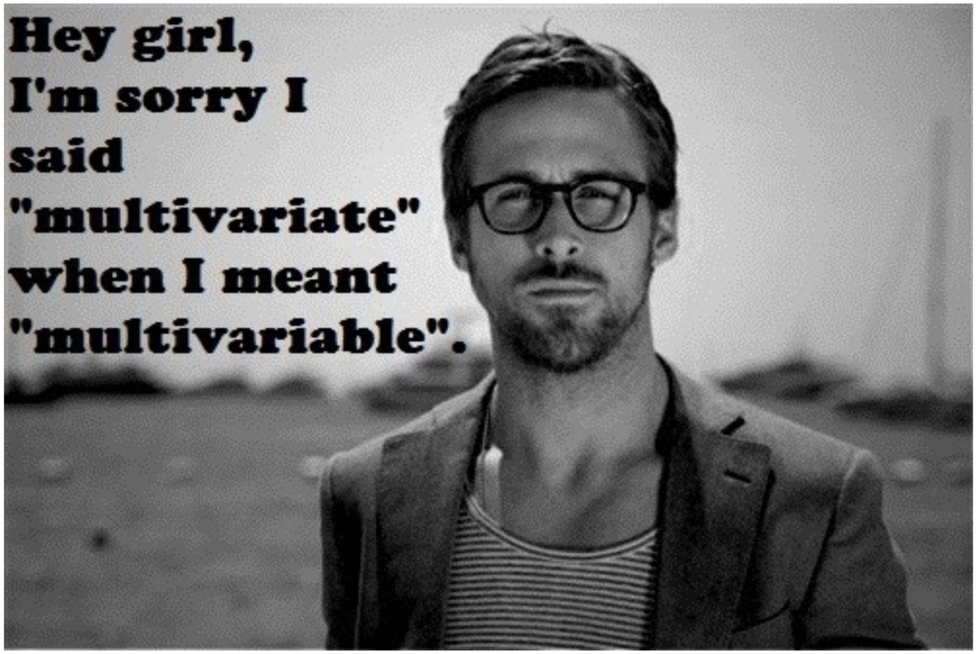
Introduction to Longitudinal Data Analysis with Linear Mixed Models (LMM)



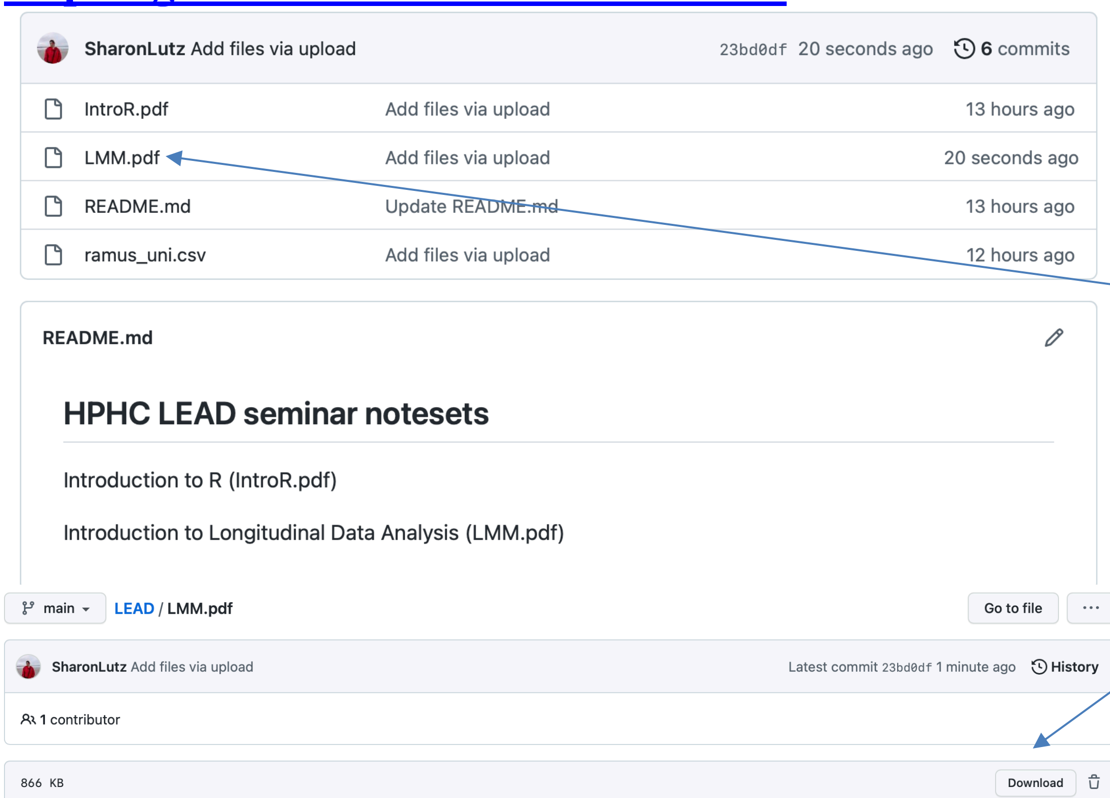
Additional Reading:

