

Introduction

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Pre-post study

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Multivariate model

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Basic Statistic for health researchers

Lecture 8: repeated measurements

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23-11-2020

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Corona guidelines

- in and outside classrooms



- Don't show up if you have symptoms of COVID-19 – even if your symptoms are mild.
- Cough/sneeze into your sleeve.
- Go home if you develop symptoms.



- Keep a minimum distance of 1 metre.
- Avoid using lifts. If you have to use a lift, keep a distance of 2 metres.
- Make room for the others when you enter or leave the classrooms, and remember to keep a distance when you are in the common rooms, the cafeteria, etc.



- Sanitise your hands when you enter the building and the rooms.
- Make sure to maintain good hand hygiene – wash and sanitise your hands frequently.
- Beware of contact points (buttons, switches, railings).



- Sit at least 1 metre apart.
- The 1-metre precaution is waived during teaching in permanent class.
- The 1-meter precaution is waived during exercises, where you use personal protective equipment.
- Beware of where you are allowed to sit and not sit.
- Avoid walking about during classes/lectures.



- Leave the classroom in an orderly fashion while observing the distance requirement.
- Let people closest to the exit leave first.



- Keep a minimum distance of 1 metre to your fellow students in your permanent teams when you are outside the class rooms.

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Pre-post study

A 3x5 grid of 15 small circles, arranged in three rows and five columns.

Multivariate model

A 3x5 grid of 15 small circles, arranged in three rows and five columns.

Conclusion

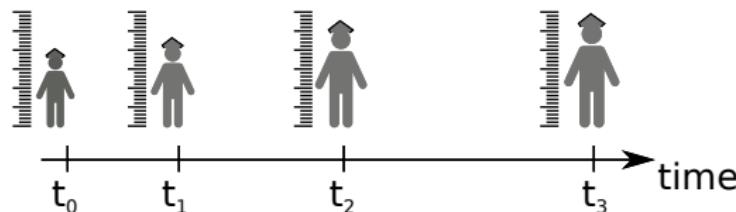
A 2x5 grid of 10 small circles, arranged in two rows of five.

General concepts

What are repeated measurements?

Measurement of a variable at different occasions on an experimental unit:

- typically **same** type of **measurement**
on the **same patient**
at **different timepoints**.



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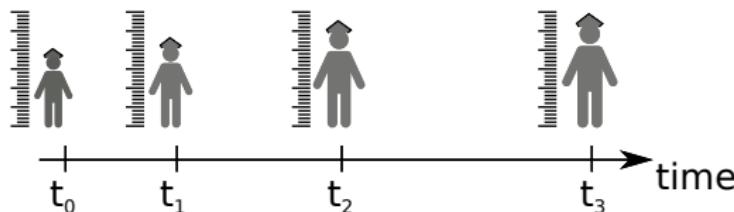
Conclusion

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What are repeated measurements?

Measurement of a variable at different occasions on an experimental unit:

- typically **same** type of **measurement** on the **same patient** at **different timepoints**.



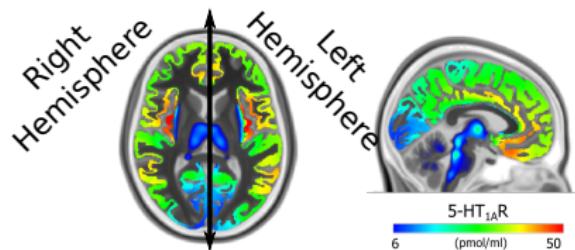
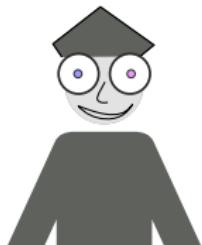
To make things simple, we will focus on:

- comparing two treatment groups
- at fixed timepoints
- no missing data

What are repeated measurements?

Measurement of a variable at different occasions on an experimental unit:

- could also be the **same** type of **measurement** on the **same patient** at **different locations**.



(brain picture from Beliveau et al. (2017))

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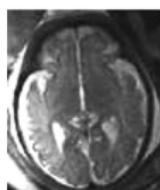
Conclusion

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What are repeated measurements?

Measurement of a variable at different occasions on an experimental unit:

- could also be **different** ways of **measuring** the same quantity on the **same patient** at the **same timpoint and location**.



Gold standard

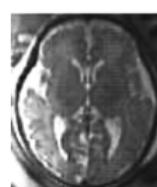


(b) Original (Coronal)

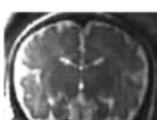


(c) Original (Sagittal)

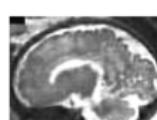
VS.



High resolution



(d) HR (Axial)



(f) HR (Sagittal)

(brain pictures from Van Reeth et al. (2012))

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Why performing repeated measurements? (1/4)

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Multivariate model

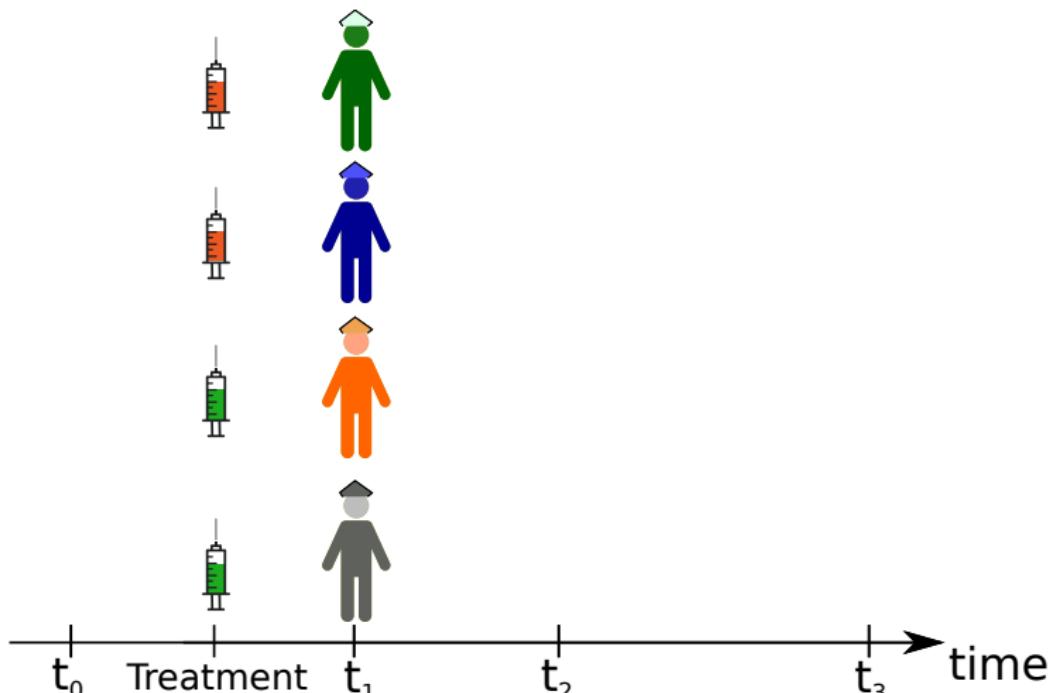
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Why performing repeated measurements? (1/4)

→ *Can you compare the two treatments?*



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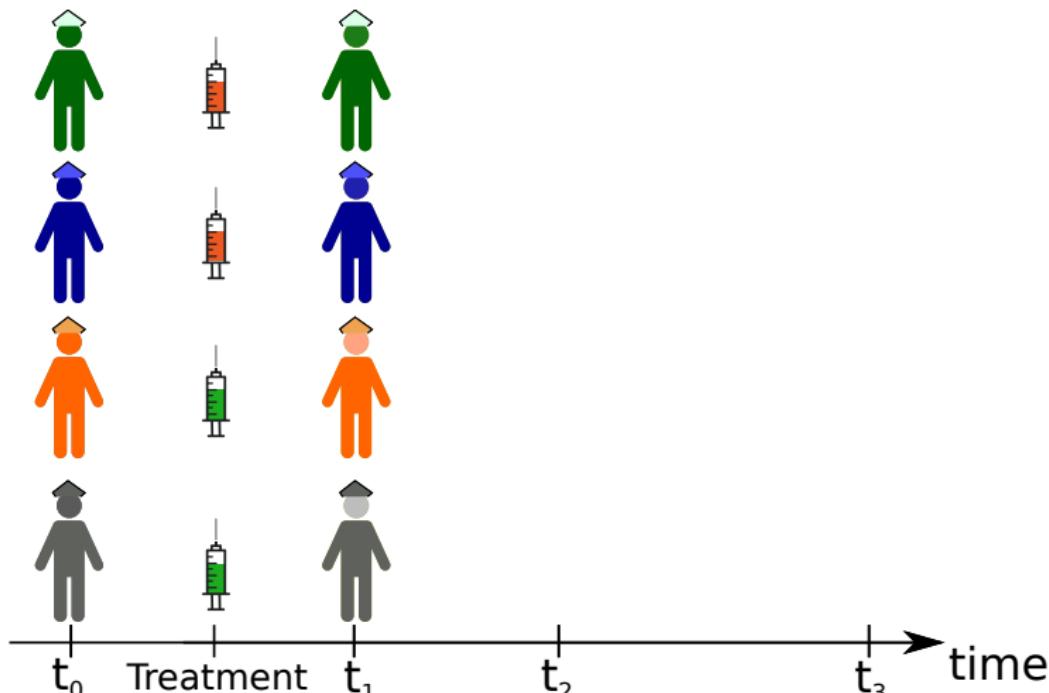
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Why performing repeated measurements? (1/4)

