# Accounting for Covariates (i.e. nuisances) with Multivariate Permutation tests

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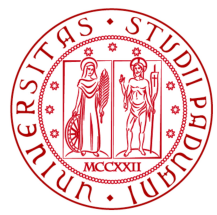
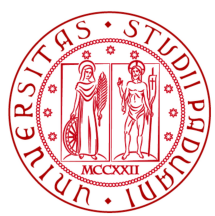


# (minimal) Bibliography

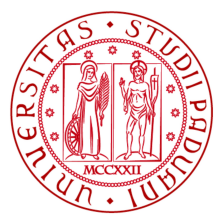

- Anderson M. Winkler, Gerard R. Ridgway, Matthew A. Webster, Stephen M. Smith, Thomas E. Nichols (2014) Permutation inference for the general linear model. NeuroImage, 92, doi.org/10.1016/j.neuroimage.2014.01.060
- Sara Kherad-Pajouh, Olivier Renaud (2010) An exact permutation method for testing any effect in balanced and unbalanced fixed effect ANOVA. Computational Statistics and Data Analysis. doi:10.1016/j.csda.2010.02.015
- Aldo Solari, Livio Finos and Jelle Goeman (2014) Rotation-based multiple testing in the multivariate linear model. Biometrics, 70, doi.org/10.1111/biom.12238

# Motivating example

- Acute Lymphoblastic Leukemia data (Chiaretti et al., 2004)
- $n = 128$ patients
- $p = 12625$ gene expression profiles
- covariate of interest: `group` (B or T-cell type patients)
- differentially expressed genes between the two groups?

$$\texttt{gene} = \gamma_0 + \beta \cdot \texttt{group} + \texttt{error}$$



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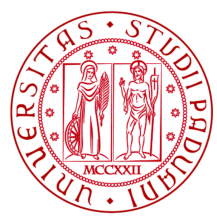
$$\begin{bmatrix} \texttt{gene}_1 \\ \vdots \\ \texttt{gene}_p \end{bmatrix} = \begin{bmatrix} \gamma_{01} \\ \vdots \\ \gamma_{0p} \end{bmatrix} + \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_p \end{bmatrix} \cdot \texttt{group} + \begin{bmatrix} \texttt{error}_1 \\ \vdots \\ \texttt{error}_p \end{bmatrix}$$



# Multivariate linear model

$$\mathbf{Y} = \mathbf{1}\mathbf{G}_{1\times p} + \mathbf{X}\mathbf{B}_{1\times p} + \mathbf{E}$$

- $\mathbf{Y}$ : $(n \times p)$ matrix of responses
- $\mathbf{X}$ : $(n \times 1)$ matrix of covariates (`group`)
- $\mathbf{E} \sim (\mathbf{0}_{n\times p}, \mathbf{I}_n \otimes \mathbf{\Sigma})$ matrix of errors

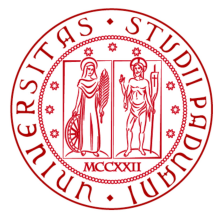
  $\mathbf{\Sigma}$ : $(p \times p)$ gene-gene covariance matrix

## Marginal model ($j$-th gene)

$$\mathbf{y}_j = \mathbf{1}\gamma_{0j} + \mathbf{X}\boldsymbol{\beta}_j + \boldsymbol{\varepsilon}_j, \qquad \boldsymbol{\varepsilon}_j \sim (\mathbf{0}_{n\times 1}, \sigma_j^2 \mathbf{I}_n)$$

## Multiple hypotheses

$$H_j : \boldsymbol{\beta}_j = \mathbf{0}, \ \forall \boldsymbol{\gamma}_j \qquad j = 1, \ldots, p$$



# The Multiple Testing Problem

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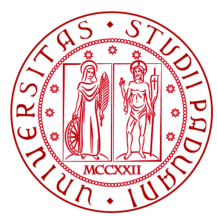

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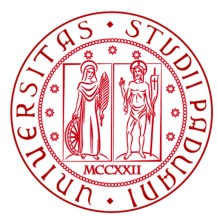

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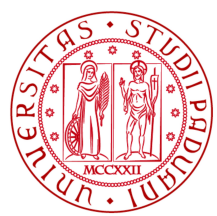
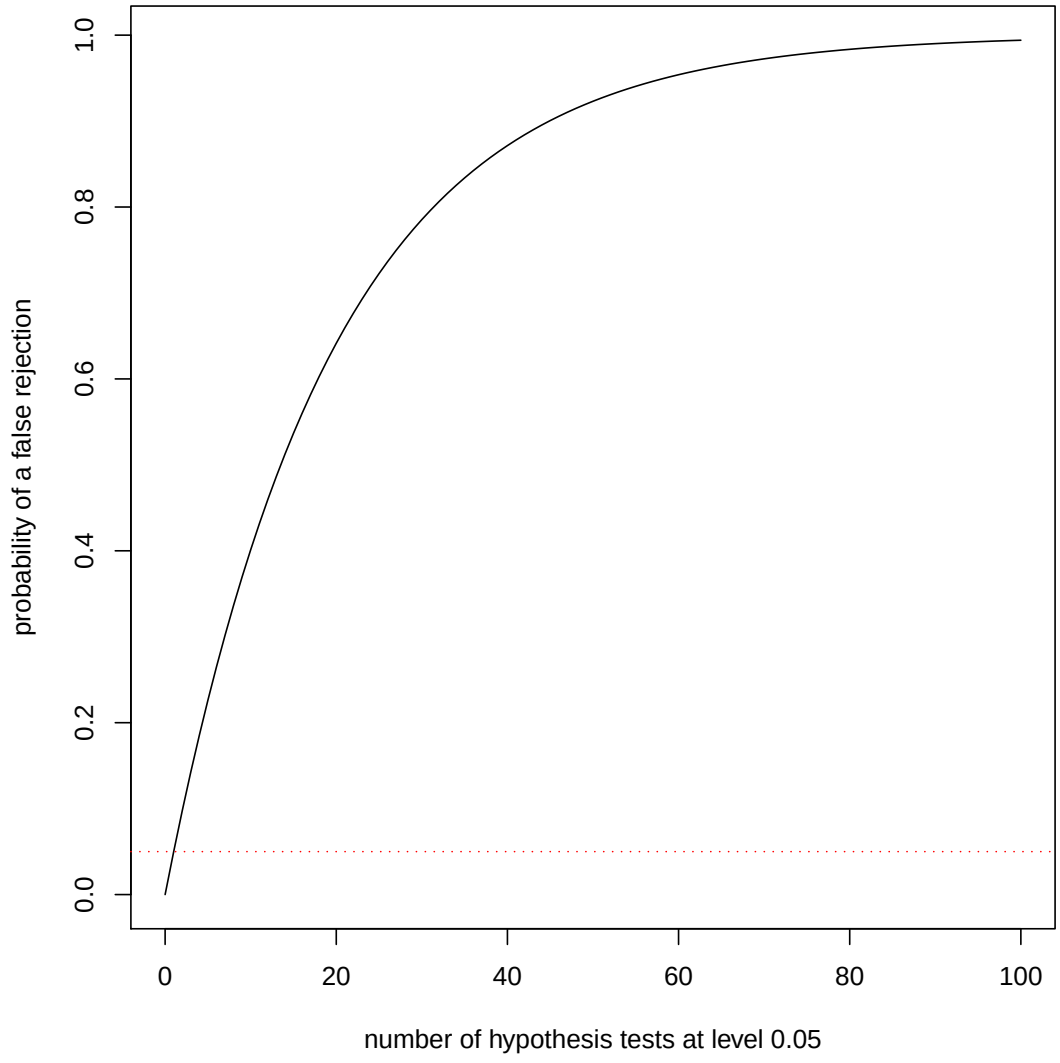
$H_{0j} : \beta_j = 0$ (= two grous are equal) $\quad j = 1, \ldots, p$

one p-value for each gene ($p$)



# Type I error if not correcting for multiple testing




# . . . a very common problem

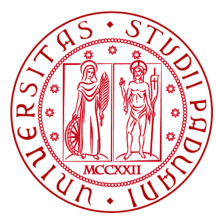
The problem of multiplicity control arises when more than one (statistical) hypothesis is tested
(12625 in this case, one for each gene).

This problem is very common in many (other) fields of medicine:

- clinical trials with multiple endpoints
- neuroimaging experiments

and in many other fields like:

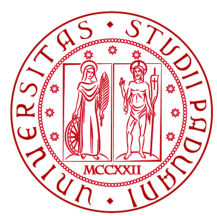
- psycho-sociological
- ecological
- quality control
- many others...



# Familywise Error Rate (FWER)

FWER:
probability of one or more false positives (i.e. wrong rejections)

The most well-known method controlling the FWER:
Holm procedure (Holm, 1979).
Based on step-wise application of Bonferroni inequality:
hence: reject genes with $p_i \leq \alpha/(\#\ \text{of genes})$, $i = 1, \ldots, 12625$



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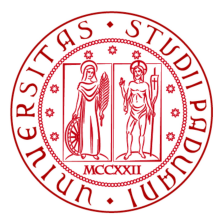

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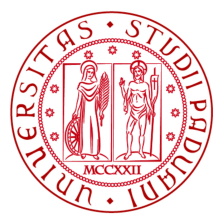
BUT becomes very conservative when dependencies are strong.



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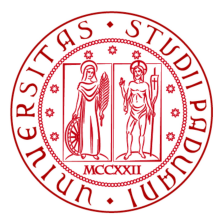
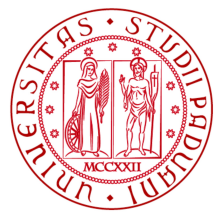
BUT becomes very conservative when dependencies are strong.
Permutation tests are often a solution.



# Outline



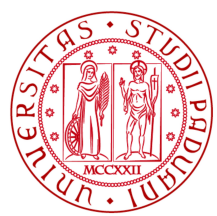


# (Multivariate) Permutation tests

Under $H_0 : \bigcap_{j=1}^{p} H_j$,

$$\mathbf{Y} \stackrel{\mathrm{d}}{=} \mathbf{\Pi Y}$$

for every permutation matrix $\mathbf{\Pi}$ (*null-invariant transformation*) i.e. Exchangeability: $f(\mathbf{Y}) = f(\mathbf{\Pi Y})$



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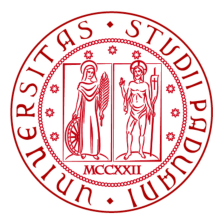
## When it holds

re-sampling null datasets is possible

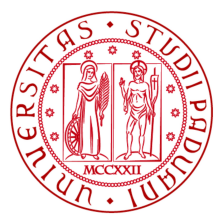
$$n\text{-vector } \mathbf{X} = \begin{cases} -1/n_B & \text{if B patient,} \\ +1/n_T & \text{if T patient.} \end{cases}$$

(vector of) Test Statistic: $t_{obs} = \mathbf{X}^\top \mathbf{Y}$
(vector of) Test Statistic of permuted data: $t_{\mathbf{\Pi}} = \mathbf{X}^\top \mathbf{\Pi Y}$



# Joint distributions of P-values

- Observed statistic is any among possible permutations ($\Pi = \mathbb{I}$)
- compute test statistics on every possible permutation or sample them (e.g. 10 000 random permutations).



