CANCER RESEARCH UK | CAMBRIDGE INSTITUTE

UNIVERSITY OF CAMBRIDGE

Introduction to Statistical Analysis

Cancer Research UK – 12^{th} of February 2018

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: Parametric tests for the mean
- $\sim$ 30mn Exercises with shiny apps & discussion

- $\sim$ 30mn Lecture: Non-parametric tests for the mean
- $\sim$ 15mn Exercises & discussion

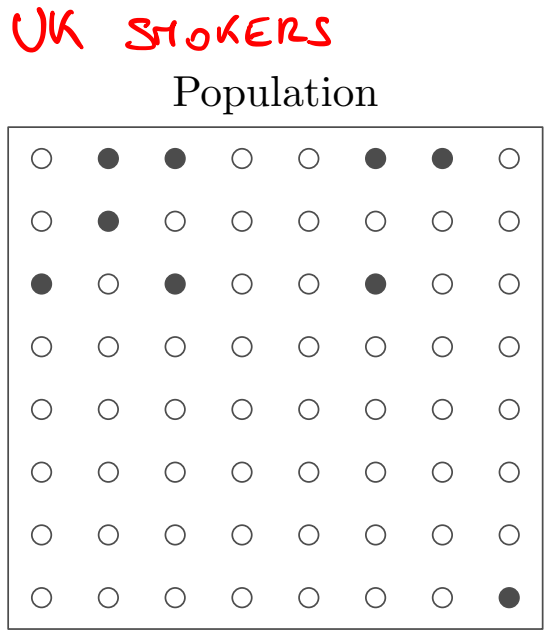
15:00 – 15mn Coffee & Tea break

- $\sim$ 15mn Lecture: Tests for categorical variables
- $\sim$ 15mn Exercises & discussion

16:00 – Group based exercises

- $\sim$ 60mn

Grand Picture of Statistics



Data Types

SUMMARY STATISTICS

LOCATION (typical value)
- MODE
- MEAN
- MEDIAN

VARIABILITY
- RANGE
- VARIANCE, ST. DEV.
- IQR
- MAD

MUTUAL EXCLUSIV.

RANKING

EQUIDIST.

QUALITATIVE (NOMINAL)

- BINARY
- CATEGORICAL
- ORDINAL

QUANTITATIVE (NUMERICAL)

- DISCRETE
- CONTINUOUS

	x_1	x_2	x_3	$\cdots$	x_n
Cancer status	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

✓ ✗ ✗
✓ ✗ ✗
✓ ✓ ✓✗
✓ ✓ ✓
✓ ✓ ✓

LOW

HIGH

GRAPHICAL DISPLAYS

- BARPLOT
- HISTOGRAM
- BOXPLOT

Summary statistics and plots for qualitative data

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

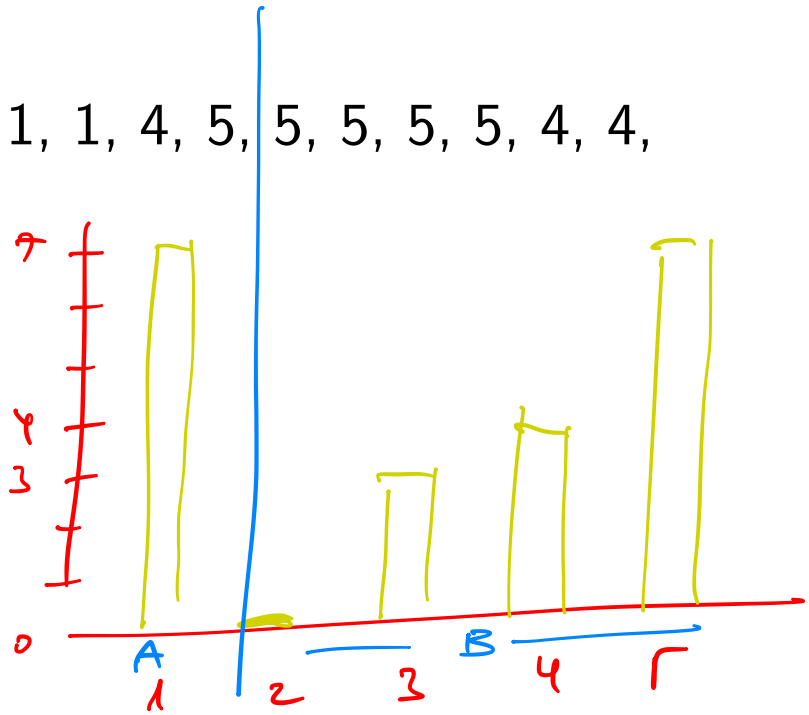
5-level answers of 21 patients to the question
"How much did pain due to your ureteric stones interfere with your day to day activities ?":

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

$\Sigma = 1$



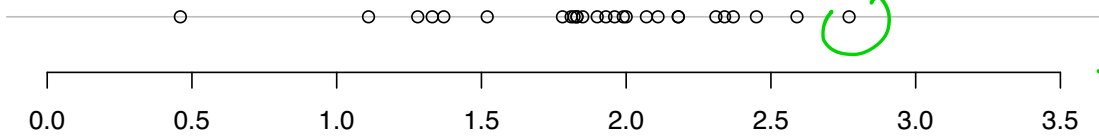
TWO-STAGE PROCESS:
A: INTERFERENCE: YES/NO MODE = YES
B: IF INTERFERENCE: INTERF. LEVEL MODE = 5

Summary statistics and plots for quantative data

LOCATION:

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

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



if replaces by by 10^3,
→ impact on mean
→ no impact on median.

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

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

Summary statistics and plots for quantative data

VARIABILITY

RANGE : $x_{(n)} - x_{(1)} = 2.77 - 0.46 = 2.31$

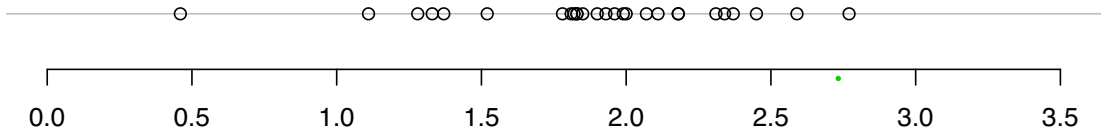
VARIANCE : $\hat{\sigma}^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i - \bar{x})^2 = \frac{(0.46 - 1.83)^2 + (1.11 - 1.83)^2 + \dots}{n} = 0.5$