→ *Can you compare the two treatments?*



Why performing repeated measurements? (1/4)

To get a **better estimation** of the **treatment effect**, using each patient as its own control:

- control for confounding → less bias
- accounting for risk factors → less uncertainty
(narrower confidence intervals)

Why performing repeated measurements? (1/4)

To get a **better estimation** of the **treatment effect**, using each patient as its own control:

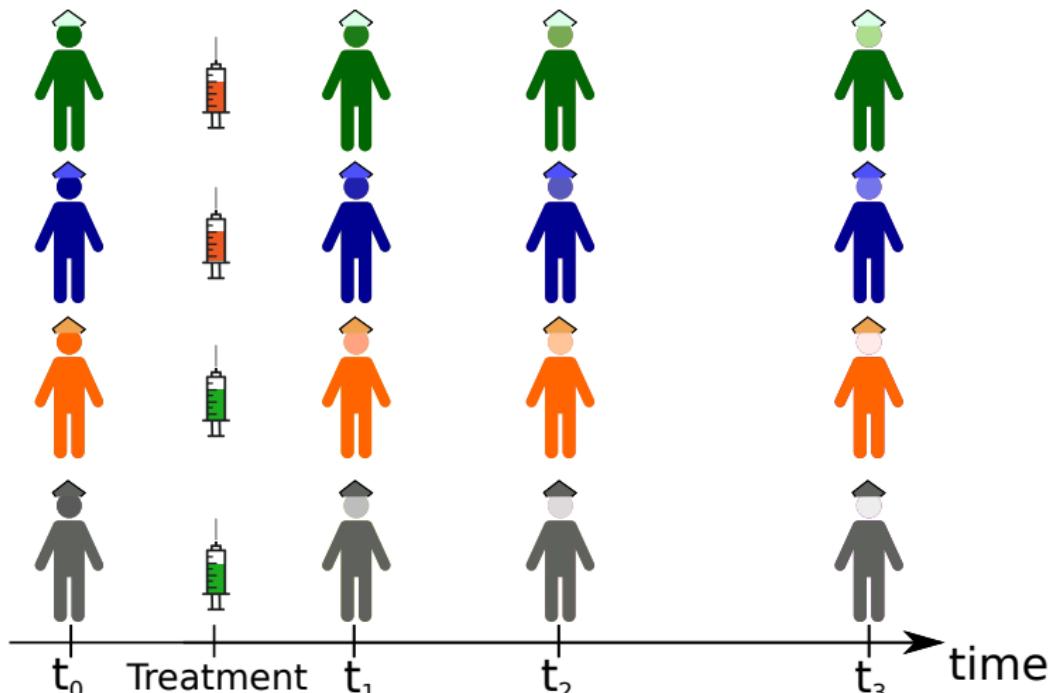
- control for confounding → less bias
- accounting for risk factors → less uncertainty
(narrower confidence intervals)

⚠ not true if confounding/risk factors change across repetitions
(in a non-predictable way), e.g.

- type of device used to make the measurement
- external events
e.g. time since previous meal when monitoring glucose level.

Why performing repeated measurements? (2/4)

→ *What about the treatment effect now?*



Why performing repeated measurements? (2/4)

To **better understand** the (time-dynamic of the) **treatment effect**:

- Is there any treatment effect?
- Is there a sustained treatment effect?
- Is there an immediate treatment effect?
- Are there side effects?
- ...

Why performing repeated measurements? (3/4)

To **save resources**:

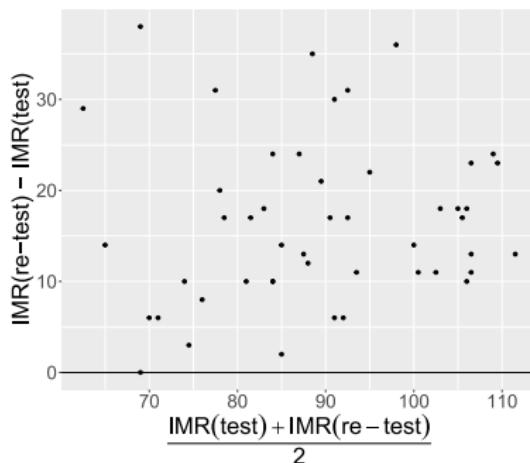
- A baseline+post-treatment study will typically require ¹ fewer subjects compared to a post-treatment only study.
... but requires 2 measurements instead of 1 per subject!
- A single study can be used for answering several research questions
e.g., Immediate treatment effect on the serotonin system.
Long-term treatment effect on depression.

¹ to achieve the same statistical power

Why performing repeated measurements? (4/4)

To validate a new instrument/device/sensor:

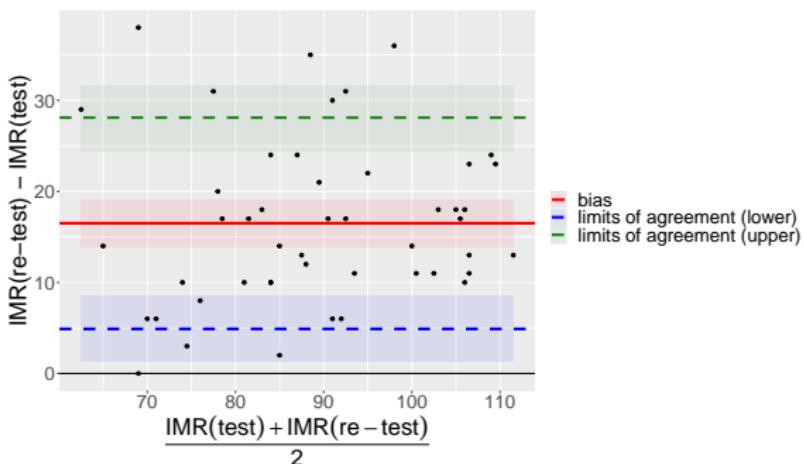
- against a gold standard: agreement with an expensive method or a long-term outcome.
- against itself: agreement between the replicates,
e.g. from [Hjordt et al. \(2020\)](#)



Why performing repeated measurements? (4/4)

To validate a new instrument/device/sensor:

- against a gold standard: agreement with an expensive method or a long-term outcome.
- against itself: agreement between the replicates,
e.g. from Hjordt et al. (2020)



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Challenges when analyzing repeated measurements (1/2)

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Challenges when analyzing repeated measurements (1/2)

The usual **assumption of independent observations** is **violated**.

If ignored, this can lead to:

- ✗ incorrect p-values/confidence intervals (almost always)
- ✗ biased estimates (unless certain assumptions are met)

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Challenges when analyzing repeated measurements (1/2)

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- ✗ biased estimates (unless certain assumptions are met)

Possible solutions:

- **modeling:**
- **one at a time:**
- **summary-statistic:**

Challenges when analyzing repeated measurements (1/2)

The usual **assumption of independent observations** is **violated**.

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Possible solutions:

- **modeling:** model the dependency
⚠ Requires more complex statistical tools
- **one at a time:**

- **summary-statistic:**

Challenges when analyzing repeated measurements (1/2)

The usual **assumption of independent observations** is **violated**.

If ignored, this can lead to:

- incorrect p-values/confidence intervals (almost always)
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Possible solutions:

- **modeling:** model the dependency
 - Requires more complex statistical tools
- **one at a time:** perform separate analyses,
e.g. baseline vs. each timepoint.
 - (possible) loss of statistical power and interpretability
- **summary-statistic:**

Challenges when analyzing repeated measurements (1/2)

The usual **assumption of independent observations** is **violated**.

If ignored, this can lead to:

- ✗ incorrect p-values/confidence intervals (almost always)
- ✗ biased estimates (unless certain assumptions are met)

Possible solutions:

- **modeling**: model the dependency
 - ⚠ Requires more complex statistical tools
- **one at a time**: perform separate analyses,
e.g. baseline vs. each timepoint.
 - ⚠ (possible) loss of statistical power and interpretability
- **summary-statistic**: summarize repetitions into one number
average, area under the curve, peak value
 - ⚠ (possible) loss of information and interpretability

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A 3x5 grid of 15 small circles, arranged in three rows and five columns.

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Challenges when analyzing repeated measurements (2/2)

Multiple testing:

Handling missing values:

Challenges when analyzing repeated measurements (2/2)

Multiple testing:

- several ways to test the treatment effect
at any time, short term, long term, ...
- several possible statistical approaches
multiple t-tests, random intercept model with linear / non-linear treatment effect ...

Handling missing values:

Challenges when analyzing repeated measurements (2/2)

Multiple testing:

- several ways to test the treatment effect
at any time, short term, long term, ...
- several possible statistical approaches
multiple t-tests, random intercept model with linear / non-linear treatment effect ...

