



CANCER
RESEARCH
UK

CAMBRIDGE
INSTITUTE



UNIVERSITY OF
CAMBRIDGE

Introduction to Statistical Analysis

Cancer Research UK – 5th of November 2018

D.-L. Couturier / M. Eldridge / M. Fernandes [Bioinformatics core]

Timeline

9:30 – Morning

- ▶ ~ 45mn Lecture: **data type, summary statistics and graphical displays**
- ▶ ~ 15mn Quiz

10:30 – 15mn Coffee & Tea break

- ▶ ~ 60mn Lecture: **some statistical distributions + CLT**
- ▶ ~ 15mn Exercises & discussion

12:00 – Lunch break

13:00 – Afternoon

- ▶ ~ 45mn Lecture: **One-sample location test**
- ▶ ~ 30mn Exercises with shiny app & discussion

- ▶ ~ 45mn Lecture: **Two-sample location test**

15:15 – 15mn Coffee & Tea break

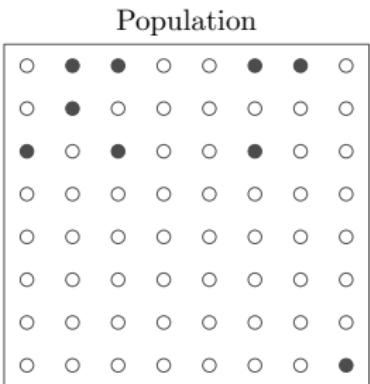
- ▶ ~ 30mn Exercises with shiny app & discussion

16:15 – Group based exercises

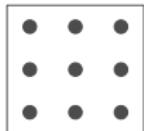
- ▶ ~ 60mn

Grand Picture of Statistics

UK SMOKERS



Sample



MEASUREMENT ERROR
MISSING VALUES

Data

(x_1, x_2, \dots, x_n)

$\text{C } \neq \neq$

POINT
ESTIMATION

OUTLIERS
ZERO INFLATED

Statistics

INFERENCE

$\hat{\mu}$

$\hat{\sigma}^2$

NO SUITABLE
TEST

$$\hat{\pi} = \frac{1}{3} = 0.\overline{3}$$

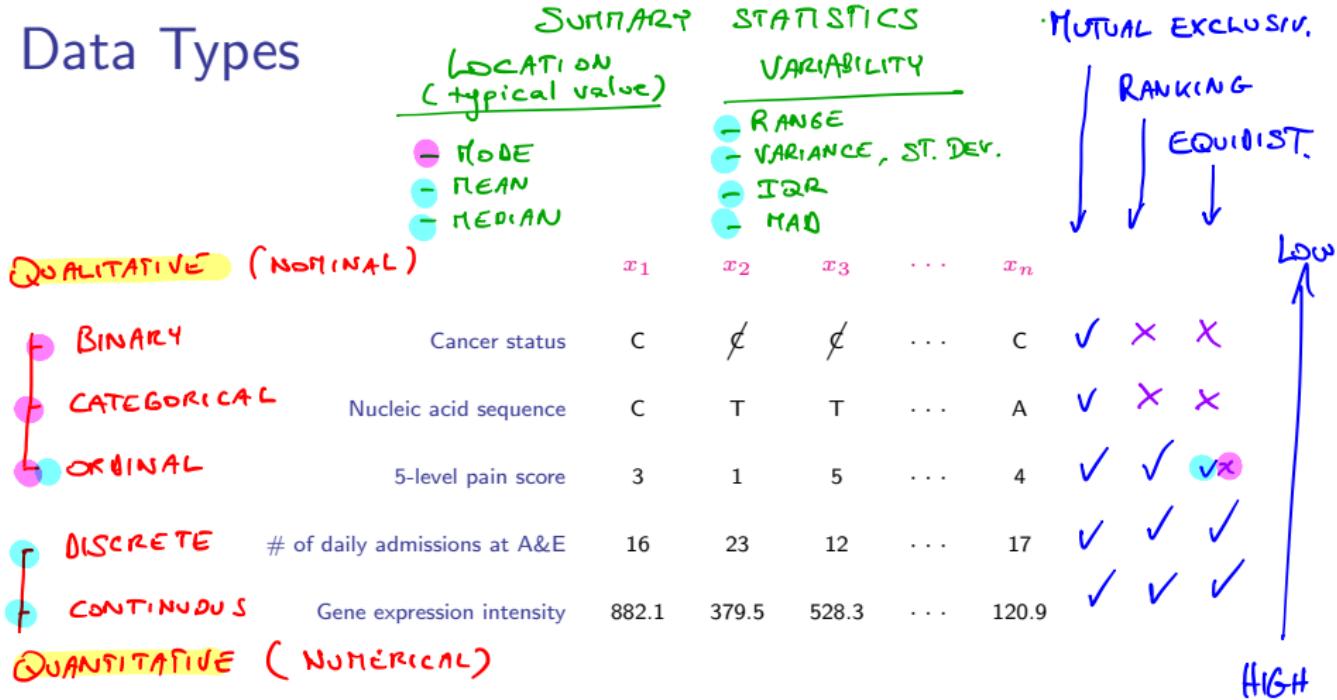
PROBABILITY OF
LUNG CANCER
AMONG SMOKERS

μ

σ^2

π

Data Types



GRAPHICAL DISPLAYS

- BARPLOT
 - HISTOGRAM
 - BoxPLOT

Summary statistics and plots for qualitative data

$$\hat{\pi}_c = \frac{\sum_{i=1}^n I(x_i = c)}{n} \quad \text{where } I(x_i = c) = 1 \text{ if } x_i = c \text{ and} \\ = 0 \text{ otherwise}$$

5-level answers of 21 patients to the question

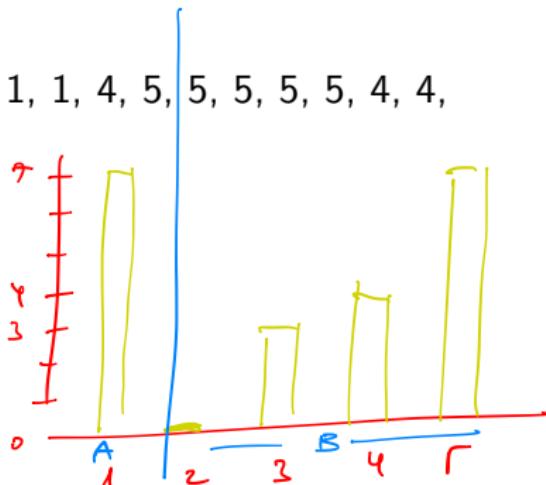
"How much did pain due to your ureteric stones interfere with your day to day activities ?":

3, 1, 5, 3, 1, 1, 1, 5, 1, 3, 4, 1, 1, 4, 5, 5, 5, 5, 5, 4, 4,

where

- 1 = "Not at all", 7/21
- 2 = "A little bit", 0/21
- 3 = "Somewhat", 3/21
- 4 = "Quite a bit", 4/21
- 5 = "Very much". 7/21

$$\sum = 1$$



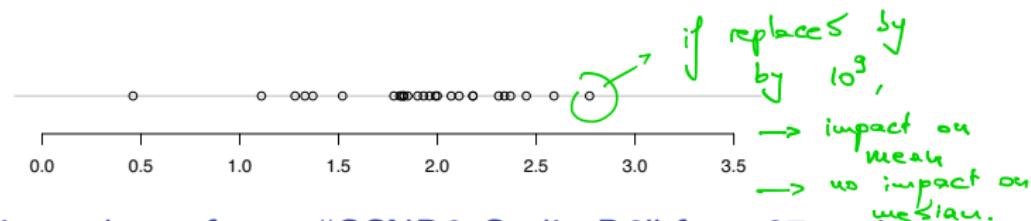
A: TWO - STAGE PROCESS :
INTERFERENCE: YES/NO MODE = YES
B: IF INTERFERENCE : INTERF. LEVEL MODE = 5

Summary statistics and plots for quantitative data

LOCATION:

$$\text{MEAN: } \hat{\mu} = \bar{x} = \frac{1}{n} \sum_{i=1}^n x_i = 1.83$$

$$\text{MEDIAN: } \hat{med} = \hat{q}_{0.5} = \begin{cases} x_{\left(\frac{n+1}{2}\right)} & \text{if } n \text{ is odd} \\ \frac{(x_{\frac{n}{2}} + x_{\frac{n}{2}+1})}{2} & \text{if } n \text{ is even} \end{cases} = 1.93$$