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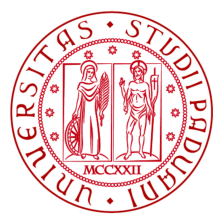

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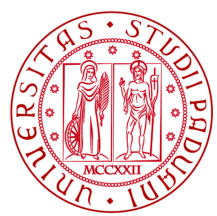
- Compute the joint distribution of p-values from joint dist. of test statistic
  (compute p-values for observed test stat. and for all permuted test stats.)



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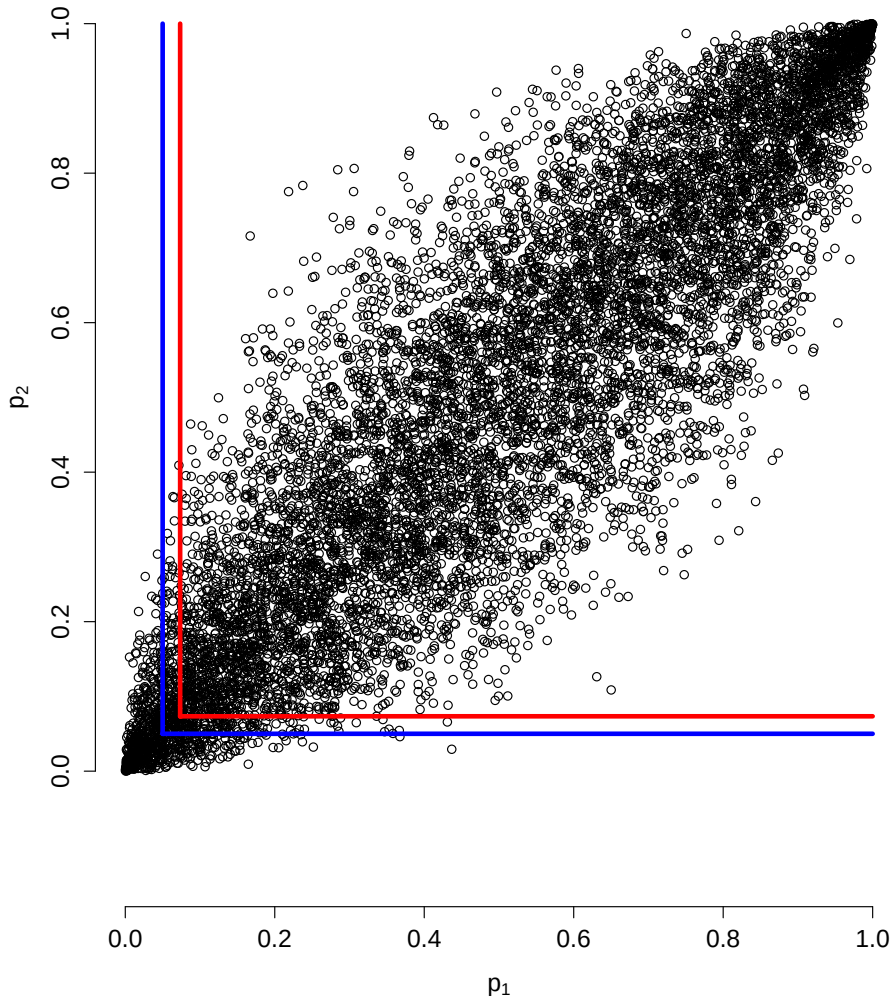



- Hypothesis:

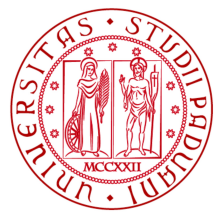
$$H : H_1 \cap H_2$$

- min-p test:

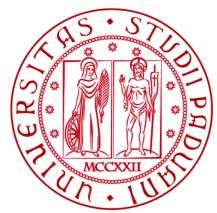
$$\Pr_H \left\{ \min(p_1, p_2) < c \right\} \leq \alpha$$

- Bonferroni inequality:

$$c = \alpha/2$$



# Holm vs Westfall & Young min-p



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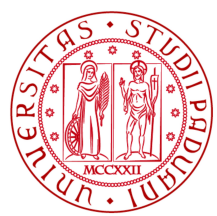

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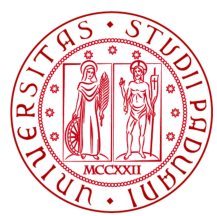

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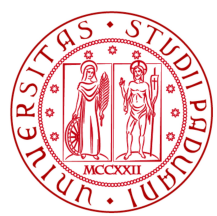
both provides a list of adjusted p-values
W&Y is usually more powerful
(i.e. lower adjusted p-values, more rejections) than Holm



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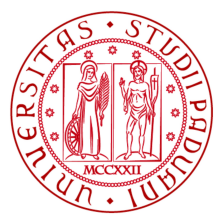

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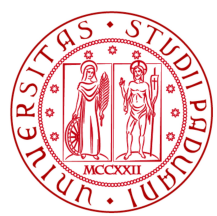
You can perform it on `R` using
`library(multtest)` or `library(flip)`



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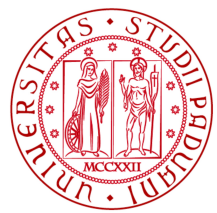

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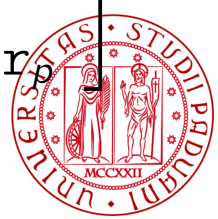
- Acute Lymphoblastic Leukemia data (Chiaretti et al., 2004)
- $n = 128$ patients
- $p = 12625$ genes
- covariate of interest: `group` (B or T-cell type patients)
- confounder: `sex`
- differentially expressed genes between the two groups?

$$\texttt{gene} = \gamma_0 + \gamma_1 \cdot \texttt{sex} + \beta \cdot \texttt{group} + \texttt{error}$$

$$\begin{bmatrix} \texttt{gene}_1 \\ \vdots \\ \texttt{gene}_p \end{bmatrix} = \begin{bmatrix} \gamma_{01} \\ \vdots \\ \gamma_{0p} \end{bmatrix} + \begin{bmatrix} \gamma_{11} \\ \vdots \\ \gamma_{1p} \end{bmatrix} \cdot \texttt{sex} + \begin{bmatrix} \beta_1 \\ \vdots \\ \beta_p \end{bmatrix} \cdot \texttt{group} + \begin{bmatrix} \texttt{error}_1 \\ \vdots \\ \texttt{error}_p \end{bmatrix}$$



# Multivariate linear model

$$\mathbf{Y} = \mathbf{ZG} + \mathbf{XB} + \mathbf{E}$$

- $\mathbf{Y}$ : $(n \times p)$ matrix of responses
- $\mathbf{X}$ : $(n \times q)$ matrix of covariates (`group`)
- $\mathbf{Z}$ : $(n \times 2)$ intercept and `sex`
- $\mathbf{E} \sim (\mathbf{0}_{n \times p}, \mathbf{I}_n \otimes \mathbf{\Sigma})$ matrix of errors

  $\mathbf{\Sigma}$ : $(p \times p)$ gene-gene covariance matrix

## Marginal model ($j$-th gene)

$$\mathbf{y}_j = \mathbf{Z}\boldsymbol{\gamma}_j + \mathbf{X}\boldsymbol{\beta}_j + \boldsymbol{\varepsilon}_j, \qquad \boldsymbol{\varepsilon}_j \sim (\mathbf{0}_{n \times 1}, \sigma_j^2 \mathbf{I}_n)$$

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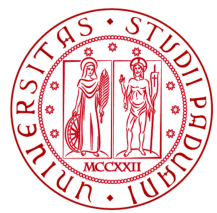
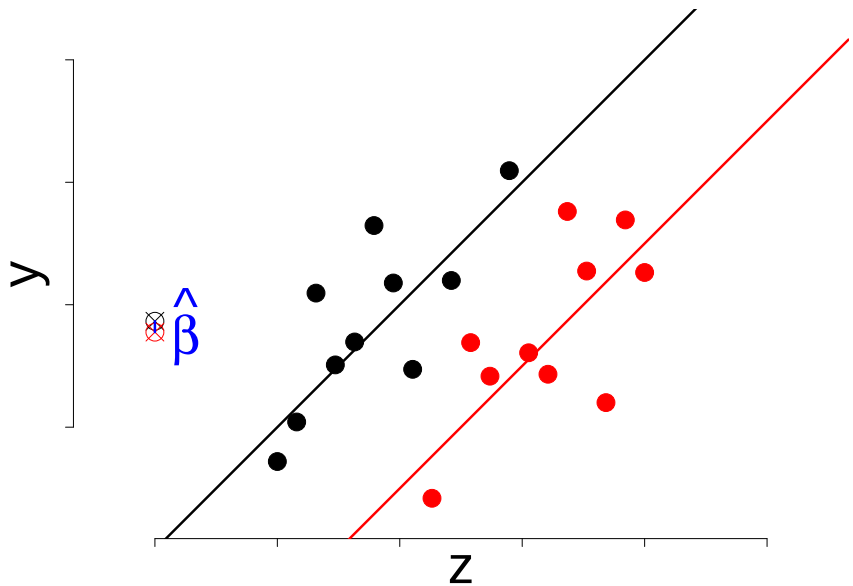


# Ignoring the confounders

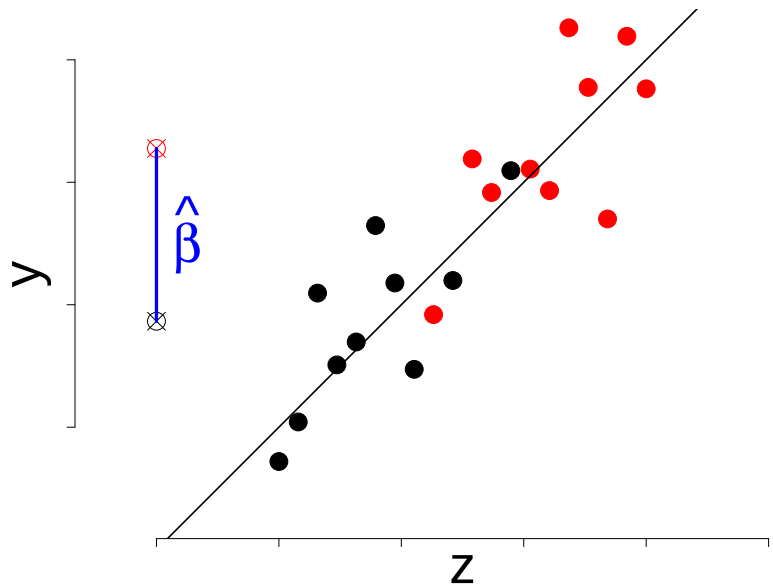
Drop **Z** from the model:

$$\mathbf{Y} = \mathbf{XB} + \mathbf{E}$$

false negative ($\beta \neq 0$, $\hat{\beta} \approx 0$)




false positive ($\beta = 0$, $\hat{\beta} \neq 0$)

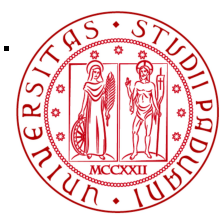


# Goal

Permutation methods are very useful in multiple testing since they easily deal with dependencies even when $p >> n$. e.g.

