01NAEX - Lecture 12
Introduction to Longitudinal Data Analysis

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Introduction to Longitudinal Data Analysis

Longitudinal Data Analysis:

- Experimental designs in which each subject is measured at several points in time.
- Often called "Repeated measures analysis".

Analysis of these data types can be done by

- Separate analysis for each time point.
- Analysis of summary statistic.
- Random effects approach with different covariance models.

Basic example

Dataset: Dental study from Pothoff and Roy (1964):

- Sample of 27 children (16 boys, 11 girls)
- Response variable: Distance in mm between the center of the pituitary and the pterygomaxillary fissure.
- Measurement repeated at 8, 10, 12, and 14 years of age.

Questions of interest:

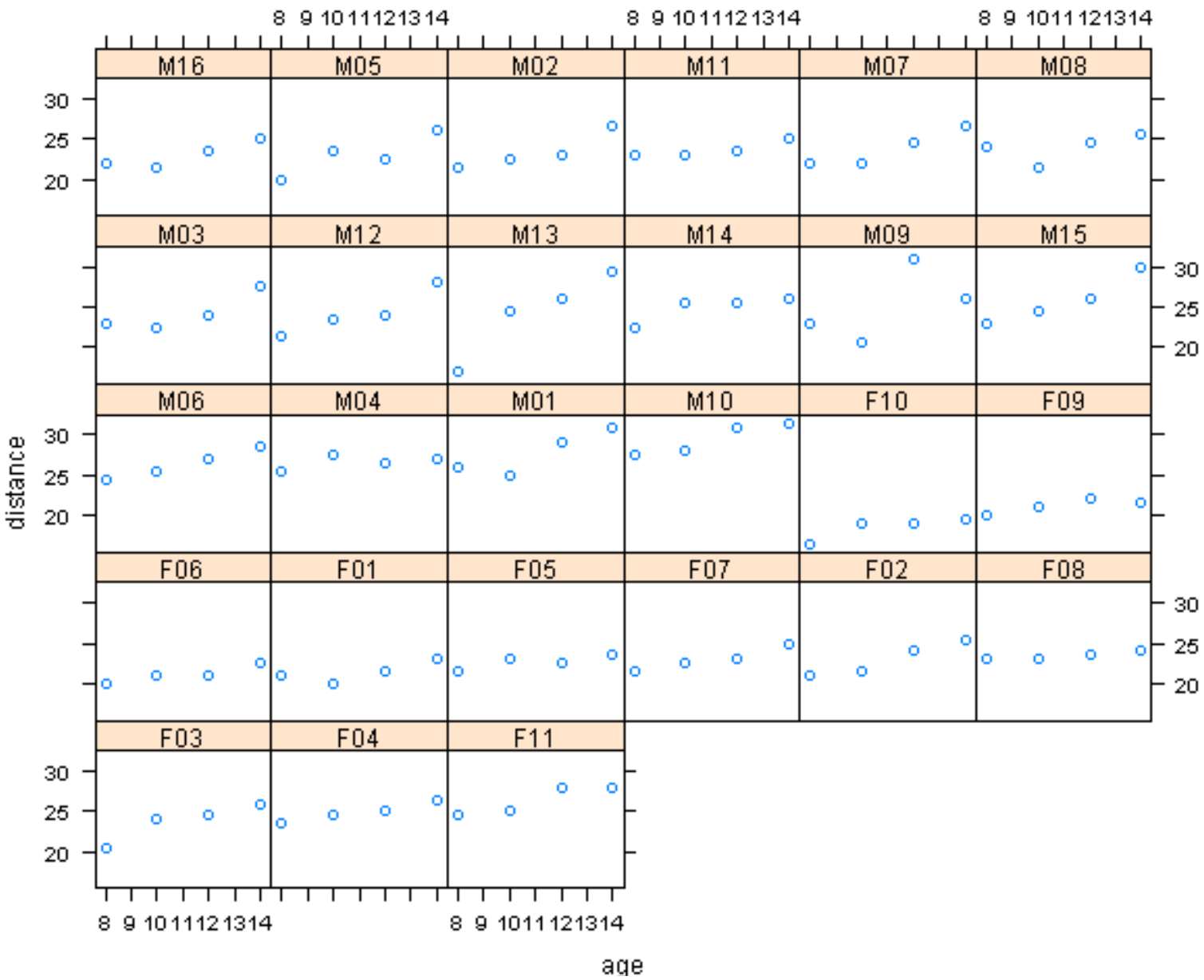
- Does distance change over time?
- What is the pattern of change?
- Is the pattern different for boys and girls and how?

