HANDOUT 10

Mixed Models Analyses

Best Linear Unbiased Prediction (BLUP)

Introduction to Best Linear Unbiased Prediction

Objectives

- Roles of the random effect parameters.
  - Random effects in the models help determining the SE for the fixed effects or the proper form of test stat.

- The best linear unbiased predictor (BLUP) and the empirical best linear unbiased predictor (EBLUP).
  - Predicted effect of one level of the random factor given the observed value of the response variable in the data.

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Random Effect Parameter

A fixed effect parameter, β, corresponds to the negative or positive contribution of a level of a factor to the mean response.

A random effect parameter, γ, corresponds to the realized value of the random effect given the observed data.

The linear mixed effect model

$$Y = X\beta + Z\gamma + \varepsilon$$

where

$$\begin{bmatrix}\gamma\\ \varepsilon\end{bmatrix} \sim N\left(\begin{bmatrix}0\\ 0\end{bmatrix}, \begin{bmatrix}G & 0\\ 0 & R\end{bmatrix}\right)$$

Given data y, what is out best guess for unobserved vector γ. Meaning: BLUP for γ.

Multicenter Clinical Trial Example

- Three drugs are compared in multicenter clinical trial for their effects on diastolic blood pressure measurements.
- Patients are given one of the three drugs, at random, at 1 of 26 clinics.
- Measurements are taken on the patients during five visits at the clinics.
- The visits are three weeks apart.
- The actual data set contains more than 3000 observations and is highly unbalanced.
- A balanced subset is selected. This set contains records on 78 patients at 26 clinics.
- Each patient receives one drug and visits the same clinic five times.

Multicenter Clinical Trial Example

		CLINIC 1			CLINIC 2			…
Drug		1	4	3	3	1	4	
Patient		4261	4269	4270	3081	3082	3085	
Visit	1	82	86	80	80	70	80	
	2	70	84	82	70	80	60	
	3	80	90	90	70	70	70	
	4	70	82	84	60	70	90	
	5	80	70	80	60	70	70	

Predicting a Random Effect--BLUP

- The variable **`drug`** is a fixed effect

- **`clinic`** and **`patient`** (or **`drug*clinic`**) are random effects.

- You suspect patients in some clinics might have more favorable responses than patients in other clinics.

- You want to predict the actual effect of a **`clinic`** based on the measurements of **`diabp`**.

- The prediction of a random effect or any linear combination involving random effects is a best linear unbiased prediction (BLUP).
  - The prediction of **diabp** value at randomly selected clinic is BLUP.

Machine Example

The manager of an automotive plant must replace the machines producing a certain component used in automatic transmissions.

2 different machines are available.

The manager wants to evaluate the productivity of the machines when operated by the plant's employees.

5 employees are randomly selected from the workforce to operate each machine.

Predicting a Random Effect--BLUP

- The variable **`machine`** is a fixed effect
- **`Operator`** and **`machine*operator`** are random effects.
- You might want to predict the actual effect of an **`operator`** based on the measurements of **`productivity`**.
- You might also want to know the performance of the j^{th} **`operator`** averaged over all machines or at one specific machine.
- You can address these objectives by estimating random effects or linear combinations involving random effects--the BLUPs.

Properties of BLUPs

– Best: minimizes the residual error.

If γ *is fixed effect,* this is the same as minimum variance among all linear and unbiased estimators

– Linear: linear estimator: $\hat{\gamma} = a+By$

– Unbiased: $E(\hat{\gamma}-\gamma) = 0$

– BLUPs are shrinkage estimators.

Properties of BLUPs

BLUPs have a so-called shrinkage property.

The predicted response for a random effect shrinks toward the overall average. In other words, they are less extreme than the observed counterparts.

For example, consider the toy example introduced earlier in the course. It can be shown that the BLUP for the toy effect, b_j is $\widehat{b_j} = \frac{\sigma_b^2}{\sigma_b^2+\frac{1}{3}\sigma^2}(\bar{y}_{.j} - \hat{\mu})$ where $\bar{y}_{.j}$ is the average pressure value for toy j and $\hat{\mu}$ is the estimated grand mean.