- Westfall & Young min-p (controls the FamilyWise Error Rate)
- Meinshausen method (controls the proportion of False Rejections)
- Statistical NonParametric Mapping (SnPM, controls the FWER at cluster-level)

There are no standard solutions accounting for covariates
Permutation of the observed response $\mathbf{Y}$ is not a valid solution.
We need a valid method to account for confounders.



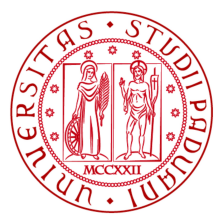
# Adjusting for confounders

Residuals of $\mathbf{Z}$ i.e.
Project $\mathbf{Y}$ into the subspace $\perp$ to $\mathrm{span}(\mathbf{Z})$:

$$\begin{aligned} \mathbf{Y} &= \mathbf{ZG} + \mathbf{XB} + \mathbf{E} \\ (\mathbf{I}_n - \mathbf{H})\mathbf{Y} &= (\mathbf{I}_n - \mathbf{H})\mathbf{ZG} + (\mathbf{I}_n - \mathbf{H})\mathbf{XB} + (\mathbf{I}_n - \mathbf{H})\mathbf{E} \\ & \quad ((\mathbf{I}_n - \mathbf{H})\mathbf{ZG} = 0) \\ (\mathbf{I}_n - \mathbf{H})\mathbf{Y} &= (\mathbf{I}_n - \mathbf{H})\mathbf{XB} + (\mathbf{I}_n - \mathbf{H})\mathbf{E} \end{aligned}$$

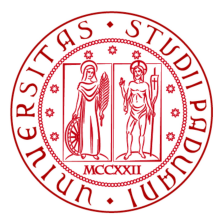
where

- $\mathbf{H} = \mathbf{Z}(\mathbf{Z}^\top\mathbf{Z})^{-1}\mathbf{Z}^\top$ is the $n \times n$ projection matrix
- $(\mathbf{I}_n - \mathbf{H})$ is the $n \times n$ 'residualizing' matrix



# Exchangeability

- Null model: $(\mathbf{I}_n - \mathbf{H})\mathbf{Y} = (\mathbf{I}_n - \mathbf{H})\mathbf{E} \sim (\mathbf{0}_{n\times p}, (\mathbf{I}_n - \mathbf{H}) \otimes \mathbf{\Sigma})$
- $(\mathbf{I}_n - \mathbf{H})\mathbf{Y} \overset{\mathrm{d}}{\neq} \Pi(\mathbf{I}_n - \mathbf{H})\mathbf{Y}$
  where $\Pi$: permutation matrix (*null-invariant transformation*)



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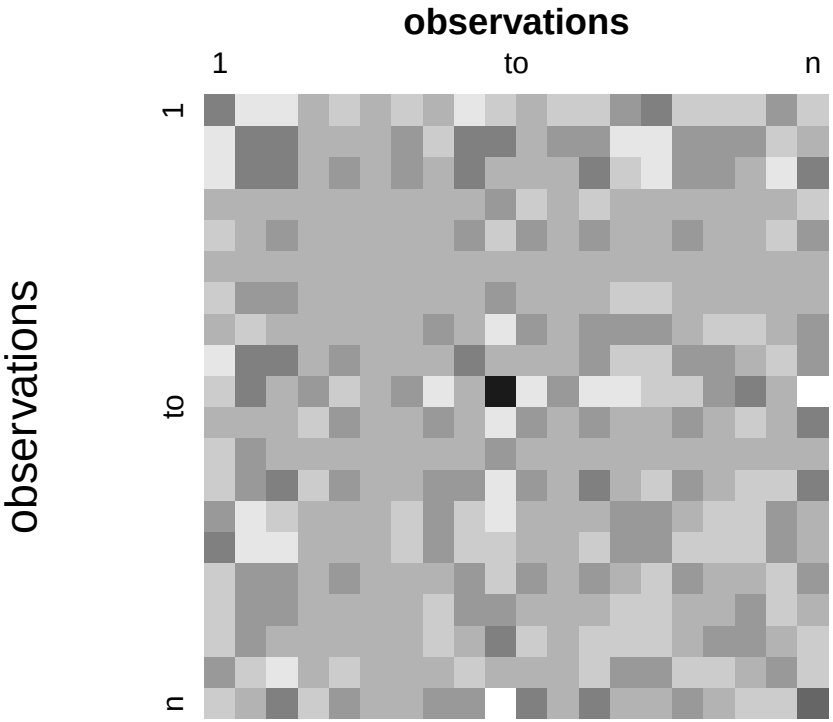
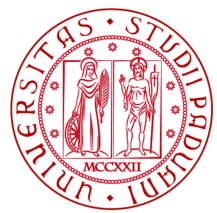
  where $\Pi$: permutation matrix (*null-invariant transformation*)
  i.e. observations are not exchangeable anymore :(

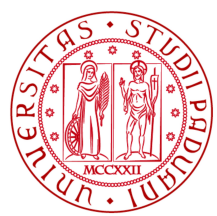
a look to $(\mathbf{I}_n - \mathbf{H})$:



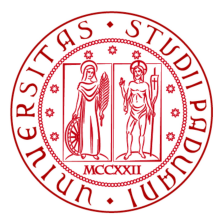
**solutions to be discussed:**

- permutation for factor (i.e. discrete)
- permutation/rotation for covariates (i.e. continuous + discrete)



# Nuisance Factors (i.e. Discrete)

In our example, `sex` is a 2-levels factor



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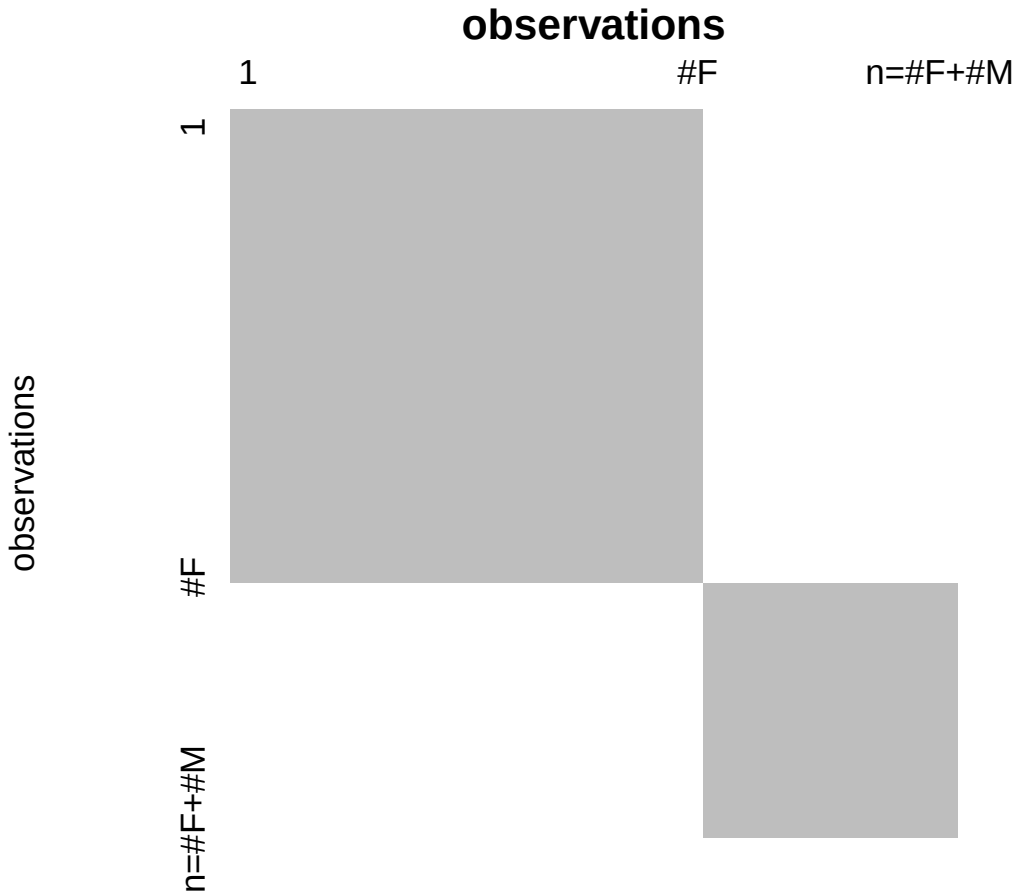
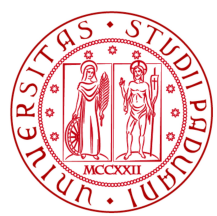
a look to $H_0$



# Nuisance Factors (i.e. Discrete)

**Solution:**

permutations within each strata of confounder:
(i.e. within Female and Male)



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Exchangeability within strata implies EXACT control of the type I error,
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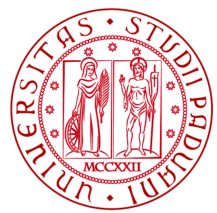

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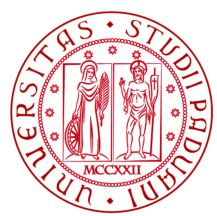
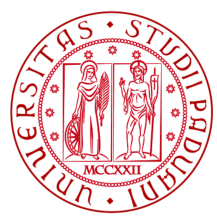
**Special case:**
exact solution for paired samples (and one-sample) test with hetheroscedastic errors (few more slides upon request)



# Paired samples

$$\mathbf{Y} = \mathbf{ZG} + \mathbf{XB} + \mathbf{E}$$

- $\mathbf{X}$ : treatments $\mathbf{X} = (-1, +1, -1, +1, \ldots, -1, +1)$
- $\mathbf{Z}$ : $n/2$ dummy variables, one for each subject.



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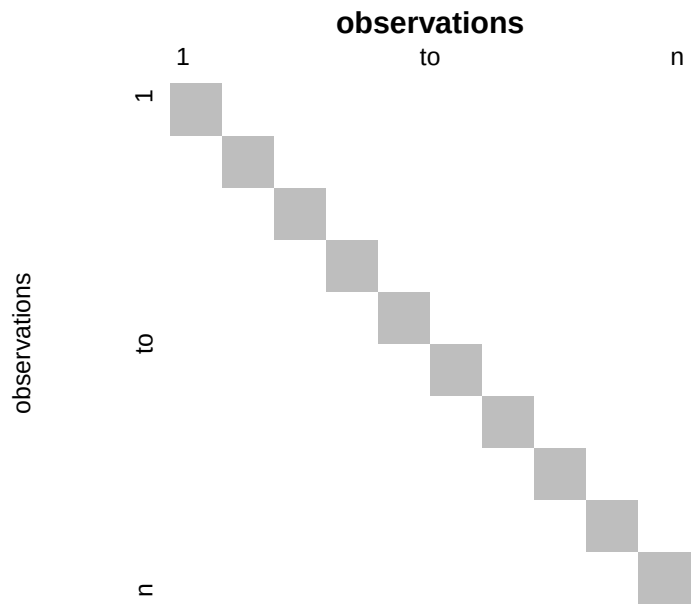
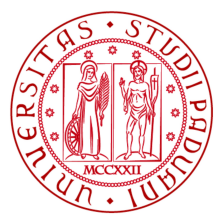
**a look to $H_0$**



# Paired samples

**Permutation solution:**

- $\Pi$: flip responses only within the same subject
- test statistic: $\mathbf{X}^\top(\mathbf{I}_n - \mathbf{H})\Pi(\mathbf{I}_n - \mathbf{H})\mathbf{Y}$
- (equivalent to standard permutation test for paired sample)
- subject-specific model (e.g. variance) is allowed.
- (still) Exact control of Type I error.



