

## Module 2: Linear Mixed Models

BIOS 526

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## Reading

- Ruppert, D., M. Wand, R. Carroll, *Semiparametric Regression*. 4.1 - 4.8 (4.9 is also interesting)
- Wood, S. *Generalized Additive Models*. Chapter 2.
- Reference for syntax: Table 2 in Bates et al. (2015), Fitting Linear Mixed-Effects Models Using lme4. *Journal of Statistical Software*.

## Concepts

- Mixed models for data that are not independent, e.g., clustered data, repeated measures.
- Structure and notation for clustered data.
- Random intercept model: motivation and interpretation.
- Shrinkage estimation and BLUPs of random effects.
- Random slope model.
- Hierarchical formulation of random effect model.

# Examples of Clustered Data

## 1. Longitudinal Data:

E.g., observations  $y_{ij}$

Repeated measurements (**level-1**), e.g.,  $j = 1, \dots, r$ ,  
on each subject (i.e., group, **level-2**), e.g.,  $i = 1, \dots, n$ .

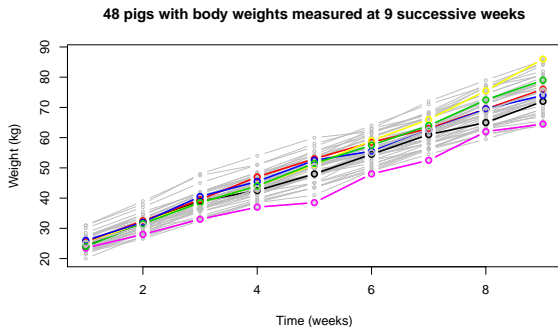
- In a sample of students across years, *annual math score* from each **student**.
- In a sample of patients, **CD4+ cell counts** of each **HIV patient** *visit* past seroconversion.

## 2. Multilevel Data: observations (**level-1**) nested within groups (**level-2**).

- Time series of **daily mortality counts** for a **city** in the US, with data from multiple cities.
- Occurrence of **medical errors** in a **hospital** in Atlanta.

Clusters or groups represent a collection of units from a **population** of similar units.

# Longitudinal data: Pig Weight



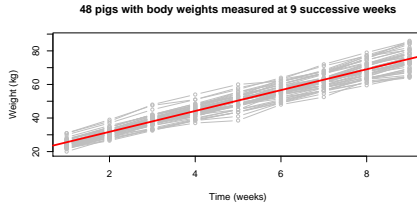
Let  $y_{ij}$  be the weight (kg) at the  $j^{\text{th}}$  week for the  $i^{\text{th}}$  pig.

## Pig Weight Data Structure

Multilevel data are often represented in the *long* format. Data are grouped by the variable *id*.

```
> pig[1:13,]  
   id weeks weight  
1   1     1   24.0  
2   1     2   32.0  
3   1     3   39.0  
4   1     4   42.5  
5   1     5   48.0  
6   1     6   54.5  
7   1     7   61.0  
8   1     8   65.0  
9   1     9   72.0  
10  2     1   22.5  
11  2     2   30.5  
12  2     3   40.5  
13  2     4   45.0
```

# Approach 1: Incorrect approach ignoring clustered structure



Note:

- 

Issues:

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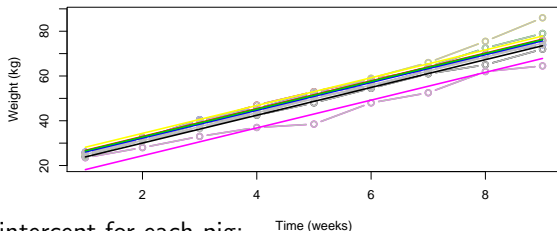
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Limitations:

- Cannot forecast individual pig's growth curve.

## Approach 2: Pig-specific Fixed Effects Model

48 pigs with body weights measured at 9 successive weeks



Separate intercept for each pig: Time (weeks)

Interpretations:

- $\beta_{0i}$  is the **pig-specific** weight at zero and  $\beta_1$  is the constant slope.
- $\sigma^2$  captures **within** pig variability.

Limitations:

- Estimating lots of parameters: subject-specific coefficients don't leverage population information and have less precision because of smaller sample size.
- Cannot forecast the growth curve of a **new** pig.

## Pig Data: Fit Comparison

```
> fit.lm = lm (weight~weeks, data = dat)
> summary(fit.lm)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
(Intercept)	19.35561	0.46054	42.03	<2e-16 ***
weeks	6.20990	0.08184	75.88	<2e-16 ***

Residual standard error: 4.392 on 430 degrees of freedom  
Multiple R-squared: 0.9305, Adjusted R-squared: 0.9303  
F-statistic: 5757 on 1 and 430 DF, p-value: < 2.2e-16

```
> fit.strat = lm (weight~weeks+factor(id)-1, data = dat)
> summary(fit.strat)
```

Coefficients:

	Estimate	Std. Error	t value	Pr(> t )
weeks	6.20990	0.03906	158.97	<2e-16 ***
factor(id)1	17.61719	0.72557	24.28	<2e-16 ***
factor(id)2	20.28385	0.72557	27.96	<2e-16 ***

.  
factor(id)48 25.67274 0.72557 35.38 <2e-16 \*\*\*  
---

Residual standard error: 2.096 on 383 degrees of freedom  
Multiple R-squared: 0.9859, Adjusted R-squared: 0.9841  
F-statistic: 557.8 on 48 and 383 DF, p-value: < 2.2e-16



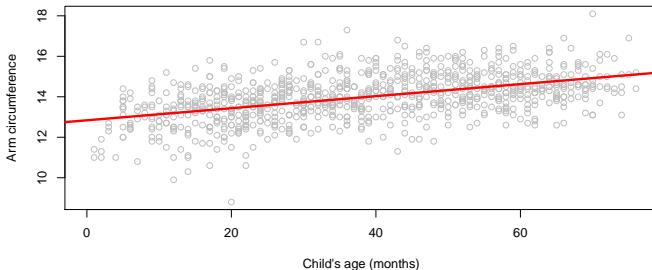
## Pig Data: Summary

- Data are balanced (same number of observations for each pig).
- Here, the slope of week is the same in the model with a single intercept and the model with an intercept for each pig.
- Here, controlling for group-specific intercepts gives a smaller standard error for the slope of weeks.
- Note that oftentimes, the standard error will be larger.  
Pseudo-replication = treating clustered observations as independent.

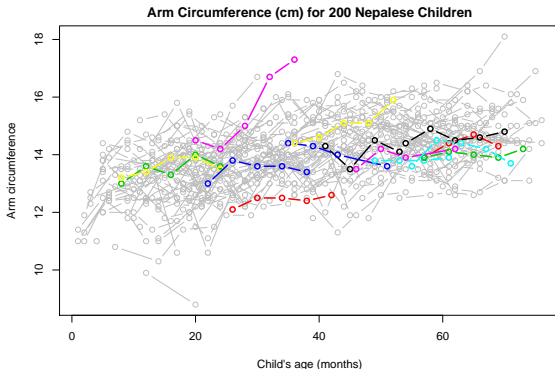
# Longitudinal Example: Nepalese Children

## Study Design:

1. **Time-varying** variables of 200 children collected at 5 time points about 4 months apart:
  - age (month), indicator for current breastfeeding status, arm circumference (cm), height (cm), weight (kg).
2. **Time-invariant** baseline information:
  - sex of the child, mother's age at birth, indicator of mother's literacy, parity.



# Longitudinal Example: Nepalese Children



**Scientific questions** about arm circumference and age:

- What is the **overall** trend?
- How much do growth patterns **differ** between children?
- Do maternal covariates **explain variability** in growth patterns between children?
- How do we **predict** the growth pattern of a **new** child?

## Nepalese Data: Fit Comparison

```
> fit.incorrect = lm (arm~age, data = nepal)
> summary (fit.incorrect)
      Estimate Std. Error t value Pr(>|t|)
(Intercept) 12.838182   0.075987  168.95  <2e-16 ***
age          0.029789   0.001798   16.56  <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Residual standard error: 0.9849 on 880 degrees of freedom

```
> nepal$fid = factor(nepal$id)
> fit.fixedeffects = lm (arm~age+fid, data = nepal)
> summary (fit.fixedeffects)
      Estimate Std. Error t value Pr(>|t|)
(Intercept) 12.626381   0.287480  43.921  < 2e-16 ***
age          0.031354   0.003073  10.204  < 2e-16 ***
fid2         -0.276657   0.354961  -0.779  0.436013
.
fid199        0.950442   0.344728   2.757  0.005988 **
fid200       -2.112362   0.364621  -5.793  1.05e-08 ***
Residual standard error: 0.4972 on 684 degrees of freedom
```

## Fit Comparison

- Note that the effects of age are different.
- Here, controlling for group-specific intercepts gives a larger standard error. (Allows for valid inference.)

