Repeated measures

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Outline

1. Repeated measures ANOVA
2. Example: Depression and Imipramin
3. Mixed-effects regression

1 Repeated measures ANOVA

Model with one repeated measurement factor

- When subjects are observed for more than two time points, we can model these data using a repeated measures ANOVA
- Data layout

	Time point					
Subject	1	2	$\cdots$	j	$\cdots$	n
1	y_{11}	y_{12}	$\cdots$	y_{1j}	$\cdots$	y_{1n}
2	y_{21}	y_{22}	$\cdots$	y_{2j}	$\cdots$	y_{2n}
$\vdots$	$\vdots$					$\vdots$
i	y_{i1}	y_{i2}	$\cdots$	y_{ij}	$\cdots$	y_{in}
$\vdots$	$\vdots$					$\vdots$
N	y_{N1}	y_{N2}	$\cdots$	y_{Nj}	$\cdots$	y_{Nn}

Statistical model

- When we observe $i = 1, \ldots, N$ subjects for $j = 1, \ldots, n$ time points, we get

$$y_{ij} = \mu_0 + \tau_j + \upsilon_i + \varepsilon_{ij}$$

with

μ_0	grand mean
τ_j	effect of time point j equal for all subjects
υ_i	effect of subject i constant over time
ε_{ij}	error term for subject i at time point j

- Assumptions
  - $\upsilon_i \sim N(0, \sigma_\upsilon^2)$ i.i.d., σ_υ^2 being the variance between subjects
  - $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., σ^2 being the variance within subjects
  - υ_i and ε_{ij} are independent

Statistical model

$$y_{ij} = \mu_0 + \tau_j + \upsilon_i + \varepsilon_{ij}$$

response	grand mean	time effect	subject effect	residual
y_{11}	μ_0	τ_1	υ_1	ε_{11}
y_{12}	μ_0	τ_2	υ_1	ε_{12}
y_{13}	μ_0	τ_3	υ_1	ε_{13}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{21}	μ_0	τ_1	υ_2	ε_{21}
y_{22}	μ_0	τ_2	υ_2	ε_{22}
y_{23}	μ_0	τ_3	υ_2	ε_{23}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{Nn}	μ_0	τ_n	υ_N	ε_{Nn}

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$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{21}	μ_0	τ_1	υ_2	ε_{21}
y_{22}	μ_0	τ_2	υ_2	ε_{22}
y_{23}	μ_0	τ_3	υ_2	ε_{23}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{Nn}	μ_0	τ_n	υ_N	ε_{Nn}
$\sigma_\upsilon^2 + \sigma^2$			σ_υ^2	σ^2

Model properties

- For the model, we have

$$\begin{aligned} E(y_{ij}) &= \mu_0 + \tau_j \\ Var(y_{ij}) &= Var(\mu_0 + \upsilon_i + \tau_j + \varepsilon_{ij}) = \sigma_\upsilon^2 + \sigma^2 \\ Cov(y_{ij}, y_{i'j}) &= 0 \text{ for subjects } i \neq i' \\ Cov(y_{ij}, y_{ij'}) &= \sigma_\upsilon^2 \text{ for observations } j \neq j' \end{aligned}$$

- The correlation between observations and subjects is

$$Corr(y_{ij}, y_{ij'}) = \frac{\sigma_\upsilon^2}{\sigma_\upsilon^2 + \sigma^2}$$

known as intraclass correlation (ICC)

Compound Symmetry

- For the covariance matrix of the observations for one subject we get the so-called compound symmetry structure

$$\mathbf{\Sigma}_{\mathbf{y}_i} = \sigma_v^2 \mathbf{1}\mathbf{1}' + \sigma^2 \mathbf{I} = \begin{pmatrix} \sigma_v^2 + \sigma^2 & \sigma_v^2 & \sigma_v^2 & \cdots & \sigma_v^2 \\ \sigma_v^2 & \sigma_v^2 + \sigma^2 & \sigma_v^2 & \cdots & \sigma_v^2 \\ \vdots & & \ddots & & \vdots \\ \sigma_v^2 & \sigma_v^2 & \sigma_v^2 & \cdots & \sigma_v^2 + \sigma^2 \end{pmatrix}$$

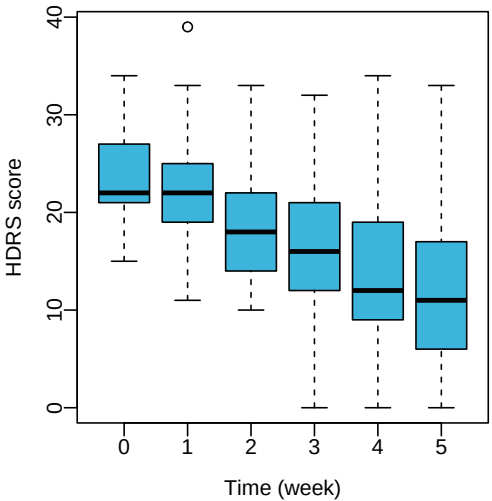
- The assumption of a compound symmetry structure is usually unrealistic for longitudinal data
- In general, successive observations are more strongly correlated than observations being farther apart (covariance is not constant)
- Variance increases with time, e. g., when some subjects are more responsive to a certain treatment than others

