Introduction to Statistical Analysis

Cancer Research UK – 12^{th} of February 2019

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

Timeline

9:30 – Morning

- $\sim$ 45mn Lecture: data type, summary statistics and graphical displays
- $\sim$ 15mn Quiz

10:30 – 15mn Coffee & Tea break

- $\sim$ 60mn Lecture: some statistical distributions + CLT
- $\sim$ 15mn Exercises & discussion

12:00 – Lunch break

13:00 – Afternoon

- $\sim$ 45mn Lecture: One-sample location test
- $\sim$ 30mn Exercises with shiny app & discussion

- $\sim$ 45mn Lecture: Two-sample location test

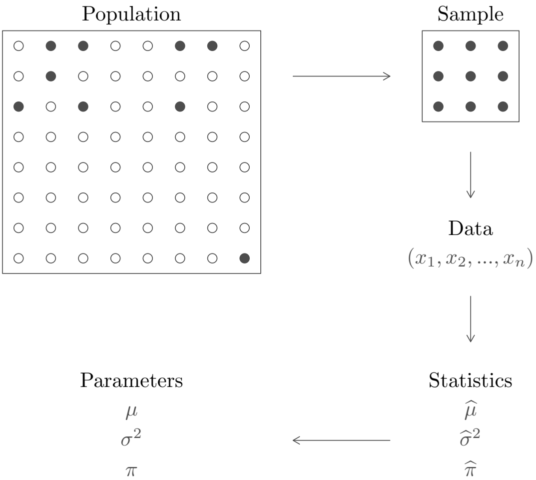
15:15 – 15mn Coffee & Tea break

- $\sim$ 30mn Exercises with shiny app & discussion

16:15 – Group based exercises

- $\sim$ 60mn

Grand Picture of Statistics



Data Types

	x_1	x_2	x_3	$\cdots$	x_n
Cancer status	C	$\not{C}$	$\not{C}$	$\cdots$	C
Nucleic acid sequence	C	T	T	$\cdots$	A
5-level pain score	3	1	5	$\cdots$	4
# of daily admissions at A&E	16	23	12	$\cdots$	17
Gene expression intensity	882.1	379.5	528.3	$\cdots$	120.9

Summary statistics and plots for qualitative data

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",
- 2 = "A little bit",
- 3 = "Somewhat",
- 4 = "Quite a bit",
- 5 = "Very much".

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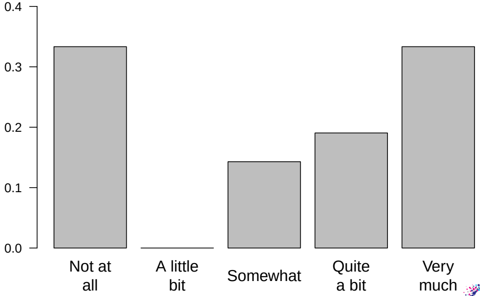
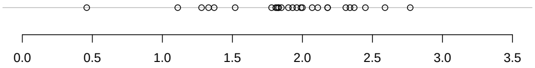


Summary statistics and plots for quantative data



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
$x_{(19)}$	$x_{(20)}$	$x_{(21)}$	$x_{(22)}$	$x_{(23)}$	$x_{(24)}$	$x_{(25)}$	$x_{(26)}$	$x_{(27)}$
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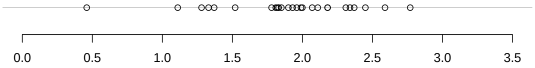

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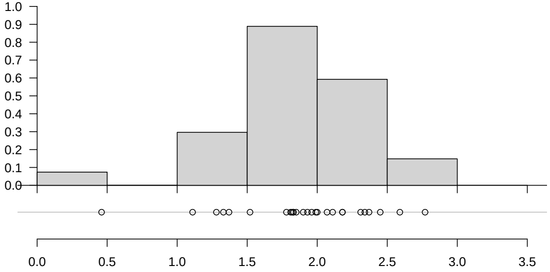

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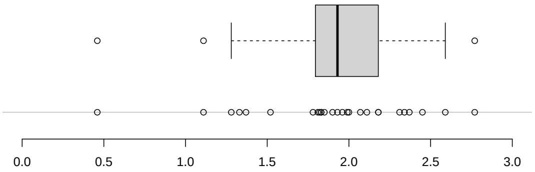

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Two-sample case: independent versus paired samples

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					

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

Quiz Time

Sections 1 to 4

https://docs.google.com/forms/d/
1C3RHisRHoWXcnFqX9JhRAk3gy_aJ6FrhouJ6ljsJ-Fc

Statistical distributions

"In probability theory and statistics, a statistical distribution is a mathematical function that provides the probabilities of occurrence of different possible outcomes in an experiment" [Wikipedia].

