

3. Linear Mixed Effects (LME) Models

1. Overview
2. Simple cases:
 - a) Random intercept
 - b) Random intercept and slope.
3. The general LME model formulation.
4. Variance and covariance structures.
5. Estimation.
6. Model selection.
7. Residual Analysis and Goodness of Fit.
8. Implementation in R and Phoenix.

3.1 Overview

Overview LME Models

- Not very common for pharmacokinetic data; however, they lead to a better grasp of the nonlinear mixed effects case.
- Mixed effects are introduced when measurements within subjects are not assumed independent.
- Data is longitudinal: multiple measurements are made on the same subject over time, e.g., blood pressure, drug concentration.

Overview

- Responses may be:
 - Unequally spaced (times between measurements may vary).
 - With an unequal number of observations per subject
 - Often correlated within a subject.
- Overall are more flexible than multiple regression models, since they:
 - Allow for greater control over the sources of variability
 - Incorporate patient-specific characteristics
 - Allow for covariates to vary over time

Mixed effects: Fixed + Random effects

Fixed effects

- Represent variables whose levels were chosen/controlled, e.g., drug doses or time points for blood draws.
- Their levels represent a set of all possible levels, e.g., gender

Random effects

- Represent variables whose levels do not constitute the set of all possible levels (e.g., countries, in multinational level analysis).
- Often represent nuisance variables: effect is not of interest but rather the variability induced by the variable.
- Are arbitrary samples from a larger pool of other equally possible samples.
- Most common example: the subjects used in an experiment
 - There is often no specific interest in the particular set of subjects, but in generalizing the results to a population at-large.

Simple cases of random and mixed effects models

- Linear random effects model:
 - Random intercept
- Linear mixed effects model (random + fixed):
 - Random intercept and slope
 - Random intercept and slope by groups

Example Random Effects – No Covariates Orthodontic Study on Maxillary Distance (Pinheiro, 2000)

- Measurements of the distance from the pituitary gland to the pterygo-maxillary fissure (abbrev. “maxillary distance”).
- Data collected from x-rays of children’s skulls.
- Taken every two years
- From 8 -14 years of age
- Sample of 27 children- 16 males and 11 females.
- Available in R with name “Orthodont” (ISwR package)

Example Random Effects, Orthodontic Study on Maxillary Distance (Pihneiro, 2000)

Response variable:

Y_{ij} = Maxillary distance (mm),

where

i indexes subjects ($i=1, \dots, n=27$),
 j indexes occasions ($j=1, \dots, m=4$)
representing 8, 10, 12 and 14 years of age.

Example Random Effects, Orthodontic Study on Maxillary Distance (Pinheiro, 2000)

Data structure (4 subjects)

| Subject i | Maxillary distance measurements (mm) Y_{ij} $i=\text{subject}, j=\text{occasion}$ | | | | Subject Mean \bar{Y}_i |
|-------------|----------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------------------|
| | $j=1$ 8 yrs | $j=2$ 10 yrs | $j=3$ 12 yrs | $j=4$ 14 yrs | |
| 1 | 26 | 25 | 29 | 31 | 27.75 |
| 2 | 21.5 | 22.5 | 23 | 26.5 | 23.38 |
| 3 | 23 | 22.5 | 24 | 27.5 | 24.25 |
| 4 | 25.5 | 27.5 | 26.5 | 27 | 26.63 |

$$\text{Grand Mean } \bar{Y} = 24.02 \\ (27 \text{ subjects})$$

Note: The arrangement of the data in R consists of multiple lines per subject.

Random effects model with no covariates

$$Y_{ij} = \mu + u_i + \varepsilon_{ij}; \quad j = 1, \dots, m_i, \quad i = 1, \dots, n.$$

$$= \mu_i + \varepsilon_{ij};$$

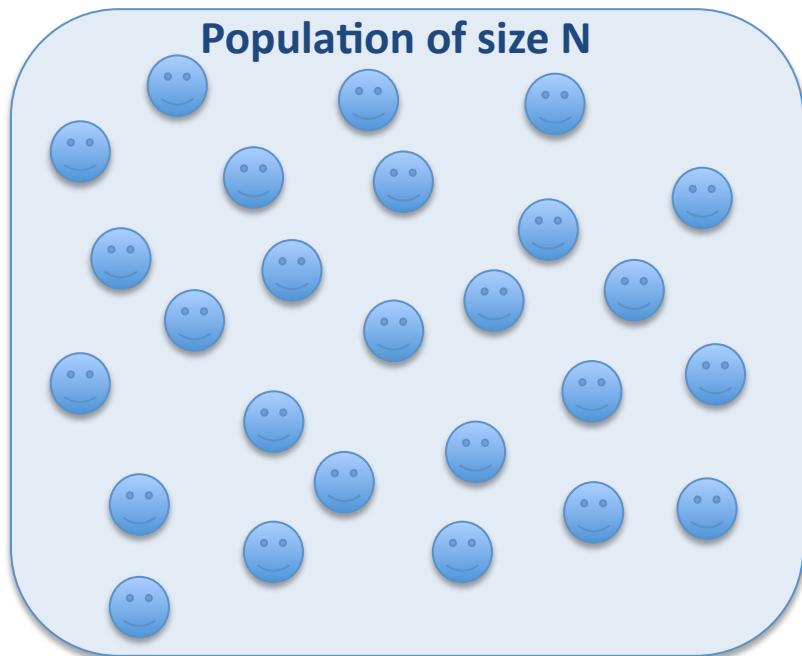
In terms of regression, think of μ as β_0 .
and $\mu_i = \beta_0 + u_i$ only here there's no line!

In our example,

- $n=4$, $m_i=4$ for all subjects $i=1, \dots, n$.
- Y_{ij} is the maxillary distance (mm) taken from subject i at occasion j .
- μ is the population overall mean maxillary distance.
- μ_i is the true (population) subject-specific mean.
- u_i is the random deviation of μ_i from μ
- ε_{ij} is the random deviation for j -th measurement on subject i from μ_i .

Random effects model with no covariates

Population: all children aged 8-14



Take subject i :

{ Y_{i1} Set of **true**
 Y_{i2} maxillary
 Y_{i3} distances
 Y_{i4} at ages
 8,10,12,14
 years.

(Unknown,
not
measured
yet)

True (population) subject-specific mean:

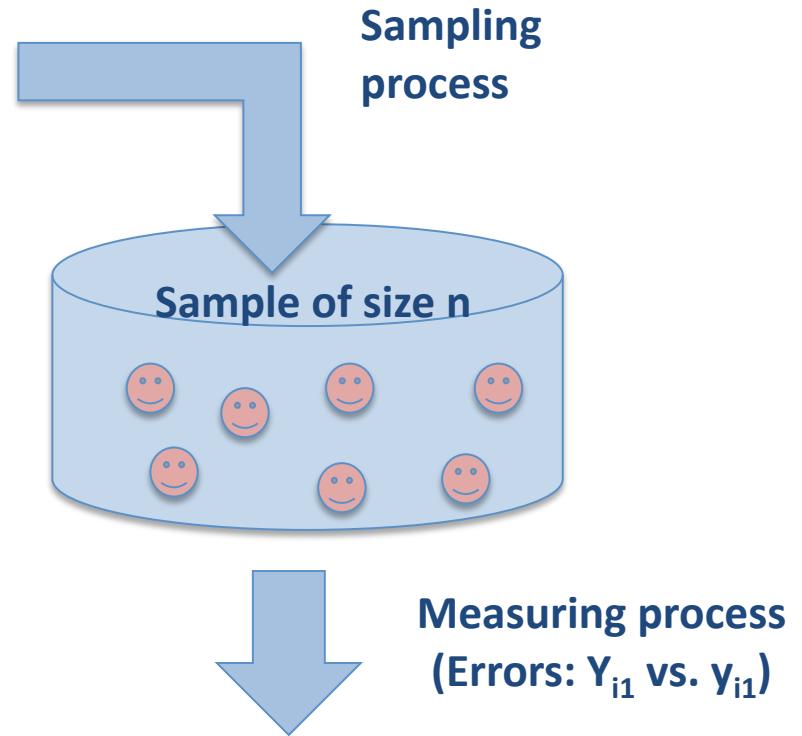
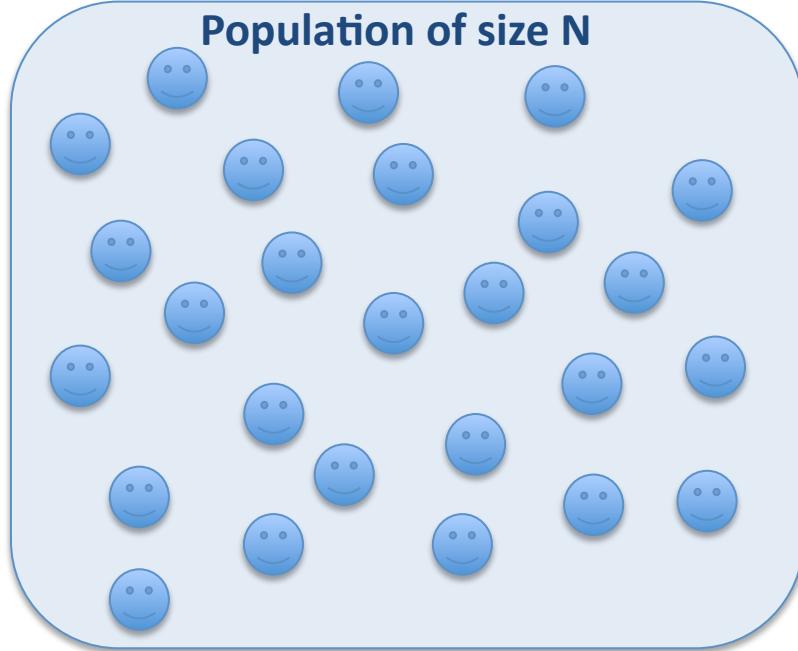
(Unknown)

$$\mu_i = \frac{1}{4} \sum_{j=1}^4 Y_{ij} \quad \xleftarrow{\text{---}} \quad u_i = \mu - \mu_i \quad \xrightarrow{\text{---}}$$

True population overall mean:
(Unknown)

$$\mu = \frac{1}{N} \sum_{i=1}^N \mu_i$$

Random effects model with no covariates



Deviation of Y_{i1} from μ_i
+ measurement error

$$\begin{aligned}\varepsilon_{i1} &= (Y_{i1} - \mu_i) + (y_{i1} - Y_{i1}) \\ &= y_{i1} - \mu_i\end{aligned}$$

Take subject i from the sample:

{ :) y_{i1} Set of
 y_{i2} **observed**
 y_{i3} maxillary
 y_{i4} distances

Example Random Effects, Orthodontic Study on Maxillary Distance (Pinheiro, 2000)

Residuals: Deviations from subject means: $\hat{\varepsilon}_{ij} = y_{ij} - \hat{\mu}_i = y_{ij} - \bar{Y}_i$.

| Subject i | Maxillary distance measurements (mm) Y_{ij} $i=\text{subject}, j=\text{occasion}$ | | | | Subject Mean \bar{Y}_i | Deviation from overall mean $\hat{\mu}_i$ $(\bar{Y}_{i\cdot} - \bar{Y})$ |
|-------------|-------------------------------------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------------------|--------------------------------------------------------------------------------|
| | $j=1$ 8 yrs | $j=2$ 10 yrs | $j=3$ 12 yrs | $j=4$ 14 yrs | | |
| 1 | 26 | 25 | 29 | 31 | 27.75 | 1.98 |
| 2 | 21.5 | 22.5 | 23 | 26.5 | 23.38 | -0.64 |
| 3 | 23 | 22.5 | 24 | 27.5 | 24.25 | 0.23 |
| 4 | 25.5 | 27.5 | 26.5 | 27 | 26.63 | 2.61 |

Grand Mean
(n=27)

$$\bar{Y} = 24.02$$

Estimate of subject-specific mean μ_i

Estimate of population mean μ

$$\hat{\varepsilon}_{11} = 26 - 27.75 = -1.75$$

| Subject i | Residuals | | | |
|-------------|-----------|--------|--------|--------|
| | 8 yrs | 10 yrs | 12 yrs | 14 yrs |
| 1 | -1.75 | -2.75 | 1.25 | 3.25 |
| 2 | -1.88 | -0.88 | -0.38 | 3.13 |
| 3 | -1.25 | -1.75 | -0.25 | 3.25 |
| 4 | -1.13 | 0.88 | -0.13 | 0.38 |

3.2 Simple cases

a) Random Intercept Model

- Model specification
- Marginal and conditional means
- How random effects induce correlation

Specific learning objectives:

1. Write the random intercept model and its assumptions.
2. Explain the interpretation of the random effects u_i .
3. Explain the marginal and conditional means.
4. Fit a random intercept model in R and identify the estimated model parameters in the output.
5. Construct graphs in R for longitudinal data using the groupedData structure.

Random Intercept Model

$$Y_{ij} = \mu_{ij} + \varepsilon_{ij} \quad \mu_{ij} \text{ is the subject-specific mean at occasion } j.$$
$$= \underbrace{\beta_0 + \beta_1 t_{ij}}_{\text{Fixed}} + u_{i1} + \varepsilon_{ij}; \quad j = 1, \dots, m_i; \quad i = 1, \dots, n.$$

Random

Re-arranging,

$$Y_{ij} = \underbrace{(\beta_0 + u_{i1})}_{\text{Intercept}} + \underbrace{\beta_1 t_{ij}}_{\text{Slope}} + \varepsilon_{ij};$$

μ_{ij} is a line with intercept $\beta_0 + u_{i1}$ and slope β_1 .

Random Intercept Model

Population subject specific mean: $\mu_{ij} = \beta_0 + \beta_1 t_{ij} + u_{i1}$

Population overall mean: $\beta_0 + \beta_1 t_{ij}$

- t_{ij} is the time variable associated with measurement Y_{ij}
- u_{i1} is the random deviation of the true subject specific intercept ($\beta_0 + u_{i1}$) from true overall intercept β_0 .
- This translates in the deviation of the true population subject specific mean μ_{ij} vs. the overall population mean $\beta_0 + \beta_1 t_{ij}$.
- ε_{ij} is the random deviation of the ij -th response from subject specific mean.

Model Assumptions

Random Intercept Model

$$Y_{ij} = \beta_0 + \beta_1 t_{ij} + u_{i1} + \varepsilon_{ij}; \quad j = 1, \dots, m_i; \quad i = 1, \dots, n.$$

$$u_{i1} \sim N(0, \sigma_u^2); \quad \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2);$$

ε_{ij} independent of ε_{ik} , u_{i1} independent of u_{j1}

u_{i1} independent of ε_{ij} .

1. Linear relationship of Y with respect to parameters β_0, β_1 .
2. Normally, independently distributed residual errors ε_{ij} .
3. Normally, independently distributed random effects u_{i1} .
4. Random effects and residuals errors are independent.

Random effects model with a time covariate
Random intercept.

