BIOS 6612
Lecture 15

Mixed Models: Random Effects
Random Intercept & Random Slope Models

Good Reference Texts:
Fitzmaurice, Laird, & Ware. "Applied Longitudinal Analysis"
Verbeke & Molenberghs "Linear Mixed Models in Practice"
Brown & Prescott "Applied Mixed Models in Medicine"

Review (14) / Current (Lecture 15)/ Preview (Lecture 16)

General Linear Mixed Effects Models (Mixed Models) are the most flexible method for analyzing repeated measures / correlated / longitudinal data**.**

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{b} + \boldsymbol{\varepsilon} \text{ and } V = Var(\mathbf{Y}) = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \mathbf{R}$$

- Lecture 14: RMANOVA
- Lecture 15: specify the random effect **b** (i.e. random intercept, random slope)
- Lecture 16: specify Var(Y)

	Repeated Measures ANOVA	Covariance Pattern Model	Random Coefficients Model
Time	Categorical	Categorical -effect of time (i.e. linear, quadratic) does not need to be specified	Continuous -must model the effect of time
Covariance Structure	Compound Symmetry (i.e. spherecity)	Attempts to account for all the potential sources of variability that have an impact on the covariance among repeated measures on the same individual	Usually assumes random effects account for most of the variation in the data and the remaining error components, ε_i, have a very simple covariance structure (e.g., $\sigma^2 I_N$)
Distinguish between-subject and within-subject sources of variability	Yes	No	Yes
Highly Unbalanced Data	No	No	Yes

Linear Mixed Models
(SAS PROC MIXED)

Linear Mixed Effects Models (Mixed Models) are the most flexible method for analyzing repeated measures / correlated / longitudinal data.

- Allows continuous predictors for repeated measures
    - i.e. time can be treated as continuous in MIXED
    - must be categorical in RM-ANOVA

- Missing data can be handled easily and subjects with missing data are still included in the analysis.

- Allows for different covariance structures to model the correlation between repeated measures.

    -Also allows for heteroscedasticity.

- Subjects are weighted according to the amount of information available for that subject (number of measurements).

    - Subjects with more data points have curves which are closer to their data, while subjects with fewer data points have curves closer to the population curve.

Linear regression in matrix notation

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

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

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

> 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).

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

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

General Linear Mixed Model

- The general linear mixed model can be defined as: $Y = X\beta + Zb + \varepsilon$

Y is the vector that contains the responses

X is a known matrix (design matrix)

β is the vector that contains the overall mean and all the fixed effects parameters

Z is a known matrix (the design matrix for the random effects)

b is the vector that contains all the random-effects variables

ε is the vector that contains the random errors

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

$$\text{and} \quad \begin{pmatrix} \mathbf{b} \\ \varepsilon \end{pmatrix} \sim N\left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \mathbf{G} & 0 \\ 0 & \mathbf{R} \end{pmatrix} \right) \quad \text{So that,} \quad V = Var(\mathbf{Y}) = \mathbf{ZGZ'} + \mathbf{R}$$

Specified by SAS RANDOM statement.

Specified by SAS REPEATED statement.

Approach 1: Random Coefficients Model
        -Specify the functional form of the effect (i.e. **b,Z**)
        -Random Intercept; Random Intercept and Random Slope
Approach 2: Covariance Pattern Model
        -Don't specify the functional form of the effect
        -Instead specify the covariance/ variance structure (i.e. Var($\mathbf{Y}$) = $\mathbf{R}$)
Approach 3: Both 1 & 2 (not recommended: need to think about $\mathbf{V}$)

General Linear Mixed Model in Matrix Notation

- Example: Random intercept model and 3 measurements for all n subjects
- Fixed effects contribute to the mean and random effects contribute to the variance

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + Z b_1 + \boldsymbol{\varepsilon}$$

$$
\mathbf{Y}_{3n\times1} =
\begin{pmatrix}
\begin{bmatrix} Y_{11} \\ Y_{12} \\ Y_{13} \end{bmatrix} \\
\begin{bmatrix} Y_{21} \\ Y_{22} \\ Y_{23} \end{bmatrix} \\
\vdots \\
\begin{bmatrix} Y_{n1} \\ Y_{n2} \\ Y_{n3} \end{bmatrix}
\end{pmatrix},
X_{3n\times(p+1)} =
\begin{pmatrix}
1 & x_{(11)1} & x_{(11)2} & \cdots & x_{(11)p} \\
1 & x_{(12)1} & x_{(12)2} & \cdots & x_{(12)p} \\
1 & x_{(13)1} & x_{(13)2} & \cdots & x_{(13)p} \\
1 & x_{(21)1} & x_{(21)2} & \cdots & x_{(21)p} \\
1 & x_{(22)1} & x_{(22)2} & \cdots & x_{(22)p} \\
1 & x_{(23)1} & x_{(23)2} & \cdots & x_{(23)p} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
1 & x_{(n1)1} & x_{(n1)2} & \cdots & x_{(n1)p} \\
1 & x_{(n2)1} & x_{(n2)2} & \cdots & x_{(n2)p} \\
1 & x_{(n3)1} & x_{(n3)2} & \cdots & x_{(n3)p}
\end{pmatrix},
\boldsymbol{\beta}_{(p+1)\times1} =
\begin{pmatrix}
\beta_0 \\ \beta_1 \\ \vdots \\ \beta_p
\end{pmatrix},
\boldsymbol{\varepsilon}_{3n\times1} =
\begin{pmatrix}
\begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{12} \\ \varepsilon_{13} \end{bmatrix} \\
\begin{bmatrix} \varepsilon_{21} \\ \varepsilon_{22} \\ \varepsilon_{23} \end{bmatrix} \\
\vdots \\
\begin{bmatrix} \varepsilon_{n1} \\ \varepsilon_{n2} \\ \varepsilon_{n3} \end{bmatrix}
\end{pmatrix},
Z_{3n\times n} =
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1
\end{pmatrix}
$$

$$\varepsilon \sim N(0, \sigma_e^2 \, I_{3n \times 3n}) \Rightarrow E[\varepsilon_i] = 0$$

$$b_1 \sim N(0, \sigma^2 \, I_{n \times n}) \Rightarrow E[b_1] = 0$$

$$Y_i = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip} + Z b_1 + \varepsilon_i \Rightarrow E(Y) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \ldots + \beta_p x_{ip}$$

General Linear Mixed Model in Matrix Notation

- Example: Random intercept model and 3 measurements for all n subjects

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + Z b_1 + \boldsymbol{\varepsilon}$$

$$
\mathbf{Y}_{3n\times1} =
\begin{pmatrix}
\begin{bmatrix} Y_{11} \\ Y_{12} \\ Y_{13} \end{bmatrix} \\
\begin{bmatrix} Y_{21} \\ Y_{22} \\ Y_{23} \end{bmatrix} \\
\vdots \\
\begin{bmatrix} Y_{n1} \\ Y_{n2} \\ Y_{n3} \end{bmatrix}
\end{pmatrix},
X_{3n\times(p+1)} =
\begin{pmatrix}
1 & x_{(11)1} & x_{(11)2} & \cdots & x_{(11)p} \\
1 & x_{(12)1} & x_{(12)2} & \cdots & x_{(12)p} \\
1 & x_{(13)1} & x_{(13)2} & \cdots & x_{(13)p} \\
1 & x_{(21)1} & x_{(21)2} & \cdots & x_{(21)p} \\
1 & x_{(22)1} & x_{(22)2} & \cdots & x_{(22)p} \\
1 & x_{(23)1} & x_{(23)2} & \cdots & x_{(23)p} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
1 & x_{(n1)1} & x_{(n1)2} & \cdots & x_{(n1)p} \\
1 & x_{(n2)1} & x_{(n2)2} & \cdots & x_{(n2)p} \\
1 & x_{(n3)1} & x_{(n3)2} & \cdots & x_{(n3)p}
\end{pmatrix},
\boldsymbol{\beta}_{(p+1)\times1} =
\begin{pmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{pmatrix},
\boldsymbol{\varepsilon}_{3n\times1} =
\begin{pmatrix}
\begin{bmatrix} \varepsilon_{11} \\ \varepsilon_{12} \\ \varepsilon_{13} \end{bmatrix} \\
\begin{bmatrix} \varepsilon_{21} \\ \varepsilon_{22} \\ \varepsilon_{23} \end{bmatrix} \\
\vdots \\
\begin{bmatrix} \varepsilon_{n1} \\ \varepsilon_{n2} \\ \varepsilon_{n3} \end{bmatrix}
\end{pmatrix},
Z_{3n\times n} =
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1
\end{pmatrix}
$$

$$
Var(\mathbf{Y}) = Z_{3n\times n}\left(\sigma^2 I_{n\times n}\right) Z^T_{n\times 3n} + \sigma_\varepsilon^2 I_{3n\times 3n} =
\begin{pmatrix}
\sigma^2+\sigma_\varepsilon^2 & \sigma^2 & \sigma^2 & & & & \\
\sigma^2 & \sigma^2+\sigma_\varepsilon^2 & \sigma^2 & & & 0 & \\
\sigma^2 & \sigma^2 & \sigma^2+\sigma_\varepsilon^2 & & & & \\
& & & \ddots & & & \\
& & & & \sigma^2+\sigma_\varepsilon^2 & \sigma^2 & \sigma^2 \\
& & & & \sigma^2 & \sigma^2+\sigma_\varepsilon^2 & \sigma^2 \\
& 0 & & & \sigma^2 & \sigma^2 & \sigma^2+\sigma_\varepsilon^2
\end{pmatrix}
$$

Random Coefficients Model (Growth Curve Model)

- Usually treats time as a continuous variable.
    - Must model the effect of time (e.g., polynomial functions, piecewise linear functions).

- Distinguishes between-subject and within-subject sources of variability.

- Usually assumes random effects account for most of the variation in the data and the remaining error components, ε_i, have a very simple covariance structure (e.g., independence $\sigma^2 I_N$).