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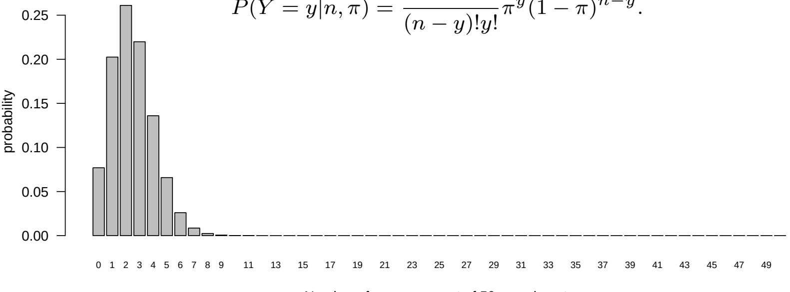
For a given cancer, mutation of the nucleic acid located at position 790 of Exon 20 is assumed to occur with a probability of $\sim 5\%$.
Probability of observing y patients out of $n = 50$ cancer patients with this mutation?

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



Some parametric distributions: Binomial distribution

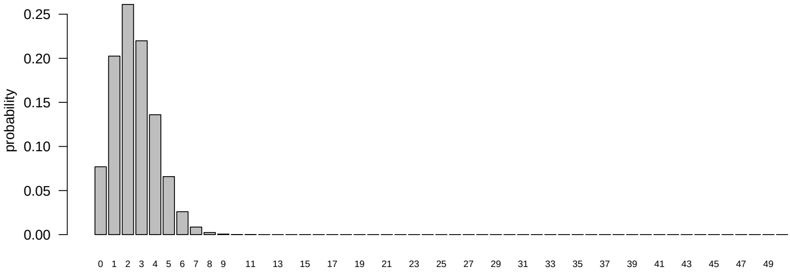
- the number of successes out of n trials (experiments), $Y = \sum_{i=1}^{n} X_i$, follows a binomial distribution with parameters n and π:

$$Y \sim Bin(n, \pi),$$

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

IF

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



Some parametric distributions: Poisson distribution

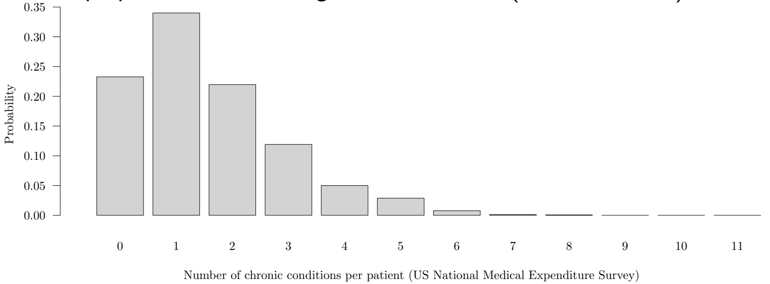
- the number of events occurring in a fixed time interval or in a given area, X, may be modelled by means of a Poisson distribution with parameter λ:

$$X \sim Poisson(\lambda),$$

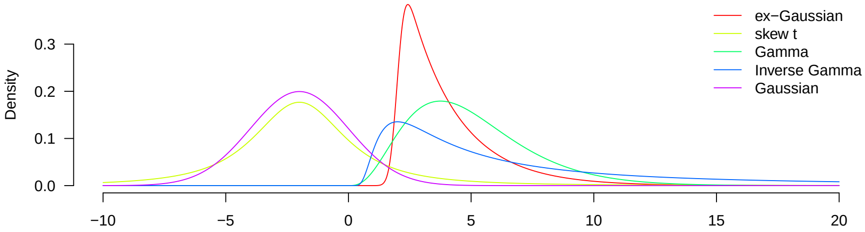
$$P(X = x|\lambda) = \frac{\lambda^x e^{-\lambda}}{x!}.$$

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),



Some parametric distributions: Continuous distrib.