Handling missing values:

- Drop-out (patients leaving the study)
reason for leaving → how it should be handled
- Competing risks, e.g. patient died during the study
informative censoring: complete case analysis usually wrong

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Content for today

✓ Specificities when analysing repeated measurements

Illustration with a pre-post study

- data management: from long to wide format
- data exploration: descriptive statistics and plots
- analysis: testing the treatment effect using the change from baseline

Multivariate modeling:

- visualizing bivariate distributions
- introduction to mixed models

Conclusion and recommendations

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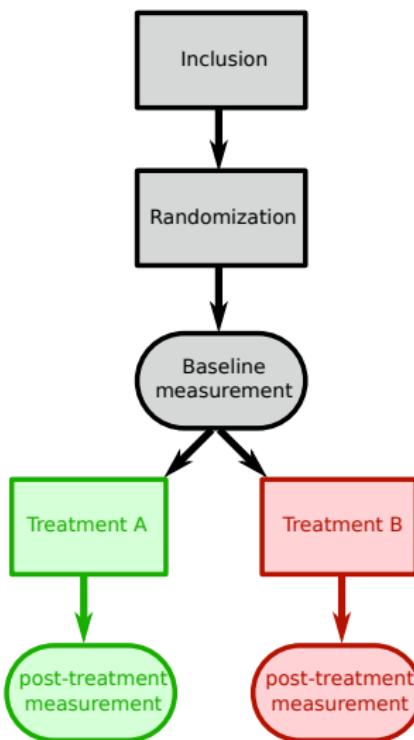
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Pre-post study

Design: pre-post study



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Illustration: ARMD trial (int, 1997)

Age-Related Macular Degeneration (ARMD) Trial:

- clinical trial comparing interferon- α and placebo
- baseline + week 4 measurements

Main outcome:

- change in vision between week 4 and baseline

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Illustration: armd dataset from the *nlmeU* package

```
dW.pp <- read.table("prepost.txt")
head(dW.pp)
```

	subject	treatment	lesion	visual0	visual4
1	1	Active	3	59	55
2	2	Active	1	65	70
3	3	Placebo	4	40	40
4	4	Placebo	2	67	64
6	6	Active	3	59	53
7	7	Placebo	1	64	68

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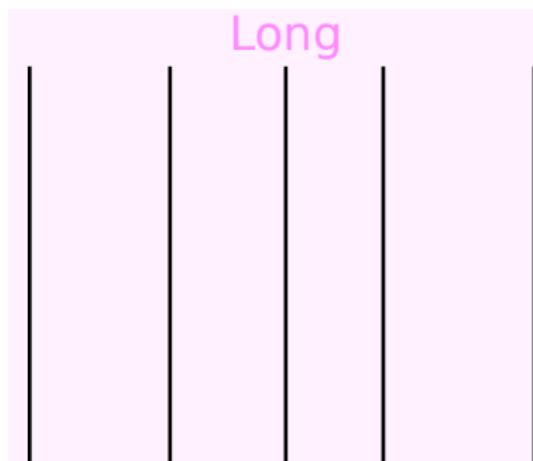
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Moving to the long format (1/3)

Wide

subject	group	outcome (time = 0)	outcome (time = 4)
1	A	59	55
2	A	65	70
3	P	40	40
..

Long



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Moving to the long format (1/3)

Wide

subject	group	outcome (time = 0)	outcome (time = 4)
1	A	59	55
2	A	65	70
3	P	40	40
..

Long

subject	group	time	outcome
		0	
		4	
		0	
		4	
		0	
		4	
		..	

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Moving to the long format (1/3)

Wide

subject	group	outcome (time = 0)	outcome (time = 4)
1	A	59	55
2	A	65	70
3	P	40	40
..

Long

subject	group	time	outcome
1	A	0	59
1	A	4	55
?	?	0	?
?	?	4	?
		0	
		4	
		..	

Moving to the long format (2/3)

```
## reshape to long format
dL.pp <- reshape2::melt(dW.pp,
  id.var = c("subject", "treatment", "lesion"),
  measure.vars = c("visual0", "visual4"),
  variable.name = "week",
  value.name = "visual")
```

```
## re-order dataset
dL.pp <- dL.pp[order(dL.pp$subject),]
## convert week as factor with appropriate values
dL.pp$week <- factor(dL.pp$week,
  level = c("visual0", "visual4"),
  labels = c(0,4))
## remove row names
rownames(dL.pp) <- NULL
```

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Multivariate model

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Conclusion

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```

Moving to the long format (3/3)

```
dW.pp[1:3,] # Wide format: 1 line = 1 subject
```

	subject	treatment	lesion	visual0	visual4
1	1	Active	3	59	55
2	2	Active	1	65	70
3	3	Placebo	4	40	40

```
head(dL.pp) # Long format: 1 line = 1 measurement
```

	subject	treatment	lesion	week	visual
1	1	Active	3	0	59
2	1	Active	3	4	55
3	2	Active	1	0	65
4	2	Active	1	4	70
5	3	Placebo	4	0	40
6	3	Placebo	4	4	40

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Multivariate model

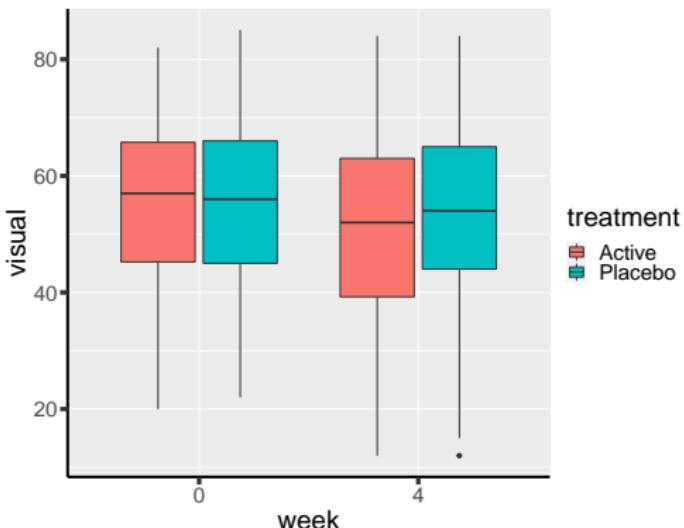
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Graphical display: boxplot

```
gg <- ggplot(data = dL.pp,  
               mapping = aes(x=week, y=visual, fill=treatment))  
gg + geom_boxplot()
```



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Multivariate model

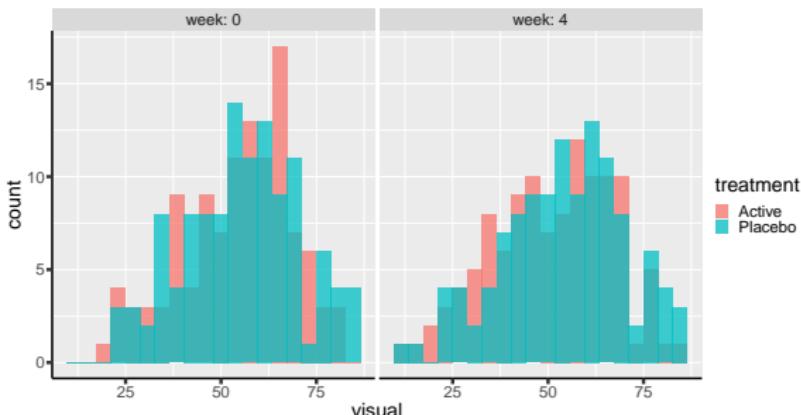
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Graphical display: histogram

```
library(ggplot2)
gg <- ggplot(data = dL.pp,
               mapping = aes(x = visual, fill=treatment))
gg <- gg + facet_wrap(~week, labeller = label_both)
gg + geom_histogram(position = "identity",
                     alpha = 0.75, bins = 20)
```



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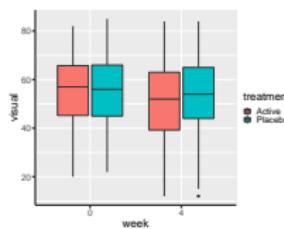
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Testing the treatment effect - exercise!

Assuming normally distributed "visual" values:

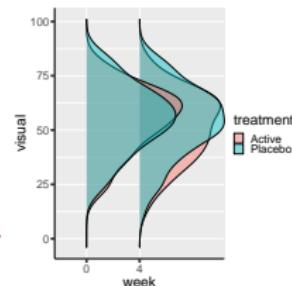
- null hypothesis relative to the treatment effect?
- how can you summarize the data?
- re-phrase the null hypothesis in mathematical terms



Testing the treatment effect - exercise!

Assuming normally distributed "visual" values:

- null hypothesis relative to the treatment effect?
- how can you summarize the data?
- re-phrase the null hypothesis in mathematical terms



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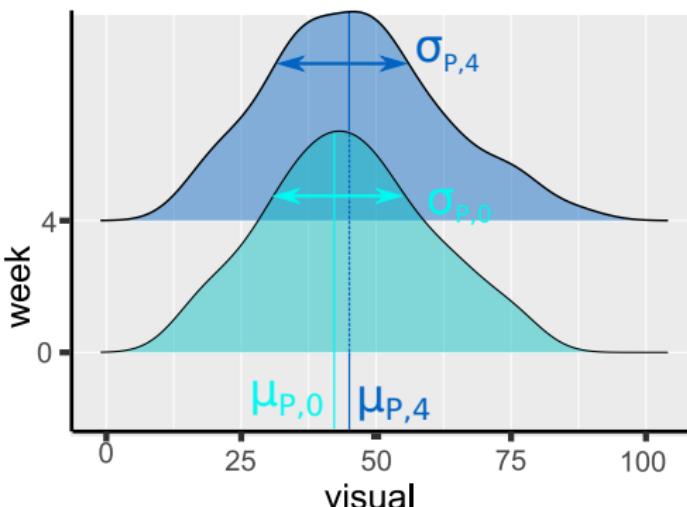
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Testing the treatment effect - solution!

In plain english:

H_0 : same expected change in "visual" value in the Active and Placebo arm

Summarize the data:



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Testing the treatment effect - solution!