Basic example - data preview

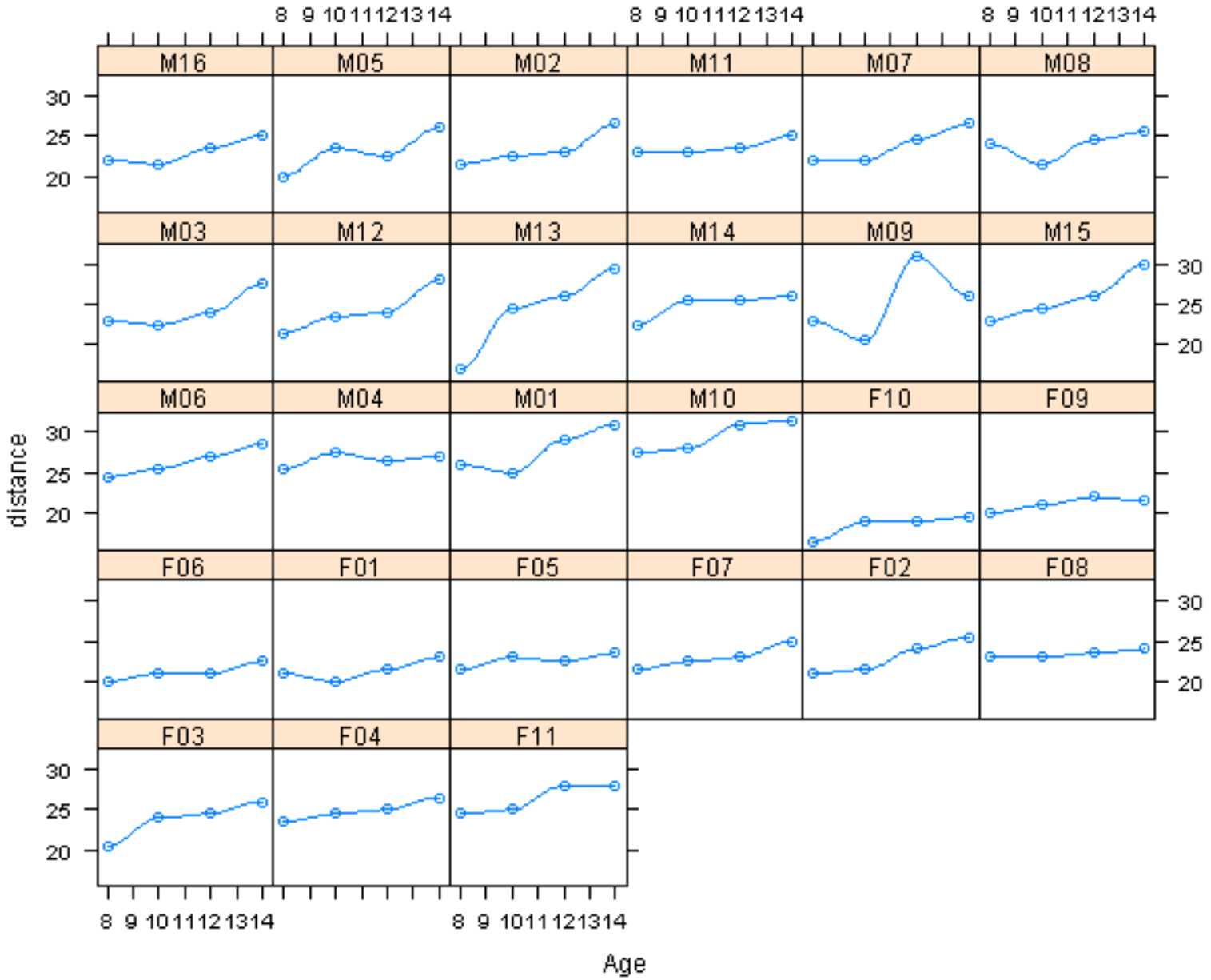
```
> library(nlme) > library(lattice)  > data(Orthodont)
> head(Orthodont)
Grouped Data: distance ~ age | Subject
 distance    age  Subject   Sex
1     26.0      8      M01  Male
2     25.0     10      M01  Male
3     29.0     12      M01  Male
4     31.0     14      M01  Male
5     21.5      8    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

> summary(Orthodont)
distance         age             Subject      Sex
Min.   :16.50   Min.   : 8.0   M16    : 4   Male  :64
1st Qu.:22.00   1st Qu.: 9.5   M05    : 4   Female:44
Median :23.75   Median :11.0   M02    : 4
Mean   :24.02   Mean   :11.0   M11    : 4
3rd Qu.:26.00   3rd Qu.:12.5   M07    : 4
Max.   :31.50   Max.   :14.0   M08    : 4
(Other):84
> attach(Orthodont)
```