Example: Maxillary Distance

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + u_{i1} + \varepsilon_{ij}; \quad j = 1, \dots, 4, \quad i = 1, \dots, 27.$$

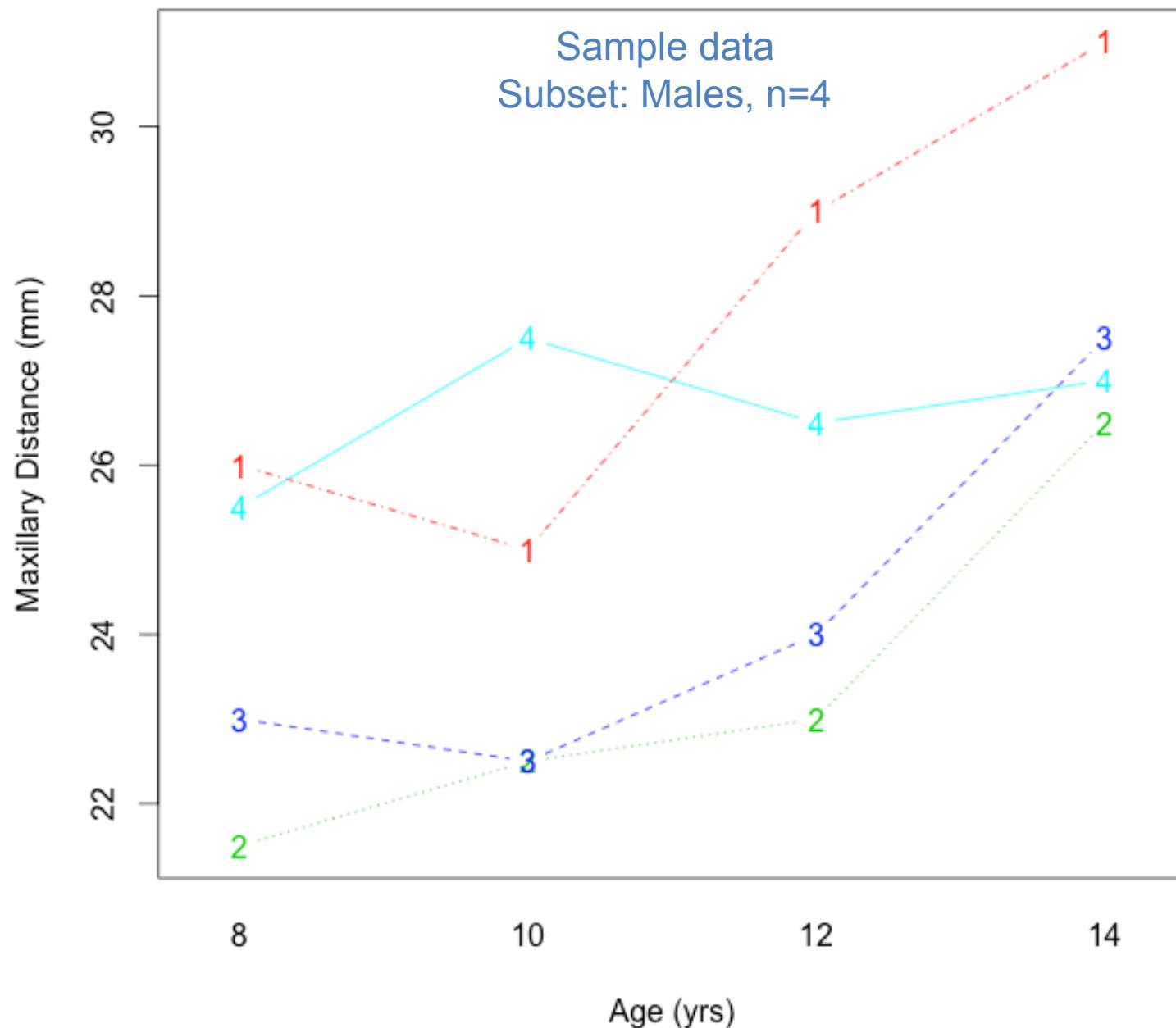
The subject-specific mean is:

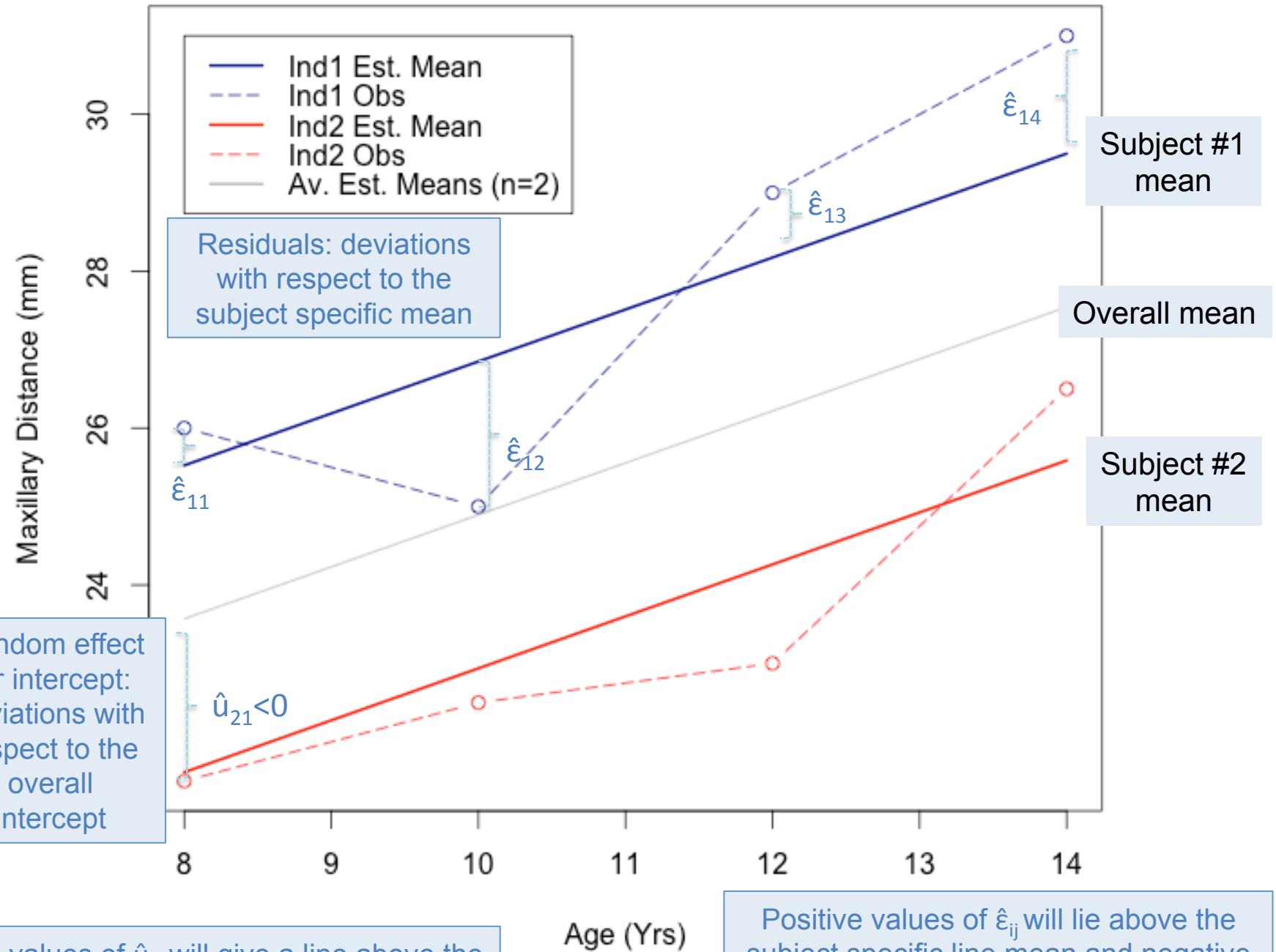
$$\begin{aligned}\mu_{ij} &= \beta_0 + \beta_1 Age_{ij} + u_{i1} \\ &= (\beta_0 + u_{i1}) + \beta_1 Age_{ij}\end{aligned}$$

The subject specific mean is the regression line.

- Y_{ij} is the maxillary distance (mm) taken from subject i at occasion j .
- μ_{ij} is the true (population) subject-specific mean.
- $(\beta_0 + u_{i1}), \beta_1$ are the intercept (random) and slope
- u_{i1} is the random deviation of the (population) subject-specific intercept from the overall (population) intercept β_0 .
- ε_{ij} is the random deviation for j -th measurement on subject i from μ_i .

Example Random Effects, Orthodontic Study on Maxillary Distance (Pinheiro, 2000)





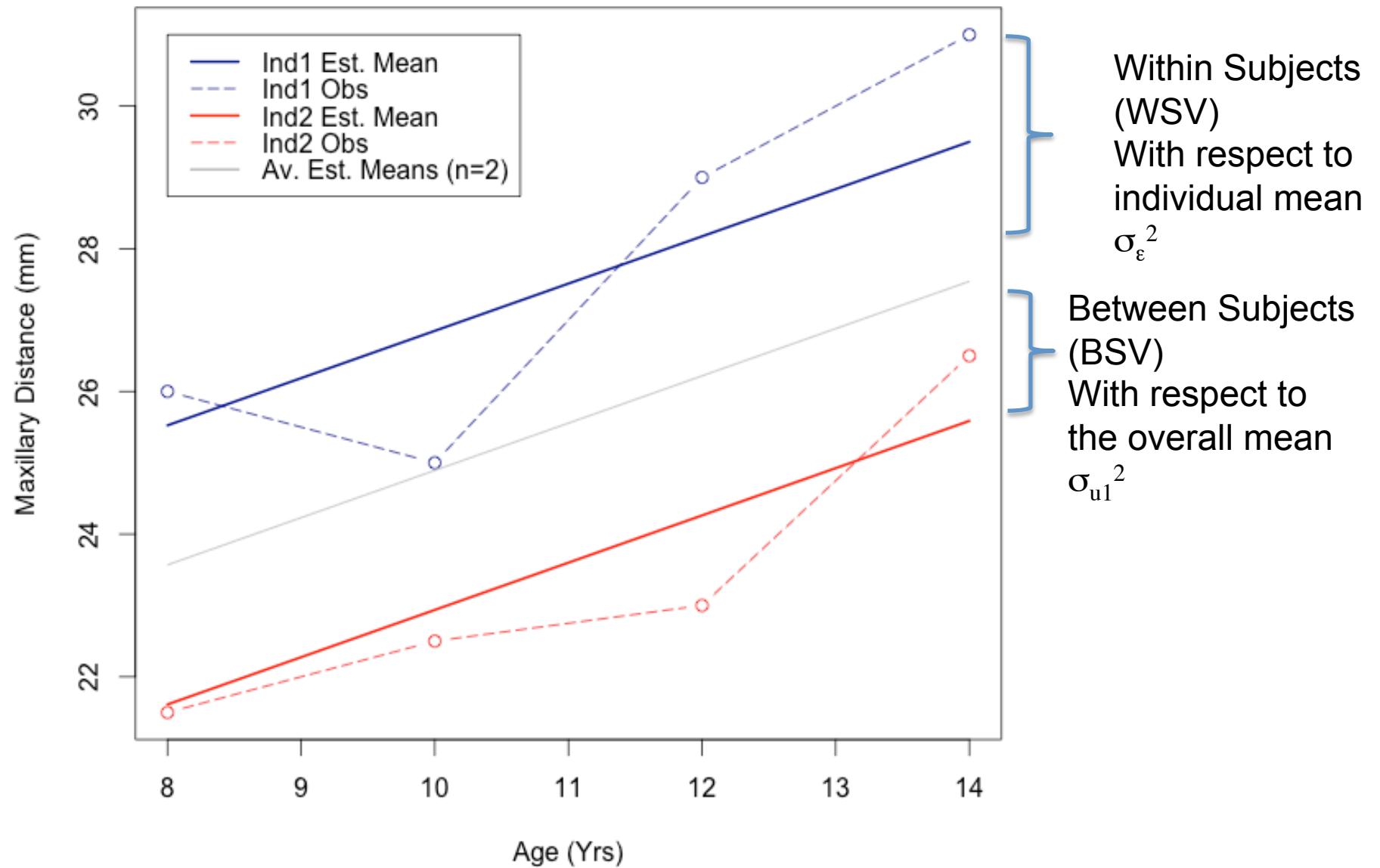
Sources of Variability

Random Intercept Model

$$u_{il} \sim N(0, \sigma_{u_l}^2), \quad \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2).$$

1. $\sigma_{u_l}^2$: Between subject variability (BSV): reflects the subject specific variability around the overall population mean.
2. σ_ε^2 : Within subject variability (WSV): includes within subject variability and measurement error.
 - Represents variability that cannot be explained with available information.
 - It is impossible to determine if the deviation of Y_{ij} from the subject specific mean μ_{ij} is really measurement error or due to true random variability within a subject.

Two random sources of variability



Fitting a Random Intercept Model

Maxillary Distance Example

$$Y_{ij} = \beta_0 + \beta_1 \text{Age}^*_{ij} + u_{il} + \varepsilon_{ij}.$$

$$u_{il} \sim N(0, \sigma_u^2); \quad \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2);$$

ε_{ij} independent of ε_{ik} , u_{il} independent of ε_{ij} .

Age is centered: $\text{Age}^* = \text{Age} - 11$

Typical call: `lme (fixed , data , random)`

```
> library(nlme)
> dat <- Orthodont
> # random intercept
> fitt1 <- lme(distance ~ I(age-11),
   data = dat, random = ~ 1 | Subject)
```

I(...) is a inside
function, inside I(...)
function 我们可以从新
中心化自变量

intercept 用 1 表示, grouped by “subject”

```
> summary(fitt1)
Linear mixed-effects model fit by REML
Data: dat
      AIC      BIC      logLik
 455.0025 465.6563 -223.5013
```

Random effects:

Formula: ~1 | Subject
 (Intercept) Residual
 StdDev: 2.114724 1.431592

$$\hat{\sigma}_u, \hat{\sigma}_\epsilon$$

Fixed effects: distance ~ I(age - 11)

| | Value | Std.Error | DF | t-value | p-value |
|-------------|-----------|-----------|----|----------|---------|
| (Intercept) | 24.023148 | 0.4296605 | 80 | 55.91193 | 0 |
| I(age - 11) | 0.660185 | 0.0616059 | 80 | 10.71626 | 0 |

This is the overall mean

Correlation:
 (Intr)
 I(age - 11) 0

$$\hat{\beta}_0, \hat{\beta}_1$$

Standardized Within-Group Residuals:

| Min | Q1 | Med | Q3 | Max |
|-------------|-------------|-------------|------------|------------|
| -3.66453932 | -0.53507984 | -0.01289591 | 0.48742859 | 3.72178465 |

Number of Observations: 108

Number of Groups: 27

Number of subjects

$$\text{Accessing fitted values } \hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}^*_{ij} + \hat{u}_{il}.$$

```
> fitt1$fitted
```

| | fixed | Subject |
|---|----------|----------------|
| 1 | 22.04259 | 25.38635 |
| 2 | 23.36296 | 26.70672 |
| 3 | 24.68333 | 28.02709 |
| 4 | 26.00370 | 29.34746 |
| 5 | 22.04259 | 21.46107 |
| 6 | 23.36296 | 22.78144 |
| 7 | 24.68333 | 24.10181 |
| 8 | 26.00370 | 25.42218 . . . |

Note that the first two subjects are male, have the same overall mean.

```
> fitt1$coef
```

| | \$fixed |
|-------------|-------------|
| (Intercept) | I(age - 11) |
| 24.0231481 | 0.6601852 |

$$\hat{\beta}_0, \hat{\beta}_1$$

```
$random
```

| | \$random\$Subject |
|-------------|-------------------|
| (Intercept) | |
| M16 | -0.9179756 |
| M05 | -0.9179756 |
| M02 | -0.5815230 |
| M11 | -0.3572213 |
| . . . | |
| M01 | 3.3437571 |
| . . . | |

$$\hat{u}_{il}'s$$

“fixed”: $\hat{\beta}_0 + \hat{\beta}_1 \text{Age}^*_{ij}$

```
> 24.0231481 + 0.6601852 *(c(8,10,12,14)-11)
[1] 22.04259 23.36296 24.68333 26.00370
```

“Subject”: $\hat{\beta}_0 + \hat{\beta}_1 \text{Age}^*_{ij} + \hat{u}_{il}$

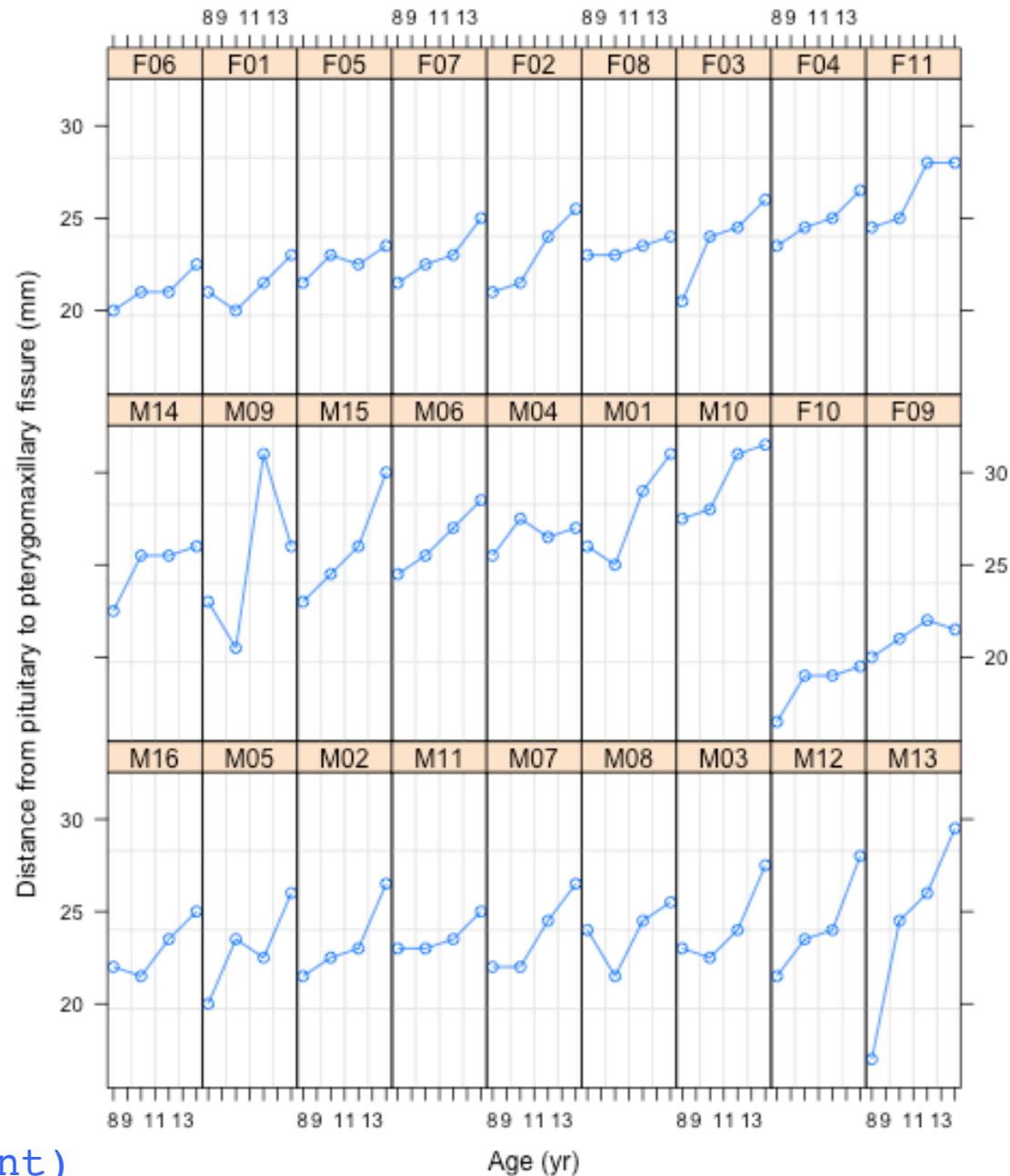
```
> 24.0231481 + 0.6601852 *(c(8,10,12,14)-11) + 3.3437571
[1] 25.38635 26.70672 28.02709 29.34746
```