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

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

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

ROBUST TO OUTLIERS



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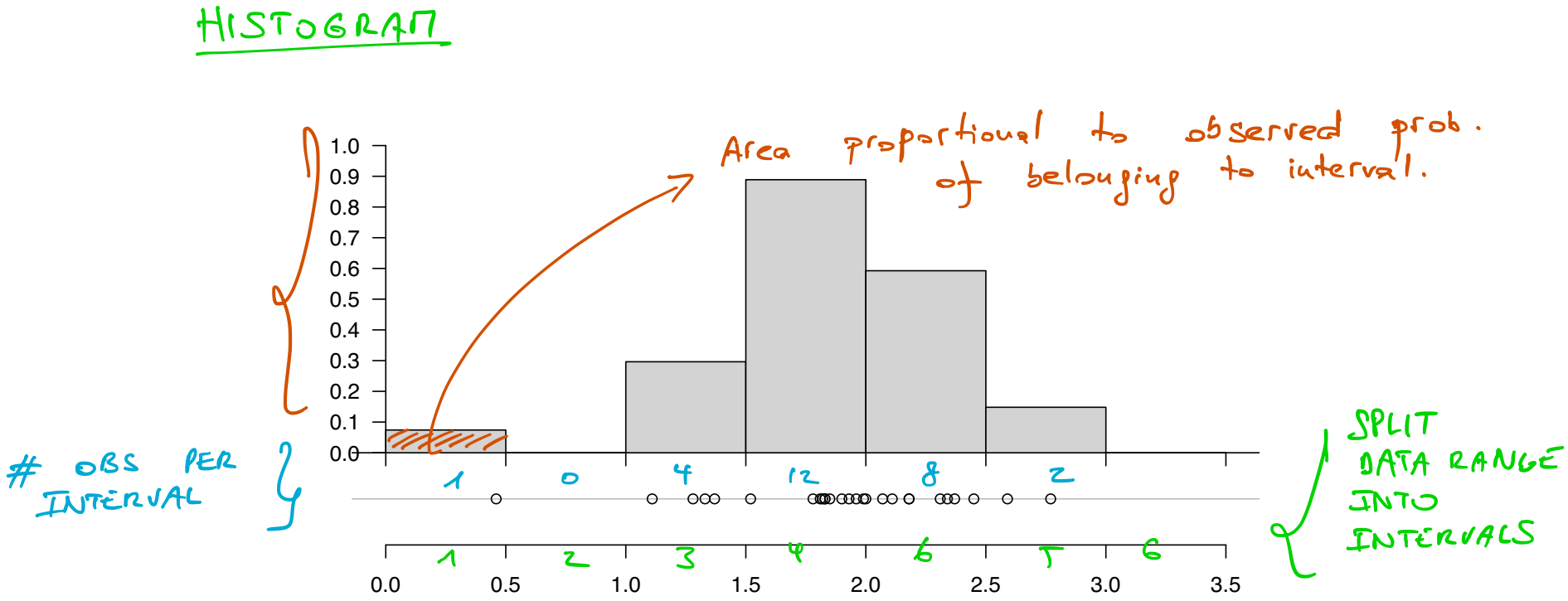

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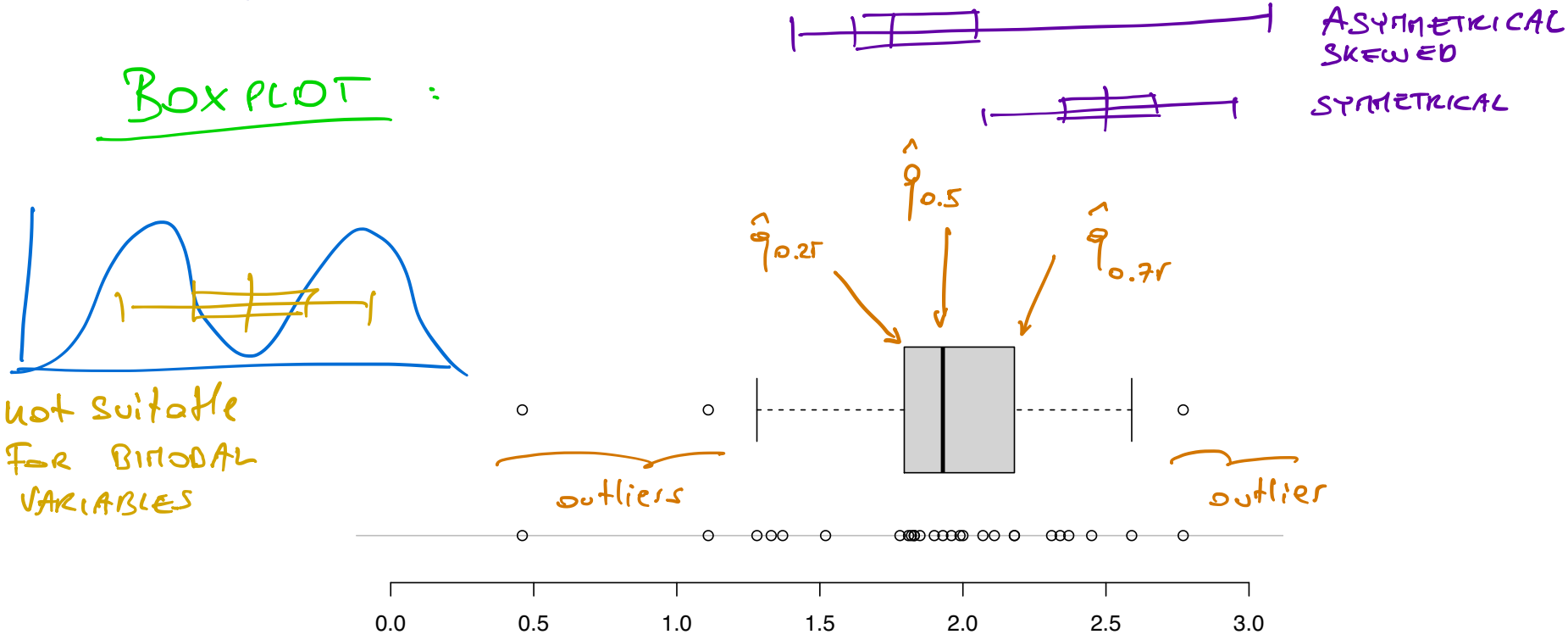

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Two-sample case: independent versus paired samples

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					

$\bar{x}$ $\bar{y}$ $\bar{y} - \bar{x}$

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

$y_i - x_i$

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

Quiz Time

Sections 1 to 4

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

Some parametric distributions: Bernoulli distribution

	x_1	x_2	x_3	$\cdots$	x_n
Cancer status	C	$\not{C}$	$\not{C}$	$\cdots$	C
	1	0	0	$\cdots$	1

If

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

then, each dichotomous experiment, X_i, follows a Bernoulli distribution with parameter π:

$$X_i \sim Bernoulli(\pi)$$

$$P(X_i = 1) = \pi$$

$$P(X_i = 0) = 1 - \pi$$

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:

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

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

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

Some parametric distributions: Binomial distribution

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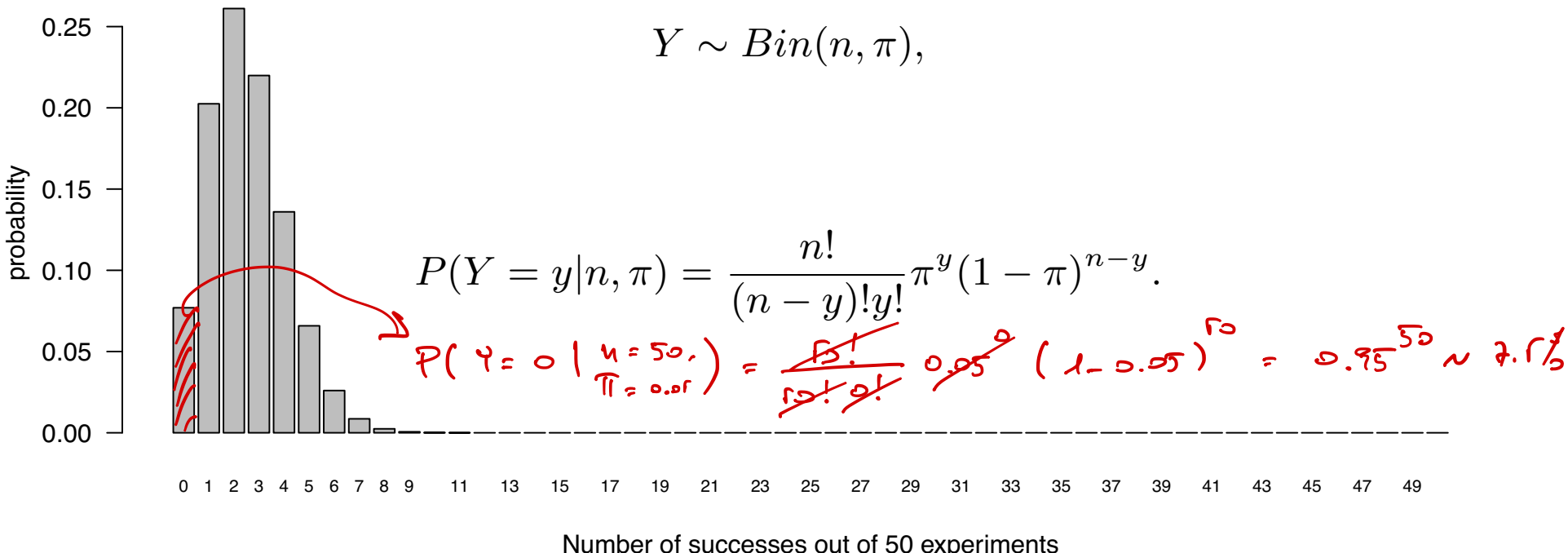

$$P(Y = y|n, \pi) = \frac{n!}{(n-y)!y!}\pi^y(1-\pi)^{n-y}.$$

$P(Y=0 \mid n=50, \pi=0.05) = \frac{50!}{50!\,0!} 0.05^0 (1-0.05)^{50} = 0.95^{50} \sim 7.7\%$