2 Example: Depression and Imipramin

Depression and Imipramin (Reisby et al., 1977)

- Reisby et al. (1977) studied the effect of Imipramin on 66 inpatients treated for depression
- Depression was measured with the Hamilton depression rating scale (HDRS)
- Additionally, the concentration of Imipramin and its metabolite Desipramin was measured in their blood plasma
- Patients were classified into endogenous and non-endogenous depressed
- Depression was measured weekly for 6 time points; the effect of the antidepressant was observed starting at week 2 for four weeks

Descriptive statistics



HDRS score

t	W0	W1	W2	W3	W4	W5
M	23.44	21.84	18.31	16.42	13.62	11.95
SD	4.53	4.70	5.49	6.42	6.97	7.22
n	61	63	65	65	63	58

Empirical correlation matrix of HDRS score

	W0	W1	W2	W3	W4	W5
Week 0	1	.49	.41	.33	.23	.18
Week 1	.49	1	.49	.41	.31	.22
Week 2	.41	.49	1	.74	.67	.46
Week 3	.33	.41	.74	1	.82	.57
Week 4	.23	.31	.67	.82	1	.65
Week 5	.18	.22	.46	.57	.65	1

Depression and Imipramin

```
dat      <- read.table("data/reisby.dat", header = TRUE)
dat$id   <- factor(dat$id)
dat$diag <- factor(dat$diag, levels = c("nonen", "endog"))
dat      <- na.omit(dat)     # drop missing values

# descriptive statistics
aggregate(hamd ~ week, dat, mean)
aggregate(hamd ~ week, dat, sd)
aggregate(hamd ~ week, dat, length)

cor(reshape(dat[, c("hamd", "id", "week")],
            direction = "wide", timevar = "week")[, 2:7],
    use = "pairwise.complete.obs")
```

Fitting repeated-measures ANOVA

```r
# week needs to be a factor when computing an ANOVA
dat$week2 <- factor(dat$week)
contrasts(dat$week2) <- "contr.sum"   # effect coding
summary(aov(hamd ~ week2 + Error(id/week2), dat))
# --> ??

library(ez)   # "SPSS"-style
ezANOVA(data = dat, dv = hamd, wid = id, within = week2, type = 3)

# check data
ezDesign(data = dat, x = week, y = id, col = diag)
replications(hamd ~ week2 + id, dat)
```

Fitting repeated-measures ANOVA

```
# remove IDs with missing observations
ids <- names(which(replications(hamd ~ id, dat)$id == 6))
dat_val <- dat[dat$id %in% ids, ]

# fit ANOVAs again
aov1 <- aov(hamd ~ week2 + Error(id/week2), dat_val)
summary(aov1)

ez1 <- ezANOVA(data = dat_val, dv = hamd, wid = id, within = week2)
ez1$ANOVA
```

Fitting repeated-measures ANOVA

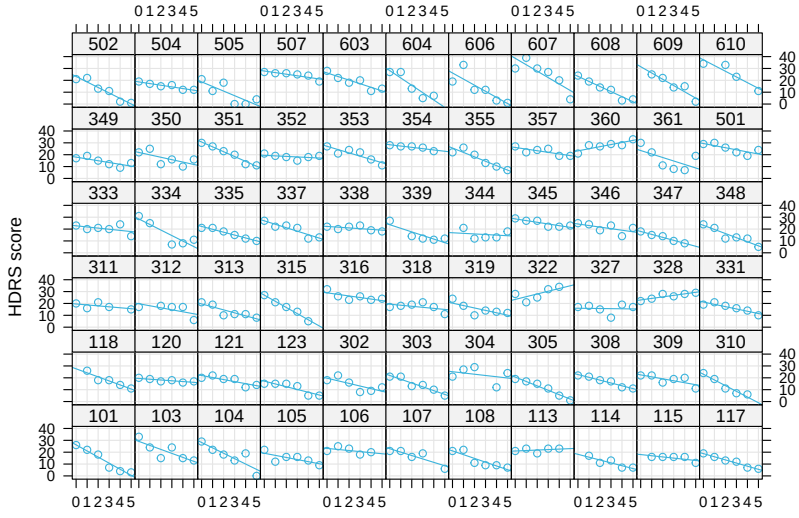
```
# How close can we get with a mixed-effects model?
library(lme4)

lme1 <- lmer(hamd ~ week2 + (1 | id), dat_val)
anova(lme1)

# calculate mean sum of squares for id by hand
sp <- attr(VarCorr(lme1)$id, "stddev")
se <- sigma(lme1)
se^2 + 6 * sp^2
```