Basic example - vizualization

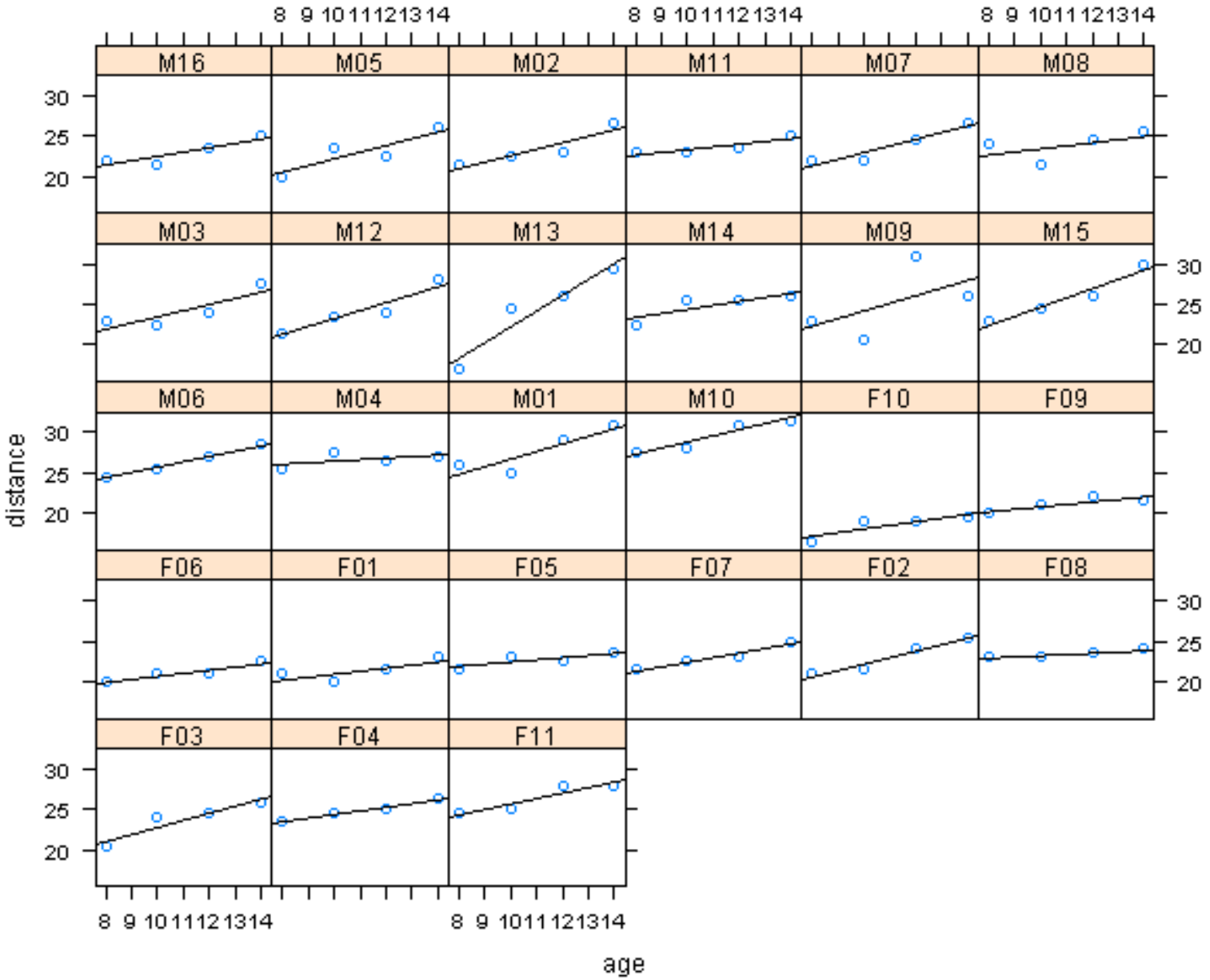
```
> xyplot(distance ~ age|Subject, data=Orthodont,as.table=T)
```