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:

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

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

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

Some parametric distributions: Poisson distribution

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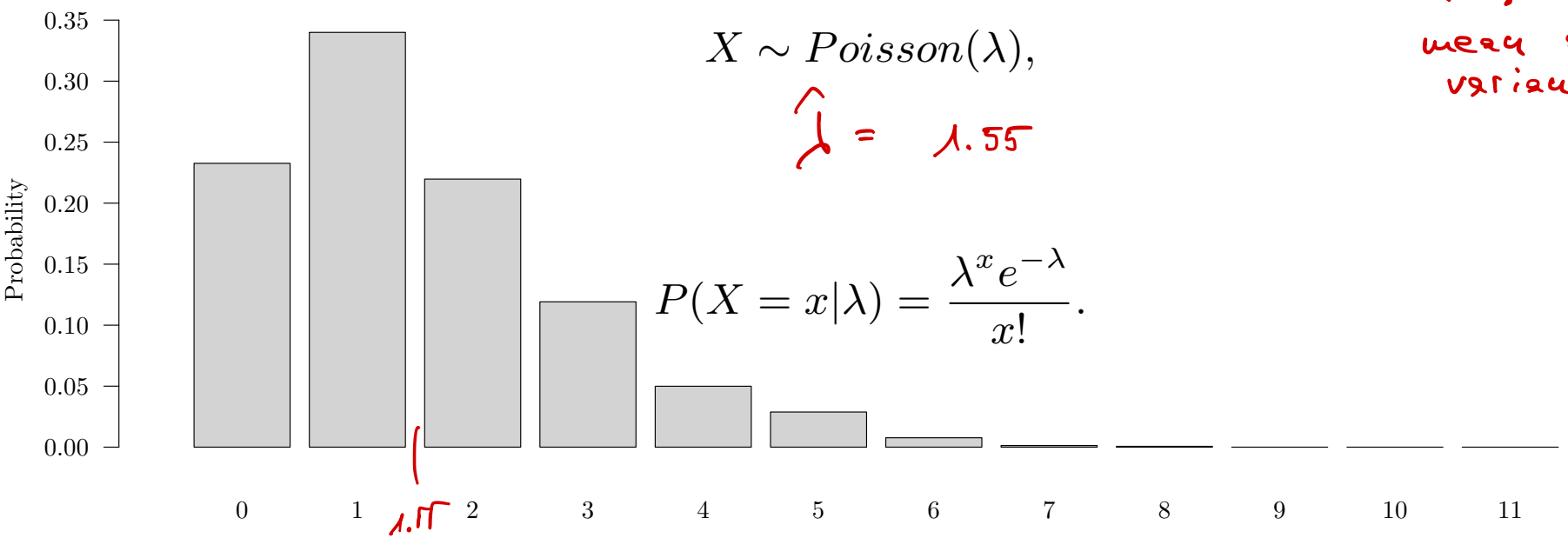
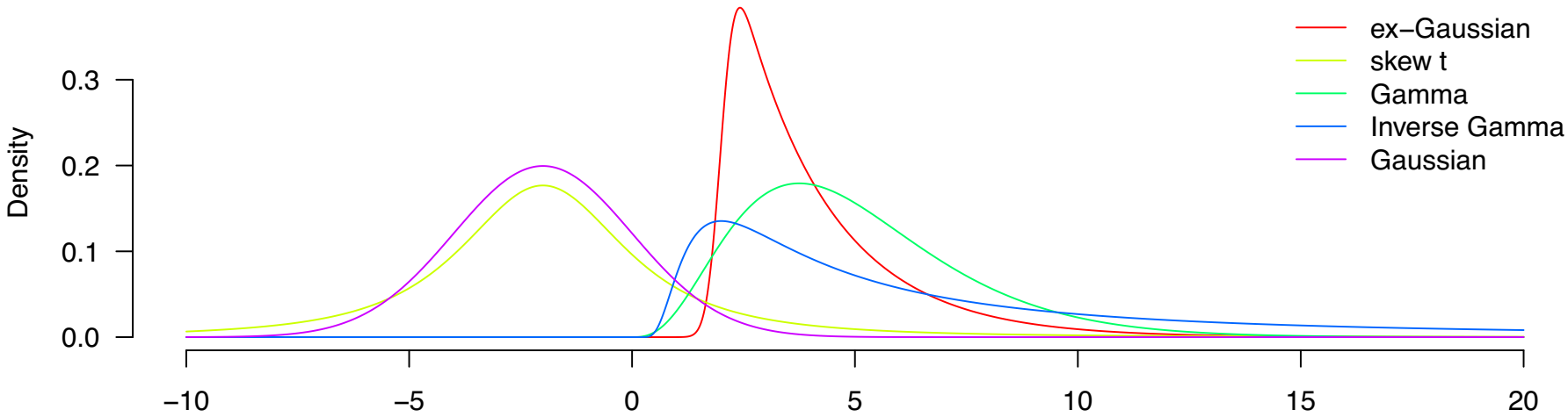


Number of chronic conditions per patient (US National Medical Expenditure Survey)

Some parametric distributions: Continuous distrib.



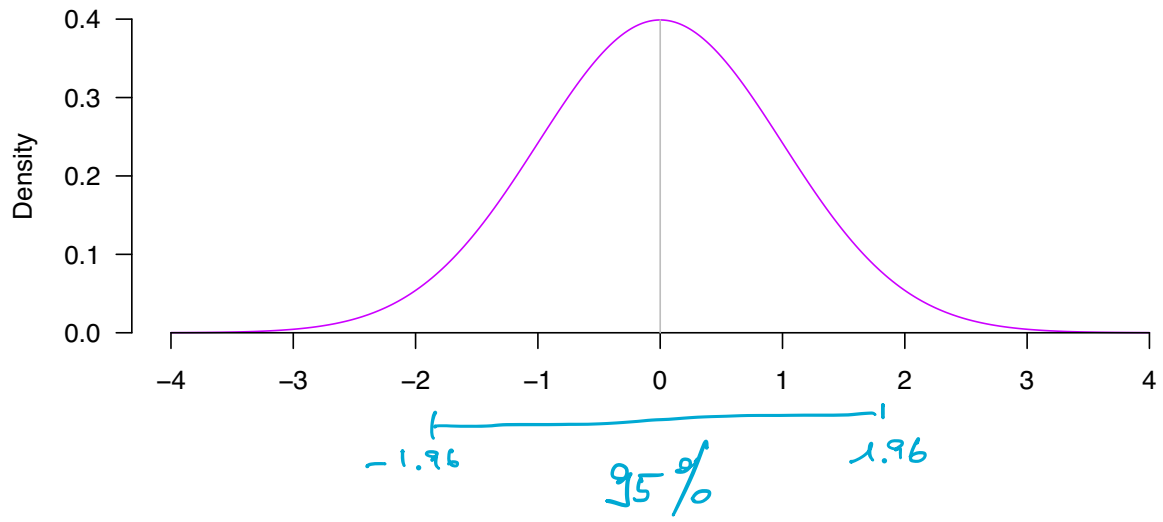
Some parametric distributions: Normal distribution