In plain english:

H_0 : same expected change in "visual" value in the Active and Placebo arm

Summarize the data:

- average value_{group,time}: $\mu_{A,0}, \mu_{A,4}, \mu_{P,0}, \mu_{P,4}$
- variance_{group,time}: $\sigma^2_{A,0}, \sigma^2_{A,4}, \sigma^2_{P,0}, \sigma^2_{P,4}$

Mathematically:

$H_0: \mu_{A,4} - \mu_{A,0} = \mu_{P,4} - \mu_{P,0}$

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Estimating the treatment effect

$$\mathcal{H}_0: \mu_{A,4} - \mu_{A,0} = \mu_{P,4} - \mu_{P,0}$$

Estimation: using the R function `mean`

- in each subgroups, subsetting (manually) the dataset

```
dW.ppA <- dW.pp[dW.pp$treatment=="Active",]
dW.ppP <- dW.pp[dW.pp$treatment=="Placebo",]
c(mu_A.0=mean(dW.ppA[, "visual0"]),
  mu_P.0=mean(dW.ppP[, "visual0"]))
```

`mu_A.0 mu_P.0`
 54.42105 55.26496

- in all subgroups at once, using the long format

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Estimating summary statistics "at once" (1/2)

Example: average outcome value **at each timepoint**

Long

subject	group	time	outcome
1	A	0	59
1	A	4	55
2	A	0	65
2	A	4	70
3	P	0	40
3	P	4	40
..

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Estimating summary statistics "at once" (1/2)

Example: average outcome value **at each timepoint**

Sort

Long

subject	group	time	outcome
1	A	0	59
1	A	4	55
2	A	0	65
2	A	4	70
3	P	0	40
3	P	4	40
..

Long

subject	group	time	outcome
1	A	0	59
2	A	0	65
3	P	0	40
..	..	0
1	A	4	55
2	A	4	70
3	P	4	40
..	..	4

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Estimating summary statistics "at once" (1/2)

Example: average outcome value **at each timepoint**

Long

subject	group	time	outcome
1	A	0	59
2	A	0	65
3	P	0	40
..	..	0

Split 1

subject	group	time	outcome
1	A	0	59
2	A	0	65
3	P	0	40
..	..	0

Split 2

subject	group	time	outcome
1	A	4	55
2	A	4	70
3	P	4	40
..	..	4

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Conclusion

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Estimating summary statistics "at once" (1/2)

Example: average outcome value **at each timepoint**

Split 1

subject	group	time	outcome
1	A	0	59
2	A	0	65
3	P	0	40
..	..	0

Summarize

mean

59
65
40
....

Split 2

subject	group	time	outcome
1	A	4	55
2	A	4	70
3	P	4	40
..	..	4

mean

55
70
40
....

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Multivariate model

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Conclusion

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```

Estimating summary statistics "at once" (2/2)

```
library(data.table)
dL.pp <- as.data.table(dL.pp)
dL.pp[,mean(visual),by = "week"]
```

	week	V1
1:	0	54.84848
2:	4	52.45887

```
dL.pp[,list(mu=mean(visual), sigma=sd(visual)),
      by = c("treatment", "week")]
```

	treatment	week	mu	sigma
1:	Active	0	54.42105	14.59718
2:	Active	4	50.91228	15.81114
3:	Placebo	0	55.26496	15.11872
4:	Placebo	4	53.96581	15.90973

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Testing the treatment effect: t-test (1/2)

Compute the change:

```
dW.ppP$visualDiff04 <- dW.ppP$visual4-dW.ppP$visual0  
dW.ppA$visualDiff04 <- dW.ppA$visual4-dW.ppA$visual0
```

t-test:

```
t.test(x=dW.ppP$visualDiff04, y=dW.ppA$visualDiff04)
```

Welch Two Sample t-test

```
data: dW.ppP$visualDiff04 and dW.ppA$visualDiff04  
t = 2.019, df = 223.08, p-value = 0.04469  
alternative hypothesis: true difference in means is not equal to  
95 percent confidence interval:  
 0.05288768 4.36636558  
sample estimates:  
mean of x mean of y  
-1.299145 -3.508772
```

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Testing the treatment effect: t-test (2/2)

Underlying statistical model:

- $\text{visual}_{\text{week } 4, \text{Active}} - \text{visual}_{\text{week } 0, \text{Active}} \sim \mathcal{N}(\mu_{A,4-0}, \sigma_{A,4-0}^2)$
- $\text{visual}_{\text{week } 4, \text{Placebo}} - \text{visual}_{\text{week } 0, \text{Placebo}} \sim \mathcal{N}(\mu_{P,4-0}, \sigma_{P,4-0}^2)$

Note 1: strictly speaking, normality is not a requirement

Note 2:

- $\mu_{A,4-0} = \mu_{A,4} - \mu_{A,0}$
- $\sigma_{A,4-0}^2 = \sigma_{A,0}^2 + \sigma_{A,4}^2 - 2\rho_A \sigma_{A,4} \sigma_{A,0}$

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Testing the treatment effect: t-test (2/2)

Underlying statistical model:

- $\text{visual}_{\text{week } 4, \text{Active}} - \text{visual}_{\text{week } 0, \text{Active}} \sim \mathcal{N}(\mu_{A,4-0}, \sigma_{A,4-0}^2)$
- $\text{visual}_{\text{week } 4, \text{Placebo}} - \text{visual}_{\text{week } 0, \text{Placebo}} \sim \mathcal{N}(\mu_{P,4-0}, \sigma_{P,4-0}^2)$

Note 1: strictly speaking, normality is not a requirement

Note 2:

- $\mu_{A,4-0} = \mu_{A,4} - \mu_{A,0}$
- $\sigma_{A,4-0}^2 = \sigma_{A,0}^2 + \sigma_{A,4}^2 - 2\rho_A \sigma_{A,4} \sigma_{A,0}$

Was it a good idea to work on the difference?

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Conclusion

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What about a standard linear regression?

```
dW.pp$visualDiff04 <- dW.pp$visual4 - dW.pp$visual0  
lm(visualDiff04 ~ treatment, data = dW.pp)
```

Call:

```
lm(formula = visualDiff04 ~ treatment, data = dW.pp)
```

Coefficients:

(Intercept)	treatmentPlacebo
-3.509	2.210

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What about a standard linear regression?

```
dW.pp$visualDiff04 <- dW.pp$visual4 - dW.pp$visual0  
lm(visualDiff04 ~ treatment, data = dW.pp)
```

Call:

```
lm(formula = visualDiff04 ~ treatment, data = dW.pp)
```

Coefficients:

(Intercept)	treatmentPlacebo
-3.509	2.210

Here we assume that $\sigma_{A,4-0}^2 = \sigma_{P,4-0}^2$.

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Linear regression for heteroschedastic data

```
library(nlme)
gls(visualDiff04 ~ treatment, data = dW.pp,
    weights = varIdent(form=~1|treatment))
```

Coefficients:

(Intercept)	treatmentPlacebo
-3.508772	2.209627

Variance function:

Structure: Different standard deviations per stratum

Formula: ~1 | treatment

Parameter estimates:

Active	Placebo
1.0000000	0.8711495

$$\hat{\sigma}_{A,4-0} \approx 0.87 \hat{\sigma}_{P,4-0}.$$

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Multivariate model

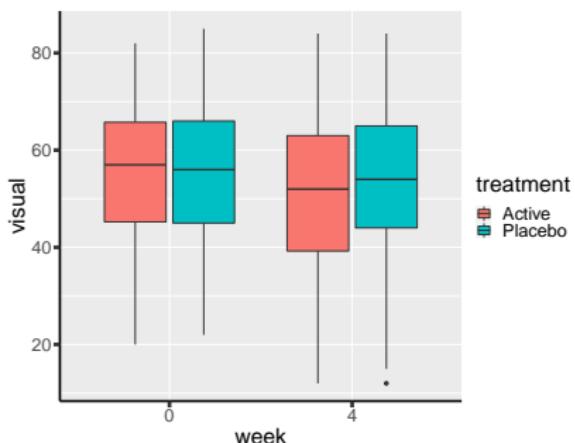
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Conclusion

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Graphical display: are we missing something?

```
gg <- ggplot(data = dL.pp,  
               mapping = aes(x=week, y=visual, fill=treatment))  
gg + geom_boxplot()
```



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Multivariate model

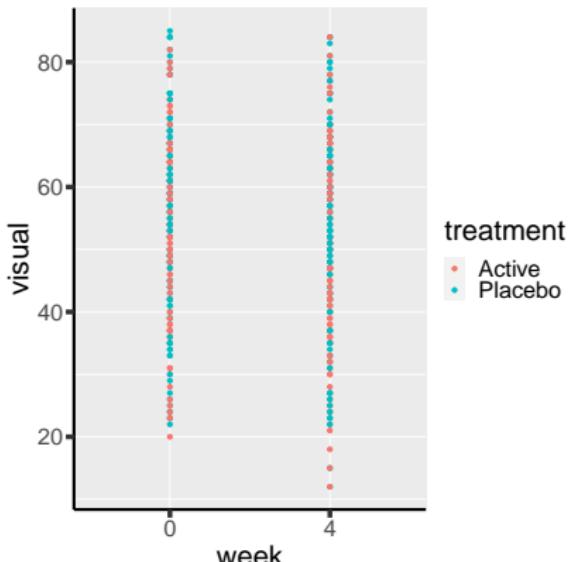
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Graphical display: spaghetti plot (1/3)

```
gg <- ggplot(data = dL.pp,  
               mapping = aes(x=week, y=visual, color=treatment))  
gg + geom_point()
```



