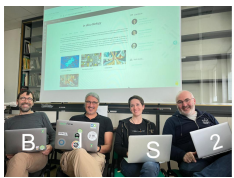
# Reminder on hypothesis testing

## Statistical test and p-value

H. Barbot




BIS2.0 Back2Basic, Mai 2025

# Guiding thread

## Differential gene expression

Goal: Identify genes which show a **difference** in expression between two experimental conditions (i.e. greater than expected just due to natural random variation).

You are Mathéo Lode, and you have acces to preclinical data. Tumoral cells are given to mice to see the efficiency of a treatment. Each condition (control and treatment) have 3 observations available of RNAseq data.

## Null and alternative hypothesis

We have two hypothesis, which one is the most likely ?

$$\begin{cases} H_0 : \text{the effect can't be observed at population scale} \\ H_1 : \text{the effect is observed at population scale} \end{cases}$$

We test the expression of one gene:

$$\begin{cases} H_0 : \text{We don't see a greater difference in expression than expected for this gene} \\ H_1 : \text{We find out a significant difference in expression for this gene} \end{cases}$$

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The **null hypothesis** $H_0$ is the presumption of innocence. We reject $H_0$ only if it is obvious that observations are incoherent with it.

*The null hypothesis is never proved or established, but is possibly disproved, in the course of experimentation* [Fisher et al., 1966],
*Absence of evidence is not evidence of absence* [Altman and Bland, 1995].

# Three keys of a statistical test

**Test** of $H_0$: rule to reject or not $H_0$ from data.

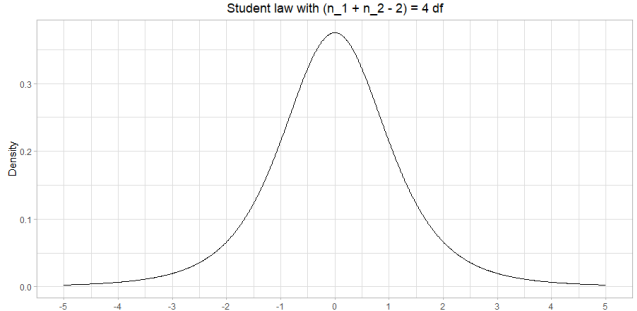
- **Test statisitic** $T$, it measure the effect: the more evident the effect, the greater the value of $T$.
- **Distribution** of $T$ under $H_0$. If the probability that $T$ being superior than 2 is below 5%, then observing $t_{gene1} = 3$ must lead to reject $H_0$.
- Test's **p-value**: the probability, under $H_0$, that the test statistic $T$ is greater than the observed value $t_{gene1}$.

If the **p-value** is smaller than a level $\alpha$ (usually $\alpha = 0.05$), then the effect is significative **at the level** $\alpha$.

# Reject zone on the distribution

We consider that the expression of the gene of interest have the same variance in the two experimental conditions, with respectively $n_1 = n_2 = 3$ observations.

We test the expression of this gene: $\begin{cases} H_0 : \mu_A = \mu_B \\ H_1 : \mu_A \neq \mu_B \end{cases}$, $T = \dfrac{\hat{\mu}_A - \hat{\mu}_B}{\sqrt{\frac{\hat{\sigma}^2}{n_1} + \frac{\hat{\sigma}^2}{n_2}}}$, $t_{gene1} = 3$



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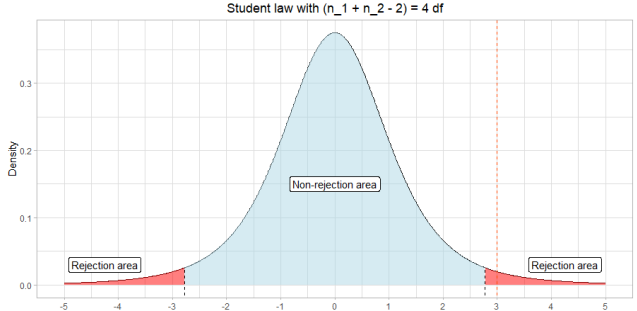
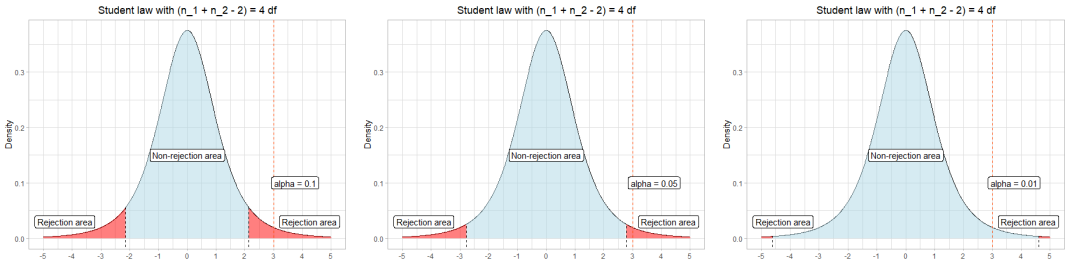


