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	Residuals
2.12	Review of Key Points \ldots

3	The Linear Mixed Effects Model	131
	3.1 The Linear Mixed Model	. 132
	3.2 Interpretation	. 138
	3.3 Hierarchical vs Marginal	. 146
	3.4 Estimation	. 155
	3.5 Mixed-Effects Models in R	. 165
	3.6 Nested and Crossed Random Effects*	. 170
	3.7 Mixed Models with Correlated Errors	. 172
	3.8 Time-Varying Covariates*	. 178
	3.9 Model Building	. 188
	3.10 Hypothesis Testing	. 191

	3.11 Residuals							
	3.12 Review of Key Points	. 202						
4	Marginal Models for Discrete Data	205						
	4.1 Review of Generalized Linear Models	. 206						
	4.2 Generalized Estimating Equations	. 219						
	4.3 Interpretation	. 227						
	4.4 Generalized Estimating Equations in R	. 234						
	4.5 Working Correlation Matrix	. 237						
	4.6 Hypothesis Testing	. 248						
	4.7 Review of Key Points	. 257						

5	Mixed Models for Discrete Data	259
	5.1 Generalized Linear Mixed Models	. 260
	5.2 Interpretation	. 262
	5.3 Estimation	. 264
	5.4 GLMMs in R	. 266
	5.5 Model Building	. 268
	5.6 Hypothesis Testing	. 270
	5.7 Review of Key Points	. 272
6	Statistical Analysis with Incomplete Grouped Data	274
	6.1 Missing Data in Longitudinal Studies	. 275

	6.2 Missing Data Mechanisms	280
	6.3 Analysis with Incomplete Data	295
	6.4 Summary	317
	6.5 Review of Key Points	319
7	Closing	321
	7.1 Concluding Remarks	322
Pr	racticals	326
	Practical 1: Marginal Models Continuous	327
	Practical 2: Mixed Models Continuous	336
	Practical 3: Marginal Models Discrete	345

Practical 4: Mixed Models Discrete											•				. 35) (
------------------------------------	--	--	--	--	--	--	--	--	--	--	---	--	--	--	------	-----

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

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,
 - **▷ MASS**, 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.
 - ▶ 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.