❸ Mixed-effects regression

Depression and Imipramin – individual processes



Alternative model with a constant time term

$$y_{ij} = \beta_0 + \beta_1 time + \upsilon_{0i} + \varepsilon_{ij}$$

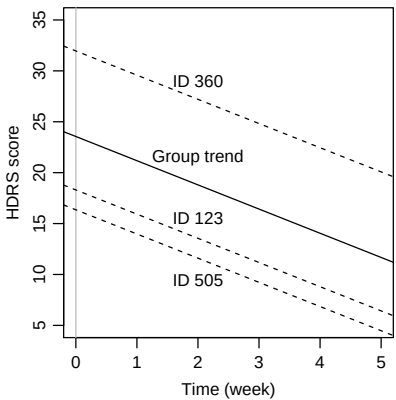
with $\upsilon_{0i} \sim N(0, \sigma_\upsilon^2)$ i.i.d., $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., υ_{0i} and ε_{ij} i.i.d.

response	intercept	time effect	time	subject effect	residual
y_{11}	β_0	β_1	0	υ_1	ε_{11}
y_{12}	β_0	β_1	1	υ_1	ε_{12}
y_{13}	β_0	β_1	2	υ_1	ε_{13}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{21}	β_0	β_1	0	υ_2	ε_{21}
y_{22}	β_0	β_1	1	υ_2	ε_{22}
y_{23}	β_0	β_1	2	υ_2	ε_{23}
$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$	$\vdots$
y_{Nn}	β_0	β_1	n	υ_N	ε_{Nn}

Random intercept model

$$y_{ij} = \beta_0 + \beta_1 time + \upsilon_{0i} + \varepsilon_{ij}$$

with $\upsilon_{0i} \sim N(0, \sigma_\upsilon^2)$ i.i.d., $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., υ_{0i} and ε_{ij} i.i.d.



- The estimated mean baseline HDRS score is $\hat{\beta}_0 = 23.55$
- However, the estimated standard deviation between patients is $\hat{\sigma}_\upsilon = 4.02$
- The mean improvement per week is $\hat{\beta}_1 = -2.38$

Implied marginal covariance matrix

- For the three time points $t_{ij} = 0, 1, 2$, $\mathbf{Z}_i = \mathbf{1}'_{n_i}$ and $\mathbf{\Sigma}_v = \sigma_v^2$ we get

$$\begin{aligned} Cov(\mathbf{y}_i) &= \mathbf{Z}_i \mathbf{\Sigma}_v \mathbf{Z}_i' + \sigma^2 \mathbf{I}_{n_i} \\ &= \sigma_v^2 \mathbf{1}_{n_i} \mathbf{1}'_{n_i} + \sigma^2 \mathbf{I}_{n_i} \\ &= \begin{pmatrix} \sigma_v^2 + \sigma^2 & \sigma_v^2 & \sigma_v^2 \\ \sigma_v^2 & \sigma_v^2 + \sigma^2 & \sigma_v^2 \\ \sigma_v^2 & \sigma_v^2 & \sigma_v^2 + \sigma^2 \end{pmatrix} \end{aligned}$$

- The random intercept model implies the compound symmetry structure

Random slope model

$$y_{ij} = \beta_0 + \beta_1 time + \upsilon_{0i} + \upsilon_{1i} time + \varepsilon_{ij}$$

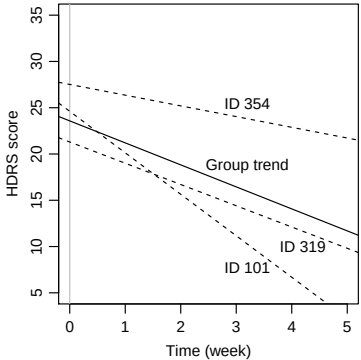
with

$$\begin{pmatrix} \upsilon_{0i} \\ \upsilon_{1i} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathbf{\Sigma}_\upsilon = \begin{pmatrix} \sigma^2_{\upsilon_0} & \sigma_{\upsilon_0\upsilon_1} \\ \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_1} \end{pmatrix} \right) \text{ i.i.d.}$$

$$\varepsilon_i \sim N(\mathbf{0}, \sigma^2 \mathbf{I}_{n_i}) \text{ i.i.d.}$$

- Individual intercepts and slopes each have a unique variance component and correlate with $\varrho_{\upsilon_0\upsilon_1} = \frac{\sigma_{\upsilon_0\upsilon_1}}{\sigma_{\upsilon_0}\,\sigma_{\upsilon_1}}$