# Risks in statistical test

| | | TRUTH | |
|---|---|---|---|
| | | There is no effect<br>$H_0$ is true | There is an effect<br>$H_1$ is true |
| DECISION | Fail to reject $H_0$ | Good decision | $\beta$ (Type II error) |
| | Reject $H_0$ | $\alpha$ (Type I error) | Good decision<br>(power $1-\beta$) |


# Influence of risk $\alpha$

→ *a priori* fixed risk: Probability we accept to be wrong when the truth is a absence of effect.



## Influence of risk $\beta$

→ **Not a priori fixed risk**: At $\alpha$ fixed, a good test try to minimise $\beta$ (i.e. maximise the statistical power).

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- Means are largely different,
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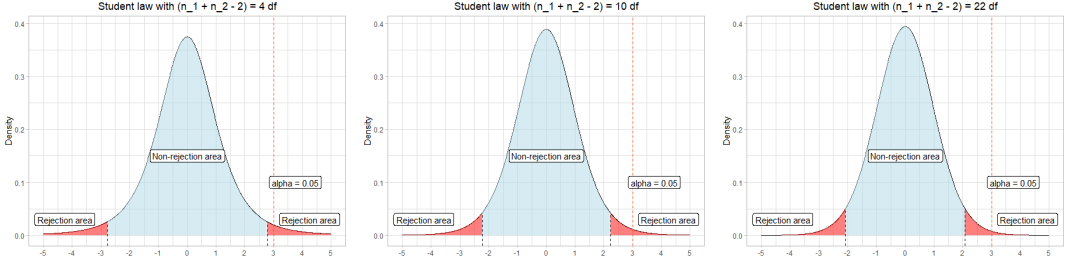

# Definition of p-value

For the distibution of $T$ under $H_0$, the p-value is the **smallest value** $\alpha$ where the test statistic $T$ is in the reject zone:

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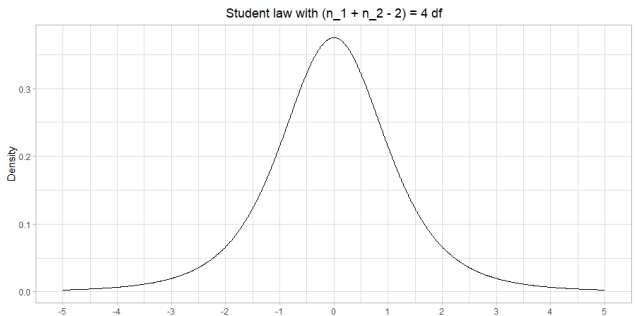

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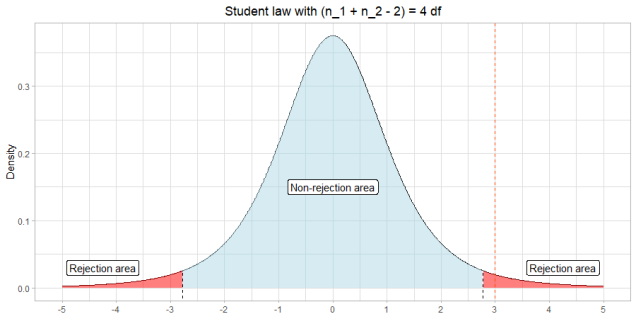

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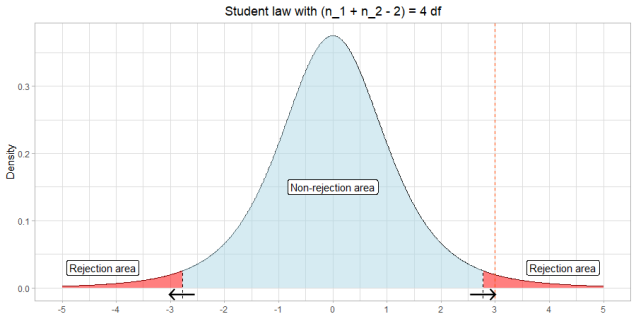

