

BIOS 755: Linear Mixed Models II

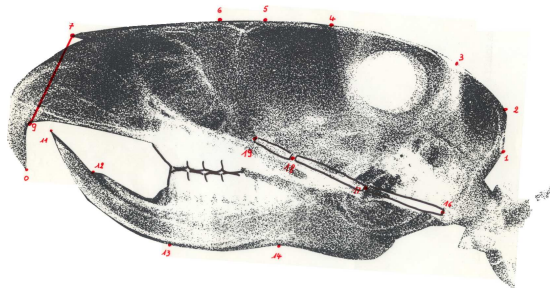
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Rat Data

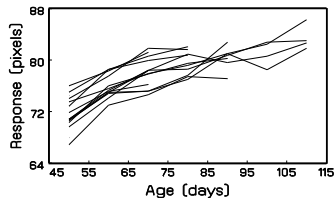
- ▶ Randomized experiment in which 50 male Wistar rats are randomized to:
 - ▶ Control (15 rats)
 - ▶ Low dose of Decapeptyl (18 rats)
 - ▶ High dose of Decapeptyl (17 rats)population.
- ▶ Question of interest: How does craniofacial growth depend on testosterone production?

Rat Data

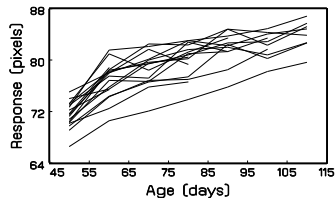
- ▶ Treatment starts at 45 days; measurements are taken every 10 days from day 50 on.
- ▶ The responses are distances (pixels) between well-defined points on x-ray pictures of the skull of each rat:



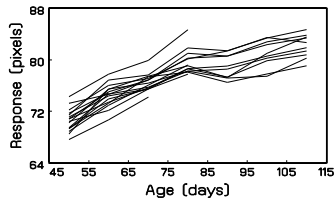
- ▶ We'll consider only one response: the height of the skull.
- ▶ Individual profiles: Control



Low dose



High dose



Models under consideration

- Let's consider the model:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 L_i + \beta_2 H_i + \beta_3 C_i + b_{1i})t_{ij} + \varepsilon_{ij}$$
$$= \begin{cases} (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \varepsilon_{ij}, & \text{if low dose} \\ (\beta_0 + b_{0i}) + (\beta_2 + b_{1i})t_{ij} + \varepsilon_{ij}, & \text{if high dose} \\ (\beta_0 + b_{0i}) + (\beta_3 + b_{1i})t_{ij} + \varepsilon_{ij}, & \text{if Control} \end{cases}$$

Where the covariance of the random effects is

$$\mathbf{D} = \text{cov}(\mathbf{b}) = \begin{pmatrix} d_{11} & d_{12} \\ d_{12} & d_{22} \end{pmatrix}$$

Linear Mixed representation

- ▶ What are the \mathbf{X} and \mathbf{Z} from the linear mixed model that corresponds to this model?
- ▶ What is the implied mean structure?
- ▶ What is the implied variance of Y_{ij} ?

Linear Mixed representation

- What is the implied marginal Variance of Y_{ij} ?

$$\begin{aligned} \text{Var}(Y_{ij}) &= \begin{pmatrix} 1 & t_{ij} \end{pmatrix} \mathbf{D} \begin{pmatrix} 1 \\ t_{ij} \end{pmatrix} + \sigma^2 \\ &= (d_{11} + \sigma^2) + 2d_{12}t_{ij} + d_{22}t_{ij}^2 \end{aligned}$$

where

Analysis

- ▶ The following model was fitted to the data

$$Y_{ij} = (\beta_0 + b_{1i}) + (\beta_1 L_i + \beta_2 H_i + \beta_3 C_i + b_{2i})t_{ij} + \varepsilon_{ij}$$

- ▶ The REML estimates obtained from PROC Mixed are:

Effect	Parameter	REMLE (s.e.)
Intercept	β_0	68.606 (0.325)
Time effects:		
Low dose	β_1	7.503 (0.228)
High dose	β_2	6.877 (0.231)
Control	β_3	7.319 (0.285)
Covariance of b_i :		
var(b_{1i})	d_{11}	3.369 (1.123)
var(b_{2i})	d_{22}	0.000 (—)
cov(b_{1i}, b_{2i})	$d_{12} = d_{21}$	0.090 (0.381)
Residual variance:		
var(ε_{ij})	σ^2	1.445 (0.145)
REML log-likelihood		-466.173

Analysis

- ▶ This suggests that the REML likelihood could be further increased by allowing negative estimates for d_{22} .
- ▶ In SAS, this can be done by adding the option `nobound` to the PROC MIXED statement.

- ▶ Results:

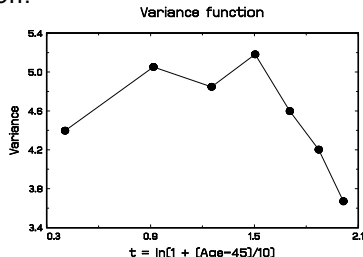
Effect	Parameter	Parameter restrictions for α	
		$d_{ii} \geq 0, \sigma^2 \geq 0$	$d_{ii} \in \mathbb{R}, \sigma^2 \in \mathbb{R}$
		REMLE (s.e.)	REMLE (s.e.)
Intercept	β_0	68.606 (0.325)	68.618 (0.313)
Time effects:			
Low dose	β_1	7.503 (0.228)	7.475 (0.198)
High dose	β_2	6.877 (0.231)	6.890 (0.198)
Control	β_3	7.319 (0.285)	7.284 (0.254)
Covariance of b_i :			
$\text{var}(b_{1i})$	d_{11}	3.369 (1.123)	2.921 (1.019)
$\text{var}(b_{2i})$	d_{22}	0.000 (—)	-0.287 (0.169)
$\text{cov}(b_{1i}, b_{2i})$	$d_{12} = d_{21}$	0.090 (0.381)	0.462 (0.357)
Residual variance:			
$\text{var}(\varepsilon_{ij})$	σ^2	1.445 (0.145)	1.522 (0.165)
REML log-likelihood		-466.173	-465.193

Meaning of a negative variance component

- Fitted variance function

$$\begin{aligned} \text{Var}(Y_{ij}) &= (\hat{d}_{11} + \hat{\sigma}^2) + 2\hat{d}_{12}t_{ij} + \hat{d}_{22}t_{ij}^2 \\ &= 4.443 + 0.924t - 0.287t_{ij}^2 \end{aligned}$$

- The suggested negative curvature in the variance function is supported by the sample variance function:



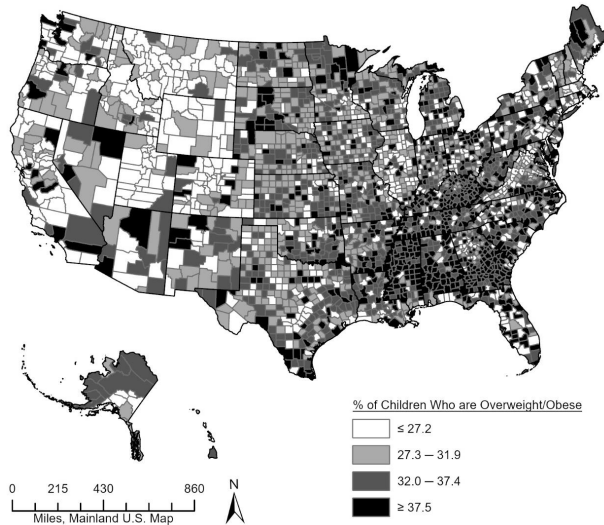
INFERENCE FOR LINEAR MIXED MODELS

Introduction

- ▶ In most applications, inference is focused on the fixed effects, β .
- ▶ However, in some studies we may want to predict (or “estimate”) subject-specific response profiles.
- ▶ Technically, because the \mathbf{b}_i ’s are random, we customarily talk of “predicting” the random effects rather than “estimating” them.
- ▶ The predicted random effects can be used to predict values for all levels in the data.