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Multivariate model

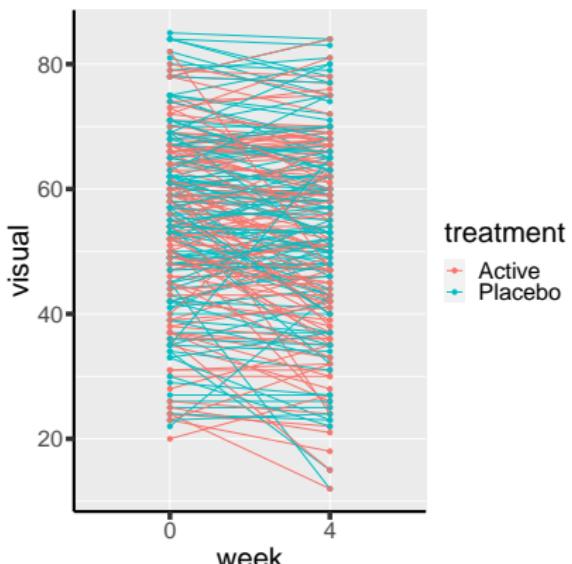
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Graphical display: spaghetti plot (2/3)

```
gg <- ggplot(data = dL.pp,  
               mapping = aes(x=week, y=visual, color=treatment))  
gg + geom_point() + geom_line(aes(group = subject))
```



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Multivariate model

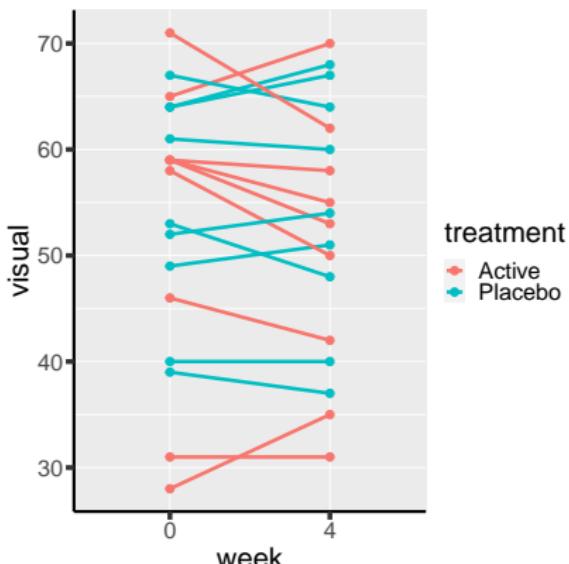
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Graphical display: spaghetti plot (2/3)

```
gg <- ggplot(data = dL.pp[dL.pp$subject < 20,],
               mapping = aes(x=week, y=visual, color=treatment))
gg + geom_point() + geom_line(aes(group = subject))
```



```
cor(dW.pp$visual0,
    dW.pp$visual4)
```

[1] 0.8543813

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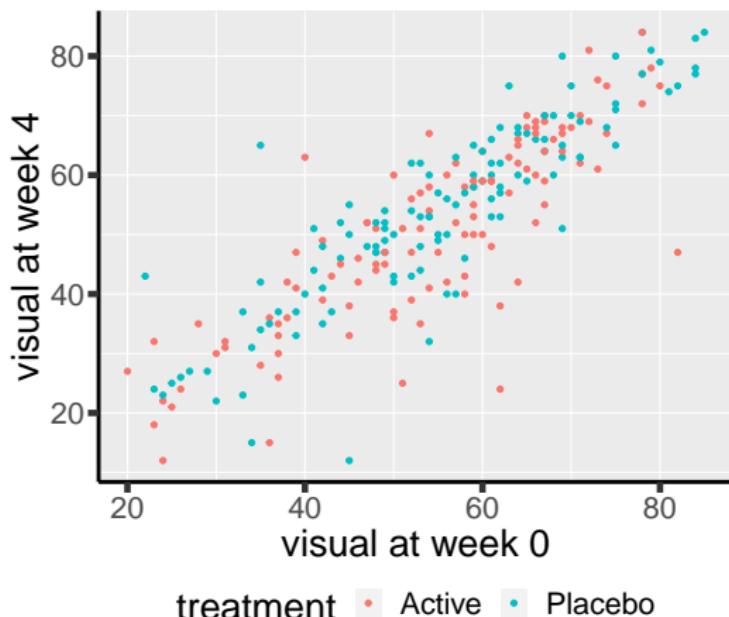
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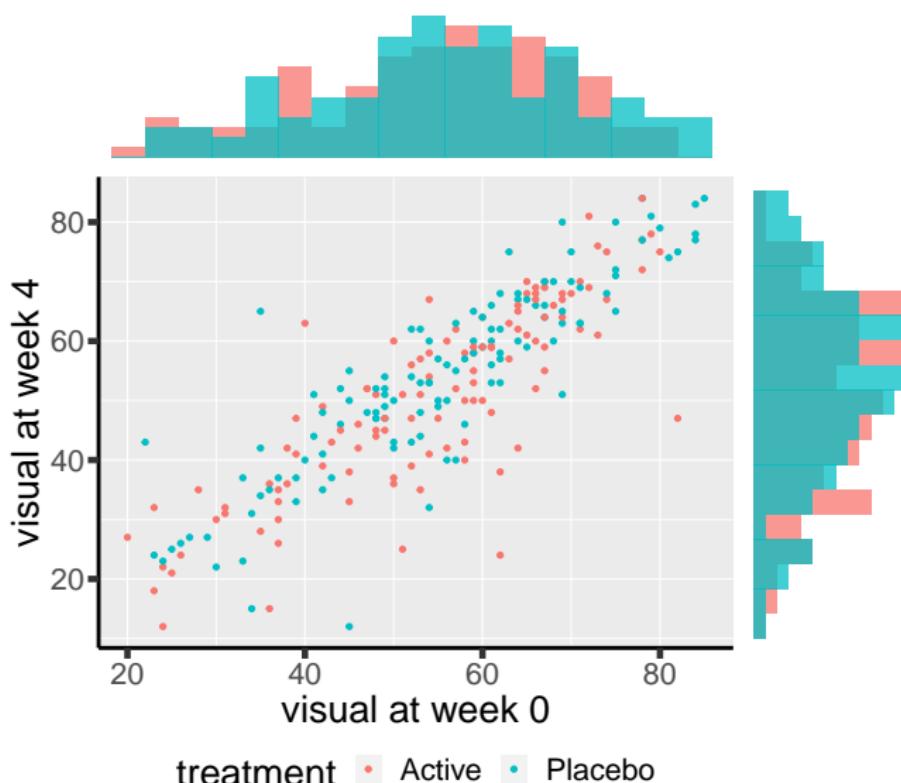
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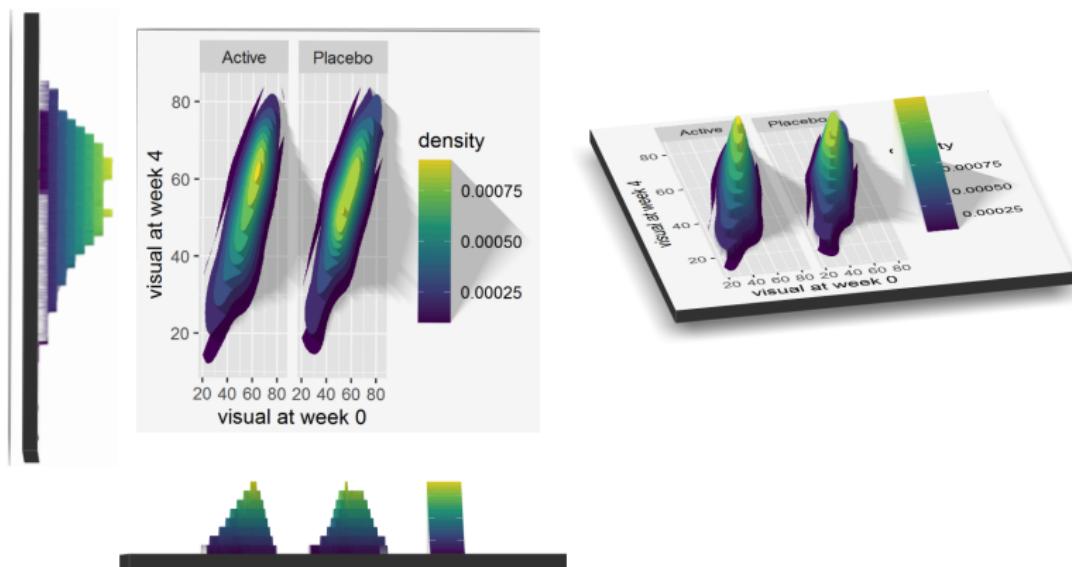
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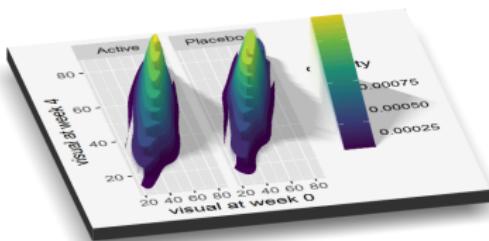
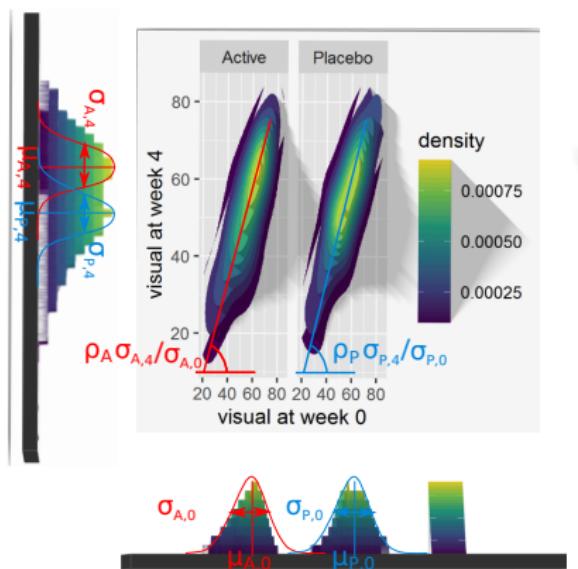
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Multivariate linear model - natural parametrisation