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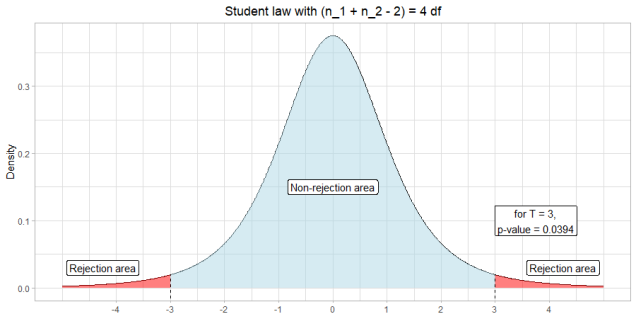
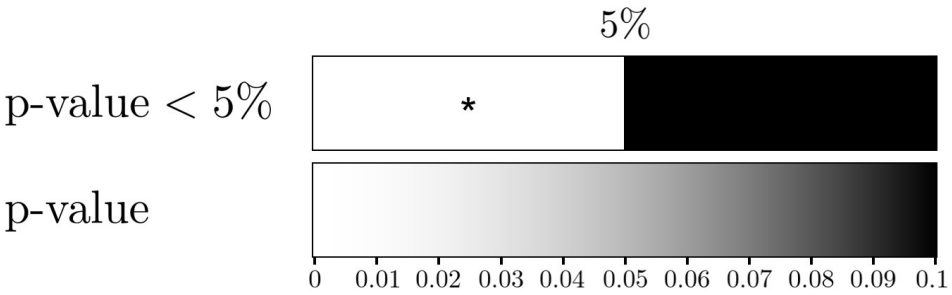


# A p-value can be interpretted




*There is a reason that the speedometer in your car doesn't just read "slow" and "fast". (F. Harrel, 'warning about the use of cutoffs after logistic regression' in R-help, 2011)*

# Non-parametric statistical tests

→ **Parametric tests** $\Longrightarrow$ Assumptions on data distribution (normality, homogeneity of variance, ...)

→ **Non-parametric tests** $\Longrightarrow$
- No assumptions of a specific distribution
- More reliable when data samples have a small size

# Non-parametric doesn't mean no assumptions

| | **parametric test** | **non-parametric test** |
|---|---|---|
| **use** | row data | row data, but a lot use ranks ▸ Supp details |
| **assume** | identically distributed and independent data, homogenous variance, ... | less needed, at least independent data |
| **power:** | optimal if assumptions are respected, drop quickly if not | stable/robust but less than parametric in the best case |

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Non-parametric test still have assumption:

- Wilcoxon-Mann-Whitney assume independent observations.
- Kruskal-Wallis is a non-parametric version of ANOVA, but assume all groups have an identically shaped and scaled distribution [Kruskal and Wallis, 1952] [Wikipedia, ].

# Testing all the genes

## Differential gene expression

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Since we fixed $\alpha = 0.05$, we expect 5% of the 20061 gene tested to be false positive, so **1003 genes or 31.1% of our list of gene differentialy expressed**.

# Multiple hypothesis

A null hypothesis collection, $H_0^{(k)}$ $k = 1, \ldots, m$, with $m_0$ true null hypothesis.

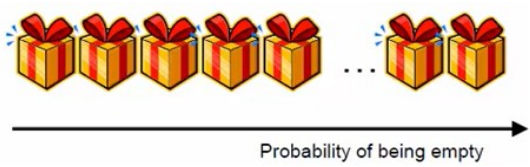
*m boxes out of which $m_0$ are empty*

*For the $k^{th}$ box, $H_0^{(k)}$: box is empty*

# Multiple p-values

For the $k^{th}$ test, the associated p-value is $p_k = \mathbb{P}_{H_0^{(k)}}\left(\text{reject } H_0^{(k)}\right)$.

*I weight each box and evaluate its probability $p_k$ of being empty*



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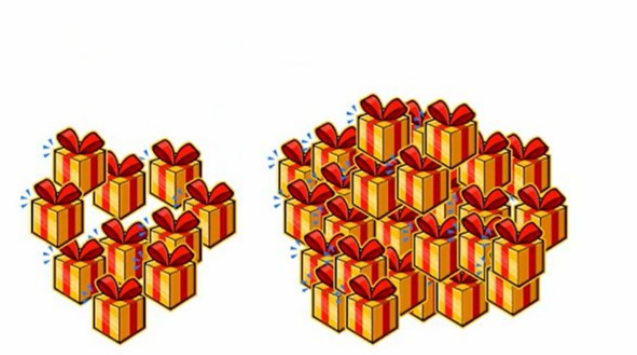