- Appropriate for highly unbalanced data with many repeated measurements per subject or when timing of assessments differ widely among individuals.

- SAS uses the RANDOM statement to model the random effects and the covariance structure for the RANDOM effects. 📝
    - The RANDOM statement defines the random effects in the model (the Z matrix containing covariates with subject-specific regression coefficients).

        - The TYPE=option specifies the covariance structure, G, for the random effects.

        - For longitudinal data analysis, one usually specifies TYPE=UN which does not assume the random-effects covariance matrix to be of any specific form.

    - A REPEATED statement can also be used to model the covariance structure for the residual components (if excluded, SAS assumes TYPE=SIMPLE and assumes that all variability in the data which is not taken into account by the random effects is purely measurement error). 📝

- R package 'nlme' function `lme()` uses a similar structure
  - `random=~1|id` argument defines a model for the random effects, structured as a formula
    - `~1` indicates random intercept only

    - `|id` gives the variable identifying independent units (patients, clusters, etc.)

    - assumes an unstructured covariance matrix for the random effects

  - `correlation=corCompSymm(form=~1|id)` argument defines a model for the correlation structure of the error term

    - `corCompSymm` specifies the correlation structure, compound symmetry in this example; other options include AR(1), ARMA, unstructured

    - `form=~1|id` specifies the model itself

    - can use `weights=varIdent(form=~1|as.numeric(time))` to complete the specification of unstructured covariance (needed for the heteroscedasticity component, as by default equal variances are assumed, so the diagonal elements of the covariance matrix are all equal)
- R package 'lme4' function `lmer()` also can fit mixed effects models
  - Specify random effects model in the formula for the mean model: `y ~ ... + (1|id)` for random intercept model

- The random Intercept model is equivalent to the covariance structure model (fitting the same fixed effects) with compound symmetry, which is also equivalent to the repeated measures ANOVA model for categorized variables.

Example: Dental Data (Wolfinger & Chang; Pothoff & Roy)

Dental measurements from the center of the pituitary to the pterygomaxillary fissure (measured in mm) for 11 girls and 16 boys at ages 8, 10, 12, and 14. The subjects are individual children, and there are four repeated measurements on each child.

Dental Measurements Data

Person	Gender	Age 8	Age 10	Age 12	Age 14
1	F	21.0	20.0	21.5	23.0
2	F	21.0	21.5	24.0	25.5
3	F	20.5	24.0	24.5	26.0
4	F	23.5	24.5	25.0	26.5
5	F	21.5	23.0	22.5	23.5
6	F	20.0	21.0	21.0	22.5
7	F	21.5	22.5	23.0	25.0
8	F	23.0	23.0	23.5	24.0
9	F	20.0	21.0	22.0	21.5
10	F	16.5	19.0	19.0	19.5
11	F	24.5	25.0	28.0	28.0
12	M	26.0	25.0	29.0	31.0
13	M	21.5	22.5	23.0	26.5
14	M	23.0	22.5	24.0	27.5
15	M	25.5	27.5	26.5	27.0
16	M	20.0	23.5	22.5	26.0
17	M	24.5	25.5	27.0	28.5
18	M	22.0	22.0	24.5	26.5
19	M	24.0	21.5	24.5	25.5
20	M	23.0	20.5	31.0	26.0
21	M	27.5	28.0	31.0	31.5
22	M	23.0	23.0	23.5	25.0
23	M	21.5	23.5	24.0	28.0
24	M	17.0	24.5	26.0	29.5
25	M	22.5	25.5	25.5	26.0
26	M	23.0	24.5	26.0	30.0
27	M	22.0	21.5	23.5	25.0

```
DATA forglm(keep=person gender y1-y4)
     formixed(keep=person gender age y);
INPUT person gender$ y1-y4;
OUTPUT forglm;
y=y1; age=8;  OUTPUT formixed;
y=y2; age=10; OUTPUT formixed;
y=y3; age=12; OUTPUT formixed;
y=y4; age=14; OUTPUT formixed;
DATALINES;
 1 F 21.0 20.0 21.5 23.0
 2 F 21.0 21.5 24.0 25.5
 3 F 20.5 24.0 24.5 26.0
 4 F 23.5 24.5 25.0 26.5
 5 F 21.5 23.0 22.5 23.5
 6 F 20.0 21.0 21.0 22.5
 7 F 21.5 22.5 23.0 25.0
 8 F 23.0 23.0 23.5 24.0
 9 F 20.0 21.0 22.0 21.5
10 F 16.5 19.0 19.0 19.5
11 F 24.5 25.0 28.0 28.0
12 M 26.0 25.0 29.0 31.0
13 M 21.5 22.5 23.0 26.5
14 M 23.0 22.5 24.0 27.5
15 M 25.5 27.5 26.5 27.0
16 M 20.0 23.5 22.5 26.0
17 M 24.5 25.5 27.0 28.5
18 M 22.0 22.0 24.5 26.5
19 M 24.0 21.5 24.5 25.5
20 M 23.0 20.5 31.0 26.0
21 M 27.5 28.0 31.0 31.5
22 M 23.0 23.0 23.5 25.0
23 M 21.5 23.5 24.0 28.0
```
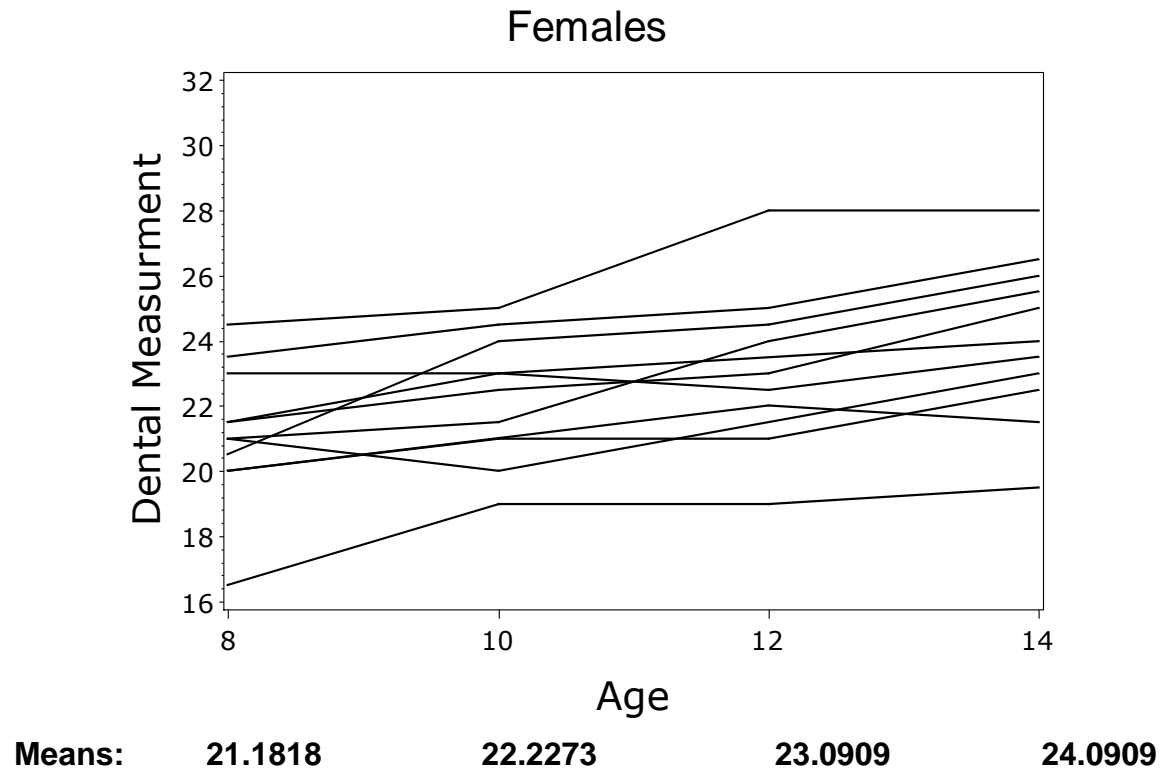
```
24 M 17.0 24.5 26.0 29.5
25 M 22.5 25.5 25.5 26.0
26 M 23.0 24.5 26.0 30.0
27 M 22.0 21.5 23.5 25.0
;


*** For GPLOT symbols ***;
%macro symbols;
%do i = 1 %to 27;
SYMBOL&i INTERPOL=JOIN COLOR=black
LINE=1
          WIDTH=2;
%end;
%mend;
%symbols;
```
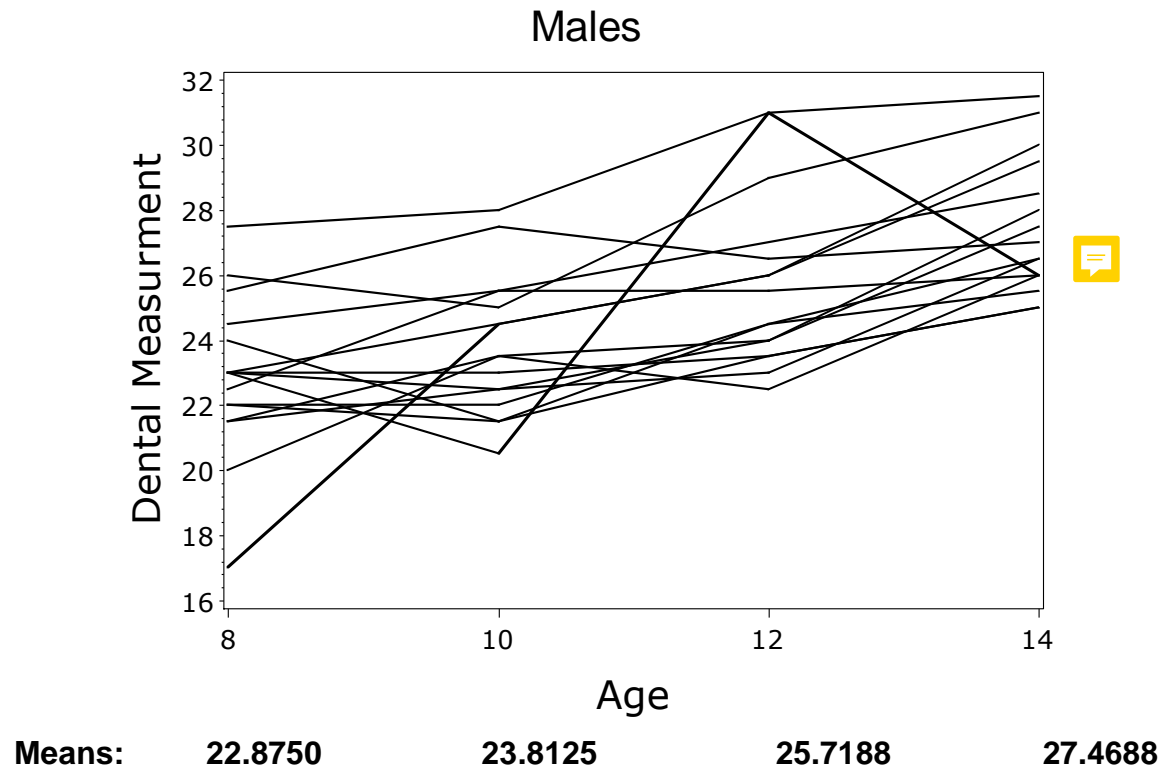
Females

