Chapter 3

The Linear Mixed Effects Model

3.1 The Linear Mixed Model

- In the previous chapter we focused on the *multivariate regression model*

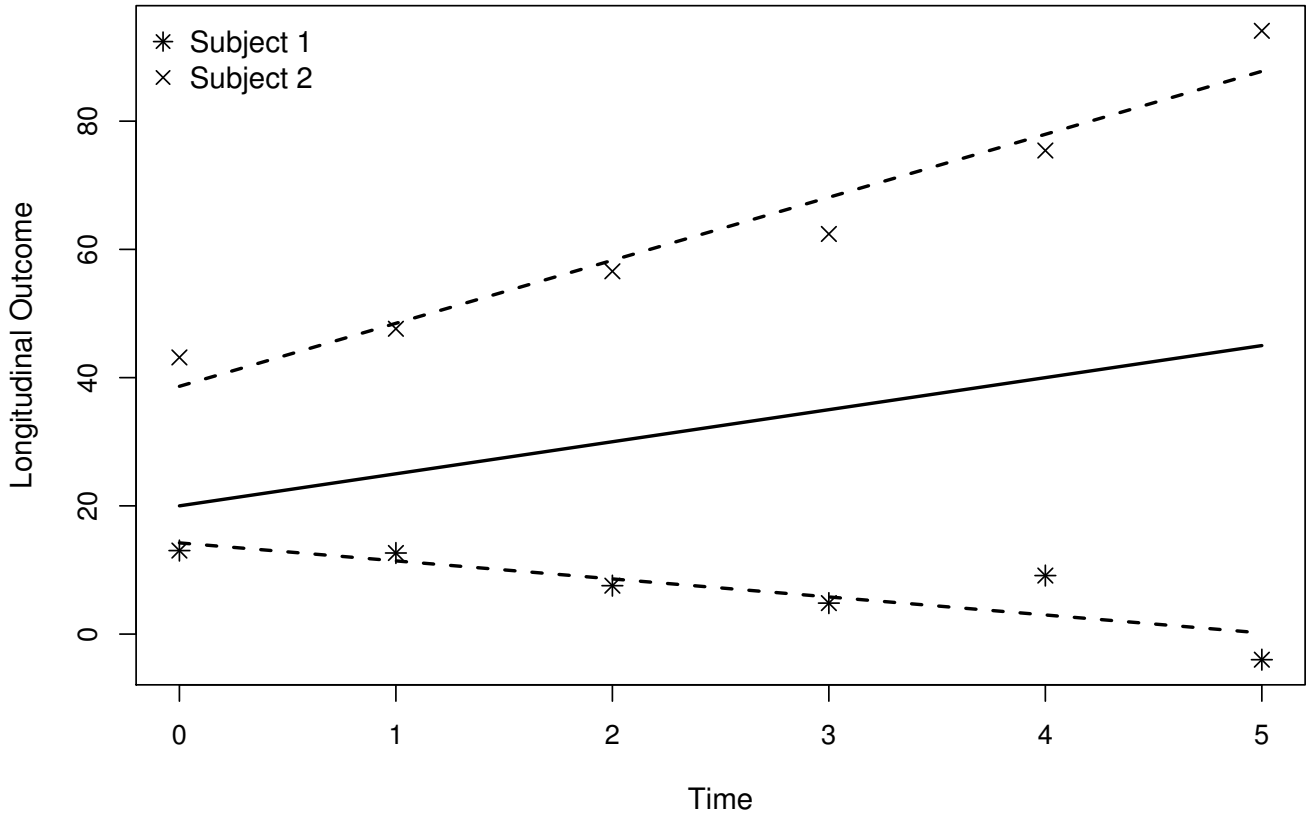
$$y_i = X_i\beta + \varepsilon_i, \quad \varepsilon_i \sim \mathcal{N}(0, V_i),$$

where

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

- **Alternative intuitive approach:** Each subject in the population has her own subject-specific mean response profile over time

3.1 The Linear Mixed Model (cont'd)



3.1 The Linear Mixed Model (cont'd)

- The evolution of each subject in time can be described by a linear model

$$y_{ij} = \tilde{\beta}_{i0} + \tilde{\beta}_{i1} t_{ij} + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2),$$

  where

  - y_{ij} the jth response of the ith subject
  - $\tilde{\beta}_{i0}$ is the intercept and $\tilde{\beta}_{i1}$ the slope for subject i

- **Assumption:** Subjects are randomly sampled from a population $\Rightarrow$ subject-specific regression coefficients are also sampled from a population of regression coefficients

$$\tilde{\beta}_i \sim \mathcal{N}(\beta, D)$$

3.1 The Linear Mixed Model (cont'd)

- We can reformulate the model as

$$y_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})t_{ij} + \varepsilon_{ij},$$

  where

  - ▷ βs are known as the *fixed effects*
  - ▷ b_is are known as the *random effects*

- In accordance for the random effects we assume

$$b_i = \begin{bmatrix} b_{i0} \\ b_{i1} \end{bmatrix} \sim \mathcal{N}(0, D)$$

3.1 The Linear Mixed Model (cont'd)

- Put in a general form

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}), \end{cases}$$

with

- ▷ X design matrix for the fixed effects β
- ▷ Z design matrix for the random effects b_i
- ▷ $b_i \perp\!\!\!\perp \varepsilon_i$

3.2 Interpretation

- Fixed and random effects:
  - ▷ β_j denotes the change in the average y_i when x_j is increased by one unit
  - ▷ b_i are interpreted in terms of how a subset of the regression parameters for the ith subject deviates from those in the population

- Advantageous feature: population + subject-specific predictions
  - ▷ β describes mean response changes in the population
  - ▷ $\beta + b_i$ describes individual response trajectories

3.2 Interpretation (cont'd)

- Example: We fit a linear mixed model for the AIDS dataset assuming
  - ▷ different average longitudinal evolutions per treatment group (fixed part)
  - ▷ random intercepts & random slopes (random part)

$$\begin{cases} y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 \{\texttt{ddI}_i \times t_{ij}\} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

- Note: We did not include a main effect for treatment due to randomization

3.2 Interpretation (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	7.189	0.222	32.359	< 0.001
β_1	-0.163	0.021	-7.855	< 0.001
β_2	0.028	0.030	0.952	0.342

- No evidence of differences in the average longitudinal evolutions between the two treatments

3.2 Interpretation (cont'd)

- Interaction & nonlinear terms: As we have seen in the previous chapter (see pp. 57–62), often
  - ▷ the effect of some predictors may be nonlinear (e.g., time effect), and/or
  - ▷ the effect of some predictors on the outcome may be influenced from other predictors (e.g., different average longitudinal evolutions per treatment group)

- In such cases, we need to consider more elaborate models that contain terms to capture these features, namely
  - ▷ polynomials or splines to model nonlinearities
  - ▷ interaction effects

3.2 Interpretation (cont'd)

- When such terms are included in the model, the interpretation of the parameters can become quite complicated

- To understand a complex mixed model we can visualize it using **effect plots**

- Example: We fit a model to the PBC dataset for serum bilirubin that contains
  - ▷ *fixed effects:*
    - * nonlinear time effect with splines, main effect of sex, age and baseline prothrombin
    - * interaction effects of sex with nonlinear time, age and baseline prothrombin
  - ▷ *random effects:* nonlinear time effect

3.2 Interpretation (cont'd)

- The model has the form:

$$\begin{aligned}\log(\texttt{serBilir}_{ij}) = {} & \beta_0 + \beta_1 N(\texttt{Time}_{ij})_1 + \beta_2 N(\texttt{Time}_{ij})_2 + \beta_3 \texttt{Female}_i + \beta_4 \texttt{Age}_i + \\ & \beta_5 \texttt{basePro}_i + \beta_6 \{\texttt{Female}_i \times \texttt{Age}_i\} + \\ & \beta_7 \{\texttt{Female}_i \times \texttt{basePro}_i\} + \beta_8 \{\texttt{Female}_i \times N(\texttt{Time}_{ij})_1\} + \\ & \beta_9 \{\texttt{Female}_i \times N(\texttt{Time}_{ij})_2\} + b_{i0} + b_{i1} N(\texttt{Time}_{ij})_1 + \\ & b_{i2} N(\texttt{Time}_{ij})_2 + \varepsilon_{ij}\end{aligned}$$

where

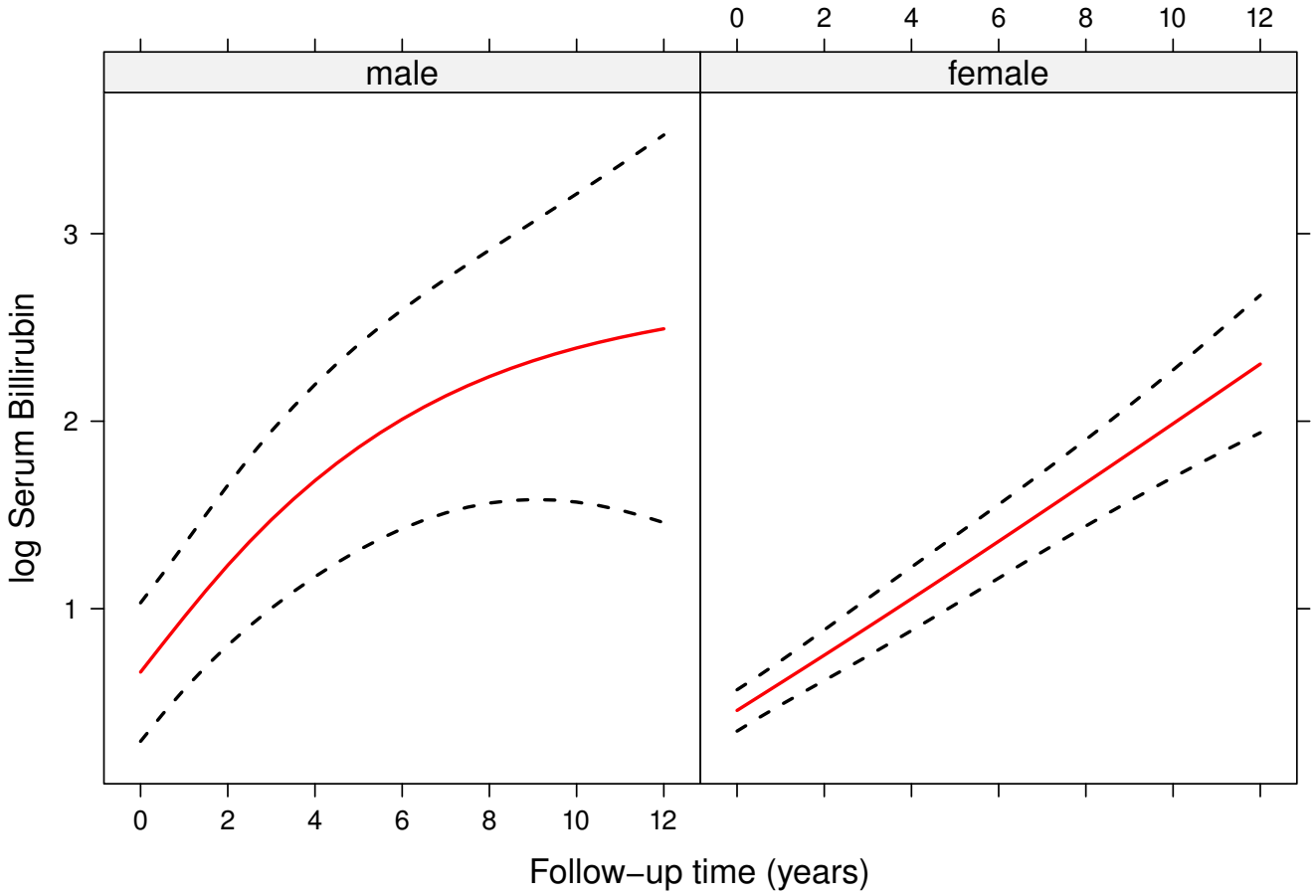
  - ▷ the terms $N(\texttt{Time}_{ij})_1$ and $N(\texttt{Time}_{ij})_2$ denote the basis for a natural spline with two degrees of freedom
  - ▷ $b_i \sim \mathcal{N}(0, D)$ and $\varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2)$