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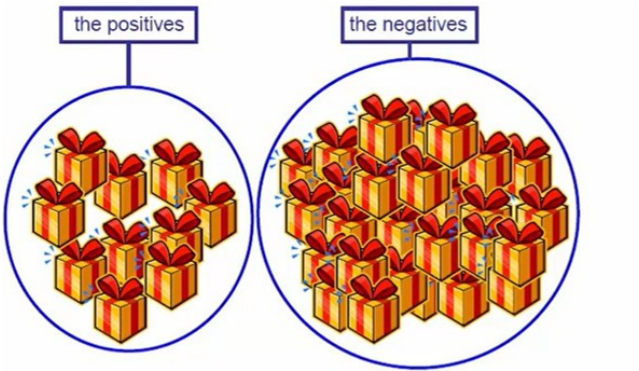


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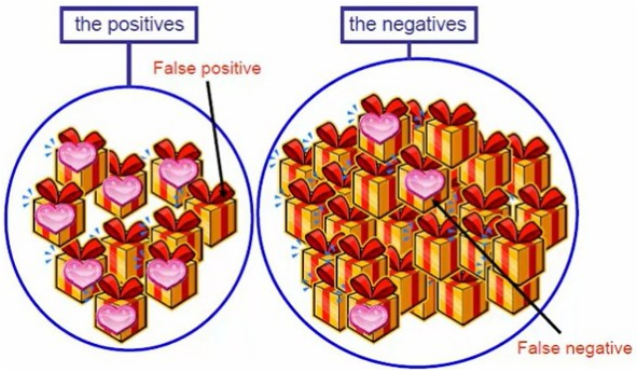


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## An efficient procedure

What is an **efficient procedure** ?

- Controlling the risk of false positive; as few disappointing discovery as possible.
- Great proportion of true positives within the positives; as much discovery as possible.
- No cofounding effects; knowing what we discover.

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What is an **efficient procedure** ?

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- No cofounding effects; knowing what we discover.

How to build an **efficient procedure** ?

1. A powerfull Design of Experiment; if the gift is much heavier than the box, it's easier.
2. A good choice for the threshold $\alpha$.

*While a good design does not guarantee a successful experiment, a suitably bad design guarantees a failed experiment—no results or incorrect results. (K.M. Kerr, 'Experimental design to make the most of microarray studies', 2003)*

# 1. Design of Experiment (DoE)

For example, we study our 2 conditions (**Control**/**Treatment**) with 8 samples each:

Day 1  8 **Control** samples

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Randomisation

# 1. Design of Experiment (DoE): Fractional plan


Especially if money is an issue, you can test multiple factors at the same time with a minimum of combination [Husson, ].

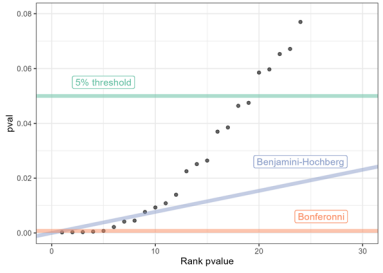
# 2. A good choice for the threshold $\alpha$

We want to have a decision rule on the $m$ p-values $p_k$, $1, \ldots, m$:

- At which threshold $\alpha$ do we reject $H_0^{(k)}$ ?
- If p-values are ordered, at which rank $\hat{k}$ p-values $p_{(1)}$ to $p_{(\hat{k})}$ lead to reject the null hypothesis, while p-values $p_{(\hat{k}+1)}$ to $p_{(m)}$ doesn't ?

For a threshold $\alpha$:

- $P_\alpha$: numbers of gene (gift box) which reject the null hypothesis (known).
- $FP_\alpha$: numbers of gene (gift box) which wrongly reject the null hypothesis (unknown).



# Family Wise error rate (FWER)

To define the new threshold $\alpha_{FWER}$, we set:

$$\text{FWER}_{\alpha_{FWER}} \leqslant \mathbb{P}\big(\text{FP}_{\alpha_{FWER}} > 0\big) = \alpha, \quad \text{equivalently } \mathbb{P}\big(\text{FP}_{\alpha_{FWER}} = 0\big) \geq 1 - \alpha$$

## Bonferroni procedure

If the number of expected false positive discovery is $\text{FP}_\alpha = m \times \alpha$ we only have to take

$$\alpha_{FWER} = \frac{\alpha}{m}.$$

The same result is obtain if we **adjust p-values**: $p_k \leqslant \frac{\alpha}{m} \Leftrightarrow \tilde{p}_k = mp_k \leqslant \alpha$. Supp details

$\Rightarrow$ FWER procedures tends to be very restrictive with few false positive.