## Mixed model: Random Intercept

Consider the random intercept model with a vector of predictors  $\mathbf{x}_{ij}$ :

- $\mu =$
- $\theta_i =$
- $\beta_{0i} = \mu + \theta_i =$
- $\beta$
- $\tau^2 =$
- $\sigma^2 =$

Mixed model:  $\theta_i$  is a **random variable**.  $\beta$  are fixed.

## Mixed model: Random Intercept

The following two models are equivalent:

$$\text{Model 1: } y_{ij} = (\mu + \theta_i) + \mathbf{x}'_{ij}\boldsymbol{\beta} + \epsilon_{ij}, \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$$

Model 1 is often referred to as a **mixed model** formulation where we assume the random coefficients  $\theta_i$  have mean zero.

Model 2:

Model 2 is often referred to as a **hierarchical model** formulation, where the random coefficients  $\beta_{0i}$  have a *higher-level* mean  $\mu$ .

Assumptions:

- $\epsilon_{ij} \perp\!\!\!\perp \theta_i$  (where  $\perp\!\!\!\perp$  = independent) for all  $i$  and  $j$ .
- $\theta_i$  are independent Normal for all  $i$ .

# Properties of the Random Intercept Model

$$y_{ij} = \mu + \theta_i + \mathbf{x}'_{ij}\boldsymbol{\beta} + \epsilon_{ij}, \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$$

- Overall (average) trend:
- Total variability around the overall trend:
- Conditional (group-specific) trend:
- Conditional (within-group) residual variance:



## Pig Data Approach 3: Random Intercept Model

```
> library(lmerTest)
> fit.randomeffects = lmer(weight~weeks+(1|id), data = pig)
> summary(fit.randomeffects)
Linear mixed model fit by REML. t-tests use Satterthwaite's method ['lmerModLmerTest']
Formula: weight ~ weeks + (1 | id)
Data: pig

REML criterion at convergence: 2033.8

Scaled residuals:
    Min       1Q   Median       3Q      Max
-3.7390 -0.5456  0.0184  0.5122  3.9313

Random effects:
Groups   Name             Variance Std.Dev.
id       (Intercept)    15.142     3.891
Residual                    4.395     2.096
Number of obs: 432, groups: id, 48

Fixed effects:
              Estimate Std. Error    df t value Pr(>|t|)
(Intercept)  19.35561    0.60314  58.55889   32.09  <2e-16 ***
weeks        6.20990    0.03906 383.00000   158.97  <2e-16 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Correlation of Fixed Effects:
      (Intr)
weeks -0.324
```

Compared to a model fitted with group dummy variables, the *weeks* slope estimate and SE are identical.

# Nepalese Children: Random Intercept Model

```
> fit = lmer (arm ~ age + (1|id), data = nepal)
> random.eff.nepal = ranef (fit)$id[,1]
> summary(fit)
```

Linear mixed model fit by REML

Formula: arm ~ age + (1 | id)

Data: nepal

AIC	BIC	logLik	deviance	REMLdev
1821	1840	-906.6	1799	1813

Random effects:

Groups	Name	Variance	Std.Dev.
id	(Intercept)	0.78073	0.88359
Residual		0.24807	0.49806

Number of obs: 882, groups: id, 197

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	12.753789	0.109667	116.30
age	0.031697	0.002357	13.45

Correlation of Fixed Effects:

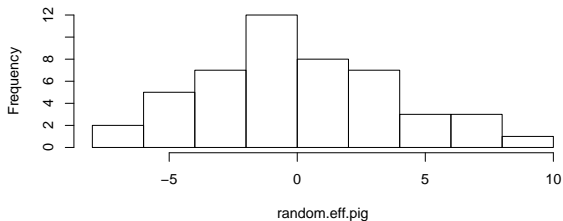
(Intr)
age -0.803

## Nepalese Children: Random Intercept Model

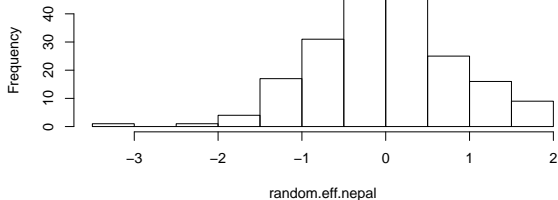
- The fixed effect model had an *age* slope estimate of 0.0313 and a SE of 0.00307
- Here, data are not balanced.
- We see a decrease in SE of slope of age with mixed model compared to fixed effects model.

# Random Effect Histograms

**Histogram of random.eff.pig**



**Histogram of random.eff.nepal**



# Nepalese Children: Random Intercept Model Interpretation

```
> fit = lmer (arm ~ age + (1|id), data = nepal)
```

Linear mixed model fit by REML

Random effects:

Groups	Name	Variance	Std.Dev.
id	(Intercept)	0.78073	0.88359
Residual		0.24807	0.49806

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	12.753789	0.109667	116.30
age	0.031697	0.002357	13.45

We found a 0.032 cm ( $CI_{95\%}$  0.027, 0.037) increase in arm circumference per month [after controlling for a child's arm circumference at birth](#).

We also found evidence of heterogeneity in arm circumference at birth. The estimated [population-average](#) arm circumference at birth is 12.8 cm, and the standard deviation of the random effect is 0.88 cm.

# Nepalese Children: Random Intercept Model Interpretation

Consider another model with an indicator for mother's literacy.

```
> fit2 = lmer(arm~age+lit+(1|id), data = nepal)
```

```
> summary (fit2)
```

Random effects:

Groups	Name	Variance	Std.Dev.
id	(Intercept)	0.74712	0.86436
Residual		0.24824	0.49823

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	12.710555	0.109304	116.29
age	0.031789	0.002338	13.60
lit	0.930247	0.316301	2.94

We found literacy to be significantly associated with arm circumference as a main effect. Also note that there is a small decrease in the degree of heterogeneity (from 0.78 to 0.75). Therefore mother's literacy may help explain some of the observed between-children variation in arm circumference at birth. Also the intercept estimate 12.71 now corresponds to the **population-average** arm circumference at birth from mothers **who are illiterate**.

# Covariance Structure

A random intercept model is also known as a two-level **variance component** model. Note that

$$y_{ij} = \mu + \theta_i + \beta x_{ij} + \epsilon_{ij}, \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2), \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2), \quad \theta_i \perp\!\!\!\perp \epsilon_{ij}$$

can be re-written as

$$y_{ij} = \mu + \beta x_{ij} + \epsilon_{ij}^*, \quad \epsilon_{ij}^* \sim N(0, \tau^2 + \sigma^2).$$

Let  $\boldsymbol{\epsilon}^* = [\epsilon_{11}^*, \epsilon_{12}^*, \dots, \epsilon_{1r}^*, \epsilon_{21}^*, \dots, \dots]'$

What is  $\text{Cov } \boldsymbol{\epsilon}^*$ , or equivalently,  $\text{Cov } \mathbf{Y}$ ?

# Covariance Structure



# Covariance Structure

## Random Intercept Model in Matrix Form

Consider the mixed model with random intercepts for  $n$  groups and define  $N = \sum_{i=1}^n r_i$ .

$$\mathbf{y} = \mathbf{Z}\boldsymbol{\theta} + \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

where

- $\mathbf{y} = N \times 1$  vector of response.
- $\mathbf{Z} = N \times n$  design matrix of indicator variables for each group.
- $\boldsymbol{\theta} = n \times 1$  vector of random intercepts.
- $\mathbf{X} = N \times p$  design matrix of fixed effects (including overall intercept).
- $\boldsymbol{\beta} = p \times 1$  vector of fixed effects.
- $\boldsymbol{\epsilon} = N \times 1$  vector of residual error.

Assumptions

- $\boldsymbol{\theta} \sim N(\mathbf{0}, \tau^2 \mathbf{I}_{n \times n})$ .
- $\boldsymbol{\epsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I}_{N \times N})$ .

## Intraclass Correlation

Note that the within-group covariance is

$$\text{Cov}(y_{ij}, y_{ij'}) = \tau^2.$$

So the correlation between observations **within** the same group is

$$\rho = \text{Corr}(y_{ij}, y_{ij'}) = \frac{\tau^2}{\tau^2 + \sigma^2} \text{ for all } j \neq j'. \quad (1)$$

The value  $\rho$  is often called the **intraclass** correlation. It measures the degree of similarity among same-group observations **compared to the residual error  $\sigma^2$** .

Application: reproducibility studies.

Example: Multiple scans of a subject's brain, and measure the connections between brain regions. We assume differences between the scans are due to measurement error. Then  **$\sigma^2$  quantifies measurement error**,  $\rho$  = reproducibility.