3.2 Interpretation (cont'd)

- 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 prothrombin time of 10.6 sec
  - ▷ for the average age of 49 years old
  - ▷ including also the corresponding 95% pointwise confidence intervals
  - ▷ (in the app different ages and prothrombin times can be selected)

3.2 Interpretation (cont'd)



3.3 Hierarchical vs Marginal

- How do the random effects capture correlation:
  - ▷ Given the random effects, the measurements of each subject are independent (*conditional independence assumption*)

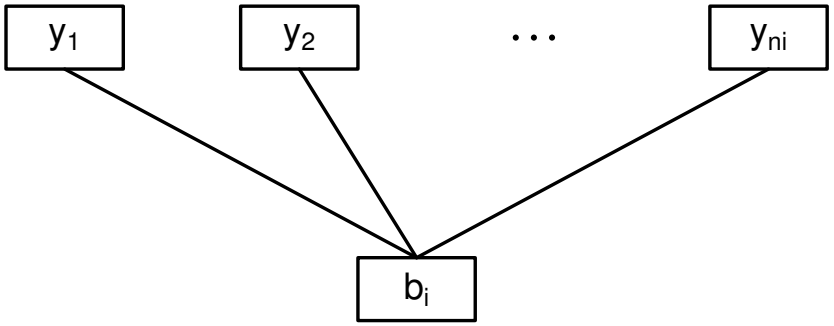
$$p(y_i \mid b_i) = \prod_{j=1}^{n_i} p(y_{ij} \mid b_i)$$

  - ▷ Marginally (integrating out the random effects), the measurements of each subject are correlated

$$p(y_i) = \int p(y_i \mid b_i)\, p(b_i)\, db_i \quad \Rightarrow \quad y_i \sim \mathcal{N}(X_i\beta,\ Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i})$$

3.3 Hierarchical vs Marginal (cont'd)

Graphical representation of the conditional independence assumption



3.3 Hierarchical vs Marginal (cont'd)

- Hence, with random effects we again model the correlations in the repeated measurements of each subject

- Notes: In using random effects for modeling the covariance matrix

  - ▷ The more random effects we include the more flexibly we capture the correlations
  - ▷ By using random effects we also directly allow for heteroscedasticity (i.e., non-constant variances in time)
  - ▷ Nevertheless, we do assume a particular type of structure for the correlations and the variances – they are **not** allowed completely free
  - ▷ Random effects work equally well with balanced or unbalanced data

3.3 Hierarchical vs Marginal (cont'd)

- Let's try the app...

3.3 Hierarchical vs Marginal (cont'd)

- Hierarchical formulation
  - ▷ a model for y_i given b_i, and a model for b_i
  - ▷ D is the covariance matrix of the random effects $\Rightarrow$ **needs to be positive definite**

- Marginal formulation
  - ▷ a model for y_i, and a specific form of the marginal covariance matrix $V_i = Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$
  - ▷ only V_i needs to be positive definite
  - ▷ V_i **can be positive definite without** D **being positive definite**

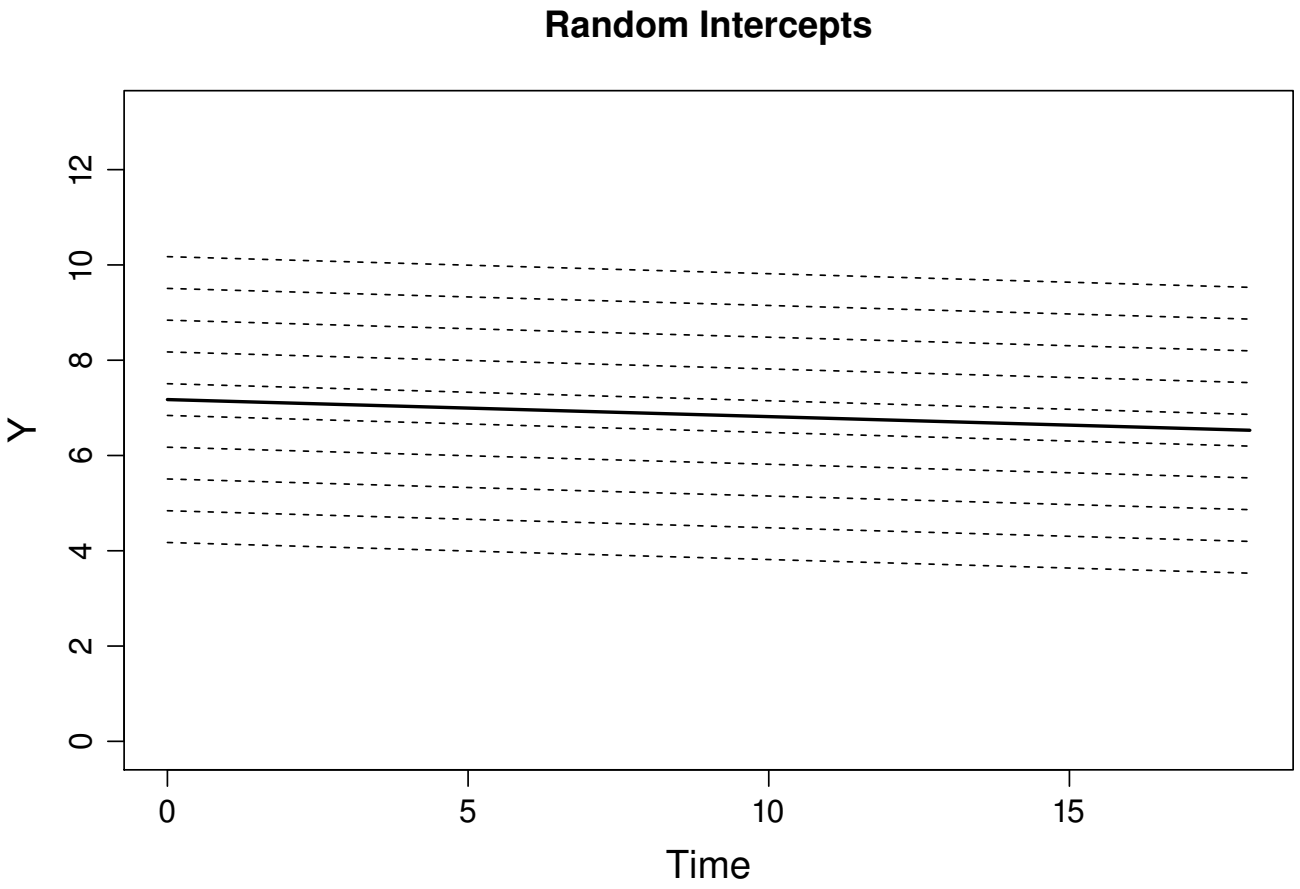
3.3 Hierarchical vs Marginal (cont'd)

The hierarchical model implies the marginal one,
not vice versa

- A simple example: Random-intercepts model

$$\begin{cases} y_{ij} = \beta_0 + \beta_1 t_{ij} + b_{i0} + \varepsilon_{ij}, \\ \\ b_{i0} \sim \mathcal{N}(0, \sigma_b^2), \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2). \end{cases}$$

3.3 Hierarchical vs Marginal (cont'd)



3.3 Hierarchical vs Marginal (cont'd)

- Implied marginal covariance matrix has the form

$$V_i = \sigma_b^2 1_{n_i} 1_{n_i}^\top + \sigma^2 \mathsf{I}_{n_i}$$

it assumes

- ▷ constant variance $\sigma_b^2 + \sigma^2$ over time, and
- ▷ equal positive correlation $\rho = \sigma_b^2/(\sigma_b^2 + \sigma^2)$ between the measurements of any two time points (aka *intra-class correlation*)
- ▷ it is known as the *compound symmetric* covariance matrix

3.3 Hierarchical vs Marginal (cont'd)

- Note that we could also have a compound symmetric covariance matrix with negative intra-class correlation
  - ▷ such a matrix could never have come from a mixed model

Random intercepts **imply** compound symmetry
but
Compound symmetry **does not imply** random intercepts

3.3 Hierarchical vs Marginal (cont'd)

- What are the implications of this?

