

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

Subject	Time point					
	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 $i = 1, \dots, N$ subjects for $j = 1, \dots, n$ time points, we get

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

with

μ_0 grand mean

τ_j effect of time point j equal for all subjects

v_i effect of subject i constant over time

ε_{ij} error term for subject i at time point j

- Assumptions
 - $v_i \sim N(0, \sigma_v^2)$ i.i.d., σ_v^2 being the variance between subjects
 - $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., σ^2 being the variance within subjects
 - v_i and ε_{ij} are independent

Statistical model

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

response	grand mean	time effect	subject effect	residual
y_{11}	μ_0	τ_1	v_1	ε_{11}
y_{12}	μ_0	τ_2	v_1	ε_{12}
y_{13}	μ_0	τ_3	v_1	ε_{13}
\vdots	\vdots	\vdots	\vdots	\vdots
y_{21}	μ_0	τ_1	v_2	ε_{21}
y_{22}	μ_0	τ_2	v_2	ε_{22}
y_{23}	μ_0	τ_3	v_2	ε_{23}
\vdots	\vdots	\vdots	\vdots	\vdots
y_{Nn}	μ_0	τ_n	v_N	ε_{Nn}

Statistical model

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y_{13}	μ_0	τ_3	v_1	ε_{13}
\vdots	\vdots	\vdots	\vdots	\vdots
y_{21}	μ_0	τ_1	v_2	ε_{21}
y_{22}	μ_0	τ_2	v_2	ε_{22}
y_{23}	μ_0	τ_3	v_2	ε_{23}
\vdots	\vdots	\vdots	\vdots	\vdots
y_{Nn}	μ_0	τ_n	v_N	ε_{Nn}
$\sigma_v^2 + \sigma^2$			σ_v^2	σ^2

Model properties

- For the model, we have

$$E(y_{ij}) = \mu_0 + \tau_j$$

$$\text{Var}(y_{ij}) = \text{Var}(\mu_0 + v_i + \tau_j + \varepsilon_{ij}) = \sigma_v^2 + \sigma^2$$

$$\text{Cov}(y_{ij}, y_{i'j}) = 0 \text{ for subjects } i \neq i'$$

$$\text{Cov}(y_{ij}, y_{ij'}) = \sigma_v^2 \text{ for observations } j \neq j'$$

- The correlation between observations and subjects is

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

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

$$\Sigma_{y_i} = \sigma_v^2 \mathbf{1}\mathbf{1}' + \sigma^2 \mathbf{I} = \begin{pmatrix} \sigma_v^2 + \sigma^2 & \sigma_v^2 & \sigma_v^2 & \cdots & \sigma_v^2 \\ \sigma_v^2 & \sigma_v^2 + \sigma^2 & \sigma_v^2 & \cdots & \sigma_v^2 \\ \vdots & & \ddots & & \vdots \\ \sigma_v^2 & \sigma_v^2 & \sigma_v^2 & \cdots & \sigma_v^2 + \sigma^2 \end{pmatrix}$$

- 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

<i>t</i>	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
<i>M</i>	23.44	21.84	18.31	16.42	13.62	11.95
<i>SD</i>	4.53	4.70	5.49	6.42	6.97	7.22
<i>n</i>	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("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

```
# Week needs to be a factor when computing an ANOVA
dat$week2 <- factor(dat$week)
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)

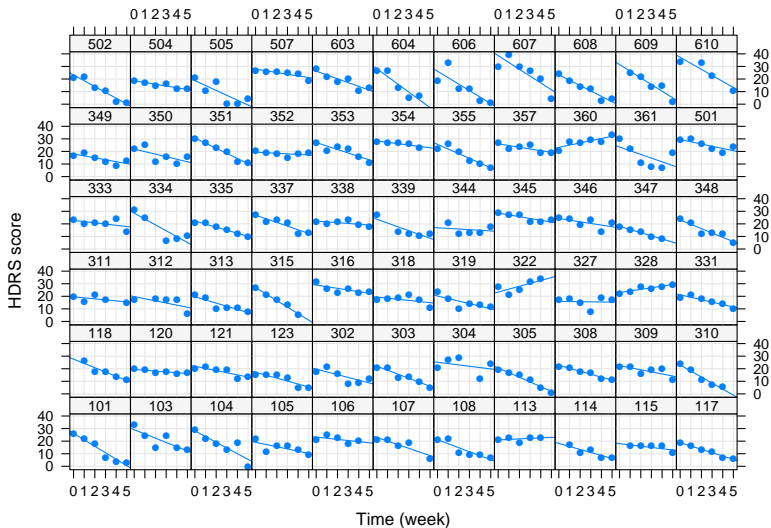
ez1 <- ezANOVA(data = dat_val, dv = hamd, wid = id, within = week2)
ez1$ANOVA
```