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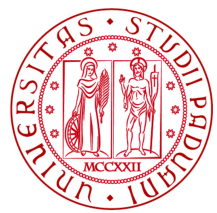
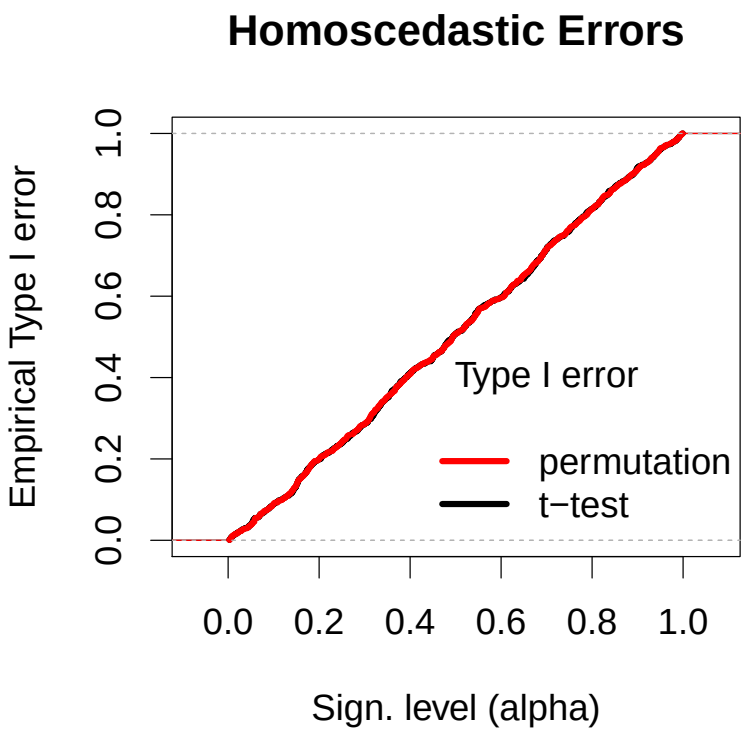
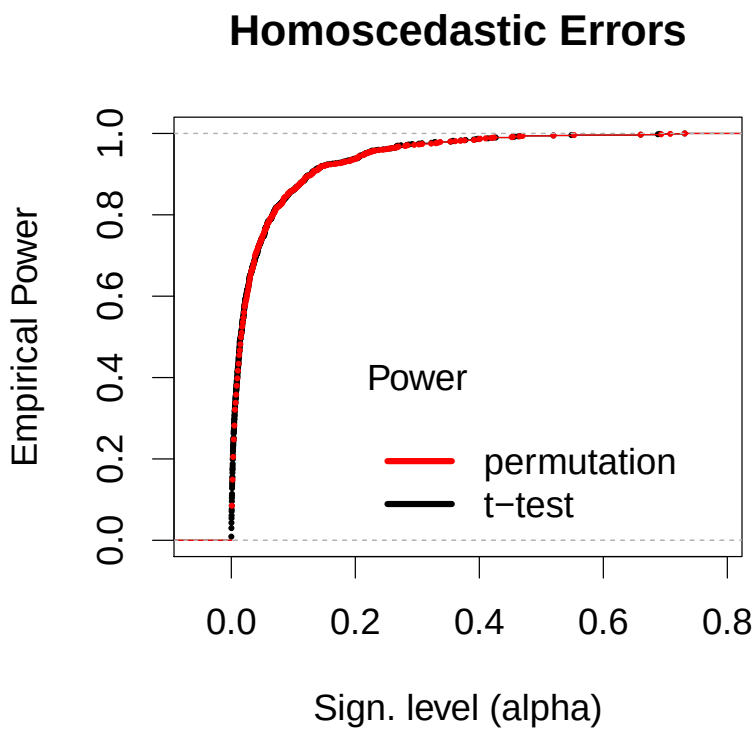
**parametric vs nonparametric: a small simulation**

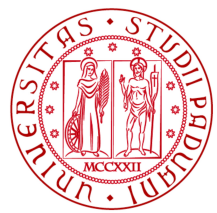
- $n = 10$,
- normal, Homoscedastic errors and
- normal, Heteroscedastic errors
  (non linear growth of variance from 1 to n)



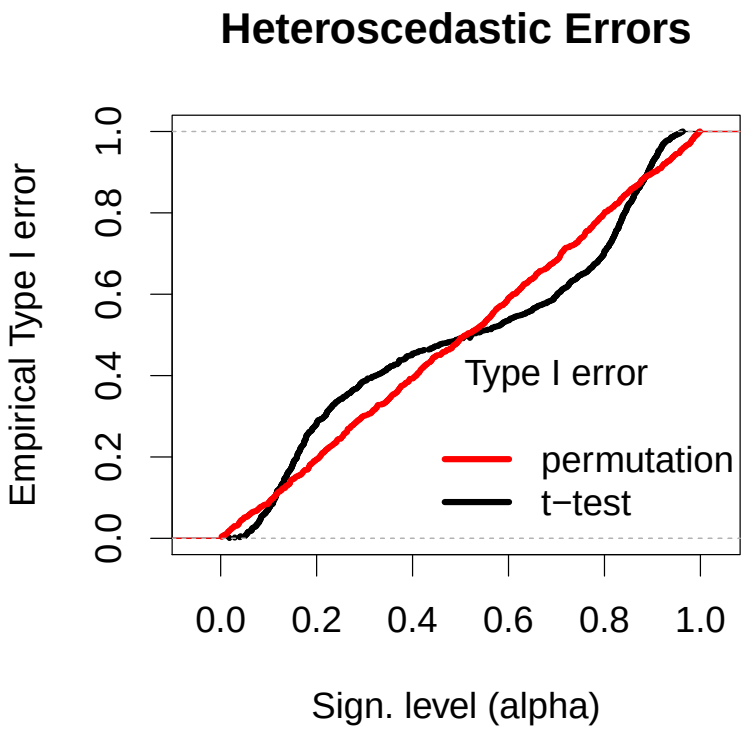
# Paired samples - Homoscedastic

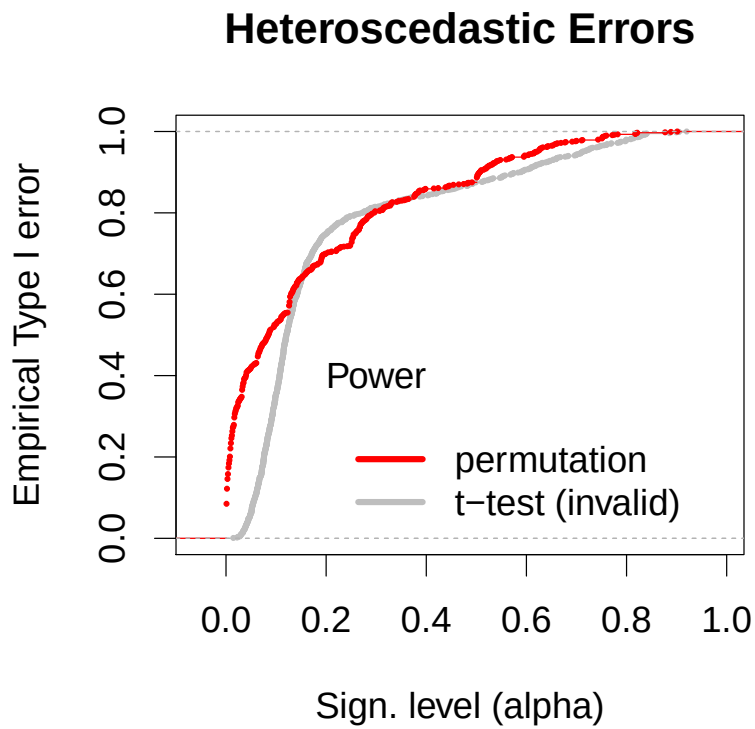


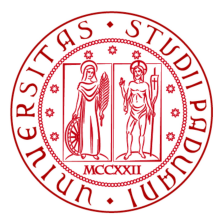
# Paired samples - Heteroscedastic




$t = \frac{\bar{x}_{diff} - \mu_{diff}}{\sqrt{\hat{\sigma}^2_{diff}/n}}$: parametric t estimates $\hat{\sigma}^2_{diff}$,

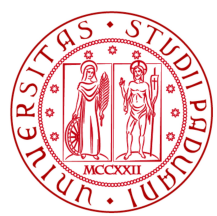
while permutation test does not!



# Nuisance Covariates (i.e. Quantitative)

- Acute Lymphoblastic Leukemia data (Chiaretti et al., 2004)
- $n = 128$ patients
- $p = 12625$ genes
- covariate of interest: `group` (B or T-cell type patients)
- quantitative confounder(s): `age` (+ `sex`)
- differentially expressed genes between the two groups?

$$\texttt{gene} = \gamma_0 + \gamma_1 \cdot \texttt{age} + \beta \cdot \texttt{group} + \texttt{error}$$



# Multivariate linear model

The Multivariate linear model of course is the same:

$$\mathbf{Y} = \mathbf{ZG} + \mathbf{XB} + \mathbf{E}$$

- $\mathbf{Y}$ : $(n \times p)$ matrix of responses
- $\mathbf{X}$ : $(n \times q)$ matrix of covariates (`group`)
- $\mathbf{Z}$ : $(n \times c)$ matrix of confounders, $c < n$
- $\mathbf{E} \sim (\mathbf{0}_{n \times p}, \mathbf{I}_n \otimes \mathbf{\Sigma})$ matrix of errors

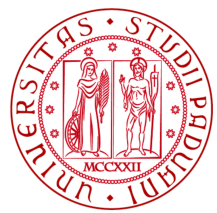
  $\mathbf{\Sigma}$ : $(p \times p)$ gene-gene covariance matrix

## Marginal model ($j$-th gene)

$$\mathbf{y}_j = \mathbf{Z}\boldsymbol{\gamma}_j + \mathbf{X}\boldsymbol{\beta}_j + \boldsymbol{\varepsilon}_j, \qquad \boldsymbol{\varepsilon}_j \sim (\mathbf{0}_{n \times 1}, \sigma_j^2 \mathbf{I}_n)$$

## Multiple hypotheses

$$H_j : \boldsymbol{\beta}_j = \mathbf{0}, \ \forall \boldsymbol{\gamma}_j \qquad j = 1, \ldots, p$$