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

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

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

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



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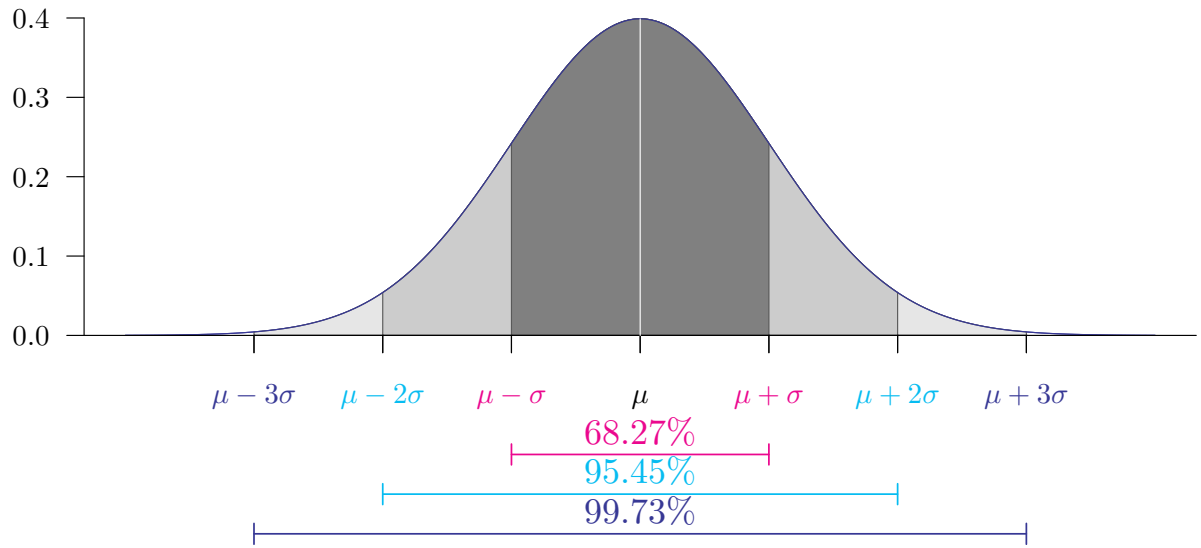

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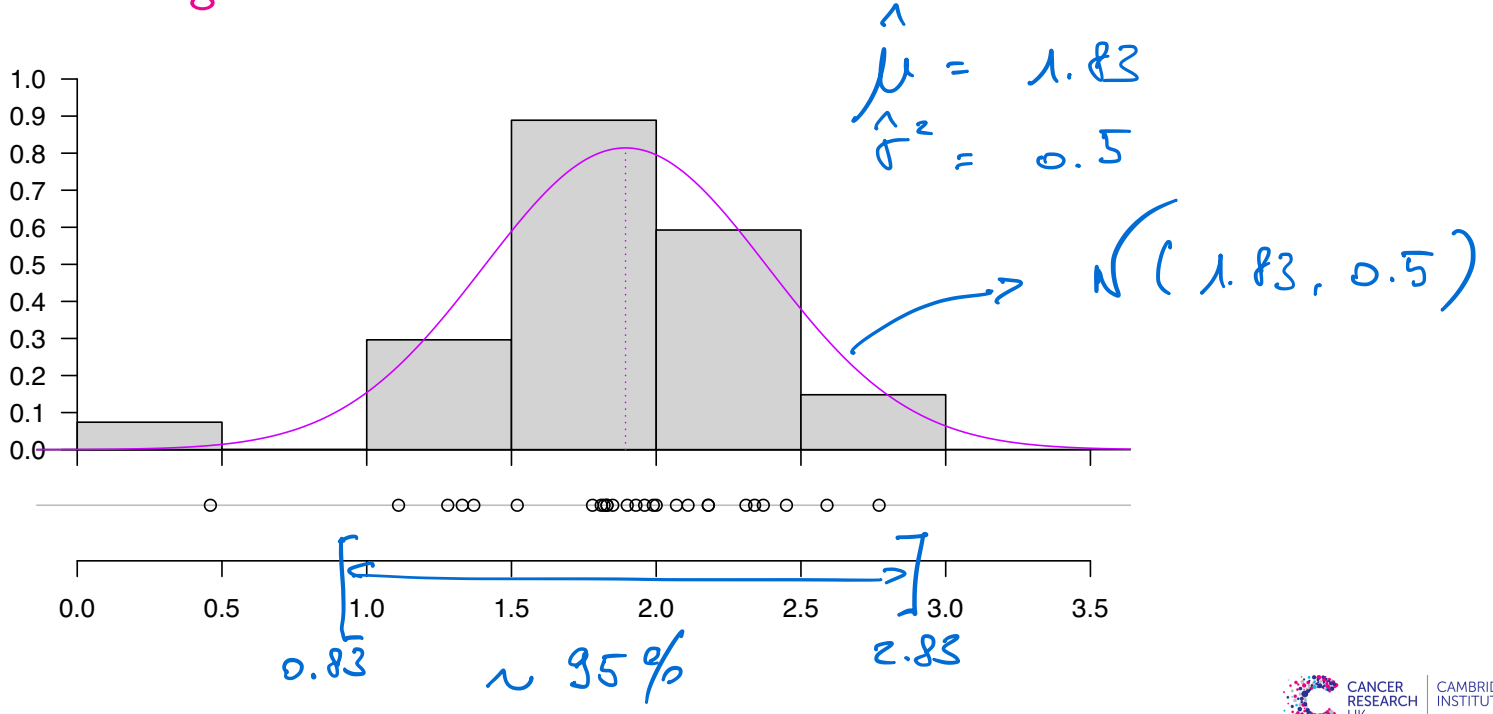
(i) Suitable modelling for a lot of variables



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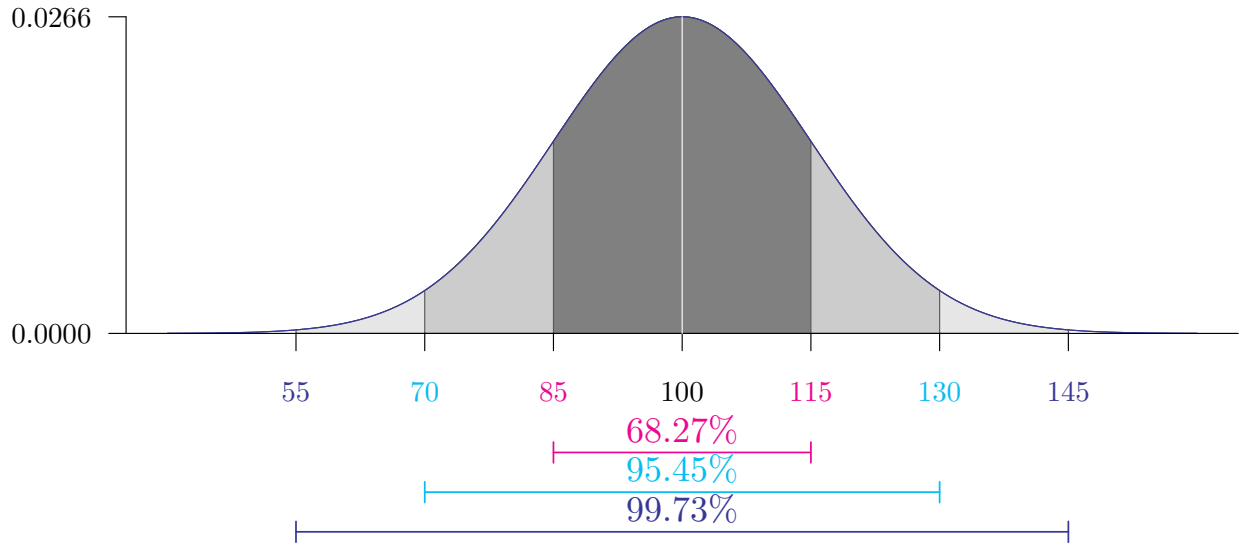
(i) Suitable modelling for a lot of variables: IQ