Gene expression values of gene "CCND3 Cyclin D3" from 27 patients diagnosed with acute lymphoblastic leukaemia:

$x_{(1)}$	$x_{(2)}$	$x_{(3)}$	$x_{(4)}$	$x_{(5)}$	$x_{(6)}$	$x_{(7)}$	$x_{(8)}$	$x_{(9)}$
0.46	1.11	1.28	1.33	1.37	1.52	1.78	1.81	1.82
$x_{(10)}$	$x_{(11)}$	$x_{(12)}$	$x_{(13)}$	$x_{(14)}$	$x_{(15)}$	$x_{(16)}$	$x_{(17)}$	$x_{(18)}$
1.83	1.83	1.85	1.9	1.93	1.96	1.99	2.00	2.07
$x_{(19)}$	$x_{(20)}$	$x_{(21)}$	$x_{(22)}$	$x_{(23)}$	$x_{(24)}$	$x_{(25)}$	$x_{(26)}$	$x_{(27)}$
2.11	2.18	2.18	2.31	2.34	2.37	2.45	2.59	2.77

Summary statistics and plots for quantitative data

VARIABILITY

$$\text{RANGE} : x_{(u)} - x_{(1)} = 2.77 - 0.46 = 2.31$$

$$\text{VARIANCE} : \hat{\sigma}^2 = \frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2 = \frac{(0.46 - 1.83)^2 + (1.11 - 1.83)^2 + \dots}{n} = 0.5$$

$$\text{ST. DEV} : \hat{\sigma} = \sqrt{\hat{\sigma}^2} = (0.25)$$

$$\text{MEDIAN ABS. DEV} : \hat{MAD} = \text{med}(|x_i - \text{med}(x)|) = 0.25$$

$$\text{INTERQUARTILE RANGE} : IQR = \hat{Q}_{0.75} - \hat{Q}_{0.25}$$

ROBUST TO OUTLIERS

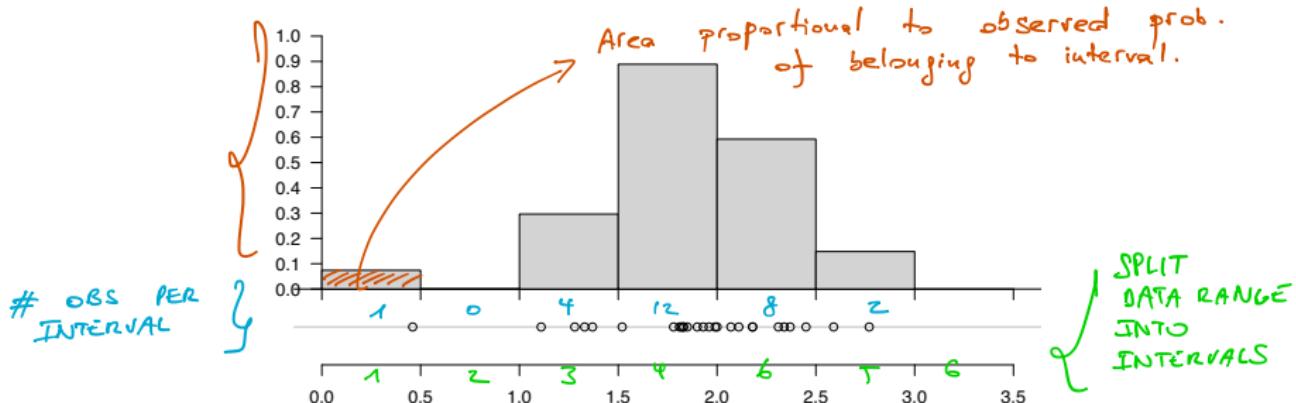


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Summary statistics and plots for quantitative data

HISTOGRAM

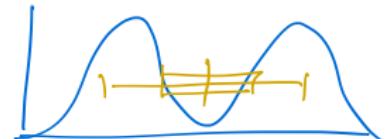


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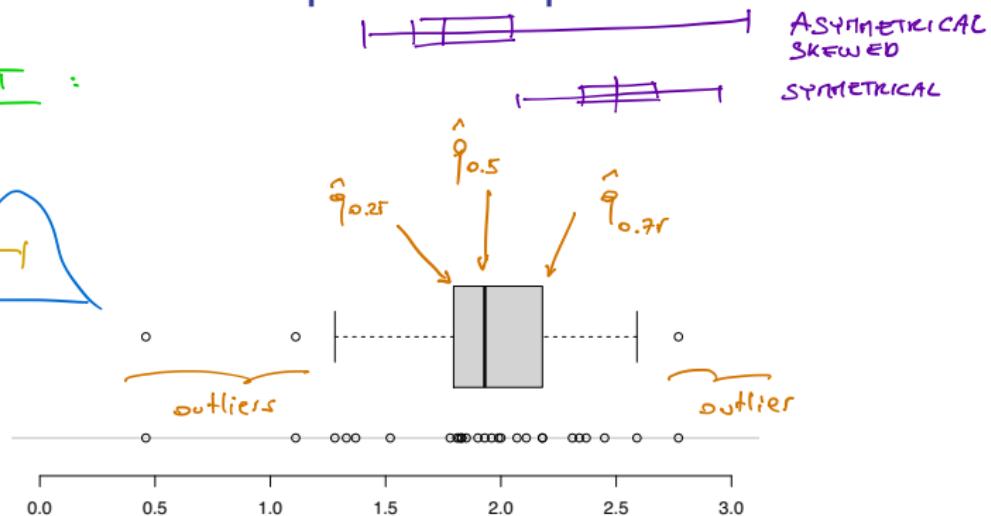
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Summary statistics and plots for quantitative data

Box PLOT :



not suitable
for BIMODAL
VARIABLES



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Two-sample case: independent versus paired samples

DIFFERENT AND UNRELATED PARTICIPANTS

SAME PARTICIPANTS MEASURED TWICE

Permeability constants of a placental membrane at term (X) and between 12 to 26 weeks gestational age (Y).

	1	2	3	4	5	6	7	8	9	10
X	0.80	0.83	1.89	1.04	1.45	1.38	1.91	1.64	0.73	1.46
Y	1.15	0.88	0.90	0.74	1.21					

$$\overline{Y} - \overline{X}$$

Hamilton depression scale factor measurements in 9 patients with mixed anxiety and depression, taken at the first (X) and second (Y) visit after initiation of a therapy (administration of a tranquilizer).

	1	2	3	4	5	6	7	8	9
X	1.83	0.50	1.62	2.48	1.68	1.88	1.55	3.06	1.30
Y	0.88	0.65	0.60	2.05	1.06	1.29	1.06	3.14	1.29
Y-X	-0.95	0.15	-1.02	-0.43	-0.62	-0.59	-0.49	0.08	-0.01

mean of the differences. { $\frac{\sum (y_i - x_i)}{n}$ }

Quiz Time

Sections 1 to 4

https://docs.google.com/forms/d/e/1FAIpQLScblQ_-ISfSCGp_EIVPPI_mnrJHttaKxln8vVoyjJFvS8BL1w/viewform

