Chapter 2

Marginal Models for Continuous Data

2.1 Simple Methods

- The reason why classical statistical techniques fail in the context of longitudinal data is that observations within subjects are correlated
  - ▷ often the correlation between two repeated measurements decreases as the time span between those measurements increases

- The paired t-test accounts for this by considering subject-specific differences $\Delta_i = Y_{i1} - Y_{i2}$
  - ▷ this reduces the number of measurements to just one per subject, which implies that classical techniques can be applied again

2.1 Simple Methods (cont'd)

- In the case of more than 2 measurements per subject, similar simple techniques are often applied to reduce the number of measurements for the ith subject, from n_i to 1

  ▷ Analysis at each time point separately

  ▷ Analysis of Area Under the Curve (AUC)

  ▷ Analysis of endpoints

  ▷ Analysis of increments

2.1 Simple Methods (cont'd)

- **Analysis at each time point separately**
  - ▷ **General idea:** The data are analyzed at each occasion separately
  - ▷ **Advantages:**
    - * simple to interpret
    - * uses all available data

    Disadvantages:
    - * does not consider 'overall' differences
    - * does not allow to study the evolution of differences
    - * problem of multiple testing
    - * possible problems with missing data

2.1 Simple Methods (cont'd)

- **Analysis of area under the curve (AUC)**
  - ▷ **General idea:** For each subject, the area under her curve is calculated

$$\text{AUC}_i = (t_{i2} - t_{i1}) \times (y_{i2} + y_{i1})/2 + (t_{i3} - t_{i2}) \times (y_{i3} + y_{i2})/2 + \ldots$$

    Afterwards, these AUCs are analyzed

  - ▷ **Advantages:**
    - * no problems of multiple testing
    - * does not explicitly assume balanced data
    - * compares 'overall' differences

2.1 Simple Methods (cont'd)

- **Analysis of area under the curve (AUC)**
  - ▷ **Disadvantages:**
    - * uses only partial information
    - * possible problems with missing data

2.1 Simple Methods (cont'd)

- **Analysis of endpoints**

  ▷ **General idea:** Assess differences only on the last time point

  ▷ **Advantages:**

  * no problems of multiple testing
  * does not explicitly assume balanced data

  Disadvantages:

  * applicable only in randomized trials
  * does not consider 'overall' differences
  * possible problems with missing data

2.1 Simple Methods (cont'd)

- **Analysis of increments**

  ▷ **General idea:** A simple method to compare evolutions between subjects, correcting for differences at baseline, is to analyze the subject-specific changes $y_{in_i} - y_{i1}$

  ▷ **Advantages:**

  * no problems of multiple testing
  * does not explicitly assume balanced data

  Disadvantages:

  * uses partial information
  * possible problems with missing data

2.1 Simple Methods (cont'd)

- The AUC, endpoints and increments are examples of summary statistics
  - ▷ such summary statistics summarize the vector of repeated measurements for each subject separately

- This leads to the following general procedure:
  - ▷ **Step 1:** Summarize the data of each subject into one statistic
  - ▷ **Step 2:** Analyze the summary statistics, e.g. analysis of covariance to compare groups after correction for important covariates

- This way, the analysis of longitudinal data is reduced to the analysis of independent observations, for which classical statistical procedures are available

2.1 Simple Methods (cont'd)

- However, all these methods have the disadvantage that (lots of) information is lost

This has led to the development of statistical techniques that overcome these disadvantages

2.2 Review of Linear Regression

- Suppose we have a continuous outcome Y measured *cross-sectionally*
  - ▷ $\boxed{\text{Example:}}$ The serum bilirubin levels from the PBC dataset at baseline (i.e., time $t = 0$)

- We are interested in making statistical inferences for this outcome, e.g.,
  - ▷ is there any difference between placebo and D-penicil corrected for the age and sex of the patients?
  - ▷ which factors best predict serum bilirubin levels?

$$\Downarrow$$

Linear Regression Model

2.2 Review of Linear Regression (cont'd)

- Definition of the linear regression model

$$\begin{cases} y_i = \beta_0 + \beta_1 x_{i1} + \ldots + \beta_p x_{ip} + \varepsilon_i \\ \\ \varepsilon_i \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

where

▷ y_i denotes the outcome for subject i

▷ $x_{i1}, \ldots, x_{ip}$ denote the p covariates for subject i

▷ $\beta_0, \beta_1, \ldots, \beta_p$ the regression coefficients

▷ ε_i the error term for subject i

2.2 Review of Linear Regression (cont'd)

- $\boxed{\text{Example:}}$ For the PBC patients we postulate the linear regression model

$$\log(\texttt{serBilir}_i) = \beta_0 + \beta_1 \texttt{Age}_i + \beta_2 \texttt{D-penicil}_i + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2)$$

  where

  ▷ $\texttt{serBilir}_i$ denotes the serum bilirubin of patient i at baseline

  ▷ $\texttt{Age}_i$ and $\texttt{D-penicil}_i$ denote the Age and whether patient i received D-penicil or placebo

  ▷ β_0, β_1, and β_2 are the regression coefficients

  ▷ ε_i are the error terms

2.2 Review of Linear Regression (cont'd)

- Behind this model there are several assumptions, some obvious, some hidden. In particular:

  ▷ serum bilirubin is assumed to be only related to Age and treatment

  ▷ the relation between serum bilirubin and Age is linear

  ▷ the effect of Age is the same whatever the treatment the patient took, and vice versa

  ▷ the error terms are normally distributed

  ▷ the variance of the error terms does not depend on neither Age nor D-penicil

  ▷ **measurements are independent with each other**

2.2 Review of Linear Regression (cont'd)

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	0.5395	0.2824	1.91	0.0570
age	0.0015	0.0056	0.28	0.7817
drugD-penicil	−0.0933	0.1174	−0.79	0.4274

- Interpretation
  - ▷ $\beta_0 =$ 0.5 average log(Ser. Bilir.) for Age $=$ 0 and placebo patients
  - ▷ $\beta_1 =$ 0.0015 increase in average log(Ser. Bilir.) for every year increase for patient with the same treatment
  - ▷ $\beta_2 =$ -0.1 decrease in average log(Ser. Bilir.) when receiving D-penicil versus placebo for patients of the same age

2.2 Review of Linear Regression (cont'd)

- Linear regression model with *matrix notation*
  - ▷ the linear regression model for the n subjects

$$
\begin{aligned}
y_1 &= \beta_0 + \beta_1 x_{11} + \ldots + \beta_p x_{1p} + \varepsilon_1 \\
y_2 &= \beta_0 + \beta_1 x_{11} + \ldots + \beta_p x_{1p} + \varepsilon_2 \\
&\vdots \\
y_n &= \beta_0 + \beta_1 x_{n1} + \ldots + \beta_p x_{np} + \varepsilon_n
\end{aligned}
$$

2.2 Review of Linear Regression (cont'd)

- Linear regression model with *matrix notation*
  - ▷ the linear regression model for the n subjects

$$\underbrace{\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix}}_{\mathbf{y}} = \underbrace{\begin{bmatrix} 1 & x_{11} & \ldots & x_{1p} \\ 1 & x_{21} & \ldots & x_{2p} \\ & \vdots & & \\ 1 & x_{n1} & \ldots & x_{np} \end{bmatrix}}_{\mathbf{X}} \underbrace{\begin{bmatrix} \beta_0 \\ \beta_1 \\ \vdots \\ \beta_p \end{bmatrix}}_{\boldsymbol{\beta}} + \underbrace{\begin{bmatrix} \varepsilon_1 \\ \varepsilon_2 \\ \vdots \\ \varepsilon_n \end{bmatrix}}_{\boldsymbol{\varepsilon}}$$

2.2 Review of Linear Regression (cont'd)

- Linear regression model with *matrix notation*
  - ▷ $\mathbf{y}$: response vector
  - ▷ $\mathbf{X}$: design matrix
  - ▷ $\boldsymbol{\beta}$: parameter vector
  - ▷ $\boldsymbol{\varepsilon}$: measurement error vector

2.2 Review of Linear Regression (cont'd)

- Maximum likelihood estimators

$$\begin{cases} \widehat{\beta} = (X^\top X)^{-1} X^\top y \\ \\ \widehat{\sigma}^2 = \dfrac{1}{n}(y - X\widehat{\beta})^\top (y - X\widehat{\beta}) \end{cases}$$

where

▷ $X^\top$ denotes the *transpose* of matrix X

▷ $X^\top X$ denotes the *matrix product* of matrices $X^\top$ and X

▷ $(X^\top X)^{-1}$ denotes the *matrix inverse* of matrix $(X^\top X)$

2.3 Marginal Models

- Let's go back to the independence assumption
  - ▷ the first five rows of the data are:

id	serBilir	age	drug
1	14.50	58.77	D-penicil
2	1.10	56.45	D-penicil
3	1.40	70.07	D-penicil
4	1.80	54.74	D-penicil
5	3.40	38.11	placebo

Each row represents a different patient, and patients are **independent** of each other

2.3 Marginal Models (cont'd)

- When we have repeated measurements data, we have the form

id	serBilir	year	age	drug
1	14.50	0.00	58.77	D-penicil
1	21.30	0.53	58.77	D-penicil
2	1.10	0.00	56.45	D-penicil
2	0.80	0.50	56.45	D-penicil
2	1.00	1.00	56.45	D-penicil
2	1.90	2.10	56.45	D-penicil
2	2.60	4.90	56.45	D-penicil

2.3 Marginal Models (cont'd)

Multiple rows per subject, rows belonging to the same subject are **correlated**

- <u>Note:</u> Long vs Wide format
  - ▷ wide format can only be used when all subjects are measured at the same time points
  - ▷ long format can always be used
  - ▷ (almost) all software accept repeated measurements data in long format

2.3 Marginal Models (cont'd)

- How correlation affects modeling of the data?