Basic example - vizualization

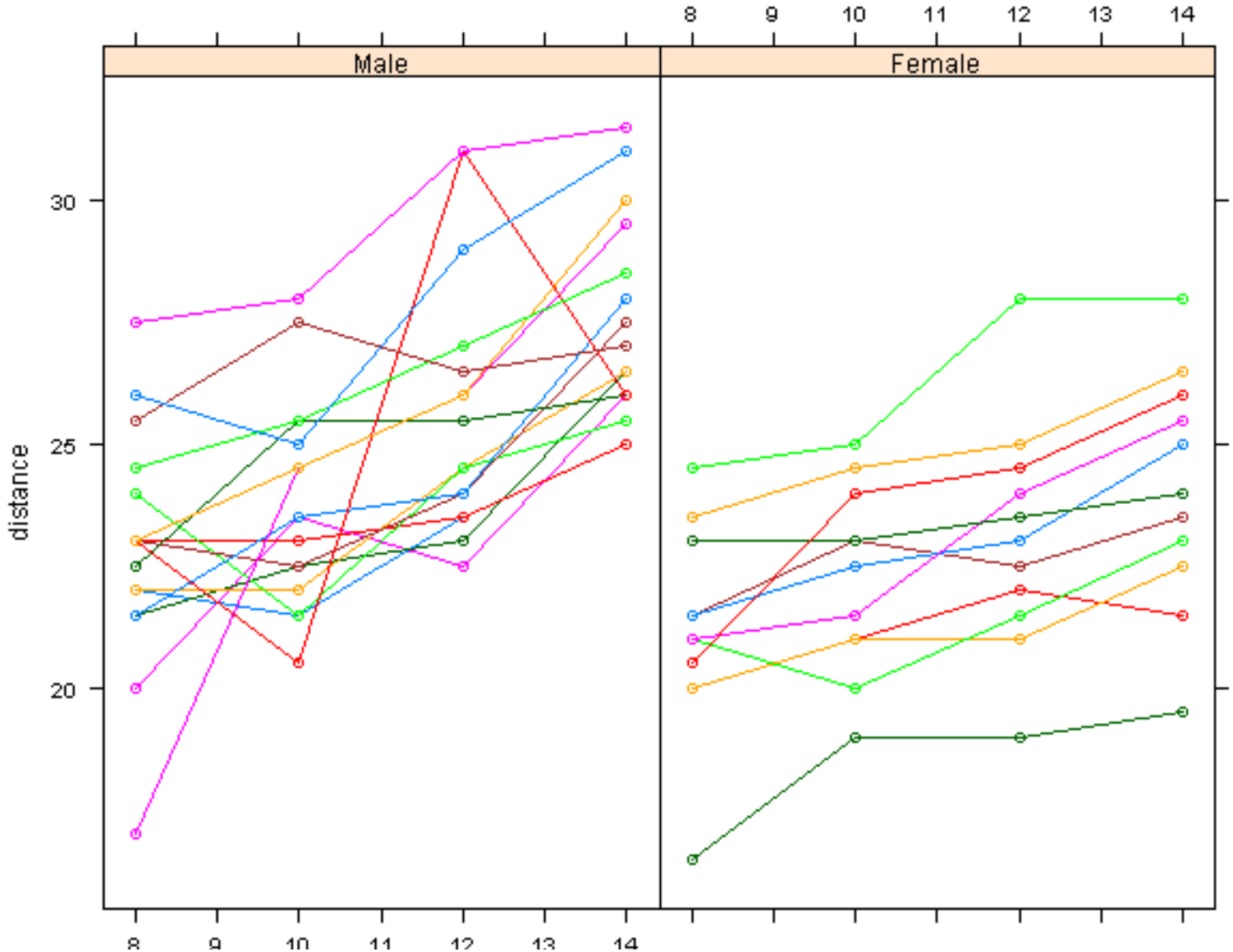


Basic example - vizualization



Basic example - vizualization (interaction plot, spaghetti plot)

```
> xyplot(distance ~ age |Sex, data = Orthodont, groups = Subje
+         type = "o", panel = panel.superpose)
```



Pooling dataset - wrong way analysis

What can we conclude from figures?

- The male trajectories appear steeper than the female ones.
- Slopes are relatively consistent within each sex.
- Male seems to be higher than female overall.
- Subject who starts high (or low) tend to stay high (or low).
- The individual pattern for most subjects follows a rough straight line increase.

Pooling dataset - Balanced data analysis:

- All subjects are measured at the same set of ages.
- Cross-sectional analysis comparing means (male vs. female) at each age 8, 10, 12, 14 by two-sample t-tests.
- Residuals within clusters are not independent; they tend to be highly correlated with each other

Basic example - results 1

```
> summary(lm ( distance ~ age * Sex , Orthodont))
Coefficients:
               Estimate  Std. Error t value Pr(>|t|)
(Intercept)    16.3406     1.4162  11.538  < 2e-16 ***
age             0.7844     0.1262   6.217 1.07e-08 ***
SexFemale       1.0321     2.2188   0.465    0.643
age:SexFemale  -0.3048     0.1977  -1.542    0.126

Residual standard error: 2.257 on 104 degrees of freedom
Multiple R-squared:  0.4227, Adjusted R-squared:  0.4061
F-statistic: 25.39 on 3 and 104 DF,  p-value: 2.108e-12
```