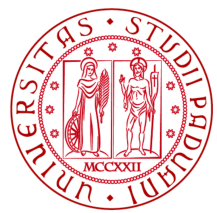


# Loss of exchangeability

For continuous variables:

$(\mathbf{I}_n - \mathbf{H})$ is not a block matrix, there are no strata

(NO permutations within strata)



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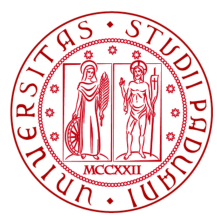

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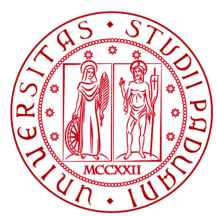

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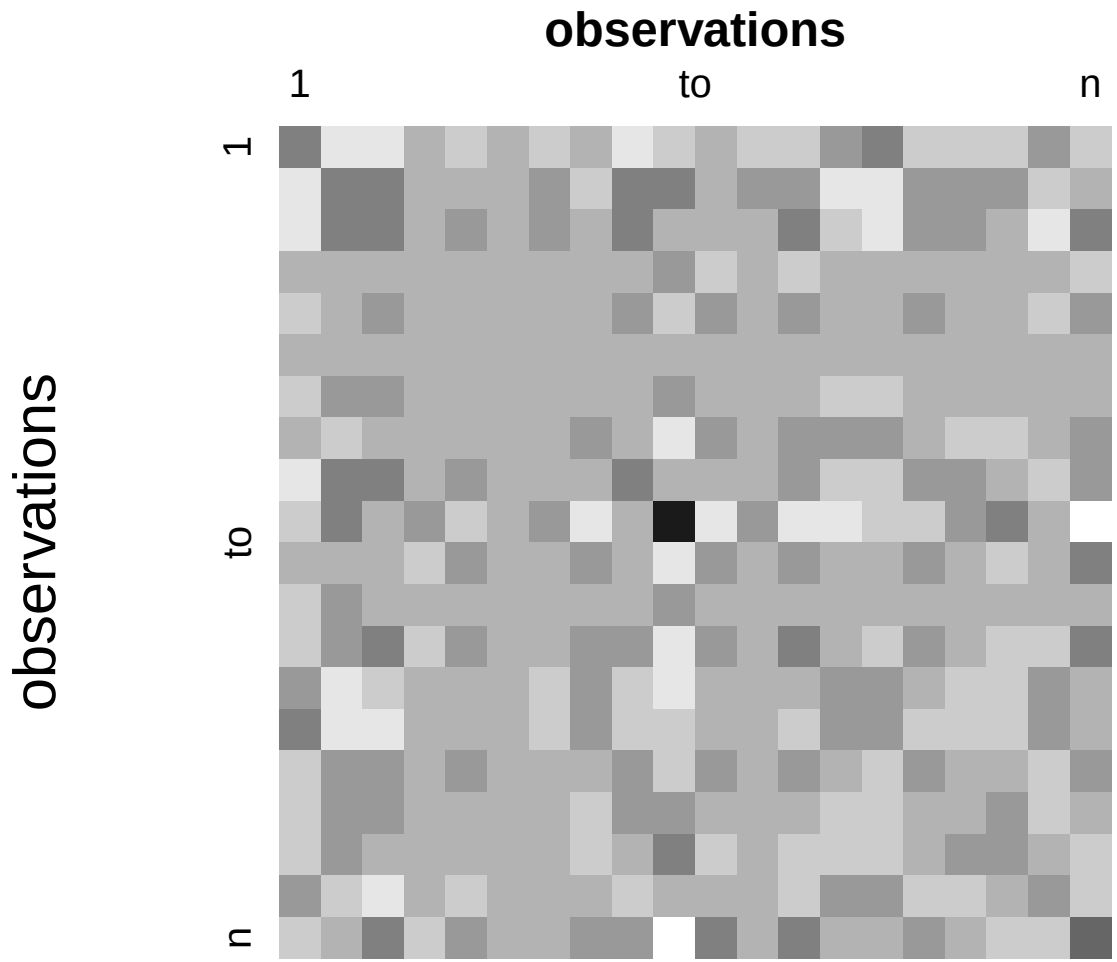
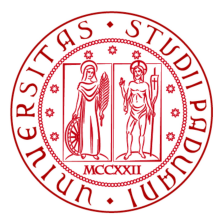


# Recovering the (weak) randomization hypothesis

- $(\mathbf{I}_n - \mathbf{H}) = \mathbf{Q}\mathbf{Q}^\top$ with $\mathbf{Q}^\top\mathbf{Q} = \mathbf{I}_{n-c}$

  $(\mathbf{I}_n - \mathbf{H})$ idempotent (i.e. eigenvalues 1 or 0),

  $\mathbf{Q}$ matrix of $n - c$ (orthogonal) eigenvectors of $(\mathbf{I}_n - \mathbf{H})$.



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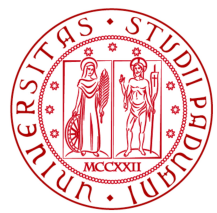

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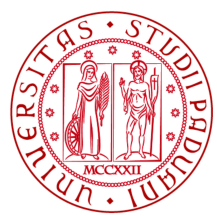
\mathbf{Q}^\top\mathbf{Y} &= \mathbf{Q}^\top\mathbf{XB} + \mathbf{Q}^\top\mathbf{E} \\
\tilde{\mathbf{Y}} &= \tilde{\mathbf{X}}\mathbf{B} + \tilde{\mathbf{E}}
\end{aligned}
$$

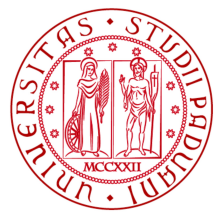


# Recovering the (weak) randomization hypothesis

- Under the Null model:

$$\begin{aligned} \mathbf{Q}^\top(\mathbf{I}_n - \mathbf{H})\mathbf{Y} &= \mathbf{Q}^\top(\mathbf{I}_n - \mathbf{H})\mathbf{E} \\ \mathbf{Q}^\top\mathbf{Y} &= \mathbf{Q}^\top\mathbf{E} \\ \tilde{\mathbf{Y}} &= \tilde{\mathbf{E}} \end{aligned}$$

- $\tilde{\mathbf{Y}} \sim (\mathbf{0}_{(n-c)\times p}, \mathbf{I}_{n-c} \otimes \mathbf{\Sigma})$
  $\tilde{\Pi}\tilde{\mathbf{Y}} \sim (\mathbf{0}_{(n-c)\times p}, \tilde{\Pi}\mathbf{I}_{n-c}\tilde{\Pi}^\top \otimes \mathbf{\Sigma})$ (n-c orthogonal rows) i.e. permute the orthogonalized residuals $\tilde{\mathbf{Y}}$ instead of $(\mathbf{I}_n - \mathbf{H})\mathbf{Y}$
- $\tilde{\mathbf{Y}}$ and $\tilde{\Pi}\tilde{\mathbf{Y}}$ have the same first two moments, therefore we can perform approximated permutation tests.
- as a consequence, asymptotic control of the type I error (hint: test stat is asymptotically normal by CLT + normal distribution has null higher moments)

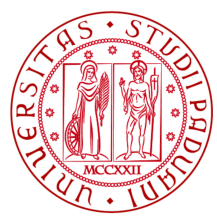


# Rotation Tests

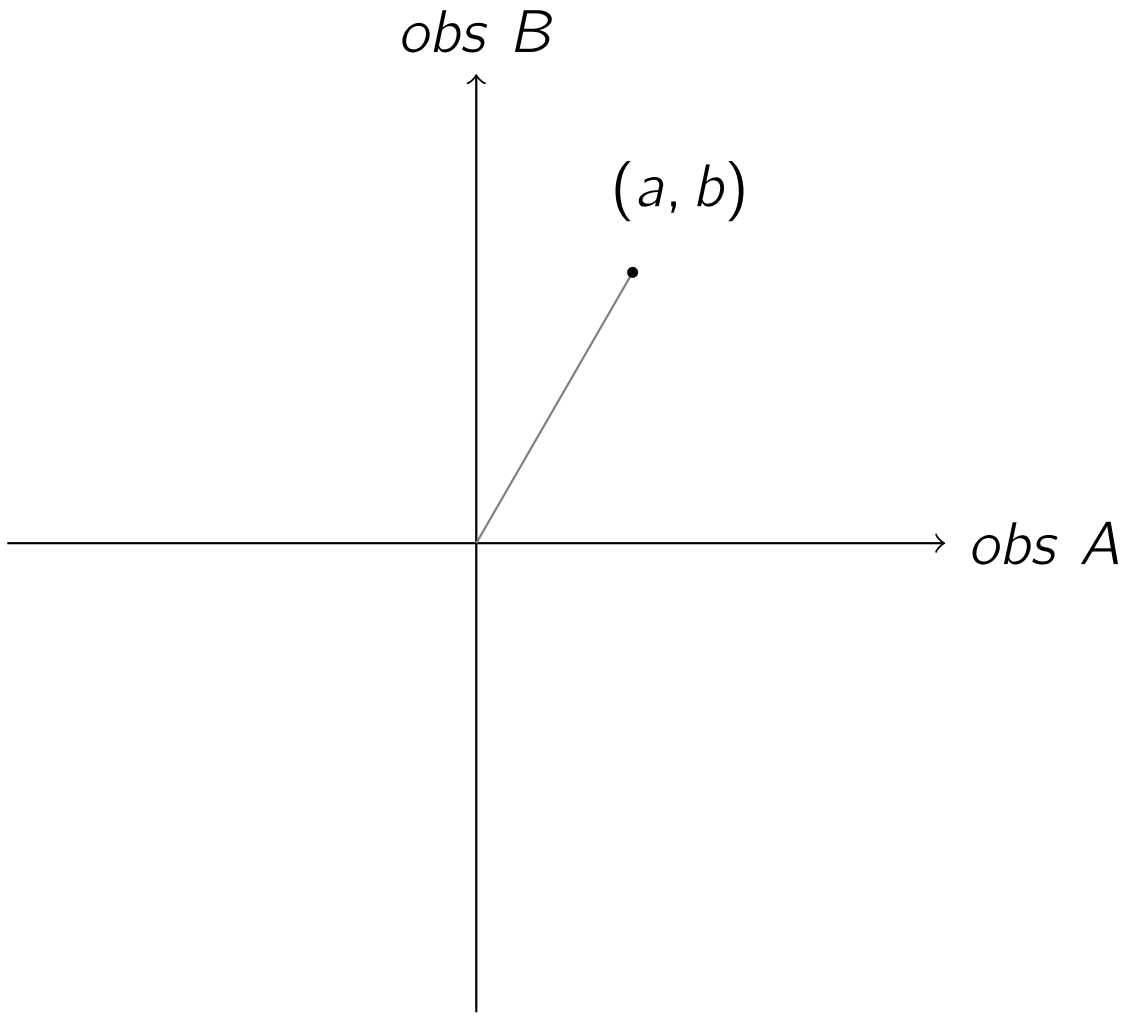
Since we renounced to exactness, we get a broader class of transformations that preserve first two moments:

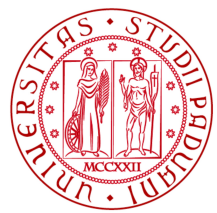
**rotation test:**

- Same as permutation but use rotations $\tilde{\mathbb{O}}$ instead of permutations $\tilde{\Pi}$.
- i.e. random generate orthogonal basis ($\tilde{\mathbb{O}}^{\mathsf{T}}\tilde{\mathbb{O}} = \mathbf{I}_{n-c}$)
- test statistic: $\tilde{\mathbf{X}}^{\mathsf{T}}\tilde{\mathbb{O}}\tilde{\mathbf{Y}}$
- Langsrud (2005), Perry and Owen (2010)



# Rotations vs Permutations



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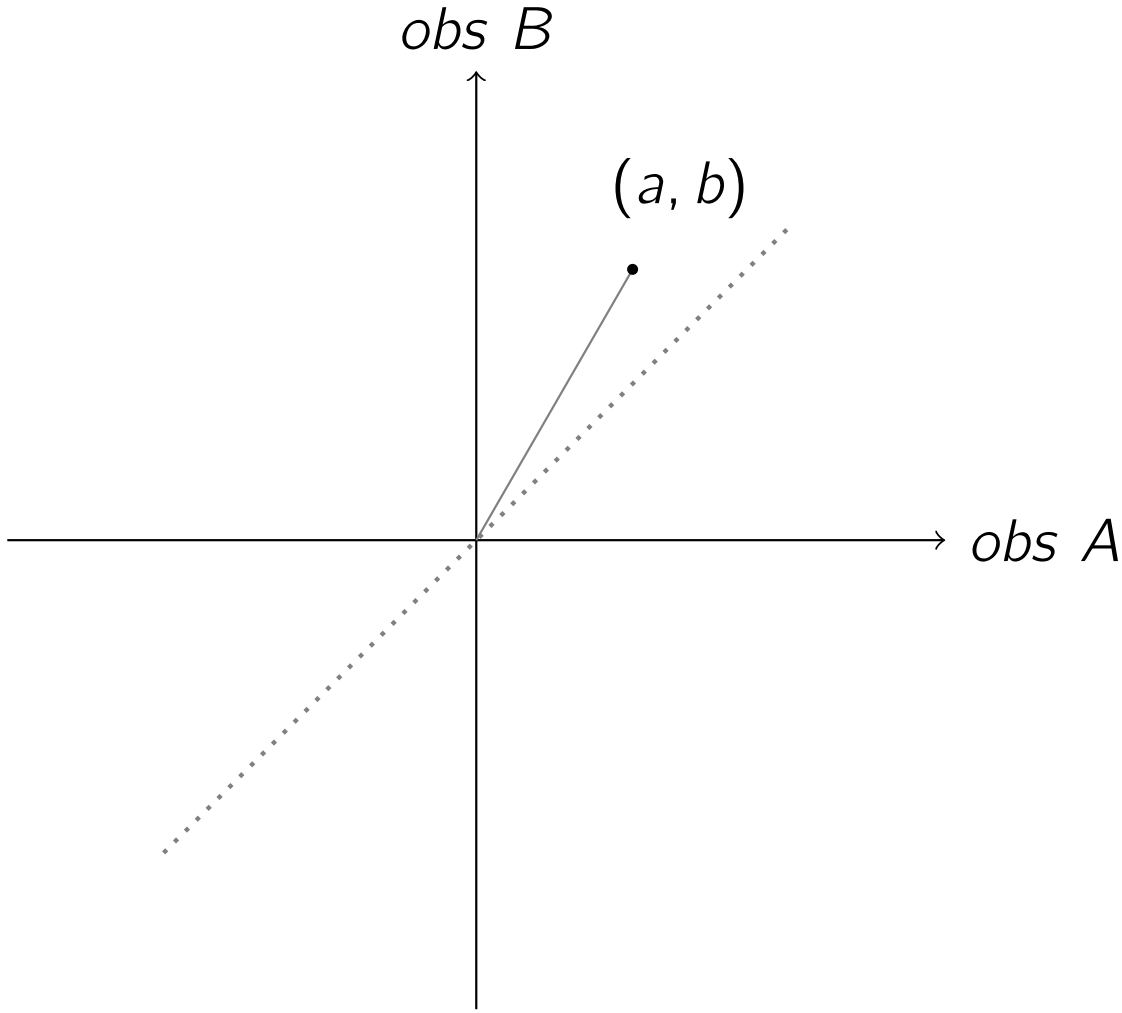

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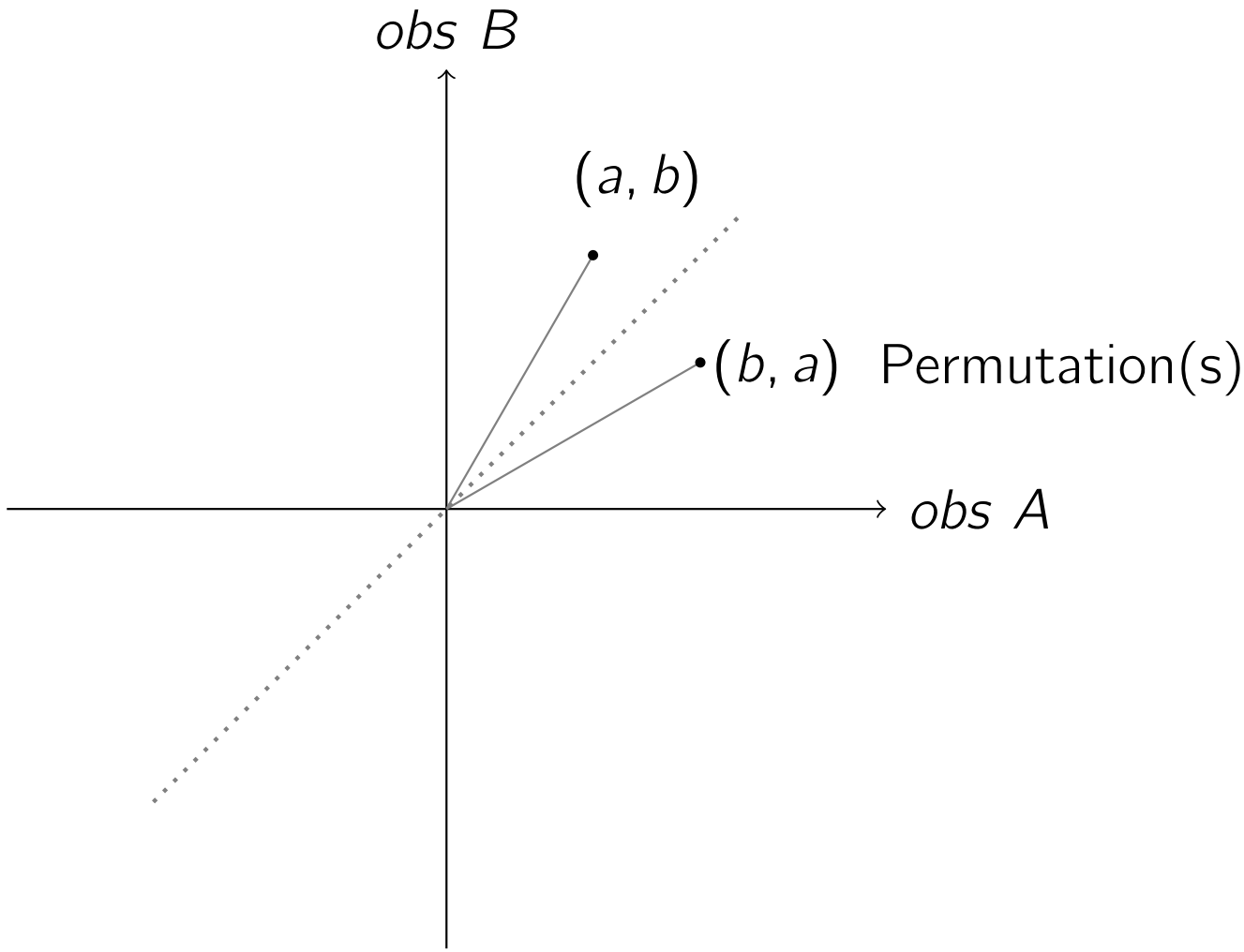

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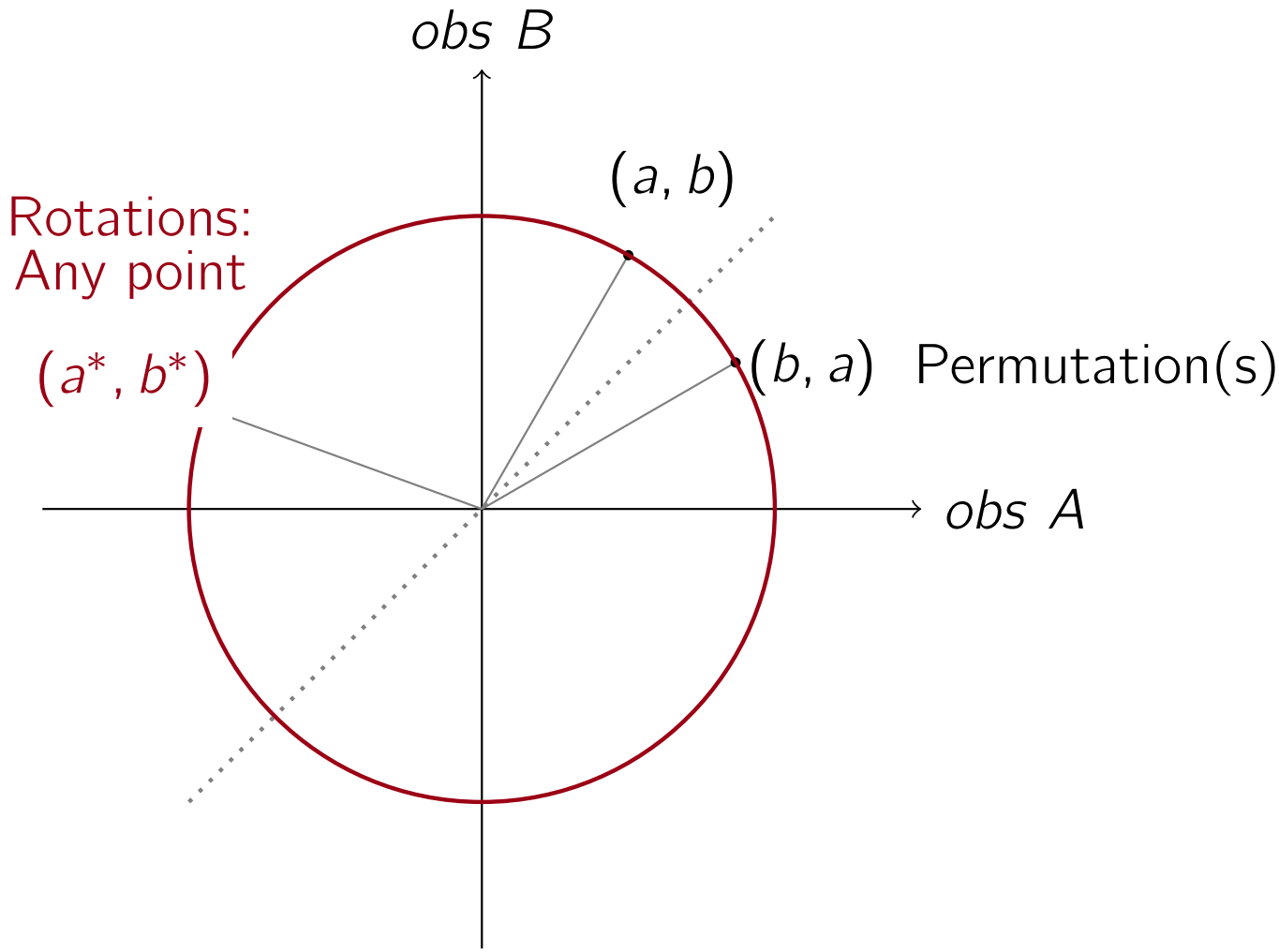
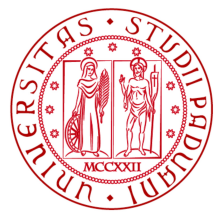


# Some properties

- Rotations of the orthogonalized residuals extends Permutations (i.e. orthogonal matrices with not all zeros and ones).
- Both tests are approximated (and asymptotically exact and consistent),
- When $\tilde{\mathbf{Y}}$ *left-spherically distributed* (e.g. normal), $\tilde{\mathbf{Y}} \stackrel{\mathrm{d}}{=} \tilde{\mathbb{O}}\tilde{\mathbf{Y}}$ i.e. exact test.



