(JC)2BIM 2018 Research School

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Introduction

Probability survival kit

Estimation

Confidence intervals

Hypothesis testing

Multiple testing (a quick introduction)

Statistical Inference

(JC)2BIM 2018 Research School

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https://github.com/jchiquet/JC2BIM18/blob/master/source_GR/Inference_Tutorial.pdf

Introduction

A short introduction

1. More and more data. . .
   - Collecting, Analyzing and Interpreting data ?
2. Statistical reasonning
   - Is now a fondamental part of experimental science

Studying a population

1. One often make statements like:
    - this gene is downregulated in lung cancer
    - in France the price of 1 kg of apple rised by 5 cents last year
    - 99% of the seeds in these bags are viable
2. In most of these cases
    - the population we are (implicitly) taking about is very large
    - collecting data is time consumming, costly and possibly it destroys the object
    - our measurements are inherently noisy

Studying a population (inference)

Hence the data we collect on this population are not “perfect”.

- How can we make statements about the whole population ?
- We need assumptions about the way data point were collected
- Those assumptions should be known and explicit
- These assumptions are formulated mathematically as a model
- Draw a schematic representation of this. . .

Undestanding statistical reasonning (1)

1. Cooking recipe level
   - if the data is such and such do this and this...
   - apply the code instructions of a vignette/tutorial online
2. **Applied statistics**
   - understand statistical models
   - under how to assess whether a method is valid (or not) to infer a model

this is understandable using mostly highschool mathematics and some R coding

Undestanding statistical reasonning (2)

3. **Apprentice statistician**
   - understand mathematical and algorithmic techniques behind statistical methods

for simple models this is understandable using mostly highschool mathematics and basic algorithmics

4. Master statistician. . .

Probability survival kit

Outline

1. **Probability**
2. Expectation, Variance and Covariance

Probability Space

Informal definition

- Ω the set of all possible outcomes
- F a set of subsets of Ω, an ω in F is called an event
- p a function from F to $[0, 1]$
  - $p(\Omega) = 1$
  - For two disjoint events ω_1, ω_2, i.e. $\omega_1 \cap \omega_2 = \emptyset$,

    $$p(\omega_1 \cup \omega_2) = p(\omega_1) + p(\omega_2)$$

  - more generally p is countably additive

Probability Space, a few examples and R

1. Throw of a coin

```r
Omega <- c("Head", "Tail")
sample(Omega, 1)
```

```
## [1] "Head"
```

```r
sample(Omega, 4, replace=TRUE)
```

```
## [1] "Tail" "Head" "Head" "Tail"
```

Probability Space, a few examples and R

2. Throw of a dice

```
Omega <- c("As", "2", "3", "4", "5", "6")
sample(Omega, 1)
```

```
## [1] "6"
```

```
sample(Omega, 4, replace=TRUE)
```

```
## [1] "4" "5" "2" "6"
```

Probability Space, a few examples and R

3. Coordinates of an arrow

```r
radius <- 2
dist_center <- runif(1, min=0, max=radius)
angle <- runif(1, min=0, max=360)
```

Probability Space, a few examples and R

4. Expression of a gene in an RNAseq experiment

```
## Poisson
rpois(n=1, lambda=100)
```

```
## [1] 95
```

```
## or Neg-Binomial
rnbinom(n=1, prob = 1/2, size = 40)
```

```
## [1] 48
```

Some usefull properties

- For an event ω

$$p(\bar{\omega}) = p(\Omega \setminus \omega) = 1 - p(\omega)$$

- For two events ω_1, ω_2

$$p(\omega_1 \cup \omega_2) = p(\omega_1) + p(\omega_2) - p(\omega_1 \cap \omega_2)$$

Independence and conditionnal probability

1. ω_1 is independent of ω_2 if

$$p(\omega_2 \cap \omega_1) = p(\omega_1)P(\omega_2)$$

2. For an event ω_1 with $p(\omega_1) > 0$ we define the conditionnal probability $p(\omega_2|\omega_1)$ as

$$p(\omega_2|\omega_1) = p(\omega_1 \cap \omega_2)/p(\omega_1)$$

Note: If ω_2 is independent of ω_1 then $P(\omega_2|\omega_1) = P(\omega_2)$

Random Variables

Definition

Y is a function from Ω to a space $Def(Y)$

- Typically $Def(Y)$ is
  - the set of integers
  - the set of real numbers
- We have:

$$p(Y \in S) = p(\{\omega \in F | Y(\omega) \in S\})$$

Random Variables

Some examples

- Y a binary variable - throw of a coin
- Y an integer smaller than 6 - a throw of a six face dice
- Y a real number - distance of a javelin throw
- Y an integer - expression of a gene in an RNAseq experiment
- $\ldots$

Independence and random variables

Definition

Two random variables Y_1 and Y_2 are independent if for all y_1 in $Def(Y_1)$ and y_2 in $Def(Y_2)$ we have

$$p(Y_1 = y_1 \cap Y_2 = y_2) = p(Y_1 = y_1)p(Y_2 = y_2)$$

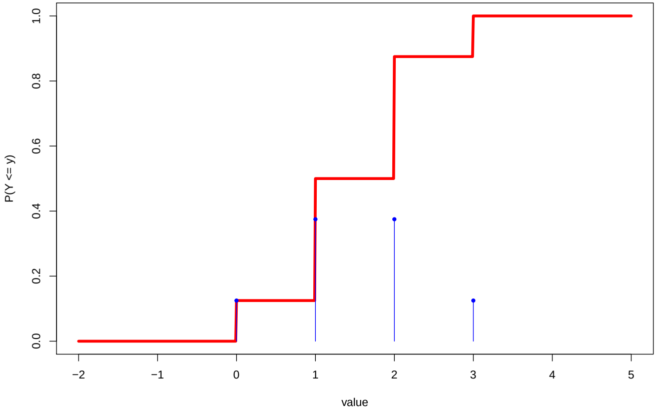
Probability and cumulative probability for discrete variables

0. We call $Def(Y)$ the discrete set of values taken by Y (e.g $\{0, 1\}$, $\mathbb{N}$)
1. For any y in $Def(Y)$ we have access to $p(Y = y) = p(y)$
2. We define the cumulative distribution function as $P(Y \leq y)$.

$$P(Y \leq y) = \sum_{\substack{y' \leq y \\ y' \in Def(Y)}} p(y')$$

Probability and cumulative probability for discrete variables

3. A graphical example Binomial with parameter $n = 3$ and $\pi = 0.5$



Density and cumulative probability for absolutely continuous random variable

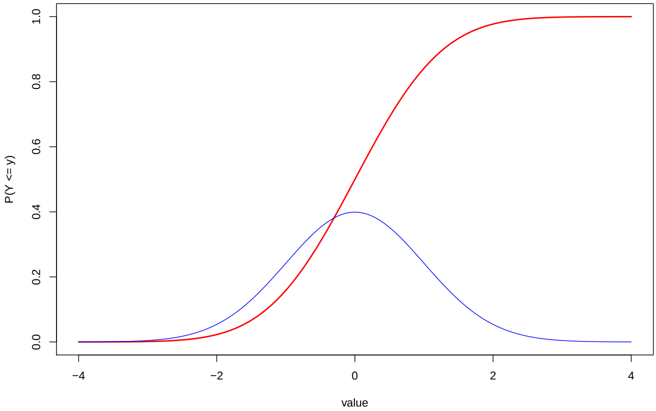
For continuous variable we can proceed fairly similarly:

0. Take $Def(Y) = \mathbb{R}$ the set of values taken by Y
1. For any y in $Def(Y)$ we have a continuous density function $p(y)$ (or $f(y)$)
2. We define the cumulative distribution function as $P(Y \leq y)$ as

$$P(Y \leq y) \int_{y' \leq y} p(y') dy'$$

Density and cumulative probability for a Gaussian

3. A graphical example with $p(y) = \frac{1}{\sqrt{2\pi}} e^{-y^2}$



Simulation exercices

Simulating simple random variables (Bernoulli)

Throw of a coin or Bernoulli variable:

- $Y = 0$ with probability π
- $Y = 1$ with probability $1 - \pi$

```
## One throw
rbinom(n=1, prob=0.5, size=1)
```

```
## [1] 1
```

Simulating simple random variables (Bernoulli)

```r
## 10^4 independent throws Y_1, Y_2, Y_3...
Y <- rbinom(n=10^4, prob=0.5, size=1)
table(Y)
```

```
## Y
##    0    1
## 5051 4949
```

Simulating simple random variables (Binomial)

```
## 10^4 independent throws Y_1, Y_2, Y_3...
Y <- rbinom(n=10^4, prob=0.5, size=5)
table(Y)
```

```
## Y
##    0    1    2    3    4    5
##  302 1544 3135 3086 1611  322
```

Simulating simple random variables (Normal)

Throw of a Normal o variable:

- Y takes continuous values $\mathcal{N}(\mu, \sigma^2)$
- the density is

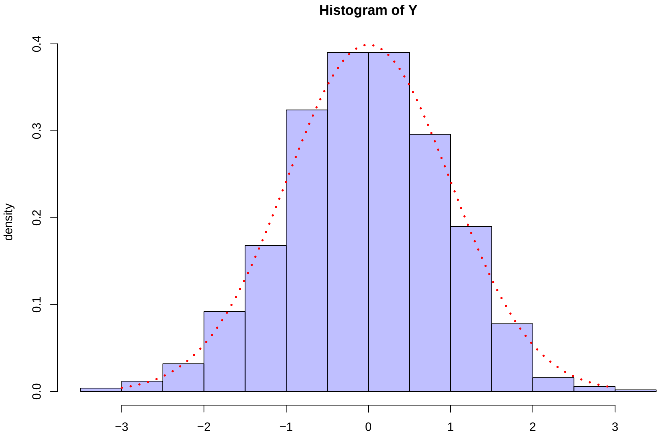
$$f(y) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{1}{\sigma^2}(y-\mu)^2}$$

```r
## One throw
rnorm(n=1, mean=0, sd=1)
```

```
## [1] -0.8303824
```

Simulating simple random variables (Normal)

```
## 10^4 independent throws Y_1, Y_2, Y_3...
Y <- rnorm(n=10^3, mean=0, sd=1)
x <- seq(-3, 3, by=0.01)
hist(Y, col=rgb(0,0,1,1/4), freq=FALSE, ylab="density")
lines(x, dnorm(x), col="red",lty=3, lwd=3)
```



Homework: simulating a Poisson random variables

Throw of a Poisson:

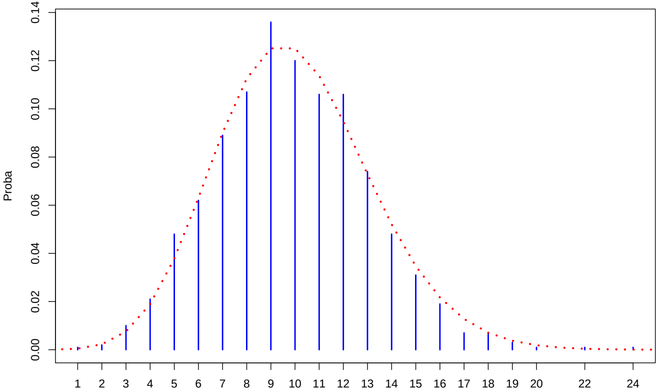
- Y takes integer values $\mathcal{P}(\lambda)$
- density $p(y) = \frac{\lambda^y e^{-\lambda}}{y!}$

```
## One throw
rpois(n=1, lambda = 10)
```

```
## [1] 14
```

Homework: simulating a Poisson random variables

```
## 10^4 independent throws Y_1, Y_2, Y_3...
Y <- rpois(n=10^3, lambda=10)
x <- 0:40
plot(table(Y)/10^3, col="blue", ylab="Proba")
lines(x, dpois(seq(0, 40), lambda=10),
      col="red",lty=3, lwd=3)
```



Outline

1. Probability
2. **Expectation, Variance and Covariance**

Expectation

Definition

1. For discrete variables with probability p

$$E(Y) = \sum_{y \in Def(Y)} yp(y)$$

2. Similarly for absolutely continuous variables with a density p

$$E(Y) = \int_{y \in Def(Y)} yp(y)dy$$

Some expectations

1. Expectation of a Bernouilli of parameter π
2. Expectation of a Binomial distribution of paramters π and n.

- number of successes in n independent experiments

$$p(Y = y) = \binom{n}{y} \pi^{y}(1 - \pi)^{n-y}$$

- a bit two difficult for now...

3. Expectation of a Normal distribution of parameters μ and σ^2

Expectation is linear

1. For two random variables Y_1, Y_2:

$$E(Y_1 + Y_2) = E(Y_1) + E(Y_2)$$

2. For a constant c and a random variable Y_1:

$$E(cY_1) = cE(Y_1)$$

3. For two random variables: $E(Y_2) = E(E(Y2|Y_1))$

Some expectations

1. Expectation of a Binomial distribution of paramters π and n

$$p(Y = y) = \binom{n}{y} \pi^{y} (1 - \pi)^{n-y}$$

Some exercices on the expectation

Ex: on the expectation (1a)

1. Expectation of the sum of 10ˆ4 throws of a dice.

We have n r.v $Y_1, ...Y_n$ taking value in $\{1,2,3,4,5,6\}$.

- We have $E(Y_i) = \sum_{i=1}^{6} \frac{i}{6} = 3.5$
- And so we get

$$E(\sum_{i=1}^{n} Y_i) = \sum_{i=1}^{n} E(Y_i) = nE(Y_1) = 3.5 \times 10^4$$

Ex: on the expectation (1b)

Using simulations and assuming the throws are independent

```
exper <- replicate(10^4, sum(
        sample.int(6, 10^4, replace=TRUE)) )
mean(exper)
```

```
## [1] 35001.99
```

Ex: on the expectation (2)

2. Expectation of the average of 10ˆ4 throws of a dice.

$$E(\frac{1}{n}\sum_{i=1}^{n} Y_i) = \frac{1}{n}\sum_{i=1}^{n} E(Y_i) = \frac{n}{n}E(Y_1) = 3.5$$

Using simulations and assuming the throws are independent

```
exper <- replicate(10^4, mean(
        sample.int(6, 10^4, replace=TRUE)) )
mean(exper)
```

```
## [1] 3.500124
```

Homework: on the expectation (1)

3. Expectation of $6(Y_1 - 1) + Y_2 - 1$ where Y_1 and Y_2 correspond to the throws of two dices.

$$E(6(Y_1 - 1) + Y_2 - 1) = 6E(Y_1) - 6 + E(Y_2) - 1 = 17.5$$

Using simulations and assuming the throws are independent

```
exper <- replicate(10^4, sum( (
  sample.int(6, 2, replace=TRUE)-1) * c(6, 1)))
mean(exper)
```

```
## [1] 17.3615
```

Homework: on the expectation (2a)

- Consider Y_1 a gaussian r.v. with parameters $\mu_1 = 0$ and $\sigma_1^2 = 1$.
- Given Y_1 the r.v. Y_2 is gaussian with parameters $\mu_2 = y_1$ and $\sigma_2^2 = 1$

4. What is the expected value of Y_2?

$$E(Y2) = E(E(Y_2|Y_1)) = E(Y_1) = 0$$

Homework: on the expectation (2b)

Using simulations and assuming independence

```r
n  <- 10^4
Y1 <- rnorm(n)
Y2 <- rnorm(n=n, mean=Y1)
mean(Y2)
```

```
## [1] 0.007585588
```

Variance

Definition

$$V(Y) = E((Y - E(Y))^2) = E(Y^2) - E(Y)^2$$

- Intuitively what does it represent ?

Variance

Properties

1. For two **independent** random variables Y_1 and Y_2:

$$V(Y_1 + Y_2) = V(Y_1) + V(Y_2)$$

2. For a constant c and a random variable Y_1,

$$V(cY_1) = c^2 V(Y_1)$$

3. For two random variables:

$$V(Y_2) = E(V(Y2|Y_1)) + V(E(Y_2|Y_1))$$

Some exercices on the variance

Ex: on the variance (1)

1. X_1 and $-X_2$ are independant so:

$$V(X_1 - X_2) = V(X_1 + (-X_2)) = V(X_1) + V(X_2)$$

Ex: on the variance (2)

2. Variance of the sum of 10ˆ4 independent throws of a dice.

- We have n r.v $Y_1, \dots Y_n$ taking value in $\{1, 2, 3, 4, 5, 6\}$.
- We have

$$V(Y_i) = E(Y_i^2) - E(Y_i)^2 = \frac{1+4+9+16+25+36}{6} - 3.5^2 = \frac{35}{12}$$

As the throws are independent we have

$$V(\sum_{i=1}^{n} Y_i) = \sum_{i=1}^{n} V(Y_i) = nV(Y_1) = \frac{35}{12} \times 10^4$$

Ex: on the variance (3)

- Using simulations and assuming the throws are independent.

```r
exper <- replicate(10^4, sum(
      sample.int(6, 10^4,replace=TRUE)) )
var(exper)
```

```
## [1] 29566.77
```

Homework: on the variance (4)

3. Variance of the average of 10ˆ4 independent throws of a dice.

- Using independence:

$$V(\frac{1}{n}\sum_{i=1}^{n} Y_i) = \frac{1}{n^2}\sum_{i=1}^{n} V(Y_i) = \frac{n}{n^2}V(Y_1) = \frac{35}{12n}$$

- Using simulations and assuming the throws are independent

```r
exper <- replicate(10^4, mean(
        sample.int(6, 10^4,replace=TRUE)) )
var(exper)
```

```
## [1] 0.000293675
```

Homework: on the variance (5)

4. Expectation of $6(Y_1 - 1) + Y_2 - 1$ where Y_1 and Y_2 correspond to the throws of two dices.

- Using independence

$$V(6(Y_1{-}1){+}Y_2{-}1) = 6^2(Y_1){+}V(Y_2) = 3{\times}35{+}\frac{35}{12} = 35{\times}(3{+}\frac{1}{12})$$

Using simulations and assuming the throws are independent

```
exper <- replicate(10^4, sum( (
  sample.int(6, 2, replace=TRUE)-1)*c(6, 1) ))
var(exper)
```

```
## [1] 108.4646
```

Homework: on the variance (6)

- Consider Y_1 a gaussian r.v. with parameters $\mu_1 = 0$ and $\sigma_1^2 = 1$.
- Given Y_1, the r.v. Y_2 is gaussian with parameters $\mu_2 = y_1$ and $\sigma_2^2 = 1$

5. What is the variance of Y_2 ?

$$V(Y_2) = E(V(Y_2|Y_1)) + V(E(Y_2|Y_1)) = E(1) + V(Y_1) = 1+1 = 2$$

Homework: on the variance (7)

Using simulations and assuming independence

```r
n  <- 10^4
Y1 <- rnorm(n)
Y2 <- rnorm(n=n, mean=Y1)
var(Y2)
```

```
## [1] 2.019936
```

Covariance

Definition

$$Cov(Y_1, Y_2) = E((Y_1 - E(Y_1))(Y_2 - E(Y_2)))$$

$$Cov(Y_1, Y_2) = E(Y_1 Y_2) - E(Y_1)E(Y_2)$$

- What is $Cov(Y_1, Y_1)$
- If Y_1 and Y_2 are independent ?
- Intuitively what does the covariance represent ?

Covariance

Properties

1. Covariance is bilinear:
   - For two random variables Y_1, Y_2: $Cov(Y_1, Y_2) = Cov(Y_2, Y_1)$
   - For three random variables Y_1, Y_2, Y_3: $Cov(Y_1 + Y_2, Y_3) = Cov(Y_1, Y_3) + Cov(Y_2, Y_3)$
   - For a constant c and two random variable Y_1: $Cov(cY_1, Y_2) = cCov(Y_1, Y_2)$
2. For three random variables $Cov(Y_1, Y_2) = E(cov(Y_1, Y_2|Y_3)) + cov(E(Y_1|Y_3)E(Y_2|Y_3))$

An exercice on the covariance

Ex: on the covariance (1)

1. Consider Y_1 a gaussian r.v. with parameter $\mu_1 = 0$ and $\sigma_1^2 = 1$. Given Y_1, the r.v. Y_2 is gaussian with parameters $\mu_2 = y_1$ and $\sigma_2^2 = 1$

What is the covariance of Y_2 and Y_1 ?

$$Cov(Y_1, Y_2) = E(Cov(Y_1, Y_2|Y_1)) + Cov(E(Y_1|Y_1), E(Y_2|Y_1))$$

$$Cov(Y_1, Y_2) = E(0) + Cov(Y_1, Y_1) = V(Y_1) = 1$$

Ex: on the covariance (2)

Using simulations and assuming independence

```r
n  <- 10^4
Y1 <- rnorm(n)
Y2 <- rnorm(n=n, mean=Y1)
cov(Y1, Y2)
```

```
## [1] 1.011137
```

Estimation

Statistical inference

- A population (possibly infinite)
- Cannot do a census
- What can we say about the whole population given a sample
- We need assumptions = a model
- Small schema (population, sample, model, inference)

Data

Given a sample of size n

- $y_1, y_2 \ldots y_n$
- Assume that they are realisations of n random variables

$$Y_1, Y_2, ..., Y_n$$

Modeling

Model of the experiment

- Define the law of the r.v $Y_1, ..., Y_n$
- Sometimes it is difficult
- In simple cases one assumes that Y_i are i.i.d:

$$Y_i \sim \mathcal{P}(\theta)$$

with distribution p_θ

- Often θ is the parameter we want to estimate.