Model predictions



- The estimated mean baseline HDRS score is $\hat{\beta}_0 = 23.58$
- The estimated standard deviation between patients is $\hat{\sigma}_{v_0} = 3.55$
- The mean improvement per week is $\hat{\beta}_1 = -2.38$
- The estimated standard deviation between patients is $\hat{\sigma}_{v_1} = 1.44$

- The estimated correlation between individual intercepts and slopes is $\hat{\varrho}_{v_0 v_1} = -0.28$
- Patients with higher (that means worse) baseline scores improve more strongly than patients with smaller baseline scores

Implied marginal covariance matrix

- For the three time points $t_{ij} = 0, 1, 2$,

$$\mathbf{Z}_i = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 2 \end{pmatrix} \text{ und } \mathbf{\Sigma}_\upsilon = \begin{pmatrix} \sigma^2_{\upsilon_0} & \sigma_{\upsilon_0\upsilon_1} \\ \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_1} \end{pmatrix}$$

we get

$$\begin{aligned} Cov(\mathbf{y}_i) &= \mathbf{Z}_i \mathbf{\Sigma}_\upsilon \mathbf{Z}_i' + \sigma^2 \mathbf{I}_{n_i} \\ &= \begin{pmatrix} \sigma^2_{\upsilon_0} & \sigma^2_{\upsilon_0} + \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} \\ \sigma^2_{\upsilon_0} + \sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} + \sigma^2_{\upsilon_1} & \sigma^2_{\upsilon_0} + 3\sigma_{\upsilon_0\upsilon_1} + 2\sigma^2_{\upsilon_1} \\ \sigma^2_{\upsilon_0} + 2\sigma_{\upsilon_0\upsilon_1} & \sigma^2_{\upsilon_0} + 3\sigma_{\upsilon_0\upsilon_1} + 2\sigma^2_{\upsilon_1} & \sigma^2_{\upsilon_0} + 4\sigma_{\upsilon_0\upsilon_1} + 4\sigma^2_{\upsilon_1} \end{pmatrix} + \sigma^2 \mathbf{I}_{n_i} \end{aligned}$$

- Hence, a more flexible covariance structure when compared to compound symmetry

Fitting mixed-effects models

```
# random intercept model
lme1 <- lmer(hamd ~ week + (1 | id), dat, REML = FALSE)
summary(lme1)

# random slope model
lme2 <- lmer(hamd ~ week + (week | id), dat, REML = FALSE)
summary(lme2)

# model comparison
anova(lme1, lme2)
```

Wald test

- For the fixed effects, based on the covariance matrix

$$Var(\hat{\boldsymbol{\beta}}) = \left(\sum_{i=1}^{N} \mathbf{X}_i' \boldsymbol{\Sigma}_i^{-1} \mathbf{X}_i \right)^{-1}$$

  we can construct Wald tests analogously to the regular linear model with approximately normally or t distributed test statistics
- First, $\boldsymbol{\Sigma}_i$ must be estimated; hence, the quality of the approximation strongly depends on the quality of the estimation of the variance and covariance components
- Many authors principally discourage using Wald tests for random effects (**HedekerGibbons06**)

Likelihood ratio test

- Hypotheses about fixed and random effects can be tested with likelihood ratio tests
- When M_0 is a model that results from a more general model M_1 by parameter restrictions, then the test statistic

$$G^2 = 2 \log \frac{L(M_1)}{L(M_0)} = 2 \left(\log L(M_1) - \log L(M_0) \right)$$

  is approximately χ^2 distributed with
  (Number of parameters in M_1) $-$ (Number of parameters in M_0) degrees of freedom
- However, for fixed effects this test can result in progressive test decisions for small samples (H_0 is rejected too often)
- For random effects and hypotheses of the form H_0: $\sigma_v^2 = 0$, the test is rather conservative

Summary

- Assumptions of repeated measures ANOVA are often too restrictive for measurements taken over time

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- Assumptions of repeated measures ANOVA are often too restrictive for measurements taken over time
- Mixed-effects models allow for a more flexible variance-covariance structure
- For unequal group sizes, repeated measures ANOVA is not defined
- (For within designs where assumptions of equal variance are more plausible, repeated measures ANOVA is well suited)

Exercise

- Expand the linear mixed-effects model two more than one factor
- Add diagnosis ("endogenous" vs. "non-endogenous") as additional between factor
- Test if this factor interacts with `week` using a likelihood-ratio test
- Use parametric bootstrapping to get a sampling distribution for your LRT statistic
- Plot the sampling distribution and add the empirical confidence interval

References

Reisby, N., Gram, L. F., Bech, P., Nagy, A., Petersen, G. O., Ortmann, J., Ibsen, I., Dencker, S. J., Jacobsen, O., Krautwald, O., Sondergaard, I., & Christiansen, J. (1977).Imipramine: Clinical effects and pharmacokinetic variability. *Psychopharmacology*, *54*, 263–272.