Some parametric distributions: Normal distribution

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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

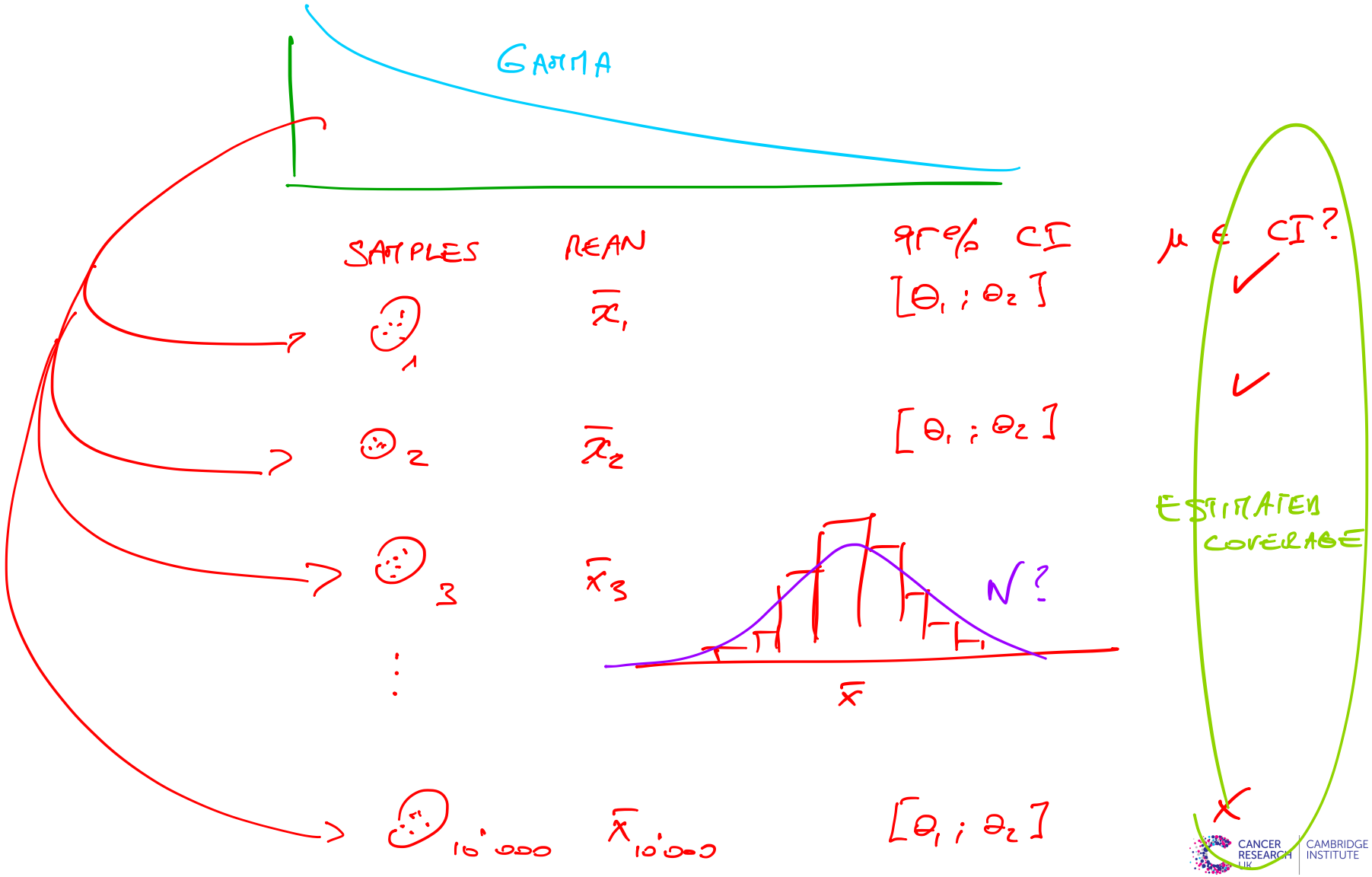
$$\widehat{\mu} = \overline{X} = \frac{\sum_{i=1}^{n} X_i}{n} \quad \xrightarrow{d} \quad N\left(\mu, \frac{\sigma^2}{n}\right).$$

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 $X_i \sim N(\mu, \sigma^2)$ or n large and X_i iid (μ, σ^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 $Z = \frac{X-\mu}{\sigma} \sim N(0,1)$,

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

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

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

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

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

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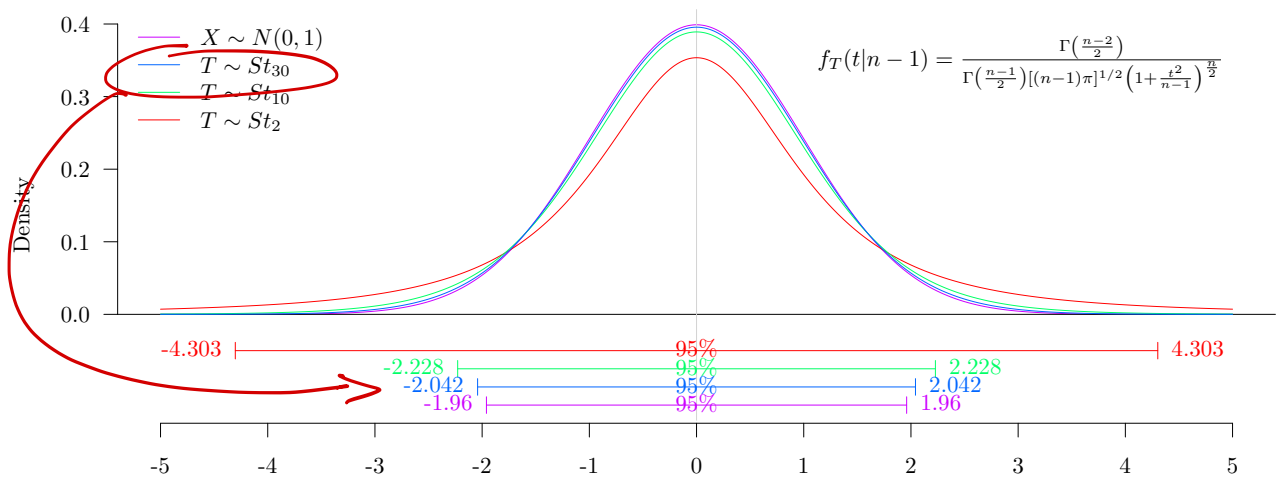
- if σ unknown, then $T = \frac{X-\mu}{s} \sim St_{n-1}$.