Estimator

An estimator is a function of $Y_1, ... Y_n$.

- It is a random variable
- A simple example:

$$\bar{Y} = \frac{\sum_i Y_i}{n}$$

- Propose an estimator for the variance of Y ?

Estimation

Realisation of an estimator

- This is not a random variable
- For example

$$\bar{y} = \frac{\sum_i y_i}{n}$$

An exercice

Exercice: viscosity of a polymer

We have 4 viscosity measurements of a polymer used by a company to make microprocessors: $78, 85, 91, 76$. For the polymer to be used we need that the viscosity is between 75 and 95

Exercice

- Data?
- Model?
- Estimator?
- Estimation?

Ex: viscosity of a polymer

- Data : $y_1 = 78, y_2 = 85, y_3 = 91, y_4 = 76$
- Model

$$Y_i \sim \mathcal{N}(\mu, \sigma^2) \quad i.i.d$$

- μ and σ^2 are respectivelythe expected value and the variance
- Estimators

1. For the mean

$$\hat{\mu} = \bar{Y} = \frac{\sum Y_i}{n}$$

2. For the variance

$$\hat{\sigma}^2 = \frac{\sum (Y_i - \hat{\mu})^2}{(n-1)}$$

Ex: viscosity of a polymer

- Estimation

```
y <- c(78, 85, 91, 76)
mean(y); var(y); sd(y)
```

```
## [1] 82.5
```

```
## [1] 47
```

```
## [1] 6.855655
```

- The mean is indeed in $[75, 95]$ but the variance seems quite large. . .

Quality of an estimator (1a)

1. The mean Squared Error (MSE)

$$E((\hat{\theta}_n - \theta)^2) = MSE(\hat{\theta}_n)$$

Quality of an estimator (1b)

1. The mean Squared Error (MSE)

```
## 1 simu
Y <- mean(rt(10, df=4))
theta_hat_obs <- mean(Y)
mse_obs <- (theta_hat_obs- 0)^2

## if n=10
mean(replicate(10^3, mean(rt(10, df=4))^2))
```

```
## [1] 0.2150205
```

```
# if n=100
mean(replicate(10^3, mean(rt(100, df=4))^2))
```

```
## [1] 0.01985605
```

Quality of an estimator (2a)

Lets try to decompose the error:

$$\hat{\theta}_n - \theta = \hat{\theta}_n - E(\hat{\theta}_n) + E(\hat{\theta}_n) - \theta$$

2. The expectation of the second part is called the bias

$$E(\hat{\theta}_n) - \theta = Bias(\hat{\theta}_n)$$

Quality of an estimator (2b)

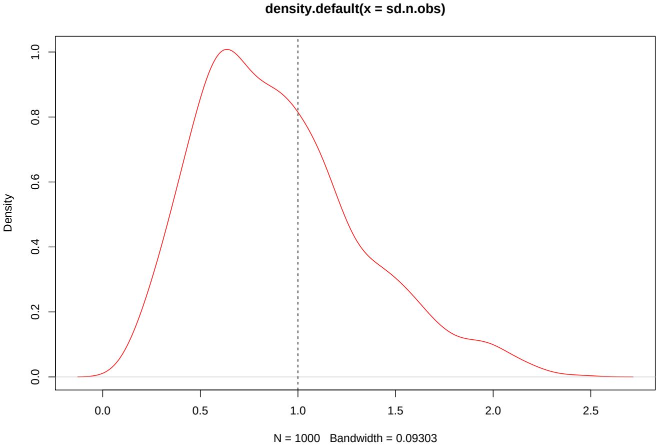
```r
## a estimator with a bias
sd.n <- function(n){
 Y <- rnorm(n)
 sum((Y-mean(Y))^2)/n
}

sd.n.obs <- (replicate(1000, sd.n(10)))
mean(sd.n.obs)
```

```
## [1] 0.9043383
```

Quality of an estimator (2c)

```
plot(density(sd.n.obs), col="red", lwd=1)
abline(v=1, lty=2)
```



Quality of an estimator (3)

3. The expectation of the first part is called the variance

$$E((\hat{\theta}_n - E(\hat{\theta}))^2) = V(\hat{\theta}_n)$$

- An estimator is a r.v

Quality of an estimator (3)

4. It can be shown that

$$MSE(\hat{\theta}_n) = E((\hat{\theta}_n - \theta)^2) = Bias(\hat{\theta}_n)^2 + V(\hat{\theta}_n)$$

- Infering a very complex model (without a little bias) is not necesarily better than infering a simpler model (with larger bias)
- Variance counts.

Quality of the empirical mean estimator

We consider a sample of size n : $y_1, ...y_n$. We assume

- Y_i are i.i.d
- $E(Y_i) = \theta$
- $V(Y_i) = \sigma^2$

$$\hat{\theta}_n = \frac{1}{n}\sum_{i=1}^{n} Y_i$$

Quality of the empirical mean estimator

1. Bias

Using the linearity of the expectation

$$E(\hat{\theta}_n) = \frac{1}{n}\sum_{i=1}^{n} E(Y_i) = \theta$$

- On average we do not make any mistake.

Quality of the empirical mean estimator

2. Variance

Using the independence:

$$V(\hat{\theta}_n) = \frac{1}{n^2} \sum_{i=1}^{n} V(Y_i) = \frac{\sigma^2}{n}$$

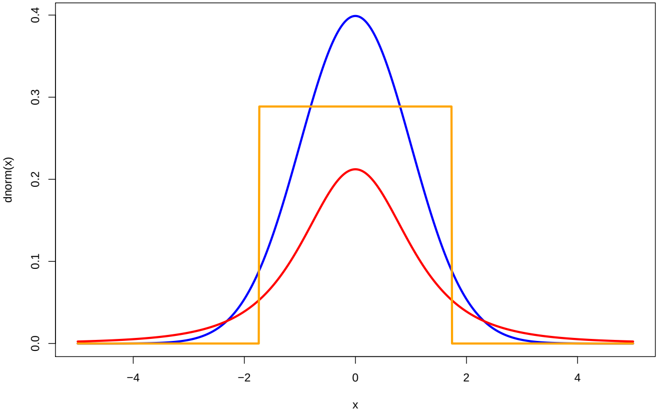
- On average we are not too far from θ
- On average we are closer if σ is smaller
- On average we are closer if we have more data.

Quality of the empirical mean estimator

- Knowing the mean and variance of a distribution is usefull but not particularly precise.
- We would like to know the distribution of $\hat{\theta}_n$

Distribution with same mean and variances

Consider the density of a Gaussian, Student and Uniform distribution with the same mean and variance.



An exercice on the mean and median

Exercice: mean or median ?

Consider a sample of size n. Assume with Y_i i.i.d.

Compare (using simulations) the Bias, Variance and MSE of the empirical mean and empirical median estimators

1. if the data are drawn from a Gaussian distribution

```
rnorm(3)
```

```
## [1]  1.2773410 -0.5756087  1.2022450
```

2. if the data are drawn from a Student distribution with a degree of freedom $k = 3$ (heavy tail)

```
rt(3,df=3)
```

```
## [1] -1.2072950 -0.7701449  0.5161675
```

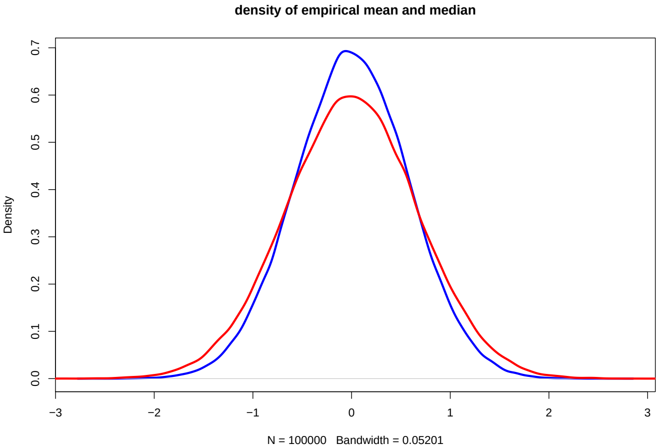
Ex: Mean or median with a Gaussian

```
## simulation function
one.simu <- function(n){
  y <- rnorm(n)
  c(mean(y), median(y))
}

## replication
es <- t(replicate(10^5, one.simu(3)))
colnames(es) <- c("mean", "median")
```

Ex: Mean or median with a Gaussian: distribution

```
plot(density(es[, 1]), col="blue", lwd=3,
     main="density of empirical mean and median")
lines(density(es[, 2]), col="red", lwd=3)
```



Ex: Mean or median with a Gaussian: bias and variance

```
colMeans(es) ## Bias (compare to 0)
```

```
##        mean      median
## 0.003787214 0.002776014
```

```
apply(es, 2, var) ## Variance
```

```
##      mean    median
## 0.3340075 0.4505219
```

Ex: Mean or median with a Gaussian: MSE

```
colMeans(es^2) ## MSE
```

```
##      mean    median
## 0.3340185 0.4505251
```

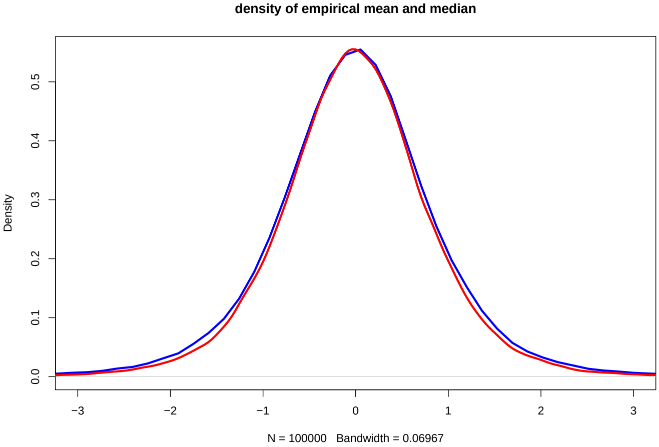
Ex: Mean or median with a Student

```r
k <- 3
one.simu <- function(n){
  y <- rt(n, df=k)
  c(mean(y), median(y))
}


es <- t(replicate(10^5, one.simu(3)))
colnames(es) <- c("mean", "median")
```

Ex: Mean or median with a Student: distribution

```
plot(density(es[, 1]), col="blue", lwd=3,
     main="density of empirical mean and median", xlim=c(-3
lines(density(es[, 2]), col="red", lwd=3)
```



Ex: Mean or median with a Student : bias and variance

```
colMeans(es) ## Bias (compare to 0)
```

```
##         mean       median
## -0.006067683 -0.003258026
```

```
apply(es, 2, var) ## Variance
```

```
##      mean    median
## 1.0181870 0.7196179
```

Ex: Mean or median with a Student : MSE

```r
colMeans(es^2) ## MSE
```

```
##      mean    median
## 1.0182136 0.7196213
```

Homework: mean or median ?