Some parametric distributions: Binomial distribution

If

- ▶ n independent experiments,
- ▶ outcome of each experiment is dichotomous (success/failure),
- ▶ the probability of success π is the same for all experiments,

then,

- ▶ the **number of successes out of n trials** (experiments), $Y = \sum_{i=1}^n X_i$, follows a binomial distribution with parameters n and π :

$$Y \sim \text{Bin}(n, \pi),$$

- ▶ the probability of observing exactly y successes out of n experiments, is given by

$$P(Y = y|n, \pi) = \frac{n!}{(n-y)!y!} \pi^y (1 - \pi)^{n-y}.$$

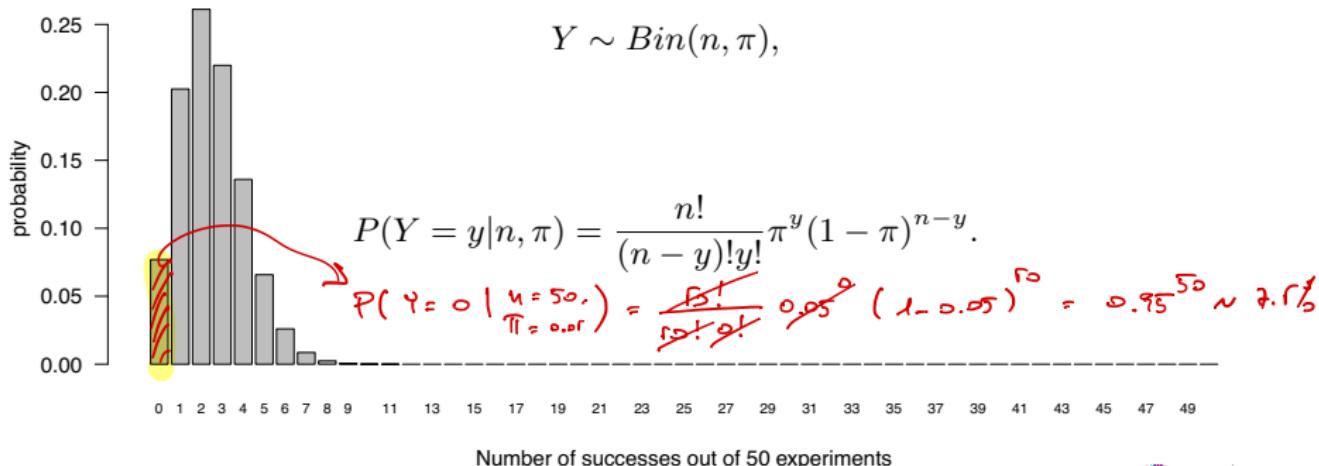
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Some parametric distributions: Poisson distribution

EVENTS PER
UNIT OF TIME AND/OR
PER AREA

HOURLY ADMISSION AT ANE
OF DAILY ORGAN DONORS IN THE UK

If, during a time interval or in a given area,

- ▶ events occur independently,
- ▶ at the same rate,
- ▶ and the probability of an event to occur in a small interval (area) is proportional to the length of the interval (size of the area),

then,

- ▶ the number of events occurring in a fixed time interval or in a given area, X , may be modelled by means of a Poisson distribution with parameter λ :

$$X \sim \text{Poisson}(\lambda),$$

- ▶ the probability of observing x during a fixed time interval or in a given area is given by

$$P(X = x|\lambda) = \frac{\lambda^x e^{-\lambda}}{x!}.$$

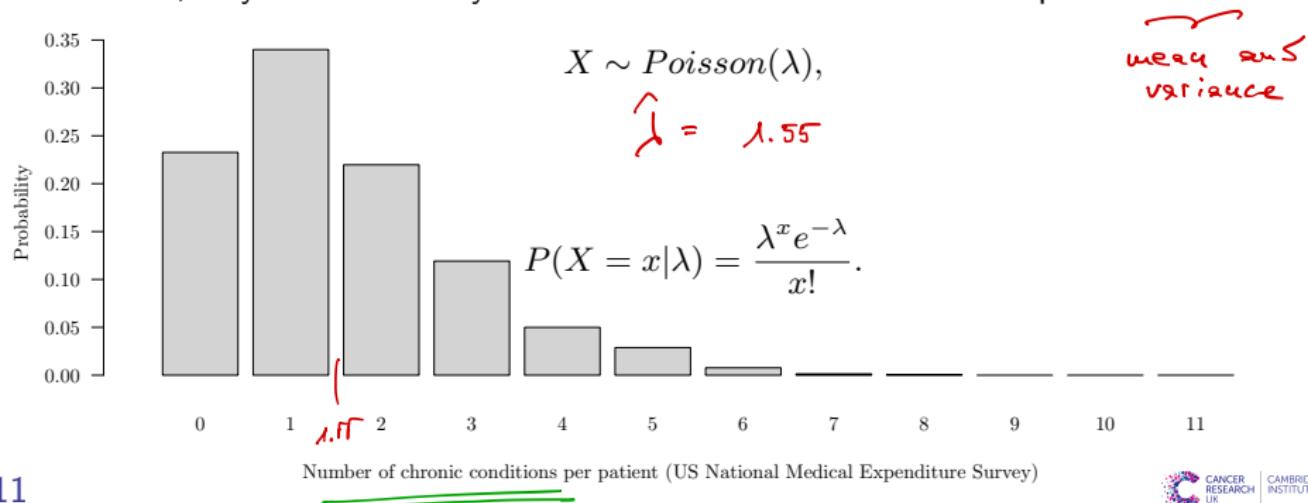
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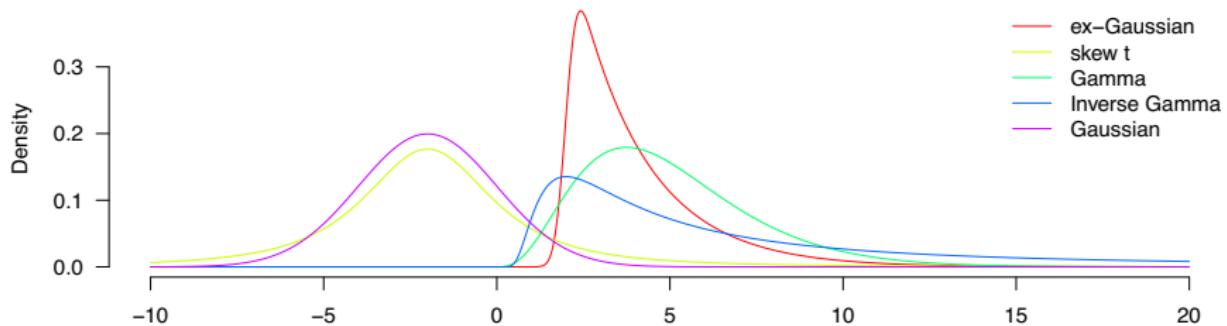
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Some parametric distributions: Continuous distrib.

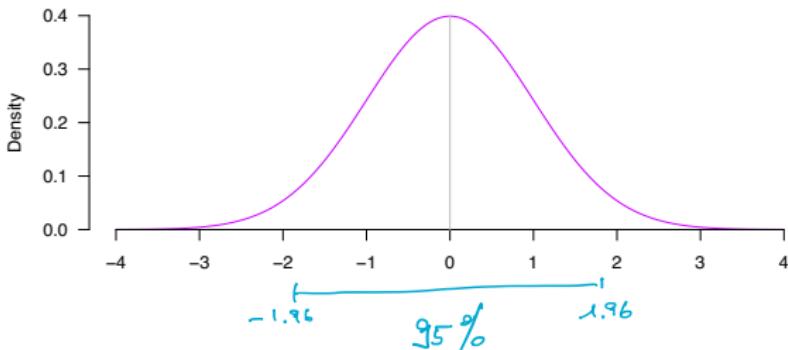


Some parametric distributions: Normal distribution

$$X \sim N(\mu, \sigma^2), \quad f_X(x) = \frac{1}{\sqrt{2\pi}\sigma^2} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$
$$\mathbb{E}[X] = \mu, \quad \text{Var}[X] = \sigma^2,$$

$$Z = \frac{X - \mu}{\sigma} \sim N(0, 1), \quad f_Z(z) = \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}}.$$

Probability density function, $f_Z(z)$, of a standard normal:

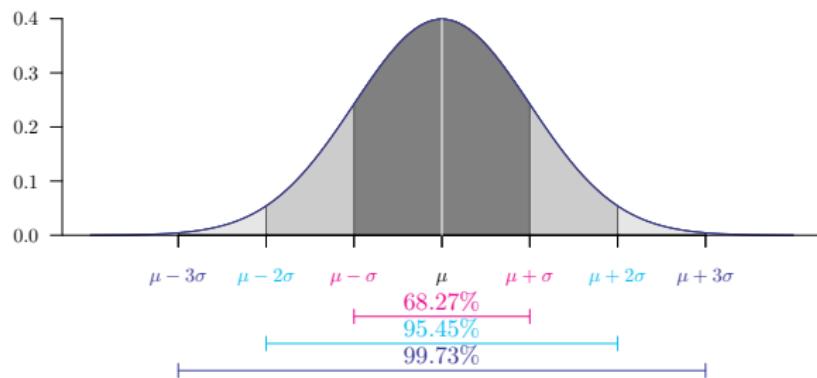


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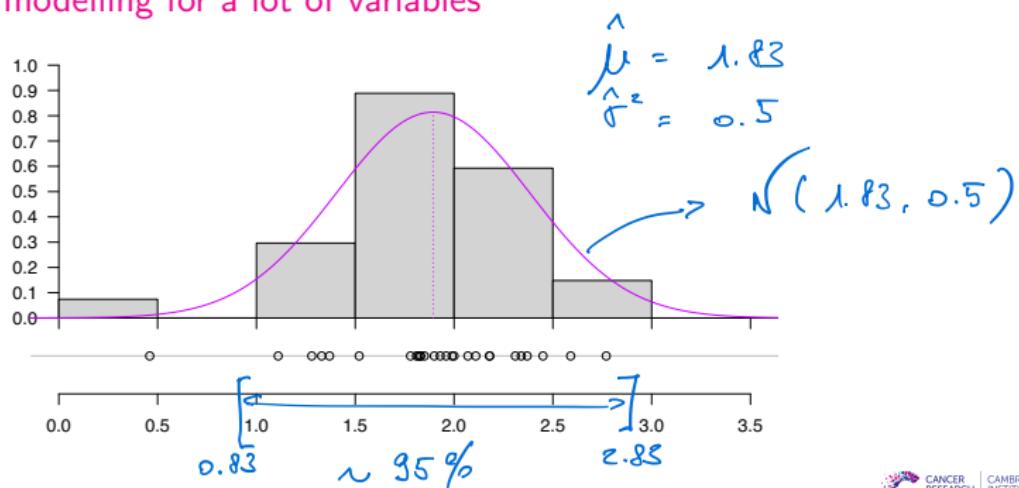


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(i) Suitable modelling for a lot of variables

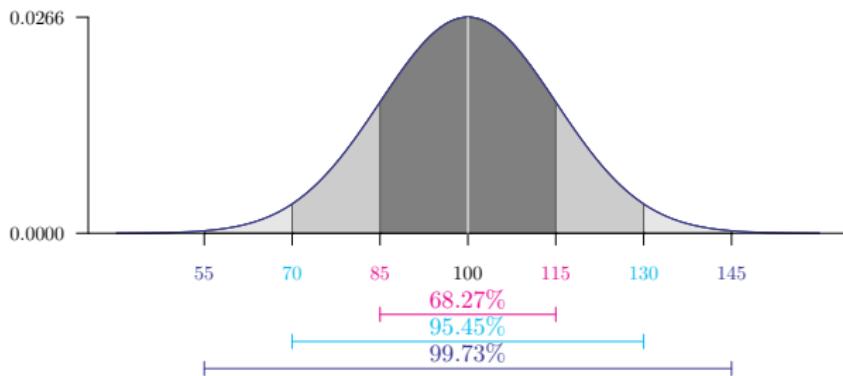


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- (i) Suitable modelling for a lot of variables: IQ



Some parametric distributions: Normal distribution

$$X \sim N(\mu, \sigma^2), \quad f_X(x) = \frac{1}{\sqrt{2\pi\sigma^2}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$$

$$\mathbb{E}[X] = \mu, \quad \text{Var}[X] = \sigma^2,$$

$$Z = \frac{X - \mu}{\sigma} \sim N(0, 1), \quad f_Z(z) = \frac{1}{\sqrt{2\pi}} e^{-\frac{z^2}{2}}.$$

(ii) Central limit theorem (Lindeberg-Lévy CLT)

- ▷ Let (X_1, \dots, X_n) be n independent and identically distributed (iid) random variables drawn from distributions of expected values given by μ and finite variances given by σ^2 ,
- ▷ then

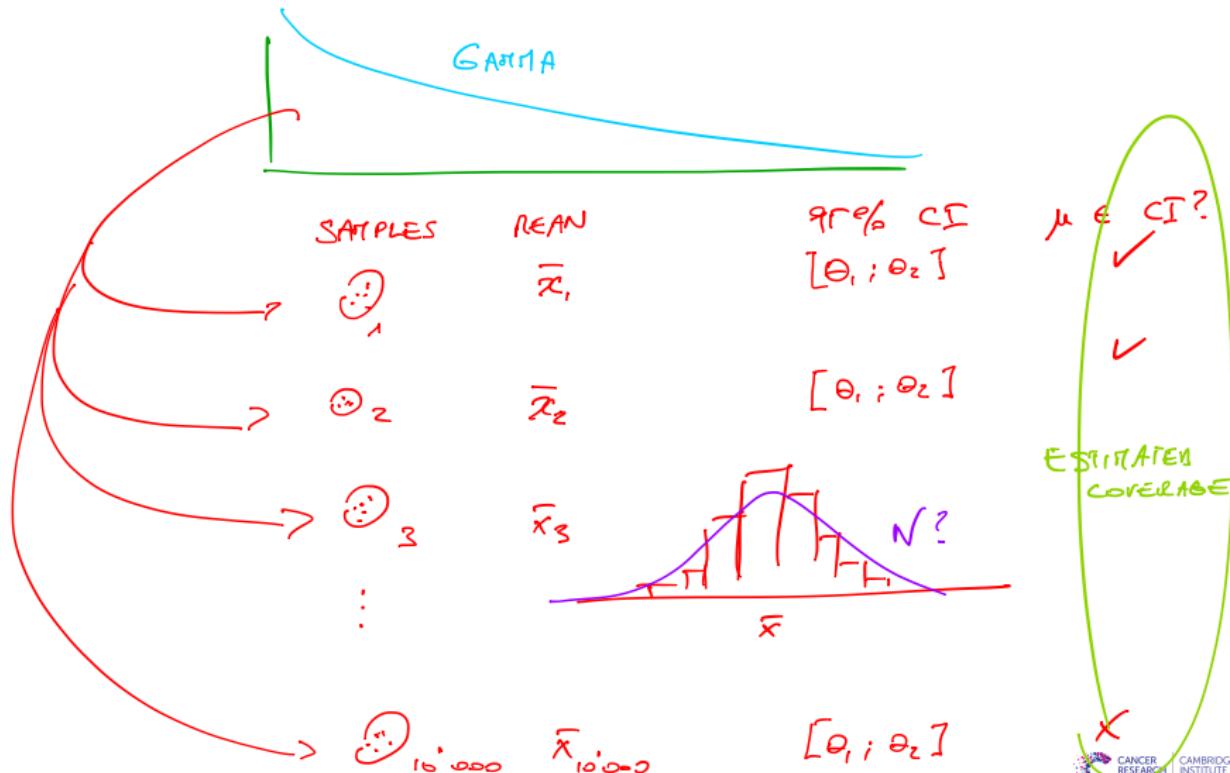
$$\hat{\mu} = \bar{X} = \frac{\sum_{i=1}^n X_i}{n} \quad \xrightarrow{d} \quad N\left(\mu, \frac{\sigma^2}{n}\right).$$

If $X_i \sim N(\mu, \sigma^2)$, this result is true for all sample sizes.

Central limit theorem shiny app:

Distribution of the mean

<http://bioinformatics.cruk.cam.ac.uk/apps/stats/central-limit-theorem/>



95% Confidence interval for μ , the population mean,
when $X_i \sim N(\mu, \sigma^2)$ or n large and $X_i \sim i.i.d. N(\mu, \sigma^2)$

- if $X \sim N(\mu, \sigma^2)$, then $\bar{X} \sim N\left(\mu, \frac{\sigma^2}{n}\right)$,
- if $X \sim N(\mu, \sigma^2)$, then $Z = \frac{X - \mu}{\sigma} \sim N(0, 1)$,

$$P\left(-1.96 < Z < 1.96\right) = 0.95$$

$$P\left(-1.96 < \frac{\bar{X} - \mu}{\sqrt{\frac{\sigma^2}{n}}} < 1.96\right) = 0.95$$

$$P\left(-1.96 \sqrt{\frac{\sigma^2}{n}} - \bar{x} < \bar{x} - \mu < 1.96 \sqrt{\frac{\sigma^2}{n}} - \bar{x}\right) = 0.95$$

