African Mathematical School

Linear mixed effect models: applications in R

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Outline

Recall: Framework of linear models

Introduction

- Types of factors and their related effects
- Model specification
- Estimation of coefficients
- Significance tests of the coefficients
- Overview on random intercept and slope models
- Applications in R

Conclusion

Recall: Framework of linear models

Example

Test whether salt water impacts blood pressure in mice.

Experiment A

10 mice fed with plain water and 10 with salt water; and the blood pressure (BP) measured.

$$BP = \alpha + \beta X + \epsilon$$

X = water type (categorical variable $\Longrightarrow$ Analysis of variance).

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Experiment B

20 mice fed with increasing concentration of salt in water starting with plain water.

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X = salt concentration
quantitative variable $\Longrightarrow$ Linear regression.

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Experiment C

Increasing salt concentration in water administrated to mice and number of death (N) is counted.

$$Log\ N = \alpha + \beta X + \epsilon$$

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Experiment D

Consideration of 10 mice that tolerate salt water and 10 other for which BP is affected by salt water; Mg^{2+} and Ca^{2+} measured.

$$Log \frac{P(T|Mg^{2+};Ca^{2+})}{1-P(T|Mg^{2+};Ca^{2+})} = \alpha + \beta_1 Mg^{2+} + \beta_2 Ca^{2+} + \epsilon$$

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Experiment E

10 mice fed with plain water and 10 with salt water; but various mice weight.

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10 mice fed with plain water and 10 with salt water; but various weight and 3 different mothers.

$$BP = \underbrace{\alpha + \beta X + \lambda Weight}_{\text{Fixed part}} + \underbrace{\gamma Mother + \epsilon}_{\text{Random part}}$$

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g(Y) = log(Y) $\Longrightarrow$ Poisson models and its extensions

g(Y) = -$\frac{1}{Y}$ $\Longrightarrow$ Gamma models

g(Y) = g(P(Y=1|X=x)) = log $\frac{P(Y=1|X=x)}{1-P(Y=1|X=x)}$

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Introduction

Example 1

30 female rats were randomly assigned to receive one of three doses (high, low,or control) of an experimental compound.

Objective: Comparison of the birth weights of pups from litters born to female rats that received the high, low-dose to those from control female.

Factor "dose" is fixed whereas factor "litter" is random.

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Analysis of variance (ANOVA)

- Applicable to mixed models
- Same estimation procedure of fixed and random effects
- Reduction of estimation bias by fixing the error term for each main factor in order to compute Fisher statistic
- **Consequences**: Some bias remained in the ANOVA model

Introduction

1861 ⇒ First known formulation of a one-way random-effects model (an model with one random factor and no fixed factors) is that by **Airy**, which was further clarified by Scheff in 1956.

Airy made several telescopic observations on the same night (clustered data) for several different angles and analyzed the data separating the variance of the random night effects from the random within-night residuals.

1863 ⇒ **Chauvenet** calculated variances of random effects in a simple random-effects model.

1947 ⇒ **Eisenhart** introduced the mixed model terminology and formally distinguished between fixed- and random-effects models.

1990s onward ⇒ Linear mixed models are becoming increasingly popular method.

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- Statistical models for continuous outcome variables in which fixed and random factors are present.
- The residuals are normally distributed but may not be independent or have constant variance contrary to *standard linear models*.

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1. Studies with clustered data, such as students in classrooms, or experimental designs with random blocks, such as batches of raw material for an industrial process
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Types of factors and their related effects

Fixed factor

A categorical or classification variable, for which the investigator has included all levels (or conditions) that are of interest in the study.

Types of factors and their related effects

Fixed factor

Fixed factors might include:

- qualitative covariates, such as gender
- classification variables implied by:
  - a survey sampling design, such as region or stratum
  - a study design, such as the treatment method in a randomized clinical trial
- ordinal classification variables in an observational study, such as age group.

Example: 3 varieties of maize compared in an experiment. Factor "variety" is fixed.

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- A classification variable with levels that can be thought of as being randomly sampled from a population of levels being studied.
- All possible levels of the random factor are not present in the data set, but it is the researchers intention to make inferences about the entire population of levels.

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Nested factor

- A factor is nested (to another) when its levels change according to the levels of the main factor.
- In addition, a nested factor is always random.
- Its effects on the response variable are known as nested effects.