Consider a sample of size n. Assume with Y_i i.i.d.

Compare (using simulations) the Bias, Variance and MSE of the empirical mean and empirical median estimators

3. if the data are drawn from a χ^2 distribution with a degree of freedom $k = 5$

```r
rchisq(3, df=5)
```

```
## [1]  0.4439805 10.4333834  6.1365275
```

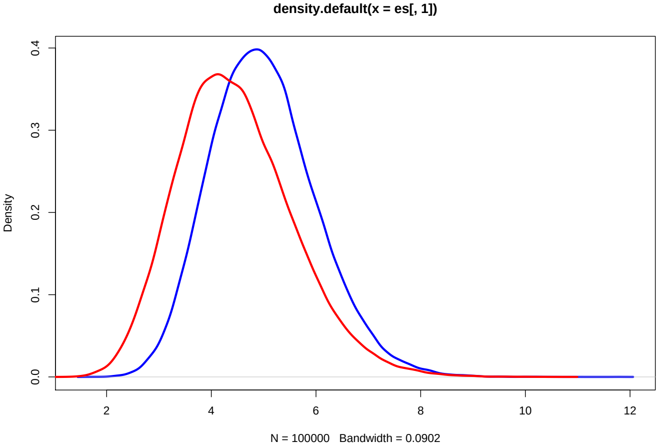
Homework: Mean or median with a χ^2

```r
k <- 5
one.simu <- function(n){
  y <- rchisq(10, df=k)
  c(mean(y), median(y))
}


es <- t(replicate(10^5, one.simu(3)))
colnames(es) <- c("mean", "median")
```

Homework: Mean or median with a χ^2: distribution

```
plot(density(es[, 1]), col="blue", lwd=3)
lines(density(es[, 2]), col="red", lwd=3)
```



Homework: Mean or median with a χ^2: distribution

- Looking at wikipedia we found that the mean and median of a χ^2 are not equal...
  1. The expectation is equal to the degree of freedom k
  2. The median is close to $k * (1 - 2/(9 * k))^3$
- So in fact we are not even trying to estimate the same thing...

Homework: Mean or median with a χ^2: bias and variance

```
mean(es[, 1])-k ## mean bias
```

```
## [1] -0.0004150696
```

```
mean(es[, 2])-k*(1-2/(9*k))^3 ## median bias
```

```
## [1] 0.09734625
```

```
apply(es, 2, var) ## Variance
```

```
##     mean   median
## 1.004363 1.209067
```

Homework: Mean or median with a χ^2: MSE

```r
mean((es[, 1] - k)^2) ## mean
```

```
## [1] 1.004353
```

```r
mean((es[, 1] - k*(1-2/(9*k))^3 )^2) ## median
```

```
## [1] 1.4102
```

Homework exercice: Sampling and estimation

- Consider Y_1 a random variable with a Poisson distribution of parameter $\lambda_1 = 10$
- Knowing $Y_1 = y_1$ Y_2 is a Poisson random variable of parameter $\lambda_2 = y_1$

1. What is the expectation and variance of Y_2 ?
2. What is the covariance of Y_1 and Y_2 ?

H-Ex: Sampling and estimation an exercice

3. Estimate the expectation, variance and covariance using sampling.

```r
n <- 10^3
Y1 <- rpois(n, lambda=10)
Y2 <- rpois(n, lambda = Y1)
mean(Y2)    # using math we know that E(Y2) = 10
```

```
## [1] 10.154
```

```r
var(Y2)     # using math we know that V(Y2) = 20
```

```
## [1] 19.99428
```

```r
cov(Y1, Y2) # using math we know that Cov(Y1, Y2) = 10
```

```
## [1] 9.947644
```

H-Ex: Estimation of $E(Y_2) = \lambda_2$

We try to estimate $E(Y_2)$ using $\sum_{i=1}^{n} Y_{2,i}/n = \hat{\lambda}_2$.

Quality of the estimator $\hat{\lambda}_2$?

4. Bias ?
5. Variance ?
6. Distribution ?

H-Ex: Estimator $\hat{\lambda}_2$

4. Bias ?

We already checked that $E(Y_2) = E(\hat{\lambda}_2)$

- No bias = on average we do not make any mistake
- This doesn't tell us anything about the magnitude of our mistakes

5. What is the variance $V(\hat{\lambda}_2)$

after some calculations we get $V(\hat{\lambda}_2) = V(Y_2)/n$

- On average we are not too far
- Still we would like to quantify the error more precisely (probability)

H-Ex: Distribution of $\hat{\lambda}_2$

6. What is the distribution of $\hat{\lambda}_2$?

- It looks a bit difficult mathematically (harder than for the expectation or variance at least).
- But using simulations . . .

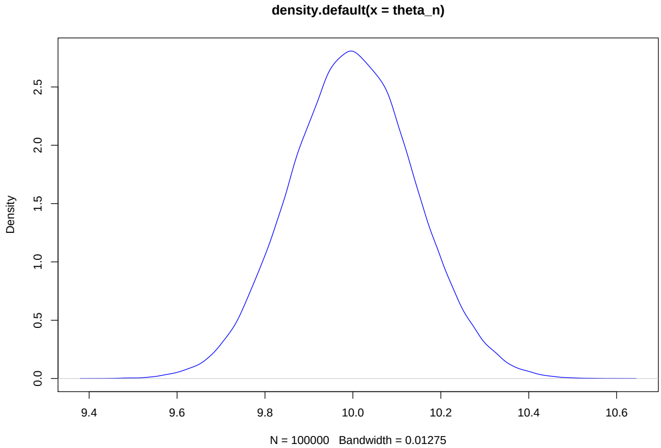
```
one.rep <- function(n=10^3){
  Y1 <- rpois(n, lambda=10)
  Y2 <- rpois(n, lambda = Y1)
  return(mean(Y2))
}

theta_n = replicate(10^5, one.rep())
```

H-Ex: Distribution of $\hat{\lambda}_2$

3. What is the distribution of $\hat{\lambda}_2$

```
plot(density(theta_n), col="blue")
```



H-Ex: To continue at home

7. Compare the density you get for larger and smaller n
8. Consider an estimator of $V(Y_2)$. Use simulations to get and idea of the bias, variance and distribution of this estimator.
9. Consider an estimator of $Cov(Y_2, Y_1)$. Use simulations to get and idea of the bias, variance and distribution of this estimator.

How do we get formula for estimators ?

- For the mean it is fairly natural to take the empirical mean.
- For the variance it is fairly natural to take the empirical variance.
- For the covariance it is fairly natural to take the empirical covariance.
- How do you get estimators for more “complex”” parameters ?
- Call a statistician
- Many more or less generic approaches
  1. Method of Moments
  2. Minimum Mean square error
  3. Maximum likelihood
  4. Bayessian inference

A brief introduction to the maximum likelihood approach

The likelihood of a sample $y_1, ...y_n$ and of parameters θ is defined as

$$\mathcal{V}(y_1, ..., y_n, \theta) = p_\theta(Y_1 = y_1, ..., Y_n = y_n)$$

Assuming all the Y_i are i.i.d

$$\mathcal{V}(y_1, ..., y_n, \theta) = \prod_{i=1}^{n} p_\theta(Y_i = y_i)$$

The log-Likelihood

The likelihood of a sample $y_1, ...y_n$ and of parameters θ is defined as

$$\mathcal{V}(y_1, ..., y_n, \theta) = p_\theta(Y_1 = y_1, ..., Y_n = y_n)$$

Assuming all the Y_i are i.i.d and taking the log

$$\mathcal{L}(y_1, ..., y_n, \theta) = \sum_{i=1}^{n} \log(p_\theta(Y_i = y_i))$$

An example with Bernouilli variables

Assume Y_i are i.i.d Bernouilli variables of parameter π

- $p_\theta(Y_i = 0) = 1 - \pi$
- $p_\theta(Y_i = 1) = \pi$
- n_1 the number of y_i equal to 1

$$\mathcal{V}(y_1, ..., y_n, \theta) = \prod_{i=1}^{n} p_\theta(Y_i = y_i) = \pi^{n_1}(1-\pi)^{n-n_1}$$

- taking the log

$$\mathcal{L}(y_1, ..., y_n, \theta) = (n_1)\log(\pi) + (n - n_1)\log(1-\pi)$$

An example with Gaussian variables

Assume Y_i are i.i.d Gaussian variables of parameter μ and σ

- $p_{\mu,\sigma}(Y_i = y_i) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(y_i-\mu)^2}{2\sigma^2}}$

$$\mathcal{V}(y_1, ..., y_n, \theta) = \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi\sigma^2}} e^{\frac{-(y_i-\mu)^2}{2\sigma^2}}$$

- taking the log

$$\mathcal{L}(y_1, ..., y_n, \theta) = -\frac{n}{2}\log(2\pi) - \frac{n}{2}\log(\sigma^2) - \frac{1}{2\sigma^2}\sum_i (y_i - \mu)^2$$

Maximum likelihood ?

1. Given some sample, what value of θ should we take ?
2. Idea: take θ that maximise the log-likelihood
3. The log-likelihood is used as a measure of fit to the data

Why should we do this:

1. Fairly generic (as soon as you have a model)
2. In a number of cases ML has good statistical properties (asymptotically unbiased and Gaussian. . .)

Maximum likelihood for *n* i.i.d Bernoulli r.v.

