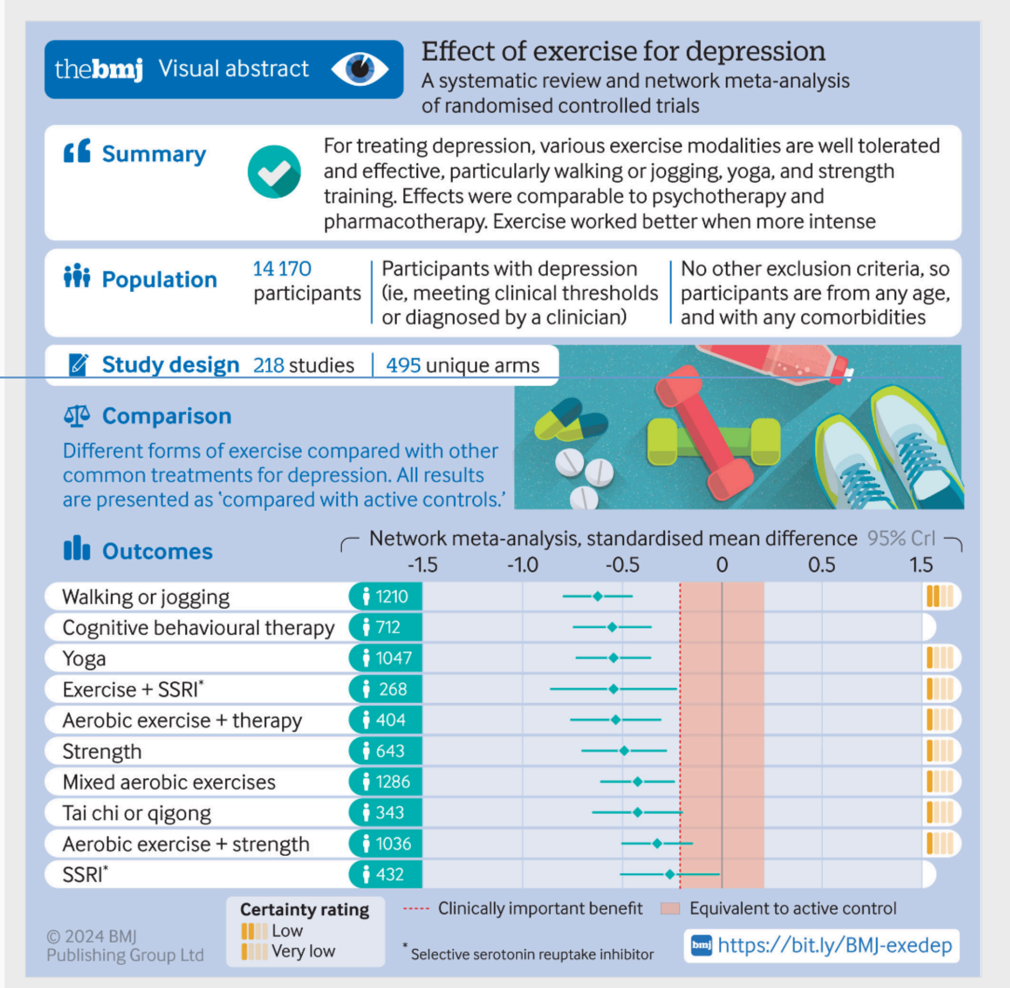
Mathematical Statistics II

STA2212H S LEC9101

Week 8

March 4 2025



thebmj Visual abstract

Effect of exercise for depression

A systematic review and network meta-analysis of randomised controlled trials

Summary For treating depression, various exercise modalities are well tolerated and effective, particularly walking or jogging, yoga, and strength training. Effects were comparable to psychotherapy and pharmacotherapy. Exercise worked better when more intense

Population 14 170 participants | Participants with depression (ie, meeting clinical thresholds or diagnosed by a clinician) | No other exclusion criteria, so participants are from any age, and with any comorbidities

