

Statistical Analysis of Repeated Measurements Data

Dimitris Rizopoulos

Department of Biostatistics, Erasmus University Medical Center



d.rizopoulos@erasmusmc.nl



@drizopoulos

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	72
2.6 Fitting Marginal Models in R	78
2.7 Covariance Matrix	82
2.8 Model Building	93
2.9 Hypothesis Testing	96
2.10 Confidence Intervals	120
2.11 Design Considerations - Sample Size	122
2.12 Residuals	127
2.13 Review of Key Points	143

3	The Linear Mixed Effects Model	145
3.1	The Linear Mixed Model	146
3.2	Interpretation	152
3.3	Hierarchical vs Marginal	160
3.4	Estimation	170
3.5	Mixed-Effects Models in R	180
3.6	Nested and Crossed Random Effects*	188
3.7	Mixed Models with Correlated Errors	199
3.8	Time-Varying Covariates*	205
3.9	Model Building	215
3.10	Hypothesis Testing	218

3.11 Residuals	241
3.12 Review of Key Points	251

4 Marginal Models for Discrete Data 254

4.1 Review of Generalized Linear Models	255
4.2 Generalized Estimating Equations	268
4.3 Interpretation	276
4.4 Generalized Estimating Equations in R	283
4.5 Working Correlation Matrix	286
4.6 Hypothesis Testing	297
4.7 Review of Key Points	306

5	Mixed Models for Discrete Data	308
5.1	Generalized Linear Mixed Models	309
5.2	Interpretation	316
5.3	Estimation	345
5.4	GLMMs in R	357
5.5	Model Building	362
5.6	Hypothesis Testing	364
5.7	Review of Key Points	369
6	Statistical Analysis with Incomplete Grouped Data	371
6.1	Missing Data in Longitudinal Studies	372

6.2	Missing Data Mechanisms	377
6.3	Analysis with Incomplete Data	392
6.4	Summary	414
6.5	Review of Key Points	416
7	Closing	418
7.1	Concluding Remarks	419
7.2	Statistical Analysis Section	422
	Practicals	424
	Practical 1: Marginal Models Continuous	425
	Practical 2: Mixed Models Continuous	435

Practical 3: Marginal Models Discrete	444
Practical 4: Mixed Models Discrete	452

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 clustered/grouped data
 - ▷ Features of grouped data
 - ▷ describe their distribution
 - ▷ inference using suitable regression models

Lexical convention

- The following terms are used interchangeably to denote multivariate outcomes
 - ▷ clustered data
 - ▷ repeated measurements data
 - ▷ multilevel data
 - ▷ grouped data

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
 - ▷ <https://cran.r-project.org/>
 - ▷ <https://www.rstudio.com/>
- Additional required packages
 - ▷ **nlme, lme4, GLMMadaptive, 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",  
                  "GLMMadaptive", "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 (<https://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)