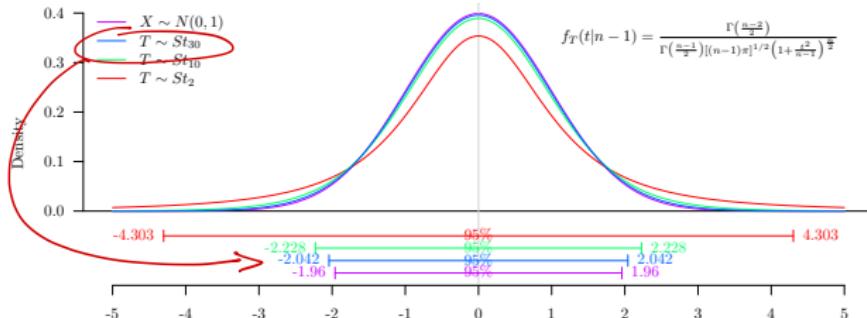
$$P\left(\bar{x} - 1.96 \sqrt{\frac{\sigma^2}{n}} < \mu < \bar{x} + 1.96 \sqrt{\frac{\sigma^2}{n}}\right) = 0.95$$

95% Confidence interval for μ , the population mean, when $X_i \sim N(\mu, \sigma^2)$ or n large and $X_i \sim i.i.d.(\mu, \sigma^2)$

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- if $X \sim N(\mu, \sigma^2)$, then $Z = \frac{X-\mu}{\sigma} \sim N(0, 1)$,
- if σ unknown, then $T = \frac{X-\mu}{s} \sim St_{n-1}$.

$$P\left(\bar{X} - T^{-1}_{n(0.975)} \frac{s}{\sqrt{n}} < \mu < \bar{X} + T^{-1}_{n(0.975)} \frac{s}{\sqrt{n}}\right) = 0.95$$

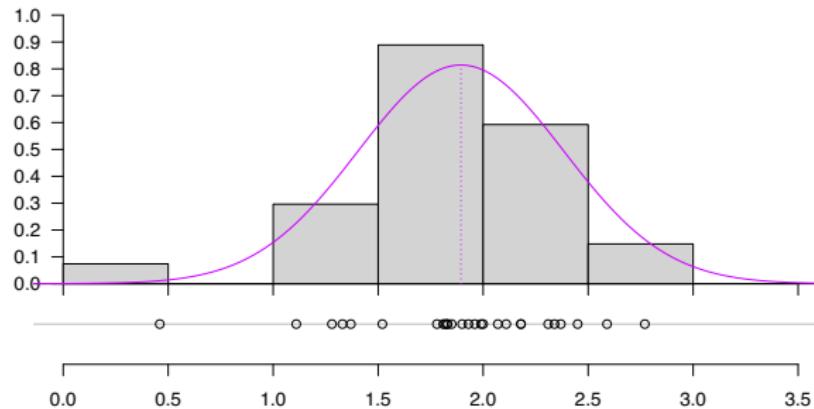
$$T^{-1}_{n(0.975)} = 2.042 \text{ for } n = 31$$



95% Confidence interval for μ , the population mean, when $X_i \sim N(\mu, \sigma^2)$

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$$P\left(\quad < \quad < \quad \right) = 0.95$$

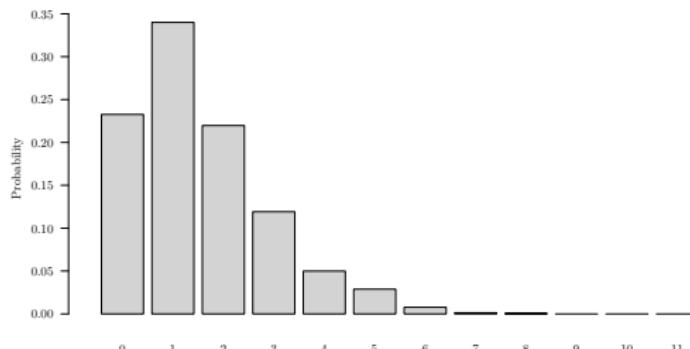


95% Confidence interval for μ , the population mean, when $X_i \sim iid(\mu, \sigma^2)$

- CLT: $\bar{X} \xrightarrow{d} N\left(\mu, \frac{\sigma^2}{n}\right)$,
- if $X \sim N(\mu, \sigma^2)$, then $Z = \frac{X-\mu}{\sigma} \sim N(0, 1)$,
- if σ unknown, then $T = \frac{X-\mu}{s} \sim St_{n-1}$.

Assuming $X_i \sim Poisson$
 $\hat{\mu} = \hat{\sigma}^2 \approx 1.55$

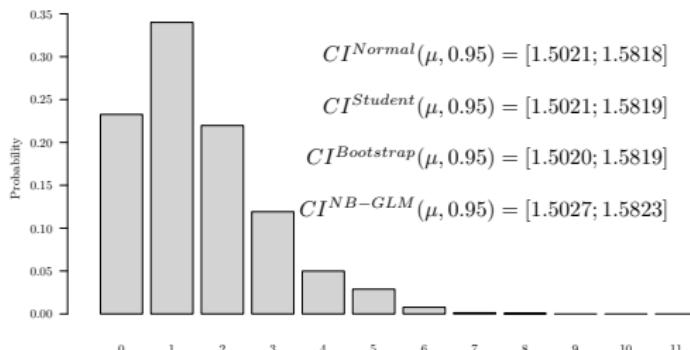
$$P\left(1.96 - 1.96 \sqrt{\frac{1.55}{4406}} < \mu < 1.96 + 1.96 \sqrt{\frac{1.55}{4406}}\right) = 0.95$$



Number of chronic conditions per patient (US National Medical Expenditure Survey: $n = 4406$, $\hat{\mu} = 1.55$)

95% Confidence interval for μ , the population mean, when $X_i \sim iid(\mu, \sigma^2)$

- CLT: $\bar{X} \xrightarrow{d} N\left(\mu, \frac{\sigma^2}{n}\right),$
- if $X \sim N(\mu, \sigma^2)$, then $Z = \frac{X-\mu}{\sigma} \sim N(0, 1),$
- if σ unknown, then $T = \frac{X-\mu}{s} \sim St_{n-1}.$



95% Confidence interval for $\mu_Y - \mu_X$, the difference between population means

If we have

- ▶ $X_i \sim iid(\mu_X, \sigma_X^2)$, $i = 1, \dots, n_X$,
- ▶ $Y_i \sim iid(\mu_Y, \sigma_Y^2)$, $i = 1, \dots, n_Y$,

then

- ▶ if $\sigma_X^2 = \sigma_Y^2$ [Student's t-test equation],

$$\triangleright CI(\mu_Y - \mu_X, 0.95) = (\bar{Y} - \bar{X}) \pm t_{1-\frac{\alpha}{2}, n_X+n_Y-2} s_p \sqrt{\frac{1}{n_X} + \frac{1}{n_Y}}$$

$$\text{where } s_p = \frac{(n_X-1)s_X^2 + (n_Y-1)s_Y^2}{n_X+n_Y-2},$$

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where $s_p = \frac{(n_X-1)s_X^2 + (n_Y-1)s_Y^2}{n_X+n_Y-2}$,
- ▶ if $\sigma_X^2 \neq \sigma_Y^2$ [Welch-Satterthwaite's t-test equation],
 - ▷ $CI(\mu_Y - \mu_X, 0.95) = (\bar{Y} - \bar{X}) \pm t_{1-\frac{\alpha}{2}, df} \sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}$, where
$$df = \frac{\left(\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y} \right)^2}{\frac{\left(\frac{s_X^2}{n_X} \right)^2}{n_X-1} + \frac{\left(\frac{s_Y^2}{n_Y} \right)^2}{n_Y-1}}$$

Central limit theorem shiny app: Coverage of Student's asymptotic confidence intervals