Study design 218 studies | 495 unique arms

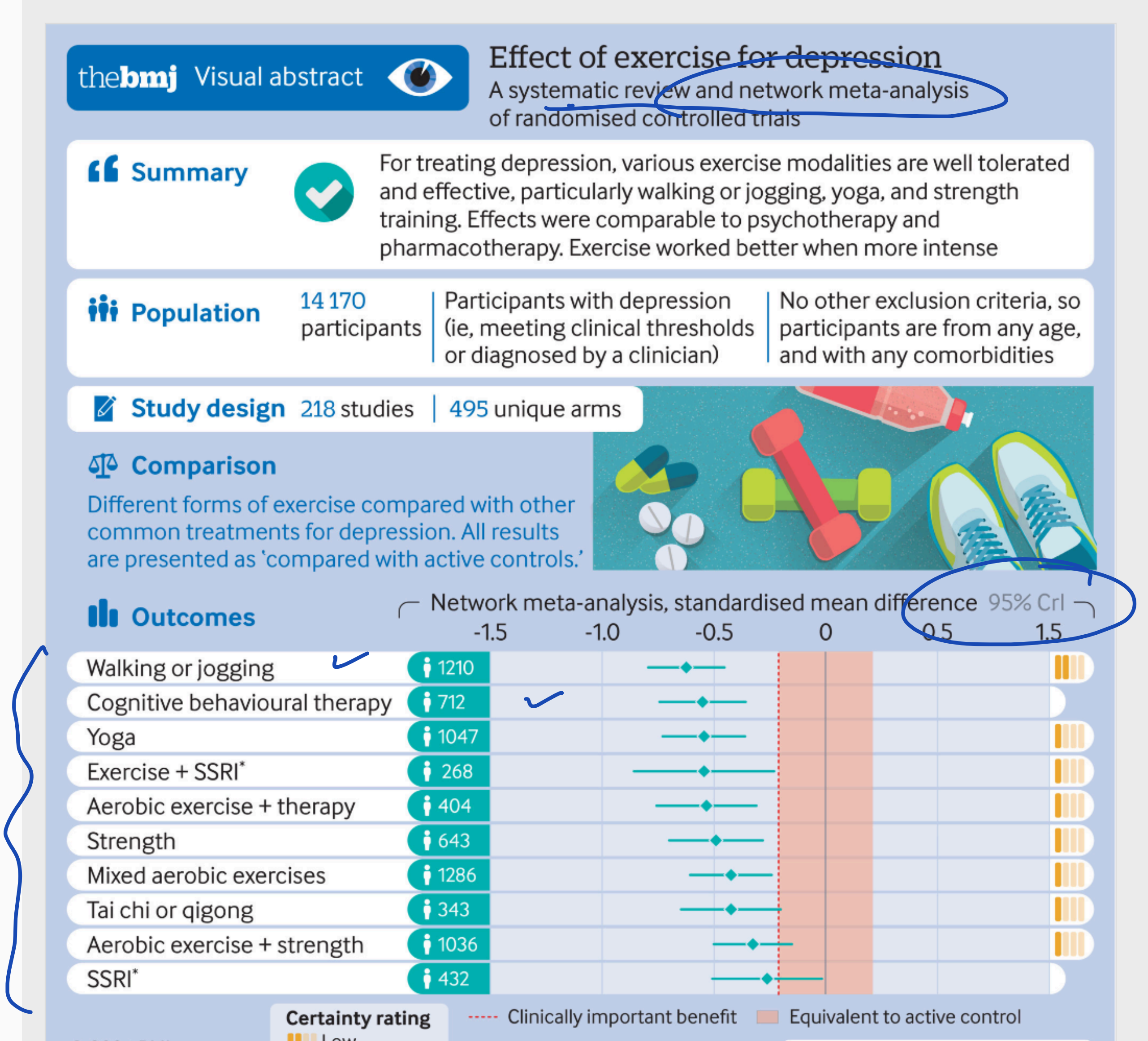
Comparison Different forms of exercise compared with other common treatments for depression. All results are presented as 'compared with active controls.'

