Statistical Analysis of Repeated Measurements Data

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April 18 – 22, 2016

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What is this Course About



Grouped data arise in wide range of disciplines

- Typical examples of grouped data
 - > repeated measurements: measuring the same outcome multiple times on the same sample unit (e.g., biomarkers in patients)

What is this Course About (cont'd)



- Statistical analysis of grouped data
 - > Features of grouped data
 - ▷ describe their distribution

Learning Objectives



- Goals: After this course participants will be able to
 - □ identify settings in which family of repeated measurements model is required,
 - > construct and fit an appropriate model to the data at hand, and
 - > correctly interpret the obtained results
- Even though the course will be primarily explanatory
 - ▷ emphasis is given on sufficient detail in order for participants to obtain a clear view on the different modeling approaches, and how they should be used in practice

Agenda



• Chapter 1: Motivating Data Sets

- Data sets that we will use throughout the course
- □ General repeated measurements settings

• Chapter 2: Marginal Models for Continuous Data

- \triangleright Features of repeated measurements data
- Naive approaches

Agenda (cont'd)



- Chapter 3: The Linear Mixed Effects Model
 - > Intuition behind mixed models
 - □ nested and cross random effects
- Chapter 4: Marginal Models for Discrete Data

Agenda (cont'd)



- Chapter 5: Mixed Models for Discrete Data
 - □ Generalized linear mixed effects models
 - □ approximations of the integrand & integral
 - > interpretation of parameters
- Chapter 6: Statistical Analysis with Incomplete Grouped Data
 - > Problems with incomplete data

 - > Valid inferential approaches

Structure of the Course & Material



• Lectures & software practicals using R

- Material:

 - R code in soft format

• Within the course notes there are several examples of R and SPSS syntax – these are denoted by the symbols 'R> ' and 'SPSS> ', respectively

Software Requirements



• The up-to-date version of R and Rstudio; downloadable from

```
> http://cran.r-project.org/
> http://www.rstudio.com/
```

- Additional required packages
 - ⊳ Ime4, MCMCgImm, geepack,
 - > shiny, curl, corrplot

Software Requirements



 Up-to-date versions of these packages and their dependencies can be installed using the command

- Up-to-date version of a modern web browser, e.g.,

 - □ Google Chrome (http://www.google.com/chrome/)

Software Requirements



- A shiny web app that replicates all analyses in the course including also some additional illustrations
- The app is available on GitHub and can be invoked using the following two-step procedure (assuming internet connection is available)
 - 1. Start R
 - 2. Run the command

```
shiny::runGitHub("Courses", "drizopoulos",
    ref = "Repeated_Measurements")
```

this will open a new web browser window (or tab) with the app

• Note: in order the app to be functional you should **not** close R

References



- Some texts in longitudinal data analysis
 - Demidenko, E. (2004). *Mixed Models: Theory and Applications*. New York: John Wiley & Sons.
 - Diggle, P., Heagerty, P., Liang, K.-Y., and Zeger, S. (2002). *Analysis of Longitudinal Data*, 2nd edition. New York: Oxford University Press.
 - □ Galecki, A. and Burzykowski, T. (2013). Linear Mixed-Effects Models Using R.
 New York: Springer-Verlag.
 - ▶ Molenberghs, G. and Verbeke, G. (2005). Models for Discrete Longitudinal Data.
 New York: Springer-Verlag.
 - ▶ Fitzmaurice, G., Laird, N., and Ware, J. (2011). Applied Longitudinal Analysis, 2nd Ed. Hoboken: John Wiley & Sons.
 - ▶ Hand, D. and Crowder, M. (1995). Practical Longitudinal Data Analysis. London: Chapman & Hall.

References (cont'd)



- Some texts in longitudinal data analysis

 - Description Lindsey, J. (1993). *Models for Repeated Measurements*. Oxford: Oxford University Press.
 - \triangleright Pinheiro, J. and Bates, D. (2000). *Mixed Effects Models in S and S-plus*. New York: Springer-Verlag.
 - Verbeke, G. and Molenberghs, G. (2000). Linear Mixed Models for Longitudinal Data. New York: Springer-Verlag.