<http://bioinformatics.cruk.cam.ac.uk/apps/stats/central-limit-theorem/>

Quiz Time

Practical 1

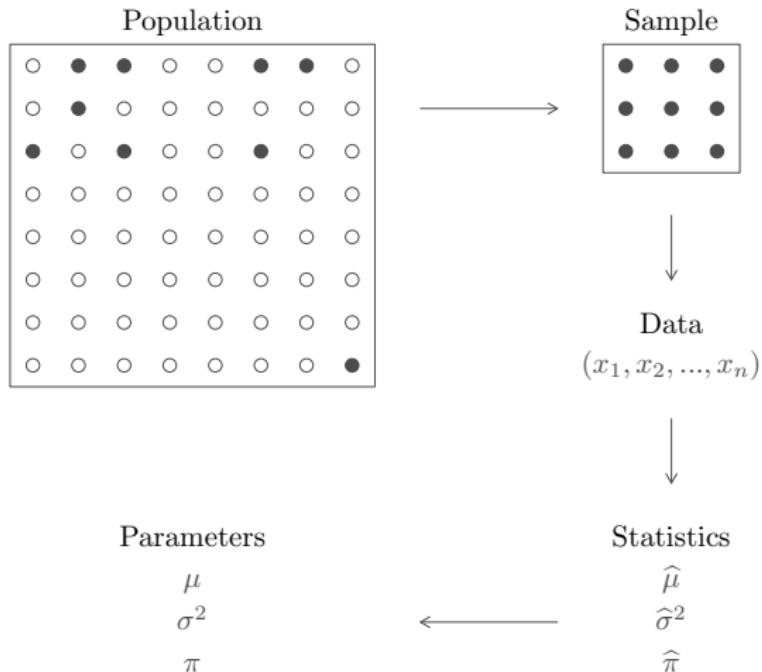
[http://bioinformatics-core-shared-training.github.io/
IntroductionToStats/practical.html](http://bioinformatics-core-shared-training.github.io/IntroductionToStats/practical.html)

PART II: Parametric and non-parametric one-sample location tests

Cancer Research UK – 5th of November 2018

D.-L. Couturier / M. Eldridge / M. Fernandes [Bioinformatics core]

Grand Picture of Statistics



Statistical hypothesis testing

A hypothesis test describes a phenomenon by means of two non-overlapping idealised models/descriptions:

- ▶ the null hypothesis **H0**, "generally assumed to be true until evidence indicates otherwise"
- ▶ the alternative hypothesis **H1**.

$$\begin{aligned} H_0 : \pi_B &= 0.5 \\ H_1 : \pi_B &> 0.5 \end{aligned}$$

The aim of the test is to **reject the null hypothesis in favour of the alternative hypothesis**, and conclude, with a probability α of being wrong, that the idealised model/description of H1 is true.

Theory 1: Dieters lose more fat than the exercisers

$$\begin{aligned} H_0 : \mu_D &= \mu_E \\ H_1 : \mu_D &> \mu_E \end{aligned}$$

Theory 2: There is no majority for Brexit now

Theory 3: Serum vitamin C is reduced in patients

$$\begin{aligned} H_0 : \mu_P &= \mu_F \\ H_1 : \mu_P &< \mu_F \end{aligned}$$

Statistical hypothesis testing

Many options:

- ▶ One-sided versus two-sided tests,
- ▶ Exact versus asymptotic tests,
- ▶ Parametric versus non-parametric tests,

Parametric or non-parametric ?

T-test		Outcome(s) normally distributed		
		Yes	Mildly	No
Sample size	Small	✓	/ / / /	✗
	Medium	✓	✓	/ / / /
	Large	✓	✓	✓

Situations which may suggest the use of non-parametric statistics:

- ▶ When there is a small sample size or **very unequal groups**,
- ▶ When the data has **notable outliers**,
- ▶ When one outcome has a **distribution other than normal**,
- ▶ When the data are **ordered** with many ties or are rank ordered.

Parametric location test (One-sided) t-test

We test:

$$\begin{aligned} H_0: \mu_{IQ} &= 100, \\ H_1: \mu_{IQ} &> 100. \end{aligned}$$

We have $X_i \sim N(\mu, \sigma^2), i = 1, \dots, n,$

We know

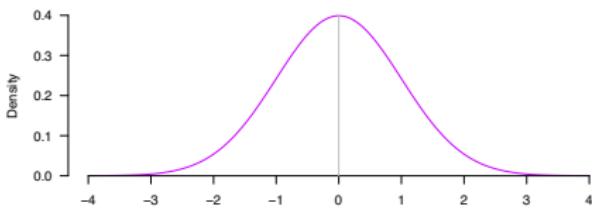
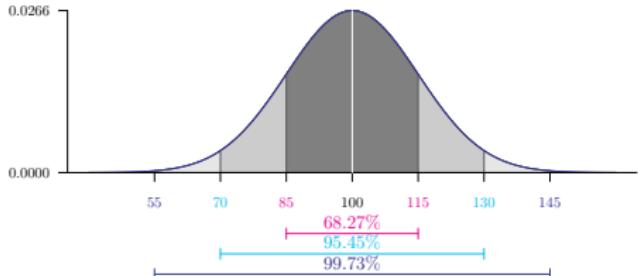
- ▶ $\bar{X} \sim N\left(\mu, \frac{\sigma^2}{n}\right),$
- ▶ $Z = \frac{\bar{X} - \mu}{\frac{\sigma}{\sqrt{n}}} \sim N(0, 1),$

Thus, if H_0 is true, we have:

- ▶ $Z = \frac{\bar{X} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \sim N(0, 1).$

Define the p-value:

- ▶ $p\text{-value} = P(T > T_{obs})$



Statistical hypothesis testing

4 possible outcomes

Conclude:

- ▶ if $p\text{-value} > \alpha \rightarrow$ do not reject H_0 .
- ▶ if $p\text{-value} < \alpha \rightarrow$ reject H_0 in favour of H_1 .

HIV test

		Test Outcome	
		H_0 (−) not rejected	H_1 (+) accepted
Unknown Truth	H_0 true (−)	$1 - \alpha$	α FALSE POS.
	H_1 true (+)	β FALSE NEG.	$1 - \beta$

where

- ▶ α is the type I error,
- ▶ β is the type II error.

Parametric location test (One-sided) binomial exact test

We test:

$$H_0: \pi = 5\%,$$

$$H_1: \pi > 5\%.$$

We have $X_i \sim Bernoulli(\pi)$, $i = 1, \dots, n$,

We know

$$\blacktriangleright Y = \sum_{i=1}^n X_i \sim Binomial(\pi, n),$$

Thus, if H_0 is true, we have:

$$\blacktriangleright Y = \sum_{i=1}^n X_i \sim Binomial(5\%, n),$$

Parametric location test (One-sided) binomial exact test

We test:

$$\begin{aligned} H_0: \pi &= 5\%, \\ H_1: \pi &> 5\%. \end{aligned}$$

We have $X_i \sim Bernoulli(\pi)$, $i = 1, \dots, n$,

We know

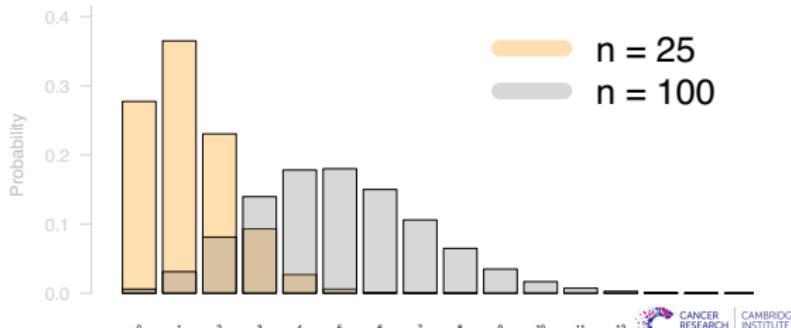
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Thus, if H_0 is true, we have:

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Define the p-value:

$$\blacktriangleright p\text{-value} = P(Y > Y_{obs})$$



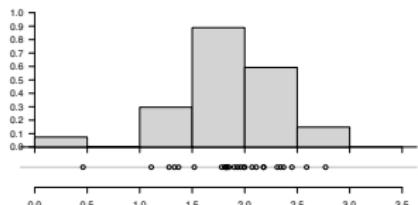
Non-parametric location test

Wilcoxon sign-rank test

A location model is assumed for $X_i, i = 1, \dots, n$:

$$X_i = \theta + e_i,$$

where $e_i \sim iid(\mu_e = 0, \sigma_e^2)$.



Interest for **H0**: $\theta = \theta_0$ against **H1**: $\theta < \theta_0$ or $\theta \neq \theta_0$ or $\theta > \theta_0$.

Test statistics : $W^+ = \sum_{i=1}^n \iota(X_i - \theta_0 > 0) \text{ Rank}(|X_i - \theta_0|)$.