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

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



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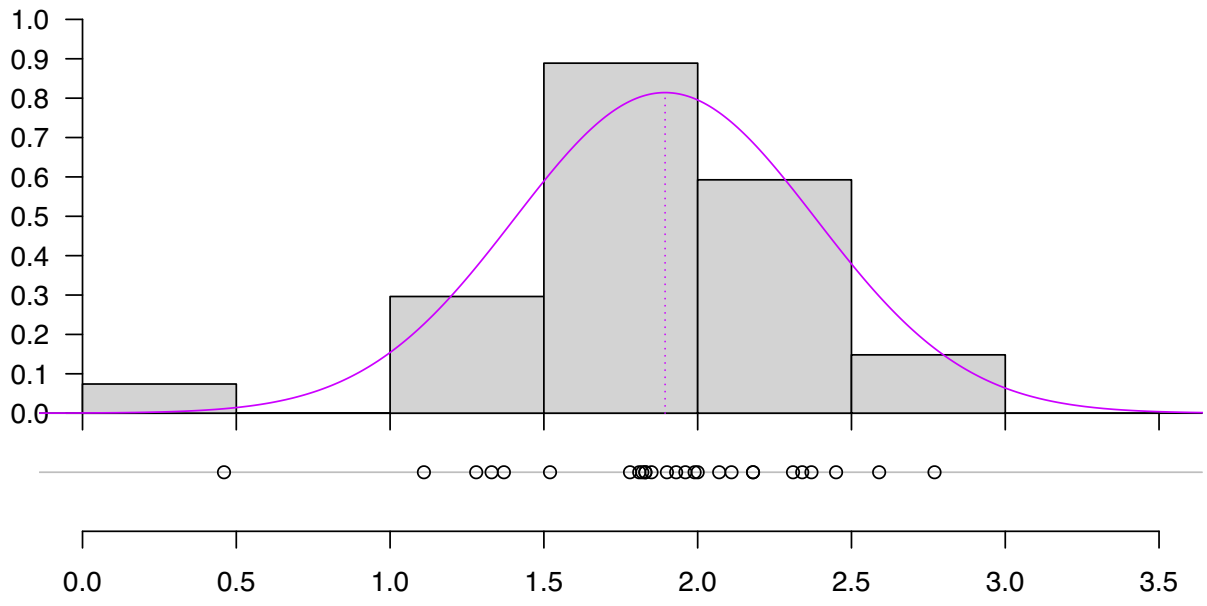
$$\mathrm{P}\left(\quad < \quad < \quad \right) = 0.95$$



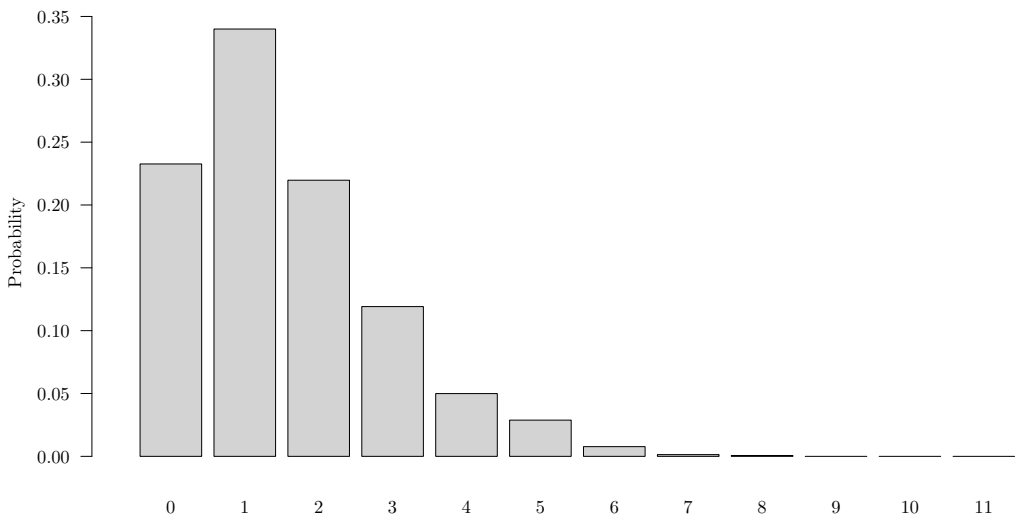
95% Confidence interval for μ, the population mean, when $X_i \sim iid(\mu, \sigma^2)$

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

Assuming $X_i \sim$ Poisson

$\hat{\mu} = \hat{\sigma}^2 \simeq 1.55$

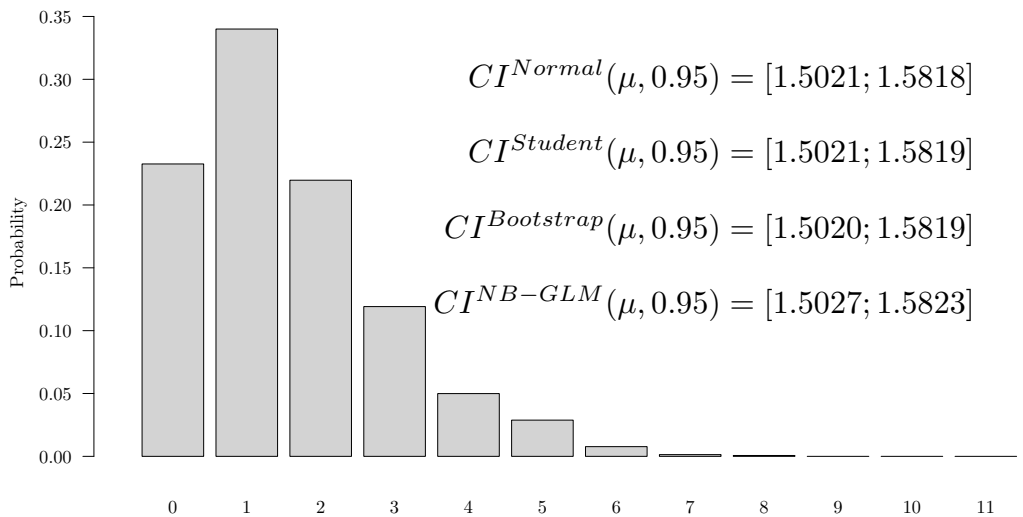
$$P\left(1.55 - 1.96\sqrt{\frac{1.55}{4406}} < \mu < 1.55 + 1.96\sqrt{\frac{1.55}{4406}}\right) = 0.95$$



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

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

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



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

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

If we have

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

then

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

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

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

If we have

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

then

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

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

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

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

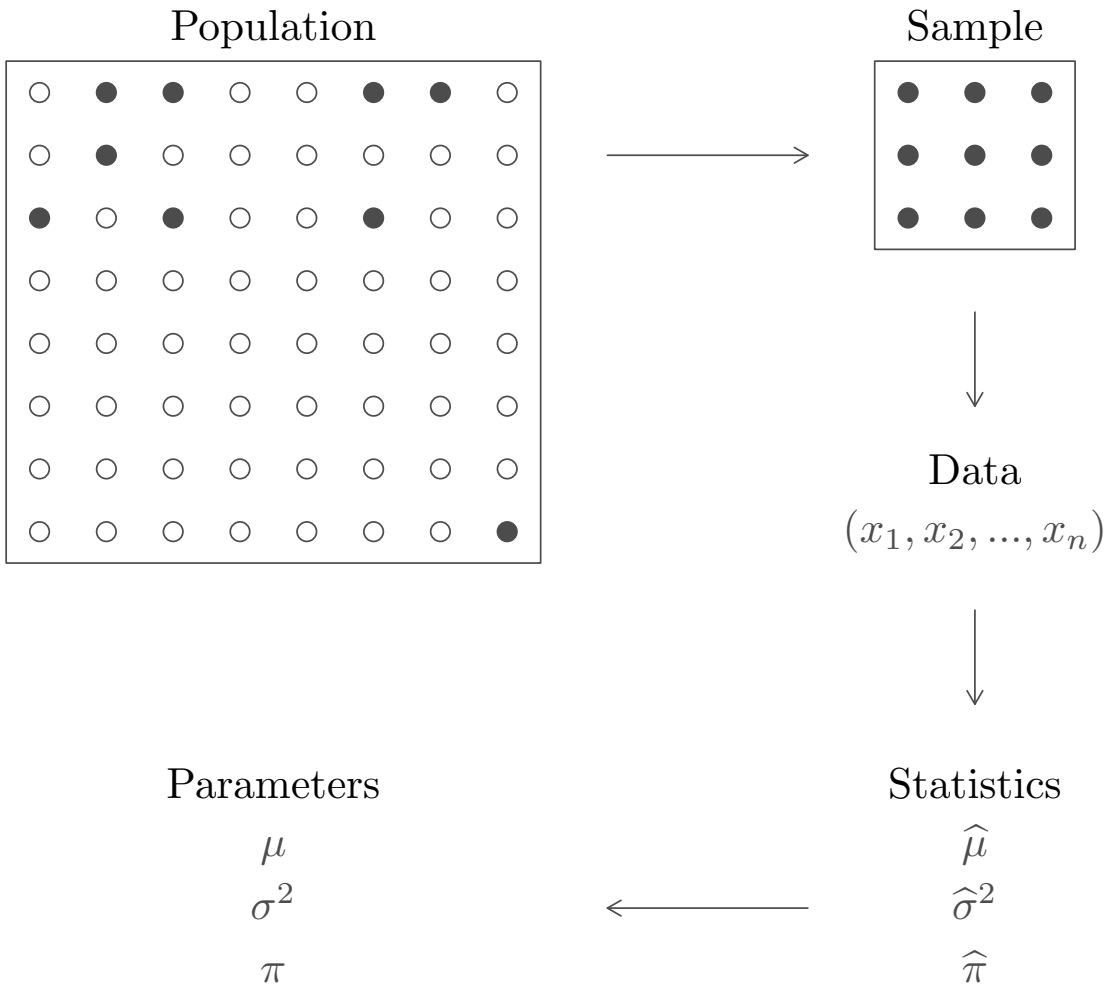
`http://bioinformatics-core-shared-training.github.io/IntroductionToStats/practical.html`