The general model (under normality assumption) in the pre-post study is:

- Active group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} .. \\ .. \\ .. \end{bmatrix}, \begin{bmatrix} .. & .. \\ .. & .. \end{bmatrix} \right)$$

- Placebo group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} .. \\ .. \\ .. \end{bmatrix}, \begin{bmatrix} .. & .. \\ .. & .. \end{bmatrix} \right)$$

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Multivariate linear model - natural parametrisation

The general model (under normality assumption) in the pre-post study is:

- Active group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{A,0} \\ \mu_{A,4} \end{bmatrix}, \begin{bmatrix} \sigma_{A,0}^2 & \rho_A \sigma_{A,0} \sigma_{A,4} \\ \rho_A \sigma_{A,0} \sigma_{A,4} & \sigma_{A,4}^2 \end{bmatrix} \right)$$

- Placebo group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{P,0} \\ \mu_{P,4} \end{bmatrix}, \begin{bmatrix} \sigma_{P,0}^2 & \rho_P \sigma_{P,0} \sigma_{P,4} \\ \rho_P \sigma_{P,0} \sigma_{P,4} & \sigma_{P,4}^2 \end{bmatrix} \right)$$

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Random intercept model - standard parametrisation

- Active group:

$$\begin{bmatrix} \mu_{A,0} = \text{visual}_{\text{week } 0} \\ \mu_{A,4} = \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{A,0} = \alpha \\ \mu_{A,4} = \alpha + \beta \end{bmatrix}, \begin{bmatrix} \sigma^2 + \tau & \tau \\ \tau & \sigma^2 + \tau \end{bmatrix} \right)$$

- Placebo group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{P,0} = \alpha + \gamma \\ \mu_{P,4} = \alpha + \beta + \gamma + \delta \end{bmatrix}, \begin{bmatrix} \sigma^2 + \tau & \tau \\ \tau & \sigma^2 + \tau \end{bmatrix} \right)$$

Can you re-express the null hypothesis using the model parameters?

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Random intercept model - standard parametrisation

- Active group:

$$\begin{bmatrix} \mu_{A,0} = \text{visual}_{\text{week } 0} \\ \mu_{A,4} = \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{A,0} = \alpha \\ \mu_{A,4} = \alpha + \beta \end{bmatrix}, \begin{bmatrix} \sigma^2 + \tau & \tau \\ \tau & \sigma^2 + \tau \end{bmatrix} \right)$$

- Placebo group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{P,0} = \alpha + \gamma \\ \mu_{P,4} = \alpha + \beta + \gamma + \delta \end{bmatrix}, \begin{bmatrix} \sigma^2 + \tau & \tau \\ \tau & \sigma^2 + \tau \end{bmatrix} \right)$$

Can you re-express the null hypothesis using the model parameters?

$$\mathcal{H}_0: \delta = 0$$

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Random intercept model in R

```
e.lme <- lme(visual ~ week*treatment,  
               random = ~1|subject,  
               data = dL.pp)  
logLik(e.lme)
```

'log Lik.' -1761.094 (df=6)

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Random intercept model in R

```
e.lme <- lme(visual ~ week*treatment,
               random = ~1|subject,
               data = dL.pp)
logLik(e.lme)
```

'log Lik.' -1761.094 (df=6)

For individual $i \in \{1, \dots, 231\}$ and week $t \in \{0, 4\}$:

$$Y_{it} = \alpha + \beta \mathbb{1}_{t=4} + \gamma \mathbb{1}_{\text{group}_i = \text{Placebo}} + \delta \mathbb{1}_{t=4} \mathbb{1}_{\text{group}_i = \text{Placebo}} + \varepsilon_{it}$$

$$\varepsilon_{it} = u_i + \xi_{it}$$

where $\mathbb{1}_x$ is the indicator function (1 if x is true and 0 otherwise)

ε_{it} is a (non iid) error term

$u_i \sim \mathcal{N}(0, \tau)$ are independent random effects

$\xi_{it} \sim \mathcal{N}(0, \sigma^2)$ are independent residuals

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Mean structure - standard parametrisation

$$\mathbb{E}[Y_{it} | \text{group}_i] = \alpha + \beta \mathbb{1}_{t=4} + \gamma \mathbb{1}_{\text{group}_i = \text{Placebo}} + \delta \mathbb{1}_{t=4} \mathbb{1}_{\text{group}_i = \text{Placebo}}$$

```
data.frame(name = c("alpha", "beta", "gamma", "delta"),
           value = fixef(e.lme),
           p.value = summary(e.lme)$tTable[, "p-value"])
```

	name	value	p.value
(Intercept)	alpha	54.4210526	2.038171e-100
week4	beta	-3.5087719	1.022514e-05
treatmentPlacebo	gamma	0.8439046	6.769226e-01
week4:treatmentPlacebo	delta	2.2096266	4.427774e-02

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Mean structure - standard parametrisation

$$\mathbb{E}[Y_{it}|\text{group}_i] = \alpha + \beta \mathbb{1}_{t=4} + \gamma \mathbb{1}_{\text{group}_i=\text{Placebo}} + \delta \mathbb{1}_{t=4} \mathbb{1}_{\text{group}_i=\text{Placebo}}$$

$$\mathbb{E}[Y_{i0}|\text{Active}] =$$

$$\mathbb{E}[Y_{i4}|\text{Active}] =$$

$$\mathbb{E}[Y_{i0}|\text{Placebo}] =$$

$$\mathbb{E}[Y_{i4}|\text{Placebo}] =$$

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data.frame(name = c("alpha", "beta", "gamma", "delta"),
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Mean structure - standard parametrisation

$$\mathbb{E}[Y_{it}|\text{group}_i] = \alpha + \beta \mathbb{1}_{t=4} + \gamma \mathbb{1}_{\text{group}_i=\text{Placebo}} + \delta \mathbb{1}_{t=4} \mathbb{1}_{\text{group}_i=\text{Placebo}}$$

$$\mathbb{E}[Y_{i0}|\text{Active}] = \alpha + \beta * 0 + \gamma * 0 + \delta * 0 * 0$$

$$\mathbb{E}[Y_{i4}|\text{Active}] = \alpha + \beta * 1 + \gamma * 0 + \delta * 1 * 0$$

$$\mathbb{E}[Y_{i0}|\text{Placebo}] = \alpha + \beta * 0 + \gamma * 1 + \delta * 0 * 1$$

$$\mathbb{E}[Y_{i4}|\text{Placebo}] = \alpha + \beta * 1 + \gamma * 1 + \delta * 1 * 1$$

```
data.frame(name = c("alpha", "beta", "gamma", "delta"),
           value = fixef(e.lme),
           p.value = summary(e.lme)$tTable[, "p-value"])
```

	name	value	p.value
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Mean structure - standard parametrisation

$$\mathbb{E}[Y_{it}|\text{group}_i] = \alpha + \beta \mathbb{1}_{t=4} + \gamma \mathbb{1}_{\text{group}_i=\text{Placebo}} + \delta \mathbb{1}_{t=4} \mathbb{1}_{\text{group}_i=\text{Placebo}}$$

$$\mathbb{E}[Y_{i0}|\text{Active}] = \alpha$$

$$\mathbb{E}[Y_{i4}|\text{Active}] = \alpha + \beta$$

$$\mathbb{E}[Y_{i0}|\text{Placebo}] = \alpha + \gamma$$

$$\mathbb{E}[Y_{i4}|\text{Placebo}] = \alpha + \beta + \gamma + \delta$$

```
data.frame(name = c("alpha", "beta", "gamma", "delta"),
           value = fixef(e.lme),
           p.value = summary(e.lme)$tTable[, "p-value"])
```

	name	value	p.value
(Intercept)	alpha	54.4210526	2.038171e-100
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Fitted values

```
UX <- unique(dL.pp[,c("week", "treatment")])  
UX
```

```
week treatment  
1    0    Active  
2    4    Active  
5    0    Placebo  
6    4    Placebo
```

```
UX$fit <- predict(e.lme, level = 0, newdata = UX)  
UX
```

```
week treatment      fit  
1    0    Active 54.42105  
2    4    Active 50.91228  
5    0    Placebo 55.26496  
6    4    Placebo 53.96581
```

