

Statistical Analysis of Repeated Measurements Data

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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	52
2.5 Estimation	63
2.6 Fitting Marginal Models in R	69
2.7 Covariance Matrix	73
2.8 Model Building	84
2.9 Hypothesis Testing	87
2.10 Confidence Intervals	111
2.11 Design Considerations - Sample Size	113
2.12 Residuals	118
2.13 Review of Key Points	134

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	232
3.12 Review of Key Points	242

4 Marginal Models for Discrete Data 245

4.1 Review of Generalized Linear Models	246
4.2 Generalized Estimating Equations	259
4.3 Interpretation	267
4.4 Generalized Estimating Equations in R	274
4.5 Working Correlation Matrix	277
4.6 Hypothesis Testing	288
4.7 Review of Key Points	297

5	Mixed Models for Discrete Data	299
5.1	Generalized Linear Mixed Models	300
5.2	Interpretation	307
5.3	Estimation	335
5.4	GLMMs in R	347
5.5	Model Building	351
5.6	Hypothesis Testing	353
5.7	Review of Key Points	358
6	Statistical Analysis with Incomplete Grouped Data	360
6.1	Missing Data in Longitudinal Studies	361

6.2 Missing Data Mechanisms	366
6.3 Analysis with Incomplete Data	381
6.4 Summary	403
6.5 Review of Key Points	405

7 Closing 407

7.1 Concluding Remarks	408
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Practicals 412

Practical 1: Marginal Models Continuous	413
Practical 2: Mixed Models Continuous	423
Practical 3: Marginal Models Discrete	432

Practical 4: Mixed Models Discrete	440
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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
- ▷ 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
 - ▷ nested and cross random effects
- **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
- ▷ approximations of the integrand & integral
- ▷ interpretation of parameters

- **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

- 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
 - ▷ 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.

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)