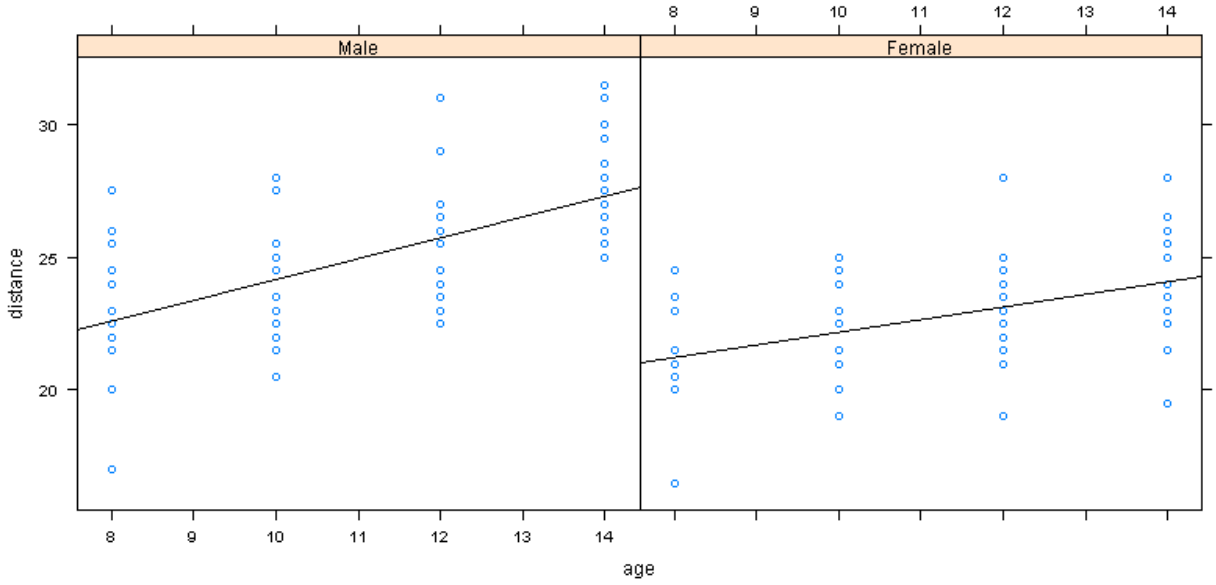
```
>  summary(aov( distance ~ age * Sex , Orthodont))
             Df Sum Sq Mean Sq F value   Pr(>F)
age           1  235.4  235.36  46.204 6.88e-10 ***
Sex           1  140.5  140.46  27.576 8.05e-07 ***
age:Sex       1   12.1   12.11   2.378    0.126
Residuals   104  529.8    5.09
```