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Multivariate model

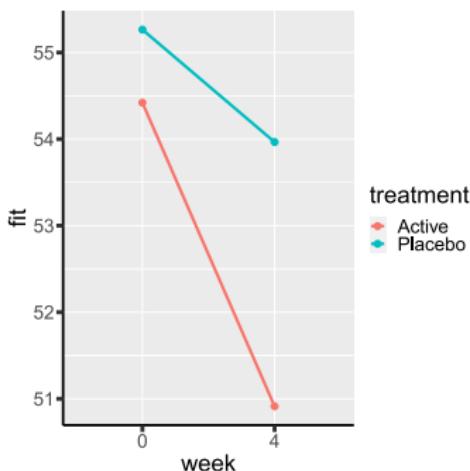
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Display fitted values

```
gg <- ggplot(UX, aes(x = week, y = fit,  
                      group = treatment, color = treatment))  
gg + geom_point() + geom_line()
```



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Multivariate model

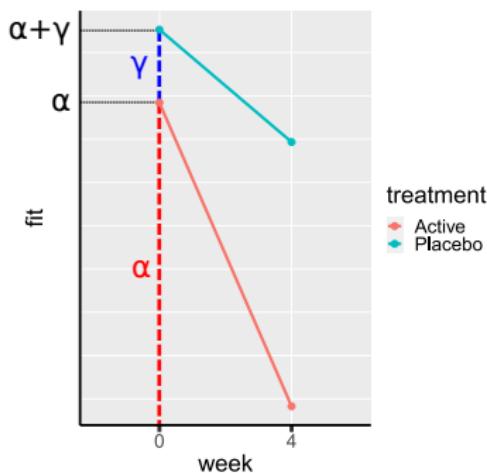
```
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```

Display fitted values

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gg <- ggplot(UX, aes(x = week, y = fit,
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Multivariate model

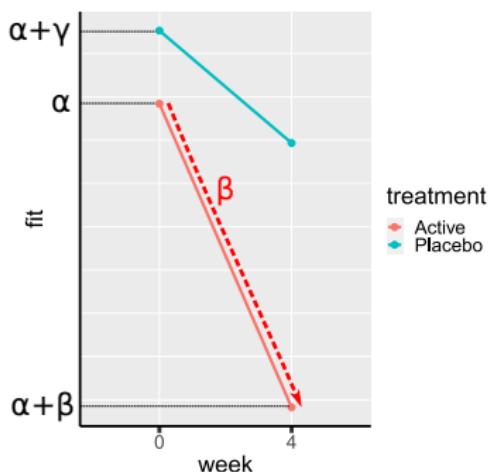
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Display fitted values

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Multivariate model

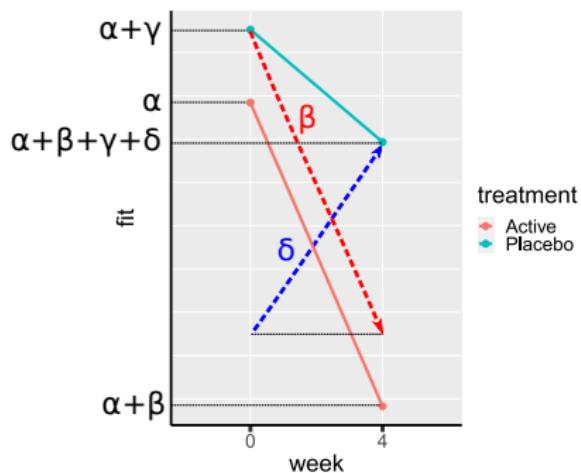
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Display fitted values

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gg <- ggplot(UX, aes(x = week, y = fit,
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gg + geom_point() + geom_line()
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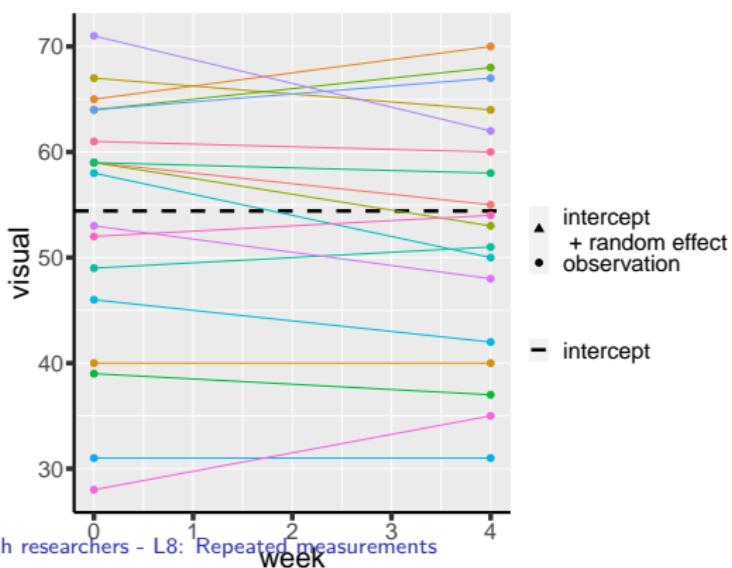
Variance-covariance structure (1/2)

For individual $i \in \{1, \dots, 231\}$ and week $t \in \{0, 4\}$:

$$\varepsilon_{it} = u_i + \xi_{it}$$

where $u_i \sim \mathcal{N}(0, \tau)$ are independent random effects

$\xi_{it} \sim \mathcal{N}(0, \sigma^2)$ are independent residuals



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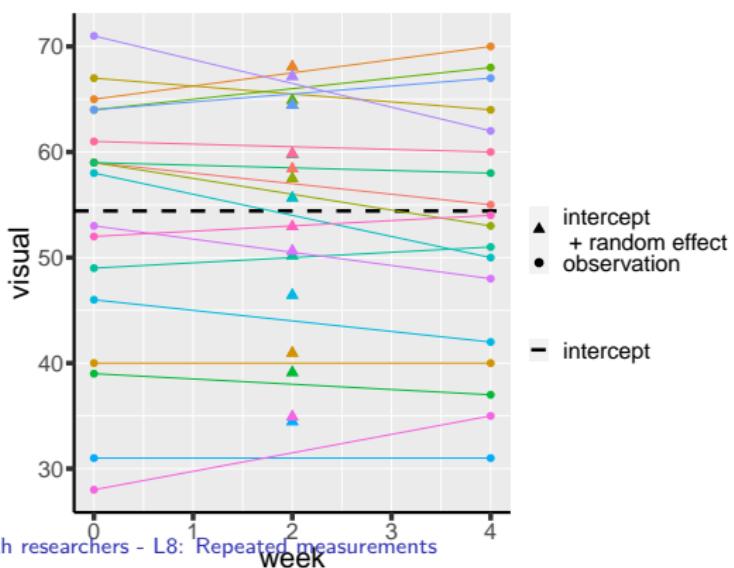
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A 3x5 grid of 15 small circles, arranged in three rows and five columns.

10

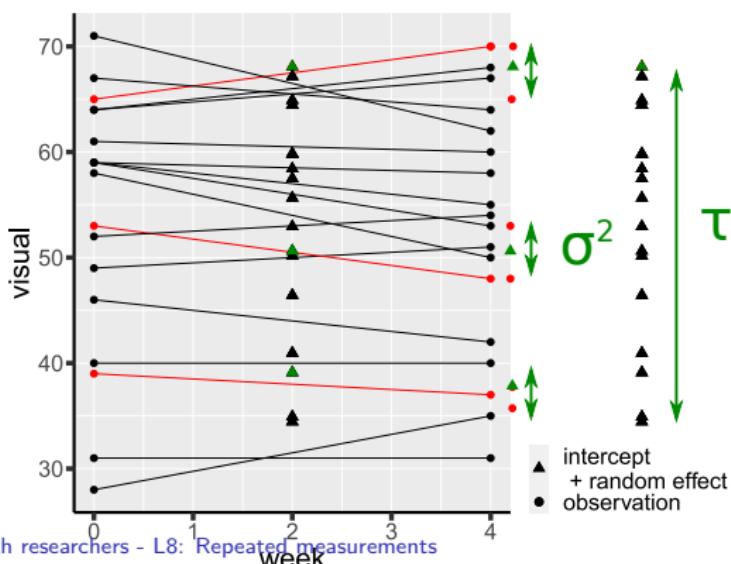
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Variance-covariance structure (2/2)