In our case, $\alpha_{FWER} = \frac{0.05}{20061} = 2.492 \times 10^{-6}$ which lead to 38 positive genes.

# False discovery rate (FDR)

To define the new threshold $\alpha_{FDR}$, we set:

$$\text{FDR}_{\alpha_{FDR}} = \mathbb{E}\left[\frac{FP_{\alpha_{FDR}}}{P_{\alpha_{FDR}}}\right] \leqslant \alpha$$

## Benjamini-Hochberg procedure

The number of false positive is unknown, so we control the number of positive and estimate the esperance of fale positive. For that, we order p-values and for the $k^{th}$ p-value we have

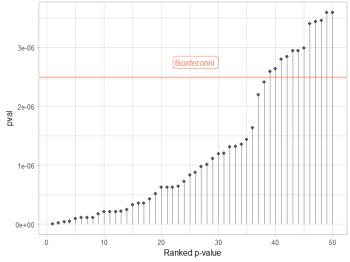
$$\alpha_{FDR} = k\frac{\alpha}{m}.$$

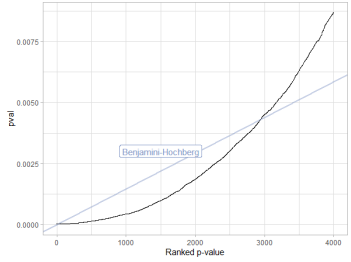
Again we can rather look at **adjust p-values**: $\tilde{p}_k = \frac{mp_k}{k} \leqslant \alpha$. Supp details

$\Rightarrow$ FDR procedures are less demanding than FWER, and provides much more positives.

In our case, $\alpha_{FDR} = k\frac{0.05}{20061}$ which lead to 1958 positive genes ($\alpha_{FDR} = 0.00488$).

# Ranked p-values



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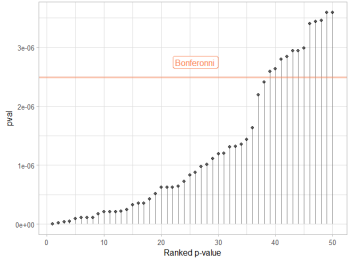


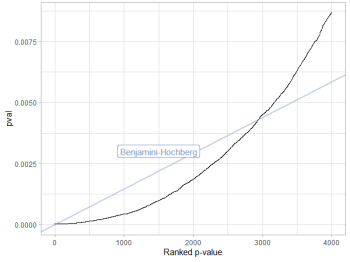


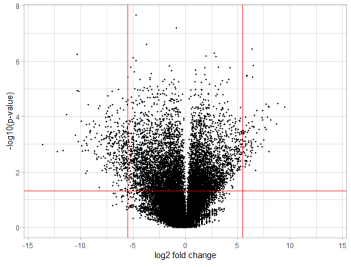

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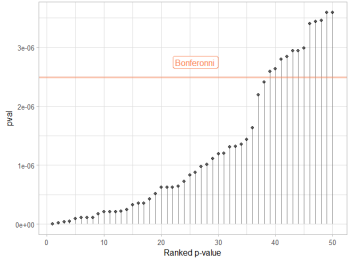
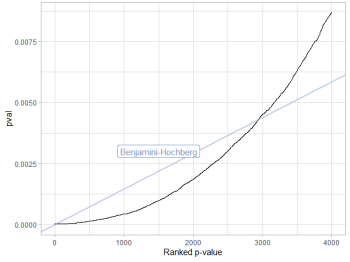
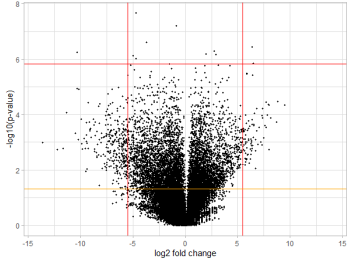
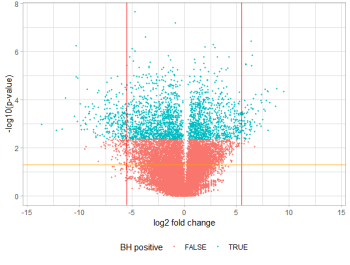
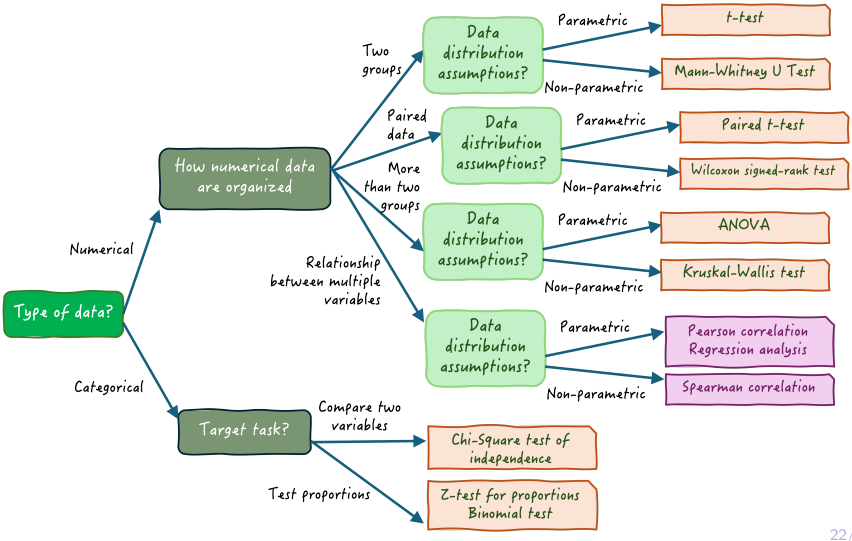