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
```


③ Mixed-effects regression

Depression and Imipramin – individual process



Alternative model with a constant time term

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

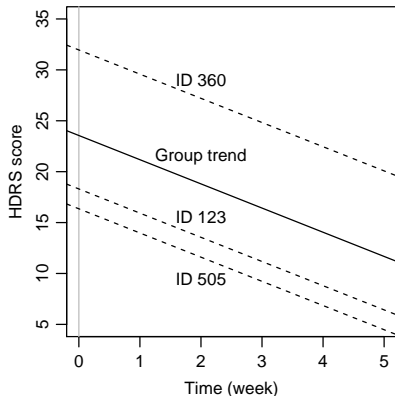
with $v_{0i} \sim N(0, \sigma_v^2)$ i.i.d., $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., v_{0i} and ε_{ij} i.i.d.

response	intercept	time effect	time	subject effect	residual
y_{11}	β_0	β_1	0	v_1	ε_{11}
y_{12}	β_0	β_1	1	v_1	ε_{12}
y_{13}	β_0	β_1	2	v_1	ε_{13}
\vdots	\vdots	\vdots	\vdots	\vdots	\vdots
y_{21}	β_0	β_1	0	v_2	ε_{21}
y_{22}	β_0	β_1	1	v_2	ε_{22}
y_{23}	β_0	β_1	2	v_2	ε_{23}
\vdots	\vdots	\vdots	\vdots	\vdots	\vdots
y_{Nn}	β_0	β_1	n	v_N	ε_{Nn}

Random intercept model

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

with $v_{0i} \sim N(0, \sigma_v^2)$ i.i.d., $\varepsilon_{ij} \sim N(0, \sigma^2)$ i.i.d., v_{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 $\hat{\sigma}_v = 4.02$
- 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

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

- The random intercept model implies the compound symmetry structure

Random slope model

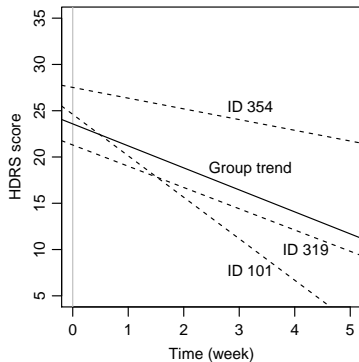
$$y_{ij} = \beta_0 + \beta_1 \text{time} + v_{0i} + v_{1i} \text{time} + \varepsilon_{ij}$$

with

$$\begin{pmatrix} v_{0i} \\ v_{1i} \end{pmatrix} \sim N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \mathbf{\Sigma}_v = \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0 v_1} \\ \sigma_{v_0 v_1} & \sigma_{v_1}^2 \end{pmatrix} \right) \text{ i.i.d.} \\ \varepsilon_i \sim N(\mathbf{0}, \sigma^2 \mathbf{I}_{n_i}) \text{ i.i.d.}$$

- Individual intercepts and slopes each have a unique variance component and correlate with $\rho_{v_0 v_1} = \frac{\sigma_{v_0 v_1}}{\sigma_{v_0} \sigma_{v_1}}$

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 $\hat{\rho}_{v_0v_1} = -0.28$
 - 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 $t_{ij} = 0, 1, 2$,

$$\mathbf{Z}_i = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ 1 & 2 \end{pmatrix} \text{ und } \mathbf{\Sigma}_v = \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0v_1} \\ \sigma_{v_0v_1} & \sigma_{v_1}^2 \end{pmatrix}$$

we get

$$\begin{aligned} \text{Cov}(\mathbf{y}_i) &= \mathbf{Z}_i \mathbf{\Sigma}_v \mathbf{Z}_i' + \sigma^2 \mathbf{I}_{n_i} \\ &= \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0}^2 + \sigma_{v_0v_1} & \sigma_{v_0}^2 + 2\sigma_{v_0v_1} \\ \sigma_{v_0}^2 + \sigma_{v_0v_1} & \sigma_{v_0}^2 + 2\sigma_{v_0v_1} + \sigma_{v_1}^2 & \sigma_{v_0}^2 + 3\sigma_{v_0v_1} + 2\sigma_{v_1}^2 \\ \sigma_{v_0}^2 + 2\sigma_{v_0v_1} & \sigma_{v_0}^2 + 3\sigma_{v_0v_1} + 2\sigma_{v_1}^2 & \sigma_{v_0}^2 + 4\sigma_{v_0v_1} + 4\sigma_{v_1}^2 \end{pmatrix} + \sigma^2 \mathbf{I}_{n_i} \end{aligned}$$

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)

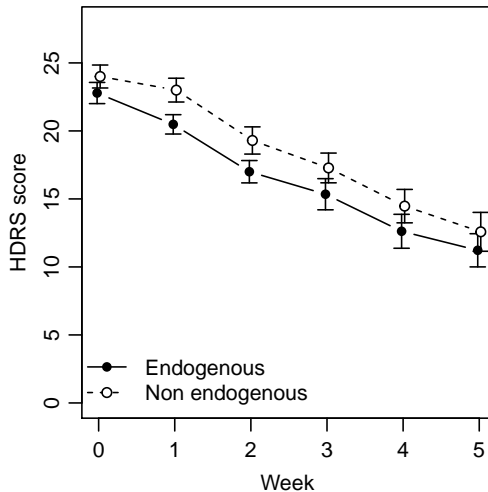
# Model comparison
anova(lme1, lme2)
```