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- Fixed effects, called regression coefficients or fixed-effect parameters, describe the relationships between the dependent variable and predictor variables (i.e., fixed factors or continuous covariates).
- Fixed effects may describe:
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Fixed effects versus Random effects

- Random effects are random values associated with the levels of a random factor (or factors).
- They represent random deviations from the relationships described by fixed effects.

For instance:

⇒ random intercepts (representing random deviations for a given subject or cluster from the overall fixed intercept).

⇒ random coefficients (representing random deviations for a given subject or cluster from the overall fixed effects).

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$$(1) \begin{cases} y_i = X_i\beta + Z_i\gamma_i + \epsilon_i \\ \gamma_i \sim N(0, G_i) \\ \epsilon_i \sim N(0, \Sigma_i) \\ \gamma_i \text{ and } \epsilon_i \text{ must be independent.} \end{cases}$$

y_i: vector of i^{th} observation of the dependent variable;
X_i: known matrix of fixed observations ;
β: fixed coefficients ;
Z_i: known matrix of random observations ;
γ_i: random coefficients ;
ϵ_i: error linked with the i^{th} observation.

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y_i: vector of i^{th} observation of the dependent variable;
X_i: known matrix of fixed observations ;
β: fixed coefficients ;
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Model specification

Example for model specification

Let consider the following dataset

Plot	Block	Variety	Dose	Yield
1	1	1	0	1.7
2	1	1	30	1.7
3	1	2	0	1.3
4	1	2	30	1.5
5	2	1	0	1.2
6	2	1	30	1.4
7	2	2	0	1.0
8	2	2	30	1.2
9	3	1	0	1.4
10	3	1	30	2.0
11	3	2	0	1.7
12	3	2	30	2.2
13	4	1	0	1.9
14	4	1	30	2.3
15	4	2	0	1.5
16	4	2	30	1.8

Model specification

Example for model specification

$$\text{Yield}_{ijk} = \underbrace{\beta_0 + \beta_j \text{Variety}_j * \text{Dose}_k}_{\text{Fixed effects}} + \underbrace{\alpha_{0i} + \alpha_{1i}\text{Block}_i}_{\text{Random effects}} + \varepsilon_{ijk}$$

$$\beta = (\beta_0, \beta_{ij})' \quad ; \quad \gamma = (\alpha_{0k}, \alpha_{1k})'$$

i=1, 2, 3; 4 ; j=1, 2 ; k=0, 30

Model specification

Example for model specification

$$\text{Yield} = X\beta + Z\gamma + \varepsilon$$

$$
\begin{pmatrix} 1.7 \\ 1.7 \\ 1.3 \\ 1.5 \\ 1.2 \\ 1.4 \\ 1.0 \\ 1.2 \\ 1.4 \\ 2.0 \\ 1.7 \\ 2.2 \\ 1.9 \\ 2.3 \\ 1.5 \\ 1.8 \end{pmatrix}
=
\begin{pmatrix}
1 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 \\
1 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 \\
1 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 \\
1 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1
\end{pmatrix}
\begin{pmatrix} b0 \\ b11 \\ b12 \\ b21 \\ b22 \end{pmatrix}
+
\begin{pmatrix}
1 & 1 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 1 & 0 \\
1 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 1 \\
1 & 0 & 0 & 0 & 1
\end{pmatrix}
\begin{pmatrix} u0 \\ u1 \\ u2 \\ u3 \\ u4 \end{pmatrix}
+
\begin{pmatrix} \varepsilon1 \\ \varepsilon2 \\ \varepsilon3 \\ \varepsilon4 \\ \varepsilon5 \\ \varepsilon6 \\ \varepsilon7 \\ \varepsilon8 \\ \varepsilon9 \\ \varepsilon10 \\ \varepsilon11 \\ \varepsilon12 \\ \varepsilon13 \\ \varepsilon14 \\ \varepsilon15 \\ \varepsilon16 \end{pmatrix}
$$

$$y \quad = \quad X \quad * \quad \beta \quad + \quad Z \quad * \quad u \quad + \quad \varepsilon$$

Estimation of coefficients

Estimation of β and $\alpha_i (i = 1, \ldots, g)$ in Gaussian models

Maximum likelihood estimation (ML)

Under a Gaussian mixed model, we have:

y$\sim N(X\beta, V)$ with $V_i(\theta_k)$=Σ_i+$Z_i G_i Z_i'$, $k = 1, \ldots, q$; $i = 1, \ldots, g$