Maximization of the likelihood for *n* i.i.d Bernouilli variables

- Idea: derivative of $\mathcal{L}$ as a function of π

Visually for *n* i.i.d Bernoulli r.v. (1)

```r
Y <- rbinom(n=20, size=1, prob=0.5)
mean(Y)
```

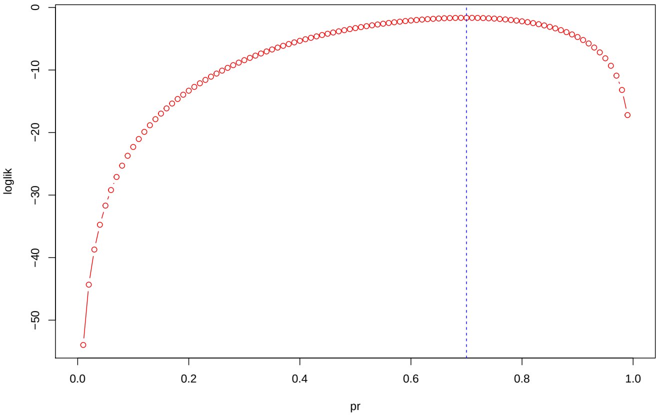
```
## [1] 0.7
```

```r
pr <- seq(0, 1, by=0.01)
loglik <- dbinom(sum(Y), size=20, prob=pr, log=TRUE)
pr[which.max(loglik)]
```

```
## [1] 0.7
```

Visually for *n* i.i.d Bernoulli r.v. (2)

```
plot(pr, loglik, col="red", type="b")
abline(v=mean(Y), lty=2, col="blue")
```



An exercice maximum likelihood of a Gaussian r.v

Ex: Maximum likelihood for a Gaussian r.v. (1)

Maximization of the likelihood for *n* i.i.d Gaussian variables

- Idea: derivative of $\mathcal{L}$ as a function of μ and σ^2

Ex: Visually for *n* i.i.d Gaussian r.v. (2)

```r
Y <- rnorm(n=10, mean=1)
mean(Y)
```

```
## [1] 1.229894
```

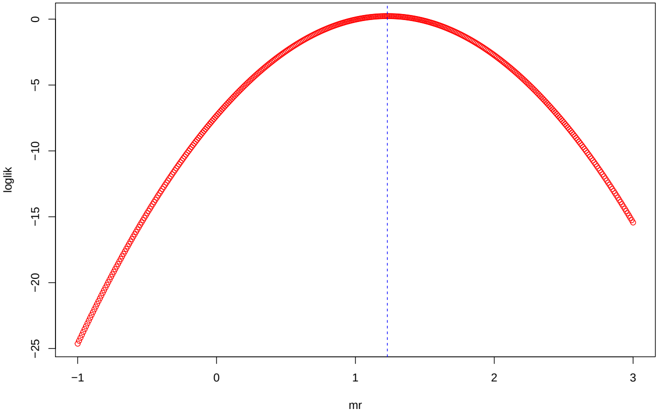
```r
mr <- seq(-1, 3, by=0.01)
loglik <- dnorm(mean(Y), mean=mr, sd=1/sqrt(10), log=TRUE)

mr[which.max(loglik)]
```

```
## [1] 1.23
```

Ex: Visually for *n* i.i.d Gaussian r.v. (3)

```r
plot(mr, loglik, col="red", type="b")
abline(v=mean(Y), lty=2, col="blue")
```



Confidence intervals

Idea / Definition

Idea: Rather than giving one value for a parameter, we aim to give two bounds B_1 and B_2 and we hope that the true value is between the two

1. Random interval

Definition: Let $B_1 = m(Y_1, ..., Y_n)$ et $B_2 = M(Y_1, ..., Y_n)$ two r.v. We define a random interval for θ with the couple (B_1, B_2). We call $P(B_1 < \theta < B_2)$ the level of confidence.

2. Confidence interval

Definition: A confidence interval at level $1 - \alpha$ for θ is a realisation $[b_1, b_2]$ of a random interval with confidence $1 - \alpha$

Confidence interval for the mean knowing the variance (1)

- Data $y_1, ..., y_n$
- Estimator

$$\bar{Y} = \sum Y_i/n$$

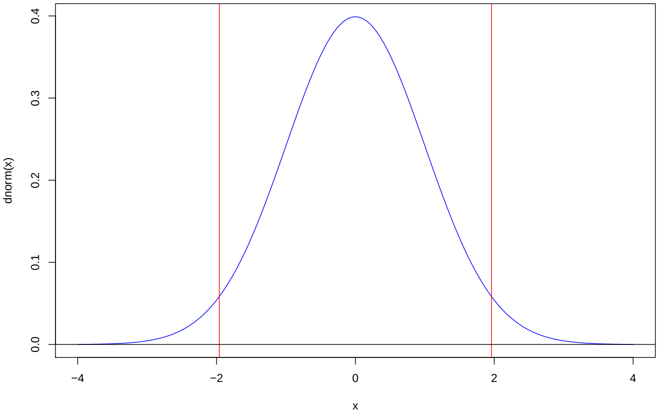
- We suppose that $V(Y_i) = \sigma^2$ is known
- Model for the estimator [using TCL]

$$\bar{Y} \sim \mathcal{N}(\mu, \sigma^2/\sqrt{n})$$

$$\frac{\bar{Y} - \mu}{\sigma/\sqrt{n}} \sim \mathcal{N}(0, 1)$$

Confidence interval for the mean knowing the variance (2)

- Visually



Confidence interval for the mean knowing the variance (3)

- So we have

$$P(u_{\frac{\alpha}{2}} \leq \frac{\bar{Y}-\mu}{\frac{\sigma}{\sqrt{n}}} \leq u_{1-\frac{\alpha}{2}}) = 1-\alpha$$

- If we study the two inequalities

$$u_{\frac{\alpha}{2}} \leq \frac{\bar{Y}-\mu}{\frac{\sigma}{\sqrt{n}}} \qquad \text{and} \qquad \frac{\bar{Y}-\mu}{\frac{\sigma}{\sqrt{n}}} \leq u_{1-\frac{\alpha}{2}}$$

- We get

$$\mu \leq \bar{Y} - u_{\frac{\alpha}{2}}\frac{\sigma}{\sqrt{n}} \qquad \text{and} \qquad \bar{Y} - u_{1-\frac{\alpha}{2}}\frac{\sigma}{\sqrt{n}} \leq \mu$$

Confidence interval for the mean knowing the variance (4)

- We get

$$P(\bar{Y} - u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}} \leq \mu \leq \bar{Y} - u_{\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}) = 1 - \alpha$$

$$B_1 = \bar{Y} - u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}} \qquad \text{and} \qquad B_2 = \bar{Y} - u_{\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$$

- The interval is larger for
  - larger σ
  - smaller α
  - smaller n

Exercice: Check that a c.i returned by a given approach works reasonably well

Exercice: First implement in R the previous c.i

Our two bounds are:

$$B_1 = \bar{Y} - u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}} \qquad \text{and} \qquad B_2 = \bar{Y} - u_{\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$$

```r
y <- rnorm(10) ## 0 mean and sd=1
n <- length(y)
theta.h <- mean(y)
alpha <- 0.05
b1 <- theta.h + qnorm(p=alpha/2)/sqrt(n)
b2 <- theta.h + qnorm(p=1-alpha/2)/sqrt(n)
```

Exercice: Check using simulations that our c.i works reasonably well (1)

- What should we check exactly ?
- The claim is : the probability that the random interval with confidence level $1-\alpha$ contains the true mean is $1-\alpha$
- We got our c.i assuming

$$\bar{Y} \sim \mathcal{N}(\mu, \sigma^2/\sqrt{n})$$

- Is it a reasonable assumption?

Ex: Check that our c.i works reasonably well (2)

A function to do that simulating uniform Y_i:

For now we simulate uniform Y_i

```
one.simu <- function(n=2, alpha=0.05){
  y <- runif(n, -0.5, 0.5)*sqrt(12) ## 0 mean and sd=1
  theta <- mean(y)
  b1 <- theta + qnorm(p=alpha/2)/sqrt(n)
  b2 <- theta + qnorm(p=1-alpha/2)/sqrt(n)
  return((b1 < 0) & (0 < b2))
}
```

Ex: Check that our c.i works reasonably well (3)

A few test

```
## n=2, clearly not perfect
res1 <- replicate(10^5, one.simu(2))
mean(res1)
```

```
## [1] 0.96051
```

```
## n=10, fairly close
res2 <- replicate(10^5, one.simu(10))
mean(res2)
```

```
## [1] 0.95103
```

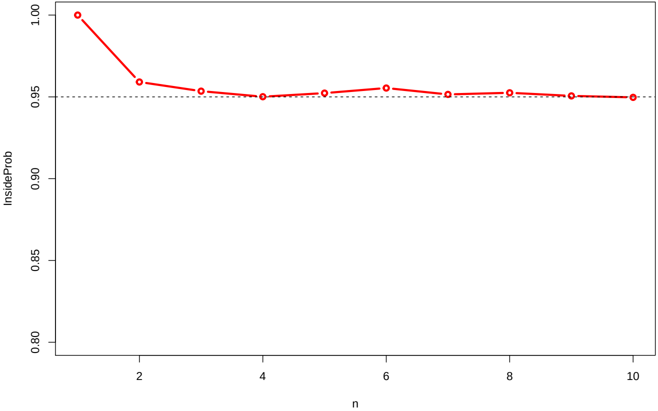
Ex: Check that our c.i works reasonably well (4)

If we now test for many values of *n*

```r
InsideProb <- numeric(10)
for(n in c(1:10)){
  InsideProb[n] <- mean( replicate(10^4, one.simu(n)) )
}
```

Ex: Check that our c.i works reasonably well (5)

```
plot(InsideProb, type="b", lwd=3, col="red", xlab="n",
     ylim=c(0.8, 1))
abline(h=0.95, lty=2)
```



For large enough (in fact not so large) it works. With probability 95% the interval

H-Ex: Check that our c.i works reasonably well (6)

- We used a uniform distribution for the Y_i
- Test for two times a Bernoulli r.v. of parameter 0.5

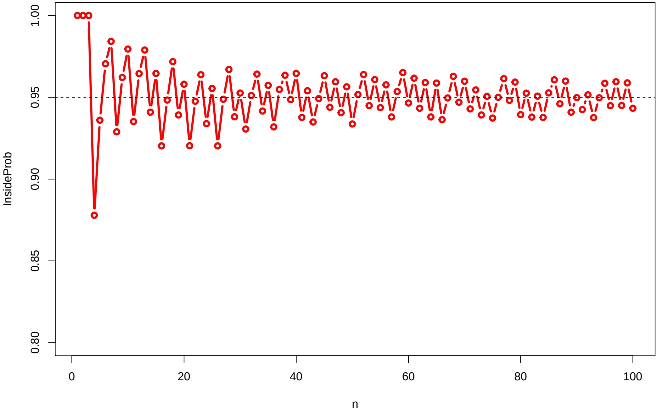
```r
one.simu <- function(n=2, alpha=0.05){
  y <- 2*rbinom(n=n, size=1, prob=0.5) ## 0 mean and sd=1
  theta <- mean(y)
  b1 <- theta + qnorm(p=alpha/2)/sqrt(n)
  b2 <- theta + qnorm(p=1-alpha/2)/sqrt(n)
  return((b1 < 1) & (1 < b2))
}
```