PART II: Parametric tests

Cancer Research UK – 24^{th} of April 2017

D.-L. Couturier / M. Dunning / M. Eldridge [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**.

$H_0 : \pi_B = 0.5$
$H_1 : \pi_B > 0.5$

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

$H_0 : \mu_D = \mu_E$
$H_1 : \mu_D > \mu_E$

Theory 2: There is no majority for Brexit now

Theory 3: Serum vitamin C is reduced in patients

$H_0 : \mu_P = \mu_P$
$H_1 : \mu_P < \mu_P$

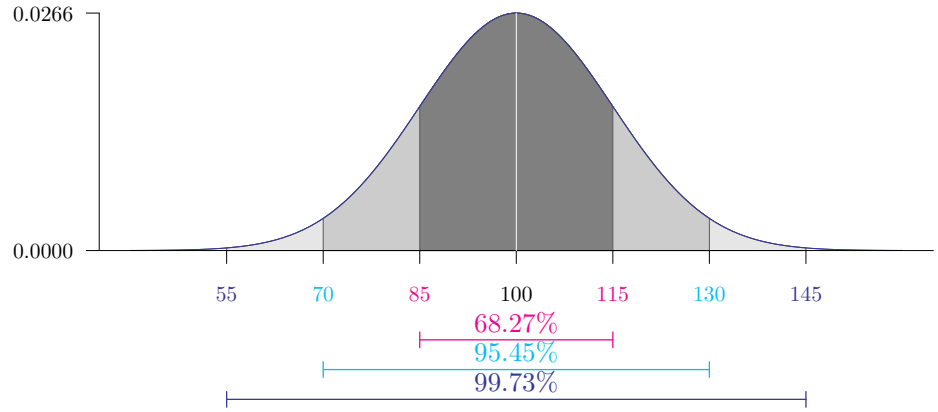
Statistical hypothesis testing

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
Example: One-sample two-sided t-test

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

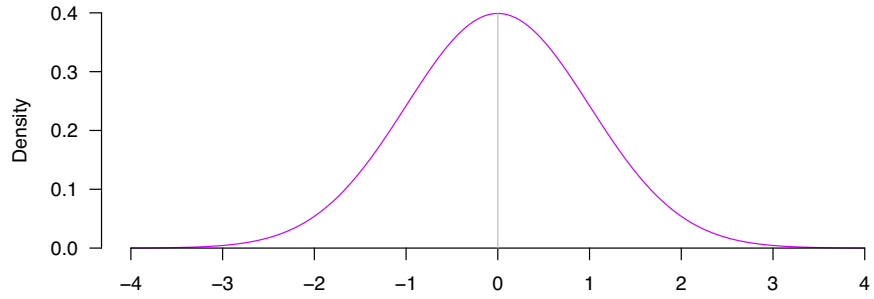


We have $X_i \sim N(\mu, \sigma^2), i = 1, ..., n,$

$\sigma^2 = 15^2$

We know

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



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:

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

$= P(Z > Z_{obs})$

$Z_{obs} = \frac{120 - 100}{\frac{15}{\sqrt{30}}}$

Statistical hypothesis testing
4 possible outcomes

Conclude:

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

HIV test

		Test Outcome	
		H0 not rejected (−)	H1 accepted (+)
Unknown Truth	H0 true (−)	$1-\alpha$	α FALSE POS.
	H1 true (+)	β FALSE NEG.	$1-\beta$ → Power function of DESIGN, Sample size, ...

where

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

Statistical hypothesis testing
Example: 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

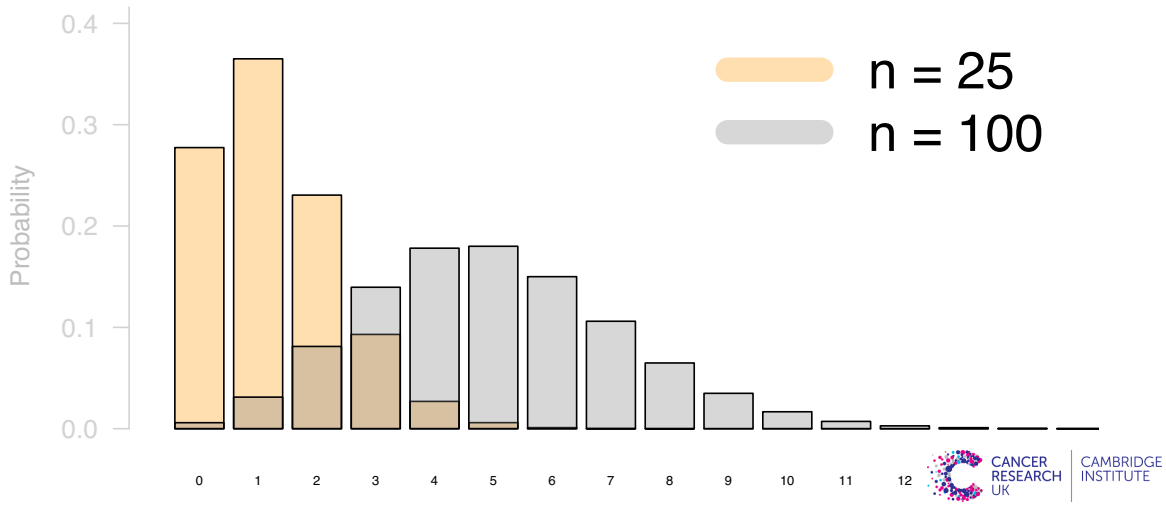
- $Y = \sum_{i=1}^{n} X_i \quad \sim \quad Binomial\,(\pi, n)\,,$

Thus, if H0 is true, we have:

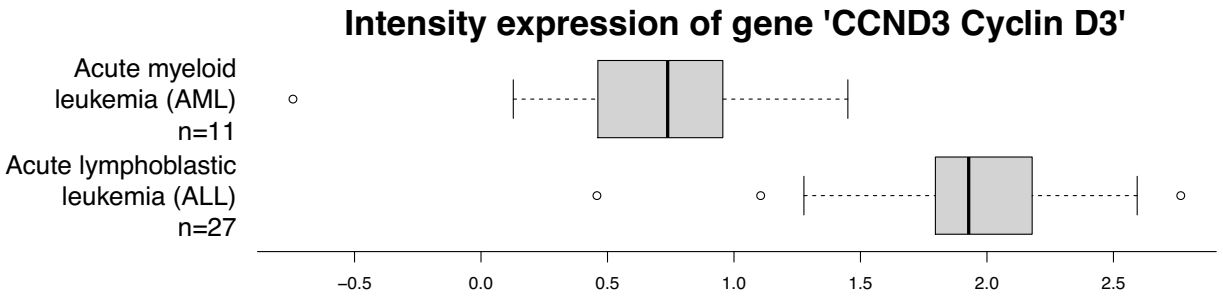
- $Y = \sum_{i=1}^{n} X_i \quad \sim \quad Binomial\,(5\%, n)\,,$