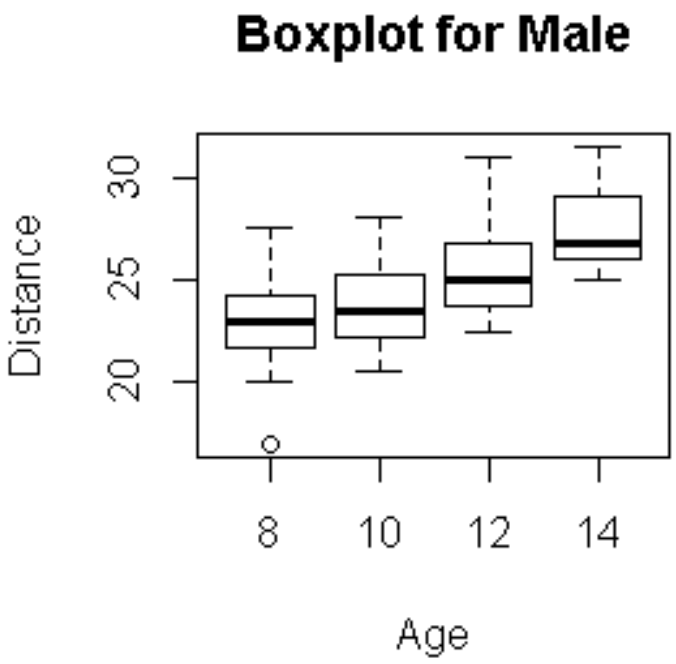
Basic example - results 2

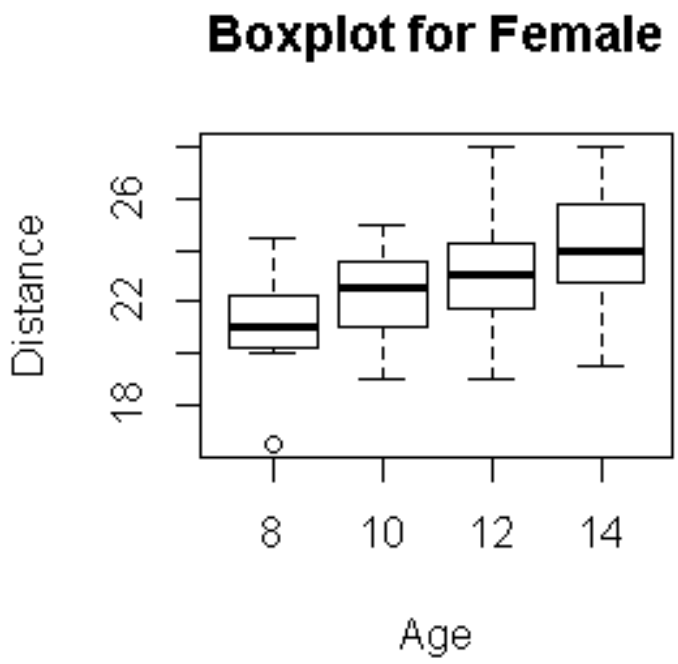
```
> summary(lm ( distance ~ age + Sex , Orthodont))
Coefficients:
Estimate Std. Error t value Pr(>|t|)
(Intercept) 17.70671    1.11221  15.920  < 2e-16 ***
age          0.66019    0.09776   6.753 8.25e-10 ***
SexFemale   -2.32102    0.44489  -5.217 9.20e-07 ***
---
Residual standard error: 2.272 on 105 degrees of freedom
Multiple R-squared:  0.4095, Adjusted R-squared:  0.3983
F-statistic: 36.41 on 2 and 105 DF,  p-value: 9.726e-13

> summary(aov( distance ~ age + Sex , Orthodont))
Df Sum Sq Mean Sq F value   Pr(>F)
age           1  235.4  235.36   45.61 8.25e-10 ***
Sex           1  140.5  140.46   27.22 9.20e-07 ***
Residuals   105  541.9    5.16
```

Same slope for all subjects and estimated variance within each subject: $\sigma^2 = 2.272^2$.

Pooling dataset - wrong way analysis







Basic example - results 3

```
> summary(lm( distance ~ age *Subject , Orthodont))
Coefficients:
Estimate Std. Error t value Pr(>|t|)
(Intercept)    16.76111    0.63281  26.487  < 2e-16 ***
age             0.66019    0.05638  11.711  < 2e-16 ***
Subject.L       5.07509    3.28817   1.543  0.12857
Subject.Q       0.59068    3.28817   0.180  0.85811
...
age:Subject.L  -0.49787    0.29293  -1.700  0.09496 .
age:Subject.Q  -0.19737    0.29293  -0.674  0.50334
age:Subject.C   0.69724    0.29293   2.380  0.02086 *
...

Residual standard error: 1.31 on 54 degrees of freedom
Multiple R-squared:  0.899, Adjusted R-squared:  0.7999
F-statistic:  9.07 on 53 and 54 DF,  p-value: 6.568e-14
```

Different slope for each subjects and estimated variance for each subject: $\sigma^2 = 1.31^2$.

Remarks to bad approach

Why is the approach "single slope for single subject" wrong?

- No estimate of sex effect .
- Can't be generalized to population. We can't estimate new observation.
- No autocorrelation in time

F-tests for no Sex effect

```
> names(fValues) <- levels(as.factor(age))
> for (i in 1:4){
+   fValues[as.integer(i)] <-
    anova(lm(distance[age == unique(age)[i]]
                ~ Sex[age == unique(age)[i]]))[1, 4]
+   }
> fValues
8        10        12        14
3.450811  3.914354  6.972702 14.917559
> qf(0.95,1,25)
[1] 4.241699
```

A few significant values are found, so we can conclude that Sex evidence of group difference have been seen.

New approach

What can we do?

- Make a correct analysis time by time, but it is weak and often confusing, because it does not combine all information into one test.
- Randomize some variables (use lme, lmer)
- Add correlation structure (use gls for fixed and lme for mixed models)

Remark: For mixed model we have

$$\mathbf{y} \sim \mathbf{N}(\mathbf{X}\beta, \mathbf{ZGZ}' + \mathbf{R}),$$

- $\mathbf{X}$ is the design matrix for the fixed effects part of the model;
- β is the fixed effects parameters;
- $\mathbf{Z}$ is the design matrix for the random effects;
- $\mathbf{G}$ the covariance between the random effects in the model;
- $\mathbf{R}$ covariance between the residual measurement errors.