$f(y) = \frac{1}{(2\pi)^{\frac{n}{2}} |V|^{\frac{1}{2}}} exp\{-0.5(y - X\beta)' V^{-1} (y - X\beta)\}$

$$V_i(\theta_k) = \begin{pmatrix} G_i & 0 \\ 0 & \Sigma_i \end{pmatrix}$$

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$$L(\beta, \theta) = \prod_{i=1}^{n} f(y_i)$$

Thus, the log-likelihood function is:

$$l(\beta, \theta) = ln[L(\beta, \theta)] = c - \frac{1}{2} ln(|V|) - \frac{1}{2}(y - X\beta)' V^{-1}(y - X\beta) \quad (2)$$

$$\frac{\partial l}{\partial \beta} = X' V^{-1} y - X' V^{-1} X\beta = 0 \quad (3)$$

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Maximum likelihood estimation (ML)

$$(3) \Rightarrow y' P \frac{\partial V}{\partial \theta_k} P y = tr(V^{-1} \frac{\partial V}{\partial \theta_k}) \quad (4)$$

with $P = V^{-1} - V^{-1}X(X'V^{-1}X)^{-1}X'V^{-1}$ (5)

In Gaussian models, $\sigma_i^2 = \sigma^2$ (equality of variances) $\Rightarrow \Sigma = \sigma^2 I_n$
σ^2 is the variance of residual error.

$$G = \sum_{i=1}^{g} \tau_i^2 Z_i Z_i'$$

τ_i^2 represent the variance of the ith random component.

$$V = \sigma^2 I_n + \sum_{i=1}^{g} \tau_i^2 Z_i Z_i' \quad (6)$$

and $\frac{\partial V}{\partial \sigma^2} = I_n$; $\frac{\partial V}{\partial \tau_i^2} = Z_i Z_i'$

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Maximum likelihood estimation (ML)

(4) becomes

$$\begin{cases} y'P^2y = tr(V^{-1}) \\ y'PZ_iZ_i'Py = tr(V^{-1}Z_iZ_i') \quad P \text{ is defined as in (5)} \end{cases} \tag{7}$$

Newton-Raphson algorithm for the computation of β and V.

Step 1. Compute β using OLE (Ordinary Least square Estimation).

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

Step 2. Use $\hat{\beta}$ to compute $l(\beta, \theta)$ using (2).

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Step 6. Repeat these steps until convergence. A convergence criterion is linked with a slight change, about 10^{-9} in $\hat{\beta}$ or 0.01 of change in $l(\beta, \theta)$

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Estimation of coefficients

Estimation of β and $\alpha_i (i = 1, \ldots, g)$ in Gaussian models

Restricted Maximum likelihood estimation (REML)

The ML of the variance components are generally biased.

In the REML approach, estimation of fixed effects is suppressed to have good estimation of the random effects (variance components) and fixed effects are only estimated using ML (robust for non Gaussian models).

Thus, under a Gaussian mixed model, we have:

$$l_R(\theta) = l(\beta, \theta) - \frac{1}{2} ln|X'V^{-1}X|$$

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The same procedure described above is used.

Estimation of coefficients

Estimation of β and $\alpha_i (i = 1, \ldots, g)$ in Gaussian models

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Estimation of coefficients

Estimation of β and $\alpha_i (i = 1, \ldots, g)$ in non-Gaussian models

REML and ML procedures

Two Non Gaussian models will be considered: ANOVA models with non normal y and longitidunal models (repeated measures).

Non Gaussian ANOVA models

Quasi-Likelihood Method

In Quasi-Likelihood Method, the idea is to use normality-based estimators of $\hat{\theta}$ using REML equations and compute $\hat{\beta}$ using ML equations. Then,

The REML equations are:

$$\begin{cases} \hat{y}'\hat{P}^2\hat{y} = tr(P) \\ \\ \hat{y}'\hat{P}Z_iZ_i'\hat{P}\hat{y} = tr(Z_i'PZ_i) \end{cases}$$

The ML equations are:

$$\begin{cases} X'\hat{V}X\hat{\beta} = X'\hat{V}^{-1}\hat{y} \\ \hat{y}'\hat{P}^2\hat{y} = tr(\hat{V}^{-1}) \\ \hat{y}'\hat{P}Z_iZ_i'\hat{P}\hat{y} = tr(Z_i'\hat{V}^{-1}Z_i) \end{cases}$$

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Estimation of coefficients

Estimation of β and $\alpha_i (i = 1, \ldots, g)$ in non-Gaussian models

REML and ML procedures

Two Non Gaussian models will be considered: ANOVA models with non normal y and longitidunal models (repeated measures).