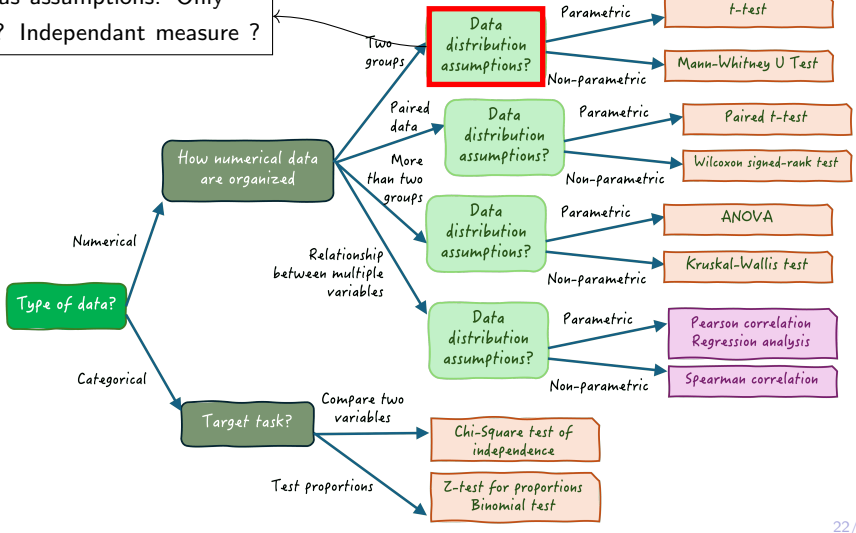



# Decision tree have gaps



# Decision tree have gaps

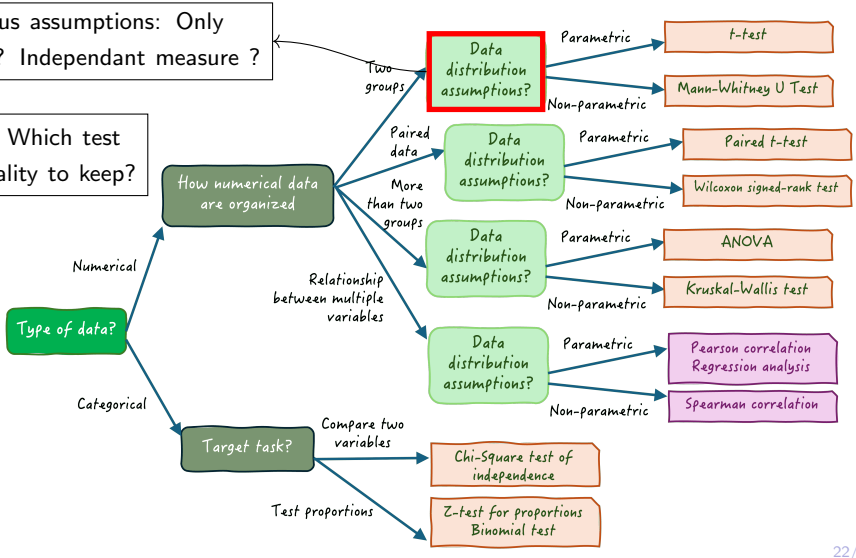
Oversimplified or ambiguous assumptions: Only normal ? same variance too ? Independant measure ?



# Decision tree have gaps

Oversimplified or ambiguous assumptions: Only normal ? same variance too ? Independant measure ?

Doesn't prevent p-hacking: Which test for homoscedasticity or normality to keep?