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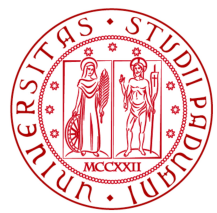
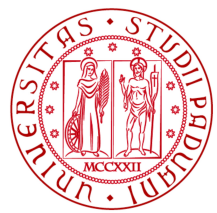
- Easy to generate from the joint distribution i.e. dependence among tests is dealt.



# ... back to motivating example: ALL results

- Acute Lymphoblastic Leukemia data (Chiaretti et al., 2004)
- $n = 128$ patients, $p = 12625$ genes
- covariate of interest: `group` (B or T-cell type patients)
- confounder(s): `age` + `sex`



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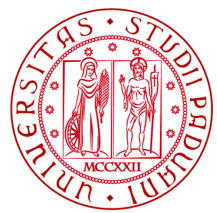
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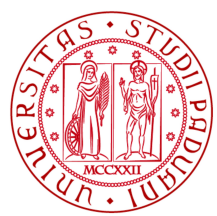
**Application to Multiplicity control:**

- Familywise Error Rate:
  parametric & Holm vs permutation & min-p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**Application to Multiplicity control:**

- Familywise Error Rate:
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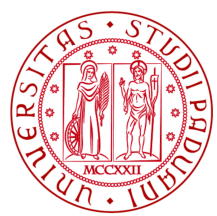
- simultaneous CI for number of rejected hypos:
  parametric & Simes vs permutation & Meinshausen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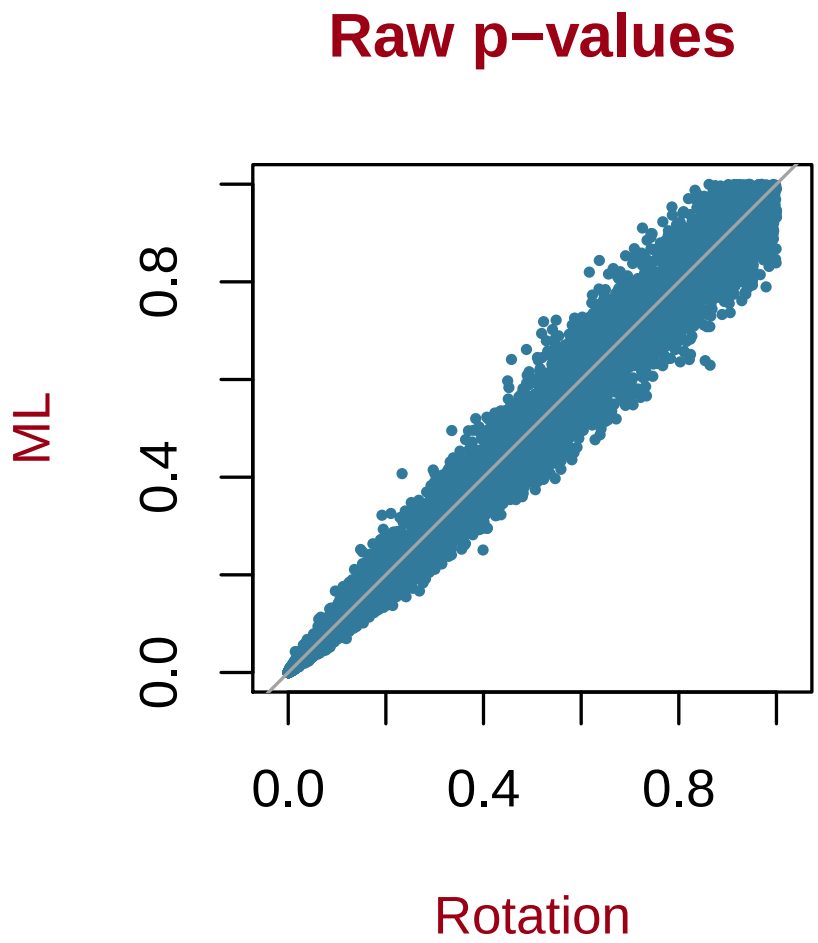