Because the factor $\frac{\sigma_b^2}{\sigma_b^2+\frac{1}{3}\sigma^2}$ is never greater than 1, the BLUPs are often referred to as shrinkage estimator.

How to Obtain the Best Linear Unbiased Prediction (BLUP)?

BLUPs can be obtained in one of the following two ways:

- Computing the expected value of the random effect given the observed data using the Bayes theorem.

- Solving the MIXED model equations (PROC MIXED).

How to Obtain the BLUP?

BLUPs can be estimated using the Bayesian approach. Because the random effects are assumed to be random variables, it is most natural to estimate them using the Bayes theorem (Box and Tiao 1992). The prior distribution of a random effect is $\gamma \sim N(0, \mathbf{G})$. The conditional distribution of y given random effects γ is $y \mid \gamma \sim N(\mathrm{X}\beta + \mathrm{Z}\gamma, \mathbf{R})$. The posterior distribution of a random effect given the observed y, $f(\gamma \mid y)$, can be calculated using the Bayes theorem:

$$f(\gamma \mid y) = \frac{f(y \mid \gamma) f(\gamma)}{\int f(y \mid \gamma) f(\gamma) d\gamma}$$, where $f(\cdot)$ represents the probability density function.

It can be shown that the above equation is the density of a multivariate normal distribution. The prediction of the random effect γ is estimated by the mean of this posterior distribution:

$$\hat{\gamma} = E(\gamma \mid y) = \int \gamma f(\gamma \mid y) d\gamma = GZ'V^{-1}(y - X\beta).$$

Henderson (1959) has shown that BLUPs can also be obtained by solving the mixed-model equations, which is analogous to the normal equations in the fixed-effect model:

$$\begin{bmatrix} X'R^{-1}X & X'R^{-1}Z \\ Z'R^{-1}X & Z'R^{-1}Z + G^{-1} \end{bmatrix} \begin{bmatrix} \hat{\beta} \\ \hat{\gamma} \end{bmatrix} = \begin{bmatrix} X'R^{-1}Y \\ Z'R^{-1}Y \end{bmatrix}.$$

How to Obtain the BLUP?

Solving these equations for $\hat{\beta}$ and $\hat{\gamma}$ yields

$\hat{\beta} = (X'V^{-1}X)^{-}X'V^{-1}y$ and

$\hat{\gamma} = GZ'V^{-1}(y - X\hat{\beta})$, where V=ZGZ′+R.

- $\hat{\beta}$ is the best linear unbiased estimator (BLUE) of the vector of the fixed effects parameters β.
- $\hat{\gamma}$ is the best linear unbiased predictor (BLUP) of the vector of random effects γ.

For a linear combination of only fixed effects (K′β), the solution of the mixed-model equations results in *best linear unbiased estimators*, or BLUEs, of K′β.

For linear combinations of random effects (M′γ), or linear combinations of fixed *and* random effects (K′β + M′γ), the solutions of the mixed-model equations result in BLUPs of M′γ or K′β + M′γ.

Which of the following is true?

a. The BLUP of a random effect is the same as the estimate of the effect if it were treated fixed.

b. The BLUP of a random effect has shrinkage property.

c. The BLUP of the response variable is the same as the population mean.

Predicted values in Linear Mixed Models

$\hat{y} = \mathbf{X}\beta$ — population average (marginal) prediction, OUTPM= option in the MODEL statement

$\hat{y} = \mathbf{X}\beta + \mathbf{Z}\gamma$ — subject-specific (conditional) prediction, OUTP= option in the MODEL statement, a BLUP

It can be shown that the BLUP of the breaking strength across all adhesives for toy j is the weighted average of the grand mean and the observed value.

$$\hat{y}_j = \hat{\mu} + \widehat{b_j} = \hat{\mu} + \frac{\sigma_b^2}{\sigma_b^2 + \frac{\sigma^2}{3}}(\bar{y}_{.j} - \hat{\mu})$$

$$= \frac{\sigma^2/3}{\sigma_b^2 + \sigma^2/3}\hat{\mu} + \left(1 - \frac{\sigma^2/3}{\sigma_b^2 + \sigma^2/3}\right)\bar{y}_{.j}$$

What is an EBLUP?