- Statistical software that fit mixed models under ML actually fit the implied marginal model
  - ▷ we can construct examples where two mixed models have exactly the same implied marginal model
  - ▷ based on the fitted model we **cannot** say under which model the data have been generated

- We can only do it under a Bayesian approach (because there we actually fit the hierarchical model)

3.4 Estimation

- Fixed effects: For known marginal covariance matrix $V_i = Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$, the fixed effects 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: The unique parameters in V_i are estimated based on either maximum likelihood (ML) or restricted maximum likelihood (REML)
  - ▷ REML provides unbiased estimates for the variance components in small samples

3.4 Estimation (cont'd)

- Two-step iterative procedure
  - ▷ Step 0: Set initial values for D and σ^2
  - ▷ Step 1: Calculate the covariance matrix $\widehat{V}_i^{it=k}$ and following the fixed effects $\hat{\beta}^{it=k}$
  - ▷ Step 2: Update $\widehat{V}_i^{it=k+1}$ using REML or ML
  - ▷ Step 3: Check convergence criterion, if not satisfied return to Step 1

Steps 1–3 are repeated until convergence is attained

3.4 Estimation (cont'd)

- Estimation of random effects
  - ▷ based on a fitted mixed model, estimates for the random effects are based on the posterior distribution:

$$p(b_i \mid y_i; \theta) = \frac{p(y_i \mid b_i; \theta)\, p(b_i; \theta)}{p(y_i; \theta)}$$

$$\propto p(y_i \mid b_i; \theta)\, p(b_i; \theta),$$

in which θ is replaced by its MLE $\hat{\theta}$

3.4 Estimation (cont'd)

- This is a whole distribution
  - ▷ in the linear mixed model we have seen, this posterior distribution has a closed-form:

$$[b_i \mid y_i; \theta] \sim \mathcal{N}\Big\{DZ_i^\top V_i^{-1}(y_i - X_i\beta),\ DZ_i^\top K Z_i D\Big\},$$

with

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

3.4 Estimation (cont'd)

- To obtain estimates for the random effects we typically use measures of location from this posterior distribution (e.g., mean or mode)

- Due to the fact that in linear mixed models we obtain a normal distribution, in which the mean and mode coincide, we use estimates of the random effects the means

$$\widehat{b}_i = DZ_i^\top V_i^{-1}(y_i - X_i\beta)$$

- These estimates are called the *empirical Bayes* estimates of the random effects

3.4 Estimation (cont'd)

- Estimates of the random effects are very useful in prediction
  - ▷ in this context there is an important difference between the marginal models we have seen in Chapter 2 and the mixed models of this chapter

- In particular, the predictions from a marginal model are

$$\widehat{y}_i^{marg} = X_i\widehat{\beta}$$

whereas as from the mixed model

$$\widehat{y}_i^{subj} = X_i\widehat{\beta} + Z_i\widehat{b}_i$$

3.4 Estimation (cont'd)

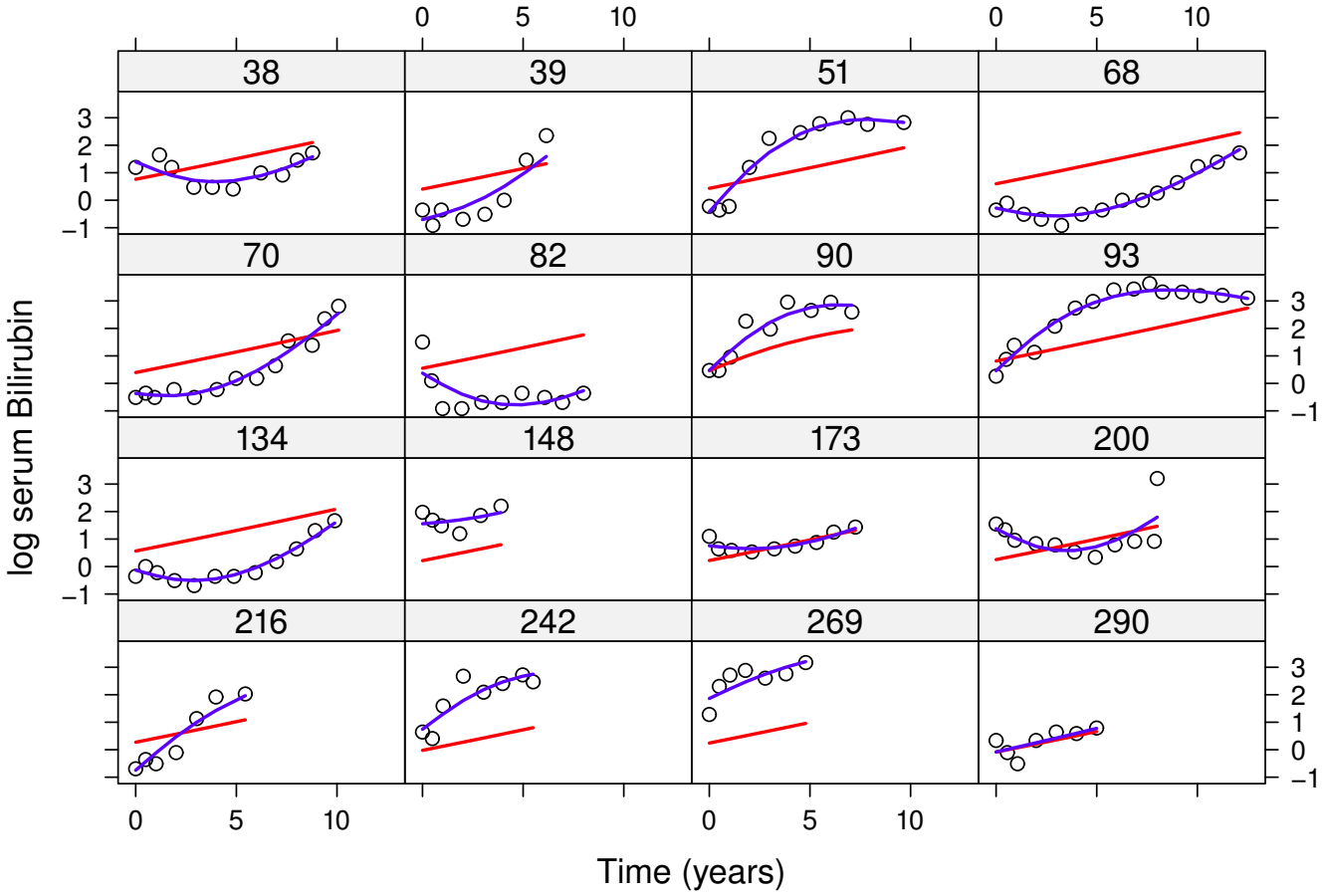
- The difference is that
  - ▷ from the marginal model we obtain predictions for the *'average'* patient having characteristics X_i (i.e., age, sex, etc.)
  - ▷ from the mixed model we obtain predictions for the *'average'* patient that has characteristics X_i and observed data y_i (i.e., they have a subject-specific nature)

- The predictions $X_i\widehat{\beta} + Z_i\widehat{b}_i$ we obtain from the mixed model are called the *Best Linear Unbiased Predictions (BLUPs)*
  - ▷ 'linear' because they are a linear combination of $\widehat{\beta}$ and $\widehat{b}_i$
  - ▷ 'unbiased' because their average equals the true subject-specific mean
  - ▷ 'best' because they have the smallest variance of all linear predictors

3.4 Estimation (cont'd)

- Example: To see an example of the difference between the marginal and subject-specific predictions, we compare the two sets of predictions for the complex linear mixed model we have seen in Section 3.2 (pp.147–150) for 16 randomly selected patients
  - ▷ red lines denote the marginal predictions,
  - ▷ blue lines denote the subject-specific predictions
  - ▷ black circles the observed data

3.4 Estimation (cont'd)



3.4 Estimation (cont'd)

- We clearly observe that the subject-specific prediction are much closer to the data of each individual patient than the marginal predictions

3.5 Mixed-Effects Models in R

R> There are two primary packages in R for mixed models analysis:

- Package **nlme**
  - * fits linear & nonlinear mixed effects models, and marginal models for normal data
  - * allows for both random effects & correlated error terms
  - * several options for covariances matrices and variance functions

- Package **lme4**
  - * fits linear, nonlinear & generalized mixed effects models
  - * uses only random effects
  - * allows for nested and crossed random-effects designs

3.5 Mixed-Effects Models in R (cont'd)

R> The basic function to fit linear mixed models in the **nlme** package is `lme()`, and has three basic arguments

- ▷ `fixed`: a formula specifying the response vector and the fixed-effects structure
- ▷ `random`: a formula specifying the random-effects structure
- ▷ `data`: a data frame containing all the variables

3.5 Mixed-Effects 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
⋮	⋮	⋮	⋮	⋮

3.5 Mixed-Effects Models in R (cont'd)

R> The code used to fit the linear mixed model for the AIDS dataset (pp.144) is as follows

```
lmeFit <- lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = ~ obstime | patient)

summary(lmeFit)
```

3.5 Mixed-Effects Models in R (cont'd)

R> The same fixed-effects structure but only random intercepts

```
lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = ~ 1 | patient)
```

R> The same fixed-effects structure, random intercepts & random slopes, with a diagonal covariance matrix (using the `pdDiag()` function)

```
lme(CD4 ~ obstime + obstime:drug, data = aids,
    random = list(patient = pdDiag(form = ~ obstime)))
```

3.5 Mixed-Effects Models in R (cont'd)

R> The basic function to fit linear mixed models in the **lme4** package is `lmer()`, and has two basic arguments

- ▷ `formula`: a formula specifying the response vector, the fixed- and random-effects structure
- ▷ `data`: a data frame containing all the variables

R> Again the data should be in the long format

3.5 Mixed-Effects Models in R (cont'd)

R> The analogous code to fit the linear mixed model for the AIDS dataset (pp.144) is as follows

```
lmerFit <- lmer(CD4 ~ obstime + obstime:drug + (obstime | patient),
                data = aids)

summary(lmerFit)
```

3.5 Mixed-Effects Models in R (cont'd)

R> To fit the same model but with a diagonal matrix for the random effects the call becomes:

```
lmerFit2 <- lmer(CD4 ~ obstime + obstime:drug + (1 | patient) +
                       (0 + obstime | patient),
                 data = aids)

summary(lmerFit2)
```

3.6 Nested and Crossed Random Effects*

- In the previous examples the primary type of correlated data we have seen is longitudinal data
  - ▷ correlations stems from the fact that we measure *the same* outcome repeatedly in time for each subject

- Another commonly encountered feature that induces correlation is clustering, e.g.,
  - ▷ patients are clustered within hospitals
  - ▷ children are clustered within schools or families
  - ▷ ...

