

Master Program in *Data Science and Business Informatics*

# Statistics for Data Science

Lesson 32 - Multiple comparisons. Multiple sample testing of the mean

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# The multiple comparisons problem

- Single test  $H_0 : \theta = 0$ , with significance level  $\alpha = 0.05$  [false positive rate]
  - ▶ test is called *significant* when we reject  $H_0$
  - ▶  $\alpha$  is Type I error, probability of rejecting  $H_0$  when it is true
- Multiple tests, say  $m = 20$ 
  - ▶ E.g.,  $H_0^i : \theta_i = 0$  for  $i = 1, \dots, m$  where  $\theta_i$  is the **expectation of a subpopulation**
- What is the probability of rejecting at least one  $H_0^i$  when all of them are true?
  - ▶ For independent tests:  $P(\cup_{i=1}^m \{p_i \leq \alpha\}) = 1 - P(\cap_{i=1}^m \{p_i > \alpha\}) = 1 - (1 - \alpha)^m$   
and then  $1 - (0.95)^{20} \approx 0.64$
  - ▶ For dependent tests:  $P(\cup_{i=1}^m \{p_i \leq \alpha\}) \leq \sum_i P(\{p_i \leq \alpha\}) = m \cdot \alpha$ , and then  $\leq 20 \cdot 0.05 = 1$

## Family-wise error rate (FWER)

The FWER is the probability of making at least one Type I error in a family of  $n$  tests. If the tests are independent:

$$\alpha_{FWER} = 1 - (1 - \alpha)^m$$

If the test are dependent:  $\alpha_{FWER} \leq m \cdot \alpha$

# Multiple comparisons: corrections

Objective: achieve significant tests ( $p \leq \alpha'$ ) such that  $\alpha_{FWER} \leq \alpha$

- *Bonferroni correction* (most conservative one):

- ▶ scale significance level  $\alpha' = \alpha/m$

[invert  $\alpha = m \cdot \alpha'$ ]

- ▶ Notice:  $p \leq \alpha'$  is equivalent to scale p-values and test  $p \cdot m \leq \alpha$

Thus  $\alpha_{FWER} \leq m \cdot \alpha' = \alpha$

- *Šidák correction* (exact for independent tests):

- ▶ scale significance level  $\alpha' = 1 - (1 - \alpha)^{1/m}$

[invert  $\alpha = 1 - (1 - \alpha')^m$ ]

- ▶ Notice:  $p \leq \alpha'$  is equivalent to scale p-values and test  $1 - (1 - p)^m \leq \alpha$

Thus  $\alpha_{FWER} = 1 - (1 - \alpha')^m = \alpha$

**See R script**

# False Discovery Rate and $q$ -values

		True state of nature	
		$H_0$ is true	$H_1$ is true
Our decision on the basis of the data	Reject $H_0$	False Positive	True Positive
	Not reject $H_0$	True Negative	False Negative

- False Positive Rate:  $FPR = FP / (FP + TN)$ 
  - ▶ Corrections control for  $FPR$  since  $FWER = P(FP > 0 | H_0^i \ i = 1, \dots, m)$
- Drawback: acting on  $\alpha$  increases  $FNR = FN / (FN + TP)$
- False Discovery Rate:  $FDR = FP / (FP + TP)$  [Korthauer et al, 2019]
  - ▶  $FDR = 0.05$  means 5% of rejected  $H_0$ 's are actually true
- **$q$ -value** is  $P(H_0 | T \geq t)$  [vs.  $p = P(T \geq t | H_0)$ ]
  - ▶  $FDR$  can be controlled by requiring  $q \leq \text{threshold}$

**See R script**

# Omnibus tests and post-hoc tests

- $H_0 : \theta_1 = \theta_2 = \dots = \theta_k$  [= 0]
- $H_1 : \theta_i \neq \theta_j$  for some  $i \neq j$
- *Omnibus tests* detect any of several possible differences
  - ▶ Advantage: no need to pre-specify which treatments are to be compared ...  
... and then no need to adjust for making multiple comparisons
- If  $H_1$  is rejected (test significant), a *post-hoc test* to find which  $\theta_i \neq \theta_j$ 
  - ▶ Everything to everything post-hoc compare all pairs
  - ▶ One to everything post-hoc compare a new population to all the others
- We distinguish a few cases:
  - ▶ Multiple linear regression (normal errors + homogeneity of variances, i.e.,  $U_i \sim N(0, \sigma^2)$ ):
    - F-test + t-test
  - ▶ Equality of means (normal distributions + homogeneity of variances):
    - ANOVA + Tukey/Dunnett
  - ▶ Equality of means (general distributions):
    - Friedman + Nemenyi

