# 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 testosteron production?
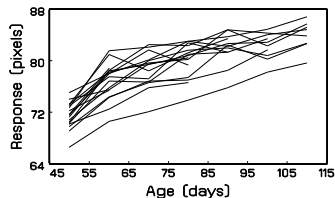
Rat Data

- ▶ Treatment starts at the age of 45 days; measurements 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:
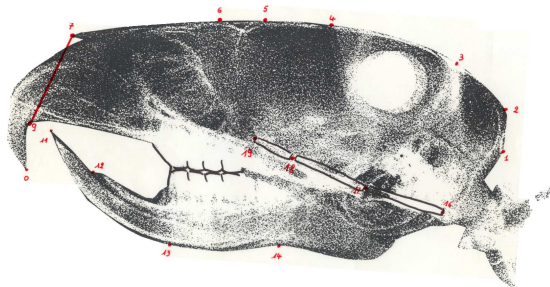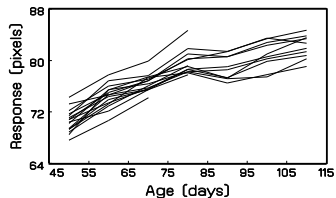
- ▶ We'll consider only one response the height of the skull.
- ▶ Individual profiles:
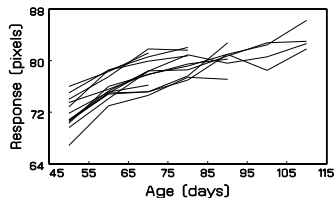
Models under consideration

- 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

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

Linear Mixed representation

- What is the X and Z from the linear mixed model that correspond 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}?

$$
\begin{aligned}
Var(Y_{ij}) &= \left(1 \; t_{ij}\right) \boldsymbol{D} \left(\begin{array}{c} 1 \\ t_{ij} \end{array} \right) + \sigma^2 \\
&= (d_{11} + \sigma^2) + 2d_{12}t_{ij} + d_{22}t_{ij}^2
\end{aligned}
$$

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 $\boldsymbol{b}_i$:		
$\mathrm{var}(b_{1i})$	d_{11}	3.369 (1.123)
$\mathrm{var}(b_{2i})$	d_{22}	0.000 (——)
$\mathrm{cov}(b_{1i}, b_{2i})$	$d_{12} = d_{21}$	0.090 (0.381)
Residual variance:		
$\mathrm{var}(\varepsilon_{ij})$	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:

		Parameter restrictions for α	
		$d_{ii} \geq 0, \sigma^2 \geq 0$	$d_{ii} \in \mathbb{R}, \sigma^2 \in \mathbb{R}$
Effect	Parameter	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:			
var(b_{1i})	d_{11}	3.369 (1.123)	2.921 (1.019)
var(b_{2i})	d_{22}	0.000 (——)	−0.287 (0.169)
cov(b_{1i}, b_{2i})	$d_{12} = d_{21}$	0.090 (0.381)	0.462 (0.357)
Residual variance:			
var(ε_{ij})	σ^2	1.445 (0.145)	1.522 (0.165)
REML log-likelihood		−466.173	−465.193

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Meaning of a negative variance component

▶ Fitted variance function

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

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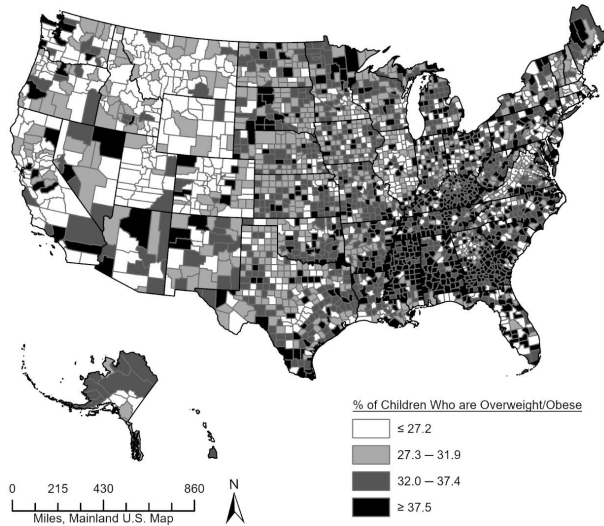

Variance function
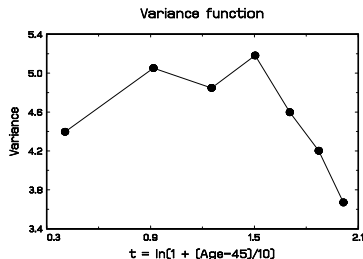
Inference for Linear Mixed Models

Introduction

- In most applications, inference is focused on the fixed effects, $\boldsymbol{\beta}$.
- However, in some studies we may want to predict (or "estimate") subject-specific response profiles.
- Technically, because the $\boldsymbol{b}_i$'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.

% of Children Who are Overweight/Obese

☐	≤ 27.2
☐	27.3 — 31.9
☐	32.0 — 37.4
■	≥ 37.5

0   215   430   860

Miles, Mainland U.S. Map

N

Conditional Expectation

► For a RE ANOVA model on $Y_{i1}, Y_{i2}, \ldots, Y_{in_i}$ we have

$$\mathbf{Y}_{ij} = \mu + b_i + e_{ij}$$

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 $Var(b_i) = G$

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 b_i is given by

$$GZ_i'\Sigma_i^{-1}(Y_i - X_i\hat{\beta}),$$

where

$$\Sigma_i = \text{var}(Y_i) = Z_iGZ_i' + R_i$$

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

Empirical BLUP

▶ In more general cases we use the Best Linear Unbiased Predictor (or BLUP) to predict the random effects.

▶ The formula for this is

$$\hat{\boldsymbol{b}}_i = \hat{\boldsymbol{G}} \boldsymbol{Z}_i' \hat{\Sigma}_i^{-1} (\boldsymbol{Y}_i - \boldsymbol{X}_i \hat{\boldsymbol{\beta}}),$$

is often referred to as the "Empirical BLUP" or the "Empirical Bayes" (EB) estimator.

▶ Furthermore, it can be shown that

$$\text{var}(\hat{\boldsymbol{b}}_i) = \boldsymbol{G} \boldsymbol{Z}_i' \Sigma_i^{-1} \boldsymbol{Z}_i \boldsymbol{G} - \boldsymbol{G} \boldsymbol{Z}_i' \Sigma_i^{-1} \boldsymbol{X}_i \left(\sum_{i=1}^{n} \boldsymbol{X}_i' \Sigma_i^{-1} \boldsymbol{X}_i \right)^{-1} \boldsymbol{X}_i' \Sigma_i^{-1} \boldsymbol{Z}_i \boldsymbol{G}$$

The BLUP Estimation of Individual Mean

- Finally, the ith subject's predicted response profile is,

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

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

BLUP As a Weighted Average

▶ When the between-subject variability is greater than the within-subject variability, more weight is given to the ith subject's observed data $\mathbf{Y}_i$.

▶ One formulation of the predicted values can be written as

$$\hat{\mathbf{Y}}_i = W_i \mathbf{X}_i \hat{\beta}_i^{OLS} + (1 - W_i) \mathbf{X}_i \hat{\beta}$$

where

$$W_i = \frac{n_i D_{11}}{n_i D_{11} + \sigma^2}$$

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

$$Y_{ijk} = \beta' \boldsymbol{X}_{ijk} + \boldsymbol{b}_i' \boldsymbol{B}_{ij} + \boldsymbol{b}_{ij}' \boldsymbol{B}_{ijk} + \epsilon_{ij}, \tag{1}$$

Overweight estimates for East and Central Africa

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