- Say we are interested in the effect of time on serum bilirubin while also correcting for the age of the patients
  - ▷ the corresponding regression equation is

$$\log(\texttt{serBilir}_{ij}) = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Age}_i + \varepsilon_{ij}$$

where

* $\texttt{serBilir}_{ij}$ denotes the level of serum bilirubin of patient i at time point $\texttt{Time}_{ij}$
* ε_{ij} is the corresponding error term

2.3 Marginal Models (cont'd)

- The fact that the responses of each patient are correlated translates to error terms that are correlated
  - ▷ based on the data of the first two patients (see pp.47) we have

$$\begin{bmatrix} \color{red}{14.5} \\ \color{red}{21.3} \\ \color{blue}{1.1} \\ \color{blue}{0.8} \\ \color{blue}{1.0} \\ \color{blue}{1.9} \\ \color{blue}{2.6} \end{bmatrix} = \begin{bmatrix} 1 & 0.0 & 58.8 \\ 1 & 0.5 & 58.8 \\ 1 & 0.0 & 56.5 \\ 1 & 0.5 & 56.5 \\ 1 & 1.0 & 56.5 \\ 1 & 1.9 & 56.5 \\ 1 & 2.6 & 56.5 \end{bmatrix} \begin{bmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} \color{red}{\varepsilon_{11}} \\ \color{red}{\varepsilon_{12}} \\ \color{blue}{\varepsilon_{21}} \\ \color{blue}{\varepsilon_{22}} \\ \color{blue}{\varepsilon_{23}} \\ \color{blue}{\varepsilon_{24}} \\ \color{blue}{\varepsilon_{25}} \end{bmatrix}$$

2.3 Marginal Models (cont'd)

- The direct approach to account for correlated data $\Rightarrow$ *multivariate regression*

$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i),$$

where

- ▷ y_i the vector of responses for the i-th subject
- ▷ X_i design matrix describing structural component
- ▷ V_i covariance matrix describing the correlation structure

The covariance matrix V_i explicitly accounts for the correlations

2.4 Interpretation

- Interpretation of β
  - ▷ β_j denotes the change in the average y_i when x_j is increased by one unit and all other covariates are fixed

- $\boxed{\text{Example:}}$ In the AIDS dataset we are interested in the effect of treatment on the average longitudinal evolutions – we fit a marginal model with
  - ▷ different average longitudinal evolutions per treatment group ($X\beta$ part)
  - ▷ compound symmetry covariance matrix (V_i part)

$$\begin{cases} \sqrt{\texttt{CD4}_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{ddI}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}, \\ \\ \varepsilon_i \sim \mathcal{N}(0, V_i) \end{cases}$$

2.4 Interpretation (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	7.189	0.221	32.593	< 0.001
β_1	-0.156	0.017	-9.247	< 0.001
β_2	0.016	0.024	0.662	0.508

▷ Coefficient β_1: For patients in the ddC group, every month the average $\sqrt{\texttt{CD4}}$ changes by -0.156

▷ Coefficient β_2:

* Is the difference of the time effect between ddI and ddC
* For patients in the ddI group, every month the average $\sqrt{\texttt{CD4}}$ changes by (-0.156 $+$ 0.016)

2.4 Interpretation (cont'd)

- The estimated covariance matrix V_i is

	$t = 0$	$t = 2$	$t = 6$	$t = 12$	$t = 18$
$t = 0$	24.15	20.30	20.30	20.30	20.30
$t = 2$	20.30	24.15	20.30	20.30	20.30
$t = 6$	20.30	20.30	24.15	20.30	20.30
$t = 12$	20.30	20.30	20.30	24.15	20.30
$t = 18$	20.30	20.30	20.30	20.30	24.15

$$\triangleright\ \textsf{corr}(CD4_{t=0}, CD4_{t=2}) = \frac{\textsf{cov}(CD4_{t=0}, CD4_{t=2})}{\sqrt{\textsf{var}(CD4_{t=0})}\sqrt{\textsf{var}(CD4_{t=2})}} = \frac{20.3}{24.15} = 0.84$$

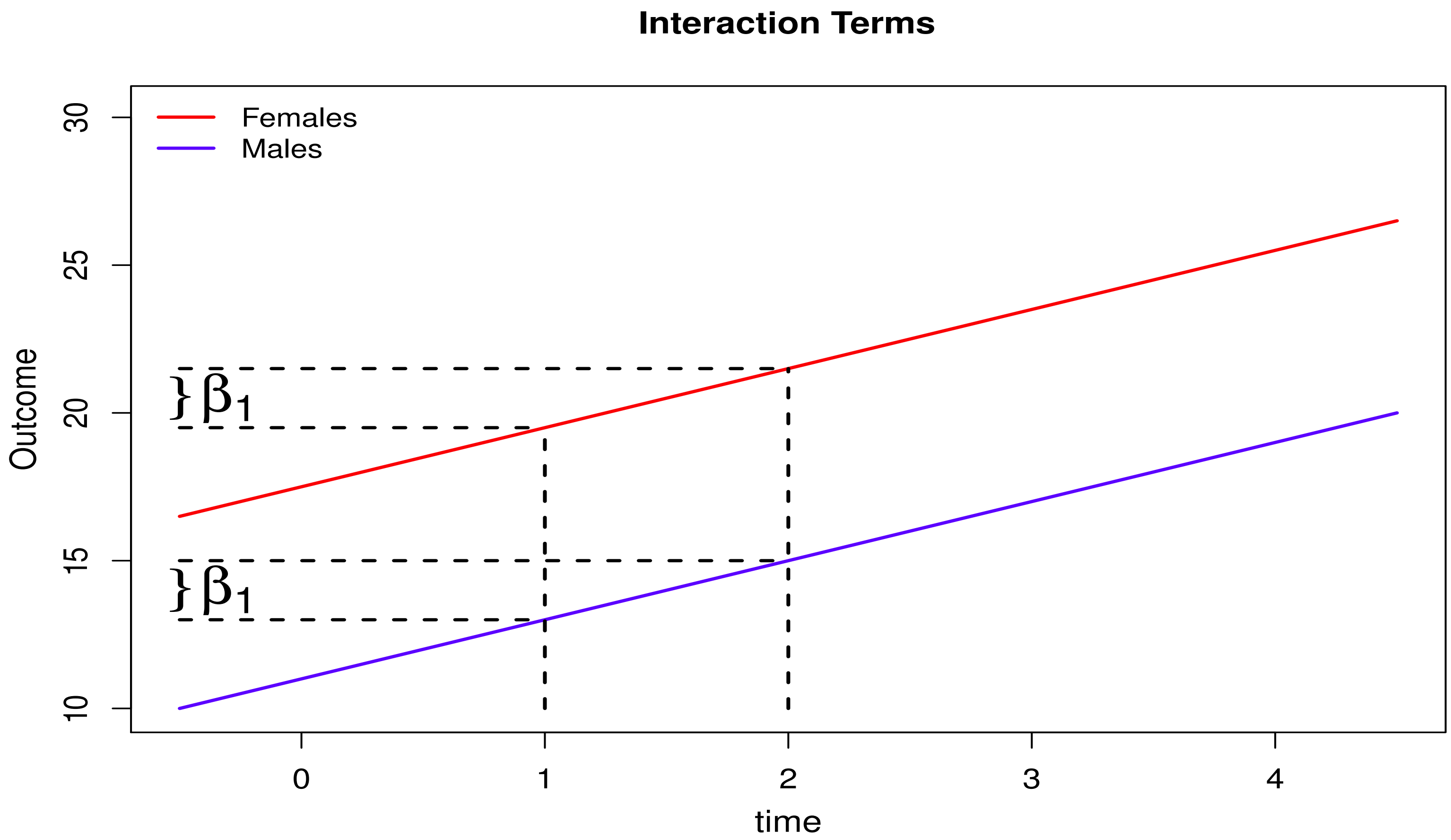
2.4 Interpretation (cont'd)

- Note: Interaction terms for longitudinal data
  - ▷ Consider the model

$$y_{ij} \; = \; \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Sex}_i + \varepsilon_{ij}, \qquad \varepsilon_i \sim \mathcal{N}(0, V_i)$$

  * we include the time effect and we also control for sex
  * the model assumes that the effect of time is the same for the two sexes (*parallel lines*)

2.4 Interpretation (cont'd)

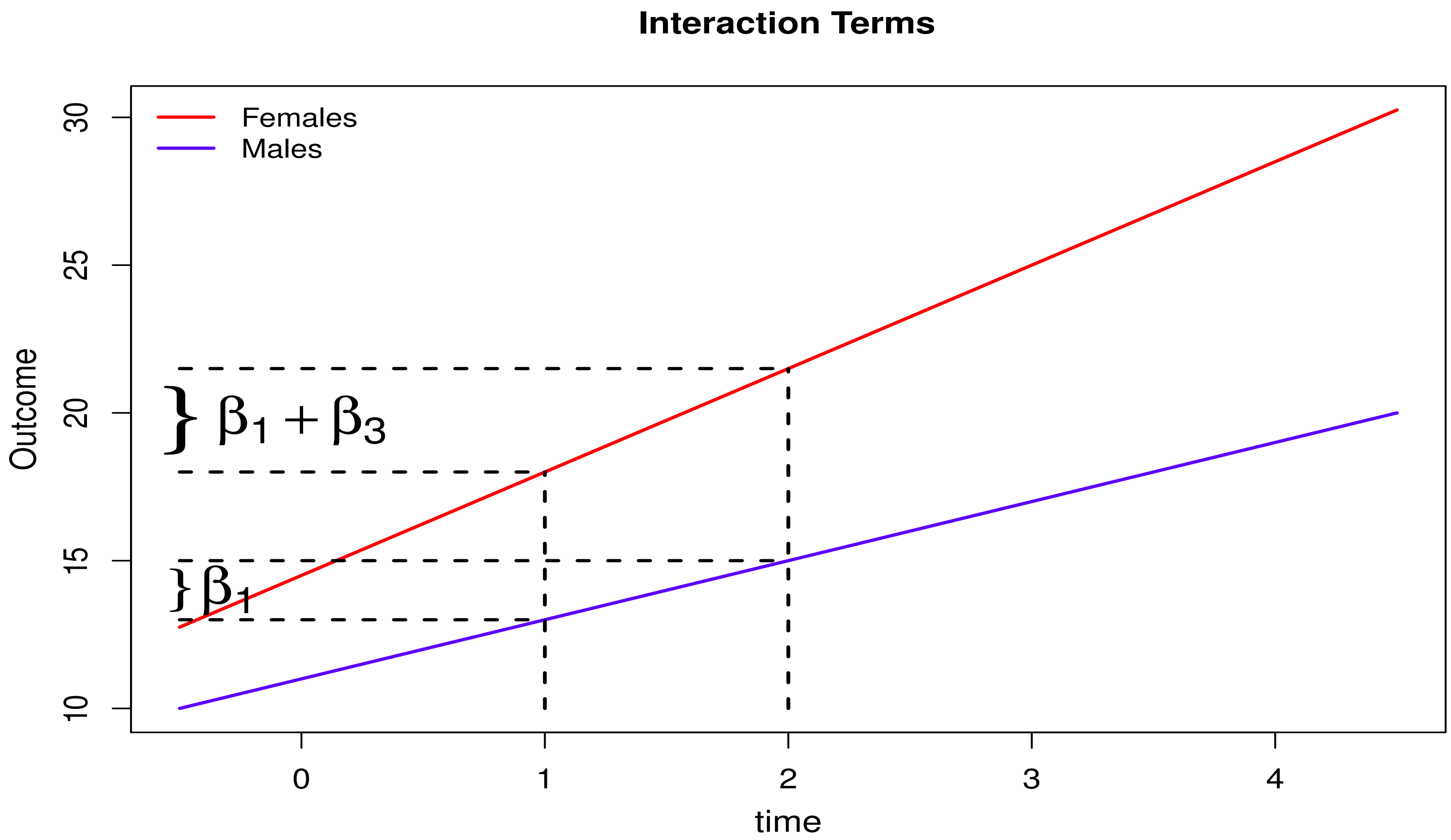


2.4 Interpretation (cont'd)

- Note: Interaction terms for longitudinal data
  - ▷ if we would like different longitudinal evolutions for the two sexes we need to include the *interaction term*