Accessing fitted values

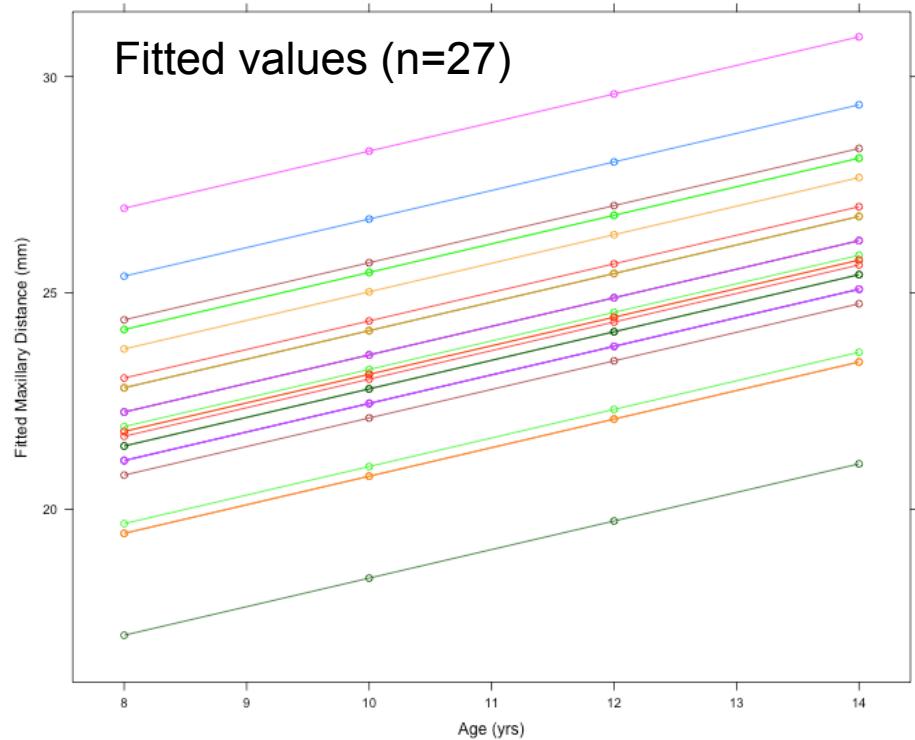
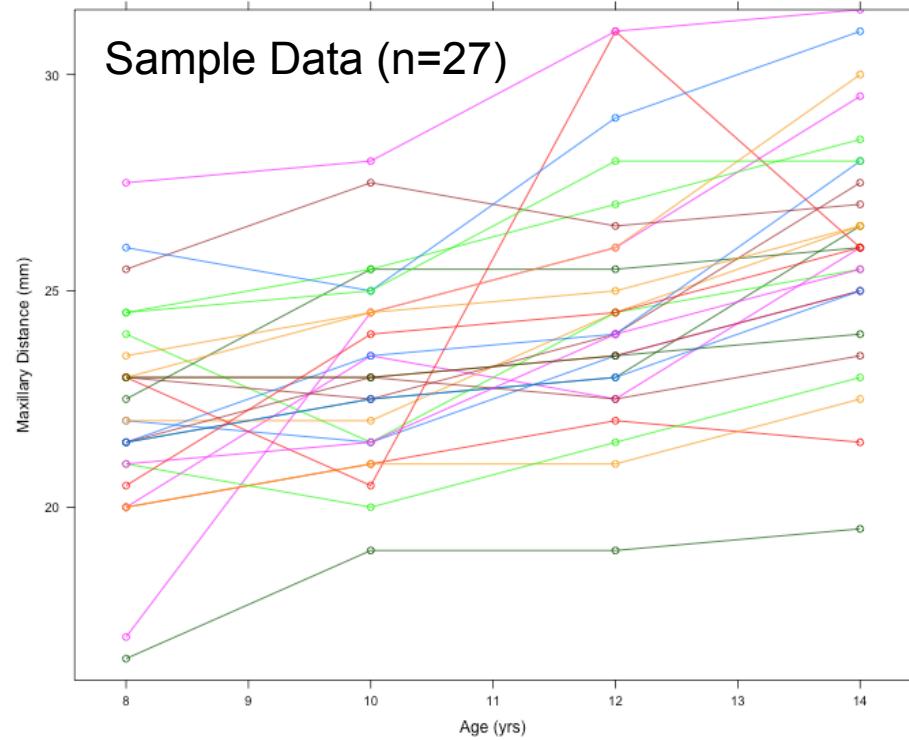
More convenient when plotting...

```
> fitted(fitt1)
M01      M01      M01      M01      M02      M02      M02      M02
25.38635 26.70672 28.02709 29.34746 21.46107 22.78144 24.10181 25.42218
      M03      M03      M03      M03      M04      M04      M04      M04
22.24613 23.56650 24.88687 26.20724 24.37699 25.69736 27.01773 28.33810
```

Individual Maxillary Growth (ages 8-14)



plot(Orthodont)



```
library(lattice)
```

```
# Sample data plot
y.lim <- c(16,31.5)
xyplot(distance~age,groups=Subject,data=dat, ylim=y.lim,type="b",
       ylab="Maxillary Distance (mm)",xlab="Age (yrs)")
```

```
# Fitted data plot
xyplot(fitted1~age,groups=Subject,data=dat,ylim=y.lim,type="b",
       ylab="Fitted Maxillary Distance (mm)",xlab="Age (yrs)")
```

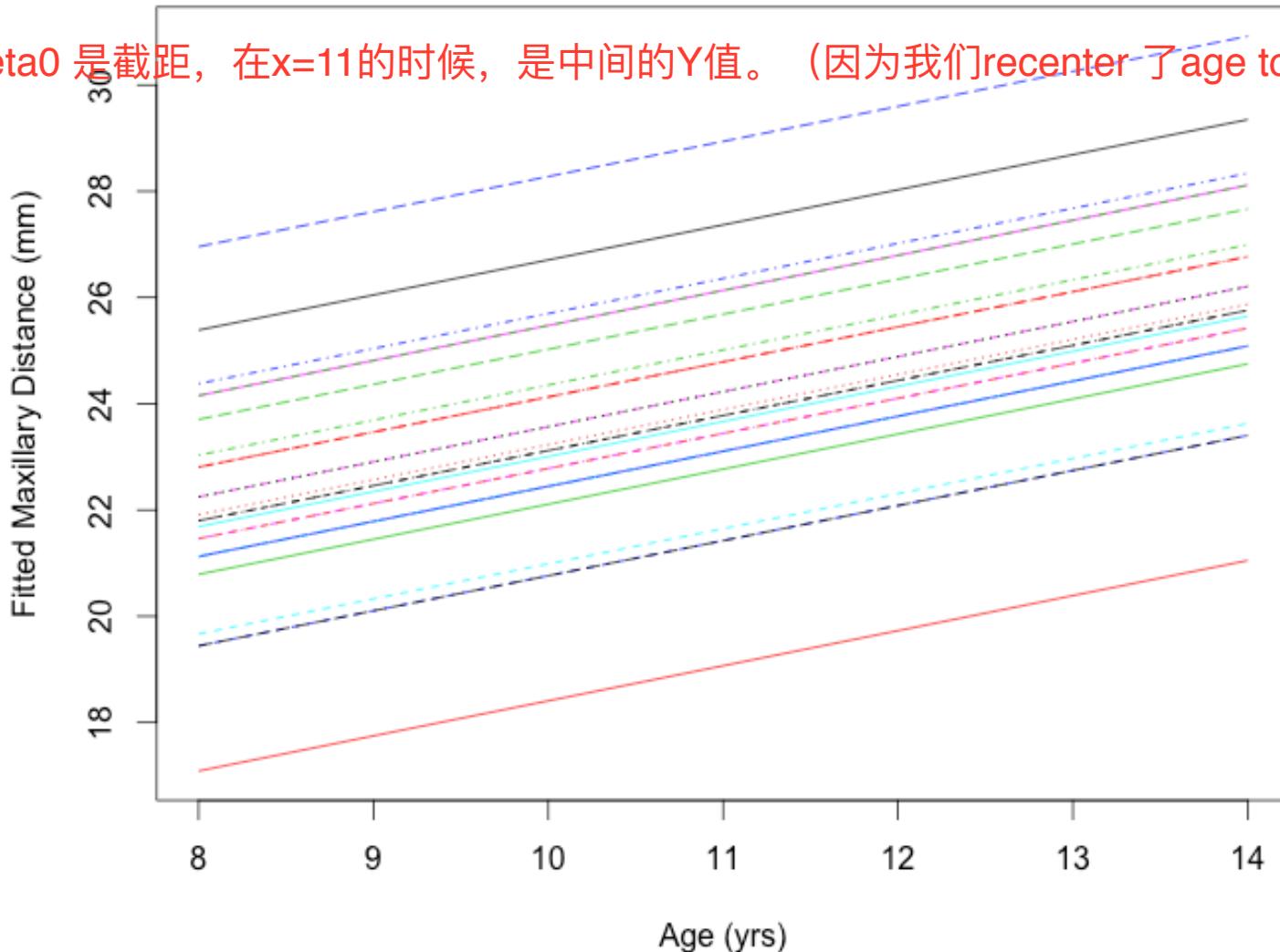
$$\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}^{*}_{ij} + \hat{u}_{il}$$

Interpreting the fitted model

$$\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 Age^{*}_{ij} + \hat{u}_{il}, \quad Age^{*}_{ij} = Age_{ij} - 11$$

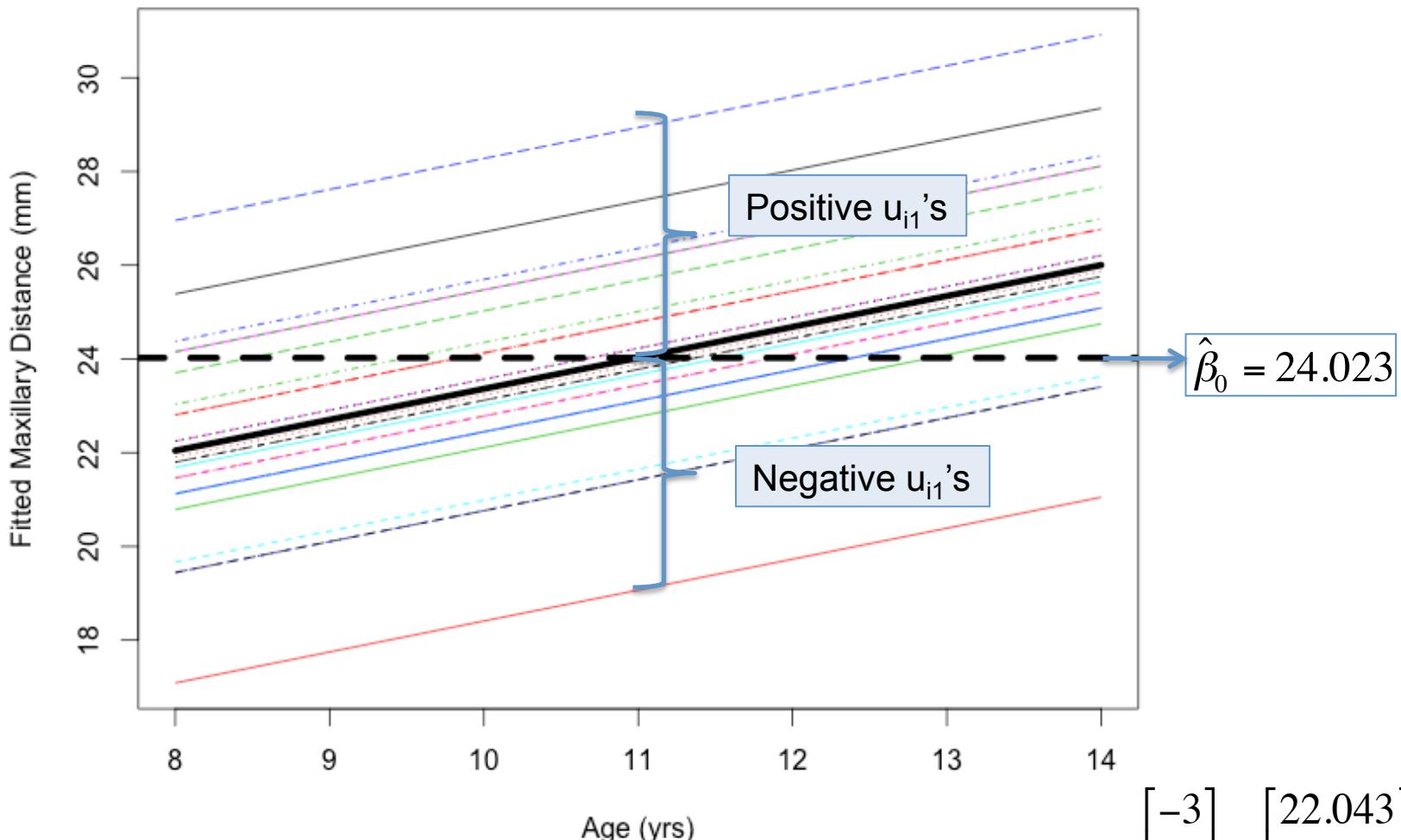
$$\hat{\beta}_0 = 24.023, \quad \hat{\beta}_1 = 0.660$$

