Longitudinal Data Modeling

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Preface

1 Introduction

1.1 Workshop Structure

This class focuses on the longitudinal modeling of data from Patient Reported Outcomes (PROs). It is meant to be hands-on class with applications in R.

Content and structure follow the book by (Mallinckrodt 2016). We would like to extend our warmest gratitude towards Dr. Mallinckrodt for providing the example data for the workshop.

The following topics will be covered:

- Welcome and Introduction (WS session 1)
- Exploration and visualization of longitudinal data (WS session 1/2)
- Inferences from longitudinal data (WS session 3 + 4)
- Assessment of missingness patterns (WS session 5)
- Sensitivity analyses to assess the impact of missingness (WS session 6)
- Annex: Inferences from longitudinal binary data (WS session 7)

1.2 Longitudinal Data

This workshop focuses on the analysis of data observed in randomized clinical trials (RCTs). Here, patients have assessments taken at the start of their treatment and then subsequently throughout the course of the trial based on a pre-specified schedule of assessments. The measurement at the start of the treatment is usually referred to as the baseline.

Researchers can be interested in

1. the occurrence of a certain event during the course of the trial, e.g. death or a cardiac event, or the time to the occurrence of such an event, or
2. the longitudinal profile from multiple repeated measurements taken, with a focus on either estimates at a landmark visit or across several time points.

The outcomes under point 1. can be handled via a comparison of the percentages of patients with events between treatment arms, or a time-to-event analysis. Both are out of scope of this workshop.

1.3 Basics about RStudio (pre-read)

Alex to add pre-read (YouTube + Cheat Sheets)

1.4 Example data

2 Longitudinal Data Exploration and Visualization

2.1 Introduction

- Data on individuals followed over time with information collected at several time points.
- Clusters are the individuals who are followed over time.
- Repeated observations may or may not be taken at regular times (balanced, fixed occasions, do not differ between subjects).
- Our interest is in the change from baseline.

Datasets used in this course: Example data is taken from (Mallinckrodt 2016). Contain data on the HAMD17 (Hamilton 17-item rating scale for depression). Two treatement arms are included: drug vs. placebo. Assessments were taken at baseline and weeks 1, 2, 4, 6, and 8

There are 3 data sets created from the original data: - *all2* Subsample of the large dataset with n=50, visits: weeks 2, 4, 8 - *high2* Large dataset with n=100, high dropout = 70% (drug), 60% (placebo) - *low2* Large dataset with n=100, low dropout = 18%

2.2 Task 1 - Exploration of dataset all2 - 15 Minutes working time

- Are the data balanced and equally spaced?
- Number of observations by week?
- Summary statistics for HAMD17 (change from baseline) by week.
- Plot trajectories for each individual, different colors for each treatment group (or panels). Add mean to your plot. ODER Mean plot separat evtl. mit CI
- Generate and interpret the group-wise boxplots of the change from baseline.
- Plot trajectories separately by gender. Comment on the plots.

2.2.1 Task 1 Discussion, possible solution

TO DO: Datensatz aufbereiten, Label, Time=Faktor (t) Alex: library gtsummary okay? Oder sollen wir es anders machen

Table: Summary statistics for HAMD17 by treatment and week in the all2 dataset

```
all2 %>%
  select(change, group, avisit) %>%
  tbl_strata(strata=group,
             ~.x %>%
               tbl_summary(by = avisit,
                           statistic = list(
      all_continuous() ~ "{mean} ({sd})"),
      digits = all_continuous() ~ 2 )
)
```

```
Table printed with `knitr::kable()`, not {gt}. Learn why at
https://www.danieldsjoberg.com/gtsummary/articles/rmarkdown.html
To suppress this message, include `message = FALSE` in code chunk header.
```

Characteristic	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25	**Week 2**, N = 25	**Week 4**, N = 25	**Week 8**, N = 25
change	-4.20 (3.66)	-6.80 (4.25)	-9.88 (4.85)	-5.24 (5.49)	-8.60 (5.39)	-13.24 (5.54)