Means: **21.1818**   **22.2273**   **23.0909**   **24.0909**

```
PROC GPLOT DATA=formixed;
 PLOT (y)*age =person
/VAXIS=AXIS1 HAXIS=AXIS2 NOLEGND;
 AXIS1 LABEL = (FONT='Verdana' HEIGHT= 3 ANGLE=90 POSITION=top "Dental Measurment" )
                VALUE=(FONT='Verdana' HEIGHT=2) ORDER=(16 to 32 by 2) ;
 AXIS2  LABEL = (FONT='Verdana' HEIGHT=3 "Age") MINOR=NONE ORDER=(8 to 14 by 2)
                VALUE=(FONT='Verdana' HEIGHT=2);
 WHERE male = 0;
 LEGEND1 ;
 TITLE1 HEIGHT=3 FONT=ARIAL "Females";
 RUN;
```

Males

| Means: | 22.8750 | 23.8125 | 25.7188 | 27.4688 |

```
PROC GPLOT DATA=formixed;
 PLOT (y)*age =person
/VAXIS=AXIS1 HAXIS=AXIS2 NOLEGND;
 AXIS1 LABEL = (FONT='Verdana' HEIGHT= 3 ANGLE=90 POSITION=top "Dental Measurment" )
               VALUE=(FONT='Verdana' HEIGHT=2) ORDER=(16 to 32 by 2) ;
 AXIS2 LABEL = (FONT='Verdana' HEIGHT=3 "Age") MINOR=NONE ORDER=(8 to 14 by 2)
               VALUE=(FONT='Verdana' HEIGHT=2);
 WHERE male = 1;
 LEGEND1 ;
 TITLE1 HEIGHT=3 FONT=ARIAL "Males";
```

- Consider a <u>Random Intercept model</u> for the Dental Measurements Example
  - $\mathbf{Z}$ matrix is just 1 column of 1's

$$\mathbf{Y} = \mathbf{X}\beta + \mathbf{Z}b + \varepsilon$$

$$\mathbf{Y}_{4(27)\times 1} = \begin{pmatrix} \begin{bmatrix} Y_{(1)1} \\ Y_{(1)2} \\ Y_{(1)3} \\ Y_{(1)4} \end{bmatrix} \\ \vdots \\ \begin{bmatrix} Y_{(11)1} \\ Y_{(11)2} \\ Y_{(11)3} \\ Y_{(11)4} \end{bmatrix} \\ \begin{bmatrix} Y_{(12)1} \\ Y_{(12)2} \\ Y_{(12)3} \\ Y_{(12)4} \end{bmatrix} \\ \vdots \\ \begin{bmatrix} Y_{(27)1} \\ Y_{(27)2} \\ Y_{(27)3} \\ Y_{(27)4} \end{bmatrix} \end{pmatrix} == \begin{pmatrix} \begin{bmatrix} 21.0 \\ 20.0 \\ 21.5 \\ 23.0 \end{bmatrix} \\ \vdots \\ \begin{bmatrix} 24.5 \\ 25.0 \\ 28.0 \\ 28.0 \end{bmatrix} \\ \begin{bmatrix} 26.0 \\ 25.0 \\ 29.0 \\ 31.0 \end{bmatrix} \\ \vdots \\ \begin{bmatrix} 22.0 \\ 21.5 \\ 23.5 \\ 25.0 \end{bmatrix} \end{pmatrix}, X_{4(27)\,X(3+1)} = \begin{pmatrix} 1 & 0 & 8 & 0 \\ 1 & 0 & 10 & 0 \\ 1 & 0 & 12 & 0 \\ 1 & 0 & 14 & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 1 & 0 & 8 & 0 \\ 1 & 0 & 10 & 0 \\ 1 & 0 & 12 & 0 \\ 1 & 0 & 14 & 0 \\ 1 & 1 & 8 & 8 \\ 1 & 1 & 10 & 10 \\ 1 & 1 & 12 & 12 \\ 1 & 1 & 14 & 14 \\ \vdots & \vdots & \vdots & \vdots \\ 1 & 1 & 8 & 8 \\ 1 & 1 & 10 & 10 \\ 1 & 1 & 12 & 12 \\ 1 & 1 & 14 & 14 \end{pmatrix}, \beta_{(3+1)\times 1} = \begin{pmatrix} \beta_0 \\ \beta_{gender} \\ \beta_{age} \\ \beta_{gender*age} \end{pmatrix}, (X\beta)_{4(27)\times 1} = \begin{pmatrix} \beta_0 + 8\beta_{age} \\ \beta_0 + 10\beta_{age} \\ \beta_0 + 12\beta_{age} \\ \beta_0 + 14\beta_{age} \\ \vdots \\ \beta_0 + 8\beta_{age} \\ \beta_0 + 10\beta_{age} \\ \beta_0 + 12\beta_{age} \\ \beta_0 + 14\beta_{age} \\ (\beta_0 + \beta_{gender}) + 8(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 10(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 12(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 14(\beta_{age} + \beta_{g*a}) \\ \vdots \\ (\beta_0 + \beta_{gender}) + 8(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 10(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 12(\beta_{age} + \beta_{g*a}) \\ (\beta_0 + \beta_{gender}) + 14(\beta_{age} + \beta_{g*a}) \end{pmatrix}$$

$$
Z_{4(27)\times 1(27)} G_{27\times 27} Z^T{}_{27\times 4(27)} =
\begin{pmatrix}
1 & 0 & & 0 \\
1 & 0 & \cdots & 0 \\
1 & 0 & & 0 \\
1 & 0 & & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & & 0 \\
0 & 1 & & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \\
0 & 0 & & 1 \\
0 & 0 & & 1 \\
0 & 0 & \cdots & 1
\end{pmatrix}
\begin{pmatrix}
\sigma_I^2 & & 0 \\
& \ddots & \\
0 & & \sigma_I^2
\end{pmatrix}
\begin{pmatrix}
1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 & \cdots & 0 & 0 & 0 & 0 \\
\vdots & & & & & & & & \vdots & \ddots & \vdots & & \vdots \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots & 1 & 1 & 1 & 1
\end{pmatrix}
$$

$$
Z_{4(27)\times 1(27)} G_{27\times 27} Z^T{}_{27\times 4(27)} = \sigma_I^2
\begin{pmatrix}
1 & \cdots & 0 \\
1 & & 0 \\
1 & & 0 \\
1 & \cdots & 0 \\
\vdots & \ddots & \vdots \\
0 & \cdots & 1 \\
0 & & 1 \\
0 & & 1 \\
0 & \cdots & 1
\end{pmatrix}
\begin{pmatrix}
1 & 1 & 1 & 1 & \cdots & 0 & 0 & 0 & 0 \\
\vdots & & & & \vdots & \ddots & \vdots & & \vdots \\
0 & 0 & 0 & 0 & \cdots & 1 & 1 & 1 & 1
\end{pmatrix}
= \sigma_I^2
\begin{pmatrix}
1 & 1 & 1 & 1 & & & & & 0 \\
1 & 1 & 1 & 1 & & & & & \\
1 & 1 & 1 & 1 & & & & & \\
1 & 1 & 1 & 1 & & & & & \\
& & & & \ddots & & & & \\
& & & & & 1 & 1 & 1 & 1 \\
& & & & & 1 & 1 & 1 & 1 \\
& & & & & 1 & 1 & 1 & 1 \\
0 & & & & & 1 & 1 & 1 & 1
\end{pmatrix}_{4(27)\times 4(27)}
$$

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

$$Var(Y)_{4(27) \times 4(27)} = Z_{4(27) \times 27} G_{27 \times 27} Z^T_{27 \times 4(27)} + \Sigma_{108 \times 108} = Z_{4(27) \times 27} G_{27 \times 27} Z^T_{27 \times 4(27)} + \sigma_e^2 I_{108 \times 108}$$

$$= \sigma_I^2 \begin{pmatrix} 1 & 1 & 1 & 1 & & & & & 0 \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ 1 & 1 & 1 & 1 & & & & & \\ & & & & \ddots & & & & \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ & & & & & 1 & 1 & 1 & 1 \\ 0 & & & & & 1 & 1 & 1 & 1 \end{pmatrix}_{4(27) \times 4(27)} + \sigma_e^2 \begin{pmatrix} 1 & 0 & 0 & 0 & & & & & 0 \\ 0 & 1 & 0 & 0 & & & & & \\ 0 & 0 & 1 & 0 & & & & & \\ 0 & 0 & 0 & 1 & & & & & \\ & & & & \ddots & & & & \\ & & & & & 1 & 0 & 0 & 0 \\ & & & & & 0 & 1 & 0 & 0 \\ & & & & & 0 & 0 & 1 & 0 \\ 0 & & & & & 0 & 0 & 0 & 1 \end{pmatrix}_{4(27) \times 4(27)}$$

$$= \begin{pmatrix} \sigma_I^2 + \sigma_e^2 & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 & & & & & 0 \\ \sigma_I^2 & \sigma_I^2 + \sigma_e^2 & \sigma_I^2 & \sigma_I^2 & & & & & \\ \sigma_I^2 & \sigma_I^2 & \sigma_I^2 + \sigma_e^2 & \sigma_I^2 & & & & & \\ \sigma_I^2 & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 + \sigma_e^2 & & & & & \\ & & & & \ddots & & & & \\ & & & & & \sigma_I^2 + \sigma_e^2 & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 \\ & & & & & \sigma_I^2 & \sigma_I^2 + \sigma_e^2 & \sigma_I^2 & \sigma_I^2 \\ & & & & & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 + \sigma_e^2 & \sigma_I^2 \\ 0 & & & & & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 & \sigma_I^2 + \sigma_e^2 \end{pmatrix}_{4(27) \times 4(27)}$$

