and high). The response variable y_{tk} is 100 times the lagarithm of the ratio of blood sugar at time t to the initial blood sugar, for t=1,2,3,4,5. This is similar to the percentage change in blood sugar analysed by volund.

For each subject the variable y_{tk} was assumed to follow a linear response over time $y_{tk} = \beta_{1k} + \beta_{2k} (t-1) + e_{tk}$ (t=1,2,...5, k=2,...,36). The first individual was ignored as it represents an odd value. Therefore m=35. The parameter β_{1k} corresponds to the response value at time t=1, where as β_{2k} represents the subsequent rate of change per hour. We have assumed two models concerning $\beta_k' = (\beta_{1k}, \beta_{2k})$. First β_k was assumed to follow the model

$$\beta_k = Ba_k + b_k, \tag{5.1}$$

where B' is a 2x4 matrix of unknown elements to be estimated and a_k is a 4x1 vector with elements zero or one depending on treatments (4 treatments) assignment to individuals. The vector of random variables b_k's are independent random variables distributed as N(0,D) [Note that MINQUE estimates do not depend on normality assumption].

The other model concerning β_k is

$$\beta_k = Ba_k + w\,\eta_k. \tag{5.2}$$

where $w' = (0,1)$ and η_k,s are independent random variables distributed as $N(0, \sigma_b^2)$.

For both models $x = \begin{vmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 2 \\ 1 & 3 \\ 1 & 4 \end{vmatrix}$ and $A = \text{diag}(1_8', 1_9', 1_9', 1_9')$

where $1_k'$ is a row vector of ones of order (1 x k).

The estimation of the fixed parameters' matrix B is the same for both models and it is the OLS estimate which is given by:

$$= \begin{vmatrix} -54.088 & -64.703 & -51.305 & -55.096 \\ 16.303 & 12.782 & 15.510 & 13.899 \end{vmatrix}.$$

For the first model as x=z, the sum of squares used in estimating σ^2 reduces to tr $(M_x\, YY'M_x)$

$$= tr(Y'Y) - tr(Y'x(x'x)^{-1} x'Y) = 220344.31 - 212630.52 = 7713.79$$

As $s=q$, $\hat{\sigma}^2_{ML} = \hat{\sigma}^2_{RML} = \hat{\sigma}^2_{MIN} = 73.465.$

$$(z'z)^{-1} z'Y M_A Y'z(z'z)^{-1} = \begin{vmatrix} 5552.34 & -1153.56 \\ -1153.56 & 485.39 \end{vmatrix}$$

Therefore:

$$\hat{D}_{ML} = \begin{vmatrix} 114.559 & -18.266 \\ -18.266 & 6.522 \end{vmatrix}$$

and

$$\hat{D}_{RML} = \hat{D}_{MIN} = \begin{vmatrix} 135.029 & -22.518 \\ -22.518 & 8.311 \end{vmatrix}$$

For the second model: $z = xw = (0,1,2,3)'$.

The sum of squares in (4.20) is given by

$$tr(Y'Y) - tr((x'x)^{-1} x'YA'(AA')^{-1}A Y'x) - tr(Y'z(z'z)^{-1}z'y)$$

$$+ tr((z'z)^{-1} z'YA'(AA')^{-1} AY'z)$$

$$= 220344.31-193378.25-31175.861+21177.489 = 16967.688$$

Therefore

$$\hat{\sigma}^2_{ML} = \frac{16967.688}{140} = 121.198 \quad \text{and} \quad \hat{\sigma}^2_{RM}, = \hat{\sigma}^2_{MIN} = \frac{1696.688}{136} = 124.762.$$

Also $(z'z)^{-1} z'Y M_A Y'z(z'z)^{-1} = 333.279.$

Hence

$$\hat{\sigma}^2_{b(ML)} = 5.482 \quad \text{and} \quad \hat{\sigma}^2_{b(RML)} = \hat{\sigma}^2_{b(MIN)} = 5.941.$$

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