Non Gaussian ANOVA models

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Iterative weighted Least Squares

Balanced case

The Best Linear Unbiased Estimator (BLUE) for β is given by:

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

where $\hat{V} = diag(\hat{V}_0, \ldots, \hat{V}_0)$;

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$$\hat{V}_{0i} = \hat{V}_0$$

The Newton-Raphson algorithm is used to compute $\hat{\beta}$ and $\hat{V}$.

Iterative Weighted Least square (I-WLS)

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Thus, the algorithm can be expressed as follows:

$\hat{\beta}^{(2h-1)} = f\{\hat{v}^{(2h-2)}\}$; $\hat{v}^{(0)} = (\delta_{q,r}) = \begin{cases} 1 & \text{if } q = r \\ 0 & \text{if } q \neq r \end{cases} = I_k$

$\hat{v}^{(2h)} = g\{\beta^{(2h-1)}\}$;

$$f\{v\} = (\sum_{i=1}^{g} X_i' V_i^{-1} X_i)^{-1} (\sum_{i=1}^{g} X_i' V_i^{-1} y_i)$$

$$g(\beta) = \frac{1}{m_{qr}} \sum_{i(q,r=1,\ldots,k)}^{m} (y_{iq} - x_{iq}'\beta)(y_{ir} - x_{ir}'\beta)$$

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Significant tests of the coefficients

These tests are used to test significance of β_i and γ_i because true values of these parameters are not available (iterative process).

Wald test

It is often used to test significance of vector β and sometimes used to test covariance parameters associated with random effects (γ_i)

In general, for each known matrix L(r,p):

$H_0 : L'\beta = 0$ and $H_1 : L'\beta \neq 0$

$$W = \hat{\beta}L'(L(\sum_i X_i' \hat{V}_i^{-1} X_i)^{-1} L')^{-1} L\hat{\beta}$$

W$\sim \chi^2$ distribution with rank(L) as the degree of freedom.

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It is often used for testing a single fixed-effect parameter.

For each parameter β_j of β a t test can be approximated. The two hypotheses are the same as for the wald test.

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F-test can be used to test linear hypotheses about multiple fixed effects. In other words, it is used to test significance of vector β.

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The number of degree of freedom of the numerator is equal to the rank of matrix L.

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Likelihood ratio test (LRT): The LRT can be used to test linear hypotheses about fixed-effect parameters based on ML estimation. However, when testing hypotheses about covariance parameters associated with random effects, REML estimation should be used.

Likelihood ratio (deviance, Neyman-Pearson)

λ = Statistic of likelihood ratio test

Under H_0 $\lambda = -2log\frac{L_R}{L_C}$

$$\lambda = -2L_R + 2L_C \rightarrow \chi^2_r$$

L_R: max of the log likelihood under the reduced model H_0

L_C: max of the log likelihood under the complete model H_1

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Overview on random intercept and random slope models

Random intercept and random slope models

It belong to the general framework of multilevel models

Suppose a model in which:

$j = 1, \ldots, N$ blocks (e.g. two varieties of maize (A and B) are considered within each block)

$i = 1, \ldots, n_j$ subjects within the groups (e.g. experimental pot)

$k = 1, \ldots, p_{ijk}$ times of measurements (e.g. everyday or month)

Y_{ij} a numerical response variable (e.g. agronomic performance of varieties in height, number of corncobs, yield)

x_{ij} explanatory variables (e.g. variety and block)

$$y_{ij} = \beta_{0j} + \beta_1 Variety + \beta_{2j} Block + \epsilon_{ij} \tag{1}$$

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β_{0j} depends on each block (1, ..., N)

β_1 is fixed in the population

β_{2j} also depends on each block (1, ..., N)

$\epsilon_{ij} \sim N(0, \sigma^2)$ and independent

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The intercept, β_{0j} can be broken down into two parts:

- An overall or average value of the intercept (constant): γ_{00}
- A block dependent part of the intercept: γ_{0j}

Thus,

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By replacing (2) and (3) in (1):

$$y_{ij} = (\gamma_{00} + \gamma_{0j}) + \beta_1 Variety + (\Psi_{00} + \Psi_{0j}) Block + \epsilon_{ij}$$

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$\Rightarrow$ Analysis of variance