- Then a Random Intercept model is equivalent to the

  -Covariance Structure Model (fitting the same fixed effects) with TYPE = CS

  - Similar to the Repeated Measures ANOVA model for categorized variables

    -If there are no covariates included
    -Sphericity is similar to the assumptions made for CS

- Adding a random slope allows for population heterogeneity in the effect of time on the mean of the outcome variable

- How does this change Var(Y)?

$$Z_{4(27)\times2(27)}\,G_{2(27)\times2(27)}\,Z^{T}_{2(27)\times4(27)} = \begin{pmatrix} 1 & 8 & \cdots & 0 & 0 \\ 1 & 10 & & 0 & 0 \\ 1 & 12 & & 0 & 0 \\ 1 & 14 & \cdots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \cdots & 1 & 8 \\ 0 & 0 & & 1 & 10 \\ 0 & 0 & & 1 & 12 \\ 0 & 0 & \cdots & 1 & 14 \end{pmatrix} \begin{pmatrix} \sigma_I^2 & \sigma_{IS} & & & 0 \\ \sigma_{IS} & \sigma_S^2 & & & \\ & & \ddots & & \\ & & & \sigma_I^2 & \sigma_{IS} \\ 0 & & & \sigma_{IS} & \sigma_S^2 \end{pmatrix} Z^{T}_{2(27)\times4(27)}$$

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

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

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

- Adding a random slope allows for change in the variance/covariance over time.
    o **Z** matrix now has 2 columns, one of 1's and one with age at each time point
    o If $\sigma_{IS} > 0$ (positive correlation between random intercept and random slope), then this will lead to an increase in both variance and covariance over time ($\sigma^2 > 0$ for I and S)
    o If $\sigma_{IS} < 0$, harder to predict the effects on variance and covariance with time (depends on values of σ_I and σ_S)

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

$$Var(Y)_{4(27)\times4(27)} = Z_{4(27)\times2(27)}G_{2(27)\times2(27)}Z^T_{2(27)\times4(27)} + \Sigma_{108\times108} = Z_{4(27)\times2(27)}G_{2(27)\times2(27)}Z^T_{2(27)\times4(27)} + \sigma_e^2 I_{108\times108}$$

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

SAS/R Code for Random Coefficients Model

Random Intercept and Slope:
[4 covariance parameters (2 variance + 1 covariance = 3 for random effects + 1 residual)]

```
PROC MIXED DATA=formixed;
 CLASS catage person;
 MODEL y = male age male*age / SOLUTION;
 RANDOM INT age /TYPE=UN SUBJECT=person G GCORR;
RUN;
```

Random Intercept:
[2 covariance parameters (1 for random Intercept variance + 1 residual)]

```
PROC MIXED DATA=formixed;
 CLASS catage person;
 MODEL y = male age male*age/ SOLUTION;
 RANDOM INT  /TYPE=UN SUBJECT=person G GCORR;
RUN;
```

catage = age

Creating a second variable "catage" that is identical to the variable "age" allows us to use age as both a continuous and categorical variable in the same model.

```
library(lme4)

dental <- read.table('dental.txt',header=TRUE)
dental.long <- reshape(dental,direction='long',
                    varying=3:6,
                    v.names='meas',
                    time=seq(8,14,by=2),
                    timevar='age',
                    idvar='Person')
dental.long$male <- 1*(dental.long$Gender=='M')

mod1 <- lmer(meas ~ male*age + (1+age|Person),data=dental.long,REML=TRUE)
mod2 <- lmer(meas ~ male*age + (1|Person),data=dental.long,REML=TRUE)
```

Random Intercept and Slope:

```
The Mixed Procedure


        Model Information


Data Set                    WORK.FORMIXED
Dependent Variable          y
Covariance Structure        Unstructured
Subject Effect              person
Estimation Method           REML
Residual Variance Method    Profile
Fixed Effects SE Method     Model-Based
Degrees of Freedom Method   Containment



        Class Level Information


  Class     Levels    Values


  catage         4    8 10 12 14
  person        27    1 2 3 4 5 6 7 8 9 10 11 12 13
                      14 15 16 17 18 19 20 21 22 23
                      24 25 26 27



            Dimensions


    Covariance Parameters           4
    Columns in X                    4
    Columns in Z Per Subject        2
    Subjects                       27
    Max Obs Per Subject             4
```
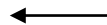
Two variances for random effects (intercept & slope)
One covariance for random effects
One residual error

Random Intercept and Slope

```
            Number of Observations
         Number of Observations Read           108
         Number of Observations Used           108
         Number of Observations Not Used         0


                 The Mixed Procedure


                 Iteration History


Iteration      Evaluations      -2 Res Log Like        Criterion
        0                1          483.55911746
        1                1          432.58166150        0.00000000



            Convergence criteria met.


                Estimated G Matrix
    Row    Effect       person        Col1        Col2
     1     Intercept      1          5.7864     -0.2896
     2     age            1         -0.2896     0.03252



            Estimated G Correlation Matrix
    Row    Effect       person        Col1        Col2
     1     Intercept      1          1.0000     -0.6676
     2     age            1         -0.6676      1.0000



            Covariance Parameter Estimates
          Cov Parm      Subject     Estimate
          UN(1,1)       person        5.7864
          UN(2,1)       person       -0.2896
          UN(2,2)       person       0.03252
          Residual                    1.7162
```

Random Intercept and Slope

```
              The Mixed Procedure
                  Fit Statistics

        -2 Res Log Likelihood          432.6
        AIC (smaller is better)        440.6
        AICC (smaller is better)       441.0
        BIC (smaller is better)        445.8



            Null Model Likelihood Ratio Test

          DF      Chi-Square      Pr > ChiSq
           3         50.98           <.0001



            Solution for Fixed Effects

                       Standard
Effect       Estimate    Error      DF    t Value    Pr > |t|

Intercept    17.3727    1.2284      25     14.14      <.0001
male         -1.0321    1.5957      54     -0.65      0.5205
age           0.4795    0.1037      25      4.62      <.0001
male*age      0.3048    0.1347      54      2.26      0.0277

            Type 3 Tests of Fixed Effects

              Num      Den
  Effect       DF       DF    F Value    Pr > F
   male         1       54       0.42    0.5205
   age          1       25      21.38    <.0001
   male*age     1       54       5.12    0.0277
```

Significant age×gender interaction

Intercept: dental distance for female at age=0

Male: Estimated difference between males and females at age=0

Slope for females: 0.4795
Slope for males: 0.4795+0.3048

Random Intercept and Slope

```
summary(mod1)

## Linear mixed model fit by REML ['lmerMod']
## Formula: meas ~ male * age + (1 + age | Person)
##    Data: dental.long
##
## REML criterion at convergence: 432.6
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.1681 -0.3859  0.0071  0.4452  3.8495
##
## Random effects:
##  Groups   Name        Variance Std.Dev. Corr
##  Person   (Intercept) 5.78640  2.4055
##           age         0.03252  0.1803   -0.67
##  Residual             1.71620  1.3100
## Number of obs: 108, groups:  Person, 27
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept)  17.3727     1.2284  14.143
## male         -1.0321     1.5957  -0.647
## age           0.4795     0.1037   4.623
## male:age      0.3048     0.1347   2.262
##
## Correlation of Fixed Effects:
##          (Intr) male   age
## male     -0.770
## age      -0.880  0.678
## male:age  0.678 -0.880 -0.770
```

- **Random Coefficient Model (Random Intercept & Slope), UN Covariance (TYPE=UN)**

$$V = Var(\mathbf{Y}) = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \Sigma$$

$$
X = \underset{108 \times 4}{}
\begin{pmatrix}
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
. & & & . \\
. & & & . \\
. & & & . \\
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
1 & 1 & 8 & 8 \\
1 & 1 & 10 & 10 \\
1 & 1 & 12 & 12 \\
1 & 1 & 14 & 14 \\
. & & & . \\
. & & & . \\
. & & & . \\
. & & & . \\
1 & 1 & 8 & 8 \\
1 & 1 & 10 & 10 \\
1 & 1 & 12 & 12 \\
1 & 1 & 14 & 14 \\
\end{pmatrix}
$$

$$
Z = \underset{108 \times 54}{}
\begin{pmatrix}
1 & 8 & 0 & 0 & & 0 & 0 \\
1 & 10 & 0 & 0 & \cdots & 0 & 0 \\
1 & 12 & 0 & 0 & & 0 & 0 \\
1 & 14 & 0 & 0 & & 0 & 0 \\
0 & 0 & 1 & 8 & & 0 & 0 \\
0 & 0 & 1 & 10 & \cdots & 0 & 0 \\
0 & 0 & 1 & 12 & & 0 & 0 \\
0 & 0 & 1 & 14 & & 0 & 0 \\
. & . & . & & . & . & \\
. & . & . & & . & . & \\
. & . & . & & & . & \\
0 & 0 & 0 & 0 & & 1 & 8 \\
0 & 0 & 0 & 0 & \cdots & 1 & 10 \\
0 & 0 & 0 & 0 & & 1 & 12 \\
0 & 0 & 0 & 0 & & 1 & 14 \\
\end{pmatrix}
$$

