

Practicals

Practical 1: Marginal Models Continuous

- We will use the PBC dataset; this is available as the object `pb2` in the R workspace available on GitHub
- To load this workspace and make the data available execute the following steps:
 1. Open a new Rstudio session
 2. Create a new R script file (File → New File → R Script)
 3. Copy-paste and execute the following three lines

```
con <- url("https://raw.githubusercontent.com/drizopoulos/Repeated_Measurements/master/Data.RData")  
load(con)  
close(con)
```

Practical 1: Marginal Models Continuous (cont'd)

- The data are available in the data frame `pbc2` – we will need the following variables
 - * `id`: patient id number
 - * `prothrombin`: prothrombin time in sec (the response variable of interest)
 - * `year`: follow-up times in years
 - * `drug`: the randomized treatment
 - * `sex`: the gender of the patients
 - * `age`: the age of the patients

Aim: To build an appropriate marginal model to investigate the relationships between the prothrombin time and the aforementioned variables

Practical 1: Marginal Models Continuous (cont'd)

- **Q1:** We will start by producing some descriptive plots for the prothrombin time, similar to those we have seen in Chapter 1, i.e.,
 - ▷ spaghetti plot per treatment group including the loess curve
 - ▷ spaghetti plot per sex including the loess curve

(hint: see code for Section 1.1)

What observations can you make?

Practical 1: Marginal Models Continuous (cont'd)

- We will continue by starting our model building exercise

Remember

- ▷ we start with a full specification of the mean structure, and investigate the covariance structure
 - ▷ based on our chosen covariance structure we can make inferences for the mean structure
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- Q2: Start by fitting a marginal model with independent error terms using `gls()` and the following specification of the mean structure (hint: see code for Section 2.4)
 - ▷ nonlinear time evolutions using natural cubic splines with 3 degrees of freedom
 - ▷ correct for `sex`, `drug` and `age`
 - ▷ interactions of the time effect with `sex` and `drug`

Practical 1: Marginal Models Continuous (cont'd)

- Q2:
 - ▷ interpret the results you obtained
 - ▷ should we simplify the model by excluding the non-significant terms?
- Q3: Continue with the same mean structure and try different covariance structures
 - ▷ first try different correlation structures, i.e., compound symmetry, continuous AR1, linear & Gaussian, and
 - ▷ then extend the above structures by assuming heteroscedastic errors, i.e., that the variance increases (or decreases) with time

(hint: see code for Section 2.9)

Practical 1: Marginal Models Continuous (cont'd)

- **Q4:** Using appropriate tools (hypothesis tests, information criteria) decide which structure is the best
 - ▷ which models are nested to which models?
- For the remainder we will use the covariance structure you have chosen in Q4
- **Q5:** Check if we can drop **all** the interaction terms
 - ▷ with an F-test
 - ▷ with a Likelihood Ratio Test

(hint: see code for Section 2.9)

Practical 1: Marginal Models Continuous (cont'd)

- **Q6:** Continue and check whether you can drop the nonlinear terms for the time effect
 - ▷ to do that fit a model that assumes a linear time trend, and
 - ▷ then do the likelihood ratio test to compare it to the model that includes the nonlinear terms
- **Q7:** Interpret the results of your final model
 - ▷ regression coefficients
 - ▷ covariance structure

Practical 1: Marginal Models Continuous (cont'd)

- **Q8:** Use an Effect Plot to depict the model with the following settings
 - ▷ **year**: in the range from 0 to 12 years of follow-up
 - ▷ **sex**: both males and females
 - ▷ **drug**: both treatment groups
 - ▷ **age**: fixed at 49 years old

(hint: see code for Section 2.4 – Effect Plot)

Practical 1: Marginal Models Continuous (cont'd)

- **Q9:** Check the assumptions of the model using scatterplots of the standardized & normalized residuals versus the fitted values,
 - ▷ overall
 - ▷ separately per sex
 - ▷ separately per treatment group

(hint: see code for Section 2.11)

What are your conclusions?

Practical 2: Mixed Models Continuous

- We will use the PBC dataset; this is available as the object `pb2` in the R workspace available on GitHub
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load(con)  
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Practical 2: Mixed Models Continuous (cont'd)

- The data are available in the data frame `pbc2` – we will need the following variables
 - * `id`: patient id number
 - * `prothrombin`: prothrombin time in sec (the response variable of interest)
 - * `year`: follow-up times in years
 - * `drug`: the randomized treatment
 - * `sex`: the gender of the patients
 - * `age`: the age of the patients

Aim: To build an appropriate linear mixed effects model to investigate the relationships between the prothrombin time and the aforementioned variables

Practical 2: Mixed Models Continuous (cont'd)

- **Q1:** Examine graphically for samples of patients
(hint: see code for Section 1.1)
 - ▷ How do the individual longitudinal trajectories of the prothrombin time look like?
 - ▷ What observations can you make?
- **Q2:** ***

Practical 2: Mixed Models Continuous (cont'd)

- **Q3:** Start by fitting a linear mixed effects model using `lme()` with the following specification of the mean fixed and random effects
(hint: see code for Section 3.2)
 - ▷ *fixed effects*:
 - * linear time evolutions, nonlinear effect of age using natural cubic splines with 2 degrees of freedom
 - * correct for `sex` and `drug`
 - * interactions of time with `sex` and `drug`, and `age` with `sex` and `drug`
 - ▷ *random effects*: random intercepts

Note: As in Practical 1, in the analysis requested above, and for the remainder of this practical exclude the prothrombin times that were above 18 sec.

Practical 2: Mixed Models Continuous (cont'd)

- **Q4:** Keeping the mean structure (i.e., the fixed effects as is), start elaborating the random-effects structure that captures the within subject correlation, i.e., consider
 - ▷ random intercepts & random slopes
 - ▷ random intercepts, linear & quadratic random slopes
 - ▷ random intercepts, linear, quadratic & cubic random slopes

For each extra random effect that you add, perform the likelihood ratio test to see if it is required to add it

- ▷ which are the null and alternative hypotheses for each of these tests?

Practical 2: Mixed Models Continuous (cont'd)

- Q5: ***

Practical 3: Marginal Models Discrete

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Practical 3: Marginal Models Discrete (cont'd)

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Practical 4: Mixed Models Discrete

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Practical 4: Mixed Models Discrete (cont'd)

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