3.6 Nested and Crossed Random Effects* (cont'd)

- Example: In the Glaucoma data we have a multilevel clustered design (see pp.11)
  - ▷ each location is nested within the hemifield
  - ▷ each hemifield is nested within the eye
  - ▷ each eye is nested within the patient

Measurements in the same cluster are expected to be **(positively) correlated**

3.6 Nested and Crossed Random Effects* (cont'd)

- To account for the correlations in each level of the multilevel structure we can include level-specific random effects

- Continuing in the Glaucoma data example, we focus (for simplicity) in the higher two levels, namely the patient and the eye

  ▷ we fit a linear mixed model with a separate random effect per level

$$\begin{cases} \texttt{VF}_{ijk} = \beta_0 + \beta_1 \texttt{Time}_{ijk} + b_i + u_{ij} + \varepsilon_{ijk} \\ b_i \sim \mathcal{N}(0, \sigma^2_{patient}), \qquad u_{ij} \sim \mathcal{N}(0, \sigma^2_{eye}), \\ \varepsilon_{ijk} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

3.6 Nested and Crossed Random Effects* (cont'd)

- where
  - ▷ $\texttt{VF}_{ijk}$ denotes the k-th visual field sensitivity measurement for the j-th eye of the i-th patient
  - ▷ $\texttt{Time}_{ijk}$ denotes the corresponding time point this measurement was taken
  - ▷ b_i is the random effect for the patients – the measurements of the i-th patient are correlated because all these measurements share the *same* random effect b_i
  - ▷ u_{ij} is the random effect for the eye within the patient – the measurements of the j-th eye of the i-th patient are more correlated than the measurements of the j'-th eye because they share the *same* random effect u_{ij}

3.6 Nested and Crossed Random Effects* (cont'd)

- The estimated variance components from the Glaucoma data are:
  - ▷ $\sigma_{patient} = 4.3$
  - ▷ $\sigma_{eye} = 5.8$
  - ▷ $\sigma = 7.9$

- Based on these variance components we can compute the corresponding correlations, i.e.,
  - ▷ measurements in the same eye have correlation

$$\frac{\sigma^2_{patient} + \sigma^2_{eye}}{\sigma^2_{patient} + \sigma^2_{eye} + \sigma^2} = 0.46$$

3.6 Nested and Crossed Random Effects* (cont'd)

▷ and measurements from different eyes

$$\frac{\sigma^2_{patient}}{\sigma^2_{patient} + \sigma^2_{eye} + \sigma^2} = 0.16$$

- It goes without saying, that if the correlations in the data are more complex we could additional random effects

- Example: Continuing in the Glaucoma example, by including only random intercepts terms we assume that the correlations are constant in time

  ▷ as we have previously discussed, this may be a simplistic assumption for longitudinal data

3.6 Nested and Crossed Random Effects* (cont'd)

- We extend the model by including a random slopes terms in the patient level, i.e.,

$$\begin{cases} \texttt{VF}_{ijk} &= \beta_0 + \beta_1 \texttt{Time}_{ijk} + b_i + u_{ij} + \varepsilon_{ijk} \\ b_i &\sim \mathcal{N}(0, D_{patient}), \qquad u_{ij} \sim \mathcal{N}(0, \sigma^2_{eye}), \\ \varepsilon_{ijk} &\sim \mathcal{N}(0, \sigma^2) \end{cases}$$

  ▷ now, in the patient level we have a covariance matrix D

3.6 Nested and Crossed Random Effects* (cont'd)

- The estimated variance components from the Glaucoma data are:
  - ▷ $\sigma_{patient,int} = 4.7$
  - ▷ $\sigma_{patient,slp} = 0.4$
  - ▷ $\text{corr}_{patient,int-slp} = -0.4$
  - ▷ $\sigma_{eye} = 5.8$
  - ▷ $\sigma = 7.8$

3.6 Nested and Crossed Random Effects* (cont'd)

- The examples we have seen so far in this section refer to settings in which the measurements of one level are *nested* within another level
  - ▷ due to this feature, the random effects we have used in the previous examples of the Glaucoma data are called *nested random effects*

- However, there are also settings in which we have different types of groupings of measurements that are not nested
  - ▷ in these cases we use *crossed random effects*

3.6 Nested and Crossed Random Effects* (cont'd)

- Example: One feature of visual field sensitivity measurements is that they exhibit the so-called *Global Visit Effect* (see pp.12)
  - ▷ in particular, for some visits some patients showed strangely low sensitivity to the stimuli
  - ▷ in the next visit, their sensitivity levels improved
  - ▷ it is not possible this low sensitivity to be due to Glaucoma because it is an irreparable disease
  - ▷ hence, the low sensitivity measurements are attributed to other reasons (e.g., tiredness)

- To capture this Global Visit Effect we can include a random effect for each visit
  - ▷ this random effect is **not** nested to the previously used random effects

3.6 Nested and Crossed Random Effects* (cont'd)

- Hence, our model now becomes

$$\begin{cases} \texttt{VF}_{ijk} = \beta_0 + \beta_1 \texttt{Time}_{ijk} + b_i + \texttt{v}_k + \varepsilon_{ijk} \\ b_i \sim \mathcal{N}(0, \sigma^2_{patient}), \qquad \texttt{v}_k \sim \mathcal{N}(0, \sigma^2_{visit}), \\ \varepsilon_{ijk} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

- The estimated variance components from the Glaucoma data are:
  - $\triangleright\ \sigma_{patient} = 5.9$
  - $\triangleright\ \sigma_{visit} = 0.8$
  - $\triangleright\ \sigma = 8.9$

3.7 Mixed Models with Correlated Errors

- We have seen two classes of models for longitudinal data, namely
  - ▷ *Marginal Models*

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

  - ▷ *Conditional Models*

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}) \end{cases}$$

3.7 Mixed Models with Correlated Errors (cont'd)

- It is also possible to combine the two approaches and obtain a linear mixed model with correlated error terms

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \\ \\ b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \Sigma_i), \end{cases}$$

where, as in marginal models, we can consider different forms for Σ_i

- The corresponding marginal model is of the form

$$y_i \sim \mathcal{N}(X_i\beta,\ Z_i D Z_i^\top + \Sigma_i)$$

3.7 Mixed Models with Correlated Errors (cont'd)

- Features
  - ▷ both b_i and Σ_i try to capture the correlation in the observed responses y_i
  - ▷ this model does not assume conditional independence

- Choice between the two approaches is to a large extent philosophical
  - ▷ *Random Effects*: trajectory of a subject dictated by time-independent random effects $\Rightarrow$ the shape of the trajectory is an inherent characteristic of this subject
  - ▷ *Serial Correlation*: attempts to more precisely capture features of the trajectory by allowing subject-specific trends to vary in time

3.7 Mixed Models with Correlated Errors (cont'd)

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Often in practice it is **not** possible to include both a serial correlation term and many random effects because of numerical problems

- Example: In the AIDS dataset we investigate the fit of a mixed model with exponential serial correlation and increasing number of random effects – in particular:
  - ▷ Model I: random intercepts
  - ▷ Model II: random intercepts & random slopes
  - ▷ Model III: random intercepts, random linear slopes & random quadratic slopes

  the fixed-effects part includes linear and quadratic slopes and their interaction with treatment

3.7 Mixed Models with Correlated Errors (cont'd)

	Model I	Model II	Model III
Intercept	7.173	7.214	7.218
$\texttt{Time}_{ij}$	−0.247	−0.251	−0.258
$\texttt{Time}_{ij}^2$	0.007	0.007	0.008
$\texttt{ddI}_i \times \texttt{Time}_{ij}$	0.186	0.154	0.158
$\texttt{ddI}_i \times \texttt{Time}_{ij}^2$	−0.013	−0.010	−0.011

- We observe small differences in the estimated fixed effects

3.7 Mixed Models with Correlated Errors (cont'd)

	Model I	Model II	Model III
ϕ	2.29	0.52	0.33
95% CI	(1.62; 3.23)	(0.08; 3.46)	(0.02; 5.89)

- However, we observe a more profound effect in the estimated parameter of the exponential serial correlation structure
  - ▷ as we include more random effects, less information is available for estimating the serial correlation structure – note length of 95% CIs

- *Numerical problems:*
  - ▷ The model is fitted with the exponential serial correlation structure,
  - ▷ but if you instead tried the Gaussian serial correlation structure, then Model III does not appropriately converge (Hessian matrix of the MLEs is not positive-definite)

3.8 Time-Varying Covariates*

- Up to now all, and with the exception of the time variable, all covariates we have included in the model were fixed from baseline

- However, often we may also be interested in assessing how a longitudinal outcome is associated with a covariate whose value changes over time

  ▷ such covariates are called *time-varying covariates*

- Example: In the PBC dataset we are interested in the effect of prothrombin time on serum bilirubin – prothrombin time has also been collected longitudinally during follow-up

3.8 Time-Varying Covariates* (cont'd)

- The handling of time-varying covariates poses some *important challenges*:

  1. Not always the longitudinal outcome and the time-varying covariate are collected at the same time points

  2. The longitudinal outcome at a particular time point t may depend not only on the value of the covariate at the same time point but also at other time points

  3. There are two types of time-varying covariates, *endogenous* and *exogenous*
     - ▷ a time-varying covariate is *exogenous* if its distribution at time t is conditionally independent of all preceding outcomes
     - ▷ a time-varying covariate is *endogenous* if it is not exogenous

3.8 Time-Varying Covariates* (cont'd)

- The formal definitions of *exogenous* and *endogenous* time-varying covariates are:

$$p\{x_i(t) \mid \mathcal{H}_i^Y(t), \mathcal{H}_i^X(t)\} = p\{x_i(t) \mid \mathcal{H}_i^X(t)\}$$

$$p\{x_i(t) \mid \mathcal{H}_i^Y(t), \mathcal{H}_i^X(t)\} \neq p\{x_i(t) \mid \mathcal{H}_i^X(t)\}$$

where

  - $\mathcal{H}_i^Y(t) = \{y_i(t_{i1}), \ldots, y_i(t_{ik}); t_{ik} \leq t\}$ denotes the set of longitudinal measurements up to time t
  - $\mathcal{H}_i^X(t) = \{x_i(t_{i1}), \ldots, x_i(t_{ik}); t_{ik} \leq t\}$ denotes the set of covariate measurements up to time t

3.8 Time-Varying Covariates* (cont'd)

- These features complicate postulating an appropriate model with such covariates

- A procedure to follow when working with time-varying covariates
  - ▷ Determine if the covariate is *endogenous* or *exogenous*
    - * if it is exogenous, then
      - we can proceed by postulating a standard mixed (or marginal) model, and
      - the longitudinal outcome at time t can only be associated with past covariate measurements, i.e., $\mathcal{H}_i^X(t)$
    - * if it is endogenous, then more complicated types of analysis are required (joint models or marginal structural models) that fall outside the scope of this course

3.8 Time-Varying Covariates* (cont'd)

▷ Next, determine how to link the time-varying covariate to the longitudinal outcome (association structure)

* the longitudinal outcome at t is associated to the covariate at which time points (the same, previous time points, etc.)