Theory of Mixed Models

Regression model of **Mixed linear model** approach:

$$y_{ij} = \beta_0 + \beta_1 Sex_i + \beta_2 Age_{ij} + \beta_3 Sex_i Age_{ij} + u_{i0} + u_{i1} Age_{ij} + e_{ij}$$

$$\underbrace{\begin{pmatrix} y_{i1} \\ y_{i2} \\ y_{i3} \\ y_{i4} \end{pmatrix}}_{\mathbf{y}} = \underbrace{\begin{pmatrix} 1 & Sex_i & Age_{i1} & Sex_i Age_{i1} \\ 1 & Sex_i & Age_{i2} & Sex_i Age_{i2} \\ 1 & Sex_i & Age_{i3} & Sex_i Age_{i3} \\ 1 & Sex_i & Age_{i4} & Sex_i Age_{i4} \end{pmatrix}}_{\mathbf{X}} \cdot \underbrace{\begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{pmatrix}}_{\beta} + \underbrace{\begin{pmatrix} 1 & Age_{i1} \\ 1 & Age_{i2} \\ 1 & Age_{i3} \\ 1 & Age_{i4} \end{pmatrix}}_{\mathbf{Z}} \cdot \underbrace{\begin{pmatrix} u_{i0} \\ u_{i1} \end{pmatrix}}_{u} + \underbrace{\begin{pmatrix} e_{i1} \\ e_{i2} \\ e_{i3} \\ e_{i4} \end{pmatrix}}_{\mathbf{e}},$$

equivalently,

$$\mathbf{Y} = \mathbf{X}\beta + \mathbf{Z}u + \mathbf{e},$$

where,

$$u_i \sim N(0, \mathbf{G}), \; e_i \sim N(0, \mathbf{R}_i) \quad i \in \{1, 2, \ldots, N\}.$$

and

$$\delta_i = Z_i u_i + e_i \quad \delta_i \sim N(0, Z_i G Z_i' + R_i) \quad y_i \sim N(\mu, \mathbf{V}).$$

Estimation of β by Generalized Least Squares:

$$\hat{\beta}^{GLS} = (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1} X'\hat{\mathbf{V}}^{-1}\mathbf{y}.$$

Correlation structures

Compound symmetry correlation structure

$$y_i \sim N(\mu, \mathbf{V})$$

$$cov(y_{i1}, y_{i2}) = V_{i_1,i_2} = \begin{cases} 0 & \text{if } Subject_{i_1} \neq Subject_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma^2_{Subj} & \text{if } Subject_{i_1} = Subject_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma^2_{Subj} + \sigma^2 & \text{if } i_1 = i_2 \end{cases}$$

Two measurements from the same individual are correlated, but equally correlated no matter how far apart the measurements were taken.
This is counterintuitive if some measurements are close (in time or space) and some are far apart. To fix this the correlation structure need to be set.

Correlation structures

AR(1) correlation structure

$$y_i \sim N(\mu, \mathbf{V}) \text{ and } e_i \sim N(0, \mathbf{R}_i), \rho \in (0,1), \text{ where}$$

$$R_i = \sigma^2 \begin{pmatrix} 1 & \rho^1 & \rho^2 & \rho^3 \\ \rho^1 & 1 & \rho^1 & \rho^2 \\ \rho^2 & \rho^1 & 1 & \rho^1 \\ \rho^3 & \rho^2 & \rho^1 & 1 \end{pmatrix}$$

Two observations "very close" together have covariance $\sigma^2_{Subj} + \tau^2$ and two observations "very far" apart have covariance σ^2_{Subj}

$$cov(y_{i1}, y_{i2}) = V_{i_1,i_2} = \begin{cases} 0 & \text{if } Subject_{i_1} \neq Subject_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma^2_{Subj} + \tau^2 \rho^{|i_1 - i_2|} & \text{if } Subject_{i_1} = Subject_{i_2} \text{ and } i_1 \neq i_2 \\ \sigma^2_{Subj} + \tau^2 + \sigma^2 & \text{if } i_1 = i_2 \end{cases}$$

Correlation structures

```
m_gls<-gls(distance ~ age + Sex,
    correlation=corCompSymm(form=~1|Subject),data=Orthodont)

> summary(m_gls)
Generalized least squares fit by REML
Model: distance ~ age + Sex
Data: Orthodont
AIC      BIC    logLik
447.5125 460.7823 -218.7563
Correlation Structure: Compound symmetry
Formula: ~1 | Subject
Parameter estimate(s):
Rho
0.6144914
Coefficients:
               Value   Std.Error   t-value p-value
(Intercept) 17.706713 0.8339225 21.233044  0.0000
age          0.660185 0.0616059 10.716263  0.0000
SexFemale   -2.321023 0.7614169 -3.048294  0.0029
Correlation:
(Intr) age
age       -0.813
SexFemale -0.372  0.000
Residual standard error: 2.305697
Degrees of freedom: 108 total; 105 residual
```