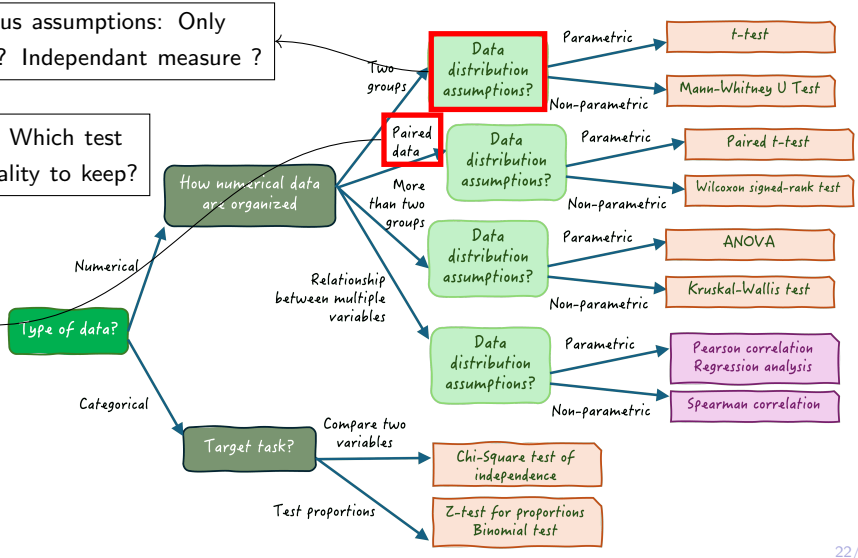


# Decision tree have gaps

Oversimplified or ambiguous assumptions: Only normal ? same variance too ? Independant measure ?

Doesn't prevent ▸ p-hacking: Which test for homoscedasticity or normality to keep?

Some knowledge require to use ▸ paired data or modern method (mixture models, ...)

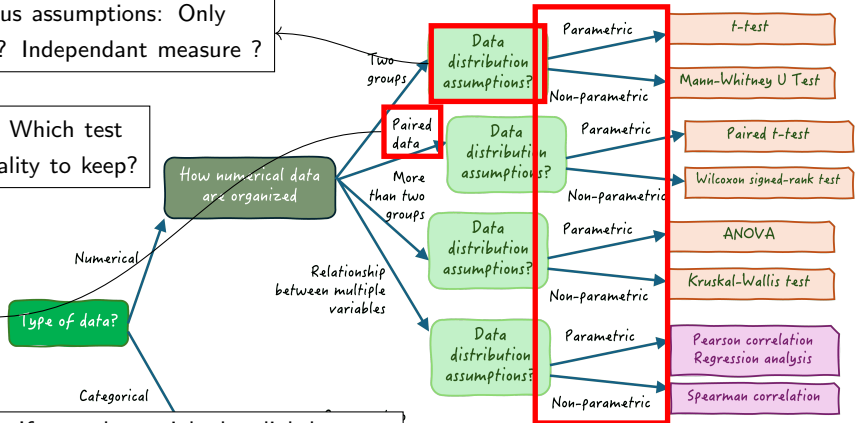


# Decision tree have gaps

Oversimplified or ambiguous assumptions: Only normal ? same variance too ? Independant measure ?

Doesn't prevent p-hacking: Which test for homoscedasticity or normality to keep?

Some knowledge require to use paired data or modern method (mixture models, permutations, . . . )




Statistics aren't sequential: If your data might be slightly non-normal (suggesting a non-parametric test) but you have a large sample size, a parametric test is robust despite non-normality.

# Decision trees are good reminders (like this presentation)

You knew 90% of all tests used, but now you better understand what you do with them: how they work and what they assume. With these new insights, you precise your limits of understanding and when you reach it.

**Take home message**

→ Use decision trees as a starting point rather than a definitive guide [MacFarland et al., 2016], consult statistical literature for complex cases.

→ With great power comes great responsability [Stan Lee, ], you make arbitrary choices (and it's ok). Always understand why each decision point matters.