## ICC, cont.

$$\rho = \text{Corr}(y_{ij}, y_{ij'}) = \frac{\tau^2}{\tau^2 + \sigma^2} \text{ for all } j \neq j'. \quad (2)$$

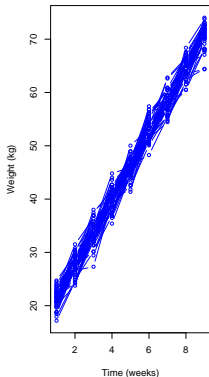
- $\rho \rightarrow 0$  when  $\tau^2 \rightarrow 0$  ( i.e. same intercept ).
- $\rho \rightarrow 0$  when  $\sigma^2 \rightarrow \infty$  ( i.e. growing measurement error ).
- $\rho \rightarrow 1$  when  $\tau^2 \rightarrow \infty$  ( i.e. large separation in intercepts ).
- $\rho \rightarrow 1$  when  $\sigma^2 \rightarrow 0$  ( i.e. zero measurement error ).

The above intraclass correlation has an **exchangeable** structure because the correlation is constant between *any pair* of within-group observations.

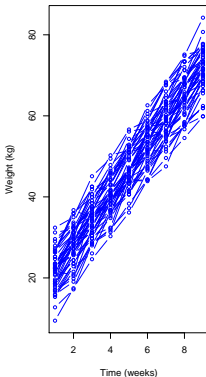
# Simulated Pig Data Ex 1 – Between subject variability

$$y_{ij} = 15 + \theta_i + 6.2 \times \text{weeks}_{ij} + \epsilon_{ij}, \quad \theta_i \sim N(0, \tau^2) \quad \epsilon_{ij} \sim N(0, 4)$$

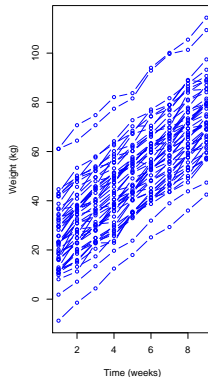
**Tau = 0.5 , ICC = 0.06**



**Tau = 4 , ICC = 0.8**

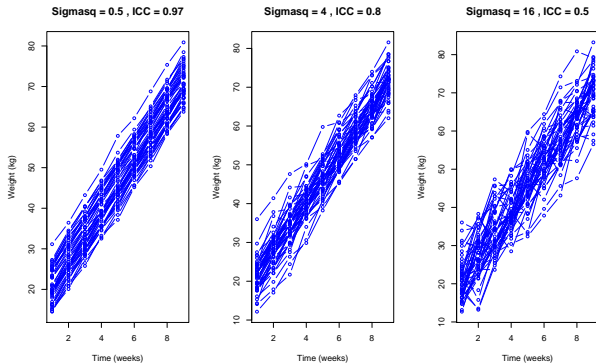


**Tau = 16 , ICC = 0.98**



## Simulated Pig Data Ex 2 – Measurement error

$$y_{ij} = 15 + \theta_i + 6.2 \times \text{weeks}_{ij} + \epsilon_{ij}, \quad \theta_i \sim N(0, 16) \quad \epsilon_{ij} \sim N(0, \sigma^2)$$



## Shrinkage and Random Effects

To simplify the derivation and make connections to ridge regression, we first consider a **special case**:

Consider a random effects model without fixed effects:

$$y_{ij} = \theta_i + \epsilon_{ij}, \quad \theta_i \stackrel{iid}{\sim} N(\mathbf{0}, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

The joint density of the data and random effects is given by

$$\begin{aligned} \prod_{i,j} f(y_{ij}, \theta_i) &= \prod_{i,j} f(y_{ij}|\theta_i) \times \prod_i g(\theta_i) \\ &\propto \exp \left[ -\frac{1}{2\sigma^2} \sum_{i,j} (y_{ij} - \theta_i)^2 \right] \times \exp \left[ -\frac{1}{2\tau^2} \boldsymbol{\theta}' \boldsymbol{\theta} \right] \\ &= \exp \left[ -\frac{1}{2\sigma^2} \sum_{i,j} (y_{ij} - \theta_i)^2 - \frac{1}{2\tau^2} \boldsymbol{\theta}' \boldsymbol{\theta} \right] \\ &= \exp \left[ -\frac{1}{2\sigma^2} \left[ \sum_{i,j} (y_{ij} - \theta_i)^2 + \frac{\sigma^2}{\tau^2} \boldsymbol{\theta}' \boldsymbol{\theta} \right] \right] \end{aligned}$$

## Shrinkage and Random Effects

Then maximizing the log likelihood is equivalent to

$$\arg \min \left[ \sum_{i,j} (y_{ij} - \theta_i)^2 + \frac{\sigma^2}{\tau^2} \sum_i \theta_i^2 \right]$$

Consider the matrix formulation

$$\mathbf{y} = \mathbf{Z}\boldsymbol{\theta} + \boldsymbol{\epsilon}$$

where  $\mathbf{Z} \in \mathbb{R}^{nr \times n}$  design matrix of indicator variables denoting the  $ij$ th observation belongs to group  $i$ , for clarity we assume  $r$  observations in all groups. Then

$$\arg \min \left[ (\mathbf{y} - \mathbf{Z}\boldsymbol{\theta})'(\mathbf{y} - \mathbf{Z}\boldsymbol{\theta}) + \frac{\sigma^2}{\tau^2} \boldsymbol{\theta}'\boldsymbol{\theta} \right]$$

Given values of  $\sigma^2$  and  $\tau^2$ , it's easy to find the closed-form solution to this. We will see it again in [ridge regression](#) in module 6:

$$\hat{\boldsymbol{\theta}} = \left( \mathbf{Z}'\mathbf{Z} + \frac{\sigma^2}{\tau^2} \mathbf{I} \right)^{-1} \mathbf{Z}'\mathbf{y}.$$



## Shrinkage and Random Effects, cont.

This is equivalent to

$$\hat{\theta}_i = \frac{\sum_{j=1}^r y_{ij}}{r + \sigma^2/\tau^2},$$

Note that

- $\hat{\theta}_i \rightarrow 0$  when  $\tau^2 \rightarrow 0$  (*i.e. shrinks all random intercepts to zero*).
- $\hat{\theta}_i \rightarrow \bar{y}_i$ . when  $\tau^2 \rightarrow \infty$  (*i.e. no shrinkage = raw group mean estimates*)
- $\hat{\theta}_i \rightarrow \bar{y}_i$ . when  $\sigma^2 \rightarrow 0$  (*i.e. no shrinkage = raw group mean estimates*).
- $\hat{\theta}_i \rightarrow \bar{y}_i$ . when  $r \rightarrow \infty$  (*i.e. no shrinkage = raw group mean estimates*)

$\tau^2$  controls the amount of **shrinkage** and how much information to **borrow across groups**

What happens if groups differ a lot?

## Shrinkage and Random Effects - EDF

In penalized regression, the notion of **effective degrees of freedom** is useful for generalizing the notion of the number of parameters to models in which parameter estimates are shrunk towards zero.

Recall in multiple regression,  $\text{tr}(\mathbf{X}(\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}') = \text{number of parameters}$ .

For ridge regression,  $\text{EDF} = \text{tr} \left[ \mathbf{X} (\mathbf{X}'\mathbf{X} + \lambda \mathbf{I})^{-1} \mathbf{X}' \right]$ .

The notion of effective degrees of freedom (EDF) can be extended to understanding random effects:

$$\text{EDF} = \text{tr} \left[ \mathbf{Z} \left( \mathbf{Z}'\mathbf{Z} + \frac{\sigma^2}{\tau^2} \mathbf{I} \right)^{-1} \mathbf{Z}' \right].$$

The amount of shrinkage depends on the ratio of between-group versus within-group variation.

## Shrinkage and Random Effects - EDF

For the pig data, we have  $\mathbf{Z}'\mathbf{Z} = 9 \times \mathbf{I}_{48 \times 48}$ . So

$$\begin{aligned}\text{EDF} &= \text{trace} \left[ \mathbf{Z} \left( 9 + \frac{\sigma^2}{\tau^2} \right)^{-1} \times \mathbf{I}\mathbf{Z}' \right] = \text{trace} \left[ \left( 9 + \frac{\sigma^2}{\tau^2} \right)^{-1} \mathbf{Z}\mathbf{Z}' \right] \\ &= \left( \frac{9\tau^2 + \sigma^2}{\tau^2} \right)^{-1} \text{trace}[\mathbf{Z}\mathbf{Z}'] = 48 \times 9 \left( \frac{\tau^2}{9\tau^2 + \sigma^2} \right) \\ &= 48 \left( \frac{9}{9 + \sigma^2/\tau^2} \right)\end{aligned}$$

## Shrinkage and Random Effects - EDF

$$\text{EDF} = 48 \left( \frac{9}{9 + \sigma^2/\tau^2} \right)$$

EDF  $\rightarrow 48$  (less shrinkage) when:

- $\sigma^2/\tau^2 \rightarrow 0$
- Within-pig variation  $\sigma^2 \ll$  between-pig variation  $\tau^2$ .
- Clear separation of the pig-specific intercepts. Estimate the intercepts close to fixed effects.