* Note: If the scientific interest is focused on a particular type of association structure but in reality the longitudinal outcomes is differently associated to the time-varying covariate, then the estimated association of interest may be diluted (biased) unless a specific type of analysis is followed (a marginal model with independent error terms, i.e., linear regression and corrected standard errors using the sandwich estimator)

3.8 Time-Varying Covariates* (cont'd)

▷ Depending on the chosen association structure in the previous step, and if the time-varying covariate is not measured at the same time points as the longitudinal outcome, then a form of interpolation may be required

- Example: In the PBC dataset we are interested in the effect of prothrombin time on serum bilirubin

$$\begin{aligned}\log(\texttt{serBilir}_{ij}) = {} & \beta_0 + \beta_1 N(\texttt{Time}_{ij})_1 + \beta_2 N(\texttt{Time}_{ij})_2 + \beta_3 \texttt{Female}_i + \beta_4 \texttt{Age}_i + \\ & \beta_5 \texttt{Prothr}_{ij} + b_{i0} + b_{i1} N(\texttt{Time}_{ij})_1 + b_{i2} N(\texttt{Time}_{ij})_2 + \varepsilon_{ij}\end{aligned}$$

the covariance matrix of the random effects is assumed to be diagonal

3.8 Time-Varying Covariates* (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	0.347	0.366	0.948	0.343
β_1	1.772	0.139	12.738	< 0.001
β_2	1.266	0.197	6.422	< 0.001
β_3	-0.233	0.184	-1.263	0.207
β_4	-0.000	0.006	-0.080	0.936
β_5	0.036	0.008	4.675	< 0.001

- Log serum bilirubin at time t is strongly related with the prothrombin time at the same time point – a unit increase of prothrombin time at follow-up time t increases the expected log serum bilirubin at the same follow-up time by 0.036

3.8 Time-Varying Covariates* (cont'd)

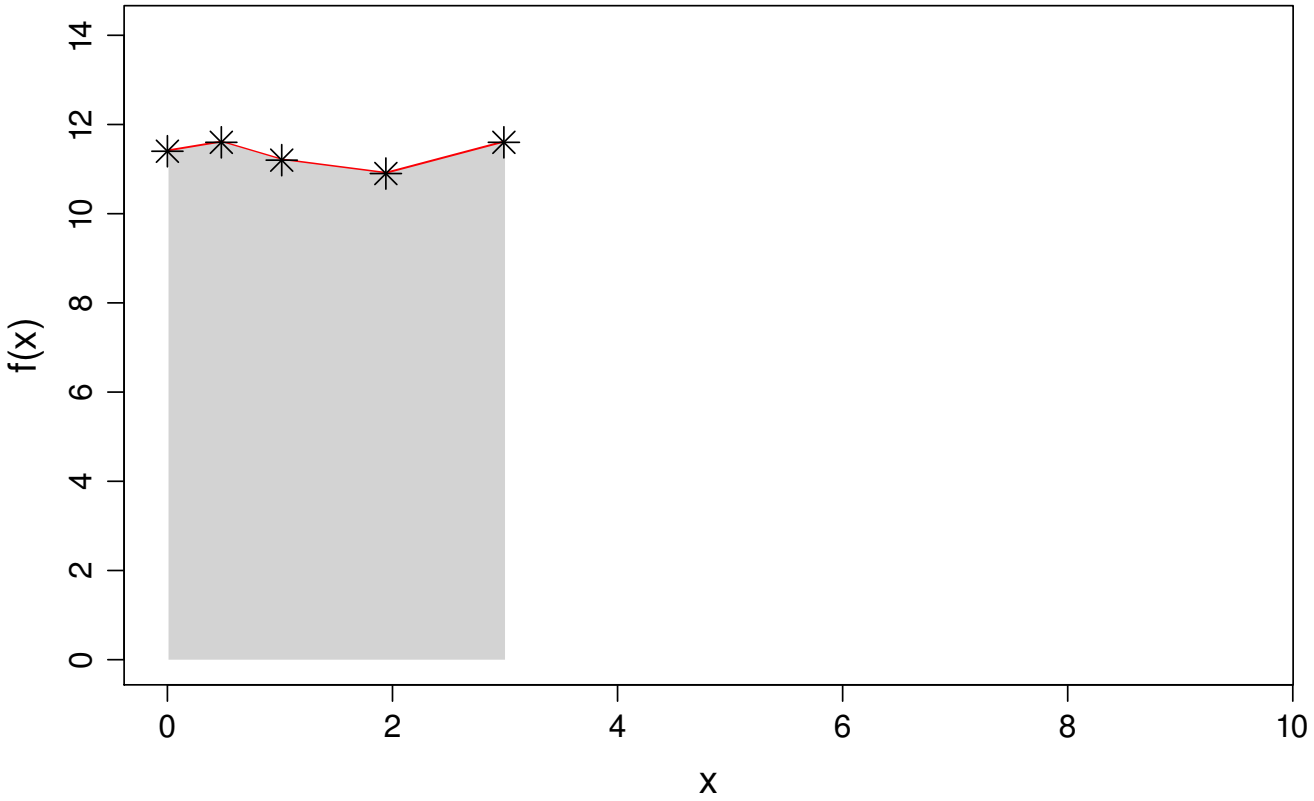
- We continue on the same example, but now we allow the log serum bilirubin at time t to be associated with the prothrombin time at previous time points as well – in particular:

$$\begin{aligned}\log(\texttt{serBilir}_{ij}) = {} & \beta_0 + \beta_1 N(\texttt{Time}_{ij})_1 + \beta_2 N(\texttt{Time}_{ij})_2 + \beta_3 \texttt{Female}_i + \beta_4 \texttt{Age}_i + \\ & \beta_5 \texttt{CumProthr}_{ij} + b_{i0} + b_{i1} N(\texttt{Time}_{ij})_1 + b_{i2} N(\texttt{Time}_{ij})_2 + \varepsilon_{ij}\end{aligned}$$

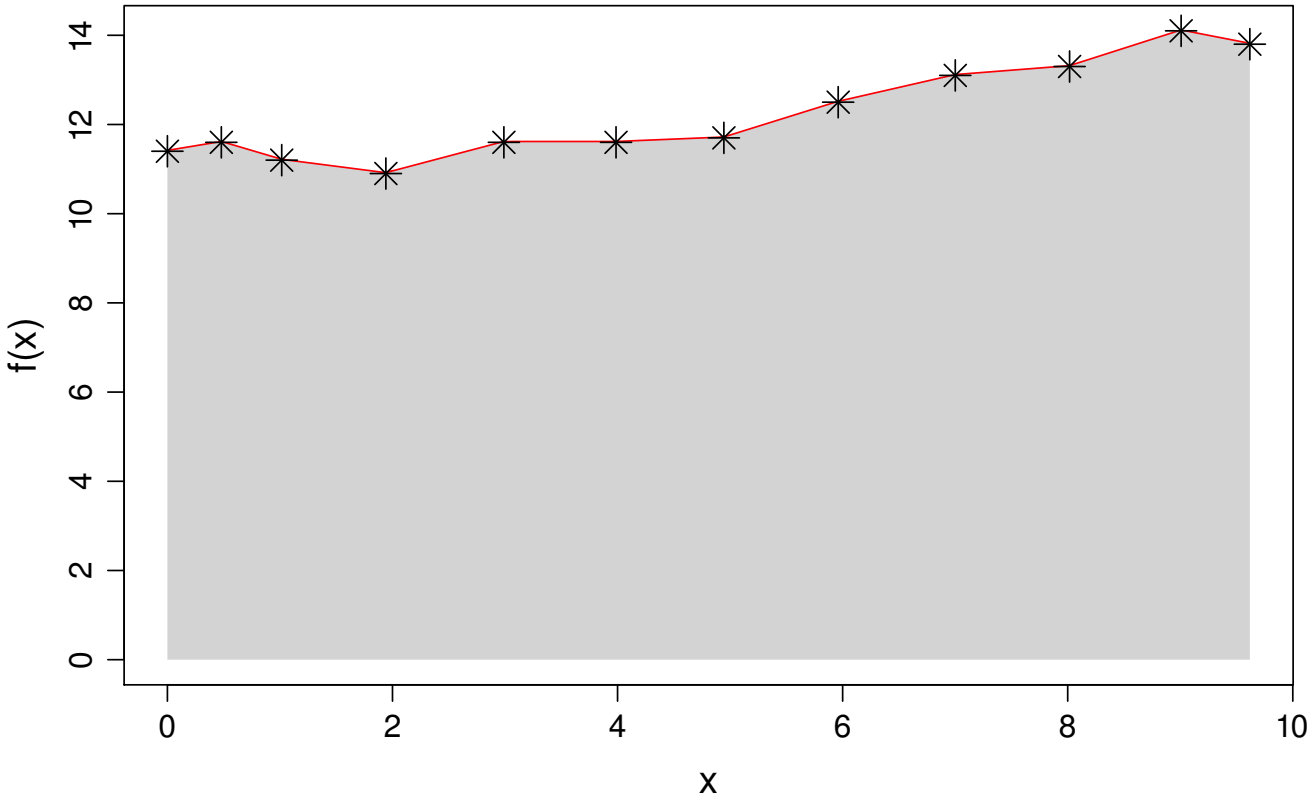
  the covariance matrix of the random effects is assumed to be diagonal

- $\texttt{CumProthr}_{ij}$ denotes the cumulative effect of prothrombin time
  - ▷ for Patient 21 and at two different follow-up times this effect is:

3.8 Time-Varying Covariates* (cont'd)



3.8 Time-Varying Covariates* (cont'd)



3.8 Time-Varying Covariates* (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	0.728	0.361	2.015	0.044
β_1	1.700	0.159	10.686	< 0.001
β_2	1.256	0.210	5.974	< 0.001
β_3	-0.245	0.187	-1.311	0.191
β_4	-0.000	0.006	-0.007	0.995
β_5	0.009	0.004	2.462	0.014