Figure: trajectories

```
ggplot(data = all2, aes(x = avisit, y = change, group=subject)) +
geom_point() + geom_line() + facet_grid(.~group)
```

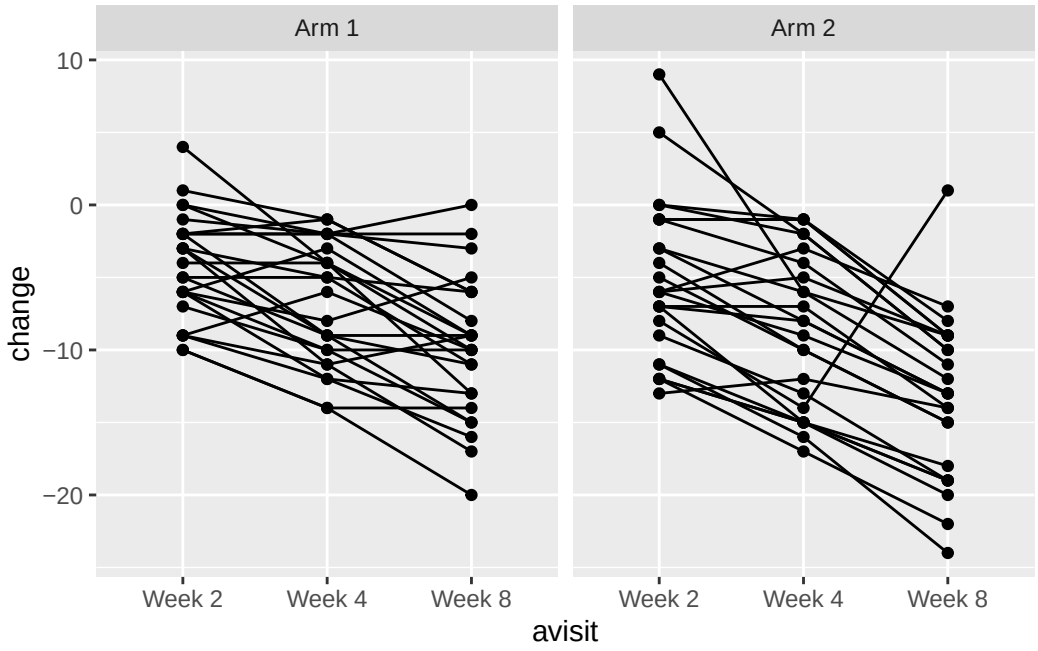

Figure 2.1: Individual trajectories of HAMD17 by treatment group

```
ggplot(data = all2, aes(x = avisit, y = change)) +
  geom_point() + facet_grid(.~group) +
  stat_summary(aes(group = 1), geom = "line", fun.y = mean,
               size = 1, col="blue") +
  stat_summary(aes(group = 1), geom = "point", fun.y = mean,
               shape=17,size = 3, col="blue")
```

```
Warning: The `fun.y` argument of `stat_summary()` is deprecated as of ggplot2 3.3.0.
i Please use the `fun` argument instead.
```

```
Warning: Using `size` aesthetic for lines was deprecated in ggplot2 3.4.0.
i Please use `linewidth` instead.
```