EDF  $\rightarrow 0$  (more shrinkage) when:

- $\sigma^2/\tau^2 \rightarrow \infty$
- Within-pig variation  $\sigma^2 \gg$  between-pig variation  $\tau^2$ .
- Random residual error  $\sigma^2$  dominates. Make estimates of the pig-specific intercepts more similar to each other, as overall mean is more informative.

Random effects are a sort of compromise between “Approach 1” (one intercept) and “Approach 2” (intercept for each subject).

## Shrinkage and Random Effects - EDF

Let  $n$  be the number of subjects/groups, and  $r$  be the number of observations within each group. Then for a simple random intercept model with no fixed effect:

$$\text{EDF} = n \left( \frac{r}{r + \sigma^2/\tau^2} \right).$$

Also note that  $\text{EDF} \rightarrow n$  when  $r$  increases. Less shrinkage is experienced because with large  $r$ , we have sufficiently large sample size per group to estimate their own intercepts. So there is no need to rely on the normality assumption to borrow information between groups.

## Shrinkage and Borrowing Information

In Slide 30, we assumed the population mean was 0. Now assume the random effects are centered around a common mean  $\mu$ :

$$y_{ij} = \theta_i + \epsilon_{ij}, \quad \theta_i \sim N(\mu, \tau^2) \quad \epsilon_{ij} \sim N(0, \sigma^2).$$

The joint density of the data and random effects is then

$$\begin{aligned} \prod_{i,j} f(y_{ij}, \theta_i) &= \prod_{i,j} f(y_{ij}|\theta_i) \times \prod_i g(\theta_i) \\ &\propto \exp \left[ -\frac{1}{2\sigma^2} [(\mathbf{y} - \mathbf{Z}\boldsymbol{\theta})'(\mathbf{y} - \mathbf{Z}\boldsymbol{\theta}) + \frac{\sigma^2}{\tau^2} (\boldsymbol{\theta} - \boldsymbol{\mu})'(\boldsymbol{\theta} - \boldsymbol{\mu})] \right] \\ &\propto \exp \left[ -\frac{1}{2\sigma^2} \left[ -2\mathbf{y}'\mathbf{Z}\boldsymbol{\theta} + \boldsymbol{\theta}'(\mathbf{Z}'\mathbf{Z})\boldsymbol{\theta} + \frac{\sigma^2}{\tau^2} \boldsymbol{\theta}'\boldsymbol{\theta} - 2\frac{\sigma^2}{\tau^2} \boldsymbol{\mu}'\boldsymbol{\theta} \right] \right] \\ &= \exp \left[ -\frac{1}{2\sigma^2} \left[ \boldsymbol{\theta}'(\mathbf{Z}'\mathbf{Z} + \frac{\sigma^2}{\tau^2} \mathbf{I})\boldsymbol{\theta} - 2(\mathbf{y}'\mathbf{Z} + \frac{\sigma^2}{\tau^2} \boldsymbol{\mu}')\boldsymbol{\theta} \right] \right] \end{aligned}$$

Recall the *completing the squares* property: let  $\mathbf{A}$  be a symmetric and invertible matrix, then

$$\boldsymbol{\theta}'\mathbf{A}\boldsymbol{\theta} - 2\boldsymbol{\alpha}'\boldsymbol{\theta} = (\boldsymbol{\theta} - \mathbf{A}^{-1}\boldsymbol{\alpha})'\mathbf{A}(\boldsymbol{\theta} - \mathbf{A}^{-1}\boldsymbol{\alpha}) - \boldsymbol{\alpha}'\mathbf{A}^{-1}\boldsymbol{\alpha}.$$

## Shrinkage and Borrowing Information, cont.

The joint density is a multivariate Normal density:

$$\prod_{i,j} f(y_{ij}|\theta_i) \times \prod_i g(\theta_i) \propto \exp \left[ -\frac{1}{2\sigma^2} (\boldsymbol{\theta} - \mathbf{A}^{-1}\boldsymbol{\alpha})' \mathbf{A} (\boldsymbol{\theta} - \mathbf{A}^{-1}\boldsymbol{\alpha}) \right]$$

where  $\mathbf{A} = (\mathbf{Z}'\mathbf{Z} + \frac{\sigma^2}{\tau^2}\mathbf{I})$  and  $\boldsymbol{\alpha} = (\mathbf{Z}'\mathbf{y} + \frac{\sigma^2}{\tau^2}\boldsymbol{\mu})$ .

For maximizing  $\boldsymbol{\theta}$ , this function is maximized at the mean:

$$\hat{\boldsymbol{\theta}} = \mathbf{A}^{-1}\boldsymbol{\alpha} = (\mathbf{Z}'\mathbf{Z} + \frac{\sigma^2}{\tau^2}\mathbf{I})^{-1}(\mathbf{Z}'\mathbf{y} + \frac{\sigma^2}{\tau^2}\boldsymbol{\mu}). \quad (3)$$

Let  $r_i$  = number of replicates for the  $i$ th group. Then,

$$\hat{\theta}_i = \frac{(\sigma^2/\tau^2)\mu + \sum_{j=1}^{r_i} y_{ij}}{r_i + \sigma^2/\tau^2}.$$

Note that

- $\hat{\theta}_i \rightarrow \mu$  when  $\tau^2 \rightarrow 0$  ( *shrink all random intercepts to a common mean* ).
- $\hat{\theta}_i \rightarrow \bar{y}_i$ . when  $\tau^2 \rightarrow \infty$  ( *no shrinkage = raw mean estimates* ).

## Shrinkage and Borrowing Information, cont. ii

We can also express  $\hat{\theta}_i$  as

$$\hat{\theta}_i = \frac{(1/\tau^2)\mu + (r_i/\sigma^2)\bar{y}_i}{1/\tau^2 + (r_i/\sigma^2)}.$$

Since  $(\sigma^2/r_i)$  is the sample variance of the estimated sample mean  $\bar{y}_i$ , the above form shows that random effects can be viewed as a **weighted average** of:

1. standard estimate without penalization:  $\bar{y}_i$ .
2. overall mean  $\mu$ .

with their corresponding **inverse-variances** as weights!

Finally, express  $\hat{\theta}_i$  in terms of intraclass correlation  $\rho = \tau^2/(\tau^2 + \sigma^2)$

$$\hat{\theta}_i = \frac{\rho^{-1}\mu + r_i(1 - \rho)^{-1}\bar{y}_i}{\rho^{-1} + r_i(1 - \rho)^{-1}}$$

and less shrinkage is expected for  $\rho \rightarrow 1$ .



## Best Linear Unbiased Prediction

For the random intercept model

$$y_{ij} = \theta_i + \epsilon_{ij}, \quad \theta_i \stackrel{iid}{\sim} N(\mu, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$$

we wish to estimate the **unobserved random variable**  $\theta_i$ .

We can also derive the estimators using the MVN distribution. Assume  $\tau^2$  and  $\sigma^2$  are known. Then

$$\begin{bmatrix} \mathbf{y}_i \\ \theta_i \end{bmatrix} \sim N \left( \begin{bmatrix} \mu \mathbf{1}_{r_i} \\ \mu \end{bmatrix}, \begin{bmatrix} \tau^2 \mathbf{1}_{r_i} \mathbf{1}_{r_i}' + \sigma^2 \mathbf{I}_{r_i \times r_i} & \tau^2 \mathbf{1}_{r_i} \\ \tau^2 \mathbf{1}_{r_i}' & \tau^2 \end{bmatrix} \right)$$

because  $cov(y_{ij}, \theta_i) = cov(\theta_i + \epsilon_{ij}, \theta_i) = \tau^2$ .

To make a **prediction** of  $\theta_i$  given the data  $\mathbf{y}_i$ , we can use the conditional distribution of the multivariate normal density. Specifically our estimator will be

$$\hat{\theta}_i = E[\theta_i | \mathbf{y}_i].$$

## Best Linear Unbiased Prediction: BLUPs

$$\begin{aligned}\hat{\theta}_i &= E[\theta_i | \mathbf{y}_i] = \mu + \tau^2 \mathbf{1}'_{r_i} [\tau^2 \mathbf{1}_{r_i} \mathbf{1}'_{r_i} + \sigma^2 \mathbf{I}_{r_i \times r_i}]^{-1} [\mathbf{y}_i - \mu \mathbf{1}_{r_i}] \\&= \mu + \tau^2 \mathbf{1}'_{r_i} \frac{1}{\sigma^2} \left[ \mathbf{I}_{r_i \times r_i} - \frac{\tau^2}{\sigma^2 + n\tau^2} \mathbf{1}_{r_i} \mathbf{1}'_{r_i} \right] [\mathbf{y}_i - \mu \mathbf{1}_{r_i}] \\&= \mu + \frac{\tau^2}{\sigma^2} \left( 1 - \frac{r_i \tau^2}{\sigma^2 + r_i \tau^2} \right) \mathbf{1}'_{r_i} [\mathbf{y}_i - \mu \mathbf{1}_{r_i}] \\&= \mu + \frac{\tau^2}{\sigma^2} \left( \frac{\sigma^2}{\sigma^2 + r_i \tau^2} \right) (r_i \bar{y}_{i\cdot} - r_i \mu) \\&= \mu + \left( \frac{\tau^2}{\sigma^2 + r_i \tau^2} \right) (r_i \bar{y}_{i\cdot} - r_i \mu) \\&= \frac{\sigma^2 \mu + \tau^2 r_i \bar{y}_{i\cdot}}{\sigma^2 + r_i \tau^2}.\end{aligned}$$

This is equivalent to (3). (Apply the Sherman-Morrison matrix inverse formula.)