H-Ex: Check that our c.i works reasonably well (7)

```
InsideProb <- numeric(100)
for(n in c(1:100)){
  InsideProb[n] <- mean( replicate(10^4, one.simu(n)) )
}
```

H-Ex: Check that our c.i works reasonably well (8)

```
plot(InsideProb, type="b", lwd=3, col="red", xlab="n",
     ylim=c(0.8, 1))
abline(h=0.95, lty=2)
```



Confidence interval for the mean not knowing the variance

- If σ is not known, similar calculations using the T distribution leads to a confidence interval:
- Namely we start from

$$\frac{\bar{X}-\mu}{\hat{\sigma}/\sqrt{n}} \sim \mathcal{T}_{n-1}$$

Confidence interval for the mean not knowing the variance

In R

```r
x <- runif(10)
t.test(x)$conf.int
```

```
## [1] 0.1622967 0.6318180
## attr(,"conf.level")
## [1] 0.95
```

Exercice and the student confidence interval

Exercice: Student confidence interval

1. Check that the Student c.i “works” when simulating Y_i as

   - independent Student r.v of degree 2.1 (in R rt).
   - (HW) independant χ^2 r.v of degree 3 (in R rchisq)

2. Study the effet of n.

```r
one.simu <- function(n=2, alpha=0.05){
  y <- rt(n=n, df=2.1) ## 0 mean and sd=1
  CI <- t.test(y)$conf.int
  return((CI[1] < 0) & (0 < CI[2]))
}
```

Ex: Student c.i

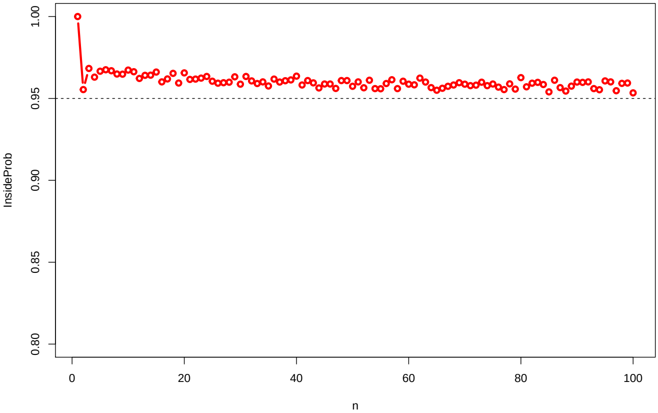
We test for various *n*

```
InsideProb <- numeric(100)
InsideProb[1] <- 1
for(n in c(2:100)){
  InsideProb[n] <- mean( replicate(10^4, one.simu(n)) )
}
```

Ex: Student c.i

We plot

```
plot(InsideProb, type="b", lwd=3, col="red", xlab="n",
     ylim=c(0.8, 1))
abline(h=0.95, lty=2)
```



H-Ex: χ^2 distribution

```r
one.simu <- function(n=2, alpha=0.05){
  y <- rchisq(n=n, df=5) ## 0 mean and sd=1
  CI <- t.test(y)$conf.int
  return((CI[1] < 5) & (5 < CI[2]))
}
```

H-Ex: χ^2 c.i

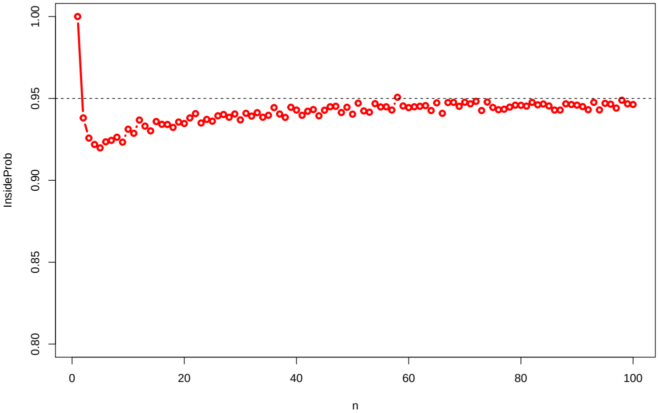
We test for various *n*

```r
InsideProb <- numeric(80)
InsideProb[1] <- 1
for(n in c(2:100)){
  InsideProb[n] <- mean( replicate(10^4, one.simu(n)) )
}
```

H-Ex: χ^2 c.i

We plot

```r
plot(InsideProb, type="b", lwd=3, col="red", xlab="n",
     ylim=c(0.8, 1))
abline(h=0.95, lty=2)
```



Confidence intervals

- Many statistical methods provide confidence intervals
- Computationnal or mathematical derivation of those c.i can be complex
- From an application point of view always the same principle

Principle A statistical model with some assumptions on the signal

1. Check that those assumptions are reasonable for your application
2. In doubt check using simulations that this is working

Exercice on polymer

Student interval

- Polymer viscosity

Is the viscocity of the polymer in the interval $[75, 95]$?

```r
## the data was
y <- c(78, 85, 91, 76)
t.test(y)$conf.int[1:2]
```

```
## [1] 71.59112 93.40888
```

What do we conclude ?

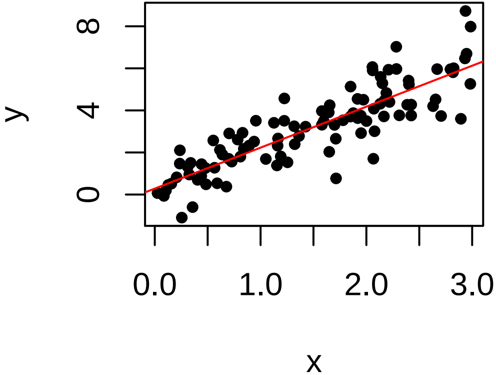
An other example simple linear regression

- Linear regression

$$Y_i = \alpha x_i + \beta + \varepsilon_i$$

$$\varepsilon_i \sim \mathcal{N}(0, \sigma^2) \quad i.i.d$$

```
model <- lm(y ~ x) ## Regression
plot(x, y, pch=20); abline(model, col="red"); ## graphe
```



Simple linear regression (2)

```r
confint(model) ## IC à 95%
```

```
##                  2.5 %    97.5 %
## (Intercept) -0.1200145 0.6829409
## x            1.7156597 2.1797113
```

- Can we conclude that the slope is different from 0?
- What about the origin ?

A schematic view of what a 95% confidence interval does

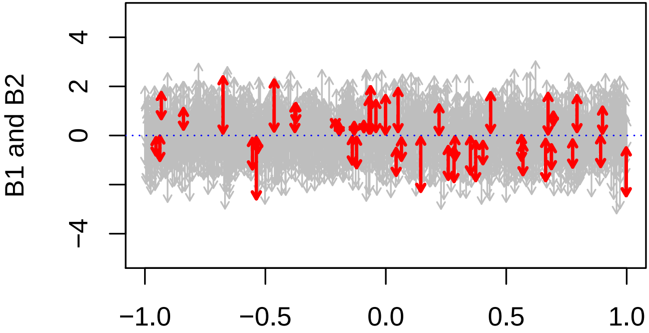


Figure 2: 200 confidence intervals

Hypothesis testing

A few examples of test-like questions

- Is the expression of gene HER2 large in breast cancer ?
- Is a new variety of tomoto more resistant to meldew than the previous one ?
- Is a drug better than a placebo ?
- Should the $+1$ increased popularity of a candidate be commented ?

When can you use a test ?

- A Yes/No question
- You have data
- These data can be considered as the result of some r.v. (known through a model)
- The question shoud be about a parameter of the distribution

Outcome of a test

Only two possibilities:

1. Either your accept the hypothesis H_0 (data are not in disagreement with your assumption)
2. Or you reject it (data are in disagreement with your assumption)

Four elements of a test

1. Data $y_1, ..., y_n$ realisation of r.v. $Y_1, ..., Y_n$
2. A statistical model:
   - distribution of $Y_1, ..., Y_n$ depending on some parameters θ
3. An assumption:
   - A statement about θ.
   - This is the so called H_0 hypothesis (H_1 is the alternative)
4. A decision rule
   - If $T = f(X_1, ..., X_n)$ is a test statistic
   - R is subset of values for T that is improbable if H_0 is true

Four elements of a test

1. Data $y_1, ..., y_n$ realisation of r.v. $Y_1, ..., Y_n$
2. A statistical model:
3. An assumption:
4. A decision rule

- A test can be viewed as a probabilistic extension of “argument to absurdity”

Efficiency of a test (intuition)

- Two types or error
  1. Reject H_0 when it is true
  2. Keep H_0 when it is false
- Typically it is not possible to control both of these errors at the same time.

Efficiency of a test (intuition)

- Type I risk: α the probability under H_0 to reject H_0
- Type II risk: β the probability under H_1 to keep H_0.
- We call power $\pi = 1 - \beta$
- Make a table. . .

Construction of a test

- Fabrication of a 100 cl bottle

1. **Data** $y_1, ..., y_n$ some measurements realisation of r.v $Y_1, ... Y_n$.
2. **Model**
$$Y_i \sim \mathcal{N}(\mu, \sigma^2) \qquad \text{i.i.d}$$
3. **Hypothesis**
$$H_0 = \{\mu = 100cl\}$$
4. **Rule**:
   - $T = \frac{1}{n} \sum Y_i$
   - Reject if $(T - 100)$ is too large:

$$\ell = u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$$

Construction of test (2)

- If all Y_i are normal and independent

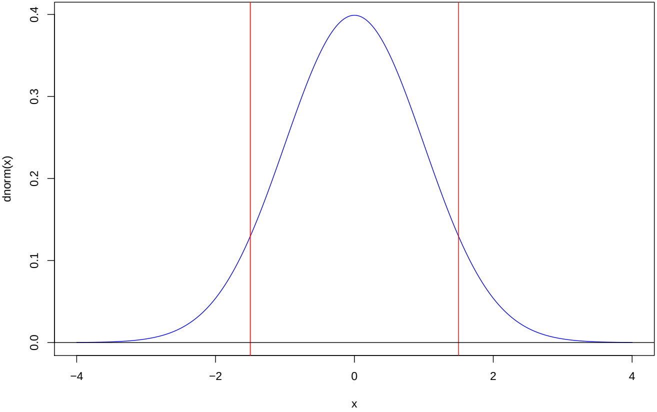
$$\bar{Y} \sim \mathcal{N}(\mu, \frac{\sigma^2}{n})$$