- Linear Mixed Models for Longitudinal Data; Verbeke and Molenberghs; Springer; 2000.
- Longitudinal Data Analysis, Hedeker and Gibbons, Wiley, 2006, Chapters 4-7.
- Applied Longitudinal Analysis, Fitzmaurice, Laird and Ware, Wiley, 2011, Chapters 8-9.
- https://m-clark.github.io/mixed-models-with-R/
- https://biostatisticsryangoslingreturns.tumblr.com

Overview

- Linear Mixed Models
  - 2 time points per persons
    - Paired t-test
    - Linear regression
    - Random intercept model
  - Linear mixed models
    - Random intercept & random intercept and slope

https://github.com/SharonLutz/LEAD



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Repeated Measures

- The terms “repeated measurements” or “repeated measures” are sometimes used as rough synonyms for “longitudinal data”
    - However, there are sometimes slight differences in the meaning of these terms
- Repeated measures are also multiple measurements on each of several individuals
    - But they are not necessarily through time
    - For example: Measurements of chemical concentration in the leaves of a plant taken at different locations (low, medium and high on the plant)
- Repeated measures could also be viewed as multiple measurements on a unit
    - For example: Standardized test scores from students in the same classroom in same school
- In all cases, however, we are referring to multiple measurements on a given subject or unit of observation

Longitudinal Data

- Longitudinal data consist of observations (i.e., measurements) taken repeatedly through time on a sample of experimental units (i.e., individuals, subjects)

- The experimental units or subjects can be human patients, animals, agricultural plots, etc

- Typically, the terms “longitudinal data” and “longitudinal study” refer to situations in which data are collected through time under controlled or uncontrolled circumstances

    - For example: dental measurements at 4 ages
        - Measure the ramus bone in lower jaw in mm
        - On 20 boys at four fixed ages: 8, 8.5, 9 & 9.5
        - Prospective study that has existed for over 40 years
        - Used by dentists to establish a growth curve for the ramus

- Longitudinal data are often contrasted with cross-sectional data

    - Cross-sectional data contains measurements on a sample of subjects at only one point in time

Advantages of Longitudinal Data

- Although time effects can be investigated in cross-sectional studies in which different subjects are examined at different time points
  - Only longitudinal data gives information on individual patterns of change
- Longitudinal studies economize on subjects
  - In investigating time effects in a longitudinal design or treatment effects in a crossover design, each subject can "serve as his or her own control"
  - Comparisons can be made within a subject rather than between subjects
  - This eliminates between-subjects sources of variability from the experimental error
    - This makes inferences more efficient/powerful
- Since the same variables are measured repeatedly on the same subjects, the reliability of those measurements can be assessed

Disadvantages of Longitudinal Data

- For longitudinal data, it is typically reasonable to assume independence across units
    - But repeated measures within a unit are almost always correlated
        - This may complicate the analysis
- Longitudinal data are often unbalanced or partially incomplete (involve missing data)
    - Loss to follow-up
        - Some subjects move away, die, miss appointments, etc.
    - For other types of clustered data, the cluster size may vary
        - Family data, where family size varies
    - This may complicate the analysis
- As a practical matter, methods and/or software may not exist or may be complex, so obtaining results and interpreting them may be difficult

Simple Longitudinal Data Analysis Example (Treatment Difference)