beta0 是截距，在x=11的时候，是中间的Y值。（因为我们recenter了age to 11）



Interpreting the fitted model

$$\hat{\beta}_0 = 24.023, \quad \hat{\beta}_1 = 0.660$$



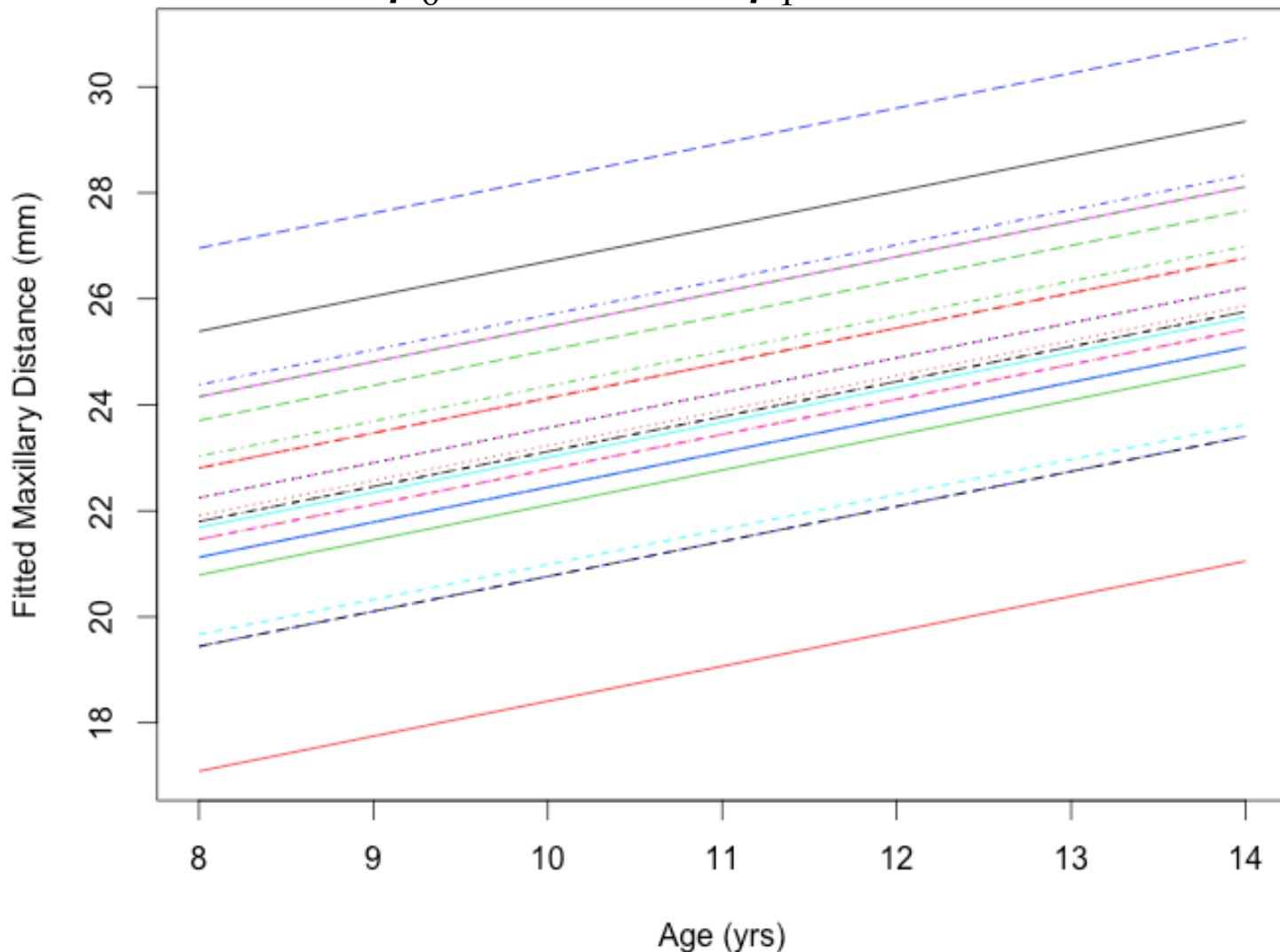
The vector of fitted values

(for each centered age value) is: $\hat{E}(Y)_{4 \times 1} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}^*_{4 \times 1} = 24.023 + 0.660$

$$\begin{bmatrix} -3 \\ -1 \\ 1 \\ 3 \end{bmatrix} = \begin{bmatrix} 22.043 \\ 23.363 \\ 24.683 \\ 26.004 \end{bmatrix}$$

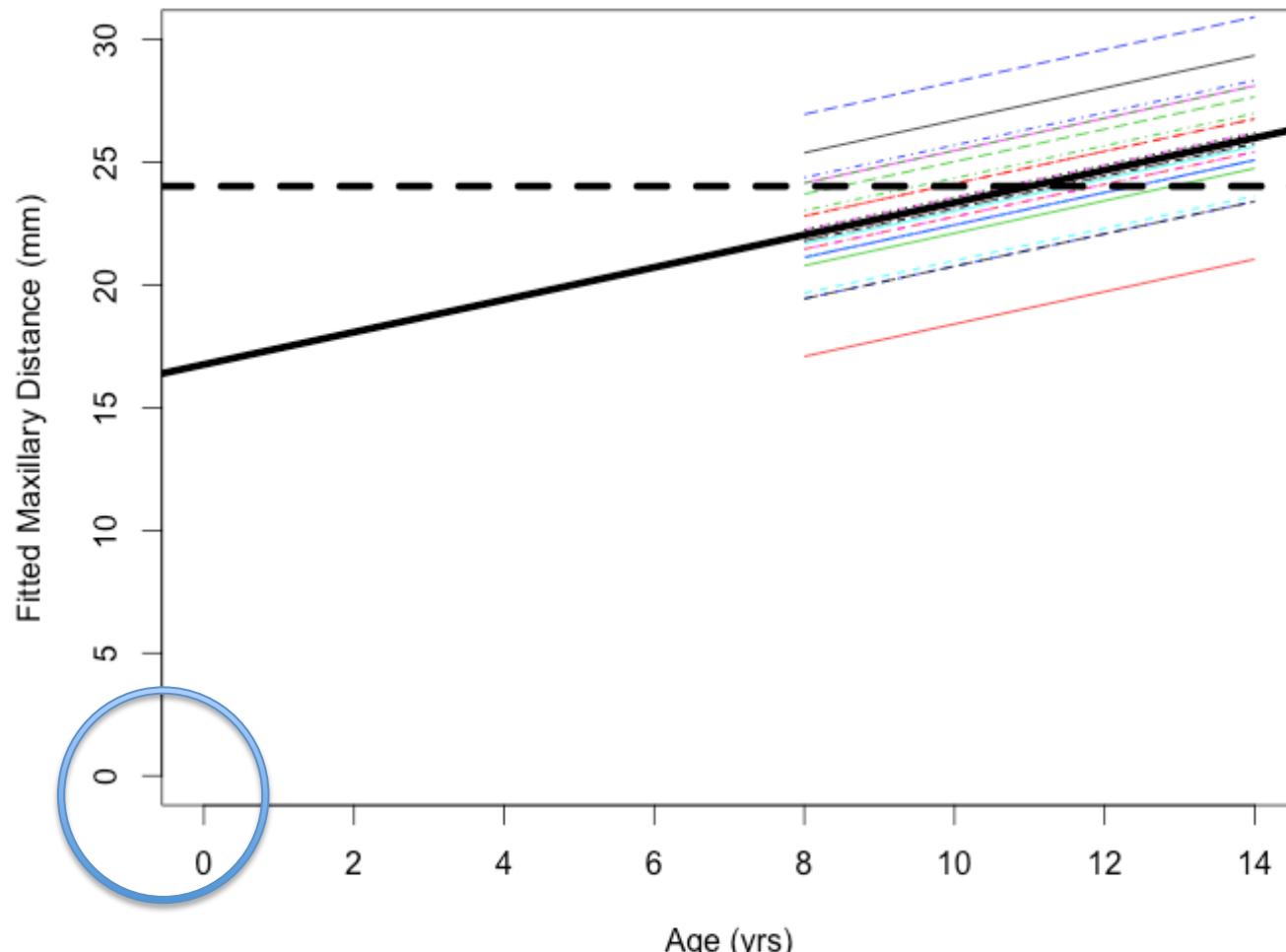
Interpreting the fitted model

$$\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}_{ij} + \hat{u}_{i1}.$$
$$\hat{\beta}_0 = 16.761, \quad \hat{\beta}_1 = 0.660$$



Fitted model: $\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}_{ij} + \hat{u}_{il}$

$$\hat{\beta}_0 = 16.761, \quad \hat{\beta}_1 = 0.660$$



The vector of fitted values
(for each age value) is:

$$\hat{E}(Y)_{4 \times 1} = \hat{\beta}_0 + \hat{\beta}_1 \text{Age}_{4 \times 1} = 16.761 + 0.660$$

i.e., the estimated Marginal Mean

$$\begin{bmatrix} 8 \\ 10 \\ 12 \\ 14 \end{bmatrix} = \begin{bmatrix} 22.043 \\ 23.363 \\ 24.683 \\ 26.004 \end{bmatrix}$$

Interpretation when centering Age

When age is not centered,

- $\beta_0 + u_{i1}$ does not have a useful interpretation since it represents the subject specific response at age 0 .
- $\text{Var}(u_{i1})$ does not have a useful interpretation.

When age is centered (at age 11, say),

- $\beta_0 + u_{i1}$ is the subject specific mean response at age 11
- $\text{Var}(u_{i1})$ is the between-subject variation in the overall mean response at age 11.

The overall mean response at age 11 is:

$$E(Y_{ij}) = \beta_0 + \beta_1 \text{Age}^*_{ij}; \quad \text{Var}(Y_{ij}) = \sigma_{u_1}^2 + \sigma_\varepsilon^2$$

Data Structure in R

- Data sets can be stored as data frames or as groupedData objects.
- Multiple lines per subject
- In R, the variable Subject will be labeled as a “grouping” variable, used for plotting and LME analysis.

```
> head(Orthodont)
Grouped Data: distance ~ age | Subject
  distance age Subject Sex
    1      26.0     8     M01 Male
    2      25.0    10     M01 Male
    3      29.0    12     M01 Male
    4      31.0    14     M01 Male
    5      21.5     8     M02 Male
    6      22.5    10     M02 Male
```

Data Structure in R

The groupedData object:

- Contains data stored as a data frame
- Designates special roles for some variables:
 - Response
 - Primary covariate
 - Grouping factor

response ~ primary | grouping

- R stores a formula with the data, which can be accessed through the `formula()` function

```
> formula(Orthodont)  
distance ~ age | Subject
```

Also useful when
fitting models

Data Structure in R

- Since there's multiple lines per subject, `dim(dat)` or `nrow(dat)` does not longer work to obtain the number of subjects.
- Also, it may be of interest to check the balance of the data.

```
> female.dat <- dat[Sex=="Female",]  
> # no. repeated measurements per subject:  
> table(female.dat$Subject)
```

```
F10 F09 F06 F01 F05 F07 F02 F08 F03 F04 F11  
4   4   4   4   4   4   4   4   4   4   4  
> # no. of subjects:  
> length(table(female.dat$Subject))  
[1] 11
```

Alternatively, the `getGroups()` function can be used if the data has the groupedData format:

```
> table(getGroups(female.dat))
```

```
F10 F09 F06 F01 F05 F07 F02 F08 F03 F04 F11  
4   4   4   4   4   4   4   4   4   4   4
```

Data Structure in R

- To check whether the data is balanced with respect of a covariate, e.g. Age in the Maxillary Distance data:

```
> table(getCovariate(female.dat),getGroups(female.dat))
```

Plotting longitudinal data in R

Plots using a groupedData object

R Code to create a groupedData object:

```
newData <-  
  groupedData( response ~ primary | grouping,  
               data = as.data.frame( dataset ),  
               outer = ~ covariate,  
               labels = list( x = "primary",  
                             y = "response" ),  
               units = list( x = "(units)", y = "(units)" ) )
```

dataset need to be a data.frame first

- The “data” option can also be used together with a function to read data, such as the `read.table()` function:

```
data = read.table(dataset, header=T)
```

- The “outer” option is designated to variables that do not vary within a subject, e.g., sex.

Plotting longitudinal data in R

Some ways to plot involve:

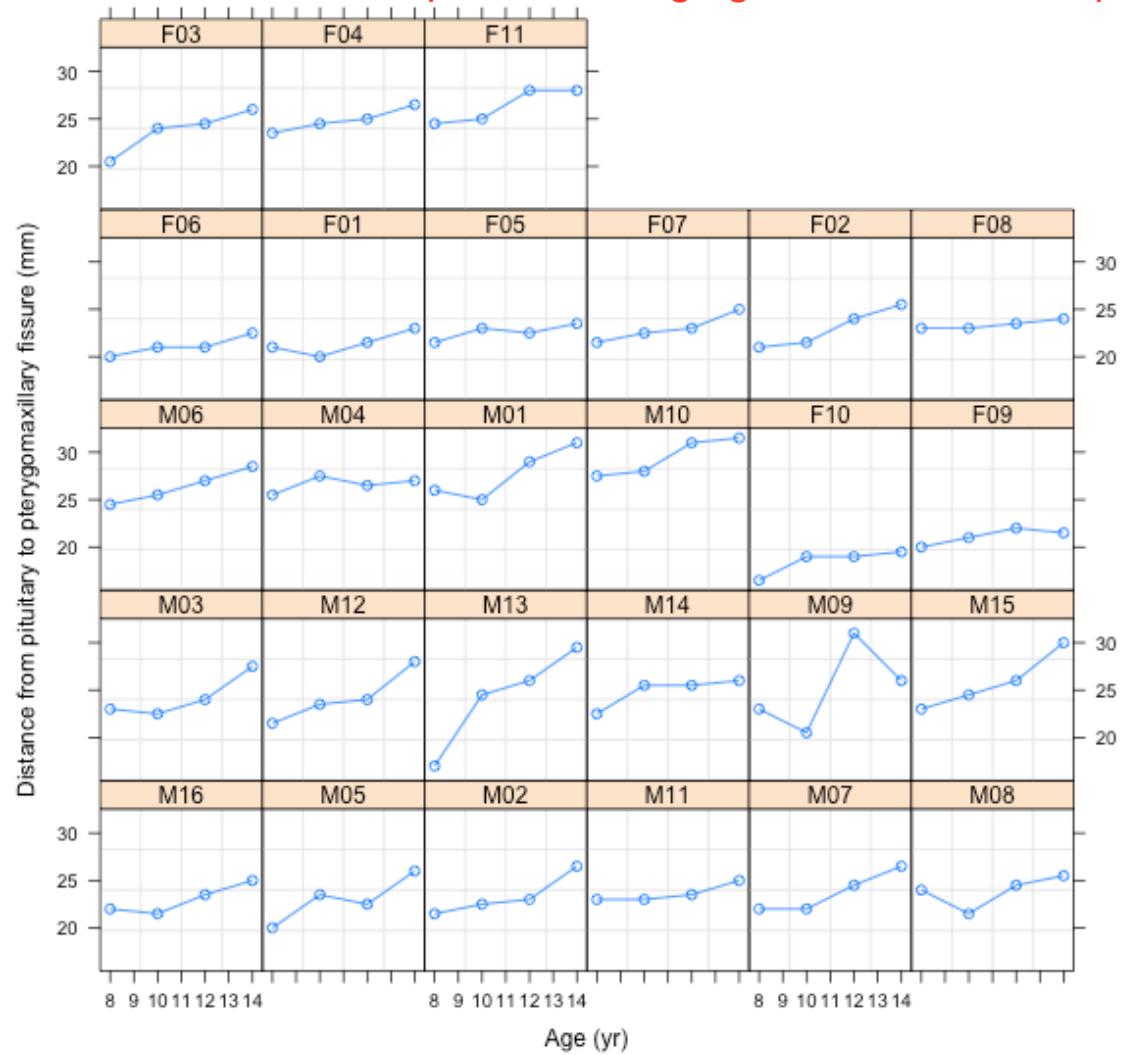
- The groupedData structure.
- The lattice library (and the “lattice” R package).
- The interaction.plot() function

Plotting longitudinal data in R

GroupedData Structure

```
plot(Orthodont, aspect=1)
```

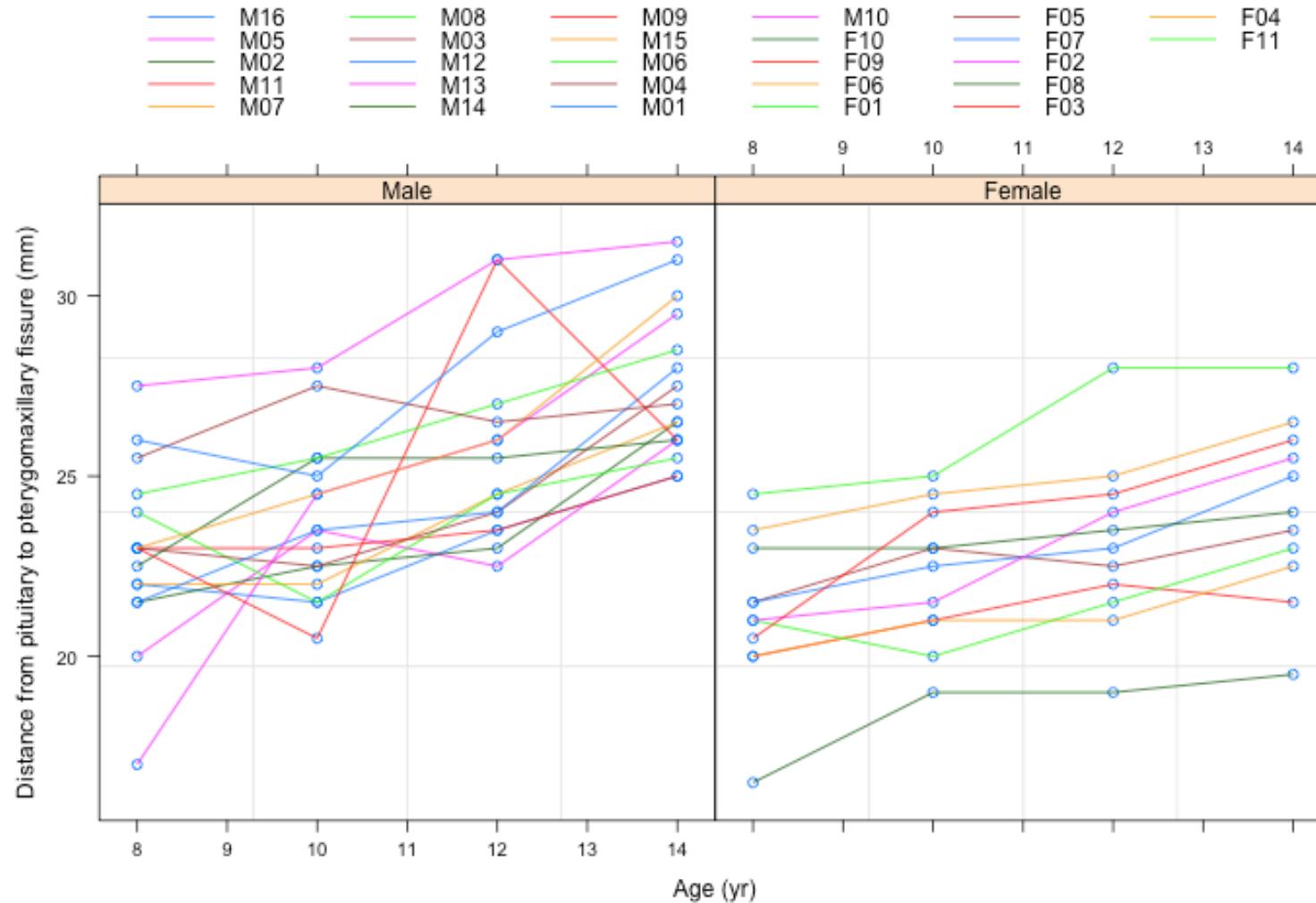
aspect -> changing the format of the plot