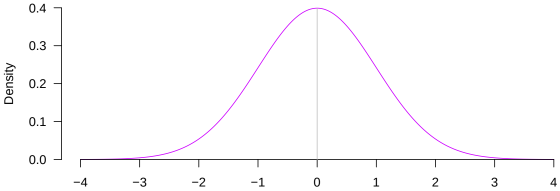
Some parametric distributions: Normal distribution

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

$$\mathsf{E}[X] = \mu, \qquad \mathsf{Var}[X] = \sigma^2,$$

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

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



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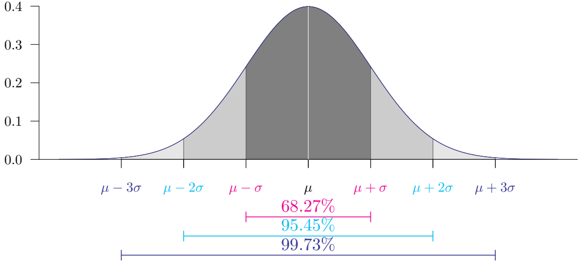

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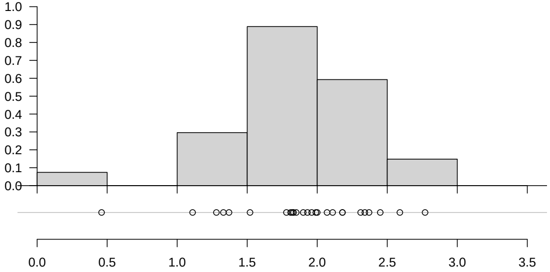

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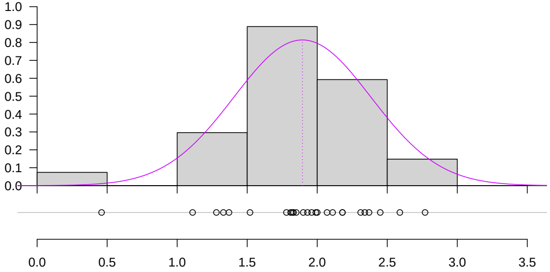

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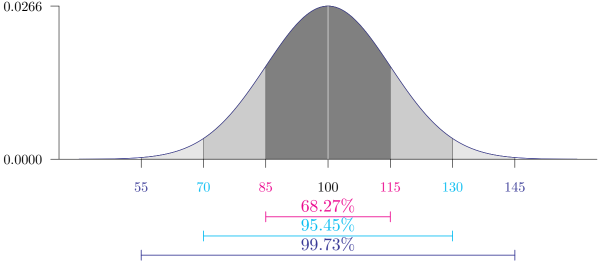
(i) Suitable modelling for a lot of variables: IQ



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

- Let $(X_1, ..., X_n)$ 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

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

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 $X_i \sim N(\mu, \sigma^2)$

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

$$\mathsf{P}\left(\qquad < \qquad < \qquad \right) = 0.95$$

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- if σ unknown, then $T = \frac{X-\mu}{s} \sim St_{n-1}$.

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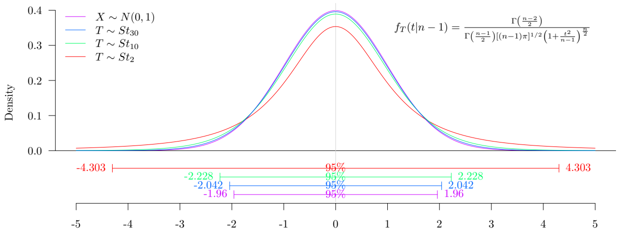

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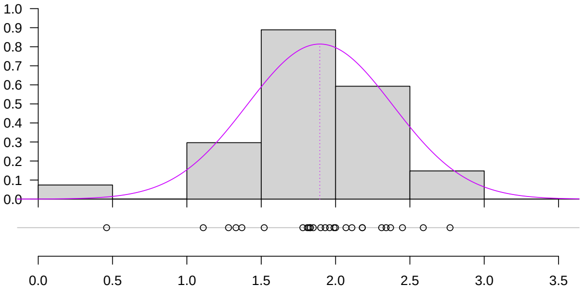

95% Confidence interval for μ, the population mean, when $X_i \sim iid(\mu, \sigma^2)$

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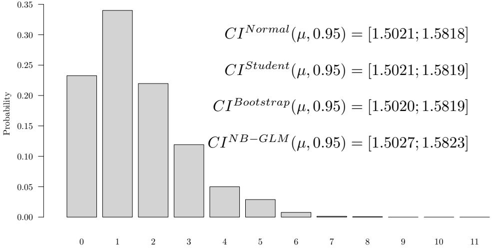

Number of chronic conditions per patient (US National Medical Expenditure Survey: $n = 4406$, $\widehat{\mu} = 1.55$)

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

If we have

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

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then

- if $\sigma_X^2 = \sigma_Y^2$ [Student's t-test equation],
  - $CI\,(\mu_Y - \mu_X, 0.95) = (\overline{Y} - \overline{X}) \pm t_{1-\frac{\alpha}{2}, n_X + n_Y - 2} s_p \sqrt{\frac{1}{n_X} + \frac{1}{n_Y}}$