- 2 roughly normally distributed measurements per person at 2 equally spaced visits
  - Visit 1: Serum cholesterol measurements (mcg/dl) on standard American diet
  - Visit 2: Serum cholesterol measurements on vegan diet one month later

- Solutions for Simple Longitudinal Data:
  - 1. Change-score model: $\Delta = Y_{post} - Y_{pre}$ as outcome
    - Fit the linear regression model with just intercept: $E[\Delta_i] = E\left[Y_{post_i} - Y_{pre_i}\right] = \beta_0$
    - $H_0 : \beta_0 = 0$ (mean cholesterol difference=0)
      - (1) Fit with linear regression or (2) paired t-test

  - 2. Baseline-as-covariate model: outcome= Y_{post} and covariate= Y_{pre}
    - Fit the linear regression model: $E\left[Y_{post_i}\right] = \alpha_0 + \alpha_b Y_{pre_i}$
    - $H_0 : \alpha_b = 0$ (mean post cholesterol is not associated with pre cholesterol levels)

  - 3. Hybrid model: $\Delta = Y_{post} - Y_{pre}$ as outcome and covariate= Y_{pre}
    - Fit the linear regression model $E[\Delta_i] = E\left[Y_{post_i} - Y_{pre_i}\right] = \gamma_0 + \gamma_b Y_{pre_i}$
      - Slope γ_b indicates whether change in cholesterol related to base line value

Article: Glymour et al. When Is Baseline Adjustment Useful in Analyses of Change? An Example with Education and Cognitive Change. AJE. 2005
Discusses when not to adjust for baseline value

  - 4. Linear Mixed Model
    - Random Intercept- allows for time varying covariates

Simple Longitudinal Data Analysis Example (Time Difference)

- 2 roughly normally distributed measurements per person
  - Measurements taken at 2 visits (2nd visit is 5 years later)
    - Not a difference in treatment, but a difference of time (i.e. FEV_1 at visit 1 & 2)

- Solutions:
  - 1. Model the average of Y_{visit2} and Y_{visit1} as the outcome
      - May NOT be appropriate given the question of interest

  - 2. Model Y_{visit2} as outcome, with Y_{visit1} as a covariate using linear regression

  - 3. Consider $\Delta = Y_{visit2} - Y_{visit1}$ as outcome
    - Y_{visit1} may be included as a covariate in this model
      - Slope indicates whether changes over time are related to base line value

  - 4. Longitudinal model for the data (i.e. linear mixed models)
    - Outcome= both base line and follow-up measurements
    - Able to model time sensitive covariates
      - Example: Random intercept model

Solutions 1-4: can include covariates for precision or to account for confounders
Solutions 1-3: Not able to estimate variances at each time or correlation between time points

You need to consider the question of interest first, before deciding on the methods!!!

Linear Mixed Models

- Linear mixed model methods are methods for analyzing clustered data
    - When the outcome variable is continuous and approximately normally distributed
    - Useful for analyzing repeated measures and longitudinal data
    - Both SAS and R can be used to fit linear mixed models
- If the outcome is not 'approximately normal', one of the following might be considered:
    - Transform the outcome
    - Mixture distribution model
    - Non-normal outcome model
- A mixed model may have random as well as fixed effects
- Mixed models allow for more complicated error covariance structures
    - Unlike simpler general linear models

Linear regression in matrix notation

$$\mathbf{Y} = \mathbf{X\beta}+\boldsymbol{\varepsilon} \ \ where \ \ \varepsilon_i \sim N(0,\sigma^2\,\mathrm{I}_{nxn})$$

$$\mathbf{Y}_{n\times 1} = \begin{pmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{pmatrix}, \quad \boldsymbol{\beta}_{(p+1)\times 1} = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix}, \quad \boldsymbol{\varepsilon}_{n\times 1} = \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{pmatrix}$$

$$\mathbf{X}_{n\times(p+1)} = \begin{pmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1p} \\ 1 & x_{21} & x_{22} & \cdots & x_{2p} \\ \vdots & \vdots & \vdots & & \vdots \\ 1 & x_{n1} & x_{n2} & \cdots & x_{np} \end{pmatrix}$$

Note that the first column of the **X** matrix of independent variables contains only 1's. This is the general convention used for any regression model containing an intercept (i.e., a constant term β_0).