Plotting longitudinal data in R

GroupedData Structure

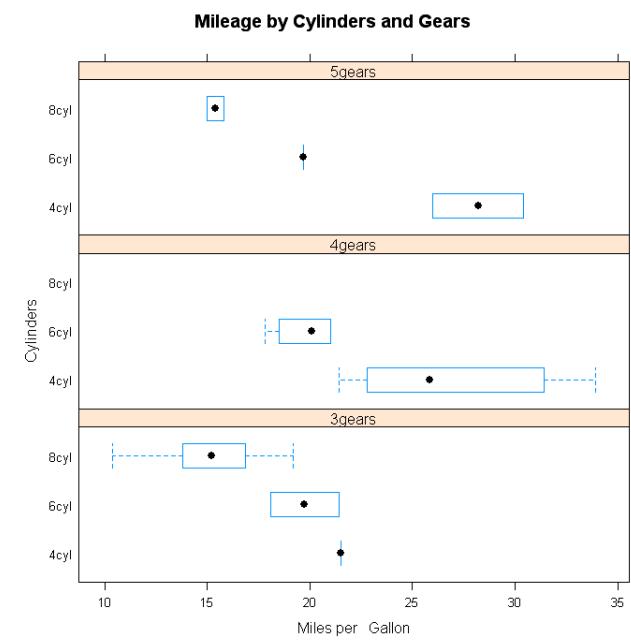
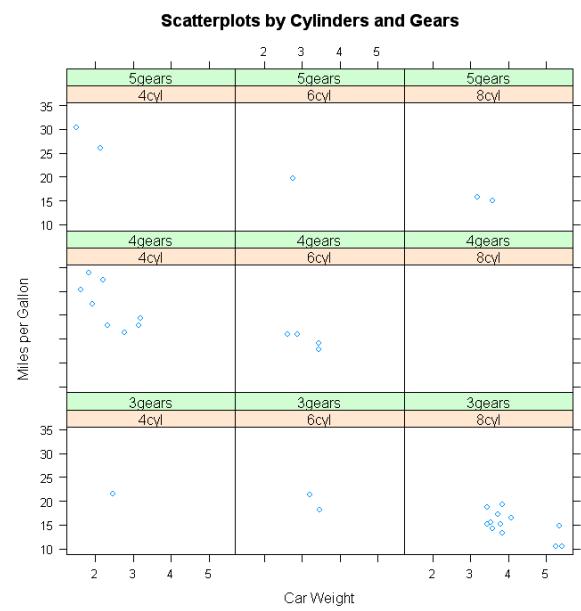
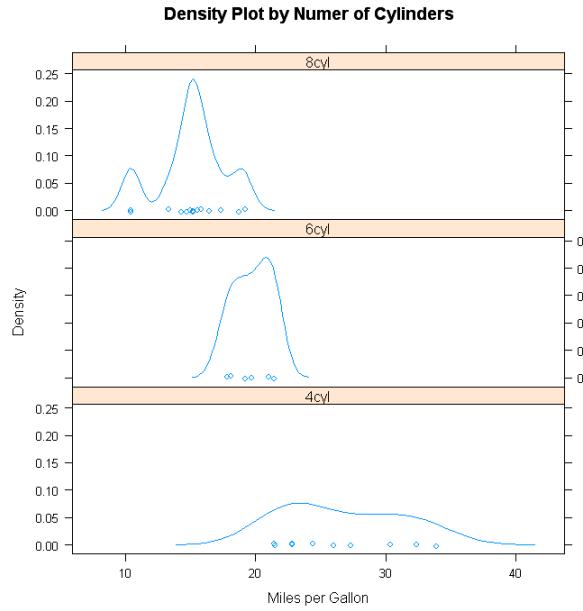
```
plot(Orthodont, outer=~Sex, aspect=1)
```



Plotting longitudinal data in R

The lattice library (lattice R package)

- Used to plot information in multiple panels: to display multivariate relationships.
- The typical format is:
 $\text{graph_type}(\text{formula}, \text{data}=)$
- In the examples below, suppose x,y are continuous variables and A,B are factors.



`densityplot()`
`x | A*B`

`xyplot()`
`y | x | A`

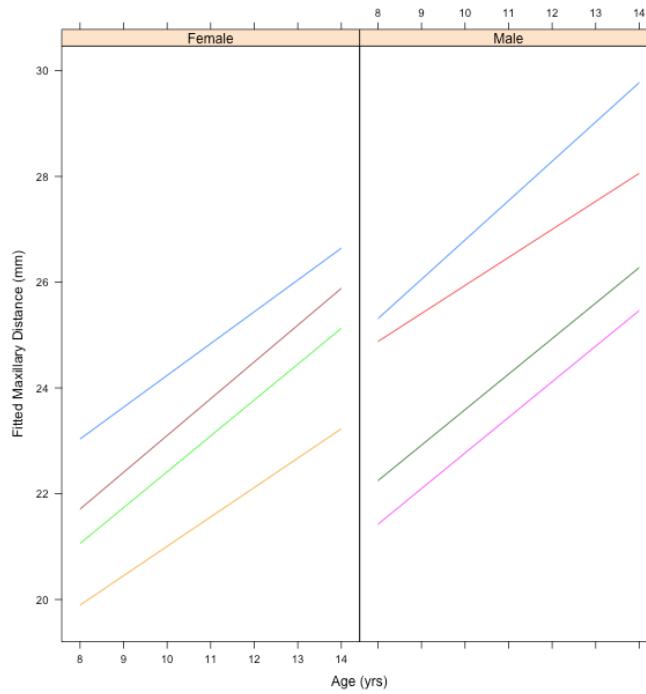
`bwplot()`
`X~A or A~x`

See <http://www.statmethods.net/advgraphs/trellis.html>

Plotting longitudinal data in R

The lattice library

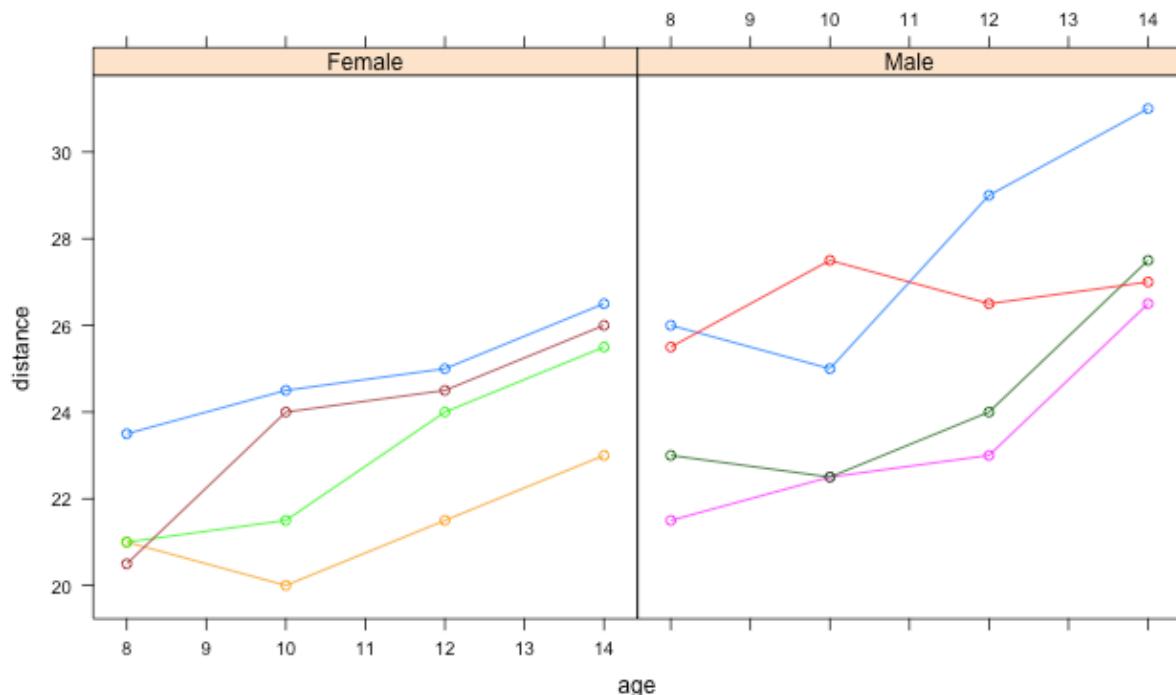
```
xyplot(fitted~age | Sex,  
       groups=Subject,  
       data=dat0,  
       type="l", line  
       ylab="Fitted Maxillary Distance (mm)",  
       xlab="Age (yrs)", aspect=2)
```



Plotting longitudinal data in R

The lattice library

```
xyplot(distance~age | Sex,  
       groups=Subject,  
       data=dat0,  
       type="b",      Both line and points  
       aspect=1)
```



Plotting longitudinal data in R

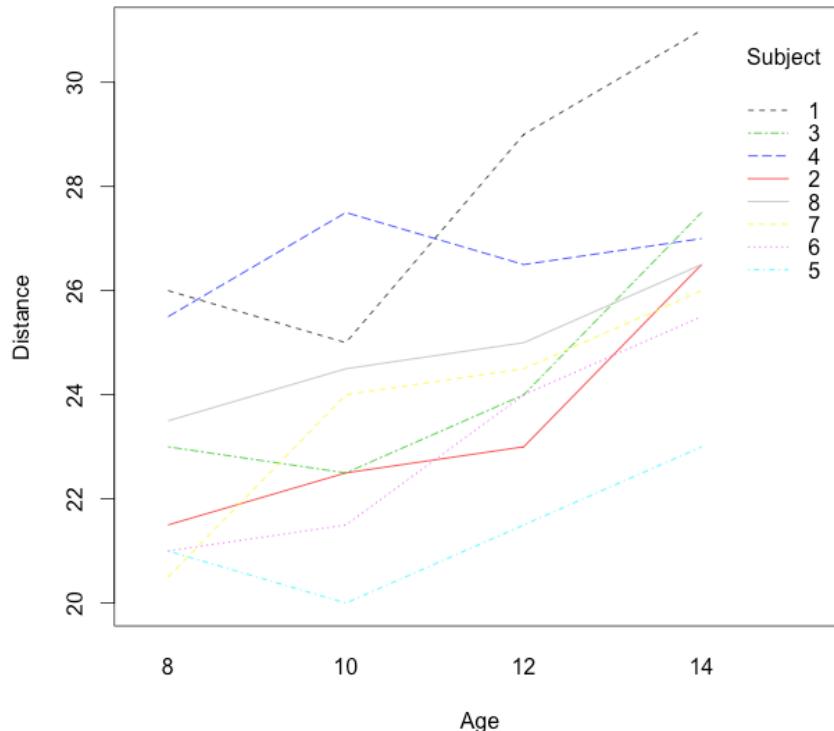
interaction.plot()

Plots trajectories (“traces”) in one single panel – useful when not too many:

```
interaction.plot(x.factor,trace.factor,response)
```

E.g.,

```
interaction.plot(age,Subject,distance,col=1:8)
```



R Code to plot fitted values

`xyplot()`, `interaction.plot()` and `plot(groupedData)`

```
# fit with random intercept
fitt1 <- lme(distance ~ I(age-11), data = dat, random = ~ 1|Subject)

# appending fitted values in data set
dat$fitted1 <- fitted(fitt1)

# plot all subjects together via xyplot
library(lattice)
xyplot(fitted1~age,groups=Subject,data=dat,type="b",
       ylab="Fitted Maxillary Distance (mm)",xlab="Age(yrs)")

# plot all subjects together via interaction.plot()
attach(dat)

interaction.plot(age,Subject,fitted1,col=1:8,
                 legend=F,ylim=y.lim,
                 ylab="Fitted Maxillary Distance (mm)",xlab="Age(yrs)")
```

R Code to plot fitted values : `xyplot()`, `interaction.plot()` and `plot(groupedData)`

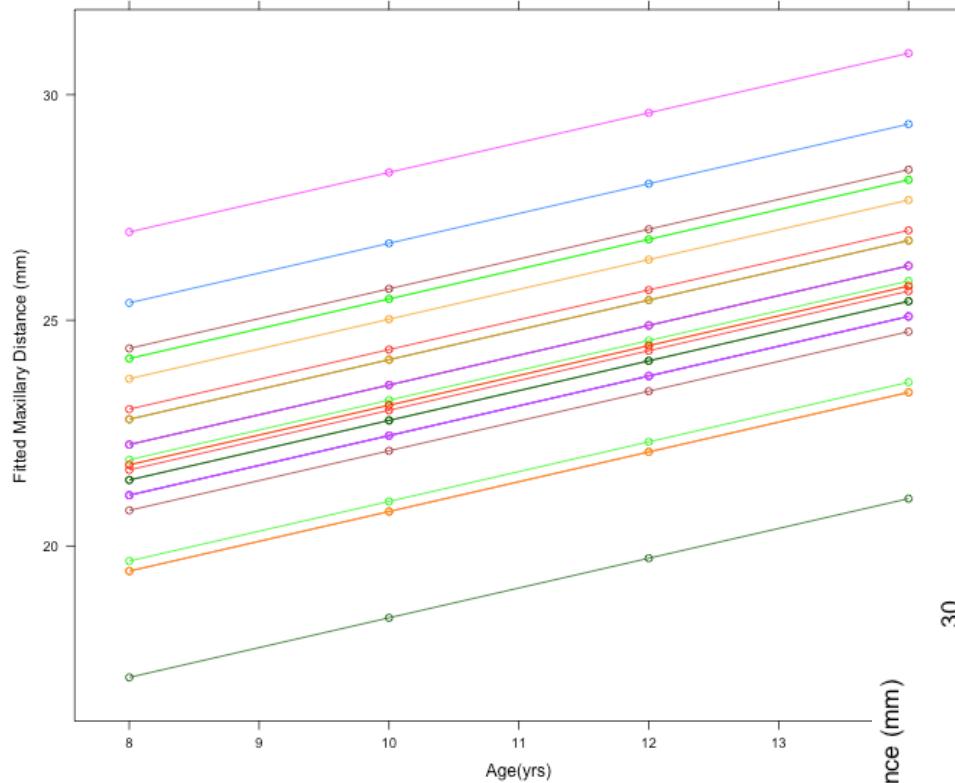
```
# plot individually via groupedData
dat.fit1 <- dat[,c("distance", "age", "Subject", "Sex", "fitted1")]

formula(dat.fit1)
# distance ~ age | Subject

dat.fit1 <- update(dat.fit1,fitted1 ~ age | Subject,
                    labels = list( x = "Age",y = "Fitted Maxillary Distance" ),
                    units = list( x = "(mm)", y = "(yrs)" ) )

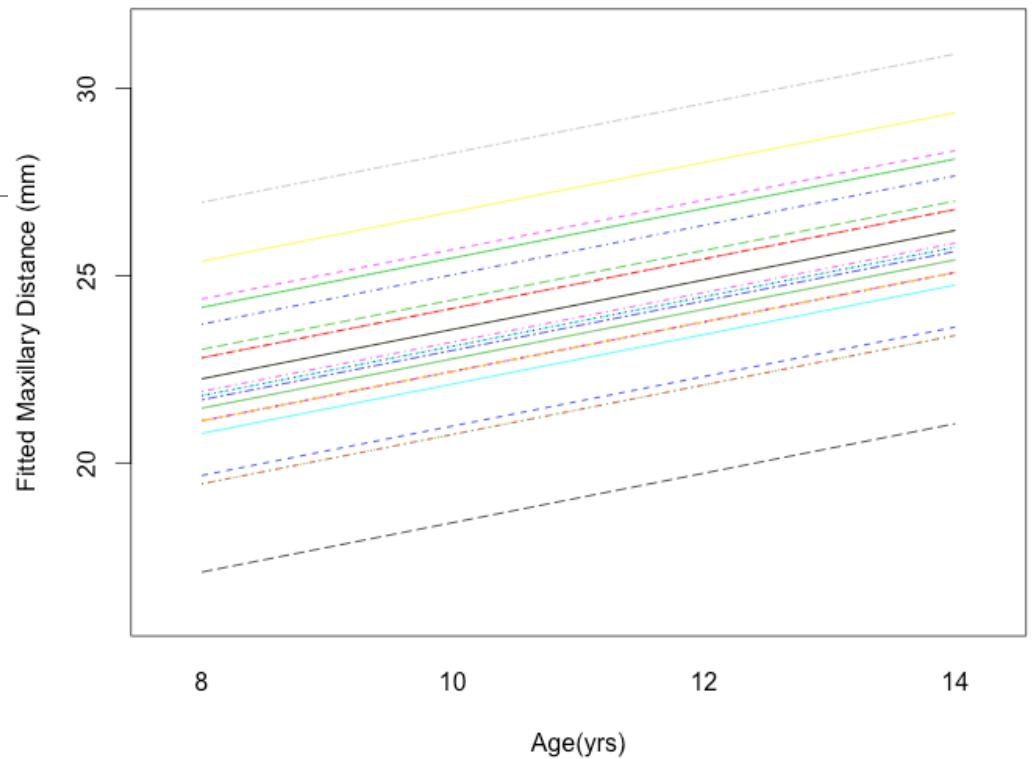
plot(dat.fit1,aspect=1)
```