    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],
  - $CI\,(\mu_Y - \mu_X, 0.95) = (\overline{Y} - \overline{X}) \pm t_{1-\frac{\alpha}{2}, \mathrm{df}} \sqrt{\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}}$, where

    $$\mathrm{df} = \frac{\left(\frac{s_X^2}{n_X} + \frac{s_Y^2}{n_Y}\right)^2}{\frac{\left(\frac{s_X^2}{n_X}\right)^2}{n_X-1} + \frac{\left(\frac{s_Y^2}{n_Y}\right)^2}{n_Y-1}}.$$

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

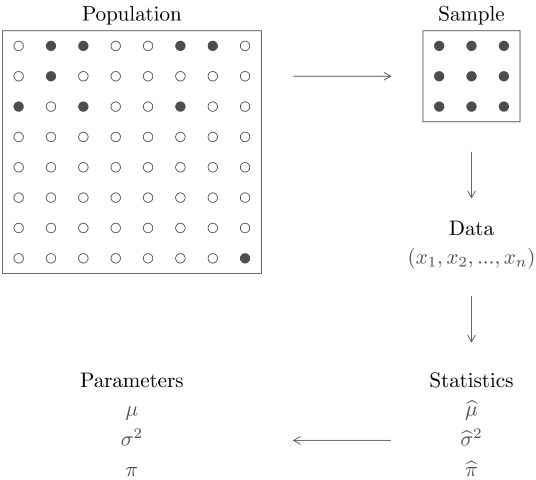
`http://bioinformatics-core-shared-training.github.io/IntroductionToStats/practical.html`

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

Cancer Research UK – 12^{th} of February 2019

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**.

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

Theory 2: There is no majority for Brexit now

Theory 3: Serum vitamin C is reduced in patients

Statistical hypothesis testing

Several-step process:

- Define H0 and H1 according to a theory
- Set α, the probability of rejecting H0 when it is true (type I error),
- Define n, the sample size, allowing you to reject H0 when H1 is true with a probability $1-\beta$ (Power),
- Determine the test statistic to be used,
- Collect the data,
- Perform the statistical test, define the p-value, and reject (or not) the null hypothesis.

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:
H0: $\mu_{\text{IQ}} = 100$,
H1: $\mu_{\text{IQ}} > 100$.

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

We know

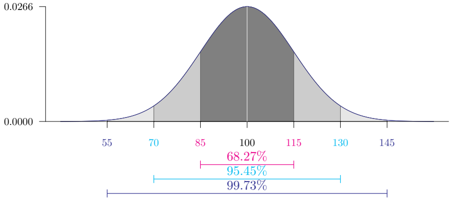
- $\overline{X} \quad \sim \quad N\left(\mu, \frac{\sigma^2}{n}\right)$,
- $Z = \frac{\overline{X}-\mu}{\frac{\sigma}{\sqrt{n}}} \sim N(0,1)$,

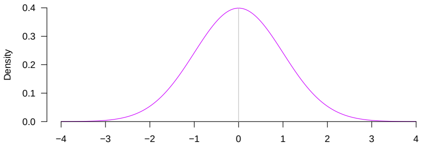
Thus, if H0 is true, we have:

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

Define the p-value:

- $p-\text{value} = P(T > T_{obs})$





Statistical hypothesis testing
4 possible outcomes

Conclude:

- if p-value $> \alpha \quad \rightarrow \quad$ do not reject H0.
- if p-value $< \alpha \quad \rightarrow \quad$ reject H0 in favour of H1.

		Test Outcome	
		H0 not rejected	H1 accepted
Unknown Truth	H0 true	$1-\alpha$	α
	H1 true	β	$1-\beta$

where

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

Parametric location test
(One-sided) binomial exact test

We test:
H0: $\pi = 5\%$,
H1: $\pi > 5\%$.