Summary

- 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 within designs where assumptions of equal variance are more plausible, repeated measures ANOVA is well suited)

④ Expanding the model to more than one factor

Two types of depression



Fitting repeated-measures ANOVA

```
# ANOVA with aov()
aov2 <- aov(hamd ~ week2 * diag + Error(id/week2), dat_val)
summary(aov2)

# Using ezANOVA()
ez2 <- ezANOVA(data = dat_val, dv = hamd, wid = id,
               within = week2, between = diag,
               type = 1)

ez2$ANOVA
```

Fitting repeated-measures ANOVA

```
# Mixed-effects model  
lme2 <- lmer(hamd ~ week2 * diag + (1 | id), dat_val)  
anova(lme2)  
  
# Calculate mean sum of squares for id by hand  
sp <- attr(VarCorr(lme2)$id, "stddev")  
se <- attr(VarCorr(lme2), "sc")  
se^2 + 6 * sp^2
```

Fitting mixed-effects model

```
# And this works on the complete data set
lme3 <- lmer(hamd ~ week2 * diag + (1 | id), dat)
anova(lme3)

# Type I sum of squares
lmerTest::anova.lmerModLmerTest(lme3)

# Or via likelihood ratio tests
m0 <- lmer(hamd ~ 1 + (1 | id), dat, REML=FALSE)
m1 <- lmer(hamd ~ week2 + (1 | id), dat, REML=FALSE)
m2 <- lmer(hamd ~ week2 + diag + (1 | id), dat, REML=FALSE)
anova(m0, m1, m2, lme3)
```

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.