## eBLUPs

- For known variance parameters,  $\hat{\theta}_i$  is the BLUP: Best Linear Unbiased Predictor.
- They are **unbiased** in the sense that  $E(\hat{\theta}_i) = E(\theta_i) = \mu$ , see Robinson 1991 (in course files /Readings).
- They are “best” in the sense that the conditional expectation minimizes the mean-squared error  $E(\hat{\theta}_i - \theta_i)^2$  among the class of linear unbiased estimators.
- Note: in ordinary linear regression,  $y_i = \mathbf{x}'_i\boldsymbol{\beta} + \epsilon_{ij}$ , the least-squares estimate of  $\boldsymbol{\beta} = (\mathbf{X}'\mathbf{X})^{-1}\mathbf{X}'\mathbf{y}$  is the Best Linear Unbiased Estimator (BLUE).
- In practice, we can't estimate BLUPs because their variances are not known.
- We use  $\hat{\sigma}_2$  and  $\hat{\tau}^2$  in place of their true values.
- The resulting random effects estimators are **eBLUPs: estimated Best Linear Unbiased Predictors**
- Connections to Bayesian statistics: see Robinson (1991).

## BLUPs: Unbiased but... biased?

Let's go back to the model  $\theta_i \sim N(0, \sigma^2)$  (slide 30), where we assume mean 0 to simplify the formulae.

Assume the conditional model  $y_{ij} \mid \theta_i = \theta_i + \epsilon_{ij}$  such that  $E[y_{ij} \mid \theta_i] = \theta_i$ . Additionally assume  $\sigma^2$  and  $\tau^2$  known.

From this perspective, the random intercepts are **biased**. For  $\tau^2 > 0$ ,

$$E[\hat{\theta}_i \mid \theta_i] = E \left[ \frac{\sum_{j=1}^r y_{ij}}{r + \sigma^2/\tau^2} \mid \theta_i \right] < E \left[ \frac{\sum_{j=1}^r y_{ij}}{r} \mid \theta_i \right] = \theta_i.$$

However, the variances are smaller.

$$Var[\hat{\theta}_i \mid \theta_i] = Var \left[ \frac{\sum_{j=1}^r y_{ij}}{r + \sigma^2/\tau^2} \mid \theta_i \right] < Var \left[ \frac{\sum_{j=1}^r y_{ij}}{r} \mid \theta_i \right].$$

We see a **trade-off between bias and variance**. Some bias is introduced, but we get smaller standard error.

## BLUPs: Matrix formulation

BLUPs can be derived as the conditional distribution of  $\boldsymbol{\theta}$  given the data  $\mathbf{y}$ . Consider the joint distribution of  $[\mathbf{y}, \boldsymbol{\theta}]$ :

$$\begin{bmatrix} \mathbf{y} \\ \boldsymbol{\theta} \end{bmatrix} \sim N \left( \begin{bmatrix} \mathbf{X}\boldsymbol{\beta} \\ 0 \end{bmatrix}, \begin{bmatrix} \tau^2 \mathbf{Z}\mathbf{Z}' + \sigma^2 \mathbf{I}_{N \times N} & \tau^2 \mathbf{Z} \\ \tau^2 \mathbf{Z}' & \tau^2 \mathbf{I}_{n \times n} \end{bmatrix} \right)$$

Then

$$E[\boldsymbol{\theta}|\mathbf{y}] = (\tau^2 \mathbf{Z}') (\tau^2 \mathbf{Z}\mathbf{Z}' + \sigma^2 \mathbf{I}_{N \times N})^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$$

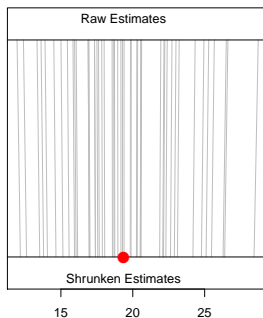
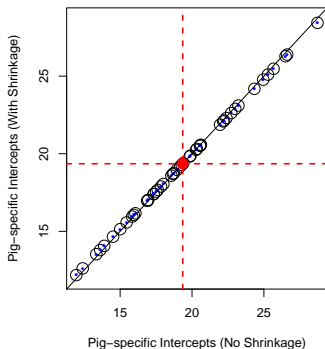
E.g., see “Conditional Distributions” at [https://en.wikipedia.org/wiki/Multivariate\\_normal\\_distribution](https://en.wikipedia.org/wiki/Multivariate_normal_distribution)

In practice, replace  $\boldsymbol{\beta}$ ,  $\sigma^2$ , and  $\tau^2$  by their estimates.

## Shrinkage: Pig Data

$$\text{weight}_{ij} = \beta_0 + \theta_i + \beta_1 \text{week}_{ij} + \epsilon_{ij} \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

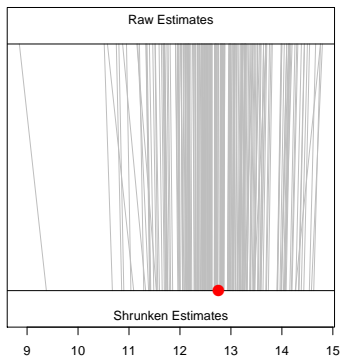
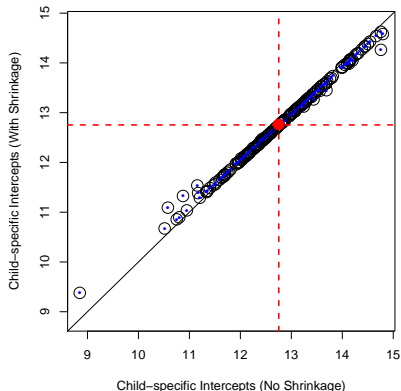
$$\hat{\tau}^2 = 15.1, \quad \hat{\sigma}^2 = 4.39, \quad \hat{\sigma}^2 / \hat{\tau}^2 = 0.29, \quad \text{ICC} = 0.77, \quad r_i = 9 \text{ for all } i$$



## Shrinkage: Nepalese Data

$$\text{armc}_{ij} = \beta_0 + \theta_i + \beta \text{age}_{ij} + \epsilon_{ij} \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

$$\hat{\tau}^2 = 0.78, \quad \hat{\sigma}^2 = 0.25, \quad \hat{\sigma}^2 / \hat{\tau}^2 = 0.32, \quad \text{ICC} = 0.76, \quad r_i \in \{1, \dots, 5\}$$



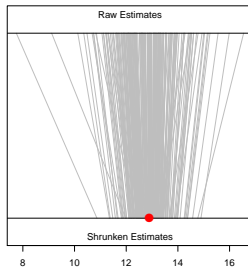
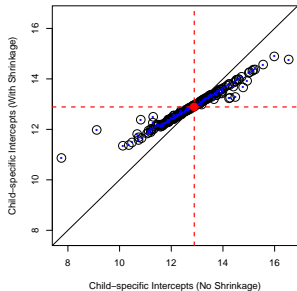
# Shrinkage: Nepalese Data with Noise

What happens if we add more random noise to the outcome? **More Shrinkage!**

$$\text{armc}^*_{ij} = \beta_0 + \theta_i + \beta_1 \text{age}_{ij} + \epsilon_{ij} \quad \theta_i \stackrel{iid}{\sim} N(0, \tau^2) \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

where  $\text{armc}^* = \text{arm} + N(0, 2)$ .

$$\hat{\tau}^2 = 0.74 \quad \hat{\sigma}^2 = 2.27 \quad \hat{\sigma}^2 / \hat{\tau}^2 = 3.07 \quad \text{ICC} = 0.24$$

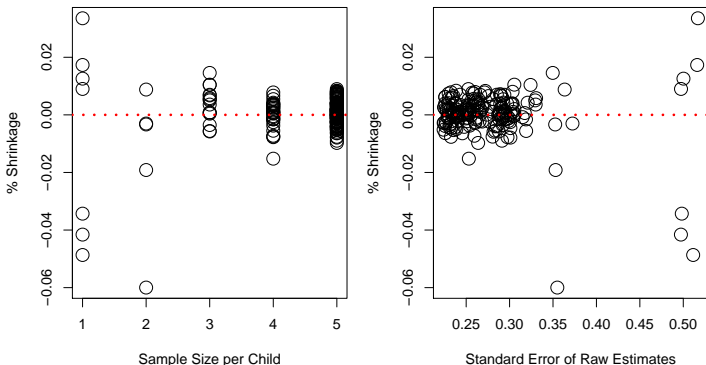




## Shrinkage and Borrowing Information, cont. iii

The Nepalese children dataset contains missing data. Not all 200 children have complete 5 visits.