$$y_{ij} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Sex}_i + \beta_3 \{\texttt{Sex}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}, \qquad \varepsilon_i \sim \mathcal{N}(0, V_i)$$

2.4 Interpretation (cont'd)



2.4 Interpretation (cont'd)

- **Communicating a model with complex terms:** Due to the elaborate structure of repeated measurements data it is often required to include complex terms in a model
  - ▷ interaction terms (e.g., between baseline and time-varying predictors)
  - ▷ nonlinear terms (e.g., nonlinear evolutions in times modeled with polynomials or splines)

- In such cases the regression coefficients β we obtain in the output do not often have a straightforward interpretation

2.4 Interpretation (cont'd)

- To overcome this issue we can use **effect plots**
  - ▷ this is a figure that depicts the average outcome along with 95% confidence intervals for specific combinations of the predictors levels

- $\boxed{\text{Example:}}$ We have fitted the following model to the PBC dataset:

$$\left\{\begin{array}{lcl}\log(\texttt{serBilir}_{ij}) & = & \beta_0 + \beta_1 N(\texttt{Time}_{ij})_1 + \beta_2 N(\texttt{Time}_{ij})_2 + \beta_3 \texttt{Female}_i + \beta_4 \texttt{Age}_i + \\ & & \beta_5 \{\texttt{Female}_i \times N(\texttt{Time}_{ij})_1\} + \beta_6 \{\texttt{Female}_i \times N(\texttt{Time}_{ij})_2\} + \\ & & \beta_7 \{\texttt{Female}_i \times \texttt{Age}_i\} + \varepsilon_{ij} \\ & & \\ \varepsilon_i \sim \mathcal{N}(0, V_i) & & V_i \text{ has a continuous AR1 structure}\end{array}\right.$$

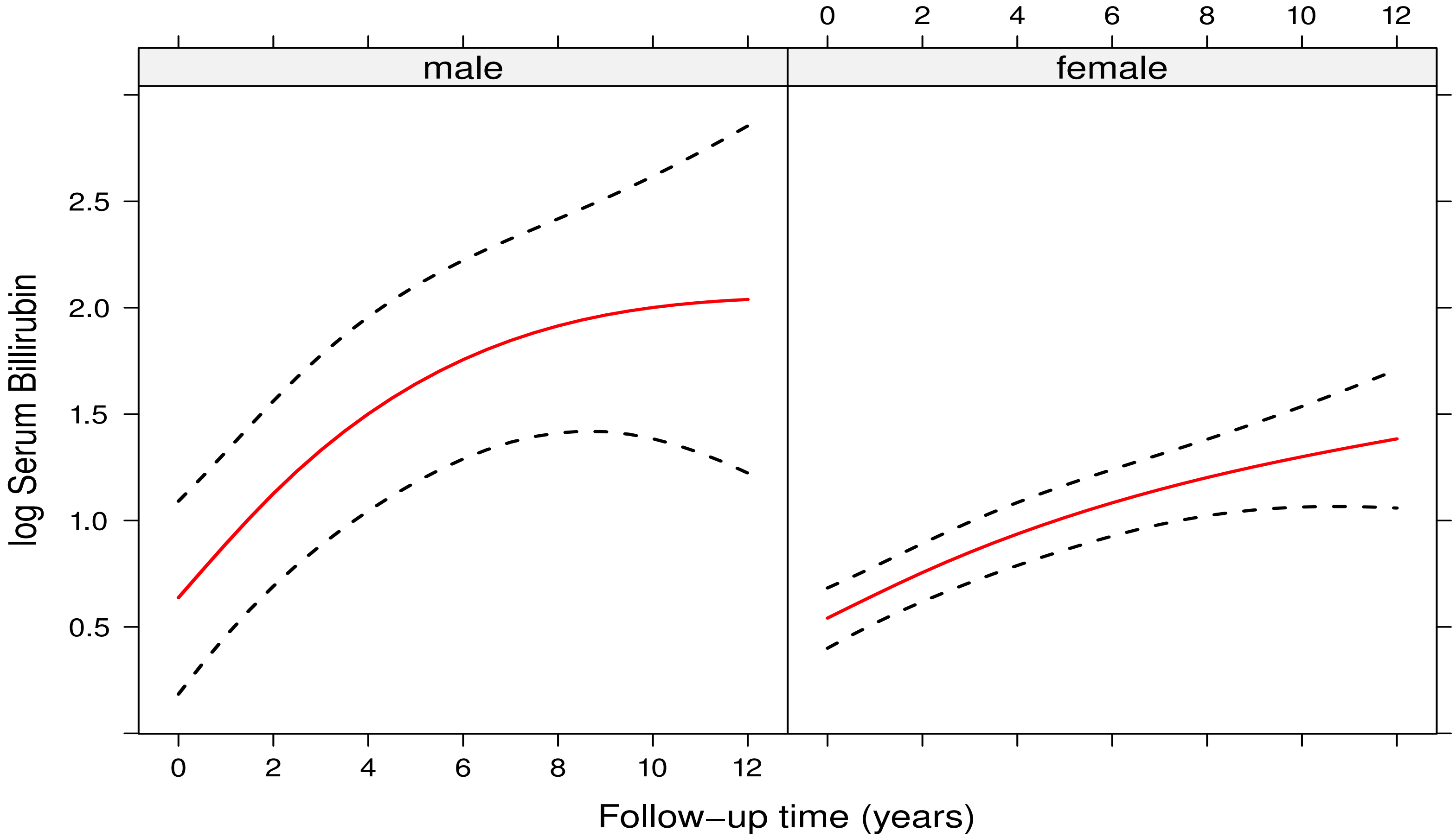
2.4 Interpretation (cont'd)

- The terms $N(\texttt{Time}_{ij})_1$ and $N(\texttt{Time}_{ij})_2$ denote the basis for a natural spline with two degrees of freedom to model possible nonlinearities in the time effect

- In this model not all coefficients have a direct interpretation in isolation

- Hence to understand the model we depict
  - ▷ how the average longitudinal profiles evolve over time time,
  - ▷ separately for males and females, and
  - ▷ for the average age of 49 years old (in the app different ages can be selected)
  - ▷ including also the corresponding 95% pointwise confidence intervals

2.4 Interpretation (cont'd)



2.5 Estimation

- Estimation of model parameters

  ▷ For known covariance matrix V_i, the regression coefficients are estimated using generalized least squares

$$\hat{\beta} = \left(\sum_{i=1}^{n} X_i^\top V_i^{-1} X_i \right)^{-1} \sum_{i=1}^{n} X_i^\top V_i^{-1} y_i$$

  ▷ Variance Components – matrix V_i:

  * Maximum Likelihood (ML)
  * restricted maximum likelihood (REML)

2.5 Estimation (cont'd)

- What's the difference between ML and REML?
  - ▷ ML estimates of variances are known to be biased in small samples
  - ▷ the simplest case: Sample variance

$$\text{var}(x) = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2$$

* to obtain an unbiased estimate we need to divide by $n - 1$

2.5 Estimation (cont'd)

The REML estimation is a generalization of this idea

- It provides unbiased estimates of the parameters in the covariance matrix V_i in small samples

- Example: To illustrate the difference between REML and ML we consider fitting the same model for the AIDS dataset we have seen before but using only the first 50 rows

2.5 Estimation (cont'd)

▷ **REML Estimation**

	$t=0$	$t=2$	$t=6$	$t=12$	$t=18$
$t=0$	16.03	13.48	13.48	13.48	13.48
$t=2$	13.48	16.03	13.48	13.48	13.48
$t=6$	13.48	13.48	16.03	13.48	13.48
$t=12$	13.48	13.48	13.48	16.03	13.48
$t=18$	13.48	13.48	13.48	13.48	16.03

▷ **ML Estimation**

	$t=0$	$t=2$	$t=6$	$t=12$	$t=18$
$t=0$	14.97	12.56	12.56	12.56	12.56
$t=2$	12.56	14.97	12.56	12.56	12.56
$t=6$	12.56	12.56	14.97	12.56	12.56
$t=12$	12.56	12.56	12.56	14.97	12.56
$t=18$	12.56	12.56	12.56	12.56	14.97

* We observe some visible differences because of small n
* In the full dataset the differences are negligible

2.5 Estimation (cont'd)

- Features of REML estimation:
  - ▷ Available in all software that fit marginal and mixed effects models
  - ▷ The way it works is by applying a transformation in the longitudinal outcome y based on the chosen structure of the design matrix X
    (i.e., which predictors you have included in the model)
  - ▷ **Hence, we <u>cannot</u> compare the likelihoods of models fitted with REML and have different $X\beta$ part**

2.6 Fitting Marginal Models in R

R> Marginal models can be fitted using function `gls()` from the **nlme** package

R> It has four basic arguments

- ▷ `model`: a formula specifying the response vector and the covariates to include in the model
- ▷ `data`: a data frame containing all the variables
- ▷ `correlation`: an object describing the assumed correlation structure
- ▷ `weights`: an object describing the assumed describing the within-group heteroscedasticity structure