- Log serum bilirubin at time t is strongly related with the cumulative prothrombin time up to the same time point – a unit increase of the cumulative prothrombin time up to follow-up time t increases the expected log serum bilirubin at the same follow-up time by 0.009

3.9 Model Building

- Mixed models consist of two parts, namely
  - ▷ *fixed effects* that describe how specific covariates influence the average longitudinal evolutions
  - ▷ *random effects* that describe how specific regression coefficients deviate from the over all mean described by the fixed effects
    - * the random effects also model the correlations in the repeated measurements

- Interest can either be
  - ▷ on the fixed-effects part alone (e.g., does treatment influence the average evolutions) or
  - ▷ on both parts (e.g., to obtain subject specific predictions)

3.9 Model Building (cont'd)

- The general model building strategy we have seen in the previous chapter for marginal models also applies in the case of mixed models – more specifically:

1. Put all the covariates of interest in the fixed-effects part, considering possible nonlinear terms and/or interactions between them – **do NOT** remove the ones that are not significant

2. Then select an appropriate random-effects structure that adequately describes the correlations in the repeated measurements
   * typically we start from random intercepts and include each time an additional random effect term to see if we improve the fit (i.e., random slopes, quadratic random slopes, etc.)
   * you should be a bit anti-conservative, i.e., do not favor a simpler covariance matrix if the p-value is just non-significant

3.9 Model Building (cont'd)

3. Finally, return to the mean part and exclude non significant covariates
   * first start by testing the nonlinear & interaction terms

3.10 Hypothesis Testing

- Similarly to the marginal models of Chapter 2, in mixed models 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 again split the types of hypothesis tests in two parts:
  - ▷ first, describe how can we choose the appropriate covariance matrix, and
  - ▷ second, focus on hypothesis testing for the mean part of the model

3.10 Hypothesis Testing (cont'd)

- **Hypothesis testing for** $V_i = Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$: Assuming the same mean structure, we can fit a series of mixed models and choose the one that best describes the covariances

- In general, we distinguish between two cases
  - ▷ comparing two mixed models with *nested* covariance matrices
  - ▷ comparing two mixed 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 obtain Model A

3.10 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)

3.10 Hypothesis Testing (cont'd)

Though, there is a **technical** complication when we compare nested mixed models for which one model has more random effects than the other

3.10 Hypothesis Testing (cont'd)

- To illustrate the issue, consider the hypothesis test between the random intercepts and the random intercepts & random slopes models
  - ▷ random intercepts model

$$y_{ij} = X\beta + b_{i0} + \varepsilon_{ij}, \qquad b_{i0} \sim \mathcal{N}(0, \sigma^2_{b_1})$$

  - ▷ random intercepts & random slopes model

$$y_{ij} = X\beta + b_{i0} + b_{i1}t + \varepsilon_{ij}, \qquad b_{i0} \sim \mathcal{N}(0, D)$$

  with

$$D = \begin{bmatrix} \sigma^2_{b_1} & \sigma_{b_{12}} \\ \sigma_{b_{12}} & \sigma^2_{b_2} \end{bmatrix}$$

3.10 Hypothesis Testing (cont'd)

- Hence, the hypotheses to be tested are

$$H_0: \quad \sigma^2_{b_2} = \sigma_{b_{12}} = 0$$

$$H_a: \quad \sigma^2_{b_2} \neq 0 \text{ or } \sigma_{b_{12}} \neq 0$$

- What is the problem? The null hypothesis for $\sigma^2_{b_2}$ is on the boundary of its corresponding parameter space
  - ▷ statistical tests derived from standard ML theory assume the H_0 is an interior point of the parameter space
  - ▷ **the classical asymptotic χ^2 distribution for the likelihood ratio test statistic does not apply**

3.10 Hypothesis Testing (cont'd)

- For simple settings (as the one above), it has been proposed to use a mixture of χ^2 distributions to derive p-values, namely
  - ▷ 50% from the χ^2 distribution with degrees of freedom the number of parameters being tested, and
  - ▷ 50% from the χ^2 distribution with degrees of freedom the number of parameters who are not on the boundary under H_0

- Nonetheless, it has been suggested that this solution does not always work satisfactorily
  - ▷ e.g., see package **RLRsim** in R and the references therein

3.10 Hypothesis Testing (cont'd)

- Example: In the AIDS dataset we compare two mixed models with linear and quadratic slopes in the fixed effects, and in the random effects
  - ▷ M_1 : random intercepts & linear random slopes
  - ▷ M_2 : random intercepts, linear random slopes & quadratic random slopes

- Hence, the covariance matrices of the random effects under the two models are

$$M_1 : D = \begin{bmatrix} \sigma^2_{b_1} & \sigma_{b_{12}} \\ \sigma_{b_{12}} & \sigma^2_{b_2} \end{bmatrix} \quad \text{and} \quad M_2 : D = \begin{bmatrix} \sigma^2_{b_1} & \sigma_{b_{12}} & \sigma_{b_{13}} \\ \sigma_{b_{12}} & \sigma^2_{b_2} & \sigma_{b_{23}} \\ \sigma_{b_{13}} & \sigma_{b_{23}} & \sigma^2_{b_3} \end{bmatrix}$$

3.10 Hypothesis Testing (cont'd)

- And, the hypotheses being tested are

$$H_0: \quad \sigma^2_{b_3} = \sigma_{b_{13}} = \sigma_{b_{23}} = 0$$

$$H_a: \quad \text{at least one different from zero}$$

- The likelihood ratio test gives:

	df	logLik	LRT	p-value	Mixture p-value
M_1	9	-3573.88			
M_2	12	-3570.71	6.34	0.0960	0.0690

3.10 Hypothesis Testing (cont'd)

- About the two p-values
  - ▷ The first p-value is based on the classic χ^2 distribution with degrees of freedom the number of parameters being tested, i.e., in this case 3
  - ▷ The second p-value is based on the mixture of χ^2 distributions with 3 degrees of freedom (i.e., the classic one) and 2 degrees of freedom (the number of parameters not on the boundary under H_0), respectively
- We observe that the classic p-value is more conservative
  - ▷ as we have seen in the previous section (see pp.207), when choosing the appropriate random effects we should be more liberal, and hence the mixture of χ^2 distribution is to be preferred

3.10 Hypothesis Testing (cont'd)

- When we have **non-nested** models we **cannot** use standard tests anymore
  - ▷ the alternative in this case is to use the information criteria AIC or BIC

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

3.10 Hypothesis Testing (cont'd)

- Example: In the PBC dataset we want to compare two mixed models with a spline effect of time and its interaction with sex in the fixed effects, and in the random effects
  - ▷ M_1 : random intercepts & linear random slopes, with an unstructured matrix for these random effects
  - ▷ M_2 : random intercepts, & nonlinear random slopes with splines, with a diagonal matrix for these random effects

  In the fixed-effects part and in the random-effects part of model M_2 : the splines are natural cubic splines with 2 internal knots

- These models are not nested and hence to compare them we use the AIC and BIC values

3.10 Hypothesis Testing (cont'd)

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

	df	logLik	AIC	BIC
M_1	10	-1522.38	3064.75	3120.45
M_2	10	-1438.53	2897.06	2952.76

  - ▷ Both AIC and BIC suggest that the model with the nonlinear random slopes is better than the model with the linear random slopes

3.10 Hypothesis Testing (cont'd)

- Notes: Hypothesis testing for the covariance matrix V_i

  ▷ The aforementioned procedures assume that the fixed-effects structure of the mixed models to be compared are the same

    * under this assumption we can compare mixed models fitted with the restricted maximum likelihood (REML) method
    * otherwise the models should be fitted with maximum likelihood (ML)

  ▷ 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

3.10 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 standard tests can be used

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

3.10 Hypothesis Testing (cont'd)

- Everything works in the same manner as we have seen for marginal models in Chapter 2 (see pp.99–102)
  - ▷ hence, we are not going to repeat the details here

- Example: We have fitted the following model to the Prothro dataset:

3.10 Hypothesis Testing (cont'd)

$$\begin{cases} \begin{aligned} \texttt{pro}_{ij} \;=\; & (\beta_0 + b_{i0}) + (\beta_1 + b_{i1}) N(\texttt{Time}_{ij})_1 + (\beta_2 + b_{i2}) N(\texttt{Time}_{ij})_2 + \\ & (\beta_3 + b_{i3}) N(\texttt{Time}_{ij})_3 + \beta_4 \texttt{predn}_i + \\ & \beta_5 \{\texttt{predn}_i \times N(\texttt{Time}_{ij})_1\} + \beta_6 \{\texttt{predn}_i \times N(\texttt{Time}_{ij})_2\} + \\ & \beta_7 \{\texttt{predn}_i \times N(\texttt{Time}_{ij})_3\} + \varepsilon_{ij} \end{aligned} \\ \\ b_i \sim \mathcal{N}(0, D) \qquad D \text{ is a diagonal matrix,} \qquad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

▷ The terms $N(\texttt{Time}_{ij})_1$, $N(\texttt{Time}_{ij})_2$ and $N(\texttt{Time}_{ij})_3$ denote the basis for a natural cubic spline with three degrees of freedom to model possible nonlinearities in the time effect

3.10 Hypothesis Testing (cont'd)

- We are interested in
  - ▷ the main of treatment,
  - ▷ the overall effect time, and
  - ▷ the overall effect of treatment (i.e., main effect + interactions)

- Under the postulated model the main effect of treatment is given by parameter β_4, i.e.,

$$\begin{aligned} H_0: &\quad \beta_4 = 0 \\ H_a: &\quad \beta_4 \neq 0 \end{aligned}$$

- The output of the model gives: ...