Note how the amount of shrinkage is related to the standard error of the fixed effects model (raw estimates = slide 12)



# Normality assumption and shrinkage

Shrinkage occurs according to the conditional mean determined by the normality assumption.

Effects of the normality assumption on random effects depend on

1. group-specific sample size,
2. within-group residual error,
3. between-group heterogeneity.

# Parameter Estimation: Maximum Likelihood Approach

$$\mathbf{y} = \mathbf{Z}\boldsymbol{\theta} + \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}, \quad \boldsymbol{\theta} \sim N(\mathbf{0}, \tau^2 \mathbf{I}) \quad \boldsymbol{\epsilon} \sim N(\mathbf{0}, \sigma^2 \mathbf{I}).$$

Since  $\boldsymbol{\theta}$  and  $\boldsymbol{\epsilon}$  are *random variables*, we can rewrite the above as

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}^*, \quad \boldsymbol{\epsilon}^* = \mathbf{Z}\boldsymbol{\theta} + \boldsymbol{\epsilon}.$$

We know  $Cov(\boldsymbol{\epsilon}^*) =$

This is equivalent to integrating out the random effects. Then the marginal model is:

$$\mathbf{y} \sim N(\mathbf{X}\boldsymbol{\beta}, \mathbf{V}).$$

# Generalized Least Squares

For known  $\mathbf{V}$ , the generalized least-squares problem is

$$\arg \min_{\boldsymbol{\beta}} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})' \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta}).$$

This is also called weighted least squares.

Note this is the kernel of the multivariate normal distribution.

Then the value of  $\boldsymbol{\beta}$  that maximizes the likelihood is given by the generalized least-squares estimate:

This estimator is the best linear unbiased estimator (BLUE).

# Parameter Estimation: Maximum Likelihood Approach

The log-likelihood  $l(\sigma^2, \tau^2)$  in terms of  $\sigma^2$  and  $\tau^2$  is:

$$l(\sigma^2, \tau^2) = -\frac{N}{2} \log(2\pi) - \frac{1}{2} |\mathbf{V}| - \frac{1}{2} (\mathbf{y} - \mathbf{X}\tilde{\boldsymbol{\beta}})' \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\tilde{\boldsymbol{\beta}}).$$

Plug in  $\tilde{\boldsymbol{\beta}} = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1}\mathbf{X}'\mathbf{V}^{-1}\mathbf{y}$

It is then straightforward to maximize the above function over the 2-D domain of  $\sigma^2$  and  $\tau^2$ .

This method of substituting some unknown parameters ( $\boldsymbol{\beta}$ ) with their MLE fixed at some other parameters ( $\sigma^2$  and  $\tau^2$ ) is known as a **profile likelihood** approach.

## REML

The MLE estimate of variances are biased. An alternative is **restricted maximum likelihood** (REML)

$$l(\sigma^2, \tau^2) - \frac{1}{2} \log |\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}|$$

to account for the degrees of freedom in the fixed effects (e.g., Ch. 6 in Searle et al. 1992, "Variance Components").

REML can be unbiased.

In the simple case of estimating  $\sigma^2$  from  $\mathbf{X}_i \stackrel{iid}{\sim} N(0, \sigma^2)$ , we have

$$\hat{\sigma}_{MLE}^2 = \frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2$$
$$\hat{\sigma}_{REML}^2 = \frac{1}{n-1} \sum_{i=1}^n (x_i - \bar{x})^2.$$

Small samples: often prefer REML.

Likelihood ratio tests and AIC: use ML.

## Parameter Estimation: MLE versus REML

```
> fit1 <- lmer (weight~weeks+(1|id), data = dat)
> summary (fit1)
Linear mixed model fit by REML
Random effects:
  Groups   Name      Variance Std.Dev.
 id        (Intercept) 15.1418  3.8913
 Residual                    4.3947  2.0964

Fixed effects:
              Estimate Std. Error t value
(Intercept) 19.35561    0.60311   32.09
weeks        6.20990    0.03906  158.97

> fit2 <- lmer (weight~weeks+(1|id), REML = FALSE,data = dat)
> summary(fit2)
Linear mixed model fit by maximum likelihood
Random effects:
  Groups   Name      Variance Std.Dev.
 id        (Intercept) 14.8175  3.8493
 Residual                    4.3833  2.0936
Number of obs: 432, groups: id, 48

Fixed effects:
              Estimate Std. Error t value
(Intercept) 19.35561    0.59737   32.4
weeks        6.20990    0.03901  159.2
```

Note that the standard errors are larger for REML.

# Fixed versus Random

Consider the model:

$$y_{ij} = \theta_i + \beta' \mathbf{x}_{ij} + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2) \theta_i : \text{either fixed or random}$$

- Fixed effects: we can treat  $\theta_i$  as fixed. Note: to make comparable to RE, we can use the sum-to-zero constraint,  $\sum_{i=1}^n \theta_i = 0$ , and estimate the intercept.
- We can treat  $\theta_i$  as random,  $\theta_i \stackrel{iid}{\sim} N(0, \tau^2)$ .

A useful paradigm: one person's covariance structure is another person's mean structure.

Random: Consider  $E(y_{ij} - \beta' \mathbf{x}_{ij})^2 = \sigma^2 + E\theta_i^2$ . (model the variance)

Fixed:  $E(y_{ij} - \theta_i - \beta' \mathbf{x}_{ij})^2 = \sigma^2$ . (model the mean structure)



## Guidelines for choosing fixed vs random

- Are we interested in predicting subject effects?
- If the experiment were repeated, would the same subjects (i.e., groups) be used?
- Or are the subjects a random sample from a population of interest?
- Are there enough subjects to estimate heterogeneity?
- Are there enough repeated measurements to estimate FE?
- Do some subjects have only 1 observation and/or is there different number of samples for each subject?

## Fixed versus Random

However, in scientific applications, we are often interested in inference on a fixed covariate, and the variable we are deciding to treat as fixed or random (subject, plot, etc.) is a “nuisance” variable.

In this case, the choice of fixed versus random may not have a big impact on inference. You can look at how sensitive your findings are to fixed versus random specification.

Pig data: data were balanced and t-statistics of week equivalent.

Nepal data: estimates of slope of age similar ( $t = 10.20$  in FE, versus  $t = 13.45$ )

The **big issue** is that we need to account for repeated observations in clustered data, and **both** approaches allow for valid inference on fixed covariates of interest.

Contrast with a model estimating a single intercept (slides 7 and 12), which results in incorrect standard errors, resulting in invalid inference.

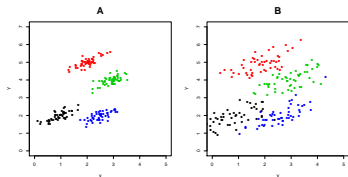
# Keywords

- Clustered / correlated / grouped / longitudinal / multi-level / hierarchical / nested data
- Random effect / (Bayesian) hierarchical / mixed / variance component model
- Between-group variability / heterogeneity / structured error
- Within-group correlation / intraclass correlation
- Within-group variability / unstructured (residual) error / measurement error
- Shrinkage / penalization / borrowing information / smoothing

# Quiz 3

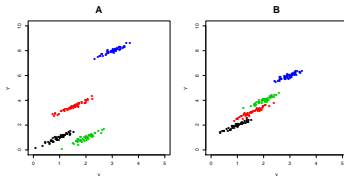
$$y_{ij} = \mu + \theta_i + \epsilon_{ij}, \quad \theta_i \sim N(0, \tau^2) \quad \epsilon_{ij} \sim N(0, \sigma^2)$$

## Part I



1. Has the larger  $\sigma^2$ ?
2. Has the larger intraclass correlation?
3.  $\hat{\theta}_i$  will experience more shrinkage?
4. Has the larger prediction SE for an observation from a within-sample group?