R Code to plot fitted values : `xyplot()`, `interaction.plot()` and `plot(groupedData)`



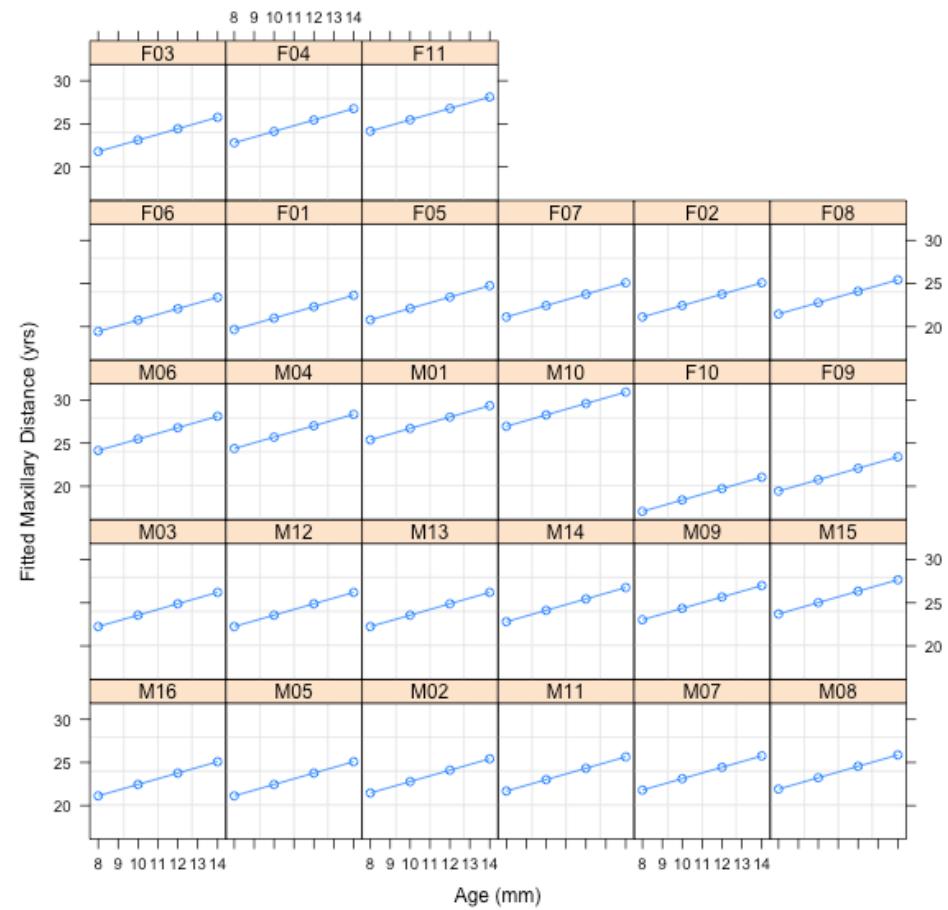
Via `interaction.plot()`

← Via `xyplot()`



R Code to plot fitted values : `xyplot()` and `plot(groupedData)`

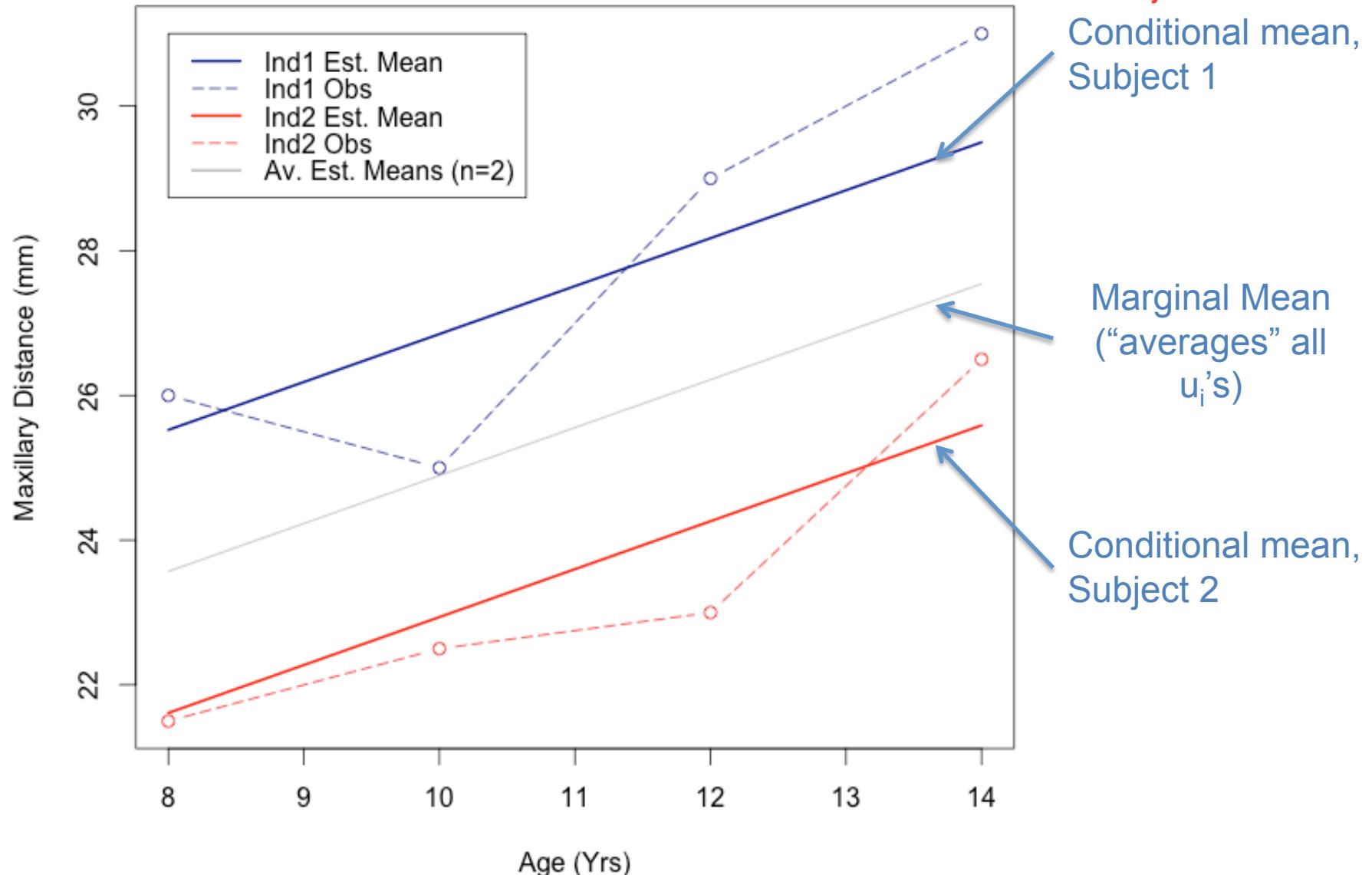
Via `plot(groupedData)` →



Two random sources of variability

Marginal and Conditional Means

Conditional mean -> is the mean conditioned to each subject



Marginal and Conditional Means

Marginal

$$Y_{ij} \sim (\mu_{ij}, \sigma_{u_1}^2 + \sigma_\varepsilon^2) \quad \text{and} \quad Y_{ij} | u_{i1} \sim (\mu_{ij} + u_{i1}, \sigma_\varepsilon^2)$$

Conditional

(u_{i1} 's as fixed)

- $E(Y)$: expected value of an individual randomly sampled from Y
- $E(Y|u_{i1})$: expected value for a particular individual
- If the expected value of individuals in their most general sense is of interest, then $E(Y)$ is of interest.
- But as soon as the discussion moves to particular subjects, $E(Y|u_{i1})$ becomes of interest.
- $Var(Y)$: total variability.
- $Var(Y|u_{i1})$: variability within a subject.

Marginal E(Y) and Var(Y)

Random intercept model

$$Y_{ij} = \beta_0 + \beta_1 t_{ij} + u_{i1} + \varepsilon_{ij}; \quad j = 1, \dots, m_i, i = 1, \dots, n.$$

$$\begin{aligned} E(Y_{ij}) &= E(\beta_0 + \beta_1 t_{ij} + u_{i1} + \varepsilon_{ij}) \\ &= \beta_0 + \beta_1 t_{ij} + E(u_{i1}) + E(\varepsilon_{ij}) \quad \text{Recall } E(\text{constant})=\text{constant} \\ &= \beta_0 + \beta_1 t_{ij}. \end{aligned}$$

The random effects induce variability into Y:

Recall $\text{Var}(\text{constant})=0$

$$\begin{aligned} \text{Var}(Y_{ij}) &= \text{Var}(\beta_0 + \beta_1 t_{ij} + u_{i1} + \varepsilon_{ij}) \\ &= \text{Var}(u_{i1} + \varepsilon_{ij}) \\ &= \text{Var}(u_{i1}) + \text{Var}(\varepsilon_{ij}) + 2\text{Cov}(u_{i1}, \varepsilon_{ij}) \\ &= \sigma_u^2 + \sigma_\varepsilon^2. \end{aligned}$$

Independence assumptions
 u_1 's vs. ε 's, and
within ε 's

Marginal $E(Y)$ and $\text{Var}(Y)$

Random intercept model

- The random errors ε induce variability into Y .
- The random effects u induce:
 - ✓ Variability into Y **AND**
 - ✓ Correlation within individual observations,
i.e., $\text{Cov}(Y_{ij}, Y_{ik}) \neq 0$.

How can we see this? By the fact that the random errors allow for
 $\text{Cov}(Y_{ij}, Y_{ik}) = \sigma_{uI}^2 \neq 0$

Marginal E(Y) and Var(Y) Random intercept model

The random effects induce correlation into subject-specific Y's:

$$\begin{aligned}
 Cov(Y_{ij}, Y_{ik}) &= Cov(\beta_0 + \beta_1 t_{ij} + u_{i1} + \varepsilon_{ij}, \beta_0 + \beta_1 t_{ik} + u_{i1} + \varepsilon_{ik}) \\
 &= Cov(u_{i1} + \varepsilon_{ij}, u_{i1} + \varepsilon_{ik}) \\
 &= Var(u_{i1}) + Cov(u_{i1}, \varepsilon_{ik}) + Cov(\varepsilon_{ij}, u_{i1}) + Cov(\varepsilon_{ij}, \varepsilon_{ik}) \\
 &= \sigma_u^2.
 \end{aligned}$$

0's due to
independence
assumptions
 u_1 's vs. ε 's, and
within ε 's

$$Corr(Y_{ij}, Y_{ik}) = \frac{Cov(Y_{ij}, Y_{ik})}{\sqrt{Var(Y_{ij})} \sqrt{Var(Y_{ik})}} = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_\varepsilon^2}.$$

Marginal E(Y) and Var(Y) Random intercept model

In summary E(Y) and Var(Y) are:

$$E(Y_{ij}) = \beta_0 + \beta_1 t_{ij}$$

$$Var(Y_{ij}) = \sigma_u^2 + \sigma_\varepsilon^2.$$

$$Cov(Y_{ij}, Y_{ik}) = \sigma_u^2 \neq 0.$$

Note non-zero covariance implies non-zero correlation, this means that the LME model accounts for within-individual correlation

$$Corr(Y_{ij}, Y_{ik}) = \frac{Cov(Y_{ij}, Y_{ik})}{\sqrt{Var(Y_{ij})} \sqrt{Var(Y_{ik})}} = \frac{\sigma_u^2}{\sigma_u^2 + \sigma_\varepsilon^2}.$$

Conditional $E(Y|u)$ and $\text{Var}(Y|u)$ Random Intercept Model

$$Y_{ij} = \mu_{ij} + u_{i1} + \varepsilon_{ij}; \quad j = 1, \dots, m_i, \quad i = 1, \dots, n$$

$$u_{i1} \sim (0, \sigma_u^2) \quad \varepsilon_{ij} \sim (0, \sigma_\varepsilon^2)$$

- When u_{i1} is stated as “given” (i.e., “ $|u_{i1}$ ”), it can be considered fixed, then Y’s ONLY inherit the distributional properties of the random component ε_{ij} .

$$E(Y_{ij} | u_{i1}) = \beta_0 + \beta_1 t_{ij} + u_{i1}$$

$$\text{Var}(Y_{ij} | u_{i1}) = \sigma_\varepsilon^2.$$

$$\text{So} \quad Y_{ij} | u_{i1} \sim (\beta_0 + \beta_1 t_{ij}, \sigma_\varepsilon^2)$$

Note that

$$\text{Cov}(Y_{ij}, Y_{ik} | u_{i1}) = \text{Cov}(\varepsilon_{ij}, \varepsilon_{ik}) = 0$$

3.2 Simple cases

b) Random Intercept & Slope:

- Model specification
- Variance & Covariance of Y

Specific learning objectives:

1. Write the random intercept & slope model and its assumptions.
2. State the features of the LME models that result from the random intercept & slope.
3. Fit a random intercept & slope model in R and identify the estimated model parameters in the output.