The covariance matrices G (for random effects) and R (random errors) are unknown.

You can substitute the REML estimates, $\hat{G}$ and $\hat{R}$.

Using the estimated covariance matrices, $\hat{G}$ and $\hat{R}$ and solving the mixed model equations yields the empirical best linear unbiased estimator, EBLUP $\hat{\beta}$ and the EBLUP $\hat{\gamma}$.

Multicenter Clinical Trial Data

clinic	patient	visit	drug	diabp
1	4261	1	1	82
1	4261	2	1	70
1	4261	3	1	80
1	4261	4	1	70
1	4261	5	1	80
1	4269	1	4	86
1	4269	2	4	84
1	4269	3	4	90
1	4269	4	4	82
1	4269	5	4	70
1	4270	1	3	80
1	4270	2	3	82
1	4270	3	3	90
1	4270	4	3	84
1	4270	5	3	80
2	3081	1	3	80
2	3081	2	3	70
2	3081	3	3	70
2	3081	4	3	60
2	3081	5	3	60
...	...	...	...	...

ClinicalTrialExample

The Model for Multicenter Clinical Data

patient effect, random

$$y_{ijk} = \mu + \alpha_i + b_j + p_{ij} + \varepsilon_{ijk}$$

drug effect, fixed

clinic effect, random

i = 1, 2, 3 (drugs)
j = 1 to 26 (clinics)
k = 1, 2, 3, 4, 5 (visits).

$$b_j \sim N(0, \sigma_b^2)$$
$$p_{ij} \sim N(0, \sigma_p^2)$$
$$\varepsilon_{ijk} \sim N(0, \sigma^2)$$

Are LSMEANS and EBLUPS different?

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The shrinkage factor for multicenter clinical trial data

$$b = \frac{Var(clinic)}{Var(clinic) + \frac{Var(patient)}{3} + \frac{Var(residual)}{15}}$$

Estimated value is $\frac{12.1253}{12.1253+\frac{37.5042}{3}+\frac{46.9962}{15}}$=0.4368

For clinic i, EBLUP = $\bar{\bar{y}} + b * (\bar{y_i} - \hat{\mu})$

For clinic 1, $EBLUP_1$=79.9256+0.4368(80.6667-79.9256)=80.2493

REVIEW

The ways to obtain EBLUPS in PROC MIXED?

The key feature of an EBLUP?

Inference Space
Objectives

- List different inference spaces in mixed models.

- Make inferences about the fixed effect over different inference spaces.

Inference Space

The inference space is determined by your choice of the coefficients associated with the random effects (**M**).

- If **M**=0, your inferences apply to the entire population from which the random effects are sampled. This is known as the *broad inference space*.
- If **M** represents averages over the appropriate random effects, your inferences apply only to the observed levels of the random effects. This is known as the *narrow inference space*.
- If **M** represents averages of some random effects and it is set to zero pertaining to other random effects, your inferences apply only to observed levels of some of the random effects. This is known as the *intermediate inference space*.

Broad Inference Space

The broad inference space is used by PROC MIXED by default.

The inferences about the linear combination of the fixed effects apply to the entire population from which the random effects are sampled.

In multicenter clinical trial example, the inferences about the drug effects apply to the population of clinics and the population of patients within a clinic in the broad inference space.

Narrow Inference Space

The narrow inference space is used by PROC GLM.

It treats clinics and patients within clinic as fixed effects.

In multicenter clinical trial example, the inferences about the drug effects apply only to the specific clinics and patients within a clinic included in the study.

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Intermediate Inference Space

The intermediate inference space is about the linear combination of the fixed effects apply on the observed levels of some of the random effects.

In multicenter clinical trial example, the inferences about the drug effects apply to the specific clinics included in the study and the population of patients within a clinic in the intermediate inference space.