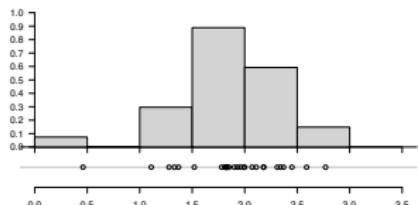
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Test statistics : $W^+ = \sum_{i=1}^n \iota(X_i - \theta_0 > 0) \text{ Rank}(|X_i - \theta_0|)$.

Distribution of W under H0: W^+ has no closed-form distribution.

Wilcoxon signed rank test

```
data: golub[1042, gol.fac == "ALL"]
V = 268, p-value = 0.05847
alternative hypothesis: true location is not equal to 1.75
95 percent confidence interval:
 1.73868 2.09106
sample estimates:
(pseudo)median
 1.926475
```

Introduction to Shiny Apps and Exercises

PART III:

Parametric and non-parametric two-sample location tests

Cancer Research UK – 5th of November 2018

D.-L. Couturier / M. Eldridge / M. Fernandes [Bioinformatics core]

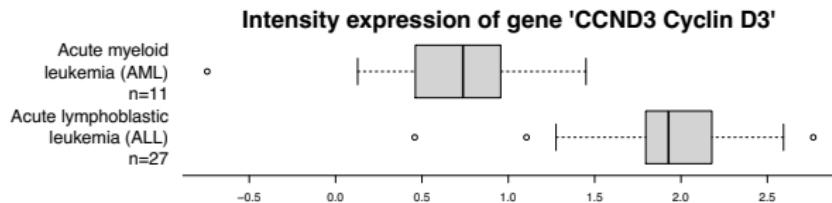
Two-sample case

Many options:

- ▶ One-sided versus two-sided tests,
- ▶ Exact versus asymptotic tests,
- ▶ Parametric versus non-parametric tests,
- ▶ Tests for paired versus independent data.

Parametric two-sample location test

Two-sample two-sided Student-s & Welch's t-tests



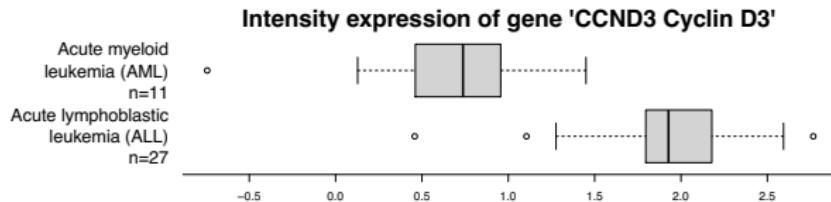
We test $H_0: \mu_Y - \mu_X = 0$ against $H_1: \mu_Y - \mu_X \neq 0$.

We know:

- ▶ Student's t-test [assume $\sigma_X^2 = \sigma_Y^2$]: $\frac{(\bar{Y} - \bar{X}) - (\mu_Y - \mu_X)}{s_p \sqrt{\frac{1}{n_X} + \frac{1}{n_Y}}} \sim t_{1 - \frac{\alpha}{2}, n_X + n_Y - 2}$
- ▶ Welch's t-test [assume $\sigma_X^2 \neq \sigma_Y^2$]: $\frac{(\bar{Y} - \bar{X}) - (\mu_Y - \mu_X)}{\sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}} \sim t_{1 - \frac{\alpha}{2}, df}$

Parametric two-sample location test

Two-sample two-sided Student-s & Welch's t-tests



We test $H_0: \mu_Y - \mu_X = 0$ against $H_1: \mu_Y - \mu_X \neq 0$.

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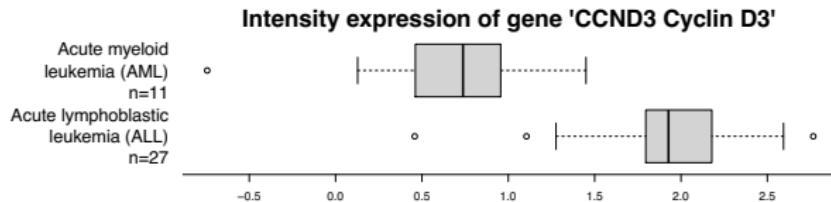
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- ▶ Welch's t-test [assume $\sigma_X^2 \neq \sigma_Y^2$]: $\frac{(\bar{Y} - \bar{X}) - (\mu_Y - \mu_X)}{\sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}} \sim t_{1 - \frac{\alpha}{2}, df}$

Two Sample t-test

```
data: golub[1042, gol.fac == "ALL"] and golub[1042, gol.fac == "AML"]
t = 6.7983, df = 36, p-value = 6.046e-08
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 0.8829143 1.6336690
sample estimates:
mean of x mean of y
1.8938826 0.6355909
```

Parametric two-sample location test

Two-sample two-sided Student-s & Welch's t-tests



We test $H_0: \mu_Y - \mu_X = 0$ against $H_1: \mu_Y - \mu_X \neq 0$.

We know:

- ▶ Student's t-test [assume $\sigma_X^2 = \sigma_Y^2$]: $\frac{(\bar{Y} - \bar{X}) - (\mu_Y - \mu_X)}{s_p \sqrt{\frac{1}{n_X} + \frac{1}{n_Y}}} \sim t_{1 - \frac{\alpha}{2}, n_X + n_Y - 2}$
- ▶ Welch's t-test [assume $\sigma_X^2 \neq \sigma_Y^2$]: $\frac{(\bar{Y} - \bar{X}) - (\mu_Y - \mu_X)}{\sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}} \sim t_{1 - \frac{\alpha}{2}, df}$

Welch Two Sample t-test

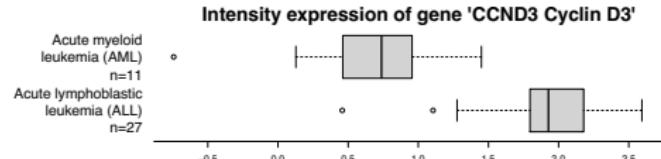
```
data: golub[1042, gol.fac == "ALL"] and golub[1042, gol.fac == "AML"]
t = 6.3186, df = 16.118, p-value = 9.871e-06
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
 0.8363826 1.6802008
sample estimates:
mean of x mean of y
1.8938826 0.6355909
```

Non-parametric two-sample location test

Mann-Whitney-Wilcoxon test

Let

- $X_i \sim iid(\mu_X, \sigma^2)$, $i = 1, \dots, n_X$,
- $Y_i \sim iid(\mu_X + \delta, \sigma^2)$, $i = 1, \dots, n_Y$.



Interest for **H0**: $\delta = \delta_0$ against **H1**: $\delta < \delta_0$ or $\delta \neq \delta_0$ or $\delta > \delta_0$.

Standardised test statistic: $z = \frac{\sum_{i=1}^{n_Y} R(Y_i) - [n_Y(n_X+n_Y+1)/2]}{\sqrt{n_X n_Y (n_X+n_Y+1)/12}}$,

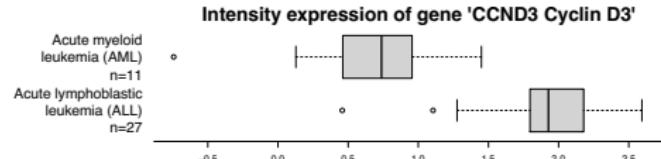
where $R(Y_i)$ denotes the rank of Y_i amongst the combined samples, i.e., amongst $(X_1, \dots, X_{n_X}, Y_1, \dots, Y_{n_Y})$.

Non-parametric two-sample location test

Mann-Whitney-Wilcoxon test

Let

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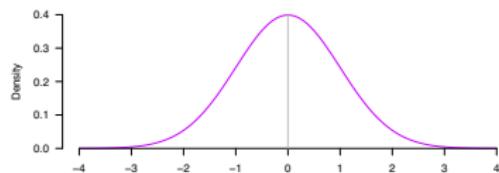
where $R(Y_i)$ denotes the rank of Y_i amongst the combined samples, i.e., amongst $(X_1, \dots, X_{n_X}, Y_1, \dots, Y_{n_Y})$.

Distribution of Z under H0: $Z \sim N(0, 1)$.