$$\begin{pmatrix} Y_1 \\ Y_2 \\ \vdots \\ Y_n \end{pmatrix} = \begin{pmatrix} 1 & x_{11} & x_{12} & \cdots & x_{1p} \\ 1 & x_{21} & x_{22} & \cdots & x_{2p} \\ \vdots & \vdots & \vdots & & \vdots \\ 1 & x_{n1} & x_{n2} & \cdots & x_{np} \end{pmatrix} \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \vdots \\ \beta_p \end{pmatrix} + \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{pmatrix} \Rightarrow \boxed{Var(Y) = \begin{pmatrix} \sigma^2 & 0 & 0 & \cdots & 0 \\ 0 & \sigma^2 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ 0 & 0 & 0 & \cdots & \sigma^2 \end{pmatrix} = \sigma^2\,\mathrm{I}_{nxn}}$$

$$Y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip} + \varepsilon_i \Rightarrow E[Y_i \mid \mathrm{X}_i] = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip}$$

$$Var(\mathrm{Y_i}) = \mathrm{cov}(\mathrm{Y_i}, \mathrm{Y}_i) = \sigma^2 \ \ and \ \ \mathrm{cov}(\mathrm{Y_i}, \mathrm{Y_j}) = 0 \ \ \forall \ i \neq j$$

Linear Mixed Model

- The general linear mixed model can be defined as:

$$\boldsymbol{Y} = \boldsymbol{X\beta} + \boldsymbol{Zb} + \boldsymbol{\varepsilon}$$

Fixed

Random

$\boldsymbol{Y}$ is the vector that contains the responses

$\boldsymbol{X}$ is a known matrix (design matrix)

$\boldsymbol{\beta}$ is the vector that contains the overall mean and all the fixed effects parameters

$\boldsymbol{Z}$ is a known matrix (the design matrix for the random effects)

$\boldsymbol{b}$ is the vector that contains all the random-effects variables

$\boldsymbol{\varepsilon}$ is the vector that contains the random errors

and

$$\begin{pmatrix} \mathbf{b} \\ \boldsymbol{\varepsilon} \end{pmatrix} \sim N\left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \mathbf{G} & 0 \\ 0 & \mathbf{R} \end{pmatrix} \right)$$

We can specify G and/or R to account for the correlation between measurements.

So that,

$$V = Var(\mathbf{Y}) = \mathbf{ZGZ'} + \mathbf{R}$$

Specified by SAS RANDOM statement.

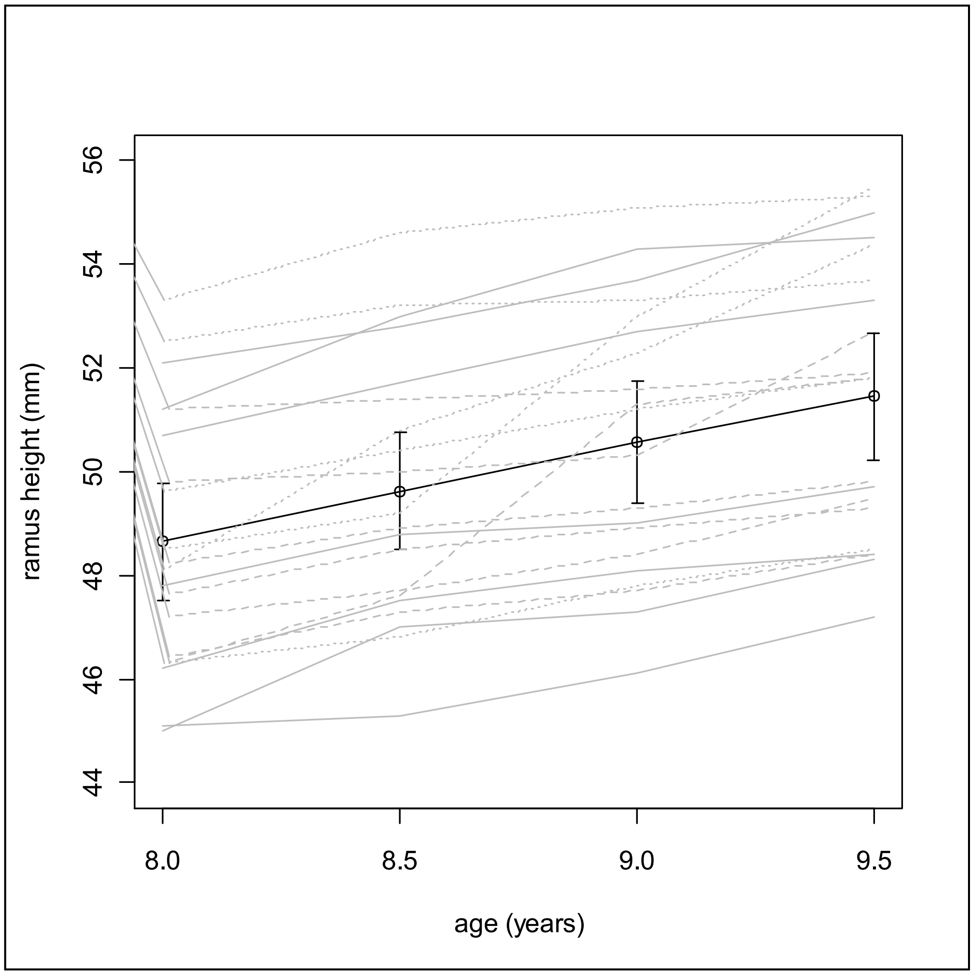
Specified by SAS REPEATED statement.