Writing an ESTIMATE Statement (Narrow Inference Space)

Estimate **`drug`** 1 mean ($\mu_{1\cdot}$) in narrow inference space.

$$\left.\begin{aligned}\mu_{1\cdot} &= \frac{1}{26}(\mu_{11} + \mu_{12} + \mu_{13} + \cdots + \mu_{126}) \\ E(y_{ijk}) &= \mu_{ij} = \mu + \alpha_i + b_j + (\alpha b)_{ij}\end{aligned}\right\}$$

$$\mu_{1\cdot} = \frac{1}{26}[26\mu + 26\alpha_1 + b_1 + b_2 + \cdots + b_{26} + (\alpha b)_{11} + (\alpha b)_{12} + \cdots + (\alpha b)_{126}]$$

$$= \mu + \alpha_1 + \frac{1}{26}[b_1 + b_2 + \cdots + b_{26} + (\alpha b)_{11} + (\alpha b)_{12} + \cdots + (\alpha b)_{126}]$$

Writing an ESTIMATE Statement (Another Approach)

```
class drug clinic;
```

drug	clinic					marginal
	1	2	…	25	26	
1	1/26	1/26	…	1/26	1/26	1
3	0	0	…	0	0	0
4	0	0	…	0	0	0
marginal	1/26	1/26	…	1/26	1/26	1

…

Question

The order of the coefficients for the interaction terms in an ESTIMATE statement is determined by which of the following?

a. The order of the variables in the CLASS statement
b. The order of the variables in the MODEL statement
c. Nothing because the order can be arbitrary
d. The specification of the interaction terms in the MODEL statement

Inference Space

This demonstration illustrates the concepts discussed previously.

ClinicalTrialExample

Inference Space and EBLUP split plot

The treatment structure used in the experiment experiment was a 3x4 factorial

with three varieties of alphalpha and four dates of third cutting.

The experimental units were arranged into six plots, each subdivided into four plots.

The varieties of alphalpha (Cossac, Ladak, Ranger) were assigned randomly to the blocks

and the dates of third cutting (1:None 2:September 1, 3:September 20, 4:-October 7) were randomly assigned to the plots.

All four dates were used in each block.

The variables are:

yield: the plot yield (T/acre)

Date: the third cutting date (1, 2, 3, 4)

Block: factor identifying the block (1 to 6)

variety: alphalpha variety (Cossack, Ladak, Ranger)

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Inference Space and EBLUP split plot

Model: $yield_{ijk}=\mu_{ijk}+\varepsilon_{ijk}$ where

$\mu_{ijk}= \mu+\alpha_i+b_j+(\alpha b)_{ij}+\gamma_k+(\alpha\gamma)_{ik}$

Mean yield for Ladak: $\mu_{2..} = \frac{\sum_j \sum_k \mu_{2jk}}{j(k)}$

$$= \frac{1}{24}\left(\begin{array}{c}\mu_{211}+\mu_{212}+\mu_{213}+\mu_{214}+\mu_{221}+\mu_{222}+\mu_{223}+\mu_{224} \\ +\ldots\ldots\ldots+\mu_{261}+\mu_{262}+\mu_{263}+\mu_{264}\end{array}\right)$$

$\mu_{211}= \mu+\alpha_2+b_1+(\alpha b)_{21}+\gamma_1+(\alpha\gamma)_{21}$

$\mu_{212}= \mu+\alpha_2+b_1+(\alpha b)_{21}+\gamma_2+(\alpha\gamma)_{22}$

$\mu_{213}= \mu+\alpha_2+b_1+(\alpha b)_{21}+\gamma_3+(\alpha\gamma)_{23}$

$\mu_{214}= \mu+\alpha_2+b_1+(\alpha b)_{21}+\gamma_4+(\alpha\gamma)_{24}$

$\mu_{221}= \mu+\alpha_2+b_2+(\alpha b)_{22}+\gamma_1+(\alpha\gamma)_{21}$

$\mu_{222}= \mu+\alpha_2+b_2+(\alpha b)_{22}+\gamma_2+(\alpha\gamma)_{22}$

$\mu_{223}= \mu+\alpha_2+b_2+(\alpha b)_{22}+\gamma_3+(\alpha\gamma)_{23}$

$\mu_{224}= \mu+\alpha_2+b_2+(\alpha b)_{22}+\gamma_4+(\alpha\gamma)_{24}$

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Inference Space and EBLUP split plot