Implementation 1:
statistic = -4.361334 , p-value = 1.292716e-05

Implementation 2:
 $W = 284$, p-value = 6.15e-07
alternative hypothesis: true location shift is not equal to 0
95 percent confidence interval:
0.89647 1.57023

sample estimates:
difference in location
1.21951



Two-sample proportion test

χ^2 goodness-of-fit test

A trial to assess the effectiveness of a new treatment versus a placebo in reducing tumour size in patients with ovarian cancer:

Observed frequencies		Binary outcome		
		Tumour did not shrink	Tumour did shrink	
Group	Treatment	44	40	(84)
	Placebo	24	16	(40)
		(68)	(56)	(124)

- ▶ **H0** : No association between treatment group and tumour shrinkage,
- ▶ **H1** : Some association.

Two-sample proportion test

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Expected frequencies under H0		Binary outcome		
		Tumour did not shrink	Tumour did shrink	
Group	Treatment			(84)
	Placebo			(40)
		(68)	(56)	(124)

We have 2 categorical variables with a total of $J = 4$ cells (categories).

- **H0** : $\pi_j = \pi_{j_0}, j = 1, \dots, J$,
- **H1** : $\pi_j \neq \pi_{j_0}, j = 1, \dots, J$.

$$\chi^2\text{-test: } \sum_{j=1}^J \frac{(O_j - E_j)^2}{E_j} \sim \chi^2(J-1).$$

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		Treatment	Placebo	Tumour did not shrink	Tumour did shrink	
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- **H1** : Some association.

		Expected frequencies under H0		Binary outcome		
		Treatment	Placebo	Tumour did not shrink	Tumour did shrink	
Group	Treatment	$\frac{84 \times 68}{124} = 46.06$	$\frac{84 \times 58}{124} = 37.94$	(84)		
	Placebo	$\frac{40 \times 68}{124} = 21.94$	$\frac{40 \times 56}{124} = 18.71$	(40)		
		(68)	(56)	(124)		

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$$\chi^2\text{-test: } \sum_{j=1}^J \frac{(O_j - E_j)^2}{E_j} \sim \chi^2(J-1).$$

Pearson's Chi-squared test with Yates' continuity correction

```
data: M  
X-squared = 0.36474, df = 1, p-value = 0.5459
```

Two-sample proportion test

Fisher's exact test of independence

χ^2 goodness-of-fit test not suitable when

- ▶ n is small
- ▶ $E_j < 5$ for at least one cell.

		Observed frequencies		Variable 1		
				Category 1	Category 2	
Variable 2	Category 1	a	b	(a+b)		
	Category 2	c	d	(c+d)		
	(a+c)	(b+d)	(a+b+c+d=n)			

Fisher showed that, under H_0 (independence),

$P(\text{observed table} \mid H_0) = P(X = a)$ and $X \sim \text{Hypergeometric}(n, a + c, a + b)$.

To compute the Fisher's test:

- ▶ Define $P(X = a)$ for all possible tables having the observed marginal counts,
- ▶ Calculate the $p - value$ by defining the percentage of these tables that get a probability equal to or smaller than the one observed.

Two-sample proportion test

Fisher's exact test of independence

χ^2 goodness-of-fit test not suitable when

- ▶ n is small
- ▶ $E_j < 5$ for at least one cell.

Observed frequencies		Binary outcome		
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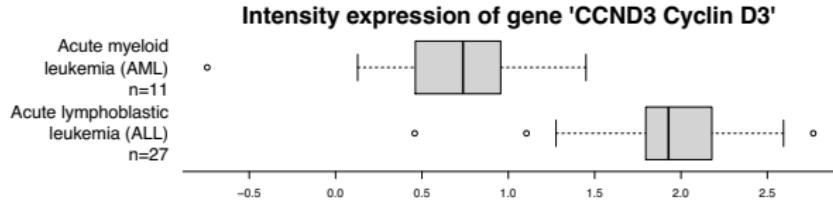
To compute the Fisher's test:

- ▶ Define $P(X = a)$ for all possible tables having the observed marginal counts,
- ▶ Calculate the $p - value$ by defining the percentage of these tables that get a probability equal to or smaller than the one observed.

Fisher's Exact Test for Count Data

```
data: M
p-value = 0.4471
alternative hypothesis: true odds ratio is not equal to 1
95 percent confidence interval:
0.3160593 1.6790135
sample estimates:
odds ratio
0.7351707
```

F-test of equality of variances

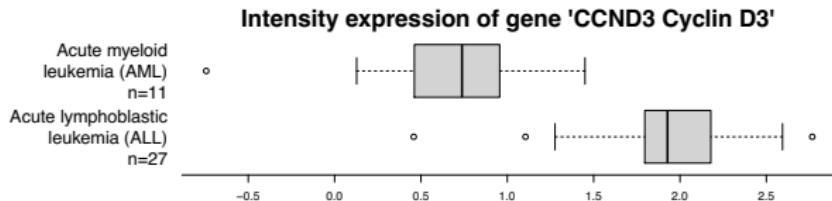


We test $\mathbf{H0}: \sigma_Y^2 = \sigma_X^2$ against $\mathbf{H1}: \sigma_Y^2 \neq \sigma_X^2$.

We know:

- ▶ F-test [assume $X_i \sim N(\mu_X, \sigma_X)$ and $Y_i \sim N(\mu_Y, \sigma_Y)$]: $\frac{s_Y^2}{s_X^2} \sim F_{n_Y-1, n_X-1}$

F-test of equality of variances



We test $H_0: \sigma_Y^2 = \sigma_X^2$ against $H_1: \sigma_Y^2 \neq \sigma_X^2$.

We know:

- ▶ F-test [assume $X_i \sim N(\mu_X, \sigma_X)$ and $Y_i \sim N(\mu_Y, \sigma_Y)$]: $\frac{s_Y^2}{s_X^2} \sim F_{n_Y-1, n_X-1}$

F test to compare two variances

```
data: golub[1042, gol.fac == "ALL"] and golub[1042, gol.fac == "AML"]
F = 0.71164, num df = 26, denom df = 10, p-value = 0.4652
alternative hypothesis: true ratio of variances is not equal to 1
95 percent confidence interval:
 0.2127735 1.8428387
sample estimates:
ratio of variances
 0.7116441
```

Warning

Multiplicity correction

For each test, the probability of rejecting H₀ (and accept H₁) when H₀ is true equals α .

For k tests, the probability of rejecting H₀ (and accept H₁) at least 1 time when H₀ is true, α_k , is given by

$$\alpha_k = 1 - (1 - \alpha)^k.$$

Thus, for $\alpha = 0.05$,

- ▶ if $k = 1$, $\alpha_1 = 1 - (1 - \alpha)^1 = 0.05$,
- ▶ if $k = 2$, $\alpha_2 = 1 - (1 - \alpha)^2 = 0.0975$,
- ▶ if $k = 10$, $\alpha_{10} = 1 - (1 - \alpha)^{10} = 0.4013$.

Idea: change the level of each test so that $\alpha_k = 0.05$:

- ▶ Bonferroni correction : $\alpha = \frac{\alpha_k}{k}$,
- ▶ Dunn-Sidak correction: $\alpha = 1 - (1 - \alpha_k)^{1/k}$.

Warning

Non-parametric is not assumption free: Type I error

Simulate 2500 samples with

- ▶ $X_i \sim Uniform(1.5, 2.5)$, $i = 1, \dots, n_X$,
- ▶ $Y_i \sim Uniform(0, 4)$, $i = 1, \dots, n_Y$,

so that $E[X_i] = E[Y_i] = 2$ (i.e., same mean, same median).

Assume

- ▶ $X_i \sim iid(\mu_X, \sigma^2)$, $i = 1, \dots, n_X$,
- ▶ $Y_i \sim iid(\mu_X + \delta, \sigma^2)$, $i = 1, \dots, n_Y$.

Test **H0**: $\delta = \delta_0$ against **H1**: $\delta \neq \delta_0$, at the 5% level, by means of

- ▶ Mann-Whitney-Wilcoxon test (MWW),
- ▶ T-test,
- ▶ Welch-test.

	$\hat{\alpha}$	Tests		
		MWW	Student's t-test	Welch's test
Sample size	$n_X = 200, n_Y = 70$	0.145	0.202	0.055
	$n_X = 20, n_Y = 7$	0.148	0.240	0.062

Exercises