Define the p-value:

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



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



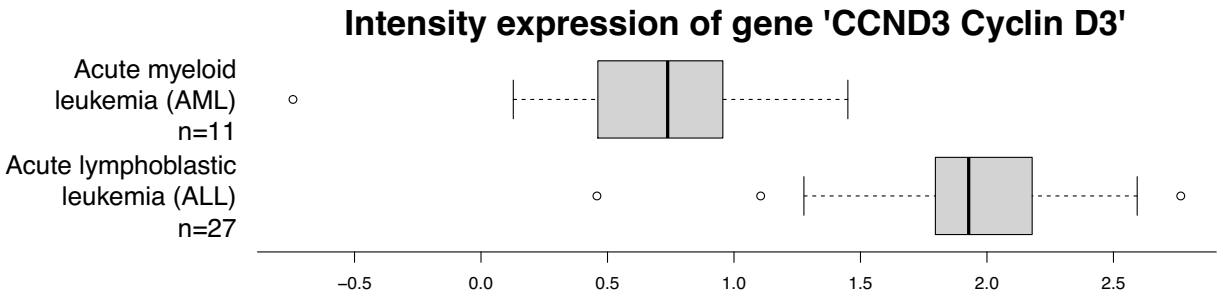
We test **H0**: $\mu_Y - \mu_X = 0$ against **H1**: $\mu_Y - \mu_X \neq 0$.

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 $\sigma_X^2 \neq \sigma_Y^2$]: $\frac{(\overline{Y}-\overline{X})-(\mu_Y-\mu_X)}{\sqrt{\frac{s_X^2}{n_X}+\frac{s_Y^2}{n_Y}}} \sim t_{1-\frac{\alpha}{2},df}$

```
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
```

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
```

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: $\alpha = 1 - (1 - \alpha_k)^{1/k}$.

Introduction to Shiny Apps and Exercises

PART III: Non-parametric tests

Cancer Research UK – 24^{th} of April 2017

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

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.

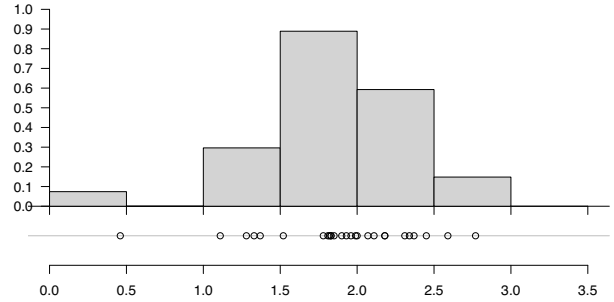
Sign test

RATHER INEFFICIENT

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

$$X_i = \theta + e_i,$$

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

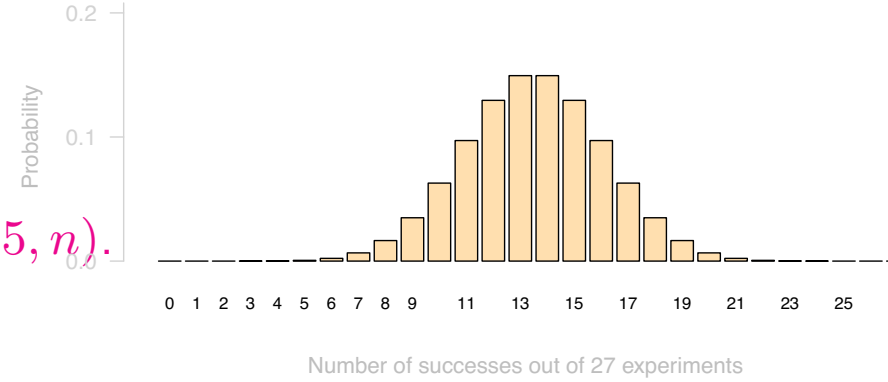


Interest for **H0**: $\theta = \theta_0$ against **H1**: $\theta < \theta_0$ or $\theta \neq \theta_0$ or $\theta > \theta_0$.

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

Distribution of S under H0:

$$S \sim Binomial(0.5, n).$$



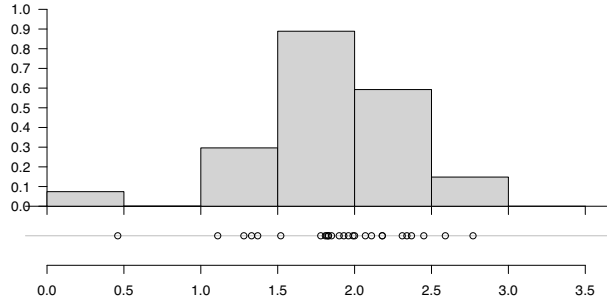

```
Exact binomial test

data:  21 and 27
number of successes = 21, number of trials = 27, p-value = 0.005925
alternative hypothesis: true probability of success is not equal to 0.5
95 percent confidence interval:
 0.5774169 0.9137831
sample estimates:
probability of success
             0.7777778
```

Wilcoxon sign-rank test

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

$$X_i = \theta + e_i,$$

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



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$(|X_i - \theta_0|)$.

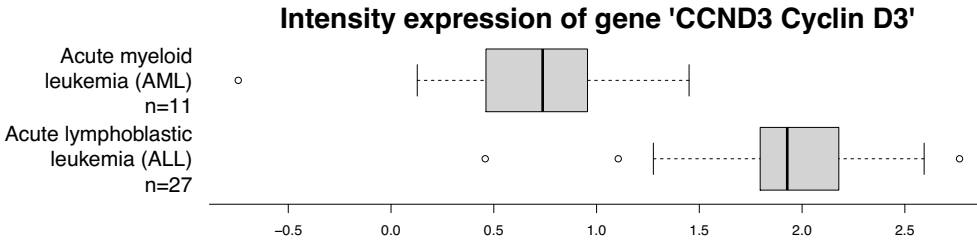
Distribution of W under H0: W^+ has no closed-form distribution.

```
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
```

Mann-Whitney-Wilcoxon test: Shift in location

Let

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

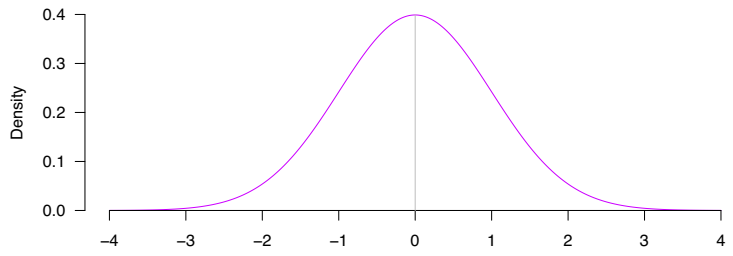


Interest for **H0**: $\delta = \delta_0$ against **H1**: $\delta < \delta_0$ or $\delta \neq \delta_0$ or $\delta > \delta_0$.

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

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
```

Non-parametric is not assumption free

Shift in location tests when H0 is true

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

PART IV: Tests for categorical variables

Cancer Research UK – 24^{th} of April 2017

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

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.

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

χ^2-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
```

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

Fisher showed that, under H0 (independence),
$P(\text{observed table} \mid \text{H0}) = P(X = a)$ and $X \sim Hypergeometric(n, a + c, a + b)$.
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.

```
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
```