```
getVarCov(e.lme, individuals = 2:3, type = "marginal")
```

subject 2

Marginal variance covariance matrix

	1	2
1	236.25	201.80
2	201.80	236.25

Standard Deviations: 15.37 15.37

subject 3

Marginal variance covariance matrix

	1	2
1	236.25	201.80
2	201.80	236.25

Standard Deviations: 15.37 15.37

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subject 3

Marginal variance covariance matrix

	1	2
1	236.25	201.80
2	201.80	236.25

Standard Deviations: 15.37 15.37

What hypotheses are we making?

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Variance-covariance structure (2/2)

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subject 2

Marginal variance covariance matrix

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Standard Deviations: 15.37 15.37

subject 3

Marginal variance covariance matrix

	1	2
1	236.25	201.80
2	201.80	236.25

Standard Deviations: 15.37 15.37

What hypotheses are we making?

$$\sigma_{A,0}^2 = \sigma_{A,4}^2 = \sigma_{P,0}^2 = \sigma_{P,4}^2 \quad \rho_A = \rho_P$$

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Conclusion

Collecting several measurements per subject is a good idea:

- reduce uncertainty/confounding (each subject is its own control)
- give more insight into the treatment effect
- scheduled measurement time is recommended

But is also challenging:

- more demanding for the patient ( drop-out!)
- more complex to organize
(e.g. ensure subjects follow the schedule)
- often require dedicated/advanced statistical tools

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Why using multivariate models?

Pro:

- generalize to more than two timepoints
- applicable in continuous time
- efficiently handles missing values
- more interpretable
 - (e.g. impose constant or linear treatment effect over time)

Cons:

- make more assumptions
- more difficult to describe (in an article)
- more complex to estimate and to perform statistical inference
 - (p-value, confidence intervals can be less reliable in small samples)

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Want to know more?

Ph.D. course:

- Statistical analysis of correlated and repeated measurements
(course director: Julie Forman)

Contents

This course is concerned with analysis of correlated quantitative data arising e.g. when taking observations from clusters of subjects, repeatedly over time on the same subjects, or by applying different treatment to different parts of the body. Pitfalls of traditional statistical analyses will be discussed and appropriate models for the analysis of e.g. baseline follow-up studies, cross-over studies, and cluster randomized trials will be exemplified.

For supplementary reading we recommend:

- FLW: G.M. Fitzmaurice, N.M. Laird and J.H. Ware, Applied Longitudinal Analysis (2nd edition), John Wiley & sons, 2011.

Please note that the book is available as e-book on KB (free download for KU students).

Day	Topics	Suggested reading*
1	Introduction to repeated measurements and clustered data. Basic theory of linear mixed models. Analysis of single group studies. Handling repeated measurements in SAS/R.	FLW 1-3. Tutorial 1.
2	Longitudinal data analysis. Models for balanced and unbalanced designs. Analysis of randomized baseline follow-up studies.	FLW 5-7. Tutorial 2.
3	Analysis of clustered data. Variance components. Multi-level models. The linear growth model.	FLW 8, 21 & 22.
4	Select topics in linear mixed models. Cross-over studies. Repeatability and reproducibility of measurement methods.	Lecture notes only.
5	Models for binary and count data. Generalized linear mixed models. Marginal models and generalized estimating equations.	FLW 10-16
6	Missing data. Consequences and statistical handling.	FLW 17-18

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Reference |

(1997). Interferon Alfa-2a Is Ineffective for Patients With Choroidal Neovascularization Secondary to Age-Related Macular Degeneration: Results of a Prospective Randomized Placebo-Controlled Clinical Trial. *Archives of Ophthalmology*, 115(7):865–872.

Beliveau, V., Ganz, M., Feng, L., Ozenne, B., Højgaard, L., Fisher, P. M., Svarer, C., Greve, D. N., and Knudsen, G. M. (2017). A high-resolution *in vivo* atlas of the human brain's serotonin system. *Journal of Neuroscience*, 37(1):120–128.

Hjordt, L. V., Ozenne, B., Armand, S., Dam, V. H., Jensen, C. G., Köhler-Forsberg, K., Knudsen, G. M., and Stenbæk, D. S. (2020). Psychometric properties of the verbal affective memory test-26 and evaluation of affective biases in major depressive disorder. *Frontiers in psychology*, 11:961.

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Reference II

Van Reeth, E., Tham, I. W., Tan, C. H., and Poh, C. L. (2012).
Super-resolution in magnetic resonance imaging: a review.
Concepts in Magnetic Resonance Part A, 40(6):306–325.

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Natural parametrisation (1/3)

Shorten names:

```
dL.pp$treat <- factor(dL.pp$treatment,  
                         levels = c("Active", "Placebo"),  
                         labels = c("A", "P"))
```

```
e2.lme <- lme(visual ~ week:treat-1,  
                 random = ~1|subject,  
                 data = dL.pp)
```

```
logLik(e2.lme)
```

'log Lik.' -1761.094 (df=6)

```
fixef(e2.lme)
```

	week0:treatA	week4:treatA	week0:treatP	week4:treatP
	54.42105	50.91228	55.26496	53.96581

Natural parametrisation (2/3)

```
library(multcomp)
C <- "week4:treatA-week0:treatA-week4:treatP+week0:
      treatP=0"
e2.glht <- glht(e2.lme, linfct = C)
rownames(e2.glht$linfct) <- "delta"
summary(e2.glht)
```

Simultaneous Tests for General Linear Hypotheses

Fit: lme.formula(fixed = visual ~ week:treat - 1, data = dL.pp,
 subject)

Linear Hypotheses:

	Estimate	Std. Error	z value	Pr(> z)
delta == 0	-2.210	1.092	-2.023	0.0431 *

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ',' 1
 (Adjusted p values reported -- single-step method)

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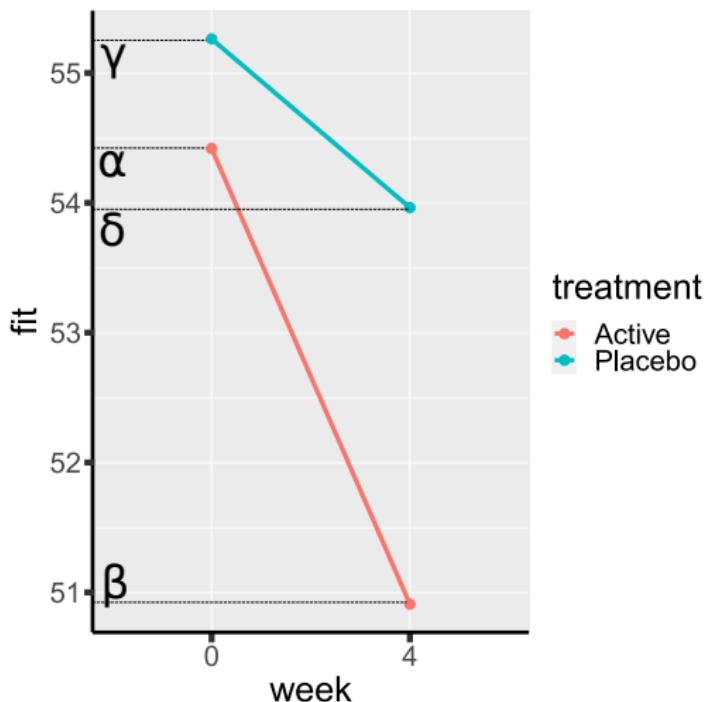
Multivariate model

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Natural parametrisation (3/3)



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Testing multiple null hypotheses

```
library(multcomp)
e.glht <- glht(e.lme,
linfct = c("week4:treatmentPlacebo=0",
          "treatmentPlacebo+week4:treatmentPlacebo=0"))
rownames(e.glht$linfct) <- c("change","final value")
summary(e.glht)
```

Simultaneous Tests for General Linear Hypotheses

Fit: lme.formula(fixed = visual ~ week * treatment, data = dL.pp
random = ~1 | subject)

Linear Hypotheses:

	Estimate	Std. Error	z value	Pr(> z)
change == 0	2.210	1.092	2.023	0.0828 .
final value == 0	3.054	2.023	1.510	0.2397
<hr/>				

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 / 44 1

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Multivariate linear model in R (no missing value)

```
e.gls <- gls(visual ~ week*treatment, data = dL.pp,
               correlation = corSymm(form=~1|subject),
               weight = varIdent(form=~1|treatment*week))
```

Correlation parameter (ρ):

```
coef(e.gls$modelStruct$corStruct, unconstrained=FALSE)
```

[1] 0.8571637

Reference variance parameter (σ^2)

Standard deviation inflation factor ($\{k_{A,4}, k_{P,0}, k_{P,4}\}$):

```
sigma(e.lme)^2
```

```
coef(e.gls$modelStruct$varStruct, unconstrained=FALSE)
```

[1] 34.45639

Active*4 Placebo*0 Placebo*4

1.0831625 0.9644284 1.0149006

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Multivariate linear model in R (no missing value)

Parametrisation

- Active group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{A,0} \\ \mu_{A,4} \end{bmatrix}, \begin{bmatrix} \sigma^2 & \rho \sigma^2 k_{A,4} \\ \rho \sigma^2 k_{A,4} & \sigma^2 k_{A,4}^2 \end{bmatrix} \right)$$

- Placebo group:

$$\begin{bmatrix} \text{visual}_{\text{week } 0} \\ \text{visual}_{\text{week } 4} \end{bmatrix} \sim \mathcal{N} \left(\begin{bmatrix} \mu_{P,0} \\ \mu_{P,4} \end{bmatrix}, \begin{bmatrix} \sigma^2 k_{P,0} & \rho \sigma^2 k_{P,0} k_{P,4} \\ \rho \sigma^2 k_{P,0} k_{P,4} & \sigma^2 k_{P,4}^2 \end{bmatrix} \right)$$

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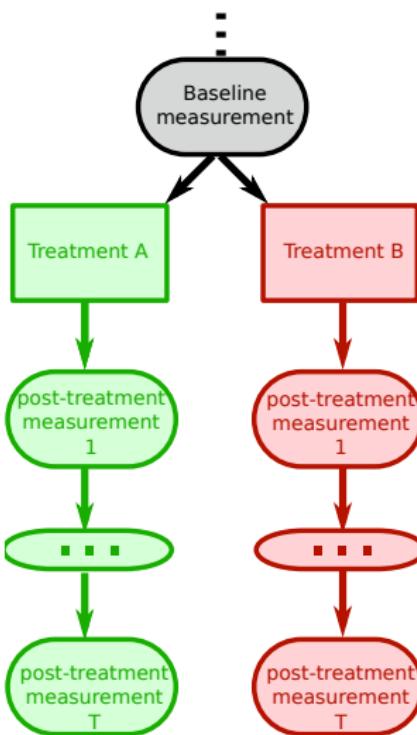
Multivariate model

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Conclusion

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○○○○○○●○

Design: longitudinal study



Introduction

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Pre-post study

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Multivariate model

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Conclusion

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Design: cross-over study