# F-test for multiple linear regression

- $\mathbf{Y} = \mathbf{X} \cdot \boldsymbol{\beta} + \mathbf{U}$ , where  $\mathbf{Y} = (Y_1, \dots, Y_n)$ ,  $\mathbf{U} = (U_1, \dots, U_n)$ , and  $\mathbf{X} = (\mathbf{x}_1, \dots, \mathbf{x}_n)$ 
  - ▶  $\boldsymbol{\beta}^T = (\alpha, \beta_1, \dots, \beta_k)$  and  $\mathbf{x}_i = (1, x_i^1, \dots, x_i^k)$
  - ▶ Unexplained (residual) error  $SSE = S(\boldsymbol{\beta}) = \sum_{i=1}^n (y_i - \mathbf{x}_i \cdot \boldsymbol{\beta})^2$
- Null model (or intercept-only model):  $\mathbf{Y} = \mathbf{1} \cdot \alpha + \mathbf{U}$ 
  - ▶ Total error  $SST = S(\alpha) = \sum_{i=1}^n (y_i - \bar{y}_n)^2$  *[residuals of the null model]*
- Explained error  $SSR = SST - SSE = \sum_{i=1}^n (\bar{y}_n - \mathbf{x}_i \cdot \boldsymbol{\beta})^2$
- Coefficient of determination  $R^2 = SSR/SST = 1 - SSE/SST$  *[See Lesson 20]*
  - ▶ Is the model useful? Fraction of explained error
- **Is the model statistically significant?** *[vs a specific  $\beta_i$  significant? See Lesson 29]*
- $H_0 : \beta_1 = \dots = \beta_k = 0$      $H_1 : \beta_i \neq 0$  for all  $i = 1, \dots, k$
- Test statistic:  $F = \frac{SSR}{SSE} \frac{n-k-1}{k} \sim F(k, n-k-1)$

**See R script**

# Equality of means: ANOVA

- $H_0 : \mu_1 = \mu_2 = \dots = \mu_k$  *[generalization of two sample t-test]*
- $H_1 : \mu_i \neq \mu_j$  for some  $i \neq j$
- datasets  $y_1^j, \dots, y_{n_j}^j$  for  $j = 1, \dots, k$ 
  - ▶ Assumption: normality (**Shapiro-Wilk test**) + homogeneity of variances (**Bartlett test**)
  - ▶ responses of  $k - 1$  treatments and 1 control group *[one way ANOVA]*
  - ▶ accuracies of  $k$  classifiers over  $n_j = n$  datasets *[repeated measures/two way ANOVA]*
- Linear regression model over dummy encoded  $j$ :

$$Y = \alpha + \beta_1 x_1 + \dots + \beta_{k-1} x_{k-1}$$

- ▶  $\alpha = \mu_k$  is the mean of the reference group ( $j = k$ )
- ▶  $\beta_j = \mu_j - \mu_k$
- ▶ in R: `lm(Y~Group)` where `Group` contains the labels of  $j = 1, \dots, k$
- $F$ -test (over linear regression):  $H_0 : \beta_1 = \dots = \beta_k = 0$ , i.e.,  $\mu_j = \mu_k$  for  $j = 1, \dots, k$
- **Tukey HSD** (Honest Significant Differences) is an all-pairs post-hoc test
- **Dunnet test** is a one-to-everything test

See R script

# Non-parametric test of equality of means: Friedman

- $H_0 : \mu_1 = \mu_2 = \dots = \mu_k$
- $H_1 : \mu_1 \neq \mu_2$  for some  $i \neq j$
- datasets  $x_1^j, \dots, x_n^j$  for  $j = 1, \dots, k$  *[paired observations/repeated measures]*
  - ▶ accuracies of  $k$  classifiers over  $n$  datasets
- Let  $r_i^j$  be the rank of  $x_i^j$  in  $x_i^1, \dots, x_i^k$ 
  - ▶ e.g.,  $j^{\text{th}}$  classifier w.r.t.  $i^{\text{th}}$  dataset
- Average rank of classifier:  $R_j = \frac{1}{n} \sum_{i=1}^n r_i^j$
- Under  $H_0$ , we have  $R_1 = \dots = R_k$  and, for  $n$  and  $k$  large:

$$\chi_F^2 = \frac{12n}{k(k+1)} \left( \sum_{j=1}^k R_j^2 - \frac{k(k+1)^2}{4} \right) \sim \chi^2(k)$$


- Nemenyi test is an all-pairs post-hoc test
- Bonferroni correction is a one-to-everything test
- For unpaired observations, use **Kruskal-Wallis test** instead of Friedman test

**See R script**




# Optional reference

- On confidence intervals and statistical tests (with R code)

 Myles Hollander, Douglas A. Wolfe, and Eric Chicken (2014)  
Nonparametric Statistical Methods.  
3rd edition, *John Wiley & Sons, Inc.*

- On False Discovery Rate

 Keegan Korthauer, Patrick K. Kimes, Claire Duvallet, Alejandro Reyes, Ayshwarya Subramanian, Mingxiang Teng, Chinmay Shukla, Eric J. Alm, and Stephanie C. Hicks (2019)  
**[A practical guide to methods controlling false discoveries in computational biology.](#)**  
Genome Biology 20, article 118