

# 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 and packages 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 lines

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

library("lattice")
library("nlme")
library("splines")
```

# Practical 1: Marginal Models Continuous (cont'd)

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- 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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- **Remove outliers:** From the plots you produced in Question 1 it was evident that we have some outlying observations
  - ▷ for the rest of this practical we will exclude prothrombin times which were larger than 18 sec – to do that use the following piece of code:

```
pbc2 <- pbc2[pbc2$prothrombin < 18, ]
```

# 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
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  3. Copy-paste and execute the following lines

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

library("lattice")
library("nlme")
library("splines")
```

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

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- 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 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 correlations, 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 marginal 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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- We will use the PBC dataset; this is available as the object `pb2` in the R workspace available on GitHub
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  3. Copy-paste and execute the following lines

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

```
library("lattice")  
library("geepack")  
library("splines")
```

## Practical 3: Marginal Models Discrete (cont'd)

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- 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 GEE model to investigate the relationships between a dichotomized version of the prothrombin time and the aforementioned variables

## Practical 3: Marginal Models Discrete (cont'd)

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- **Q1:** A normal prothrombin time is between 11 and 13 sec
  - ▷ create a dichotomous variable, with '0' denoting a normal prothrombin time, and '1' an abnormal one
- **Q2:** Examine graphically the probability of abnormal prothrombin time  
(hint: see code for Section 1.1)
  - ▷ separately per treatment including the loess curve
  - ▷ separately per sex including the loess curve
  - ▷ separately for each age category [25, 43], [43, 50], [50, 55] and [55, 80] including the loess curve
  - ▷ what observations can you make?

## Practical 3: Marginal Models Discrete (cont'd)

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- **Q3:** The researchers in this study made the following conjectures
  - ▷ the log odds of abnormal prothrombin time may evolve nonlinearly during follow-up;
  - ▷ in addition, it is plausible that the log odds evolutions in time are different between males and females, and between placebo and treated patients;
  - ▷ furthermore, age is an important risk factor, and the effect of age may be modified by sex

Translate the above conjectures into a suitable GEE model for the log odds of abnormal prothrombin time

- ▷ use the exchangeable working correlation matrix, and
- ▷ for the nonlinear terms use natural cubic splines with 2 degrees of freedom

(hint: see code for Section 4.3)



## Practical 3: Marginal Models Discrete (cont'd)

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- Q4: Re-fit the model you fitted in Question 3 by assuming
  - ▷ an independence working correlation matrix, and
  - ▷ an AR1 working correlation matrix
  
- ▷ Compare the estimated coefficients and the corresponding naive and sandwich standard errors using a coefficients' plot  
(hint: see code for Section 4.5)
  
- ▷ Which working correlation matrix do you choose and why?

## Practical 3: Marginal Models Discrete (cont'd)

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- Q5: The researchers in the study want to see if the model can be simplified by dropping the *interaction terms*
  - ▷ 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: Do the same for the *nonlinear terms*, i.e.,
  - ▷ 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 3: Marginal Models Discrete (cont'd)

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- Q7: Interpret the results of your final model
- 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**: 49 years old

(hint: see code for Section 4.3 – Effect Plot)

Do the plot in both the log odds and probability scales

## Practical 3: Marginal Models Discrete (cont'd)

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- **Q9:** From the effect plot we observe that the trajectories of the log odds for males and females in the D-penicillamine group are nonlinear (more so for the females)
  - ▷ test in males and females separately
  - ▷ with age 49 years old
  - ▷ whether there are differences in the log odds of abnormal prothrombin time
  - ▷ at the follow-up years 2, 6, 8 and 10
  - ▷ in other words, perform all the pairwise comparisons for the aforementioned follow-up times
  - ▷ should you adjust for multiple comparisons?

(hint: see code for Section 4.6 – complex effects)

# Practical 4: Mixed Models Discrete

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  2. Create a new R script file (File → New File → R Script)
  3. Copy-paste and execute the following lines

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

```
library("lattice"); library("splines")  
library("lme4"); library("MASS")
```

## Practical 4: Mixed Models Discrete (cont'd)

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- 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 GLMM to investigate the relationships between a dichotomized version of the prothrombin time and the aforementioned variables

## Practical 4: Mixed Models Discrete (cont'd)

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- **Q1:** A normal prothrombin time is between 11 and 13 sec
  - ▷ create a dichotomous variable, with '0' denoting a normal prothrombin time, and '1' an abnormal one
- **Q2:** Examine graphically the probability of abnormal prothrombin time for each patient  
(hint: see code for Section 1.1)
  - ▷ create the subject-specific smooth trajectories of abnormal prothrombin time *for patients who had more than five measurements*
  - ▷ use as a smoother the "splines" option in the 'type' argument of `xyplot()`
  - ▷ what observations can you make?

## Practical 4: Mixed Models Discrete (cont'd)

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- **Q3:** The researchers in this study made the following conjectures
  - ▷ the subject-specific log odds of abnormal prothrombin time evolve linearly during follow-up;
  - ▷ in addition, it is plausible that the subject-specific log odds evolutions in time are different between males and females;
  - ▷ furthermore, drug is expected to affect prothrombin time, and its effect may be modified by sex

Translate the above conjectures into a suitable GLMM for the log odds of abnormal prothrombin time using random intercepts, and 15 quadrature points for the adaptive Gauss-Hermite rule

(hint: see code for Section 5.2)



## Practical 4: Mixed Models Discrete (cont'd)

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- Q4: Test whether it is required to also include a random slopes component using a likelihood ratio test
  - ▷ depending on the result keep the model that best fits the data
- Q5: Continue by testing whether you can drop all interaction terms from the model using a likelihood ratio test
- Q6: Interpret the parameters in your final selected model

## Practical 4: Mixed Models Discrete (cont'd)

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- **Q7:** Use an Effect Plot to depict the marginal log odds ratios for the following settings
  - ▷ **year**: in the range from 0 to 12 years of follow-up
  - ▷ **sex**: both males and females
  - ▷ **drug**: both treatment groups

(hint: see code for Section 5.2 – Effect Plot)
- **Q8:** Create a second effect plot with the same settings as in Question 7 but for the marginal probabilities
  - ▷ also include the probabilities of the median subject