Random Intercept and Slope Model

A Mixed Effects Model

This is a mixed effects model because we are allowing a fixed effect (t_{ij}) to vary randomly.

$$Y_{ij} = \underbrace{\beta_0 + \beta_1 t_{ij}}_{\text{Fixed}} + \underbrace{u_{i1} + u_{i2} t_{ij}}_{\text{Random}} + \varepsilon_{ij}; \quad j = 1, 2, 3, 4, \quad i = 1, \dots, 26.$$

+ random effect for slope

Rearranging,

$$Y_{ij} = (\underbrace{\beta_0 + u_{i1}}_{\text{Intercept}}) + (\underbrace{\beta_1 + u_{i2}}_{\text{Slope}}) t_{ij} + \varepsilon_{ij};$$

u_{i1} 是个体的截距与总体平均的差值

u_{i2} 是个体斜率与总体平均的差值

The subject specific mean is $\mu_{ij} = \beta_0 + \beta_1 t_{ij} + u_{i1} + u_{i2} t_{ij}.$

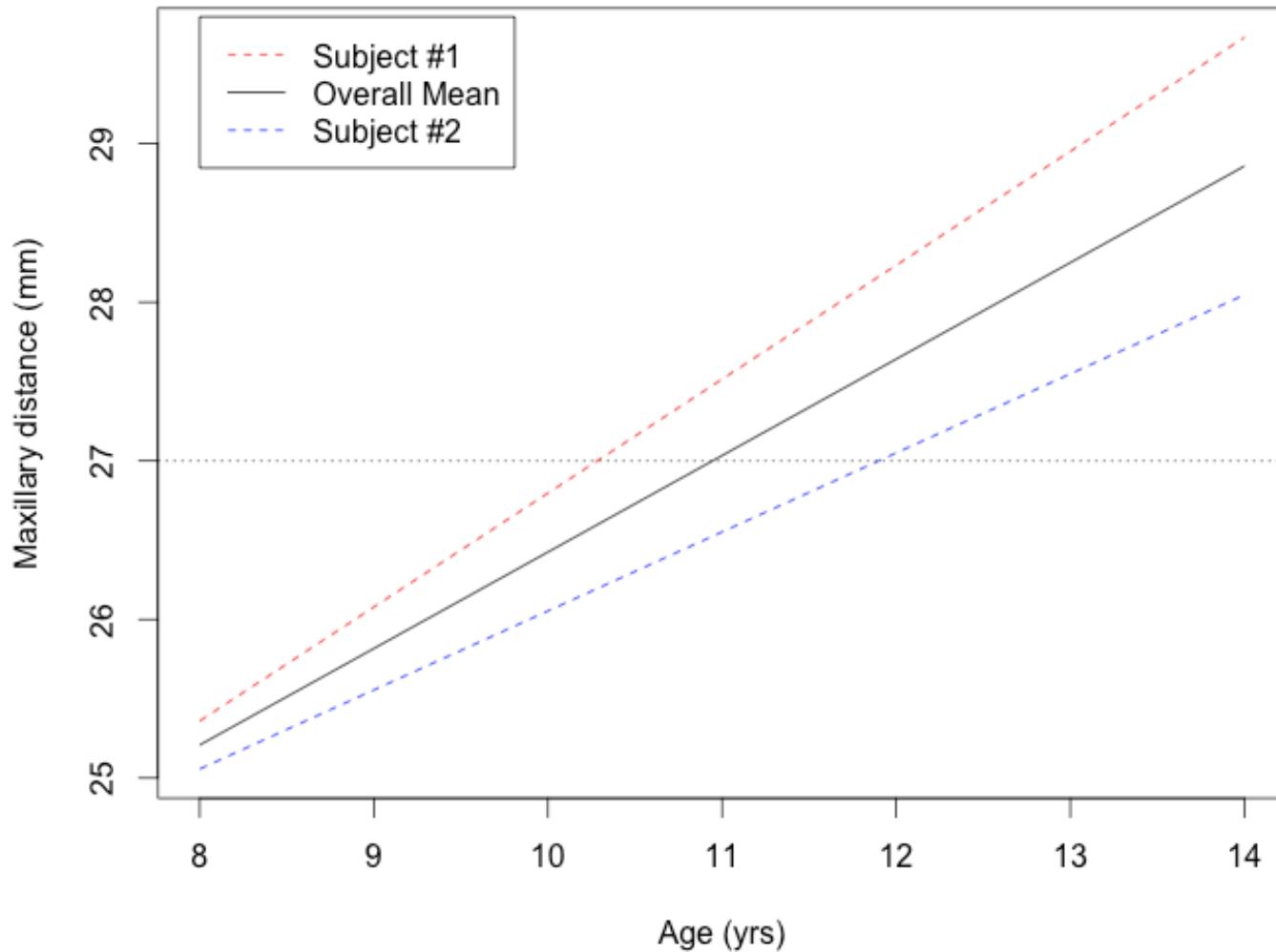
Random Intercept and Slope Model

- t_{ij} is the time variable associated with measurement Y_{ij}
- u_{i1} is the random deviation of true subject specific intercept and overall population intercept β_0 .
- u_{i2} is the random deviation of true subject specific slope and overall population slope β_1 .
- ε_{ij} is the random deviation of the ij-th response from from subject specific mean.

$$Y_{ij} = (\underbrace{\beta_0 + u_{i1}}_{\text{Intercept}}) + (\underbrace{\beta_1 + u_{i2}}_{\text{Slope}}) t_{ij} + \varepsilon_{ij};$$

Random Intercept and Slope Model

Suppose that age was centered at age 11 years and the overall estimated population mean at age 11 is $\hat{\beta}_0 = 27$ mm.



Subject #1 has a higher estimated intercept (baseline level at age=11) $\hat{\beta}_0 + \hat{u}_{11}$ than the estimated population intercept $\hat{\beta}_0$ and thus $\hat{u}_{11} > 0$.

Subject #2 has a lower estimated intercept, thus $\hat{u}_{21} < 0$.

Subject #1 has a steeper rate of increase over time $\hat{\beta}_1 + \hat{u}_{12}$ than the estimated population slope $\hat{\beta}_1$.

Subject #2 has a less steep rate of increase over time than the estimated population slope, $\hat{u}_{22} < 0$.

Random Intercept and Slope Model

Model Assumptions

$$Y_{ij} = \beta_0 + \beta_1 t_{ij} + u_{i1} + u_{i1} t_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i; \quad i = 1, \dots, n.$$

$$u_{i1} \sim N(0, g_{11}); \quad u_{i2} \sim N(0, g_{22});$$

$$\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2);$$

ε_{ij} independent of ε_{ik} , u_{i1} independent of u_{j1}

u_{i2} independent of u_{j2} , $Cov(u_{i1}, u_{i2}) = g_{12} \neq 0$

u_{i1} independent of ε_{ij} .

1. Linear relationship of Y with respect to parameters β_0, β_1 .
2. Normally, independently distributed residual errors ε_{ij} .
3. Normally, independently distributed random effects u_{i1} .
4. Random effects u_{i1} and u_{i2} are correlated.
5. Random effects and residuals errors are independent.

Random Intercept and Slope Model

Variance and correlation of Y

Recall the variance and covariance of the random effects are denoted as follows:

- $\text{Var}(u_{i1}) = g_{11}$
- $\text{Var}(u_{i2}) = g_{22}$
- $\text{Cov}(u_{i1}, u_{i2}) = g_{12}$

It can be shown that (see Fitzmaurice, Ch.8):

$$\begin{aligned}\text{Var}(Y_{ij}) &= \text{Var}(\beta_0 + \beta_1 t_{ij} + u_{i1} + u_{i2} t_{ij} + \varepsilon_{ij}) \\ &= g_{11} + 2t_{ij}g_{12} + t_{ij}^2 g_{22} + \sigma_\varepsilon^2.\end{aligned}$$

Var(Y) = between variance + within variance

Var(Y) increases when $g_{12}>0$
Var(Y) decreases when $g_{12}<0$

$$\text{Cov}(Y_{ij}, Y_{ik}) = g_{11} + (t_{ij} + t_{ik})g_{12} + t_{ij}t_{ik}g_{22}.$$

Cov(Y when age=2, Y when age=4)
 \neq

Cov(Y when age=2, Y when age=8)

Features of LME models

1. Explicitly distinguish between subject-specific and within-subject sources of variability:
greater precision of estimates than those from ordinary regression.
2. Covariance for two within-individual observations Y_{ij}, Y_{ik} can be expressed as a function of time,
and the magnitude of covariance depends on the time separation between them:
the time spacing between measurements does not have to be uniform between subjects.
3. Variance of Y_{ij} increases over time when $\text{cov}(u_{i1}, u_{i2}) > 0$ but decreases when $\text{cov}(u_{i1}, u_{i2}) < 0$:
allow for heteroscedasticity (or non-constant variance).
4. $\text{Cov}(Y_{ij}, Y_{ik})$ is expressed as an explicit function of t_{ij} 's, each subject can have a unique sequence of measurement times:
a balanced longitudinal design is not required.

Random Intercept and Slope Model

Fitting a Random Intercept and Slope Model

$$Y_{ij} = \beta_0 + \beta_1 \text{Age}^*_{ij} + u_{i1} + u_{i2} \text{Age}^*_{ij} + \varepsilon_{ij}.$$
$$u_{i1} \sim N(0, \sigma_{u_1}^2); \quad u_{i2} \sim N(0, \sigma_{u_2}^2); \quad \varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2);$$

u_{i1} not independent of u_{i2} , ε_{ij} independent of ε_{ik} ,

u_{i1} independent of ε_{ij} ,

Age* is centered at 11 yrs.

```
# library(nlme)
```

```
# random intercept and slope
fitt2 <- lme(distance ~ I(age-11),
              data = dat, random = ~ I(age-11) | Subject)
```

```
> summary(fitt2)
Linear mixed-effects model fit by REML
Data: dat
      AIC      BIC      logLik
 454.6367 470.6173 -221.3183
```

Random effects:

Formula: ~I(age - 11) | Subject

Structure: General positive-definite, Log-Cholesky parametrization

| | StdDev | Corr |
|-------------|-----------|--------|
| (Intercept) | 2.1343289 | (Intr) |
| I(age - 11) | 0.2264278 | 0.503 |
| Residual | 1.3100402 | |

$$\hat{\sigma}_{u_1}, \hat{\sigma}_{u_2}, \hat{\sigma}_\epsilon$$

$$\text{Corr}(u_{i1}, u_{i2})$$

Fixed effects: distance ~ I(age - 11)

| | Value | Std. Error | DF | t-value | p-value |
|-------------|-----------|------------|----|----------|---------|
| (Intercept) | 24.023148 | 0.4296601 | 80 | 55.91198 | 0 |
| I(age - 11) | 0.660185 | 0.0712533 | 80 | 9.26533 | 0 |

$$\hat{\beta}_0, \hat{\beta}_1$$

Correlation:

| | (Intr) |
|-------------|--------|
| I(age - 11) | 0.294 |

Standardized Within-Group Residuals:

| Min | Q1 | Med | Q3 | Max |
|--------------|--------------|-------------|-------------|-------------|
| -3.223106888 | -0.493760896 | 0.007316481 | 0.472151221 | 3.916031742 |

Number of Observations: 108

Number of Groups: 27

Number of subjects

Accessing fitted values $\hat{Y}_{ij} = \hat{\beta}_0 + \hat{\beta}_1 Age^*_{ij} + \hat{u}_{i1} + \hat{u}_{i2} Age^*_{ij}$

```
> fitt2$fitted
```

| | fixed | Subject |
|---|----------|---------------|
| 1 | 22.04259 | 24.81965 |
| 2 | 23.36296 | 26.57139 |
| 3 | 24.68333 | 28.32313 |
| 4 | 26.00370 | 30.07487 |
| 5 | 22.04259 | 21.43115 |
| 6 | 23.36296 | 22.78054 |
| 7 | 24.68333 | 24.12993 |
| 8 | 26.00370 | 25.47931. . . |

```
> fitt2$coef
```

| | \$fixed | $\hat{\beta}_0, \hat{\beta}_1$ |
|-------------|-------------|--------------------------------|
| (Intercept) | I(age - 11) | 24.0231481 |
| | | 0.6601852 |

| | \$random | $\hat{u}_{i1}, \hat{u}_{i2}' s$ |
|--|----------|---------------------------------|
|--|----------|---------------------------------|

| | \$random\$Subject | |
|-------------|-------------------|-------------|
| (Intercept) | I(age - 11) | |
| M16 | -0.9451479 | -0.06885385 |
| M05 | -0.8950636 | 0.02560005 |
| M02 | -0.5679151 | 0.01450765 |

| | ... | |
|-----|-----------|-----------------|
| M01 | 3.4241123 | 0.21568501. . . |

$$\hat{\beta}_0 + \hat{\beta}_1 Age^*_{ij}$$

```
> 24.0231481 + 0.6601852 * (c(8,10,12,14)-11)
```

```
[1] 22.04259 23.36296 24.68333 26.00370
```

$$\hat{\beta}_0 + \hat{\beta}_1 Age^*_{ij} + \hat{u}_{i1} + \hat{u}_{i2} Age^*_{ij}$$

```
> 24.0231481 + 0.6601852*(c(8,10,12,14)-11)
```

```
+ 3.4241123 + 0.21568501*(c(8,10,12,14)-11)
```

```
[1] 24.81965 26.57139 28.32313 30.07487
```

Simplification of lme() with groupedData

Since

- the data set used has a groupedData structure
- by default, the random effects have the same form as the fixed effects,

... the following two fits give the same results:

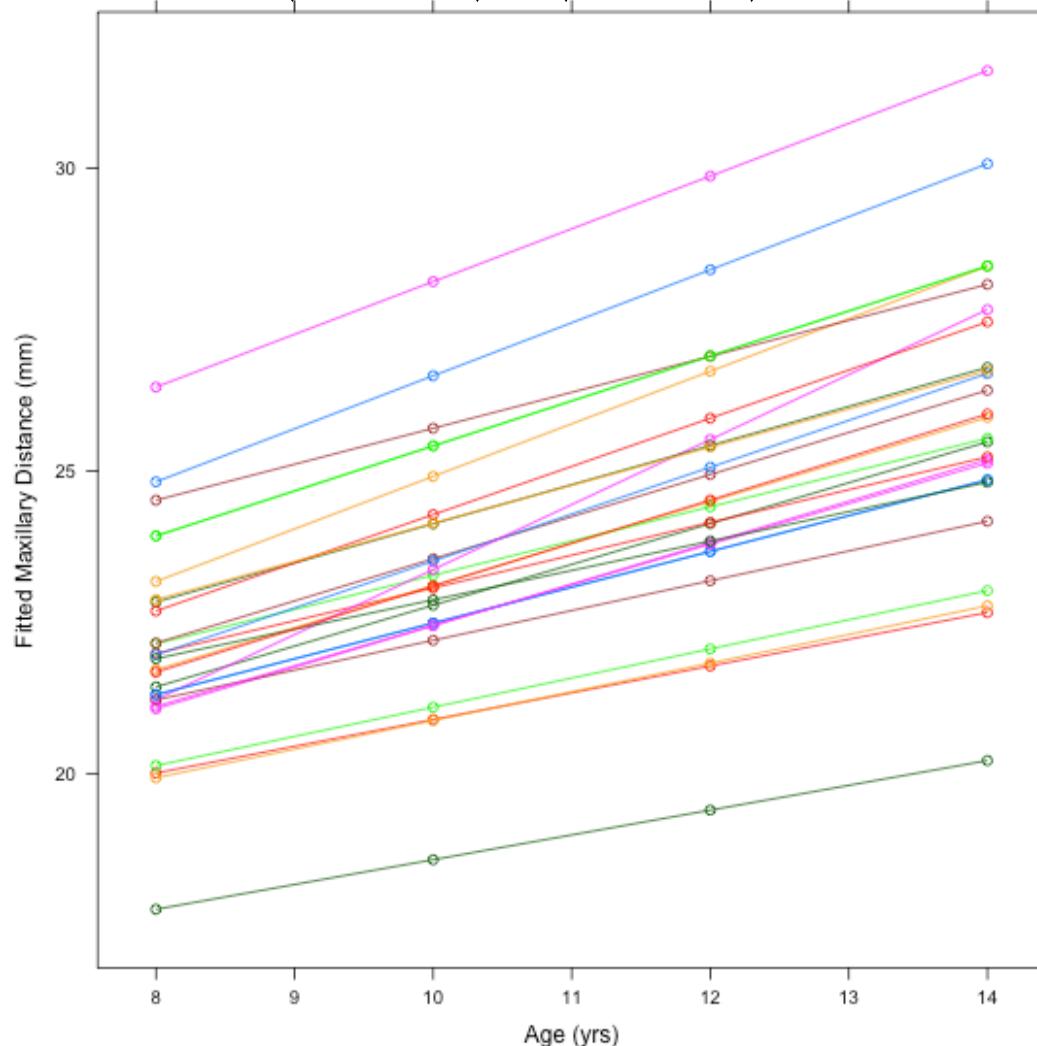
```
# fit with random intercept & slope

fitt2 <- lme(distance ~ I(age-11),
              data = dat,
              random = ~ I(age-11) | Subject)

fitt2.same <- lme(distance ~ I(age-11), data = dat)
```

Random intercept & slope
Fitted model (n=27)

$$\hat{Y}_{ij} = (\hat{\beta}_0 + \hat{u}_{i1}) + (\hat{\beta}_1 + \hat{u}_{i2}) Age^{*}_{ij}$$