2.6 Fitting Marginal Models in R (cont'd)

R> The data frame that contains all variables should be in the *long format*

Subject	y	time	gender	age
1	5.1	0.0	male	45
1	6.3	1.1	male	45
2	5.9	0.1	female	38
2	6.9	0.9	female	38
2	7.1	1.2	female	38
2	7.3	1.5	female	38
⋮	⋮	⋮	⋮	⋮

2.6 Fitting Marginal Models in R (cont'd)

R> Using formulas in R

▷ CD4 = Time + Gender

⇒ `cd4 ~ time + gender`

▷ CD4 = Time + Gender + Time*Gender

⇒ `cd4 ~ time + gender + time:gender`

⇒ `cd4 ~ time*gender` (the same)

▷ CD4 = Time + Time^2

⇒ `cd4 ~ time + I(time^2)`

R> Note: the intercept term is included by default

2.6 Fitting Marginal Models in R (cont'd)

R> The following code fits a marginal model for CD4 cell count with an AR1 correlation structure

```
glsFit <- gls(CD4 ~ obstime + obstime:drug, data = aids,
    correlation = corAR1(form = ~ 1 | patient))

summary(glsFit)
```

2.7 Covariance Matrix

- Reminder: What is a variance-covariance matrix?
  - ▷ we have the dataset:

Subject	Y_1	Y_2	Y_3	Y_4
1	2.1	3.2	2.9	3.3
2	1.8	3.1	4.2	5.1
3	3.1	3.2	3.5	3.3
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$

2.7 Covariance Matrix (cont'd)

- The variance-covariance matrix is the matrix whose element in the i, j-th position is the covariance between Y_i and Y_j, e.g.,

$$\begin{bmatrix} \text{var}(Y_1) & \text{cov}(Y_1, Y_2) & \text{cov}(Y_1, Y_3) & \text{cov}(Y_1, Y_4) \\ \text{cov}(Y_2, Y_1) & \text{var}(Y_2) & \text{cov}(Y_2, Y_3) & \text{cov}(Y_2, Y_4) \\ \text{cov}(Y_3, Y_1) & \text{cov}(Y_3, Y_2) & \text{var}(Y_3) & \text{cov}(Y_3, Y_4) \\ \text{cov}(Y_4, Y_1) & \text{cov}(Y_4, Y_2) & \text{cov}(Y_4, Y_3) & \text{var}(Y_4) \end{bmatrix}$$

- Properties

  ▷ on the diagonal the variances, of diagonal covariances

  ▷ symmetric $\Rightarrow$ $\text{cov}(Y_1, Y_2) = \text{cov}(Y_2, Y_1)$

2.7 Covariance Matrix (cont'd)

- Variances, covariances and correlations
  - ▷ variance measures how far a set of numbers is spread out (always positive)
  - ▷ covariance is a measure of how much two random variables change together (positive or negative)
  - ▷ correlation a measure of the linear correlation (dependence) between two variables (between -1 and 1; 0 no correlation)

$$\text{corr}(Y_1, Y_2) = \frac{\text{cov}(Y_1, Y_2)}{\sqrt{\text{var}(Y_1)}\sqrt{\text{var}(Y_2)}}$$

2.7 Covariance Matrix (cont'd)

- Due to the fact that the magnitude of the covariance between Y_1 and Y_2 depends on their variability, we translate the covariance matrix to a correlation matrix

$$\begin{bmatrix} 1 & \text{corr}(Y_1, Y_2) & \text{corr}(Y_1, Y_3) & \text{corr}(Y_1, Y_4) \\ & 1 & \text{corr}(Y_2, Y_3) & \text{corr}(Y_2, Y_4) \\ & & 1 & \text{corr}(Y_3, Y_4) \\ & & & 1 \end{bmatrix}$$

2.7 Covariance Matrix (cont'd)

- Coming back to our model

$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i)$$

- We need an appropriate choice for V_i in order to appropriately describe the correlations between the repeated measurements

  ▷ compound symmetry
  ▷ autoregressive process
  ▷ exponential spatial correlation
  ▷ Gaussian spatial correlation
  ▷ Toeplitz
  ▷ ...

2.7 Covariance Matrix (cont'd)

- Let's see some of those
  - ▷ General/Unstructured

$$\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 \end{bmatrix}$$

  - ▷ Diagonal

$$\begin{bmatrix} \sigma_1^2 & 0 & 0 \\ 0 & \sigma_2^2 & 0 \\ 0 & 0 & \sigma_3^2 \end{bmatrix} \quad \text{or} \quad \begin{bmatrix} \sigma^2 & 0 & 0 \\ 0 & \sigma^2 & 0 \\ 0 & 0 & \sigma^2 \end{bmatrix}$$

2.7 Covariance Matrix (cont'd)

▷ First-order autoregressive

$$\begin{bmatrix} \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 \end{bmatrix}$$

▷ Toeplitz

$$\begin{bmatrix} \sigma_1^2 & \rho_1\sigma_1\sigma_2 & \rho_2\sigma_1\sigma_3 \\ \rho_1\sigma_1\sigma_2 & \sigma_2^2 & \rho_1\sigma_2\sigma_3 \\ \rho_2\sigma_1\sigma_3 & \rho_1\sigma_2\sigma_3 & \sigma_3^2 \end{bmatrix} \quad \text{or} \quad \begin{bmatrix} \sigma^2 & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma^2 & \sigma_{12} \\ \sigma_{13} & \sigma_{12} & \sigma^2 \end{bmatrix}$$

2.7 Covariance Matrix (cont'd)

- The aforementioned structure for the covariance matrix are applicable in cases we have discrete and equally spaced time points

- For continuous time and unbalanced data, alternative options are:
  - ▷ continuous AR1
  - ▷ exponential serial correlation
  - ▷ linear correlation
  - ▷ Gaussian serial correlation

2.7 Covariance Matrix (cont'd)

- These serial correlation structures are defined using the semi-variogram
  - ▷ which we are not going to cover here because it is a bit technical (more info in any standard text for mixed models / longitudinal data analysis)

- the basic assumption is that correlations decay with the time lag $|t_i - t_j| \Rightarrow$ measurements at closer time points are more strongly correlated than measurements at more distant time points
  - ▷ each of these structure how one parameter that controls how correlation decay in time

2.7 Covariance Matrix (cont'd)

- Notes: on building covariance matrices

  ▷ *variance function:* in some cases, and especially for longitudinal data quite often, it may **not** be reasonable to assume that the variance of the outcome remains constant in time

  * we have seen versions of heteroscedastic covariance matrices, but these are only applicable when we have balanced data and few time points
  * for unbalanced designs we can specify other variance functions, e.g., that variances increase linearly or exponentially with time

  ▷ *correlation at the same point:* is it **always** reasonable that the correlation of the outcome at the same point is set to 1?

2.7 Covariance Matrix (cont'd)

- Let's try the app...

2.8 Model Building

- We have seen that marginal models consist of two parts:
  - ▷ Mean part – $X\beta$: that describes how covariates we have put in the model explain the average of the repeated measurements
  - ▷ Covariance part – V_i: assumed covariance structure between the repeated measurements

- In the majority of the cases scientific interest focuses on the mean part

However, to obtain valid and efficient inferences for this part, the covariance part need to be adequately specified

2.8 Model Building (cont'd)

- Hence, the general strategy for building models for repeated measurements data proceeds as follows:

  1. Put all the covariates of interest in the mean part, considering possible interactions between them – **do NOT** remove the ones that are not significant

  2. Then select an appropriate covariance matrix V_i that adequately describes the correlations in the repeated measurements

     * in this step you should be a bit conservative, i.e., do not favor a simpler covariance matrix if the p-value is just non-significant

  3. Finally, return to the mean part and exclude non significant covariates

     * first start by testing the interaction terms

2.8 Model Building (cont'd)

- How many covariates we can put in the mean part?

- It depends on how strong are the correlation between the repeated measurements
  - ▷ weak correlations $\Rightarrow N/10$ (N total number of measurements)
  - ▷ strong correlations $\Rightarrow n/10$ (n number of subjects)

2.9 Hypothesis Testing

- Having fitted a marginal model using maximum likelihood we can use standard inferential tools for performing hypothesis testing
  - ▷ Wald tests / t-tests / F-tests
  - ▷ Score tests
  - ▷ Likelihood ratio tests

- Following the model building strategy described above, we will
  - ▷ first, describe how can we choose the appropriate covariance matrix
  - ▷ and following focus on hypothesis testing for the mean part of the model

2.9 Hypothesis Testing (cont'd)

- **Hypothesis testing for V_i:** Assuming the same mean structure we can fit a series of model and choose the that best describes the covariances

- In general, we distinguish between two cases
  - ▷ comparing two models with *nested* covariance matrices
  - ▷ comparing two models with *non-nested* covariance matrices

- Note: Model A is nested in Model B, when Model A is a special case of Model B, i.e.,
  - ▷ by setting some of the parameters of Model B at some specific value we then obtain Model A

2.9 Hypothesis Testing (cont'd)

- For **nested** models the preferable test for selecting V_i is the likelihood ratio test (LRT):

$$\text{LRT} = -2 \times \{\ell(\hat{\theta}_0) - \ell(\hat{\theta}_a)\} \sim \chi^2_p$$

where

- ▷ $\ell(\hat{\theta}_0)$ the value of the log-likelihood function under the null hypothesis, i.e., the special case model
- ▷ $\ell(\hat{\theta}_1)$ the value of the log-likelihood function under the alternative hypothesis, i.e., the general model
- ▷ p denotes the number of parameters being tested

- **Note:** Provided that the mean structure in the two models is the same, we can either compare the REML of ML likelihoods of the models (preferable is REML)

2.9 Hypothesis Testing (cont'd)

- $\boxed{\text{Example:}}$ In the model we fitted for the AIDS dataset (see pp.52) we had assumed a compound symmetry covariance matrix – we would like to see if this option was sufficient