$$
Y = \underset{108 \times 1}{}
\begin{pmatrix}
21.0 \\
20.0 \\
21.5 \\
23.0 \\
21.0 \\
21.5 \\
24.0 \\
25.5 \\
. \\
. \\
. \\
24.5 \\
25.0 \\
28.0 \\
28.0 \\
26.0 \\
25.0 \\
29.0 \\
31.0 \\
. \\
. \\
. \\
22.0 \\
21.5 \\
23.5 \\
25.0 \\
\end{pmatrix}
$$

$$\mathbf{G} = \begin{pmatrix} 5.7864 & -0.2896 & 0 & 0 & & \cdots & 0 & 0 \\ -0.2896 & 0.03252 & 0 & 0 & & & 0 & 0 \\ 0 & 0 & 5.7864 & -0.2896 & & \cdots & 0 & 0 \\ 0 & 0 & -0.2896 & 0.03252 & & & 0 & 0 \\ & & \cdot & & & \cdot & \cdot & \\ & & \cdot & & & \cdot & \cdot & \\ & & \cdot & & & \cdot & \cdot & \\ 0 & 0 & 0 & 0 & & \cdots & 5.7864 & -0.2896 \\ 0 & 0 & 0 & 0 & & & -0.2896 & 0.03252 \end{pmatrix}$$

$$\boldsymbol{\Sigma} = \mathbf{I}_{108} \begin{bmatrix} 1.7162 \end{bmatrix}$$
$$108 \times 108$$

$\mathbf{G} =$ is 54×54

$$\boxed{V = Var(\mathbf{Y}) = \mathbf{ZGZ'} + \boldsymbol{\Sigma}}$$

$$V = \begin{pmatrix} 4.950 & 3.175 & 3.116 & 3.057 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\ 3.175 & 4.963 & 3.318 & 3.387 & 0 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\ 3.116 & 3.318 & 5.235 & 3.720 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\ 3.057 & 3.389 & 3.720 & 5.768 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 4.950 & 3.175 & 3.116 & 3.057 & & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 3.175 & 4.963 & 3.318 & 3.387 & \cdots & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 3.116 & 3.318 & 5.235 & 3.720 & & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 3.057 & 3.389 & 3.720 & 5.768 & & 0 & 0 & 0 & 0 \\ & & \cdot & & & \cdot & & \cdot & & & \cdot & & \\ & & \cdot & & & \cdot & & & \cdot & & \cdot & & \\ & & \cdot & & & \cdot & & \cdot & & & \cdot & & \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 4.950 & 3.175 & 3.116 & 3.057 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots & 3.175 & 4.963 & 3.318 & 3.387 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 3.116 & 3.318 & 5.235 & 3.720 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 3.057 & 3.389 & 3.720 & 5.768 \end{pmatrix}$$

$V =$ is 108×108

Random Intercept

```
                         The Mixed Procedure


                         Model Information


   Data Set                      WORK.FORMIXED
   Dependent Variable            y
   Covariance Structure          Unstructured
   Subject Effect                person
   Estimation Method             REML
   Residual Variance Method      Profile
   Fixed Effects SE Method       Model-Based
   Degrees of Freedom Method     Containment



                     Class Level Information


     Class      Levels    Values


     catage         4     8 10 12 14
     person        27     1 2 3 4 5 6 7 8 9 10 11 12 13
                          14 15 16 17 18 19 20 21 22 23
                          24 25 26 27



                          Dimensions


         Covariance Parameters          2
         Columns in X                   4
         Columns in Z Per Subject       1
         Subjects                      27
         Max Obs Per Subject            4
```

One variance for random effects (intercept)
One residual error

Random Intercept

```
        Number of Observations
      Number of Observations Read           108
      Number of Observations Used           108
      Number of Observations Not Used         0


            Iteration History


Iteration    Evaluations     -2 Res Log Like        Criterion
       0              1        483.55911746
       1              1        433.75724920       0.00000000
           Convergence criteria met.



            Estimated G Matrix


    Row    Effect        person        Col1
     1     Intercept       1          3.2986



        Estimated G Correlation Matrix


    Row    Effect        person        Col1
     1     Intercept       1          1.0000



        Covariance Parameter Estimates


    Cov Parm      Subject     Estimate
    UN(1,1)       person        3.2986
    Residual                    1.9221
```

Random Intercept

```
                Fit Statistics

-2 Res Log Likelihood              433.8
AIC (smaller is better)            437.8
AICC (smaller is better)           437.9
BIC (smaller is better)            440.3
```

Compare to
Covariance Structure
Model with TYPE=CS.

```
            Solution for Fixed Effects

                        Standard
Effect       Estimate     Error    DF   t Value   Pr > |t|
Intercept    17.3727     1.1835    25    14.68     <.0001
male         -1.0321     1.5374    79    -0.67     0.5040
age           0.4795     0.09347   79     5.13     <.0001
male*age      0.3048     0.1214    79     2.51     0.0141
```

Same parameter estimates,
different SEs than with
Random slope.

Significant
age×gender
interaction

Intercept:
dental
distance for
female at
age=0

Estimated difference
between males and
females at age=0

Slope for females: 0.4795
Slope for males: 0.4795+0.3048

```
        Type 3 Tests of Fixed Effects

                   Num    Den
Effect              DF     DF    F Value   Pr > F
male                 1     79     0.45     0.5040
age                  1     79    26.32     <.0001
male*age             1     79     6.30     0.0141
```

Random Intercept only

```r
summary(mod2)

## Linear mixed model fit by REML ['lmerMod']
## Formula: meas ~ male * age + (1 | Person)
##    Data: dental.long
##
## REML criterion at convergence: 433.8
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.5980 -0.4546  0.0158  0.5024  3.6862
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  Person   (Intercept) 3.299    1.816
##  Residual             1.922    1.386
## Number of obs: 108, groups:  Person, 27
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept) 17.37273    1.18351  14.679
## male        -1.03210    1.53742  -0.671
## age          0.47955    0.09347   5.130
## male:age     0.30483    0.12142   2.511
##
## Correlation of Fixed Effects:
##          (Intr) male   age
## male     -0.770
## age      -0.869  0.669
## male:age  0.669 -0.869 -0.770
```
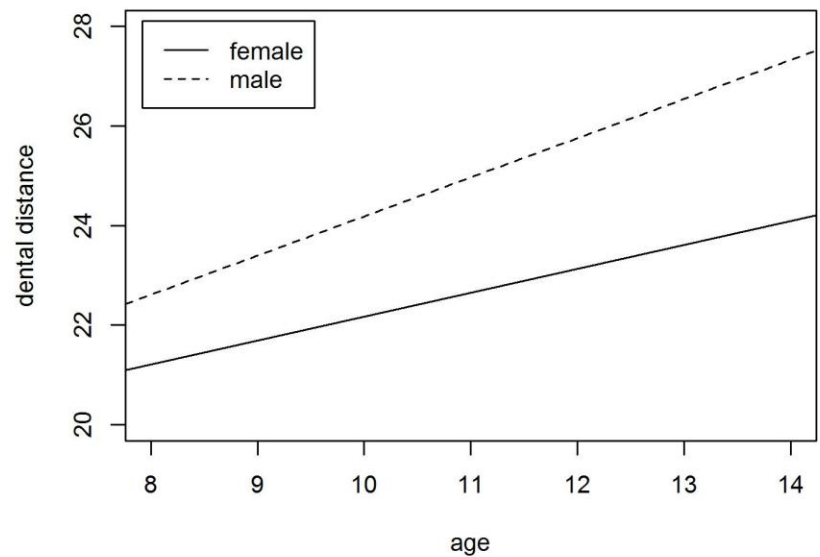
Comparing models with different fixed effects (random intercept and slope)

- If we want to determine the best model for the fixed effects, we need to use ML (not REML)
- Think about 4 possible models for the effect of gender on dental growth
    - o Model 1: Full model (age, male, age*male)
    - o Model 2: Force same slope of age (age, male)
    - o Model 3: Force same intercept (age, age*male)
    - o Model 4: Force same slope and intercept (age only)
- Models 2-4 are nested within model 1, so we can compare each of them to the full model with formal statistical tests
- If we want to make pairwise comparisons between the models, we need to use AIC/BIC

```
anova(mod1full,mod1nointerxn)

## Data: dental.long
## Models:
## mod1nointerxn: meas ~ male + age + (1 + age | Person)
## mod1full: meas ~ male * age + (1 + age | Person)
##                Df    AIC    BIC  logLik deviance  Chisq Chi Df Pr(>Chisq)
## mod1nointerxn   7 446.84 465.61 -216.42   432.84
## mod1full        8 443.81 465.26 -213.90   427.81 5.0292      1    0.02492 *
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

anova(mod1full,mod1agemale)

## Data: dental.long
## Models:
## mod1agemale: meas ~ age + age:male + (1 + age | Person)
## mod1full: meas ~ male * age + (1 + age | Person)
##                Df    AIC    BIC  logLik deviance  Chisq Chi Df Pr(>Chisq)
## mod1agemale     7 442.25 461.03 -214.13   428.25
## mod1full        8 443.81 465.26 -213.90   427.81 0.4481      1    0.5033
```

```
anova(mod1full,mod1ageonly)

## Data: dental.long
## Models:
## mod1ageonly: meas ~ age + (1 + age | Person)
## mod1full: meas ~ male * age + (1 + age | Person)
##              Df    AIC    BIC  logLik deviance  Chisq Chi Df Pr(>Chisq)
## mod1ageonly  6 451.21 467.30 -219.61   439.21
## mod1full     8 443.81 465.26 -213.90   427.81 11.406      2   0.003337 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Conclusions: age and gender

- Only model where we fail to reject the null is the comparison between the full model and the model with age and age*male
  - Model 3 also has lower AIC than Model 1
  - Think about interpretation: we don't generally include interactions without main effects
  - Thus, even though there is statistical evidence that Model 3 is adequate (failure to reject on likelihood ratio test comparing with full model), we would probably report the results of the full model
- Interpretation of the full model (age, male, age*male)
  - Interpretation of age effect: different slope (rate of growth of mean dental measurement with age) between males and females. Rate of growth in males is 0.4795+0.3048=0.7844 per year, rate of growth in females is 0.4795 per year. Positive sign of these estimates indicates growth is occurring (as opposed to getting smaller).

