

# Practicals

# Practical 1: Marginal Models Continuous

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- 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)

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- 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)

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- **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)

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- 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)

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- 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)

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- 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)

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- **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)

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- **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)

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- **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

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- 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 2: Mixed Models Continuous (cont'd)

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- 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)

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- **Q1:** Compute summary statistics for the number of repeated measurements per patient
  - ▷ do we have enough information to model potential nonlinearities in the subject-specific trajectories?
- **Q2:** 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?

## Practical 2: Mixed Models Continuous (cont'd)

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- **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 & quadratic time evolutions, nonlinear effect of age using natural cubic splines with 3 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)

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- **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)

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- **Q5:** Based on the model you selected Question 4, test whether you can drop all the *interaction terms* in order to simplify the model
  - ▷ first perform the omnibus test for all the interaction terms
  - ▷ if it is (highly) non-significant, you can drop them
  - ▷ if it is significant, find which group(s) are the significant ones
- **Q6:** In the same spirit as in Question 5, test whether you can drop all the *nonlinear terms* to simplify the model
  - ▷ first perform the omnibus test for all the nonlinear terms
  - ▷ if it is (highly) non-significant, you can drop them
  - ▷ if it is significant, find which group(s) are the significant ones



## Practical 2: Mixed Models Continuous (cont'd)

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- **Q7:** Interpret the results of your final model
  - ▷ regression coefficients
  - ▷ covariance structure
  
- **Q8:** Compare the marginal and subject-specific predictions from your final model, i.e.,
  - ▷ add in you data frame the marginal and subject-specific fitted values from the final model (remember to use the dataset that excludes the outliers)
  - ▷ select the following patients from the data set: 133, 36, 180, 11, 168, 116, 70, 58, 82, 104, 43, 21, 101, 210, 176, 157
  - ▷ create the plot that compares the predictions

(hint: see code for Section 3.4)

## Practical 2: Mixed Models Continuous (cont'd)

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- **Q9:** 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**: the median age from the original data for the respective four groups of patients (i.e., the median age of male in placebo, females in placebo, males in active treatment & females in active treatment)

(hint: see code for Section 3.2 – Effect Plot)

## Practical 2: Mixed Models Continuous (cont'd)

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- **Q10:** Check the assumptions of the model using scatterplots of the standardized subject-specific & standardized marginals residuals versus the fitted values,
  - ▷ overall
  - ▷ separately per sex
  - ▷ separately per treatment group

(hint: see code for Section 3.11)

What are your conclusions?

# 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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