  ▷ we will compare the compound symmetry model:

$$H_0 : V_i = \begin{array}{c} \begin{array}{ccccc} t=0 & t=2 & t=6 & t=12 & t=18 \end{array} \\ \begin{bmatrix} \sigma^2 & \tilde{\sigma} & \tilde{\sigma} & \tilde{\sigma} & \tilde{\sigma} \\ & \sigma^2 & \tilde{\sigma} & \tilde{\sigma} & \tilde{\sigma} \\ & & \sigma^2 & \tilde{\sigma} & \tilde{\sigma} \\ & & & \sigma^2 & \tilde{\sigma} \\ & & & & \sigma^2 \end{bmatrix} \end{array}$$

2.9 Hypothesis Testing (cont'd)

▷ versus the unstructured model

$$
H_a : V_i = \begin{array}{c} \begin{array}{ccccc} t=0 & t=2 & t=6 & t=12 & t=18 \end{array} \\ \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} & \sigma_{15} \\ & \sigma_2^2 & \sigma_{23} & \sigma_{24} & \sigma_{25} \\ & & \sigma_3^2 & \sigma_{34} & \sigma_{35} \\ & & & \sigma_4^2 & \sigma_{45} \\ & & & & \sigma_5^2 \end{bmatrix} \end{array}
$$

2.9 Hypothesis Testing (cont'd)

- We can rewrite the two hypothesis as

$$H_0 : \quad \begin{cases} \sigma_1^2 = \sigma_2^2 = \ldots = \sigma_5^2 = \sigma^2 \\ \sigma_{12} = \sigma_{13} = \ldots = \sigma_{45} = \tilde{\sigma} \end{cases}$$

$H_a :$ at least one variance of covariance is not equal to the others

- The likelihood ratio test gives:

	df	logLik	LRT	p-value
Comp Symm	5	-3586.91		NA
General	18	-3547.72	78.39	<0.0001

2.9 Hypothesis Testing (cont'd)

- When we have **non-nested** models we **cannot** use standard tests anymore

- As an alternative for this case we use information criteria – the two standard ones are:

$$\begin{aligned} \text{AIC} &= -2\ell(\hat{\theta}) + 2n_{par} \\ \text{BIC} &= -2\ell(\hat{\theta}) + n_{par}\log(n) \end{aligned}$$

  where

  ▷ $\ell(\hat{\theta})$ is the value of the log-likelihood function

  ▷ n_{par} the number of parameters in the model

  ▷ n the number of subjects (independent units)

2.9 Hypothesis Testing (cont'd)

When we compare two **non-nested** models we choose the model that has the **lowest** AIC/BIC value

- Example: For the Prothrobin data we compare the exponential and Gaussian serial correlation structures – the model are:

$$\left\{ \begin{array}{l} M_1 : \texttt{pro}_{ij} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{predn}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}, \quad \varepsilon_i \sim \mathcal{N}(0, V_i^{Exp}) \\ \\ M_2 : \texttt{pro}_{ij} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{predn}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}, \quad \varepsilon_i \sim \mathcal{N}(0, V_i^{Gauss}) \end{array} \right.$$

2.9 Hypothesis Testing (cont'd)

- The AIC and BIC values for the two models are:

	df	logLik	AIC	BIC
Exp	5	-13468.84	26947.67	26977.65
Gauss	5	-13750.88	27511.76	27541.73

  ▷ Both AIC and BIC suggest that the model with the exponential correlation structure is better

2.9 Hypothesis Testing (cont'd)

- The models we have assumed for the Prothrobin data assumed constant variance in time – as we have mentioned (see pp. 82), this assumption is not often justified for longitudinal data

- We extend models M_1 and M_2 by assuming that the variances are an exponential function of time, i.e.,

$$\text{var}(\varepsilon_{ij}) = \sigma^2 \exp\big(\delta \texttt{Time}_{ij}\big)$$

where

▷ δ is a parameter that controls how fast the variance changes with time

* if $\delta < 0$, the variance decreases with time
* if $\delta = 0$, the variance remains constant
* if $\delta > 0$, the variance increases with time

2.9 Hypothesis Testing (cont'd)

- This means that models M_1 and M_2 are nested within their heteroscedastic cousins, i.e.,

$$\begin{aligned} H_0 : \delta &= 0 \quad \text{homoscedastic model} \\ H_a : \delta &\neq 0 \quad \text{heteroscedastic model} \end{aligned}$$

- This implies that we can perform a likelihood ratio test

	df	logLik	AIC	BIC	LRT	p-value
Exp - homoscedastic	5	-13468.84	26947.67	26977.65		NA
Exp - heteroscedastic	6	-13459.99	26931.97	26967.94	17.70	<0.0001
Gauss - homoscedastic	5	-13750.88	27511.76	27541.73		NA
Gauss - heteroscedastic	6	-13748.10	27508.21	27544.18	17.70	0.0185

2.9 Hypothesis Testing (cont'd)

- Notes: Hypothesis testing for the covariance matrix V_i

  ▷ The unstructured covariance matrix is the most general matrix we can assume:
    * all other covariance matrices are a special case of the unstructured matrix
    * **but** realistically it can only be fitted when we have balanced data and relatively few time points

  ▷ The AIC and BIC do not always select the same model – when they disagree
    * AIC typically selects the more elaborate model, whereas
    * BIC the more parsimonious model

2.9 Hypothesis Testing (cont'd)

- **Hypothesis testing for the regression coefficients** β: We assume that first a suitable choice for the covariance matrix has been made

- In the majority of the cases we compare nested models, and hence the standard test can be used

- We distinguish between two cases
  - ▷ tests for individual coefficients
  - ▷ tests for groups of coefficients

2.9 Hypothesis Testing (cont'd)

- Tests for individual coefficients are based on the Wald-type statistic but assume the t distribution for calculating p-values
  - ▷ the set of hypotheses is:

$$H_0 : \beta = 0$$
$$H_a : \beta \neq 0$$

  - ▷ and we use the t test statistic

$$\frac{\hat{\beta}}{s.e.(\hat{\beta})} \sim t_{df}$$

    where $\hat{\beta}$ is the MLE, $s.e.(\hat{\beta})$ is the standard error of the MLE, and df are specified according to the number of subjects and number of repeated measurements per subject

2.9 Hypothesis Testing (cont'd)

- Tests for groups of coefficients are based on the F-test
  - ▷ the set of hypotheses is:

$$\begin{aligned} H_0: &\quad L\beta = 0 \\ H_a: &\quad L\beta \neq 0 \end{aligned}$$

where L is the contrasts matrix

  - ▷ the F test statistic is

$$\frac{\hat{\beta}^\top L^\top \left\{ L \left(\sum_{i=1}^{n} X_i^\top V_i^{-1} X_i \right)^{-1} L^\top \right\}^{-1} L\hat{\beta}}{\text{rank}(L)} \sim F_{df_1, df_2}$$

2.9 Hypothesis Testing (cont'd)

- Tests for groups of coefficients are based on the F-test
  - ▷ The numerator degrees of freedom are always equal to the rank of the contrast matrix L
  - ▷ Denominator degrees of freedom need to be estimated from the data:
    - * Containment method
    - * Satterthwaite approximation
    - * Kenward and Roger approximation

2.9 Hypothesis Testing (cont'd)

- $\boxed{\text{Example:}}$ We have fitted the following model to the PBC dataset:

$$\begin{cases} \log(\texttt{serBilir}_{ij}) = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Female}_i + \beta_3 \texttt{Age}_i + \\ \qquad\qquad \beta_4 \{\texttt{D-penicil}_i \times \texttt{Time}_{ij}\} + \beta_5 \{\texttt{Female}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij} \\ \\ \varepsilon_i \sim \mathcal{N}(0, V_i) \end{cases}$$

where V_i has a continuous AR1 structure

- We are interested in
  - ▷ the effect of Age, and
  - ▷ the overall effect of Sex

2.9 Hypothesis Testing (cont'd)

- For the effect of Age we set the hypotheses:

$$H_0: \quad \beta_3 = 0$$
$$H_a: \quad \beta_3 \neq 0$$

- The output of the model gives: ...

2.9 Hypothesis Testing (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	0.940	0.395	2.382	0.017
β_1	0.154	0.034	4.546	< 0.001
β_2	-0.281	0.218	-1.291	0.197
β_3	-0.002	0.006	-0.361	0.718
β_4	-0.014	0.020	-0.670	0.503
β_5	-0.064	0.034	-1.862	0.063

- Hence, a non-significant Age effect
  - ▷ the t-value in the output is the estimated coefficient divided by its standard error

2.9 Hypothesis Testing (cont'd)

- For the overall effect of Sex we set the hypotheses:

$$\begin{array}{ll} H_0: & \beta_2 = \beta_5 = 0 \\ H_a: & \text{either } \beta_2 \text{ or } \beta_5 \text{ are not equal to } 0 \end{array}$$

- We **cannot** obtain the p-value for this test directly from the output

- We have six parameters, the contrast matrix L is

$$L = \begin{bmatrix} \beta_0 & \beta_1 & \beta_2 & \beta_3 & \beta_4 & \beta_5 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{bmatrix}$$

2.9 Hypothesis Testing (cont'd)

- We obtain

F-value	df_1	df_2	p-value
4.458	2	1939	0.0117

- Hence, a significant overall sex effect

- We could also test the same hypotheses using a likelihood ratio test
  - ▷ in this case we compare the models under the null and alternative hypothesis

2.9 Hypothesis Testing (cont'd)

- The two models are:

$$H_0 : \log(\texttt{serBilir}_{ij}) = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_3 \texttt{Age}_i + \beta_4 \{\texttt{D-penicil}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij}$$

$$\begin{aligned} H_a : \log(\texttt{serBilir}_{ij}) &= \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Female}_i + \beta_3 \texttt{Age}_i + \\ &\quad \beta_4 \{\texttt{D-penicil}_i \times \texttt{Time}_{ij}\} + \beta_5 \{\texttt{Female}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij} \end{aligned}$$

  ▷ for both models V_i has a continuous AR1 structure

- If we compare the two models we again end up in the same hypotheses:

$$\begin{aligned} H_0 &: \quad \beta_2 = \beta_5 = 0 \\ H_a &: \quad \text{either } \beta_2 \text{ or } \beta_5 \text{ are not equal to } 0 \end{aligned}$$

2.9 Hypothesis Testing (cont'd)

- The likelihood ratio test gives

	df	logLik	AIC	BIC	LRT	p-value
without Sex	6	-1618.23	3248.46	3281.90		NA
with Sex	8	-1613.76	3243.52	3288.10	8.94	0.0114