```
## Fixed effects:
##               Estimate Std. Error t value
## (Intercept)   17.3727      1.2284  14.143
## male          -1.0321      1.5957  -0.647
## age            0.4795      0.1037   4.623
## male:age       0.3048      0.1347   2.262
```

  - Interpretation of gender effect: different intercept (mean value of dental measurement at age 0). This difference is not statistically significant, but the estimated mean measurement at age 0 in females is 17.3727 and in males is 17.3727 - 1.0321=16.34. This is not very meaningful since no subjects in our sample were evaluated at age 0.
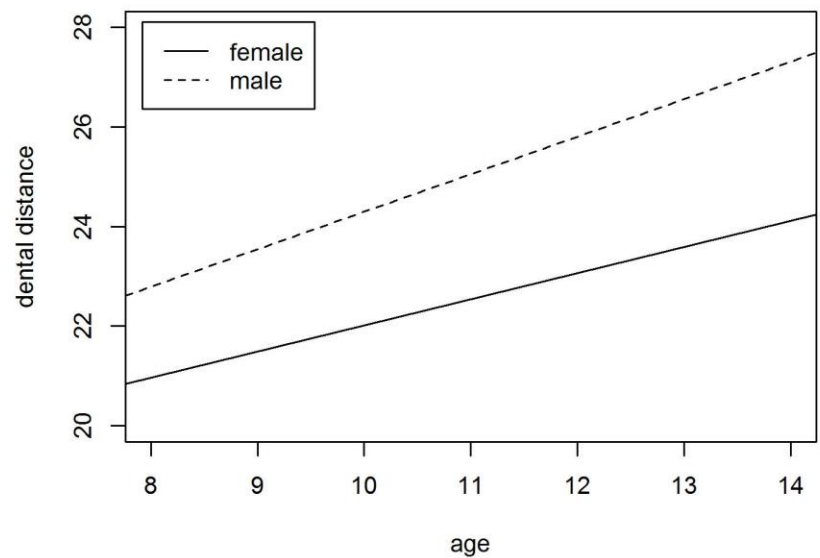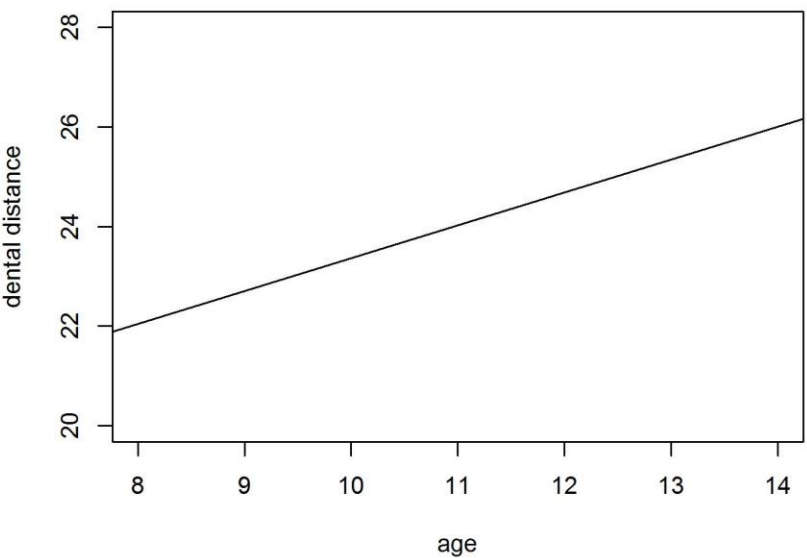
```
mod1age8 <- lmer(meas ~ male*I(age-8) +
(1+age|Person),data=dental.long,REML=TRUE)
summary(mod1age8)$coef

##                   Estimate Std. Error t value
## (Intercept)        21.2091     0.6350  33.401
## male                1.4065     0.8249   1.705
## I(age - 8)          0.4795     0.1037   4.623
## male:I(age - 8)     0.3048     0.1347   2.262
```
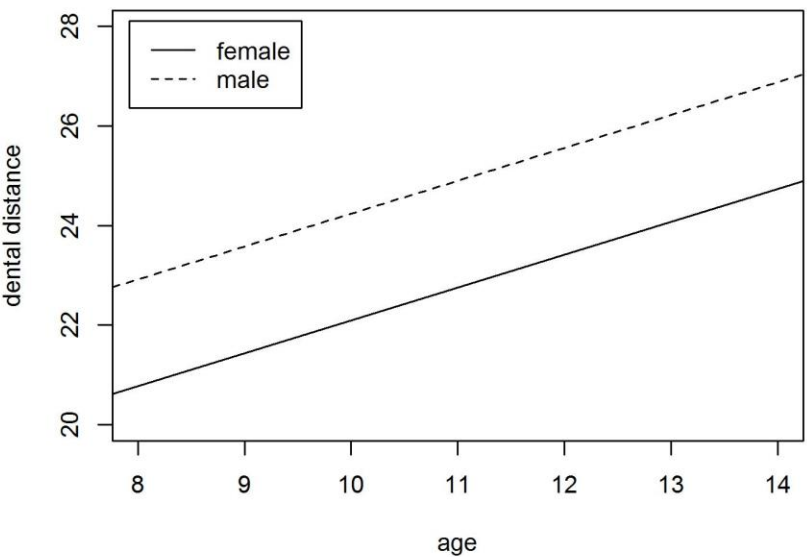
Comparing models with different random effects

- In general, this is more complicated than comparisons with fixed effects
    - Can compare AIC/BIC from REML fits, but formal testing is challenging
- <u>Example:</u> is a random slope necessary?
    - NOT just a likelihood ratio test with χ^2 (2 df) null
    - Assumptions are violated:
        - The null hypothesis has the variance of the random slope equal to 0, which is on the boundary of the parameter space.
        - What about the correlation between the random slope and intercept? This doesn't even exist in the model with only a random intercept
    - LRT: 433.8-432.6 = 1.2 is the test statistic, but we need to get the correct reference critical values under the null.
    - We can do this in SAS with PROC GLIMMIX using the covtest statement

```
PROC GLIMMIX DATA=formixed;
  CLASS gender person;
  MODEL y = gender age gender*age;
  RANDOM INT age /TYPE=UN SUBJECT=person;
  covtest 'no random slope' . 0 0/EST;
RUN;
```

Tests of Covariance Parameters
Based on the Restricted Likelihood

Label	DF	-2 Res Log Like	ChiSq	Pr > ChiSq	Estimates H0				Note
					Est1	Est2	Est3	Est4	
no random slope	2	433.76	1.18	0.4169	3.2986	0	0	1.9221	MI

MI: P-value based on a mixture of chi-squares.

In R, we can base inference on simulations of the null distribution of the test statistic

```r
# set a value for the number of simulated data sets
B <- 5000
# estimated random intercept standard deviation under the null
sigma.b <- sqrt(summary(mod2)$varcor$Person)
# estimated residual standard deviation under the null
sigma.e <- summary(mod2)$sigma
# get the model matrix
mod0 <- lm(meas ~ male*age,data=dental.long,x=TRUE)
# vector for the simulated likelihood ratio statistic values
lrstat <- numeric()
system.time(
for(i.b in 1:B) {
  set.seed(i.b)
  # generate random effects
  # subject
  b <- rnorm(27,sd=sigma.b)
  # residual
  e <- rnorm(27*4,sd=sigma.e)
  # mean
  eta <- mod0$x %*% summary(mod2)$coef[,1]
  # observed outcome
  y <- eta + rep(b,times=4) + e
  # model fits
  bmod1 <- suppressWarnings(lmer(y ~ 0+mod0$x + (1|dental.long$Person)))
  bmod2 <- suppressWarnings(lmer(y ~ 0+mod0$x + (1+mod0$x[,3]|dental.long$Person)))
  # test statistic
  lrstat[i.b] <- -2*(logLik(bmod1)-logLik(bmod2))
}
)

##    user  system elapsed
## 327.26    0.03  328.48
```

- Figure shows simulated null distribution along with reference chi-square(2) distribution (not correct in this case)

```
# unadjusted for location of parameter on boundary
pchisq(-2*(logLik(mod2)-logLik(mod1)),2,lower.tail=FALSE)