$\mu_{231}= \mu+\alpha_2+b_3+(\alpha b)_{23}+\gamma_1+(\alpha\gamma)_{21}$
$\mu_{232}= \mu+\alpha_2+b_3+(\alpha b)_{23}+\gamma_2+(\alpha\gamma)_{22}$
$\mu_{233}= \mu+\alpha_2+b_3+(\alpha b)_{23}+\gamma_3+(\alpha\gamma)_{23}$
$\mu_{234}= \mu+\alpha_2+b_3+(\alpha b)_{23}+\gamma_4+(\alpha\gamma)_{24}$
$\mu_{241}= \mu+\alpha_2+b_4+(\alpha b)_{24}+\gamma_1+(\alpha\gamma)_{21}$
$\mu_{242}= \mu+\alpha_2+b_4+(\alpha b)_{24}+\gamma_2+(\alpha\gamma)_{22}$
$\mu_{243}= \mu+\alpha_2+b_4+(\alpha b)_{24}+\gamma_3+(\alpha\gamma)_{23}$
$\mu_{244}= \mu+\alpha_2+b_4+(\alpha b)_{24}+\gamma_4+(\alpha\gamma)_{24}$
$\mu_{251}= \mu+\alpha_2+b_5+(\alpha b)_{25}+\gamma_1+(\alpha\gamma)_{21}$
$\mu_{252}= \mu+\alpha_2+b_5+(\alpha b)_{25}+\gamma_2+(\alpha\gamma)_{22}$
$\mu_{253}= \mu+\alpha_2+b_5+(\alpha b)_{25}+\gamma_3+(\alpha\gamma)_{23}$
$\mu_{254}= \mu+\alpha_2+b_5+(\alpha b)_{25}+\gamma_4+(\alpha\gamma)_{24}$
$\mu_{261}= \mu+\alpha_2+b_6+(\alpha b)_{26}+\gamma_1+(\alpha\gamma)_{21}$
$\mu_{262}= \mu+\alpha_2+b_6+(\alpha b)_{26}+\gamma_2+(\alpha\gamma)_{22}$
$\mu_{263}= \mu+\alpha_2+b_6+(\alpha b)_{26}+\gamma_3+(\alpha\gamma)_{23}$
$\mu_{264}= \mu+\alpha_2+b_6+(\alpha b)_{26}+\gamma_4+(\alpha\gamma)_{24}$

sum= $24\mu+24\alpha_2+ 4b_1+ 4b_2+ 4b_3+4 b_4+ 4b_5+ 4b_6+4(\alpha b)_{21}+4(\alpha b)_{22}+4(\alpha b)_{23}+4(\alpha b)_{24}+ 4(\alpha b)_{25}+ 4(\alpha b)_{26}+$
$6\gamma_1+ 6\gamma_2+6 \gamma_3+6 \gamma_4+6(\alpha\gamma)_{21}+6(\alpha\gamma)_{22}+ 6(\alpha\gamma)_{23}+6(\alpha\gamma)_{24}$
Mean yield for Ladak=sum/24

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Inference Space and EBLUP split plot

<u>mean of Ladak in narrow inference space:</u>

int 24 variety 0 24 0 date 6 6 6 6 variety*date 0 0 0 0 6 6 6 6 |

block 4 4 4 4 4 4 variety*block 0 0 0 0 0 0 4 4 4 4 4 4 / divisor=24;

<u>mean of Ladak in intermediate inference space:</u>

int 24 variety 0 24 0 date 6 6 6 6 variety*date 0 0 0 0 6 6 6 6 |
block 4 4 4 4 4 4 / divisor=24;

<u>mean of Ladak in broad inference space:</u>

int 24 variety 0 24 0 date 6 6 6 6 variety*date 0 0 0 0 6 6 6 6 /
divisor=24;

splitplotinferencespace