3.10 Hypothesis Testing (cont'd)

	Value	Std.Err.	t-value	p-value
β_0	72.357	1.435	50.423	< 0.001
β_1	-12.131	3.953	-3.069	0.002
β_2	31.954	3.445	9.274	< 0.001
β_3	34.015	4.706	7.228	< 0.001
β_4	-4.154	2.057	-2.019	0.044
β_5	14.621	5.679	2.575	0.010
β_6	-7.809	5.040	-1.549	0.121
β_7	-3.253	7.177	-0.453	0.650

3.10 Hypothesis Testing (cont'd)

- Hence, a significant treatment effect at baseline (strange!)
  - ▷ the t-value in the output is the estimated coefficient divided by its standard error

- For the overall effect of time, we are interested in the hypothesis:

$$\begin{aligned} H_0: &\quad \beta_1 = \beta_2 = \beta_3 = \beta_5 = \beta_6 = \beta_7 = 0 \\ H_a: &\quad \text{at least on coefficient different from 0} \end{aligned}$$

- To test this hypothesis we can use an F-test but appropriately constructing the contrasts matrix

3.10 Hypothesis Testing (cont'd)

- We obtain

F-value	df_1	df_2	p-value
23.555	6	1939	< 0.0001

  - ▷ Hence, a significant overall time effect

3.10 Hypothesis Testing (cont'd)

- For the all treatment effect, we obtain the hypothesis:

$$H_0: \quad \beta_4 = \beta_5 = \beta_6 = \beta_7 = 0$$
$$H_a: \quad \text{at least on coefficient different from 0}$$

- This cannot be tested with an F-test because of a technical reasons
  - ▷ the denominator degrees of freedom are not the same for the main effect and the terms involving time

- As an alternative we can use the likelihood ratio test
  - ▷ i.e., we compare the model we fitted with the model that only has the nonlinear effect of time in the fixed effects

3.10 Hypothesis Testing (cont'd)

- The likelihood ratio test gives

	df	logLik	AIC	BIC	LRT	p-value
without Treatment	9	−13240.53	26499.06	26553.02		
with Treatment	13	−13229.80	26485.59	26563.53	21.47	0.0003

  - ▷ Hence, we obtain a significant overall treatment effect

3.11 Residuals

- As we have similarly done for marginal models in Chapter 2, before extracting conclusions from mixed models, we will first need to validate the underlying assumptions they make

- To do this we can use the residuals of the model

- In the setting of mixed models we have two types of residuals
  - ▷ *Marginal residuals:* These are based on the implied marginal model behind a linear mixed model (see pp.151)
  - ▷ *Conditional residuals:* These are based on the hierarchical representation of the mixed model and utilize the empirical Bayes estimates of the random effects (see pp.165)

3.11 Residuals (cont'd)

- The exact definitions are as follows:
  - ▷ *Marginal residuals:*

$$\begin{cases} y_i & = X_i\beta + \varepsilon_i^*, \quad \varepsilon_i^* \sim \mathcal{N}(0, Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}) \\ r_i^{marg} & = y_i - X_i\widehat{\beta} \end{cases}$$

  - ▷ These residuals predict the marginal errors ε_i^*
  - ▷ They can be used to
    - * investigate misspecification of the mean structure $X_i\beta$
    - * validate the assumptions for the within-subjects covariance structure $Z_i D Z_i^\top + \sigma^2 \mathsf{I}_{n_i}$

3.11 Residuals (cont'd)

▷ *Conditional residuals*

$$\begin{cases} y_i = X_i\beta + Z_i b_i + \varepsilon_i, \quad b_i \sim \mathcal{N}(0, D), \quad \varepsilon_i \sim \mathcal{N}(0, \sigma^2 \mathsf{I}_{n_i}) \\ \\ r_i^{cond} = y_i - X_i\widehat{\beta} - Z_i\widehat{b}_i \end{cases}$$

▷ These residuals predict the conditional errors ε_i

▷ They can be used to

* investigate misspecification of the hierarchical mean structure $X_i\beta + Z_i b_i$
* validate the assumptions for the within-subjects variance structure σ^2

3.11 Residuals (cont'd)

- Example: We evaluate the assumptions behind the following model fitted to the Prothro dataset:

$$\begin{cases} \texttt{pro}_{ij} = (\beta_0 + b_{i0}) + (\beta_1 + b_{i1})N(\texttt{Time}_{ij})_1 + (\beta_2 + b_{i2})N(\texttt{Time}_{ij})_2 + \\ \quad (\beta_3 + b_{i3})N(\texttt{Time}_{ij})_3 + \beta_4\texttt{predn}_i + \beta_5\{\texttt{predn}_i \times N(\texttt{Time}_{ij})_1\} + \\ \quad \beta_6\{\texttt{predn}_i \times N(\texttt{Time}_{ij})_2\} + \beta_7\{\texttt{predn}_i \times N(\texttt{Time}_{ij})_3\} + \varepsilon_{ij}, \\ \\ b_i \sim \mathcal{N}(0, \text{diag}\{D\}), \quad \varepsilon_{ij} \sim \mathcal{N}(0, \sigma^2) \end{cases}$$

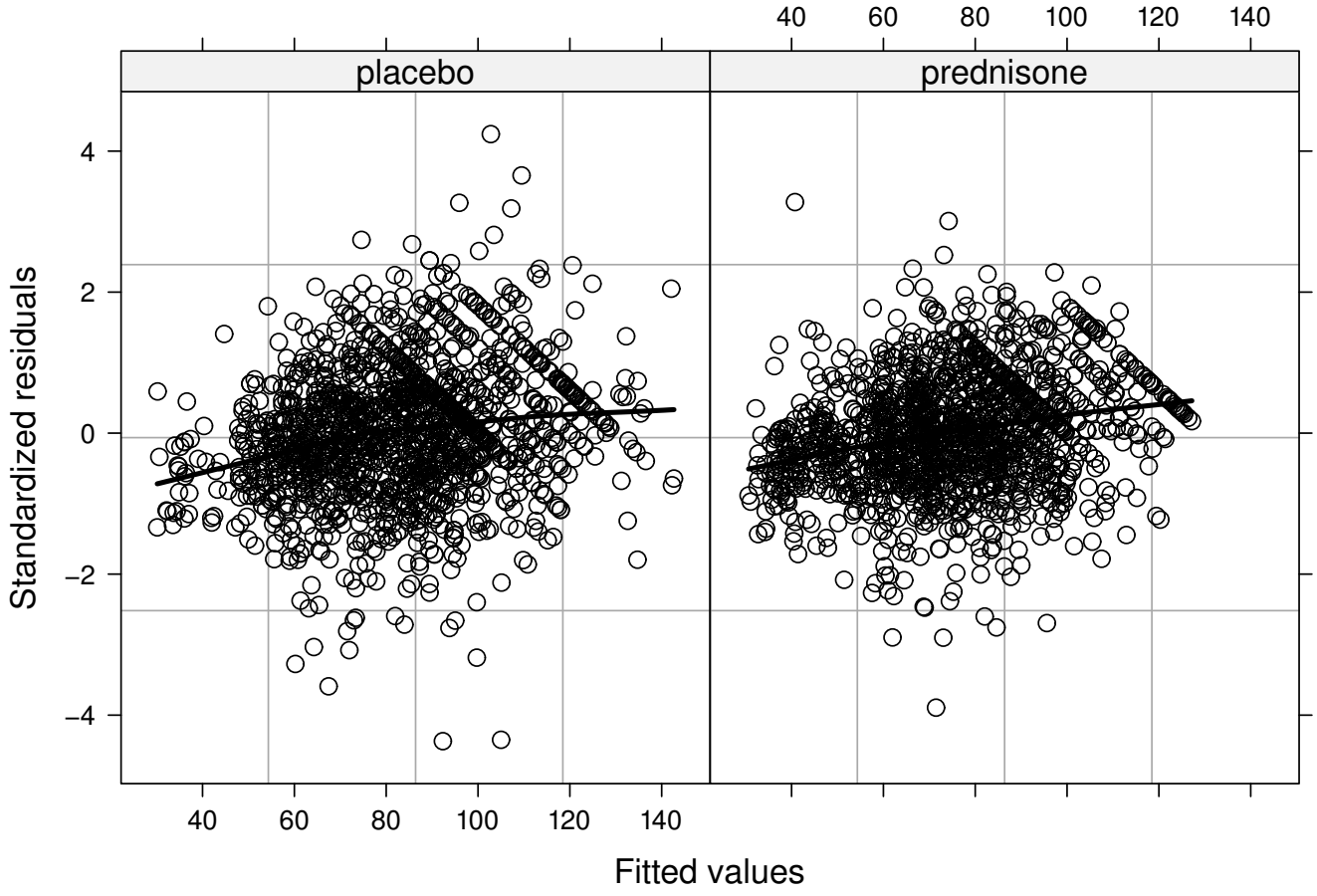
$N(\cdot)$ denotes a natural cubic spline basis