## 'log Lik.' 0.5555516 (df=6)
```
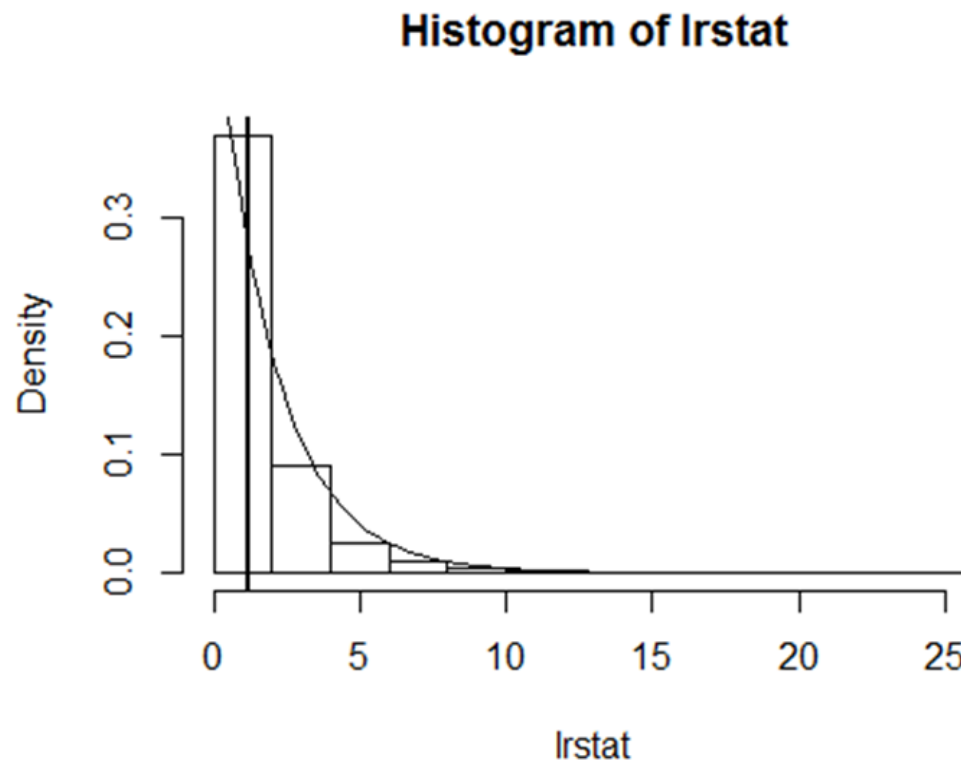
- Looking for area to the right of the observed value

```
# approximation based on simulated null distribution
mean(lrstat>-2*(logLik(mod2)-logLik(mod1)))

## [1] 0.4034
```

- Compare this with p-value from SAS (0.4169)

Histogram of lrstat

Random Coefficient Model (Random Intercept), UN Covariance (TYPE=UN)

$$X = \begin{pmatrix}
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
\cdot & & & \cdot \\
\cdot & & & \cdot \\
\cdot & & & \cdot \\
1 & 0 & 8 & 0 \\
1 & 0 & 10 & 0 \\
1 & 0 & 12 & 0 \\
1 & 0 & 14 & 0 \\
1 & 1 & 8 & 8 \\
1 & 1 & 10 & 10 \\
1 & 1 & 12 & 12 \\
1 & 1 & 14 & 14 \\
\cdot & & & \cdot \\
\cdot & & & \cdot \\
\cdot & & & \cdot \\
1 & 1 & 8 & 8 \\
1 & 1 & 10 & 10 \\
1 & 1 & 12 & 12 \\
1 & 1 & 14 & 14
\end{pmatrix}$$

X is 108×4

$$Z = \begin{pmatrix}
1 & 0 & & 0 \\
1 & 0 & \cdots & 0 \\
1 & 0 & & 0 \\
1 & 0 & & 0 \\
0 & 1 & & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & & 0 \\
0 & 1 & & 0 \\
\cdot & \cdot & & \cdot \\
\cdot & & \cdot & \cdot \\
\cdot & & & \cdot \\
0 & 0 & & 1 \\
0 & 0 & \cdots & 1 \\
0 & 0 & & 1 \\
0 & 0 & & 1 \\
0 & 0 & & 1
\end{pmatrix}$$

Z is 108×27

$$Y = \begin{pmatrix}
21.0 \\
20.0 \\
21.5 \\
23.0 \\
21.0 \\
21.5 \\
24.0 \\
25.5 \\
\cdot \\
\cdot \\
\cdot \\
24.5 \\
25.0 \\
28.0 \\
28.0 \\
26.0 \\
25.0 \\
29.0 \\
31.0 \\
\cdot \\
\cdot \\
\cdot \\
22.0 \\
21.5 \\
23.5 \\
25.0
\end{pmatrix}$$

Y is 108×1

Random Coefficient Model (Random Intercept), UN Covariance (TYPE=UN)

$$\Sigma = \underset{108\times108}{I_{108}} \begin{bmatrix} 1.9221 \end{bmatrix}$$

$$\underset{27\times27}{G} = I_{21} \begin{bmatrix} 3.2986 \end{bmatrix}$$

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

$$\underset{108\times108}{V} = \begin{pmatrix}
5.2207 & 3.2986 & 3.2986 & 3.2986 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\
3.2986 & 5.2207 & 3.2986 & 3.2986 & 0 & 0 & 0 & 0 & \cdots & 0 & 0 & 0 & 0 \\
3.2986 & 3.2986 & 5.2207 & 3.2986 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\
3.2986 & 3.2986 & 3.2986 & 5.2207 & 0 & 0 & 0 & 0 & & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 5.2207 & 3.2986 & 3.2986 & 3.2986 & & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 3.2986 & 5.2207 & 3.2986 & 3.2986 & \cdots & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 3.2986 & 3.2986 & 5.2207 & 3.2986 & & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 3.2986 & 3.2986 & 3.2986 & 5.2207 & & 0 & 0 & 0 & 0 \\
& & \vdots & & & \vdots & & \ddots & & & \vdots & \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 5.2207 & 3.2986 & 3.2986 & 3.2986 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \cdots & 3.2986 & 5.2207 & 3.2986 & 3.2986 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 3.2986 & 3.2986 & 5.2207 & 3.2986 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & & 3.2986 & 3.2986 & 3.2986 & 5.2207
\end{pmatrix}$$

Random Intercept Model Identical to fitting a Covariance Pattern Model (Compound Symmetry)

Random Intercept:
```
PROC MIXED DATA=formixed;
 CLASS catage person;
 MODEL y = male age male*age/ SOLUTION;
 RANDOM INT  /TYPE=UN SUBJECT=person G GCORR;
RUN;
```

Covariance Pattern Model (type=CS):
```
*** Mixed Model, CS Covariance***;
*** Continuous Age *****;
PROC MIXED DATA=formixed ;
 CLASS gender catage person;
 MODEL y = male age male*age /SOLUTION;
 REPEATED catage /TYPE=CS SUBJECT=person R RCORR;
RUN;
```

True in this example because:
- Age is categorical
- Balanced design

```
library(nlme)

# random intercept
mod1 <- lme(meas ~ Gender*age,
            random=~1|Person,
            data=dental.long)
summary(mod1)
```

```
## Linear mixed-effects model fit by REML
##  Data: dental.long
##        AIC      BIC    logLik
##   445.7572 461.6236 -216.8786
##
## Random effects:
##  Formula: ~1 | Person
##        (Intercept) Residual
## StdDev:   1.816214 1.386382
##
## Fixed effects: meas ~ Gender * age
##                Value Std.Error DF   t-value p-value
## (Intercept) 17.372727 1.1835071 79 14.679023  0.0000
## GenderM     -1.032102 1.5374208 25 -0.671321  0.5082
## age          0.479545 0.0934698 79  5.130483  0.0000
## GenderM:age  0.304830 0.1214209 79  2.510520  0.0141
##  Correlation:
##             (Intr) GendrM age
## GenderM     -0.770
## age         -0.869  0.669
## GenderM:age  0.669 -0.869 -0.770
##
## Standardized Within-Group Residuals:
##         Min          Q1         Med          Q3         Max
## -3.59804400 -0.45461690  0.01578365  0.50244658  3.68620792
##
## Number of Observations: 108
## Number of Groups: 27
```

```r
# specifying compound symmetry as the covariance structure
mod2 <- gls(meas ~ Gender*age,
            correlation=corCompSymm(form=~1|Person),
            data=dental.long)
summary(mod2)
```

```
## Generalized least squares fit by REML
##   Model: meas ~ Gender * age
##   Data: dental.long
##        AIC      BIC    logLik
##   445.7572 461.6236 -216.8786
```

```
##
## Correlation Structure: Compound symmetry
##  Formula: ~1 | Person
##  Parameter estimate(s):
##       Rho
## 0.6318381
##
## Coefficients:
##                 Value Std.Error    t-value p-value
## (Intercept) 17.372727 1.1835071 14.679023  0.0000
## GenderM     -1.032102 1.5374208 -0.671321  0.5035
## age          0.479545 0.0934699  5.130481  0.0000
## GenderM:age  0.304830 0.1214209  2.510519  0.0136
##
##  Correlation:
##             (Intr) GendrM age
## GenderM     -0.770
## age         -0.869  0.669
## GenderM:age  0.669 -0.869 -0.770
##
## Standardized residuals:
##         Min          Q1         Med          Q3         Max
## -2.45773173 -0.57853118 -0.07360637  0.58204364  2.29634478
##
## Residual standard error: 2.284881
## Degrees of freedom: 108 total; 104 residual
```

Induced covariance structures

```r
library(nlme)
# random intercept and slope model fit
mod3 <- lme(meas ~ male*age,
            random=~1+age|Person,
            data=dental.long)
# random intercept only model fit
mod4 <- lme(meas ~ male*age,
            random=~1|Person,data=dental.long)

# random intercept and slope
Z <- cbind(1,seq(8,14,by=2))
# ZGZ'
Z %*% getVarCov(mod3) %*% t(Z) +
  # + R
  diag(summary(mod3)$sigma^2,4)

##           [,1]     [,2]     [,3]     [,4]
## [1,] 4.950168 3.175102 3.116239 3.057376
## [2,] 3.175102 4.962541 3.317572 3.388807
## [3,] 3.116239 3.317572 5.235109 3.720238
## [4,] 3.057376 3.388807 3.720238 5.767873

getVarCov(mod3,type='marginal')

## Person 1
## Marginal variance covariance matrix
##        1      2      3      4
## 1 4.9502 3.1751 3.1162 3.0574
## 2 3.1751 4.9625 3.3176 3.3888
## 3 3.1162 3.3176 5.2351 3.7202
## 4 3.0574 3.3888 3.7202 5.7679
##   Standard Deviations: 2.2249 2.2277 2.288 2.4016
```

```r
# random intercept only
Z[,1] %*% getVarCov(mod4) %*% t(Z[,1]) +
diag(summary(mod4)$sigma^2,4)

##           [,1]     [,2]     [,3]     [,4]
## [1,] 5.220689 3.298634 3.298634 3.298634
## [2,] 3.298634 5.220689 3.298634 3.298634
## [3,] 3.298634 3.298634 5.220689 3.298634
## [4,] 3.298634 3.298634 3.298634 5.220689

getVarCov(mod4,type='marginal')

## Person 1
## Marginal variance covariance matrix
##        1      2      3      4
## 1 5.2207 3.2986 3.2986 3.2986
## 2 3.2986 5.2207 3.2986 3.2986
## 3 3.2986 3.2986 5.2207 3.2986
## 4 3.2986 3.2986 3.2986 5.2207
##   Standard Deviations: 2.2849 2.2849 2.2849 2.2849
```

Other random slopes

- What about a random slope for gender?