Linear Mixed Models: Random Intercept

- Special case of linear mixed models: random intercept model
  - A general linear model with an additional random effect called a random intercept
  - This random intercept can be defined for any cluster unit, but here we consider it for subjects
  - This model offers one simple way to account for longitudinal data
- Considering longitudinal studies, a random intercept term for subjects will
  - Account for between-subject variability
  - Induce a correlation structure for the responses
  - Often over simplistic for longitudinal data
    - But generally an improvement over no correlation structure at all

Ramus Data Example

- Ramus bone in lower jaw was measured on 20 boys at four fixed ages: 8, 8½, 9 & 9½
  - Prospective study that has existed for over 40 years
  - Used by dentists to establish a growth curve for the ramus
  - Ages 8 (h1), 8½ (h2), 9 (h3) and 9½ (h4) in mm
  - Balanced design- all 20 boys at all 4 time points



Consider a Random Intercept model for the Dental Measurements Example

- 20 boys at four fixed ages: 8, 8½, 9 & 9½
- Subject-time level: (i= 1,..,n subjects, j=1,..,4 ages)

$$Y_{ij} = \beta_0 + \beta_{age} age_{ij} + b_i + \varepsilon_{ij}$$

Where $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$ and $b_i \sim N(0, \sigma_b^2)$

- Then for full or complete data level

$\mathbf{Y} = \mathbf{X}\beta + \mathrm{Zb} + \varepsilon$

$$\mathbf{Y}_{4(20)\times 1} = \begin{pmatrix} \begin{bmatrix} Y_{(1)1} \\ Y_{(1)2} \\ Y_{(1)3} \\ Y_{(1)4} \end{bmatrix} \\ \vdots \\ \begin{bmatrix} Y_{(n)1} \\ Y_{(n)2} \\ Y_{(n)3} \\ Y_{(n)4} \end{bmatrix} \end{pmatrix} =, \mathbf{X}_{4(20)\,x(1+1)} = \begin{pmatrix} \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} & \begin{bmatrix} age1 \\ age2 \\ age3 \\ age4 \end{bmatrix} \\ \vdots & \vdots \\ \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} & \begin{bmatrix} age1 \\ age2 \\ age3 \\ age4 \end{bmatrix} \end{pmatrix}, \boldsymbol{\beta}_{(1+1)\times 1} = \begin{pmatrix} \beta_0 \\ \beta_{age} \end{pmatrix}, (\mathbf{X}\boldsymbol{\beta})_{4(20)\times 1} = \begin{pmatrix} \beta_0 + age1 * \beta_{age} \\ \beta_0 + age2 * \beta_{age} \\ \beta_0 + age3 * \beta_{age} \\ \beta_0 + age4 * \beta_{age} \\ \vdots \\ \beta_0 + age1 * \beta_{age} \\ \beta_0 + age2 * \beta_{age} \\ \beta_0 + age3 * \beta_{age} \\ \beta_0 + age4 * \beta_{age} \end{pmatrix}$$