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# Common non-parametric tests

non-parametric tests assumptions

| Test | Data Type Used | Note |
|---|---|---|
| **Rank-based tests** | | |
| Mann–Whitney U (Wilcoxon rank-sum) | Ranks | Compares ranks between two independent groups. |
| Wilcoxon signed-rank test | Ranks of differences | Based on the ranks of paired differences. |
| Kruskal–Wallis | Ranks | Extension of Mann–Whitney to $k$ independent groups. |
| Friedman | Ranks within blocks | For $k$ repeated measures or blocks, ranks computed within each block. |
| Spearman's $\rho$ | Ranks | Monotonic rank correlation. |
| Kendall's $\tau$ | Pair orderings | Measures concordance/discordance. |
| **Tests using raw data (or categories)** | | |
| Sign test | Signs ($\pm$) | Uses only the sign of differences, not their magnitude or rank. |
| McNemar's test | Binary categories | Counts discordances in a $2 \times 2$ before/after contingency table. |
| Chi-squared test of independence | Counts | Works on cell frequencies in a contingency table. |
| Kolmogorov–Smirnov test | Raw values | Compares empirical distribution functions. |
| Lilliefors test | Raw values | Adaptation of KS for normality testing without fixed parameters. |
| Log-rank test | Survival times | Compares survival curves based on exact event times. |

# Bonferroni procedure

FWER

$$\begin{aligned} \text{FWER} &= \mathbb{P}\big([p_1 \leqslant \alpha_{FWER}] \text{ or } \ldots \text{ or } [p_m \leqslant \alpha_{FWER}]\big) \\ &\leqslant \mathbb{P}\big([p_1 \leqslant \alpha_{FWER}]\big) + \ldots + \mathbb{P}\big([p_m \leqslant \alpha_{FWER}]\big) \\ &\leqslant m_0 \times \alpha_{FWER} \end{aligned}$$

If $\alpha_{FWER} = \frac{\alpha}{m}$, then FWER $= \frac{m_0}{m}\alpha \leqslant \alpha$.

# Benjamini-Hochberg procedure

$$\begin{aligned} \text{FDR} &= \mathbb{E}\left[\frac{FP_{\alpha_{FDR}}}{P_{\alpha_{FDR}}}\right] = \frac{\mathbb{E}\left[FP_{\alpha_{FDR}}\right]}{P_{\alpha_{FDR}}} \\ &= \frac{m_0\ \alpha_{FDR}}{P_{\alpha_{FDR}}} = \frac{m_0}{m}\frac{m\ \alpha_{FDR}}{P_{\alpha_{FDR}}} \leq \frac{m\ \alpha_{FDR}}{P_{\alpha_{FDR}}}. \end{aligned}$$

If, for the $k^{th}$ p-value, $\alpha_{FDR} = k\frac{\alpha}{m}$, then $\text{FDR} \leqslant \alpha$.

# p-hacking

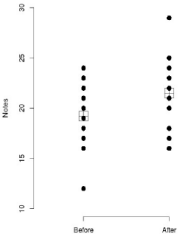
Decision tree doesn't prevent p-hacking [Head et al., 2015]: Which normal test will you keep, qq-plot, $\chi^2$ adequation, Kolmogorov-Smirnov, Lilliefors, Anderson-Darling, Shapiro-Wilks,... Same question for homoscedasticity.

A comparison of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling test concluded that Shapiro-Wilk have the best power for the same significance level, followed by Anderson-Darling [Razali et al., 2011].

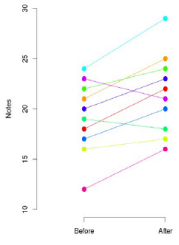
# Example of paired data

Statistical tree

| Before | After |
|---|---|
| 18 | 22 |
| 21 | 25 |
| 16 | 17 |
| 22 | 24 |
| 19 | 18 |
| 24 | 29 |
| 17 | 20 |
| 20 | 23 |
| 23 | 21 |
| 12 | 16 |




| | Before | After |
|---|---|---|
| Louise | 18 | 22 |
| Léo | 21 | 25 |
| Emma | 16 | 17 |
| Gabriel | 22 | 24 |
| Chloé | 19 | 18 |
| Adam | 24 | 29 |
| Lola | 17 | 20 |
| Timéo | 20 | 23 |
| Inès | 23 | 21 |
| Raphaël | 12 | 16 |




```
R> wilcox.test(x, y, paired = FALSE)
Wilcoxon rank sum test with continuity
correction

W = 35, p-value = 0.2716
alternative hypothesis: true location shift
is not equal to 0


R> t.test(x, y, paired = FALSE)
Two Sample t-test

t = -1.3529, df = 18, p-value = 0.1928
alternative hypothesis: true difference in
means is not equal to 0
```

```
R> wilcox.test(x, y, paired = TRUE)
Wilcoxon rank sum test with continuity
correction

V = 5, p-value = 0.02428
alternative hypothesis: true location shift
is not equal to 0


R> t.test(x, y, paired = TRUE)
Two Sample t-test

t = -3.1461, df = 9, p-value = 0.01181
alternative hypothesis: true difference in
means is not equal to 0
```