Correlation structures

```
> m_lme<-lme(distance ~ age * Sex,
+          random=~1+age|Subject,
+          correlation=corAR1(form=~1|Subject),
+          data=Orthodont)

> summary(m_lme)
Linear mixed-effects model fit by REML
Data: Orthodont
AIC       BIC       logLik
446.8076 470.6072 -214.4038

Random effects:
Formula: ~1 + age | Subject
Structure: General positive-definite, Log-Cholesky parametrization
             StdDev    Corr
(Intercept) 3.3730482 (Intr)
age         0.2907673 -0.831
Residual    1.0919754

Correlation Structure: AR(1)
Formula: ~1 | Subject
Parameter estimate(s):
Phi
-0.47328
```

Correlation structures

```
> m_lme<-lme(distance ~ age * Sex,
+          random=~1+age|Subject,
+          correlation=corAR1(form=~1|Subject),
+          data=Orthodont)

> summary(m_lme) (..continue)

Fixed effects: distance ~ age * Sex
                    Value Std.Error DF   t-value p-value
(Intercept)    16.152435 0.9984616 79 16.177323  0.0000
age             0.797950 0.0870677 79  9.164702  0.0000
SexFemale       1.264698 1.5642886 25  0.808481  0.4264
age:SexFemale  -0.322243 0.1364089 79 -2.362334  0.0206
Correlation:
(Intr) age    SexFml
age           -0.877
SexFemale     -0.638  0.559
age:SexFemale  0.559 -0.638 -0.877

Standardized Within-Group Residuals:
Min            Q1           Med            Q3           Max
-3.288886631 -0.419431536 -0.001271185  0.456257976  4.203271248

Number of Observations: 108
Number of Groups: 27
```

Correlation structures

```
>intervals(m_lme)
Approximate 95% confidence intervals
Fixed effects:
                  lower       est.       upper
(Intercept)   14.1650475 16.1524355 18.13982351
age            0.6246456  0.7979496  0.97125348
SexFemale     -1.9570145  1.2646982  4.48641100
age:SexFemale -0.5937584 -0.3222434 -0.05072829
attr(,"label")
[1] "Fixed effects:"

Random Effects:
Level: Subject
                         lower       est.      upper
sd((Intercept))       2.2057787  3.3730482  5.1580217
sd(age)               0.1848096  0.2907673  0.4574740
cor((Intercept),age) -0.9377525 -0.8309622 -0.5806162

Correlation structure:
         lower     est.       upper
Phi -0.7560625 -0.47328 -0.04159463
```

Correlation Matrix G

```
> VarCorr( m_lme )
Subject = pdLogChol(1 + age)
Variance   StdDev    Corr
(Intercept) 11.3774543 3.3730482 (Intr)
age          0.0845456 0.2907673 -0.831
Residual     1.1924103 1.0919754


> getVarCov( m_lme )
Random effects variance covariance matrix
(Intercept)       age
(Intercept)    11.37700 -0.814980
age            -0.81498  0.084546

Standard Deviations: 3.373 0.29077
```

Summary

Check and Study

- Variogram nlme: Calculate Semi-variogram
- corClasses nlme: Correlation Structure Classes

Summary of the example:

- The estimated autocorrelation is negative and $\rho = -0.47328$.
- Strong positive autocorrelation can be a symptom of lack of fit.
- Occasional large measurement errors will contribute negatively to the estimate of autocorrelation.

Random effects approach in Longitudinal Data Analysis:

- Good method for short series.
- Uses all observations
- Usually not good for long series.

Today Exercises

Final Project Assignment.
Discussion about the final project - individual consultation.

Solve pig problem: .

Investigate the effect of injection of Porcine Growth Hormone (PGH) on pH. Experiment was carried out with two pigs from each of 6 litters. There were two treatments: 1) control and 2) pgh (daily injection with 0.08 mg PGH)

The pH in the meat was measured 20 times from 30 minutes after until 24 hours after slaughter. There were 10 litters in the experiment but pH was measured for only 6 of these. The order of the data is: treatment, litter, pig number, followed by pH measurements at 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 1440 minutes after slaughter.

In this analysis the focus should be on the effect of the treatment over time.

Today Exercises

Solve pig problem.

1. Make one or more plots of the data. Comment on the plot(s).
2. Setup a suitable model for this data set, including both fixed and random effects, but no correlation structure. (Notice that besides the pig variable we also have information about litter, which could be included as an additional random effect.)
3. Reduce the initial model (if possible), both the random effects and fixed effects parts.
4. Extend the model by adding a correlation structure.
5. Use information criteria and/or semi-variograms to select an appropriate correlation structure.
6. Explain in words the correlation structure that was chosen.
7. Repeat the model reduction process.
8. What is the conclusion about the treatment?

Hint: Use time transformation: $\frac{1}{log()}$.