3.11 Residuals (cont'd)

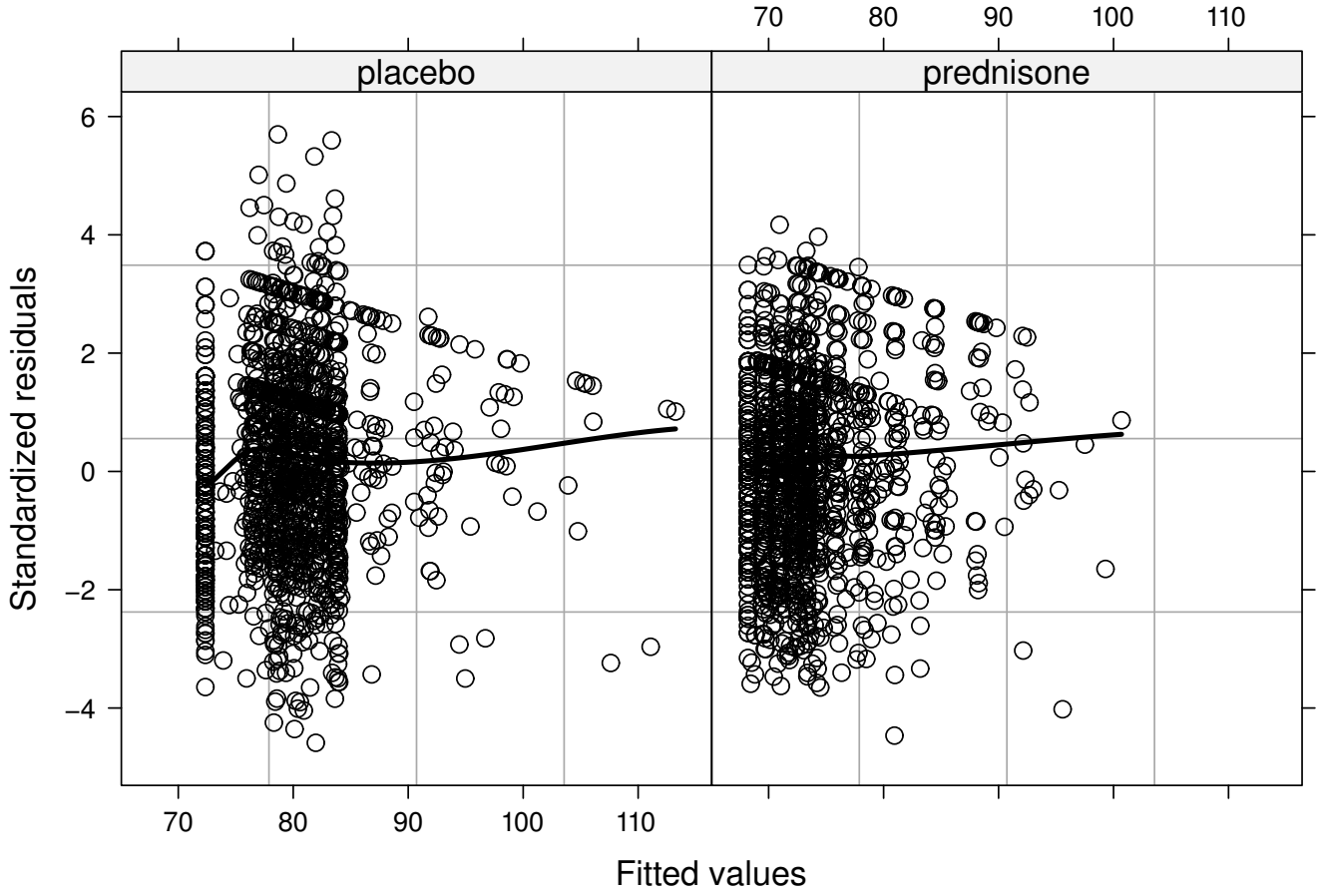
by plotting

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

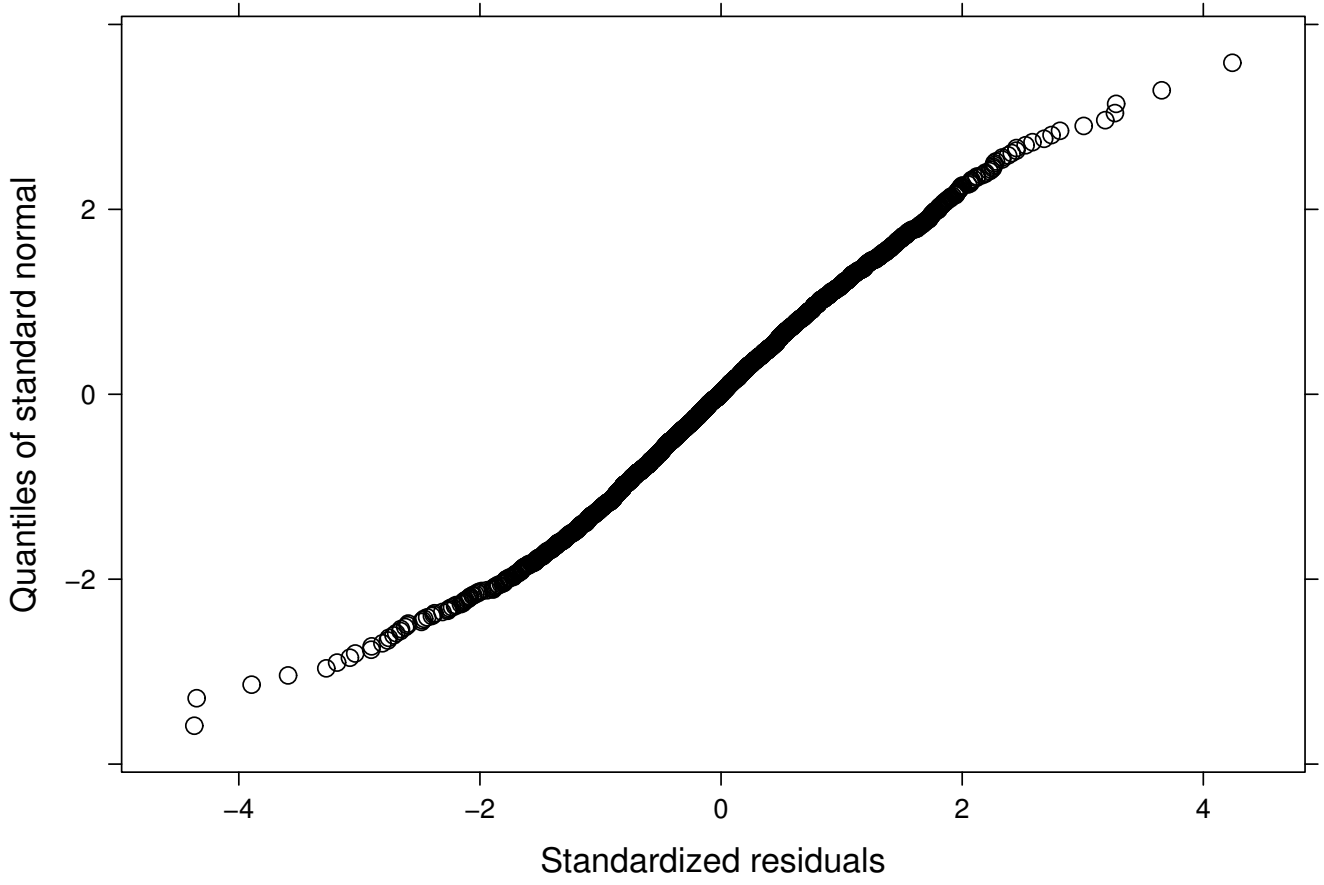
3.11 Residuals (cont'd)



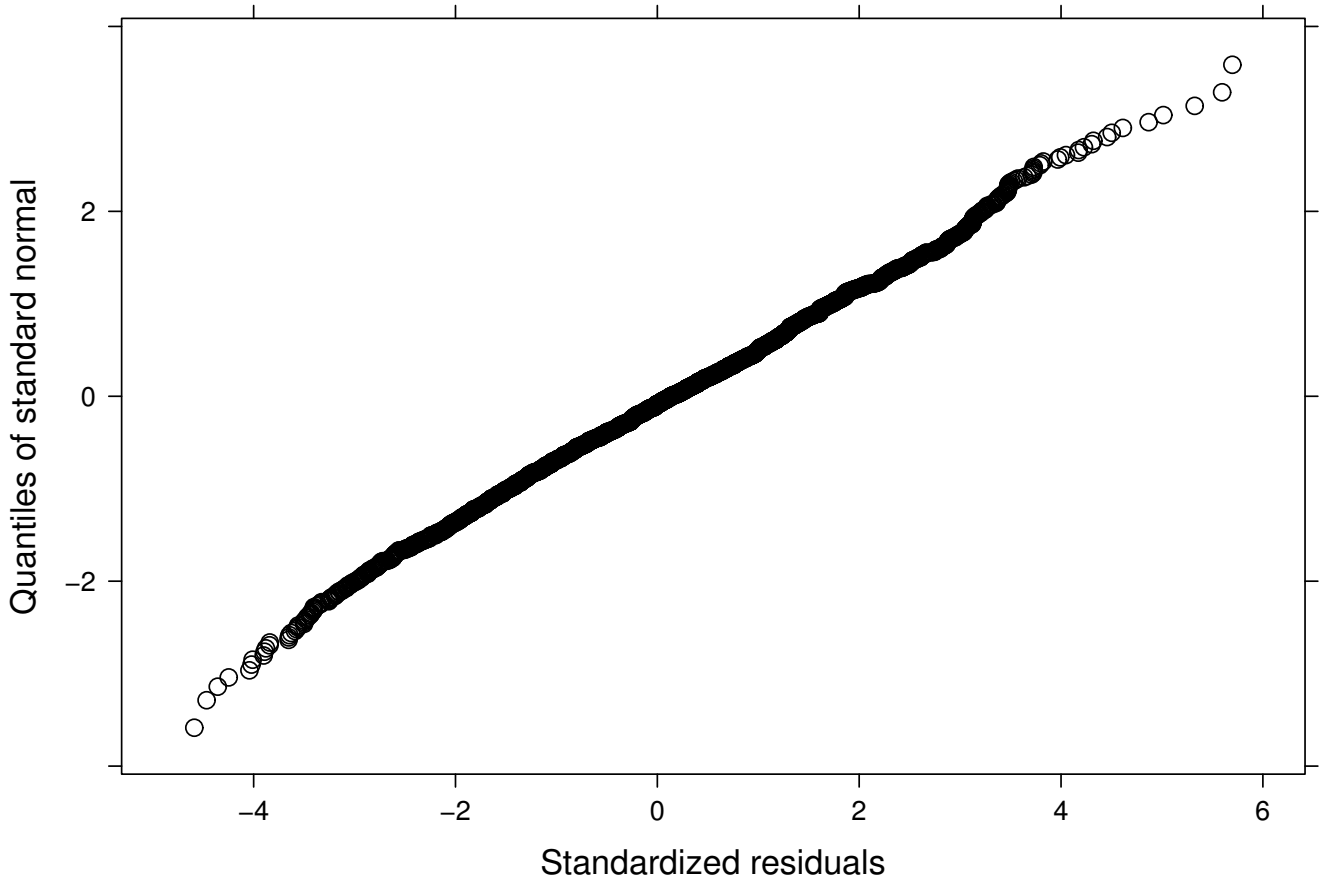
3.11 Residuals (cont'd)



3.11 Residuals (cont'd)



3.11 Residuals (cont'd)



3.11 Residuals (cont'd)

- Observations
  - ▷ the plots of the residuals versus the fitted values do show a slightly systematic behavior
  - ▷ the QQ-plots do not show big discrepancies from normality

3.12 Review of Key Points

- Mixed effects models constitute an alternative modeling framework for analyzing grouped/cluster data
  - ▷ basic idea: sample units in the same group/cluster share the same random effects
  - ▷ the random effects are *unobserved* variables that induce correlation

- From a practical viewpoint mixed models provide a more flexible manner to model correlations when
  - ▷ we have unbalanced data and/or
  - ▷ the correlation structure has a complicated form (e.g., multilevel designs)

3.12 Review of Key Points (cont'd)

- The random effects can be estimated using empirical Bayes methodology
  - ▷ mixed models provide subject-specific predictions that are more accurate than marginal predictions

- Mixed models can be extended to include correlated error terms
  - ▷ this is in the same spirit as the marginal models of Chapter 2
  - ▷ however, this extension often makes the model computationally unstable

3.12 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
  - ▷ marginal and conditional residuals available