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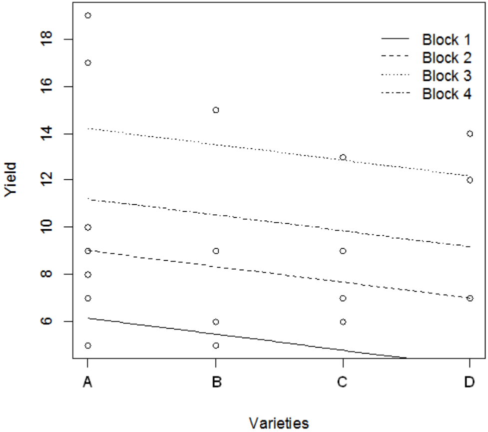
If only γ_{0j} are random parameters in the population

$\Rightarrow$ Random intercept model



Overview on random intercept and random slope models

$$y_{ij} = (\gamma_{00} + \gamma_{0j}) + \beta_1 Variety + (\Psi_{00} + \Psi_{0j}) Block + \epsilon_{ij}$$

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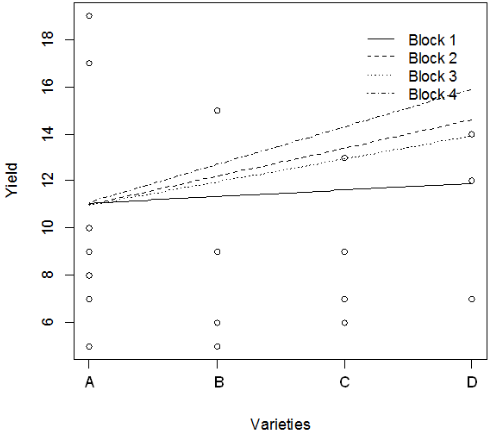
$\Rightarrow$ Random slope model



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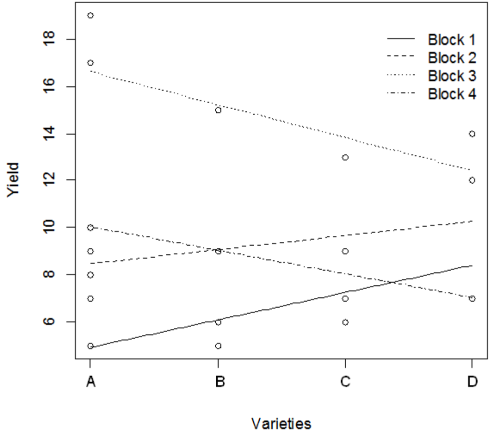
If γ_{0j} and Ψ_{0j} are random parameters in the population

$\Rightarrow$ Random intercept and random slope model



Applications in R

Recall of fixed and random models

A $<-$ **as.factor(A)** # for a non-categorical variable

B $<-$ **as.factor(B)** # for a non-categorical variable

- Two fixed factors: A and B

  lm(Y $\sim$ A*B) or lm(Y $\sim$ A+B+A:B)

- Two random factors: A and B

  library(lmerTest) or require(lmerTest)

  lmer(Y $\sim$ 1+(1|A)+(1|B)) # Restricted maximum likelihood

  lmer(Y $\sim$ 1+(1|A)+(1|B), REML = FALSE) # Maximum likelihood

  The package "nlme" is not used because of the nested order implicitly considered between random factors.

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Applications in R

Recall of fixed and random models

- Three fixed factors: A, B and C

  lm(Y ~ A*B*C) or lm(Y ~ A+B+C+A:B+A:C+B:C+A:B:C)

- Three random factors: A, B and C

  library(lmerTest) or require(lmerTest)

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Applications in R

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Applications in R

Implementation of LMEMs

- Function *lme* in package *nlme*
- Function *lmer* in package *lme4* or *lmerTest*
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  - Full model

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  - Random intercept and random slope model

  lme(Y $\sim$ A, random = $\sim$A|B)
  lmer(Y $\sim$ A + (A|B))

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Applications in R

Implementation of LMEMs

- Three factors: A and B fixed; C random

  - Full model

  lmer(Y ∼ A*B + (1|C) + (1|A:C)) + (1|B:C) + (1|A:B:C))

  - Random intercept and random slope model

  lme(Y ∼ A*B, random = ∼1+A+B|C)
  lmer(Y ∼ A*B + (1+A+B|C))

  - Random intercept model

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Applications in R

Implementation of LMEMs

- Three factors: A and B fixed; C random

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lmer(Y ~ A*B + (1|C) + (1|A:C)) + (1|B:C) + (1|A:B:C))

