

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	27
2	Marginal Models for Continuous Data	28
2.1	Simple Methods	29
2.2	Review of Linear Regression	39
2.3	Marginal Models	48

2.4 Interpretation	54
2.5 Estimation	65
2.6 Fitting Marginal Models in R	71
2.7 Covariance Matrix	75
2.8 Model Building	86
2.9 Hypothesis Testing	89
2.10 Confidence Intervals	113
2.11 Design Considerations - Sample Size	115
2.12 Residuals	120
2.13 Review of Key Points	136

3	The Linear Mixed Effects Model	138
3.1	The Linear Mixed Model	139
3.2	Interpretation	145
3.3	Hierarchical vs Marginal	153
3.4	Estimation	163
3.5	Mixed-Effects Models in R	173
3.6	Nested and Crossed Random Effects*	181
3.7	Mixed Models with Correlated Errors	192
3.8	Time-Varying Covariates*	198
3.9	Model Building	208
3.10	Hypothesis Testing	211

3.11 Residuals	234
3.12 Review of Key Points	244

4 Marginal Models for Discrete Data 247

4.1 Review of Generalized Linear Models	248
4.2 Generalized Estimating Equations	261
4.3 Interpretation	269
4.4 Generalized Estimating Equations in R	276
4.5 Working Correlation Matrix	279
4.6 Hypothesis Testing	290
4.7 Review of Key Points	299

5	Mixed Models for Discrete Data	301
5.1	Generalized Linear Mixed Models	302
5.2	Interpretation	309
5.3	Estimation	337
5.4	GLMMs in R	349
5.5	Model Building	353
5.6	Hypothesis Testing	355
5.7	Review of Key Points	360
6	Statistical Analysis with Incomplete Grouped Data	362
6.1	Missing Data in Longitudinal Studies	363

6.2 Missing Data Mechanisms	368
6.3 Analysis with Incomplete Data	383
6.4 Summary	405
6.5 Review of Key Points	407

7 Closing 409

7.1 Concluding Remarks	410
----------------------------------	-----

Practicals 414

Practical 1: Marginal Models Continuous	415
Practical 2: Mixed Models Continuous	425
Practical 3: Marginal Models Discrete	434

Practical 4: Mixed Models Discrete	442
--	-----

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)
 - ▷ *multilevel data*: outcomes measured on sample units that are organized in different levels (e.g., patients in medical centers or students in schools)

What is this Course About (cont'd)

- Statistical analysis of grouped data
 - ▷ Features of grouped data
 - ▷ describe their distribution
 - ▷ inference using suitable regression models

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
- ▷ Formulation of possible research questions

- **Chapter 2:** Marginal Models for Continuous Data

- ▷ Features of repeated measurements data
- ▷ Naive approaches
- ▷ Review linear regression
- ▷ Marginal models

Agenda (cont'd)

- **Chapter 3:** The Linear Mixed Effects Model

- ▷ Intuition behind mixed models
- ▷ Mixed models with correlated errors
- ▷ Nested and cross random effects
- ▷ Time-varying covariates

- **Chapter 4:** Marginal Models for Discrete Data

- ▷ Review generalized linear models
- ▷ Generalized estimating equations

Agenda (cont'd)

- **Chapter 5:** Mixed Models for Discrete Data

- ▷ Generalized linear mixed effects models
- ▷ interpretation of parameters
- ▷ approximations of the integrand & integral

- **Chapter 6:** Statistical Analysis with Incomplete Grouped Data

- ▷ Problems with incomplete data
- ▷ Missing data mechanisms
- ▷ Valid inferential approaches

Structure of the Course & Material

- Lectures & software practicals using R
- Material:
 - ▷ Course Notes
 - ▷ R code in soft format
- 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
 - ▷ **nlme, lme4, MCMCglmm, geepack,**
 - ▷ **MASS, lattice, shiny, corrplot**

Software Requirements

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

```
install.packages(c("shiny", "nlme", "lattice", "lme4",  
                  "MCMCglmm", "geepack", "MASS", "corrplot"),  
                dependencies = TRUE)
```

- Up-to-date version of a modern web browser, e.g.,
 - ▷ Mozilla Firefox (<https://www.mozilla.org/firefox/>)
 - ▷ Google Chrome (<http://www.google.com/chrome/>)

Software Requirements

- We will use 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 and you have installed the aforementioned packages)
 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
 - ▷ Hedeker, D. and Gibbons, R. (2006). *Longitudinal Data Analysis*. New York: John Wiley & Sons.
 - ▷ 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.

... 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)