$$V = Var(\mathbf{Y}) = \mathbf{ZGZ}' + \mathbf{R}$$

$$\mathbf{Z}_{4(20)\times 1(20)}\mathbf{G}_{20\times 20}\mathbf{Z}^{T}{}_{20\times 4(20)} = \begin{pmatrix} 1 & 0 & & 0 \\ 1 & 0 & \cdots & 0 \\ 1 & 0 & & 0 \\ 1 & 0 & & 0 \\ 0 & 1 & \cdots & 0 \\ 0 & 1 & & 0 \\ 0 & 1 & & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & 1 \\ 0 & 0 & & 1 \\ 0 & 0 & & 1 \\ 0 & 0 & \cdots & 1 \end{pmatrix} \begin{pmatrix} \sigma_b^2 & & 0 \\ & \ddots & \\ 0 & & \sigma_b^2 \end{pmatrix} \begin{pmatrix} 1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & \cdots & 0 & 0 & 0 & 0 \\ \vdots & & & & & & & \vdots & \ddots & \vdots & & & \vdots \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots & 1 & 1 & 1 & 1 \end{pmatrix}$$

$$\mathbf{Z}_{4(20)\times 1(20)}\mathbf{G}_{20\times 20}\mathbf{Z}^{T}{}_{20\times 4(20)} = \sigma_b^2 \begin{pmatrix} 1 & \cdots & 0 \\ 1 & & 0 \\ 1 & & 0 \\ 1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & 1 \\ 0 & & 1 \\ 0 & & 1 \\ 0 & \cdots & 1 \end{pmatrix} \begin{pmatrix} 1 & 1 & 1 & 1 & \cdots & 0 & 0 & 0 & 0 \\ \vdots & & & \vdots & \ddots & \vdots & & & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 & 1 & 1 & 1 \end{pmatrix} = \sigma_b^2 \begin{pmatrix} 1 & 1 & 1 & 1 & & & & & 0 \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ & & & & \ddots & & & & \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ 0 & & & & & 1 & 1 & 1 & 1 \end{pmatrix}_{4(20)\times 4(20)}$$

$$\begin{pmatrix} \mathbf{b} \\ \boldsymbol{\varepsilon} \end{pmatrix} \sim N\left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \mathbf{G} & 0 \\ 0 & \mathbf{R} \end{pmatrix} \right)$$

$$Var(\mathbf{Y})_{4(20)\times 4(20)} = \mathbf{Z}_{4(20)\times 20}\mathbf{G}_{20\times 20}\mathbf{Z}^{T}{}_{20\times 4(20)} + \mathbf{R}_{80\times 80} = \mathbf{Z}_{4(20)\times 20}\mathbf{G}_{20\times 20}\mathbf{Z}^{T}{}_{20\times 4(20)} + \sigma_e^2\mathbf{I}_{80\times 80}$$

$$= \sigma_b^2 \begin{pmatrix} 1 & 1 & 1 & 1 & & & & & 0 \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ & & & & \ddots & & & & \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ 0 & & & & & 1 & 1 & 1 & 1 \end{pmatrix}_{4(20)\times 4(20)} + \sigma_e^2 \begin{pmatrix} 1 & 0 & 0 & 0 & & & & & 0 \\ 0 & 1 & 0 & 0 & & & & & \\ 0 & 0 & 1 & 0 & & & & & \\ 0 & 0 & 0 & 1 & & & & & \\ & & & & \ddots & & & & \\ & & & & & 1 & 0 & 0 & 0 \\ & & & & & 0 & 1 & 0 & 0 \\ & & & & & 0 & 0 & 1 & 0 \\ 0 & & & & & 0 & 0 & 0 & 1 \end{pmatrix}_{4(20)\times 4(20)}$$