## Part II

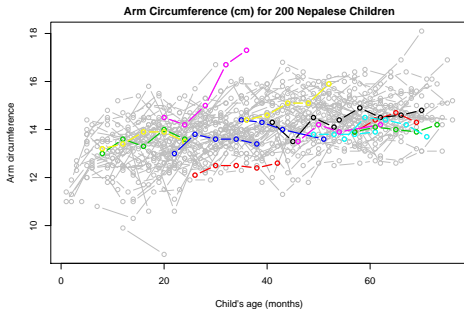


Which plot:

5. Has the larger  $\tau^2$ ?
6. Has the larger intraclass correlation?
7.  $\hat{\theta}_i$  will experience more shrinkage?
8. Has the larger prediction SE for an observation from an out-of-sample group?

# Random Slope Model

# Nepalese Children Data



**Scientific questions** about arm circumference and age:

- What is the **overall** trend?
- How much do growth patterns **differ** between children?
- Do maternal covariates **explain variability** in growth patterns between children?

## Random Intercept and Random Slope Model

Let  $ageC_{ij}$  be the child's *age* in months minus 36.

$$\begin{bmatrix} \theta_{0i} \\ \theta_{1i} \end{bmatrix}$$

The above model treats both intercept and slope of age as child-specific. These random effects represent child-specific **deviations** from the overall trend. We typically assume  $\theta_{0i}$  and  $\theta_{1i}$  are **bivariate normal**.

- $\tau_1^2$  describes between-children variation in baseline arm circumferences at **at age three**.
- $\tau_2^2$  describes between-children variation in the linear effects of age.
- $\rho$  describes the correlation between child-specific intercept and slope.
- $\sigma^2$  describes within-child variation around a child-specific linear growth trend.



## Mixed Model: Nepalese Children

```
> nepal$ageC = nepal$age - 36  
> fit = lmer (arm~ageC+(ageC|id), data = nepal)
```

Linear mixed model fit by REML

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	0.71937744	0.848161	
	ageCenter	0.00043572	0.020874	0.090
Residual		0.22657451	0.475998	

Number of obs: 882, groups: id, 197

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	13.943962	0.066677	209.13
ageC	0.032527	0.002754	11.81

Population distribution of random intercepts and slopes:

- Child-specific intercept:  $\beta_0 + \theta_{0i}$
- Child-specific slope:  $\beta_1 + \theta_{1i}$

Very high heterogeneity in the age effects. The central 95% of this distribution includes zero. Thus it's possible that a child's arm circumference does not increase with age.

- $\rho = \text{cor}(\beta_{0i}, \beta_{1i}) = 0.09$

## Comparing models: AIC, but doesn't work well

Is the model preferred to the model with a random intercept only?

AIC often used in model selection. Popular approach to choosing which variables should be included in a model.

Lower is better.

RoT: Difference of 2 or more is substantially better.

To compare models with different variance structures, one approach is to use Akaike's Information Criterion:

$$AIC = -2\ell(\boldsymbol{\theta}) + 2p$$

where  $\ell(\boldsymbol{\theta})$  is the log likelihood for all parameters  $\boldsymbol{\theta}$  and  $p$  is the number of parameters.

For nested models (one model contains a subset of parameters of the other model), we can use a likelihood ratio test.

Both these approaches use the MLE, so should use **REML=FALSE**

## Comparing models: caveat

Testing the significance of a variance component is problematic because the null hypothesis is on the boundary of the parameter space, e.g.,  $\tau_2^2 = 0$ .

This makes the  $\chi_1^2$  approximation of the LRT a poor approximation of the distribution of the test statistic under the null.

Generally, this makes the p-value too large (i.e., favors simpler models).

The homework describes a preferred approach.

For additional details, see Section 2.5, Pinheiro and Bates, *Mixed-Effects Models in S and S-Plus*, 2000.

## Compare to model without random slope

```
> fit = lmer (arm~ ageC + (ageC|id), data = nepal,REML=FALSE)
> fit.randomintercept = lmer (arm~ageC+(1|id),data=nepal,REML=FALSE)
> AIC(fit)
[1] 1802.579
> AIC(fit.randomintercept)
[1] 1807.264
```

Likelihood ratio test:

```
> anova(fit.randomintercept,fit)
Data: nepal
Models:
fit.randomintercept: arm ~ ageC + (1 | id)
fit: arm ~ ageC + (ageC | id)

```

	Df	AIC	BIC	logLik	deviance	Chisq	Chi	Df	Pr(>Chisq)
fit.randomintercept	4	1807.3	1826.4	-899.63	1799.3				
fit	6	1802.6	1831.3	-895.29	1790.6	8.6854		2	0.013 *

```
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Both AIC and LRT indicate model with random slopes is preferred.

# Mixed Model: Nepalese Children

Other options (not recommended).

Assume Independent Random Effects:

```
> fit.indep = lmer (arm~ ageC + (1|id) + (0+ageC|id), data = nepal)
> summary(fit.indep)
```

Linear mixed model fit by REML ['lmerMod']

Formula: arm ~ ageC + (1 | id) + (0 + ageC | id)

Data: nepal

REML criterion at convergence: 1804.5

Scaled residuals:

	Min	1Q	Median	3Q	Max
	-3.5914	-0.4923	0.0625	0.5651	2.9879

Random effects:

Groups	Name	Variance	Std.Dev.
id	(Intercept)	0.7170900	0.8468
id.1	ageC	0.0004122	0.0203
Residual		0.2279327	0.4774

Number of obs: 882, groups: id, 197

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	13.94277	0.06650	209.66
ageC	0.03225	0.00273	11.81

## Fixed effect model

An alternative framework would treat the intercepts as fixed.

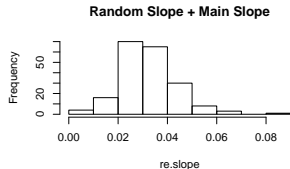
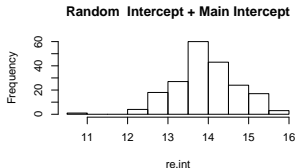
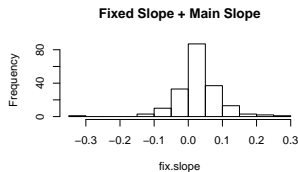
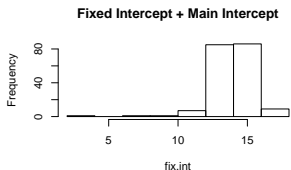
$$\text{arm}_{ij} = \beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i}) \text{ageC}_{ij} + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$$

We can use the sum-to-zero contrasts:

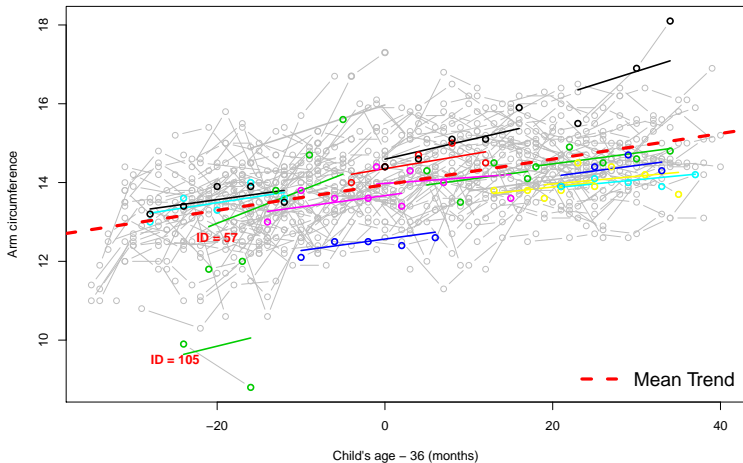
$$\sum_{i=1}^n \hat{\theta}_{0i} = 0$$

Then fixed effect interaction terms for each subject have similarities with random slopes (but don't leverage pop info), as the total age effect for each subject becomes  $\hat{\beta}_1 + \hat{\theta}_{1i}$ .

# Distributions of Child-specific Intercepts and Slopes



# Mixed Model



- Mean trend =  $\beta_0 + \beta_1 \text{ ageC}_{ij}$
- $i^{\text{th}}$  individual trend =  $\beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i}) \text{ ageC}_{ij}$



## Mixed Model: Drop ID 57 and ID 105