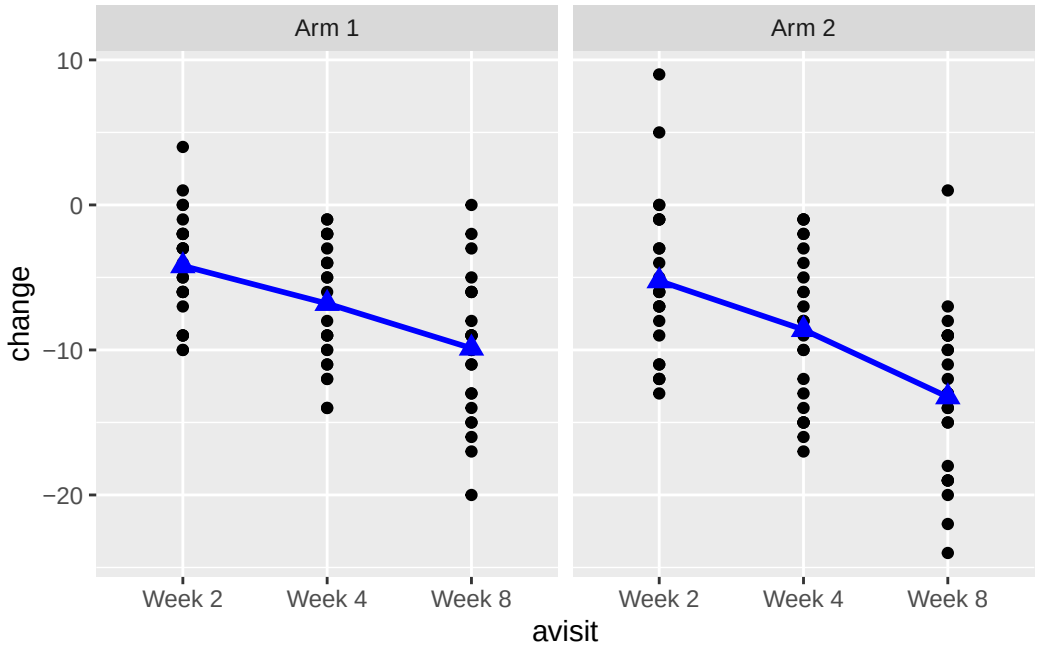

Figure 2.2: Mean change from baseline by treatment group

3 Correlation structure, covariance matrices

- model within-subject error correlation
- different residual covariance structures can be implemented

3.1 Overview - different covariance matrices

- Variance components (VC) independence structure
- Compound symmetry (CS) also known as exchangeable
- Toeplitz (TOEP)
- First order auto regressive (AR(1))
- Unstructured (UN)

Selected covariance structures for data with three assessment times are shown below. Note that with three assessment times, the number of parameters estimated for the various structures did not differ as much as would be the case with more assessment times. Thus, results from different covariance structures are more similar than would be the case with more assessment times.

3.1.1 Independence structure (VC)

Constant variance. It is assumed to be no correlation between assessments.

$$\begin{bmatrix} \sigma^2 & 0 & 0 \\ 0 & \sigma^2 & 0 \\ 0 & 0 & \sigma^2 \end{bmatrix}$$

3.1.2 Compound symmetry (CS)

Constant variance and constant covariance across all assessments. Also known as exchangeable.

$$\begin{bmatrix} \sigma^2 + \sigma_1 & \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma^2 + \sigma_1 & \sigma_1 \\ \sigma_1 & \sigma_1 & \sigma^2 + \sigma_1 \end{bmatrix}$$

3.1.3 Unstructured (UN)

This is the most general (saturated) model

$$\begin{bmatrix} \sigma_1^2 & \sigma_{21} & \sigma_{31} \\ \sigma_{21} & \sigma_2^2 & \sigma_{32} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 \end{bmatrix}$$

3.1.4 Toeplitz structure (TOEP)

Homogenous variances and heterogenous correlations. Same correlation value is used whenever the degree of adjacency is the same e.g. correlation between times 1 and 2 = correlation between times 2 and 3.

$$\begin{bmatrix} \sigma^2 & \sigma^2\rho_1 & \sigma^2\rho_2 \\ \sigma^2\rho_1 & \sigma^2 & \sigma^2\rho_1 \\ \sigma^2\rho_2 & \sigma^2\rho_1 & \sigma^2 \end{bmatrix}$$

3.1.5 Autoregressive structure (AR(1))

Correlation decreases as time between observations increases.

$$\begin{bmatrix} \sigma^2 & \sigma^2\rho & \sigma^2\rho^2 \\ \sigma^2\rho & \sigma^2 & \sigma^2\rho \\ \sigma^2\rho^2 & \sigma^2\rho & \sigma^2 \end{bmatrix}$$

3.1.6 Spatial (SP)

Spatial covariance structures does not require that the timepoints are consistent between subjects. Instead, as long as the distance between visits can be quantified in terms of time and/or other coordinates, the spatial covariance structure can be applied.

