Statistical Analysis of Repeated Measurements Data

Dimitris Rizopoulos

Department of Biostatistics, Erasmus University Medical Center

d.rizopoulos@erasmusmc.nl

April 18 – 22, 2016

Contents

| 1 | Motivating Data Sets | 1 |
|---|-------------------------------------|----|
| | 1.1 Motivating Longitudinal Studies | 2 |
| | 1.2 Features of Longitudinal Data | 14 |
| | 1.3 Review of Key Points | 26 |
| | | |
| 2 | Marginal Models for Continuous Data | 27 |
| | 2.1 Simple Methods | 28 |
| | 2.2 Review of Linear Regression | 37 |
| | 2.3 Marginal Models | 46 |

| 2.4 | Interpretation |
|------|--|
| 2.5 | Estimation |
| 2.6 | Fitting Marginal Models in R $$ |
| 2.7 | Covariance Matrix |
| 2.8 | Model Building |
| 2.9 | Hypothesis Testing |
| 2.10 | Confidence Intervals |
| 2.11 | Design Considerations - Sample Size |
| 2.12 | Residuals |
| 2.13 | Review of Key Points \ldots |

| 3 | The Linear Mixed Effects Model | 136 |
|---|---|-------|
| | 3.1 The Linear Mixed Model | . 137 |
| | 3.2 Interpretation | . 143 |
| | 3.3 Hierarchical vs Marginal | . 151 |
| | 3.4 Estimation | . 161 |
| | 3.5 Mixed-Effects Models in R | . 171 |
| | 3.6 Nested and Crossed Random Effects* | . 179 |
| | 3.7 Mixed Models with Correlated Errors | . 190 |
| | 3.8 Time-Varying Covariates* | . 196 |
| | 3.9 Model Building | . 206 |
| | 3.10 Hypothesis Testing | . 209 |

| | 3.11 Residuals | . 210 |
|---|---|-------|
| | 3.12 Review of Key Points | . 220 |
| 4 | Marginal Models for Discrete Data | 223 |
| | 4.1 Review of Generalized Linear Models | . 224 |
| | 4.2 Generalized Estimating Equations | . 237 |
| | 4.3 Interpretation | . 245 |
| | 4.4 Generalized Estimating Equations in R | . 252 |
| | 4.5 Working Correlation Matrix | . 255 |
| | 4.6 Hypothesis Testing | . 266 |
| | 4.7 Review of Key Points | . 275 |

| 5 | Mixed Models for Discrete Data | 277 |
|---|---|-------|
| | 5.1 Generalized Linear Mixed Models | . 278 |
| | 5.2 Interpretation | . 285 |
| | 5.3 Estimation | . 313 |
| | 5.4 GLMMs in R | . 325 |
| | 5.5 Model Building | . 329 |
| | 5.6 Hypothesis Testing | . 331 |
| | 5.7 Review of Key Points | . 336 |
| | | |
| 6 | Statistical Analysis with Incomplete Grouped Data | 338 |
| | 6.1 Missing Data in Longitudinal Studies | . 339 |

| | 6.2 Missing Data Mechanisms | 344 |
|----|---|-----|
| | 6.3 Analysis with Incomplete Data | 359 |
| | 6.4 Summary | 381 |
| | 6.5 Review of Key Points | 383 |
| | | |
| 7 | Closing | 385 |
| | 7.1 Concluding Remarks | 386 |
| Pr | racticals | 390 |
| | Practical 1: Marginal Models Continuous | 391 |
| | Practical 2: Mixed Models Continuous | 401 |
| | Practical 3: Marginal Models Discrete | 410 |

| Practical 4: Mixed Models Discrete $\dots \dots \dots$ |
|--|
|--|

What is this Course About



Grouped data arise in a 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

 - ▷ describe their distribution

Learning Objectives



- Goals: After this course participants will be able to
 - ▷ identify settings in which a repeated measurements model is required,
 - > construct and fit an appropriate model to the data at hand, and
 - > correctly interpret the results
- Even though the course will be primarily explanatory
 - > sufficient mathematical detail will be provided in order 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

- > 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:

 Within the course notes there are several examples of R syntax – these are denoted by the symbol 'R> '

Software Requirements



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

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

- Additional required packages

 - **▷ MASS**, lattice, shiny, 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("Repeated_Measurements", "drizopoulos")
```

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.

Use of Statistical Models



... the megalomaniacal strategy of fitting a grand unified model, supposedly capable of answering any conceivable question that might be posed, is, in our view, dangerous, unnecessary and counterproductive.

Drum and McCullach (1993, Statistical Science 8, 300-301)