Mixed Effects Model

Random Intercept & Slope Model

Adding Categorical Covariate

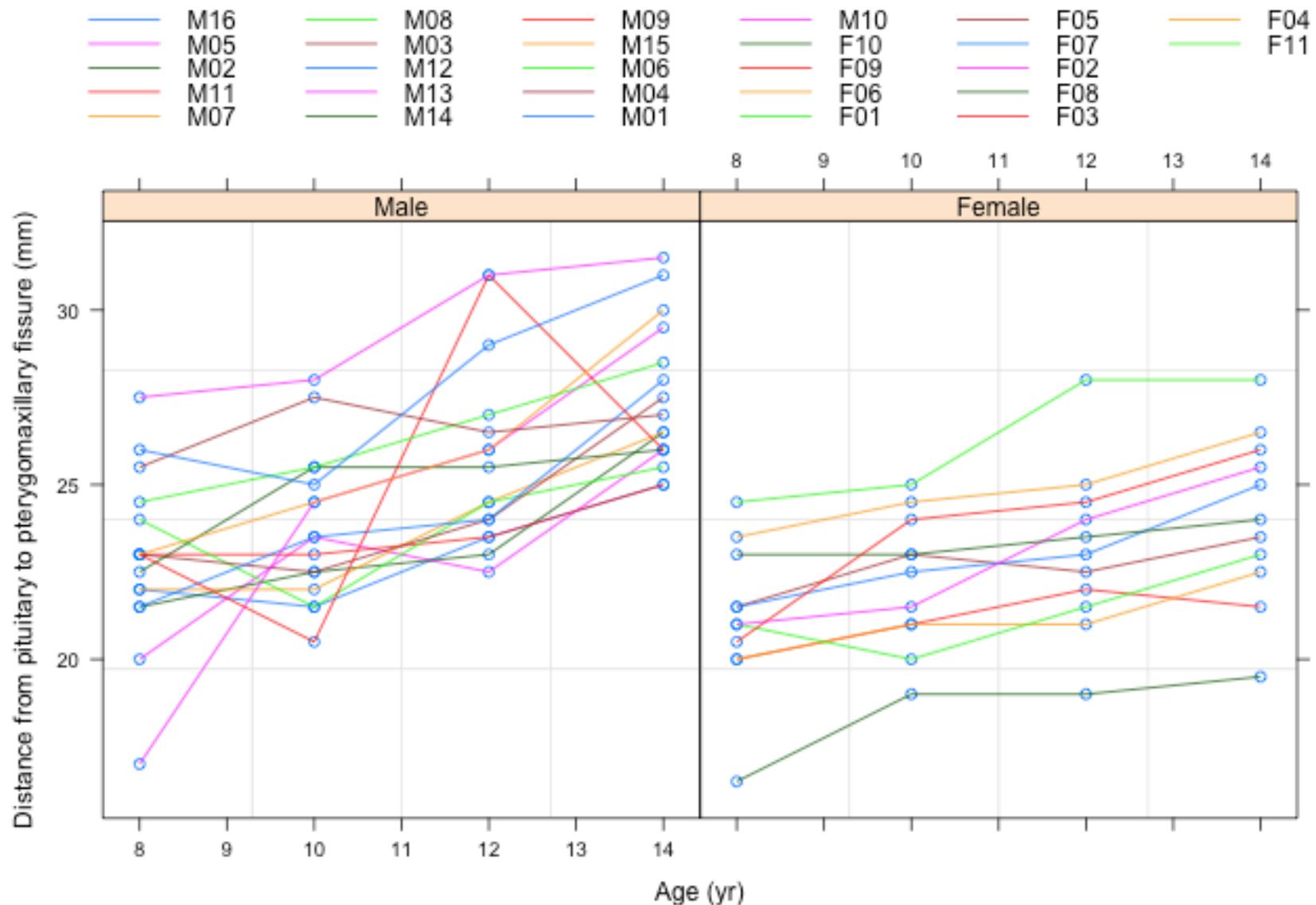
Random Intercept and Slope + Categorical Covariate

Data structure

| Subject i | Sex (1=M,0=F) | Maxillary distance measurements (mm) Y_{ij} $i=\text{subject}, j=\text{occasion}$ | | | | Subject Mean |
|-------------|---------------|-------------------------------------------------------------------------------------------|--------|--------|--------|--------------|
| | | 8 yrs | 10 yrs | 12 yrs | 14 yrs | |
| 1 | 1 | 26 | 25 | 29 | 31 | 27.75 |
| 2 | 1 | 21.5 | 22.5 | 23 | 26.5 | 23.38 |
| 3 | 1 | 23 | 22.5 | 24 | 27.5 | 24.25 |
| 4 | 1 | 25.5 | 27.5 | 26.5 | 27 | 26.63 |
| 5 | 0 | 21 | 20 | 21.5 | 23 | 21.38 |
| 6 | 0 | 21 | 21.5 | 24 | 25.5 | 23.00 |
| 7 | 0 | 20.5 | 24 | 24.5 | 26 | 23.75 |
| 8 | 0 | 23.5 | 24.5 | 25 | 26.5 | 24.88 |

Random Intercept and Slope + Categorical Covariate

Sample data, n=27, 11 female, 16 male.



Random Intercept and Slope + Categorical Covariate

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Sex_i + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i.$$

Fixed Random effects for intercept and slope + error
(Stays the same)

Rearranging....

When $Sex_i=1$
(Males)

$$\begin{aligned} Y_{ij} &= \beta_0 + \beta_1 Age_{ij} + \beta_2 + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij} \\ &= (\beta_0 + \beta_2 + u_{i1}) + (\beta_1 + u_{i2}) Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i. \end{aligned}$$

Intercept Slope

When $Sex_i=0$
(Females)

$$\begin{aligned} Y_{ij} &= \beta_0 + \beta_1 Age_{ij} + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij} \\ &= (\beta_0 + u_{i1}) + (\beta_1 + u_{i2}) Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i. \end{aligned}$$

Intercept Slope

Random Intercept and Slope + Categorical Covariate

```
> fitt.sex <- update(fitt2,.~.+Sex)
> summary(fitt.sex)
Linear mixed-effects model fit by REML
Data: dat
      AIC      BIC      logLik
 449.2339 467.8116 -217.6169
```

Random effects:

```
Formula: ~I(age - 11) | Subject
Structure: General positive-definite, Log-Cholesky parametrization
           StdDev   Corr
(Intercept) 1.8320242 (Intr)
I(age - 11) 0.2264279  0.19
Residual     1.3100396
```

Fixed effects: distance ~ I(age - 11) + Sex

| | Value | Std.Error | DF | t-value | p-value |
|-------------|-----------|-----------|----|----------|---------|
| (Intercept) | 24.897236 | 0.4852090 | 80 | 51.31239 | 0.000 |
| I(age - 11) | 0.660185 | 0.0712533 | 80 | 9.26533 | 0.000 |
| SexFemale | -2.145489 | 0.7574536 | 25 | -2.83250 | 0.009 |

Correlation:

| | (Intr) | I(-11) |
|-------------|--------|--------|
| I(age - 11) | 0.085 | |
| SexFemale | -0.636 | 0.000 |

Standardized Within-Group Residuals:

| Min | Q1 | Med | Q3 | Max |
|-------------|-------------|------------|------------|------------|
| -3.08141614 | -0.45675578 | 0.01552687 | 0.44704106 | 3.89437718 |

Number of Observations: 108

Number of Groups: 27

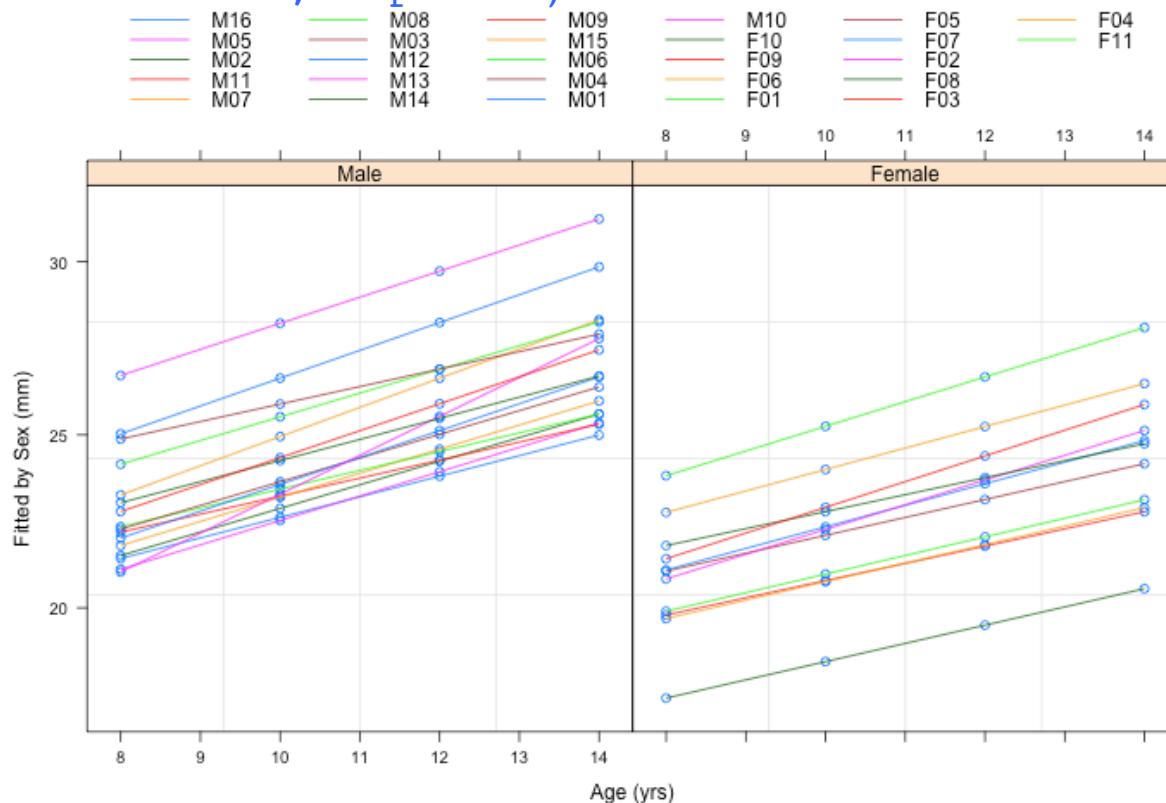
Plotting fitted values vs. sex in R

```
dat$fitted.sex <- fitted(fitt.sex)

dat.sex <- dat[,c("distance", "age", "Subject", "Sex", "fitted.sex")]
formula(dat.sex)
# distance ~ age | Subject

dat.sex <- update( dat.sex , fitted.sex ~ age | Subject)
# fitted.sex ~ age | Subject

plot(dat.sex, outer=~Sex, aspect=1)
```



Random Intercept and Slope Model, Adding Categorical Variable + Interaction

$$Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 Sex_i + \beta_3 (Age \times Sex)_{ij} + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i.$$

Rearranging....

When $Sex_i=1$ $Y_{ij} = \beta_0 + \beta_1 Age_{ij} + \beta_2 + \beta_3 Age_{ij} + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij}$
 (Males)

$$= (\underbrace{\beta_0 + \beta_2 + u_{i1}}_{\text{Intercept}}) + (\underbrace{\beta_1 + \beta_3 + u_{i2}}_{\text{Slope}}) Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i.$$

When $Sex_i=0$ $Y_{ij} = \beta_0 + \beta_1 Age_{ij} + u_{i1} + u_{i2} Age_{ij} + \varepsilon_{ij}$
 (Females)

$$= (\underbrace{\beta_0 + u_{i1}}_{\text{Intercept}}) + (\underbrace{\beta_1 + u_{i2}}_{\text{Slope}}) Age_{ij} + \varepsilon_{ij}; \quad j = 1, \dots, m_i.$$

```
> fitt.sexage <- update(fitt.sex,.~.+Sex:I(age-11))
> summary(fitt.sexage)
Linear mixed-effects model fit by REML
Data: dat
      AIC      BIC      logLik
 448.5817 469.7368 -216.2908
```

Random effects:

```
Formula: ~I(age - 11) | Subject
Structure: General positive-definite, Log-Cholesky parametrization
          StdDev   Corr
(Intercept) 1.8303267 (Intr)
I(age - 11) 0.1803454 0.206
Residual     1.3100397
```

Fixed effects: distance ~ I(age - 11) + Sex + Sex * I(age - 11)

| | Value | Std.Error | DF | t-value | p-value |
|-----------------------|-----------|-----------|----|----------|---------|
| (Intercept) | 24.968750 | 0.4860007 | 79 | 51.37596 | 0.0000 |
| I(age - 11) | 0.784375 | 0.0859995 | 79 | 9.12069 | 0.0000 |
| SexFemale | -2.321023 | 0.7614168 | 25 | -3.04829 | 0.0054 |
| I(age - 11):SexFemale | -0.304830 | 0.1347353 | 79 | -2.26243 | 0.0264 |

Correlation:

| | (Intr) | I(g-11) | SexFml |
|-----------------------|--------|---------|--------|
| I(age - 11) | 0.102 | | |
| SexFemale | -0.638 | -0.065 | |
| I(age - 11):SexFemale | -0.065 | -0.638 | 0.102 |

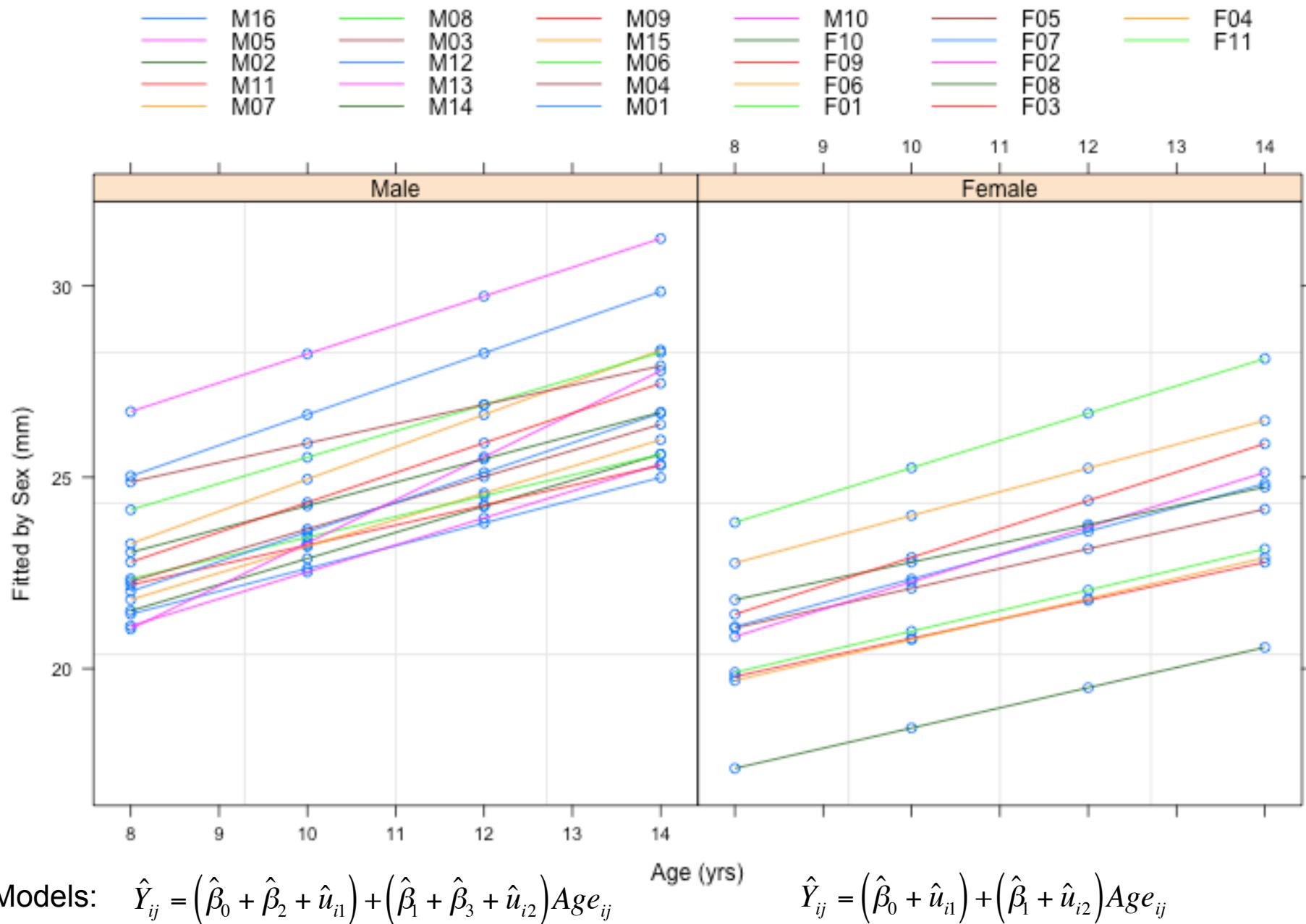
Standardized Within-Group Residuals:

| Min | Q1 | Med | Q3 | Max |
|--------------|--------------|-------------|-------------|-------------|
| -3.168078484 | -0.385939134 | 0.007103929 | 0.445154686 | 3.849463230 |

Number of Observations: 108

Number of Groups: 27

Random intercept and slope, adding a categorical variable (fixed)



Exercise in R

Obtain the Maxillary Distance Data set called “Orthodont” from nlme library.

1. Fit the following models for maxillary distances:
 - a) Random intercept
 - b) Random intercept & slope
 - c) Add Sex covariate
2. Make the following plots:
 - a) Observed maxillary distances vs. Age
 - b) Fitted maxillary distances vs. Age from models 1(a), 1(b).
 - c) Fitted maxillary distances vs. Age by Sex from model 1(c).
3. For model 1(c), use the estimated fixed and random coefficients to reproduce the fitted values for subjects M01 and F01 in the data set (procedure analogous to slides 26 and 67, done for models 1(a) and 1(b)).

Hint: use the following lines to identify M01 and F01:

```
fitted.dat <- data.frame(fit1c$fitted)  
fitted.dat$SubjectID <- Orthodont$Subject
```