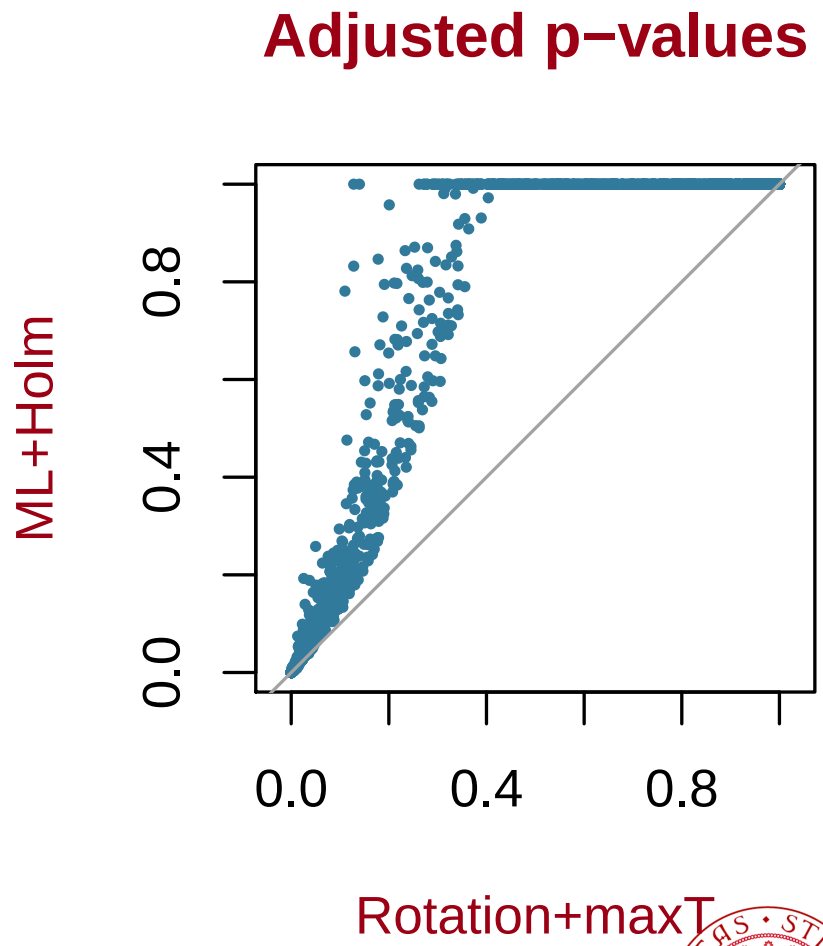

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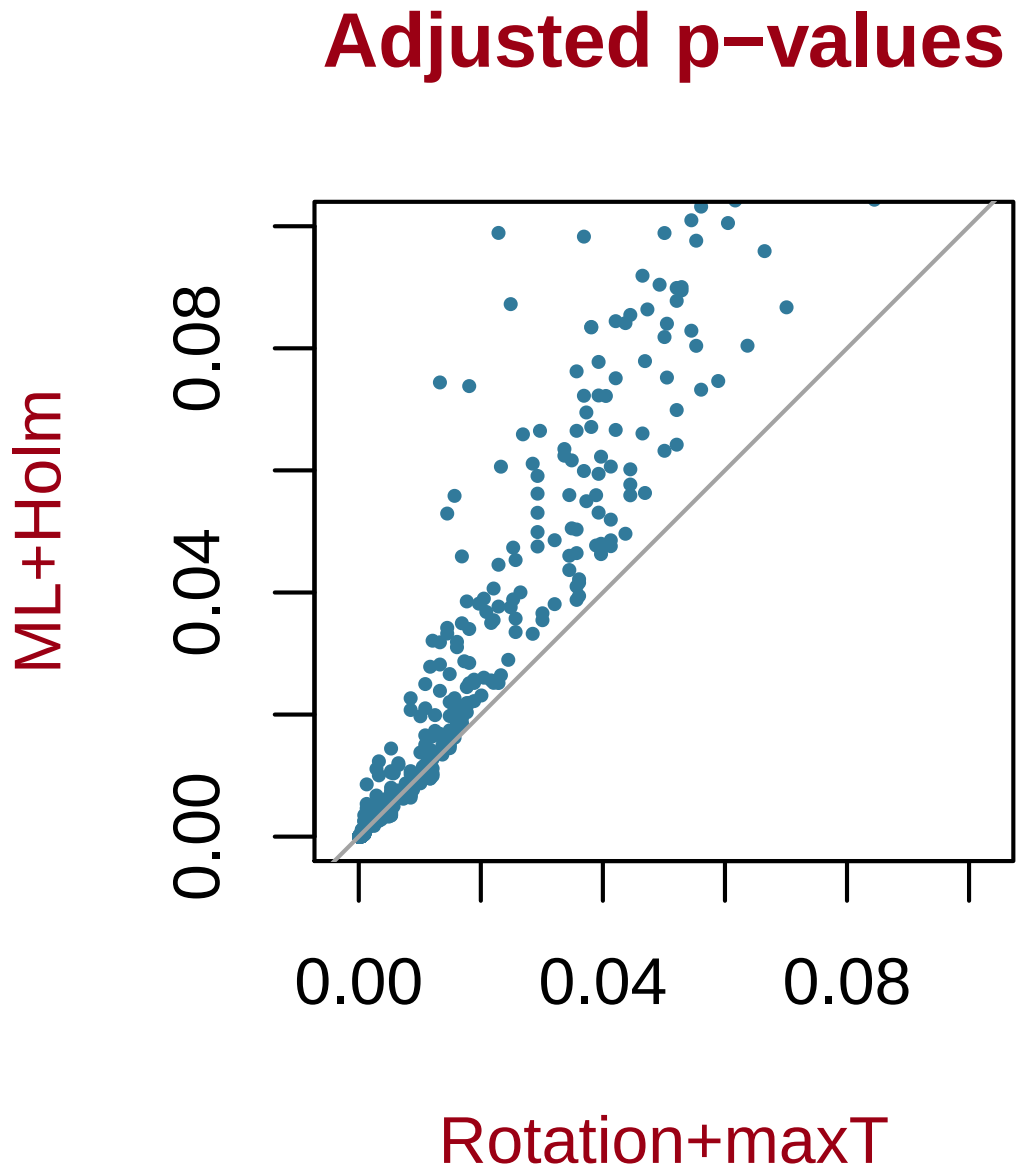
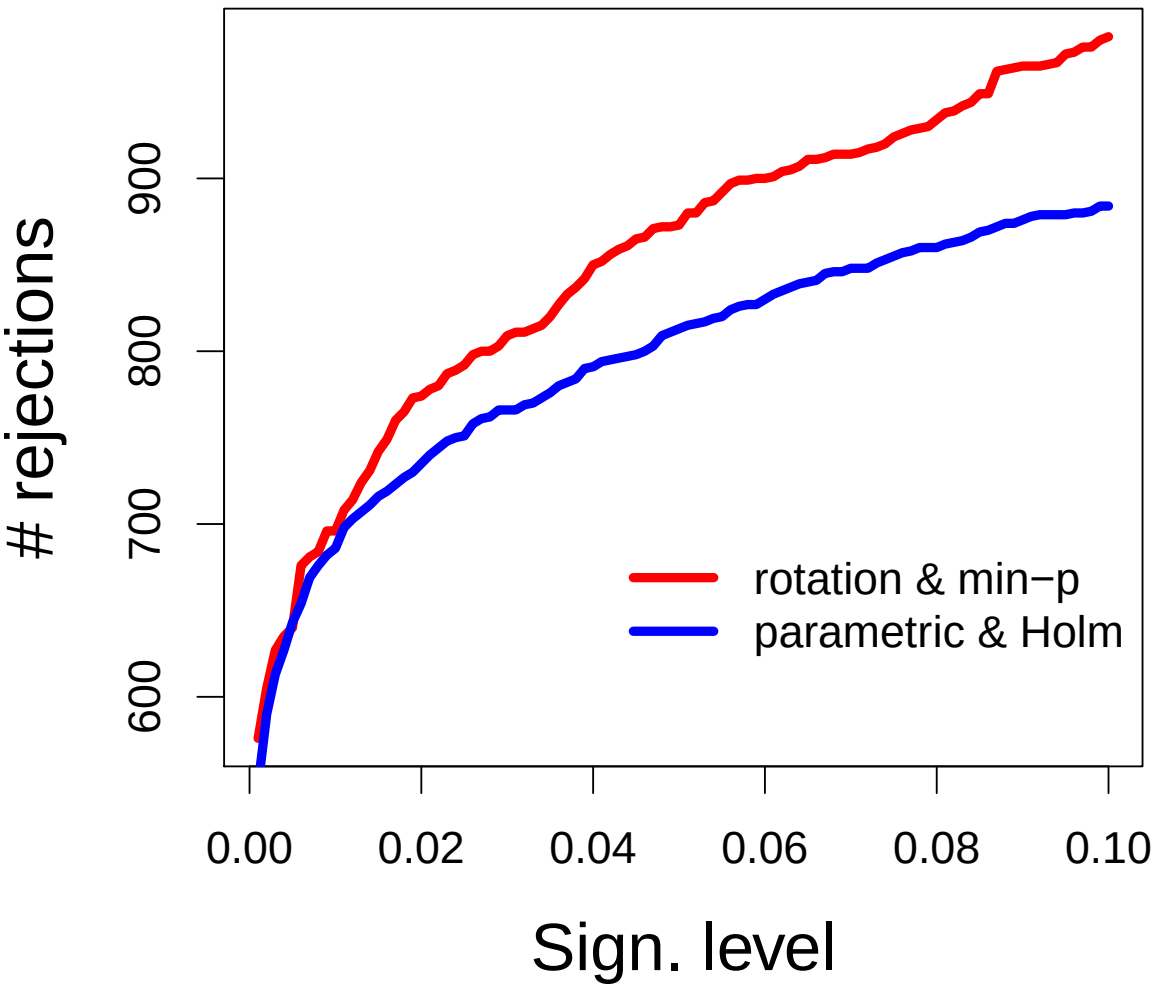


# Familywise Error Rate (Holm vs min-p)

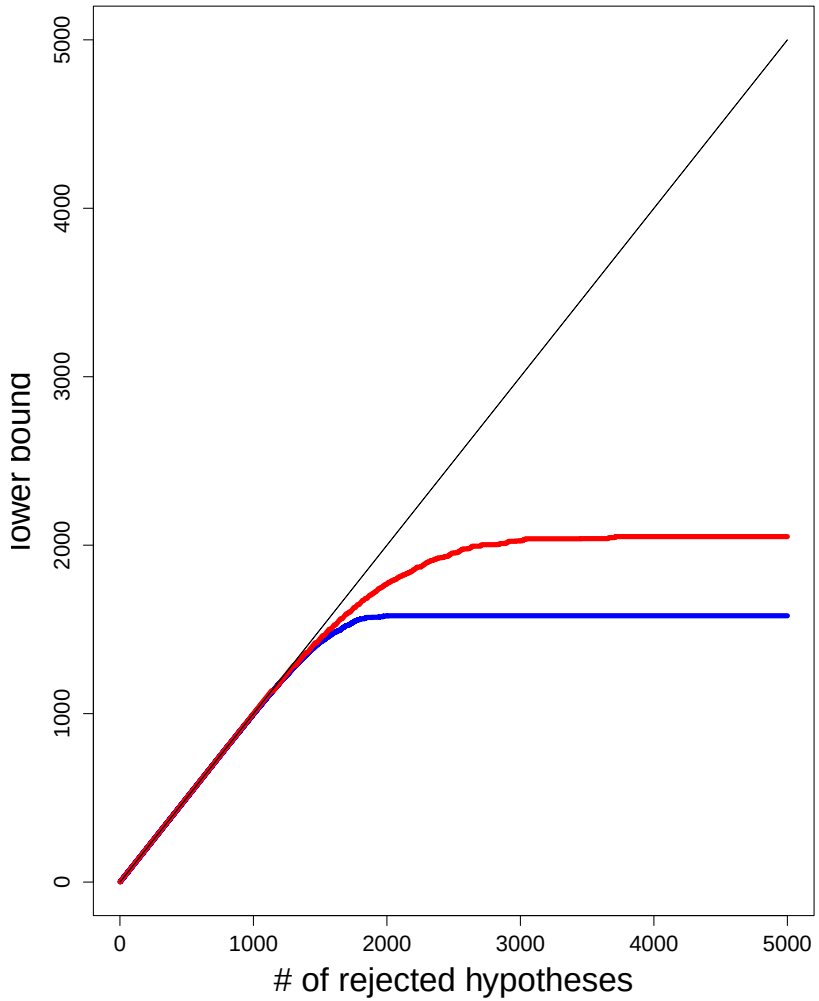
```
res=flip.adjust(pvalues,'maxT')
```




# Simes vs Meinshausen

```
library(cherry); curveMeinshausen(pvalues)
```

# of false rejections
(lower bound .95)

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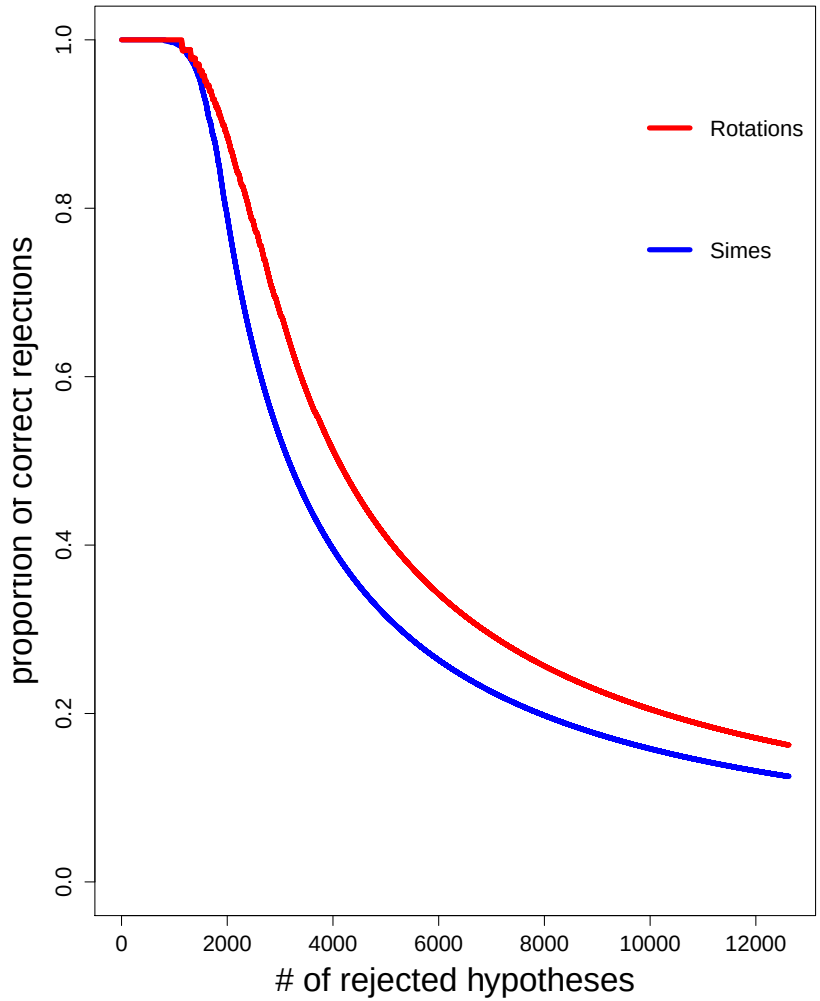
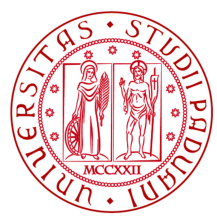


# Take-home message

- Permutations and Rotations
  - easily deal with dependence, even when $p >> n$,
  - more powerful multiplicity control



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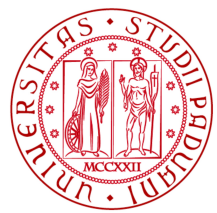

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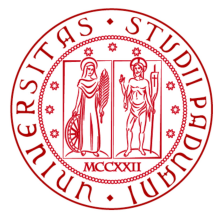

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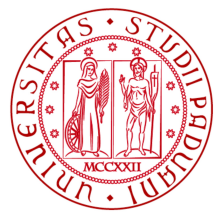

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  continuous: use orthogonal residuals (with permutations or rotations):
  - Approximated test in general
  - Exact for multivariate left-spherical (e.g. normal)
- simple algorithm even for high dimensional data
- R packages `'flip'` and `'cherry'`