- So under H_0 (taking $\mu_0 = 100$)

$$P(u_{\frac{\alpha}{2}} \leq \frac{\bar{X} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \leq u_{1-\frac{\alpha}{2}}) = 1 - \alpha$$

Construction of test (3)

- Visually, we observed $\bar{y} = 1.5$



Construction of a test (4)

- So we get

$$P(u_{\frac{\alpha}{2}} \leq \frac{\bar{X} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \leq u_{1-\frac{\alpha}{2}}) = 1 - \alpha$$

- If we study the two inequalities

$$u_{\frac{\alpha}{2}} \leq \frac{\bar{X} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \qquad \text{et} \qquad \frac{\bar{X} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \leq u_{1-\frac{\alpha}{2}}$$

- we get

$$\mu_0 + u_{\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}} \leq \bar{X} \qquad \text{et} \qquad \bar{X} \leq \mu_0 + u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$$

Construction of a test (5)

- Fabrication of a 100 cl bottle

1. **Data** $y_1, ..., y_n$ some measurements realisation of r.v $Y_1, ... Y_n$.
2. **Model**
$$Y_i \sim \mathcal{N}(\mu, \sigma^2) \qquad \text{i.i.d}$$
3. **Hypothesis**
$$H_0 = \{\mu = 100cl\}$$
4. **Rule**:
   - $T = \frac{1}{n} \sum Y_i$
   - Reject if $(T - 100)$ is too large:

$$\ell = u_{1-\frac{\alpha}{2}} \frac{\sigma}{\sqrt{n}}$$

Implementation in R

- We know the variance and scale the data using the variance

```r
## simulate some bottles
Y <- rnorm(10, mean=101, sd=2)
Y.scaled <- Y/2
mu0 <- 100/2

## probability of a value so far from 0 under H0
p.val <- 2*pnorm(abs(mean(Y)-mu0),
                 sd= 1/sqrt(10), lower.tail=FALSE)
```

Exercice: Check that this is working ?

What should we check ?

- control that we indeed control at level α
- control that under H_1 we have some power

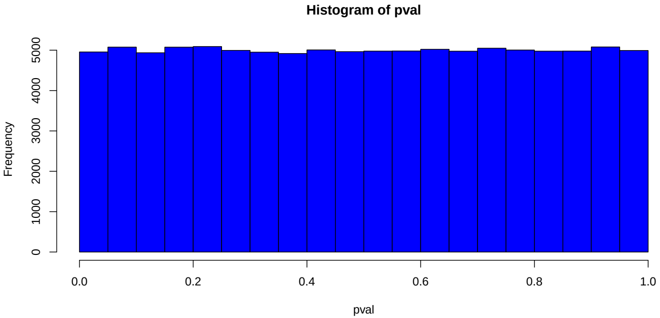
```r
n.test <- function(Y.sc, mean.H0=0){
  min(1, 2*pnorm(abs(mean(Y.sc-mean.H0)),
                 sd= 1/sqrt(length(Y.sc)),
                 lower.tail=FALSE) )
}

one.simu <- function(n, mean){
  ## no-need to scale here (sd=1)
  Y <- rnorm(n, mean=mean, sd=1)
  return( n.test(Y, 0) )
}
```

Ex: Type I error control

- If we make *n* simulations under H_0 a proportion α of those experiements should have a p-value under α.
- That is the p-values should be uniform

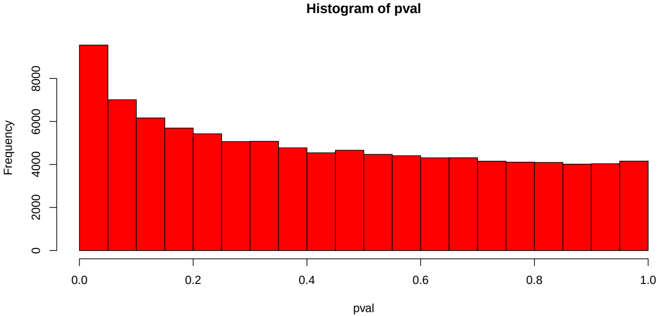
```
pval <- replicate(10^5, one.simu(10, 0))
hist(pval, col="blue")
```



Ex: Power

- If we make n simulations under H_1 a proportion higher than α of those experiements should have a p-values under α.

```r
pval <- replicate(10^5, one.simu(10, 0.2))
hist(pval, col="red")
```



Ex: Power

- At level $\alpha = 0.05$ and $\alpha = 0.01$ the power is

```r
mean(pval <= 0.05)
```

```
## [1] 0.09549
```

```r
mean(pval <= 0.01)
```

```
## [1] 0.02664
```

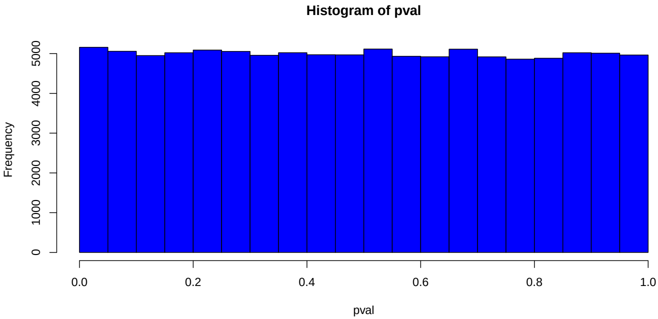
Ex:

- What happens when *n* increases ?

Ex: Type I error control

- Larger *n*
- The p-values should still be uniform

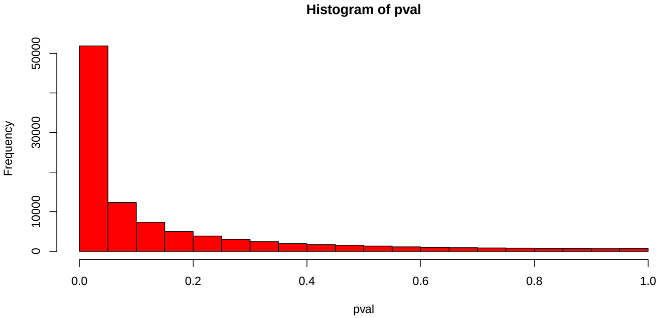
```
pval <- replicate(10^5, one.simu(100, 0))
hist(pval, col="blue")
```



Ex: Power

- We should have more power

```
pval <- replicate(10^5, one.simu(100, 0.2))
hist(pval, col="red")
```



Ex: Power

- At level $\alpha = 0.05$ and $\alpha = 0.01$ the power is

```r
mean(pval <= 0.05)
```

```
## [1] 0.51867
```

```r
mean(pval <= 0.01)
```

```
## [1] 0.28616
```

Homework:

- What happens if you change the distrubution of the Y_i

Test if σ^2 is not know

- If σ is not known, similar calculations using the student distribution with $n-1$ degrees of freedom lead to the famous T-test
- Namely we start from

$$\frac{\bar{X}-\mu}{\hat{\sigma}/\sqrt{n}} \sim \mathcal{T}_{n-1}$$

In R

```
Y <- runif(10, min=0, max=1)
t.test(Y)$p.value
```

```
## [1] 0.0001358614
```

Many other test…

1. In general many statistical methods provide hypothesis testing
2. Computationnal or mathematical derivation of those is often complex
3. But same principle

- A statistical model: check that it is reasonable for your application
- An H_0 hypothesis: check that it adress your question
- In doubt check using simulations that the test is working

Two populations t-test with same variance

- $Y_{11}, ... Y_{1n}$ i.i.d with mean θ_1 and variance σ^2
- $Y_{21}, ... Y_{2n'}$ i.i.d with mean θ_2 and variance σ^2
- H_0 $\theta_1 = \theta_2$
- H_1 $\theta_1 \neq= \theta_2$

Similar calculations lead to another student statistics. In R:

```
Y1 <- rnorm(10, sd=2)
Y2 <- rnorm(8, sd=2)

t.test(Y1, Y2, var.equal = TRUE)$p.value
```

```
## [1] 0.8927863
```

Exercice: Power of the two sample t-test

Ex: Power of two sample t-test

Two populations

- $Y_{11}, \dots Y_{1n}$ i.i.d with mean θ_1 and variance σ^2
- $Y_{21}, \dots Y_{2n'}$ i.i.d with mean θ_2 and variance σ^2

We fix $N = n + n'$.

1. Check that the t-test is indeed controling α
2. Assess the power of the t-test to detect a difference of 0.5 for an α level of 5%

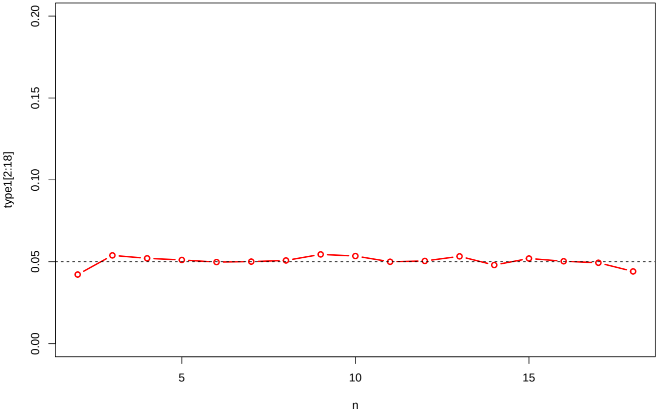
```
one.simu <- function(n=10, N=20, diff=0){
  Y1 <- runif(n, min=0, max=1)
  Y2 <- runif(N-n, min=0, max=1)+diff
  t.test(Y1, Y2, var.equal = TRUE)$p.value
}
```

Ex: Type I error control

```r
type1 <- numeric(19)
for(n in 2:18){
  type1[n] <- mean( replicate(10^4,
                         one.simu(n=n)) <= 0.05)
}
```

Ex: Type I error control

```
plot(2:18, type1[2:18], ylim=c(0, 0.2), type="b", xlab="n",
abline(h=0.05, lty=2)
```

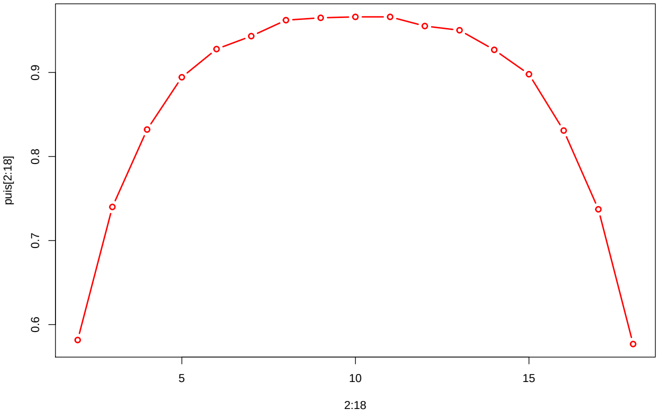


Ex: Power

```r
puis <- numeric(19)
for(n in 2:18){
  puis[n] <- mean( replicate(10^4,
                    one.simu(n=n, diff=0.5)) <= 0.05)
}
```