- Hence, again the same conclusion, i.e., a significant overall sex effect

2.9 Hypothesis Testing (cont'd)

- Notes: Hypothesis testing for the regression coefficients β

  ▷ The likelihood ratio test, and the classical univariate and multivariate Wald tests (i.e., using the χ^2 distribution instead of the t or F distributions) are 'liberal'

  * they give smaller p-values than the ones they should give, especially in small samples

  ▷ **Important:** The likelihood ratio test for comparing models with different $X\beta$ parts is only valid when the models have been fitted using maximum likelihood and **not** REML (see also pp. 64–68)

2.10 Confidence Intervals

- Confidence intervals for model parameters are obtained from the approximate distribution of the maximum likelihood estimates (MLEs)

$$\hat{\beta} \sim \mathcal{N}(\beta^*, \mathrm{var}(\hat{\beta}))$$

where

▷ $\hat{\beta}$ are the MLEs

▷ β^* the true parameter values

▷ $\mathrm{var}(\hat{\beta}) = \Big(\sum_{i=1}^n X_i^\top V_i^{-1} X_i \Big)^{-1}$ is the covariance matrix of the MLEs

2.10 Confidence Intervals (cont'd)

- For example, for the k-th regression coefficient β_k, the 95% CI is

$$\hat{\beta} \pm 1.96 \times \text{s.e.}(\hat{\beta})$$

- To obtain confidence intervals for the whole mean evolution we need to multiply with a corresponding design matrix X (see pp. 43–44), i.e.,

$$X\hat{\beta} \pm 1.96 \times \sqrt{\text{diag}\{X\text{var}(\hat{\beta})X^\top\}}$$

  - ▷ this type of confidence intervals have been used in the effects plots we have seen earlier (see pp. 59–145)

2.11 Residuals

All statistical models are based on assumptions

- Hence, to extract meaningful conclusions we need to check whether these assumptions are (crudely) violated

2.11 Residuals (cont'd)

- The marginal model for continuous data makes analogous assumptions as the linear regression model

$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i)$$

namely

▷ the error terms ε_i follow the normal distribution $\mathcal{N}(0, V_i)$

▷ the error terms are independent from the covariates X

▷ the covariates act linearly on the average outcome (here 'linearly' means with respect to the parameters β)

2.11 Residuals (cont'd)

- To validate these assumptions we need an estimate of the error terms ε_{ij}

- Based on the fitted model we obtain the estimate

$$r_{ij} = y_{ij} - x_{ij}^\top \hat{\beta}$$

  ▷ $\hat{\beta}$ are the (restricted) maximum likelihood estimates

  ▷ the r_{ij} are called *residuals*

When the model is correctly specified, we expect these residuals to have a $\mathcal{N}(0, V_i)$ distribution

2.11 Residuals (cont'd)

- Hence, we expect these residuals to be correlated and possibly also heteroscedastic
  - ▷ 'heteroscedastic' means that they exhibit non-constant variance

- This feature complicates matters because it is not easy to assess if the residuals exhibit the assumed properties

- To overcome this problem we need to transform r_{ij} to a scale that has easier to check properties
  - ▷ for example, in general, it is easier to assess whether a particular variable has a standard normal distribution

2.11 Residuals (cont'd)

- To achieve this we multiply the residual with the inverse Choleski factor

$$r_i^{norm} = \widehat{H}_i^{-1} r_i = \widehat{H}_i^{-1}(y_i - X_i \hat{\beta})$$

where

▷ $\widehat{H}_i$ is an upper-triangular matrix with the property $\widehat{H}_i^\top \widehat{H}_i = \widehat{V}_i$, with $\widehat{V}_i$ denoting the estimated covariance matrix

▷ r_{ij}^{norm} are called *normalized residuals* and when the covariance matrix is correctly specified, they should be approximately distributed as $\mathcal{N}(0, 1)$ random variables

2.11 Residuals (cont'd)

- When we have assumed a homoscedastic covariance matrix (i.e., variance remains constant), another transformation that it is often used is

$$r_i^{Pears} = \hat{\sigma}^{-1} r_i = \sigma^{-1}(y_i - X_i \hat{\beta})$$

where

▷ $\hat{\sigma}$ denotes the estimated standard deviation of the error term, i.e., V_i has the structure $\sigma^2 R_i$, with R_i denoting a correlation matrix

▷ r_{ij}^{Pears} are called *Pearson residuals* and when the covariance matrix is correctly specified, they should be approximately distributed as $\mathcal{N}(0, R_i)$ random variables

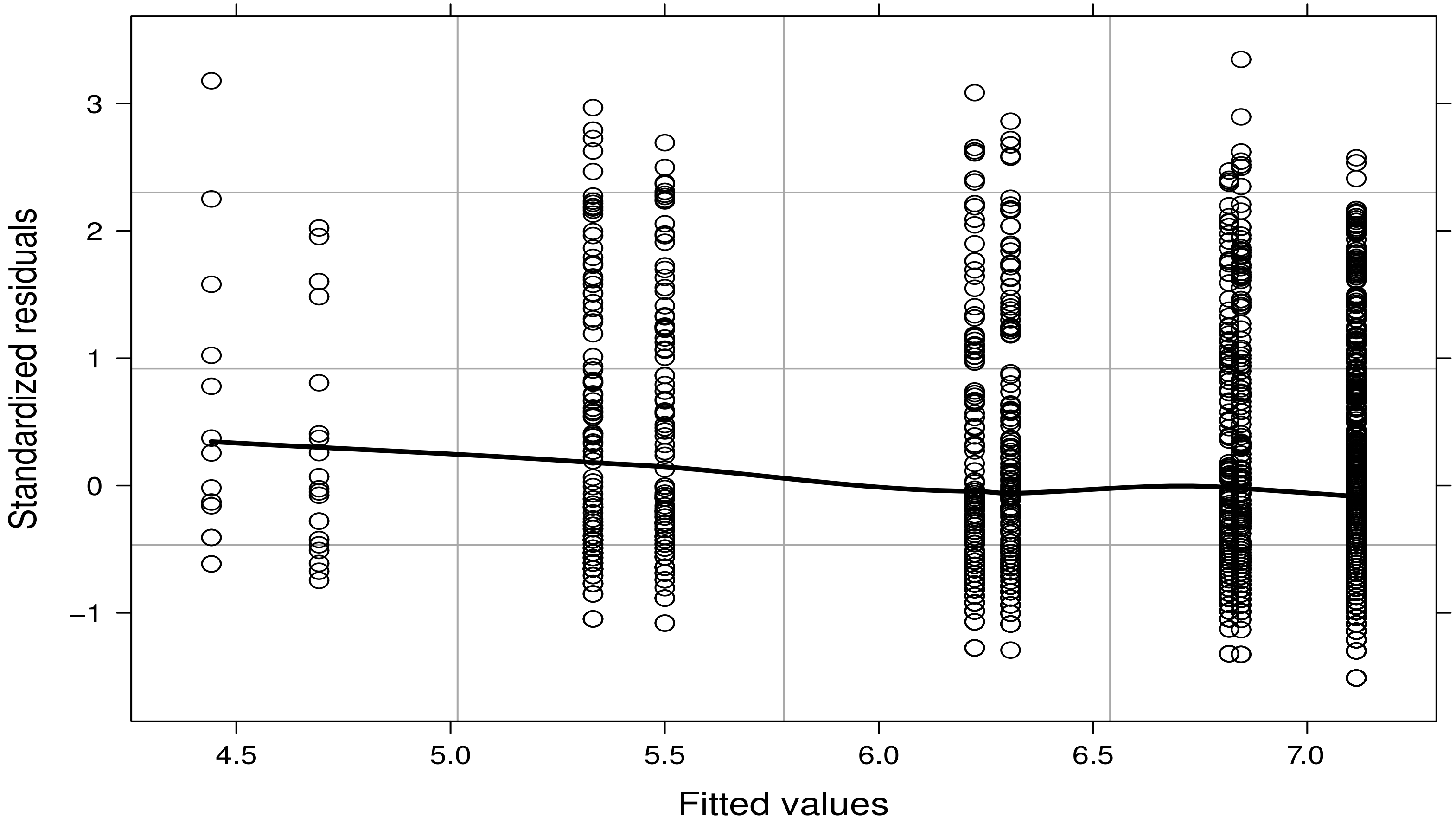
2.11 Residuals (cont'd)

- $\boxed{\text{Example:}}$ We evaluate the assumptions behind the following model fitted to the AIDS dataset:

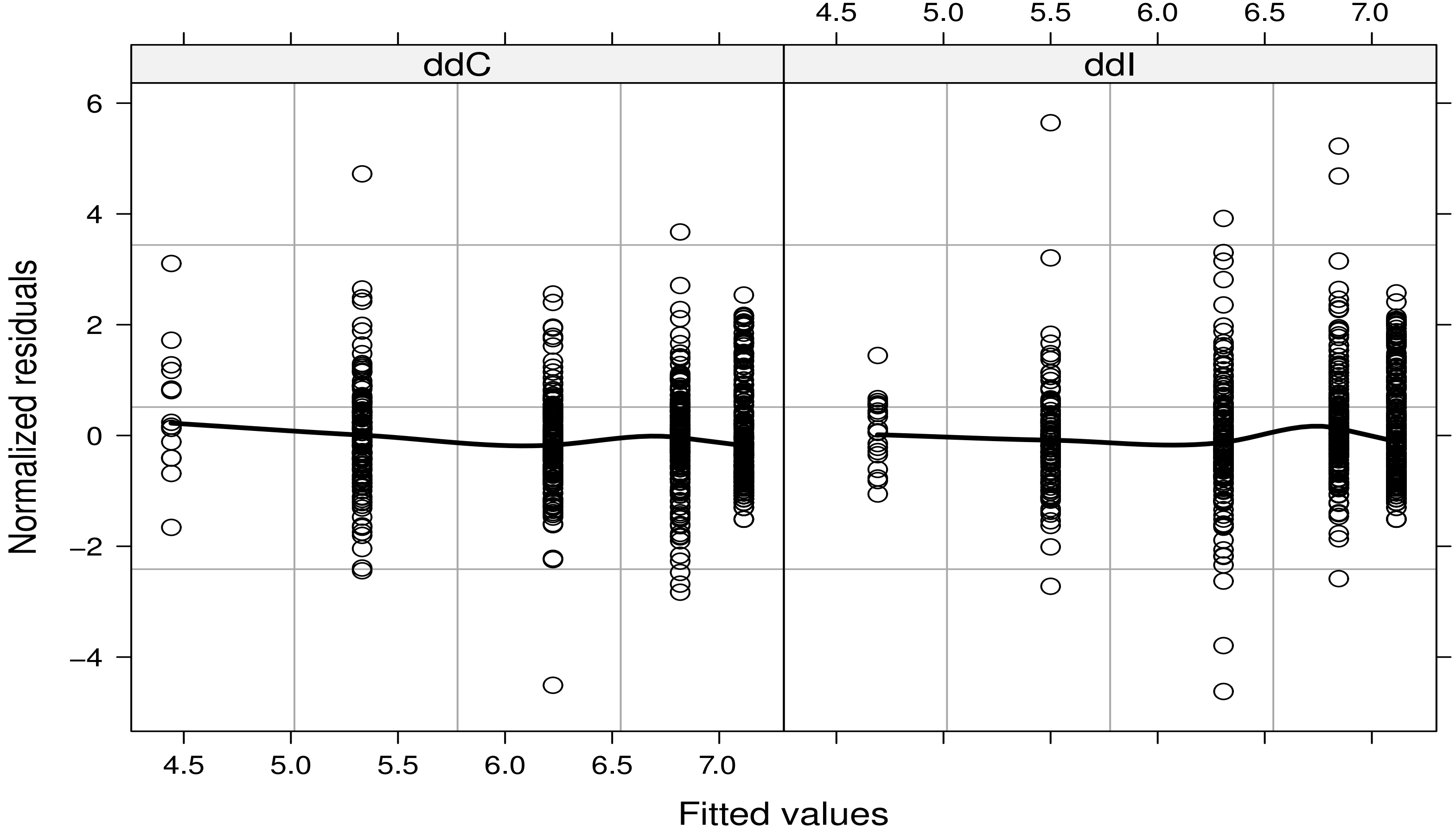
$$\left\{\begin{array}{l}\sqrt{\texttt{CD4}_{ij}} = \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \{\texttt{ddI}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij},\\[2em] \varepsilon_i \sim \mathcal{N}(0, V_i), \quad V_i \text{ is unstructured}\end{array}\right.$$

by plotting

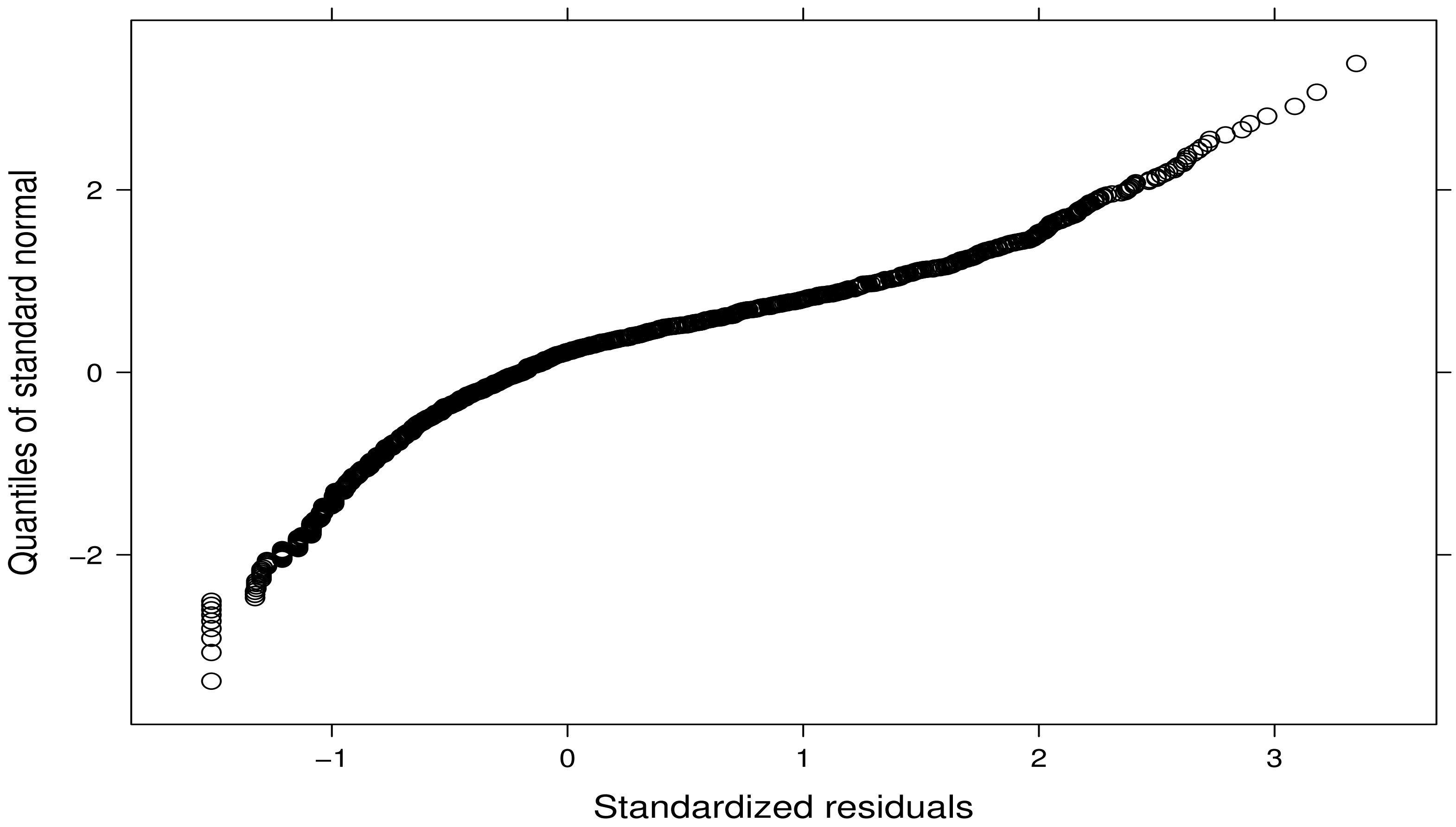
- ▷ the standardized residuals versus fitted values
- ▷ the normalized residuals versus fitted values per treatment group
- ▷ QQ-plot of the standardized residuals


Standardized residuals
Fitted values
3
2
1
0
−1
4.5
5.0
5.5
6.0
6.5
7.0

2.11 Residuals (cont'd)



2.11 Residuals (cont'd)



2.11 Residuals (cont'd)

- Observations
  - ▷ the plots of the residuals versus the fitted values do show a slightly systematic behavior with more positive residuals in the range of low fitted values
  - ▷ the QQ-plot is not perfect, but does not show a big discrepancy from normality

2.11 Residuals (cont'd)

- $\boxed{\text{Example:}}$ We continue by evaluating the assumptions of the model we have fitted to the PBC dataset:

$$\begin{cases} \log(\texttt{serBilir}_{ij}) \;=\; \beta_0 + \beta_1 \texttt{Time}_{ij} + \beta_2 \texttt{Female}_i + \beta_3 \texttt{Age}_i + \\ \qquad\qquad\qquad\quad \beta_4 \{\texttt{D-penicil}_i \times \texttt{Time}_{ij}\} + \beta_5 \{\texttt{Female}_i \times \texttt{Time}_{ij}\} + \varepsilon_{ij} \\ \\ \varepsilon_i \sim \mathcal{N}(0, V_i) \qquad\qquad V_i \text{ has a continuous AR1 structure} \end{cases}$$