$$= \begin{pmatrix} \sigma_b^2+\sigma_e^2 & \sigma_b^2 & \sigma_b^2 & \sigma_b^2 & & & & & 0 \\ \sigma_b^2 & \sigma_b^2+\sigma_e^2 & \sigma_b^2 & \sigma_b^2 & & & & & \\ \sigma_b^2 & \sigma_b^2 & \sigma_b^2+\sigma_e^2 & \sigma_b^2 & & & & & \\ \sigma_b^2 & \sigma_b^2 & \sigma_b^2 & \sigma_b^2+\sigma_e^2 & & & & & \\ & & & & \ddots & & & & \\ & & & & & \sigma_b^2+\sigma_e^2 & \sigma_b^2 & \sigma_b^2 & \sigma_b^2 \\ & & & & & \sigma_b^2 & \sigma_b^2+\sigma_e^2 & \sigma_b^2 & \sigma_b^2 \\ & & & & & \sigma_b^2 & \sigma_b^2 & \sigma_b^2+\sigma_e^2 & \sigma_b^2 \\ 0 & & & & & \sigma_b^2 & \sigma_b^2 & \sigma_b^2 & \sigma_b^2+\sigma_e^2 \end{pmatrix}_{4(20)\times 4(20)}$$

Variance does NOT change as a function of age

Different forms of the Var(Y)

- Consider different structures for the variance covariance matrix
    - Allow for random intercept and random slope
        - Adding a random slope allows for a linear increase in the variance/covariance over time
        - How does this change the Var(Y)?

$$Z_{4(27)\times 2(27)} G_{2(27)\times 2(27)} {Z^T}_{2(27)\times 4(27)} = \begin{pmatrix} 1 & 8 & \cdots & 0 & 0 \\ 1 & 10 & & 0 & 0 \\ 1 & 12 & & 0 & 0 \\ 1 & 14 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 8 \\ 0 & 0 & & 1 & 10 \\ 0 & 0 & & 1 & 12 \\ 0 & 0 & \cdots & 1 & 14 \end{pmatrix} \begin{pmatrix} \sigma_I^2 & \sigma_{IS} & & & 0 \\ \sigma_{IS} & \sigma_S^2 & & & \\ & & \ddots & & \\ & & & \sigma_I^2 & \sigma_{IS} \\ 0 & & & \sigma_{IS} & \sigma_S^2 \end{pmatrix} {Z^T}_{2(27)\times 4(27)}$$

Ages should be 8, 8.5, 9, 9.5 instead of 8,10,12,14

$$ZGZ^T = \begin{pmatrix} 1 & 8 & \cdots & 0 & 0 \\ 1 & 10 & & 0 & 0 \\ 1 & 12 & & 0 & 0 \\ 1 & 14 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 8 \\ 0 & 0 & & 1 & 10 \\ 0 & 0 & & 1 & 12 \\ 0 & 0 & \cdots & 1 & 14 \end{pmatrix} \begin{pmatrix} \sigma_I^2 & \sigma_{IS} & & & 0 \\ \sigma_{IS} & \sigma_S^2 & & & \\ & & \ddots & & \\ & & & \sigma_I^2 & \sigma_{IS} \\ 0 & & & \sigma_{IS} & \sigma_S^2 \end{pmatrix} Z^T$$

$$= \begin{pmatrix} \sigma_I^2 + 8\sigma_{IS} & \sigma_{IS} + 8\sigma_S^2 & \cdots & 0 & 0 \\ \sigma_I^2 + 10\sigma_{IS} & \sigma_{IS} + 10\sigma_S^2 & & 0 & 0 \\ \sigma_I^2 + 12\sigma_{IS} & \sigma_{IS} + 12\sigma_S^2 & & 0 & 0 \\ \sigma_I^2 + 14\sigma_{IS} & \sigma_{IS} + 14\sigma_S^2 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & \sigma_I^2 + 8\sigma_{IS} & \sigma_{IS} + 8\sigma_S^2 \\ 0 & 0 & & \sigma_I^2 + 10\sigma_{IS} & \sigma_{IS} + 10\sigma_S^2 \\ 0 & 0 & & \sigma_I^2 + 12\sigma_{IS} & \sigma_{IS} + 12\sigma_S^2 \\ 0 & 0 & \cdots & \sigma_I^2 + 14\sigma_{IS} & \sigma_{IS} + 14\sigma_S^2 \end{pmatrix} \begin{pmatrix} 1 & 1 & 1 & 1 & \cdots & 0 & 0 & 0 & 0 \\ 8 & 10 & 12 & 14 & \cdots & 0 & 0 & 0 & 0 \\ \vdots & & & \vdots & \ddots & \vdots & & & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 & 1 & 1 & 1 \\ 0 & 0 & 0 & 0 & \cdots & 8 & 10 & 12 & 14 \end{pmatrix}$$