Example: County level disease rates/summaries.

- ▶ The National Study of Children's Health (NSCH) gathers data from roughly 50K 2–17 year-old children at each survey.
- ▶ The NSCH variables include indicators of ADHD, ASD, and many other conditions.
- ▶ It also includes BMI percentile, and other continuous variables.
- ▶ A regression model with a random county level intercept was fitted.
- ▶ To predict (estimate) county level values, we needed to predict the value of the random effect.



Conditional Expectation

- ▶ For a RE ANOVA model on $Y_{i1}, Y_{i2}, \dots, Y_{in_i}$ we have

$$Y_{ij} = \mu + b_i + e_{ij}$$

with $b_i \sim N(0, G)$ and $e_i \sim N(0, \sigma^2)$.

- ▶ Under this model, the predicted value of the random intercept is

$$E(b_i | Y_i) = \frac{n_i G}{n_i G + \sigma^2} (\bar{Y}_i - \mu)$$

where $\text{Var}(b_i) = G$

Best Linear Unbiased Predictor (BLUP)

- ▶ When Σ_i is known, the estimator for β can be obtained by using ML weighted least square. Then the prediction of \mathbf{b}_i is given by

$$\mathbf{G}\mathbf{Z}_i'\Sigma_i^{-1}(\mathbf{Y}_i - \mathbf{X}_i\hat{\beta}),$$

where

$$\Sigma_i = \text{var}(\mathbf{Y}_i) = \mathbf{Z}_i\mathbf{G}\mathbf{Z}_i' + \mathbf{R}_i$$

- ▶ This is known as the Best Linear Unbiased Predictor (or BLUP).

The BLUP Estimation of Individual Mean

- Finally, the i th subject's predicted response profile is,

$$\begin{aligned}\hat{\mathbf{Y}}_i &= \mathbf{X}_i\hat{\boldsymbol{\beta}} + \mathbf{Z}_i\hat{\mathbf{b}}_i \\ &= \mathbf{X}_i\hat{\boldsymbol{\beta}} + \mathbf{Z}_i\hat{\mathbf{G}}\mathbf{Z}_i'\hat{\boldsymbol{\Sigma}}_i^{-1}(\mathbf{Y}_i - \mathbf{X}_i\hat{\boldsymbol{\beta}}) \\ &= \left(\hat{\mathbf{R}}_i\hat{\boldsymbol{\Sigma}}_i^{-1}\right)\mathbf{X}_i\hat{\boldsymbol{\beta}} + \left(\mathbf{I} - \hat{\mathbf{R}}_i\hat{\boldsymbol{\Sigma}}_i^{-1}\right)\mathbf{Y}_i\end{aligned}$$

- That is, the i th subject's predicted response profile is a weighted combination of the population-averaged mean response profile, $\mathbf{X}_i\hat{\boldsymbol{\beta}}$, and the i th subject's observed response profile \mathbf{Y}_i .

Example: Country level rates of malnutrition.

- ▶ Ending malnutrition is a key outcome in the Sustainable Development Goal (SDG)
- ▶ The 2nd SDG calls for achieving, by 2025, a reduction of stunting and wasting and halt the rise in overweight in children under 5 years of age.
- ▶ Monitoring countries' progress toward the achievement of their SDG targets is an important task, but data sparsity makes monitoring trends challenging.
- ▶ The model fitted for this analysis was

$$Y_{ijk} = \beta' \mathbf{X}_{ijk} + \mathbf{b}'_i \mathbf{B}_{ij} + \mathbf{b}'_{ij} \mathbf{B}_{ijk} + \epsilon_{ij}, \quad (1)$$

for region i , country j , and observation k .

Overweight estimates for East and Central Africa