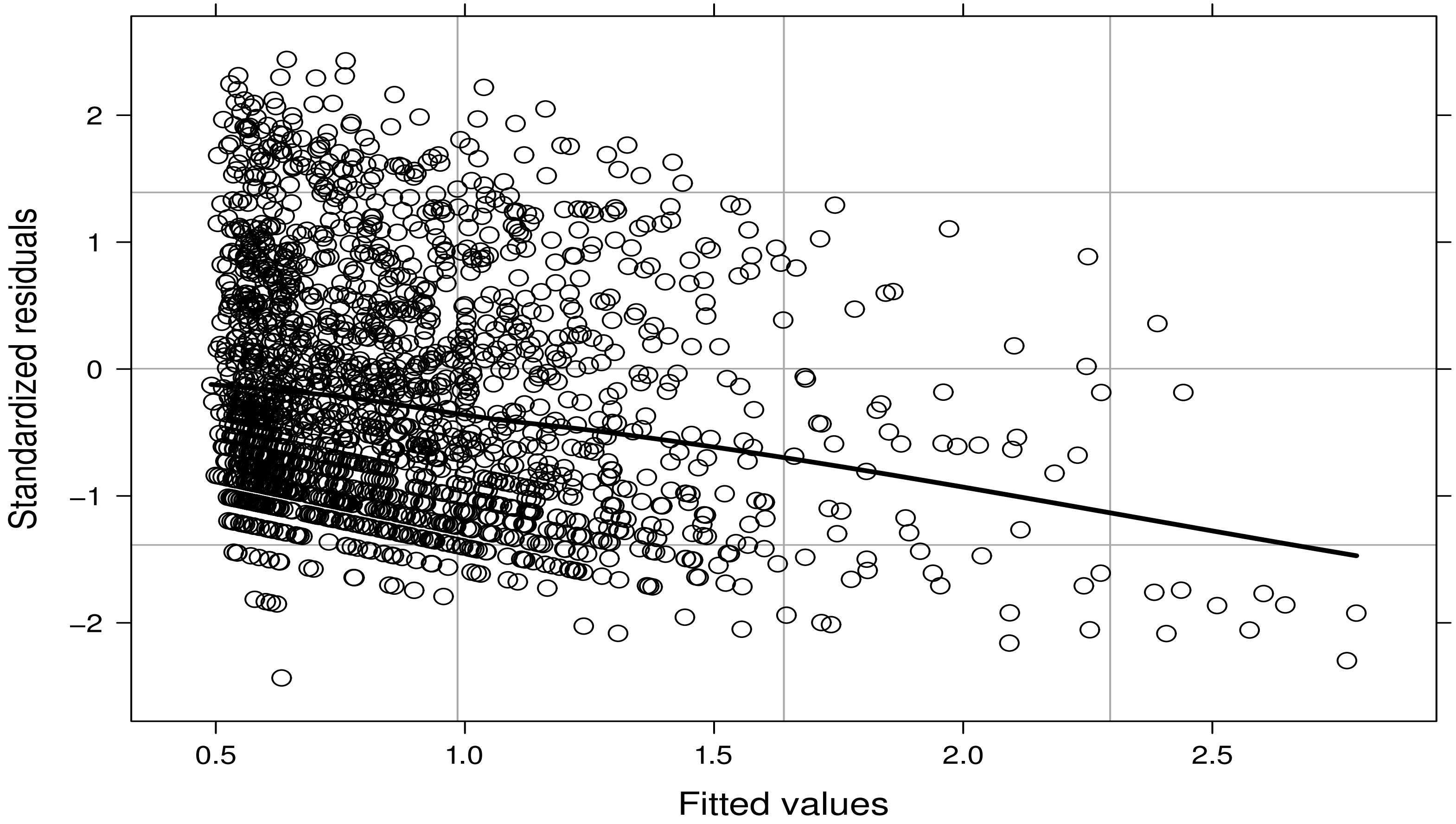
by plotting again

▷ the standardized residuals versus fitted values

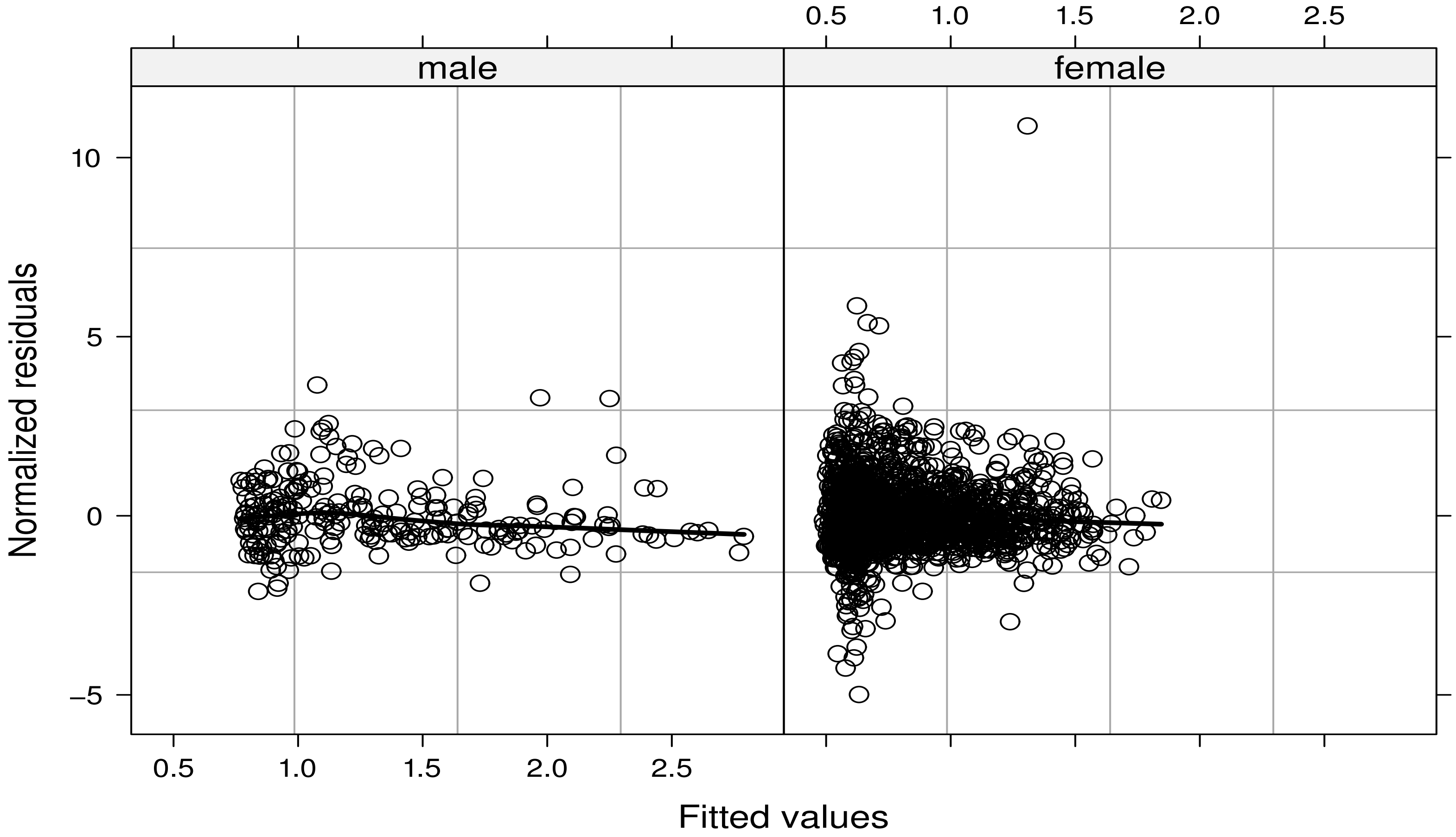
▷ the normalized residuals versus fitted values per gender

▷ QQ-plot of the standardized residuals

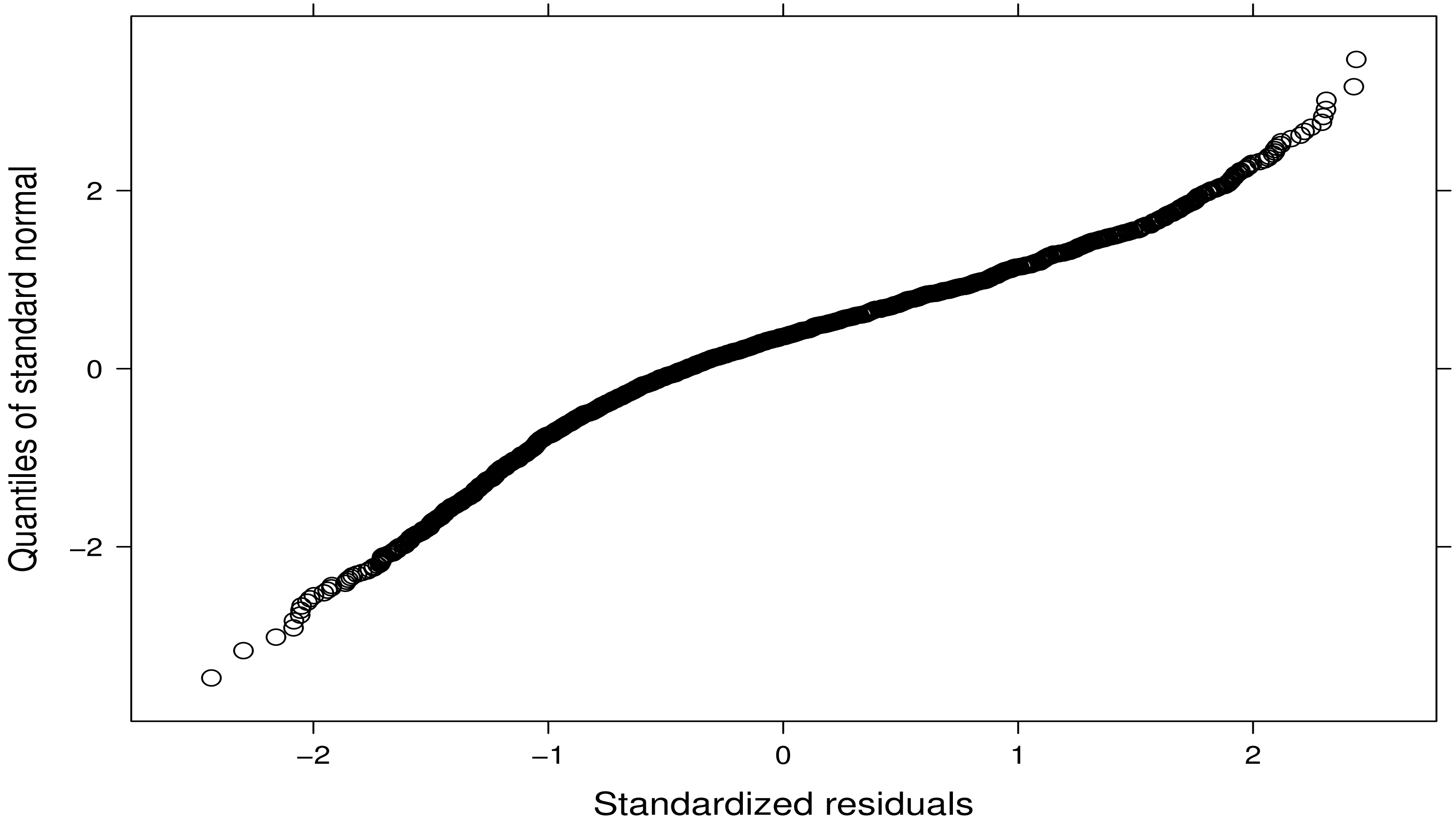
2.11 Residuals (cont'd)



2.11 Residuals (cont'd)



2.11 Residuals (cont'd)



2.11 Residuals (cont'd)

- Observations
  - ▷ the plot of the standardized residuals versus fitted values shows a clear systematic trend with more negative residuals in the range of high fitted values
  - ▷ the plot of normalized residuals versus fitted values shows an outlying observation for female and some slight heteroscedasticity (higher spread of residuals for low fitted values than for high)
  - ▷ the QQ-plot suggests a good fit of the normal distribution

2.12 Review of Key Points

- Methods for analyzing grouped/correlated data
  - ▷ naive approached working on parts or summaries of the data ⇒ loss of information
  - ▷ marginal models ⇒ extension of simple linear regression to the context of correlated data

- Marginal models: Features
  - ▷ error terms are assumed correlated ⇒ we need to make an appropriate assumption
  - ▷ mean structure is build as in standard regression models – however, need to account for potential nonlinear effects of time and/or interaction terms
  - ▷ model building: we start from a 'fully' specified mean structure, we select an appropriate covariance structure, and then the return to make inference for the mean

2.12 Review of Key Points (cont'd)

- Hypothesis testing
  - ▷ for the covariance structure and for nested models likelihood ratio tests are most often used, for non-nested models AIC/BIC
  - ▷ for the mean structure t and F tests with appropriate degrees of freedom

- Residuals
  - ▷ standard residuals plots are used to check the model assumptions
  - ▷ standardized and normalized residuals