For spatial exponential, the covariance structure is defined as follows:

$$\rho_{ij} = \rho^{d_{ij}}$$

where

$$d_{ij}$$

is the distance between time point i and time point j.

3.2 Selecting the covariance structure

There are a variety of considerations when selecting the covariance structure: - number of parameters - interpretation of the structure - model fit UN is the most flexible. Choose a reasonable covaraiance structure which is the best compromise between model fit and complexity. E.g. use AIC as it penalises more complex models.

3.3 Task - Exploration of correlation in the data

- Compute the empirical correlations between measurement timepoints (e.g. correlation between baseline and post-baseline changes).
- Looking at these correlations, comment on the suitability of the correlation structures VC, CS, UN, AR(1).

```
1 + 1
```

```
[1] 2
```

4 Inference from Longitudinal Data

Continuous endpoints

4.1 Categorical Time

avisit with three distinct values -> 2 df

```
?mmrm
```

```
fit_cat_time <- mmrm::mmrm(
  formula = change ~ basval*avisit + trt*avisit + us(avisit | subject),
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)

summary(fit_cat_time)
```

```
mmrm fit

Formula:     change ~ basval * avisit + trt * avisit + us(avisit | subject)
Data:        all2 (used 150 observations from 50 subjects with maximum 3
timepoints)
Covariance:  unstructured (6 variance parameters)
Method:      Kenward-Roger
Vcov Method: Kenward-Roger
Inference:   REML

Model selection criteria:
     AIC      BIC   logLik deviance
   822.4    833.9   -405.2    810.4

Coefficients:
                    Estimate Std. Error        df t value Pr(>|t|)
```

```
(Intercept)           1.98452    3.27479  47.00000   0.606  0.54743
basval               -0.31235    0.15905  47.00000  -1.964  0.05548 .
avisitWeek 4         -0.90862    2.39866  47.00000  -0.379  0.70654
avisitWeek 8        -10.58630    3.45922  47.00000  -3.060  0.00365 **
trt2                 -1.18993    1.27265  47.00000  -0.935  0.35457
basval:avisitWeek 4  -0.08542    0.11650  47.00000  -0.733  0.46704
basval:avisitWeek 8   0.24779    0.16801  47.00000   1.475  0.14691
avisitWeek 4:trt2    -0.80100    0.93217  47.00000  -0.859  0.39454
avisitWeek 8:trt2    -2.20106    1.34432  47.00000  -1.637  0.10825
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Covariance estimate:
        Week 2  Week 4  Week 8
Week 2 20.6112 15.3034 12.2766
Week 4 15.3034 21.3565 17.6648
Week 8 12.2766 17.6648 27.6127
```

Can extract covariance matrix via

```r
summary(fit_cat_time)$varcor
```

```
         Week 2   Week 4   Week 8
Week 2 20.61117 15.30339 12.27661
Week 4 15.30339 21.35648 17.66478
Week 8 12.27661 17.66478 27.61271
```

4.2 Continuous Time

Time as continuous effect -> single df for time and trt-by-time interaction

Modeling: - Need avisit for structure of covariance matrix - Implicit assumption is for the covariance between values for two timepoints to be equal, regardless of the specific timing

```r
fit_cont_time <- mmrm::mmrm(
  formula = change ~ basval*time + trt*time + us(avisit | subject),
  weights = all2$time,
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)
```