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

We know

- $Y = \sum_{i=1}^{n} X_i \quad \sim \quad Binomial\left(\pi, n\right),$

Thus, if H0 is true, we have:

- $Y = \sum_{i=1}^{n} X_i \quad \sim \quad Binomial\left(5\%, n\right),$

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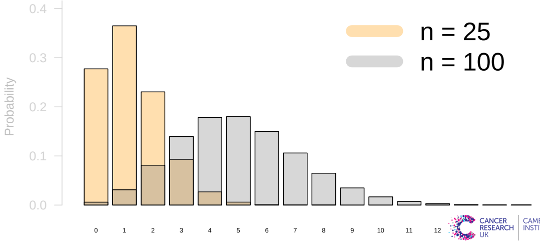
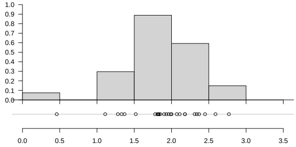
Define the p-value:
- $p -$ value $= P(Y > Y_{obs})$



Non-parametric location test
Wilcoxon sign-rank test



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

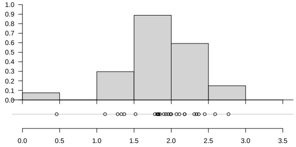
$$X_i = \theta + e_i,$$

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

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

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

Non-parametric location test
Wilcoxon sign-rank test



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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 – 12^{th} of February 2019

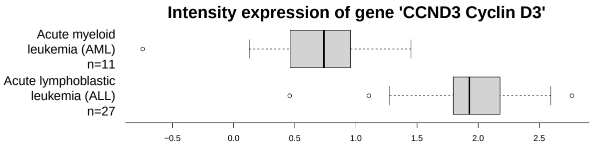
D.-L. Couturier / M. Eldridge / M. Fernandes [Bioinformatics core]

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

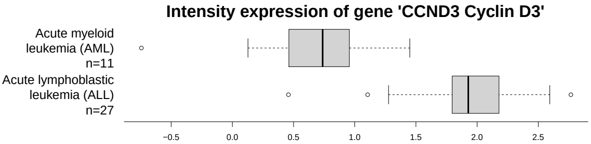


We test **H0**: $\mu_Y - \mu_X = 0$ against **H1**: $\mu_Y - \mu_X \neq 0.$

We know:

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

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



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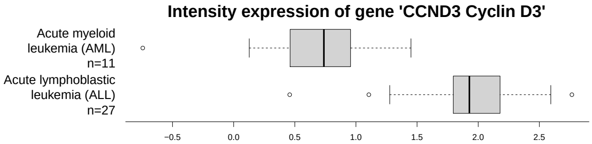
- Welch's t-test [assume $\sigma_X^2 \neq \sigma_Y^2$]: $\frac{(\overline{Y}-\overline{X})-(\mu_Y-\mu_X)}{\sqrt{\frac{s_X^2}{n_X}+\frac{s_Y^2}{n_Y}}} \sim t_{1-\frac{\alpha}{2},df}$

```
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 **H0**: $\mu_Y - \mu_X = 0$ against **H1**: $\mu_Y - \mu_X \neq 0$.

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

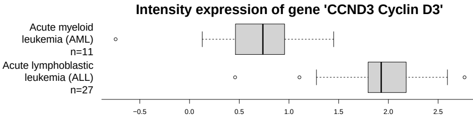
```
Welch Two Sample t-test

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

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



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 $(X_1, ..., X_{n_X}, Y_1, ..., Y_{n_Y})$.

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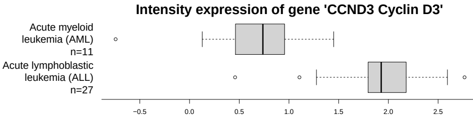
Non-parametric two-sample location test
Mann-Whitney-Wilcoxon test

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



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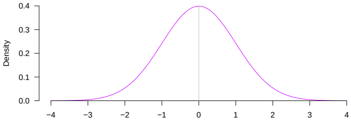
where $R(Y_i)$ denotes the rank of Y_i amongst the combined samples, i.e., amongst $(X_1, ..., X_{n_X}, Y_1, ..., Y_{n_Y})$.

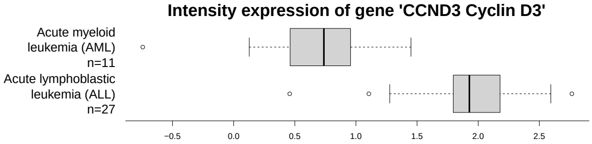
Distribution of Z under H0: $Z \sim N(0, 1)$.




```
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
```

F-test of equality of variances

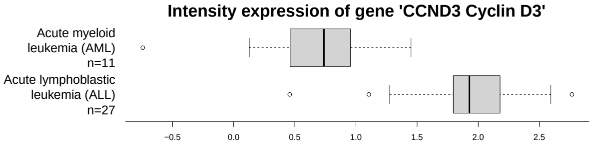


We test **H0**: $\sigma_Y^2 = \sigma_X^2$ against **H1**: $\sigma_Y^2 \neq \sigma_X^2$.

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 **H0**: $\sigma_Y^2 = \sigma_X^2$ against **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 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

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

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

Assume

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

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.

$\widehat{\alpha}$		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