```
mod3 <- try(lme(meas ~ Gender*age,
          random=~1+age+Gender|Person,
          data=dental.long),silent=FALSE)
mod3

## [1] "Error in lme.formula(meas ~ Gender * age, random = ~1 + age + Gender |  : \n  nlminb problem, convergence error
code = 1\n  message = iteration limit reached without convergence (10)\n"
## attr(,"class")
## [1] "try-error"
## attr(,"condition")
## <simpleError in lme.formula(meas ~ Gender * age, random = ~1 + age + Gender |    Person, data = dental.long):
nlminb problem, convergence error code = 1
##   message = iteration limit reached without convergence (10)>
```

- Function $\text{lme}()$ is unable to fit this model
    - Strategy: try a different package

```
mod4 <- lmer(meas ~ Gender*age+(1+age+Gender|Person),
          data=dental.long)

## Warning in optwrap(optimizer, devfun, getStart(start, rho$lower, rho$pp), :
## convergence code 1 from bobyqa: bobyqa -- maximum number of function
## evaluations exceeded

## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control$checkConv, : Model is nearly unidentifiable: large
eigenvalue ratio
##  - Rescale variables?

summary(mod4)

## Linear mixed model fit by REML ['lmerMod']
## Formula: meas ~ Gender * age + (1 + age + Gender | Person)
##    Data: dental.long
##
## REML criterion at convergence: 431
##
```

```
## Scaled residuals:
##    Min      1Q Median     3Q     Max
## -3.044 -0.400  0.023  0.457  3.875
##
## Random effects:
##  Groups   Name        Variance Std.Dev. Corr
##  Person   (Intercept) 0.0224   0.150
##           age         0.0346   0.186     0.95
##           GenderM     7.6611   2.768    -0.60 -0.80
##  Residual             1.7027   1.305
## Number of obs: 108, groups:  Person, 27
##
## Fixed effects:
##             Estimate Std. Error t value
## (Intercept)   17.373      0.989   17.57
## GenderM       -1.032      1.448   -0.71
## age            0.480      0.104    4.60
## GenderM:age    0.305      0.136    2.25
##
## Correlation of Fixed Effects:
##            (Intr) GendrM age
## GenderM    -0.683
## age        -0.802  0.548
## GenderM:age 0.618 -0.842 -0.770
## convergence code: 1
## Model is nearly unidentifiable: large eigenvalue ratio
##  - Rescale variables?
```

- More warning messages
  - Strategy: rescale variables as suggested and try again

```
dental.long$scaled.age <- scale(dental.long$age)
mod5 <- lmer(meas ~ Gender*scaled.age+(1+scaled.age+Gender|Person),
          data=dental.long)

## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control
## $checkConv, : unable to evaluate scaled gradient
```

```
## Warning in checkConv(attr(opt, "derivs"), opt$par, ctrl = control
## $checkConv, : Hessian is numerically singular: parameters are not uniquely
## determined
```

```
summary(mod5)
```

```
## Linear mixed model fit by REML ['lmerMod']
## Formula: meas ~ Gender * scaled.age + (1 + scaled.age + Gender | Person)
##    Data: dental.long
##
## REML criterion at convergence: 427.8
##
## Scaled residuals:
##    Min     1Q Median     3Q    Max
## -3.044 -0.400  0.022  0.457  3.875
##
## Random effects:
##  Groups   Name        Variance Std.Dev. Corr
##  Person   (Intercept) 4.792    2.189
##           scaled.age  0.175    0.418     1.00
##           GenderM     7.791    2.791    -0.79 -0.79
##  Residual             1.703    1.305
## Number of obs: 108, groups:  Person, 27
##
## Fixed effects:
##                   Estimate Std. Error t value
## (Intercept)         22.648      0.689    32.9
## GenderM              2.321      0.827     2.8
## scaled.age           1.077      0.234     4.6
## GenderM:scaled.age   0.685      0.304     2.2
##
## Correlation of Fixed Effects:
##            (Intr) GendrM scld.g
## GenderM    -0.833
## scaled.age  0.515 -0.429
## GndrM:scld. -0.397  0.328 -0.770
## convergence code: 0
## unable to evaluate scaled gradient
##  Hessian is numerically singular: parameters are not uniquely determined
```

- Different warning messages
    - o Have to admit defeat sometimes
- What happened here?
    - o Think about the **Z** matrix for this model: depends on gender

```
Z.female <- cbind(1,seq(8,14,by=2),0)
Z.male <- cbind(1,seq(8,14,by=2),1)
Z.female

##      [,1] [,2] [,3]
## [1,]    1    8    0
## [2,]    1   10    0
## [3,]    1   12    0
## [4,]    1   14    0

Z.male

##      [,1] [,2] [,3]
## [1,]    1    8    1
## [2,]    1   10    1
## [3,]    1   12    1
## [4,]    1   14    1
```

   - o What do we see here? Answer: multicollinearity
- Essentially, within each subject, the **Z** matrix is not full-rank
- In general, we can't estimate random slopes for covariates that don't vary within subjects

More on Longitudinal Data

Longitudinal data are characterized by repeated measurements of the same experimental unit over time (usually repeated measurements of the outcome).

- Observations are correlated in longitudinal data

    - Many standard statistical procedures assume independence of the observations.
    - Ignoring correlation in a data set generally leads to standard errors and p-values that are too small.

    - Other examples of correlated data:

        o Repeated measurements on an individual (e.g., measurements on multiple body parts or organs).
        o Clustered data (e.g., families, classrooms, communities)

- Unbalanced designs and/or missing data are common in longitudinal data

    - Timing of measurements can differ
    - Number of measurements can differ
    - Missing data is common
    - Loss to follow-up is common

Analysis of Correlated Data

- <u>Option 1</u>: Simplify the data by reducing each individual's data to a single summary measure. Use this summary measure as the data in the analysis. <u>Usually not recommended!</u>

  - Change from first to last visit.
  - Mean/Sum of all measurements (ignores time).
  - Slope of a line.
  - Height of a peak.
  - Area under the curve.

  The choice of the summary measure should reflect the study objectives.

- <u>Option 2</u>: Use special methods available for analyzing correlated data.

  - Repeated Measures ANOVA (excludes observations with missing data; same timepoints for all observations)
  - Generalized Estimating Equations (GEE)
  - Mixed Effects Models
    1. Covariance pattern models
    2. Random coefficient models

Missing Data

- Types of Missing Data:

  - Missing Completely at Random (MCAR): Probability of missing observations is independent of the observed and missing values.

  - Missing at Random (MAR): Probability of missing observations may depend on observed values, but is conditionally independent of the missing values.

  - Missing Not at Random (MNAR): Probability of missing observations is NOT conditionally independent of the missing values given the observed values.

- Strategies:

  - Analyze only those with complete data. (MCAR)
  - Available case analysis. (MCAR)
  - Replace missing values with imputed values. *General idea*: Replace missing values with a "guess." And then use analysis method for complete data. (MCAR or MAR)

        - Single Imputation
        - Multiple Imputation

  - Use methods not requiring complete data, such as mixed effects models. (MCAR or MAR)

Mixed Effects Models

Mixed Effects Models are the most flexible method for analyzing longitudinal data**.**

- Missing data can be handled easily and subjects with missing data are still included in the analysis.

- Subjects are weighted according to the amount of information available for that subject (number of measurements).

    - Subjects with more data points have curves which are closer to their data, while subjects with fewer data points have curves closer to the population curve.

- You can characterize individual variation relative to the population mean.

APPENDIX
Summary Comparison of GLM & MIXED Procedures
for Repeated-Measures Analysis

PROC GLM	*PROC MIXED*
Ordinary Least Squares estimation	Maximum Likelihood or Restricted Maximum Likelihood estimation
Requires balanced data –ignores subjects with missing observations	Allows data that are *missing at random*
Handles between-and within-subject effects differently with regard to syntax and tests	Handles between-and within-subject effects similarly
Requires a dimension-reducing orthogonal transformation for the repeated measures variables	Analyzes the data in their original form
Assumes a full ANOVA (cell means) model for within-subject effects	Allows a full ANOVA and/or a reduced mean model for within-subject effects
Assumes covariates are constant within a subject	Allows covariates to vary within a subject
Automatically performs a sphericity test with the PRINTE option	Can produce sphericity test results either by running both TYPE=UN and TYPE=HF or by using TYPE=UN on transformed data

PROC GLM	*PROC MIXED*
Assumes either a Type H or unstructured within-subject covariance matrix	Allows a wide variety of within-subject covariance structures including CS,AR(1),HF,FA,UN, spatial, and random coefficients
Estimates covariance parameters using a method of moments	Estimates covariance parameters using restricted maximum likelihood, and MIVQUEO
Is computationally fast and prints all significance tests in one run	Can be computationally intensive and requires different covariance structures
Computes F-statistics that are ratios of mean squares	Computes F-statistics that are Wald-type quadratic forms
Computes standard,G-G, and H-F univariate repeated measures tests	Computes only standard univariate repeated measures tests (using TYPE=CS or TYPE=HF)
Computes four multivariate repeated measures tests: Wilk's Lambda, Pillai's Trace, Hotelling-Lawley Trace, and Roy's Greatest Root	Computes a Wald-type F (using TYPE=UN) and two versions of Hotelling-Lawley Trace
Computes LSMEANS only for each separate variable	Computers LSMEANS which are averaged across repeated measures and whose standard errors reflect the appropriate covariance structure