Quadratic trend

```
all2$timesq <- all2$time^2

fit_cont_timesq <- mmrm::mmrm(
  formula = change ~ basval*timesq + trt*timesq + us(avisit | subject),
  weights = all2$time,
  data = all2,
  control = mmrm_control(method = "Kenward-Roger")
)
```

model checks - residuals per time point

4.3 Baseline as a Response (cLDA + LDA)

4.3.1 Adjustment of LS Means Calculations

observed vs. balanced margins -> interpretation comparison to arithmetic (observed means)

4.3.2 Addendum on RS&I Models

Different dosing/ assessment frequency between treatment arms in parallel design -> oncology (chemo with fixed cycles vs immune-therapy)

5 Missing Data

6 Sensitivity Analyses

Sensitivity analyses with respect to missing data - only?

- MMRM is an appropriate choice for the primary analysis in many longitudinal clinical trials under the MAR assumption.
- MCAR and MAR missingness can be ignored in likelihood-based analyses. MAR: future outcomes for subjects who discontinued should be similar to the future outocmes of subjects who continued if they had the same values of past (observed) outcomes, covariates,...
- Flexibility in modeling treatment effects over time and the within-patient error correlation structure makes MMRM a widely useful analysis.
- Consider sensivitiy analyses to check model assumptions e.g. MNAR methods
- Comparing results from sensitivity analyses: how much inference rely on the assumptions
- Here, inference with regard to the treatment effect. Thus, investigate how treatment effects vary depending on assumptions e.g. about missing data.
- Uncertainty from incompleteness cannot be objectively evaluated from observed data so there is a need for missing data sensitivity analyses.

Mit Alexandra abstimmen: was genau, machst du MI in deinem Teil, MMRM vs. MI+ANCOVA?, was ist eure primary analysis + typische sensitivity analyses MI: eingehen auf welche Variablen im Modell e.g. at least those from the primary model

6.1 Simple approaches

In general, not recommended for use. Methods are of histroic interest and provide a useful starting point - LOCF: used in the past, justified as it was thought that it provides conservative estimates - complete case (observed case/completers analysis): creates selection bias, may cause overestimation of within group effects particularly at the last scheduled visit

6.2 Missing covariates (baseline data)

- missing baseline value of the outcome: MI or use of mean imputation (Paper:),
- MMRM not efficient or potential biased estimates as subjects with missing covariates are excluded from the analysis

6.3 Baseline complete, missingness in post-baseline values

- for MMRM: at least one post-baseline value needed
- Alternative: LDA where baseline is part of the response vector
- when implemented in similar manners: MI and MMRM have similar assumptions and yield similar results. Thus, MI implemented similarly to MMRM is not a sensitivity analysis

6.4 Multiple imputation

- MI very useful for sensitivity analyses

6.5 Handling nonignorable missingness (MNAR)

- Assumption of MAR is often reasonable, but possibility of data missing not at random (MNAR) is difficult to rule out.
- Thus, analysis under MNAR needed
- Analysis under MNAR: these methods are heavily assumption driven and the assumptions are not testable as we do not have the missing data
- Consider a sensitivity analsyis framework allowing assessment of robustness of results to the various assumptions
- MNAR methods: Pattern-mixture, delta-adjustment method (controlled imputation; another method is reference-based imputation)

7 Inferences from binary longitudinal data

References

Craig Mallinckrodt, Ilya Lipkovich. 2016. *Analyzing Longitudinal Clinical Trial Data: A Practical Guide*. Vol. 1. USA: Chapman; Hall/CRC. https://doi.org/10.1201/9781315186634.

Little, Roderick, and Donald Rubin. 2019. "Statistical Analysis with Missing Data, Third Edition." *Wiley Series in Probability and Statistics*, April. https://doi.org/10.1002/9781119482260.

Mallinckrodt, Craig. 2016. *Analyzing Longitudinal Clinical Trial Data*. Chapman; Hall/CRC. https://doi.org/10.1201/9781315186634.

(Little and Rubin 2019)

(Craig Mallinckrodt 2016)