$$= 27 Blocks_{4\times4} \begin{pmatrix} \sigma_I^2 + 16\sigma_{IS} + 64\sigma_S^2 & \sigma_I^2 + 18\sigma_{IS} + 80\sigma_S^2 & \sigma_I^2 + 20\sigma_{IS} + 96\sigma_S^2 & \sigma_I^2 + 22\sigma_{IS} + 112\sigma_S^2 \\ & \sigma_I^2 + 20\sigma_{IS} + 100\sigma_S^2 & \sigma_I^2 + 22\sigma_{IS} + 120\sigma_S^2 & \sigma_I^2 + 24\sigma_{IS} + 140\sigma_S^2 \\ & & \sigma_I^2 + 24\sigma_{IS} + 144\sigma_S^2 & \sigma_I^2 + 26\sigma_{IS} + 168\sigma_S^2 \\ & & & \sigma_I^2 + 28\sigma_{IS} + 196\sigma_S^2 \end{pmatrix}$$

- Adding a random slope allows for a linear increase in the variance/covariance over time.

Fitting a Random Intercept Model in R

- Using lme function in nlme package (many other choices)

```
library(nlme)
ramus<- read.csv("/Users/sharon/Data/ramus_uni.csv", header = T)

ramus[1:8,]
#  boy age height
#1   1   8   47.8
#2   2   8   46.4
#3   3   8   46.3
#4   4   8   45.1
#5   5   8   47.6
#6   6   8   52.5
#7   7   8   51.2
#8   8   8   49.8

results<-lme(height~age,random=~1|boy,data=ramus)
summary(results)

# useful if p-value reported as 0
summary(results)$tTable
```

Fitting a Random Intercept Model in R

- Age is associated with the height of the ramus bone (p= 1.93e-16)

```
Linear mixed-effects model fit by REML
  Data: ramus
       AIC      BIC    logLik
  275.2223 284.6492 -133.6112

Random effects:
 Formula: ~1 | boy
        (Intercept)  Residual
StdDev:    2.468872 0.8233468

Fixed effects:  height ~ age
              Value Std.Error DF t-value p-value
(Intercept) 33.7475 1.5457389 59 21.8326       0
age          1.8660 0.1646694 59 11.3318       0
```

```
> summary(results)$tTable
              Value Std.Error DF t-value      p-value
(Intercept) 33.7475 1.5457389 59 21.8326 5.983862e-30
age          1.8660 0.1646694 59 11.3318 1.933433e-16
```

Fitting a Random Intercept and Slope Model in R

- Code

```
results2<-lme(height~age,random=~1+age|boy,data=ramus)
# same as
results2<-lme(height~age,random=~age|boy,data=ramus)
summary(results2)
```

```
Linear mixed-effects model fit by REML
  Data: ramus
       AIC      BIC    logLik
  246.2155 260.3558 -117.1078

Random effects:
 Formula: ~1 + age | boy
 Structure: General positive-definite, Log-Cholesky parametrization
            StdDev    Corr
(Intercept) 9.5949030 (Intr)
age         1.0970305 -0.966
Residual    0.4398295

Fixed effects:  height ~ age
              Value Std.Error DF   t-value p-value
(Intercept) 33.7475 2.2799050 59 14.802152       0
age          1.8660 0.2605989 59  7.160429       0
```

- Use AIC (Akaike information criterion) to compare models (275.2 vs 246.2)
    - Smaller is better

Recap: Longitudinal Data Analyses

- Linear mixed models can be used for longitudinal data analyses
- Models may not converge
  - Need to estimate both random and fixed effects
  - Certain models not possible: random intercept and slope on 2 time points
- Considered code in R
  - SAS has more choices and flexibility
  - More tutorials
    - https://m-clark.github.io/mixed-models-with-R/
- A lot more options than explored here
  - More than random intercept and slope
  - Covariance structure models for balanced data (SAS)
  - GLMM (generalized linear mixed models), GEE (generalized estimating equation)