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lme(Y ~ A*B, random = ~1+A+B|C)
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Applications in R

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Applications in R

Implementation of LMEMs

- Two factors: A fixed; B nested in A

  - Random intercept and random slope model

  lme(Y ~ A, random = ~1+A|B)
  lmer(Y ~ A + (1+A|B))

  - Random intercept model

  lme(Y ~ A, random = ~1|B) instead of lme(Y ~ A, random = ~1|A/B)

  lmer(Y ~ A + (1|B)) instead of lmer(Y ~ A + (1|A/B))

Applications in R

Implementation of LMEMs

- Two factors: A fixed; B nested in A

  - Random intercept and random slope model

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Applications in R

Implementation of LMEMs

- Two factors: A fixed; B nested in A

  - Random intercept and random slope model

  lme(Y ~ A, random = ~1+A|B)
  lmer(Y ~ A + (1+A|B))

  - Random intercept model

  lme(Y ~ A, random = ~1|B) instead of lme(Y ~ A, random = ~1|A/B)

  lmer(Y ~ A + (1|B)) instead of lmer(Y ~ A + (1|A/B))

Applications in R

Implementation of LMEMs

- Two factors: A random; B nested in A

  lme(Y $\sim$ 1, random = $\sim$1|A/B)
  lmer(Y $\sim$ 1 + (1|A/B))

Applications in R

Implementation of LMEMs

- Two factors: A random; B nested in A

  lme(Y ~ 1, random = ~1|A/B)
  lmer(Y ~ 1 + (1|A/B))

Applications in R

Implementation of LMEMs

- Three factors: A and B fixed; C nested in A and B

  - Random intercept and random slope model

  lme(Y ∼ A*B, random = ∼1+A*B|C)
  lmer(Y ∼ A*B + (1+A*B|C))

  - Random intercept model

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Applications in R

Implementation of LMEMs

- Three factors: A fixed ; B random; C nested in A and B

  - Full model

  lmer(Y ∼ A + (1|B) + (1|A:B) + (1|B/C))

  - Random intercept and random slope model

  lme(Y ∼ A, random = ∼1+A|B/C)
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Implementation of LMEMs

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  \- Random intercept and random slope model

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Applications in R

Implementation of LMEMs

- Three factors: A fixed ; B random; C nested in A and B

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- library(nlme) or require(nlme)
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Applications in R

Comment of results

Case of *lmerTest* package

The fixed effects are analysed using probability values [**Pr**($>$ |**t**|)].

The random effects are analysed by:

- Using the function *rand* followed by the name of the model in bracket to get *p-value*
- Comparing the variance of random factor (σ_r^2) to the one of experimental error (σ_e^2)

- If p-value $< \alpha$ (0.05) or $\sigma_r^2 \geq \sigma_e^2$, the random effect is significant. It must be considered in the model.
- If p-value $\geq \alpha$ (0.05) or $\sigma_r^2 < \sigma_e^2$, the random effect is not significant. A standard linear model can be considered instead of linear mixed effect model.

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Applications in R

Exercise 1

Four leaves were randomly sampled from a larger population of leaves and four discs were taken from each leaf. The calcium contents were measured (see worksheet 1).

Test first of all effect of leaves and then effects of leaves and discs using R (maximum likelihood estimation and restricted maximum likelihood estimation) and compare their outputs.

Exercise 2

Four plants were randomly sampled from a larger population of plants, and three leaves were randomly taken from each plant, and two discs were taken from each leaf. The calcium Contents were measured. (See worksheet 2.).

Test effect first of all effect of plants and leaves and then effect of plants, leaves and discs using R (maximum likelihood estimation and restricted maximum likelihood estimation) and compare their outputs.

Exercise 3

A pig farmer wants to compare the genetic quality of male pigs. He has five sires and 10 dams, and allocates two dams to each sire. The weight of two piglets per litter is then monitored and their weight gain over a 2-week period was measured.

Test effect of sire and dams using R (maximum likelihood estimation and restricted maximum likelihood estimation) and compare their outputs.

Exercise 4

Glycogen was measured on 2 rats allocated per Treatment (3 treatments were considered). Each rats liver was cut into 3 pieces and each piece was further divided into two.

Test effect of treatment, rat and liver on the glycogen using R (maximum likelihood estimation and restricted maximum likelihood estimation) and compare their outputs.

Thank You
For Your Kind Attention!