```
> fit = lmer (arm~ageC+(ageC|id), data = subset(nepal, id != 57 & id != 105) )
```

Random effects:

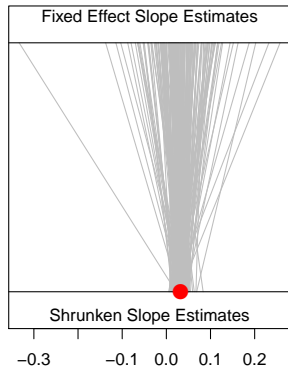
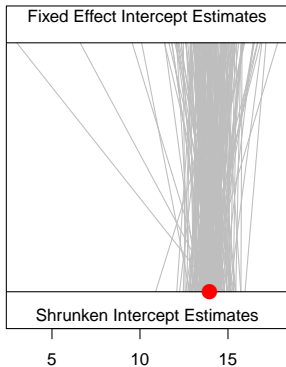
Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	0.66724471	0.816850	
	ageC	0.00029806	0.017264	0.123
Residual		0.22133729	0.470465	

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	13.949133	0.063888	218.34
ageC	0.031182	0.002581	12.08

- Changes in the fixed effects are minor:
  - Intercept: 13.944  $\rightarrow$  13.949.
  - AgeC: 0.0325  $\rightarrow$  0.0312.
- As expected, heterogeneity standard deviations become smaller:
  - Intercept: 0.848  $\rightarrow$  0.817.
  - AgeC: 0.021  $\rightarrow$  0.017.

# Shrinkage!

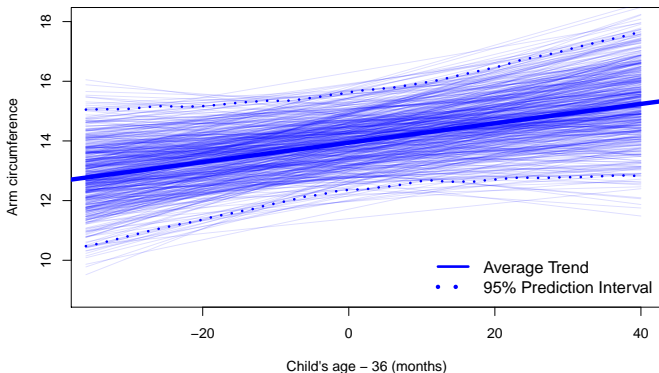


# Simulating Out-of-Sample Growth Curves

$$y_{ij} = (13.94 + \theta_{0i}) + (0.0325 + \theta_{1i}) x_{ij} + \epsilon_{ij} \quad \epsilon_{ij} \sim N(0, 0.48^2)$$

$$\begin{bmatrix} \theta_{0i} \\ \theta_{1i} \end{bmatrix} \sim N \left( \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0.85^2 & 0.09 \times 0.85 \times 0.021 \\ 0.09 \times 0.85 \times 0.021 & 0.021^2 \end{bmatrix} \right).$$

**Predicted Growth Curves for 500 Children**



## Hierarchical Formulation

Consider the following model now including interactions:

$$\text{arm}_{ij} = \beta_0 + \theta_{0i} + (\beta_1 + \theta_{1i}) \text{ageC}_{ij} + \epsilon_{ij} \quad (4)$$

$$[\theta_{0i}, \theta_{1i}]' \stackrel{iid}{\sim} N(\mathbf{0}, \Sigma), \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

In (4), the random effects are viewed as **deviations from population averages**. The model can also be written in a hierarchical (multilevel) model form:

$$\text{arm}_{ij} = \beta_{0i} + \beta_{1i} \text{ageC}_{ij} + \epsilon_{ij} \quad (5)$$

$$[\beta_{0i}, \beta_{1i}]' \sim N([\beta_0, \beta_1]', \Sigma), \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

Equation (5) can also be written as:

$$\text{Level 1:} \quad \beta_{0i} = \mu_0 + \theta_{0i} \quad \beta_{1i} = \mu_1 + \theta_{1i}$$

$$\text{Level 2:} \quad \text{arm}_{ij} = \beta_{0i} + \beta_{1i} \text{ageC}_{ij} + \epsilon_{ij}$$

$$[\theta_{0i}, \theta_{1i}]' \sim N(\mathbf{0}, \Sigma), \quad \epsilon \stackrel{iid}{\sim} N(0, \sigma^2)$$

## Hierarchical Formulation: Back to Random Intercepts

First consider the random intercept model with covariate *age* and *lit* (indicator for mother's literacy).

$$\text{arm}_{ij} = \beta_0 + \theta_{0i} + \beta_1 \text{ageC}_{ij} + \beta_2 \text{lit}_{ij} + \epsilon_{ij}$$
$$\theta_{0i} \stackrel{iid}{\sim} N(0, \tau^2), \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

What is the interpretation of  $\beta_2$ ?

- Because  $\text{lit}_{ij}$  is an indicator variable,  $\beta_2$  describes the difference in intercept (arm circumference at age 3) between literate mothers and illiterate mothers (reference).

However  $\text{lit}_{ij}$  is constant within each child. We can drop the  $j$  subscript and rewrite the model as

$$\beta_{0i} \sim N(\beta_0 + \beta_2 \text{lit}_i, \tau^2)$$
$$\text{arm}_{ij} = \beta_{0i} + \beta_1 \text{ageC}_{ij} + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2).$$

Therefore an equivalent interpretation of  $\beta_2$  is

- $\beta_2$  describes the difference in population averages in intercepts between literate and illiterate mothers.

## Hierarchical Formulation

The hierarchical (multilevel) formulation is particularly useful when covariates are available or collected at different levels. Higher level ( $i$ ) covariate values are constant in lower level ( $j$ ).

Consider the following model:

Level 1:

Level 2:

Note how we explicitly present covariates *lit* and *sex* as predictors that explain between-subjects heterogeneity. For example,

- $\alpha_{12}$  is the effect of a child's sex on the association between age and arm circumference after controlling for child-specific intercept and weight.
- $\beta_2$  is the effect of a child's weight on arm circumference adjusting for individual linear growth trend in age.

## Cross-level Interactions

Level 1:

$$\beta_{0i} = \mu_0 + \alpha_{01}lit_i + \alpha_{02}sex_i + \theta_{0i}$$
$$\beta_{1i} = \mu_1 + \alpha_{11}lit_i + \alpha_{12}sex_i + \theta_{1i}, \quad [\theta_{0i}, \theta_{1i}]' \stackrel{iid}{\sim} N(\mathbf{0}, \Sigma)$$

Level 2:

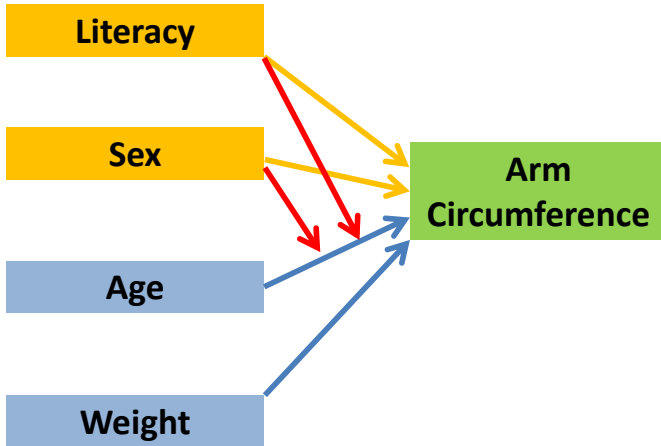
$$arm_{ij} = \beta_{0i} + \beta_{1i} ageC_{ij} + \beta_2 weightC_{ij} + \epsilon_{ij}, \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2)$$

By substituting Level 1 regressions into Level 2:

$$\begin{aligned} arm_{ij} &= \mu_0 + \alpha_{01}lit_i + \alpha_{02}sex_i + \theta_{0i} \\ &\quad + (\mu_1 + \alpha_{11}lit_i + \alpha_{12}sex_i + \theta_{1i}) ageC_{ij} + \beta_2 weightC_{ij} + \epsilon_{ij} \\ &= \mu_0 + \alpha_{01}lit_i + \alpha_{02}sex_i + \theta_{0i} \\ &\quad + \mu_1 ageC_{ij} + \alpha_{11}lit_i \times ageC_{ij} + \alpha_{12}sex_i \times ageC_{ij} + \theta_{1i} ageC_{ij} \\ &\quad + \beta_2 weightC_{ij} + \epsilon_{ij}, \\ &\quad [\theta_{0i}, \theta_{1i}]' \stackrel{iid}{\sim} N(\mathbf{0}, \Sigma), \quad \epsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma^2). \end{aligned}$$

Note that  $\alpha_{11}$  and  $\alpha_{12}$  can be interpreted as an **interaction** between two variables **across levels**.

## Cross-level Interactions





## Cross-level Interactions

```
> nepal$wtC = scale(nepal$wt,center=TRUE,scale=FALSE)
> fit.sexwtlit = lmer (arm~sex+lit+sex*ageC + lit*ageC + wt+ (ageC|id), data = nepal)
```

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	0.689381	0.83029	
	ageC	0.000427	0.02066	0.07
Residual		0.224295	0.47360	

Number of obs: 882, groups: id, 197

Fixed effects:

	Estimate	Std. Error	t value
(Intercept)	13.785990	0.095554	144.27
sex2	0.024052	0.131598	0.18
lit	0.811968	0.322324	2.52
ageC	0.029034	0.003854	7.53
wt	0.009867	0.002751	3.59
sex2:ageC	0.002838	0.005493	0.52
lit:ageC	0.007405	0.015026	0.49

- Heterogeneity decreases
- This is because we are now accounting for variation between subjects in the fixed effects, i.e., sex, lit, wt
- Mother's literacy and child's weight associated with baseline arm circum.