Ex: Power

```
plot(2:18, puis[2:18], type="b", col="red", lwd=2)
```



Homework: Compare the t-test and wilocoxon-test

Compare the following three following testin R for various normal distributed data and χ^2 distributed data. You should assess for various sample sizes:

1. The type I error control
2. The power to detect a mean difference of 0.5 at level $\alpha = 0.01$

```r
Y1 <- runif(10)
Y2 <- runif(12)

wilcox.test(Y1, Y2)$p.value
```

```
## [1] 0.5824145
```

```r
t.test(Y1, Y2, var.equal=FALSE)$p.value
```

```
## [1] 0.6209135
```

```r
t.test(Y1, Y2, var.equal=TRUE)$p.value
```

H-Ex

Simulation function

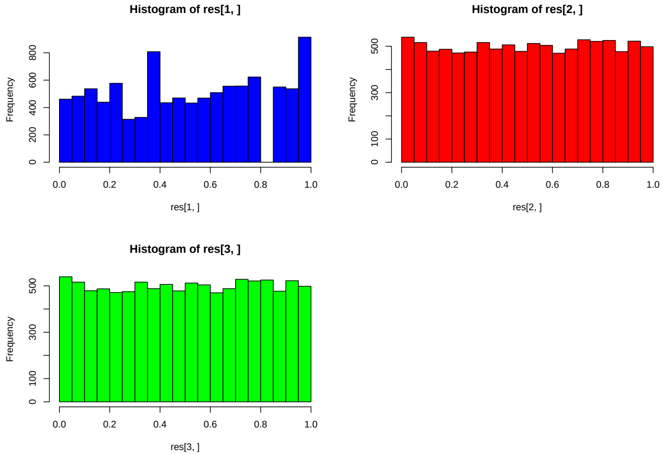
```r
one.simu <- function(n1, n2, diff){
  Y1 <- runif(n1, min=0, max=1)
  Y2 <- runif(n2, min=0, max=1)+diff
  p1 <- wilcox.test(Y1, Y2)$p.value
  p2 <- t.test(Y1, Y2, var.equal = TRUE)$p.value
  p3 <- t.test(Y1, Y2, var.equal = TRUE)$p.value
  return(c(p1, p2, p3))
}
```

H-Ex: Type I error control (a)

```r
res <- replicate(10^4, one.simu(10, 10, 0))
```

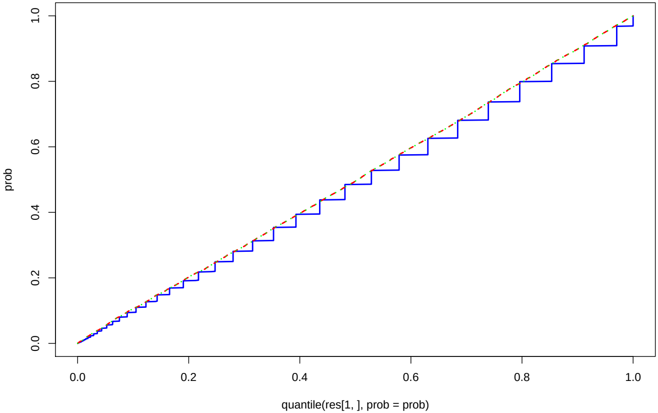
H-Ex: Type I error control (b)

```
par(mfrow=c(2, 2))
hist(res[1, ], col="blue")
hist(res[2, ], col="red")
hist(res[3, ], col="green")
```



H-Ex: Type I error control (c)

```
prob <- seq(0, 1, by=0.001)
plot(quantile(res[1, ], prob=prob), prob, type="l", col="bl
lines(quantile(res[2, ], prob=prob), prob, type="l", col="r
lines(quantile(res[2, ], prob=prob), prob, type="l", col="g
```



H-Ex: Power

```r
res <- replicate(10^4, one.simu(10, 10, 0.5))
rownames(res) <- c("Wil", "T.E", "T.I")
## for alpha at 0.05
rowMeans(res <=0.05)
```

```
##    Wil    T.E    T.I
## 0.9175 0.9683 0.9683
```

```r
## for alpha at 0.01
rowMeans(res <=0.01)
```

```
##    Wil    T.E    T.I
## 0.7370 0.8324 0.8324
```

Multiple testing (a quick introduction)

Multiple testing in genomics

- Differential analysis : one test per gene
- ChipSeq : one test per window
- GWAS : one test per SNP

Why performing many tests is a problem?

Suppose you are performing G tests at level α.

$$P(\text{at least one FP if } \mathrm{H}_0 \text{ is always true}) = 1 - (1-\alpha)^G$$

- Ex: for $\alpha = 5\%$ and $G = 20$,

$$P(\text{at least one FP if } \mathrm{H}_0 \text{ is always true}) \simeq 64$$

- This probability increases with the number of test G
- For more than 75 tests
- if H_0 is always true the probability to have at least one false positive is very close to 100%!

Error Rate for G tests

Instead of the risk α, control:

- the Family-Wise Error Rate: $\text{FWER} = \mathbb{P}(U > 0)$
  - probability to have at least one false positive decision
- the False Discovery Rate: $\text{FDR} = \mathbb{E}(Q)$ with

$$Q = \begin{cases} U/R & \text{if } R > 0 \\ 0 & \text{otherwise} \end{cases}$$

Adjusted p-values

Settings: p-values $p_1, \ldots, p_G$ ({*e.g.*}, *corresponding to G tests)*

Adjusted p-values *adjusted p-values are $\tilde{p}_1, \ldots, \tilde{p}_G$ such that*

Rejecting tests such that $\tilde{p}_g < \alpha$

is equivalent to

$$P(U > 0) \leq \alpha \quad \textit{or} \quad \mathbb{E}(Q) \leq \alpha$$

Calculating adjusted p-values

1. order the p-values $p_{(1)} \leq p_{(2)} \leq \ldots \leq p_{(G)}$
2. calculate $\tilde{p}_{(g)} = a_g p_{(g)}$
   - with Bonferroni method: $a_g = G$ (FWER)
   - with Benjamini and Hochberg method: $a_g = G/g$ (FDR)
3. if $\tilde{p}_{(g)}$ is larger than 1 replace it by 1

Implementation in R

We simulate 1000 test under H0.

```r
pval <- replicate(1000, t.test(rnorm(10))$p.value)

## adjustement
fdr <- p.adjust(pval, method="BH")
bfr <- p.adjust(pval, method="bonferroni")
```

Exercice: Check that the “BH” approach is working reasonable well

- What should we do ?
- For a given threshold α check that the average proportion of false positive is indeed less than α.

```r
one.simu <- function(n0=90, n1=10, p=20,
                     alpha=0.05, meanH1=0.5){
  pval0 <- replicate(n0, t.test(rnorm(p))$p.value)
  pval1 <- replicate(n1, t.test(rnorm(p)+meanH1)$p.value)
  pval <- c(pval0, pval1)
  padj <- p.adjust(pval, method="BH")
  sum(padj[1:n0] <= alpha) / max(1, sum(padj <= alpha))
}
```

Ex: Check that “BH” is working reasonable well (1)

One simulation:

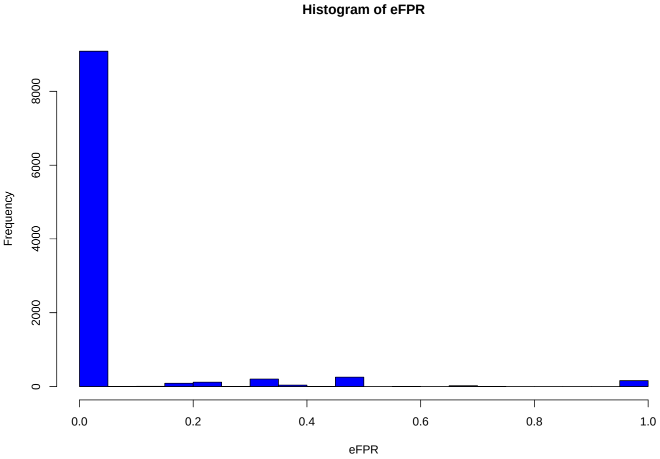
```
eFPR <- replicate(10^4, one.simu())
mean(eFPR)
```

```
## [1] 0.04402909
```

We do control the FPR on average.

Ex: Check that “BH” is working reasonable well (2)

```r
hist(eFPR, col="blue")
```



Sometimes we are a bit unlucky. . .

Ex: Check that “BH” is working reasonable well (3)

For various proportion of H1 and H0

```
res <- lapply(10*1:9, FUN=function(i)
  replicate(10^3, one.simu(n0=i, n1=100-i)))

mat <- do.call(cbind, res)
colnames(mat) <- paste0("n0=", 10*1:9)
```

Ex: Check that “BH” is working reasonable well (4)

On average we get

```
signif(colMeans(mat), 1)
```

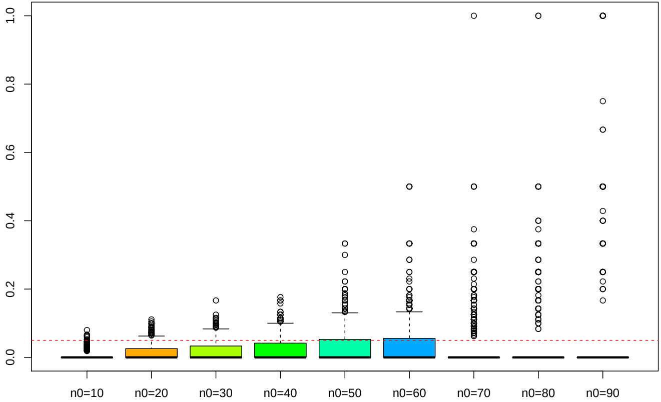
```
## n0=10 n0=20 n0=30 n0=40 n0=50 n0=60 n0=70 n0=80 n0=90
## 0.005 0.010 0.020 0.020 0.030 0.030 0.030 0.030 0.050
```

- **We indeed control the FDR**
- Our control is not always tight.

Ex: Check that "BH" is working reasonable well (5)

In details things are even more complex:

```
boxplot(mat, col=rainbow(9));
abline(h=0.05, lty=2, col="red")
```



Homework: Check that “bonferroni” is working reasonable well

Conclusion FDR, BH and beyound...

- There are other approaches
- possibly more complex mathematically
- see for example: https://mathforgenomics.github.io/neuvial.pdf