Outcomes

Walking or jogging	1210
Cognitive behavioural therapy	712
Yoga	1047
Exercise + SSRI*	268
Aerobic exercise + therapy	404
Strength	643
Mixed aerobic exercises	1286
Tai chi or qigong	343
Aerobic exercise + strength	1036
SSRI*	432

*Selective serotonin reuptake inhibitor

https://bit.ly/BMJ-exedep



Effect of exercise for depression

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For treating depression, various exercise modalities are well tolerated and effective, particularly walking or jogging, yoga, and strength training. Effects were comparable to psychotherapy and pharmacotherapy. Exercise worked better when more intense

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Study design 218 studies | 495 unique arms

Comparison

Different forms of exercise compared with other common treatments for depression. All results are presented as 'compared with active controls.'

Outcomes

Network meta-analysis, standardised mean difference 95% CrI

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Mixed aerobic exercises	1286
Tai chi or qigong	343
Aerobic exercise + strength	1036
SSRI*	432

Certainty rating

Low

Clinically important benefit

Equivalent to active control

Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials

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ABSTRACT

OBJECTIVE

To identify the optimal dose and modality of exercise for treating major depressive disorder, compared with psychotherapy, antidepressants, and control conditions.

DESIGN

Systematic review and network meta-analysis.

METHODS

Screening, data extraction, coding, and risk of bias assessment were performed independently and in duplicate. Bayesian arm based, multilevel network meta-analyses were performed for the primary

g −0.42, −0.65 to −0.21). The effects of exercise were proportional to the intensity prescribed. Strength training and yoga appeared to be the most acceptable modalities. Results appeared robust to publication bias, but only one study met the Cochrane criteria for low risk of bias. As a result, confidence in accordance with CINeMA was low for walking or jogging and very low for other treatments.

CONCLUSIONS

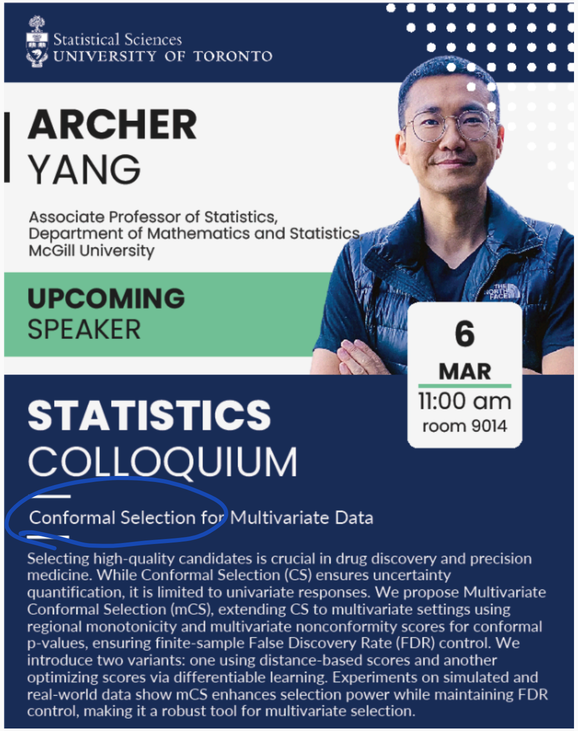
Exercise is an effective treatment for depression, with walking or jogging, yoga, and strength training more effective than other exercises, particularly when intense. Yoga and strength training were well

Today

1. Recap Feb 25 Formal testing, NP Lemma, size and power, *p*-values
2. Significance testing, nonparametric tests
3. Diagnostic testing
4. Multiple testing
5. Project Selections and Guidelines, HW 7

Upcoming seminar

Department Seminar Thursday March 6 11.00 – 12.00
Hydro Building, Room 9014 Conformal selection
Archer Yang, McGill University



Statistical Sciences
UNIVERSITY OF TORONTO

ARCHER
YANG

Associate Professor of Statistics,
Department of Mathematics and Statistics,
McGill University

UPCOMING
SPEAKER

6
MAR
11:00 am
room 9014

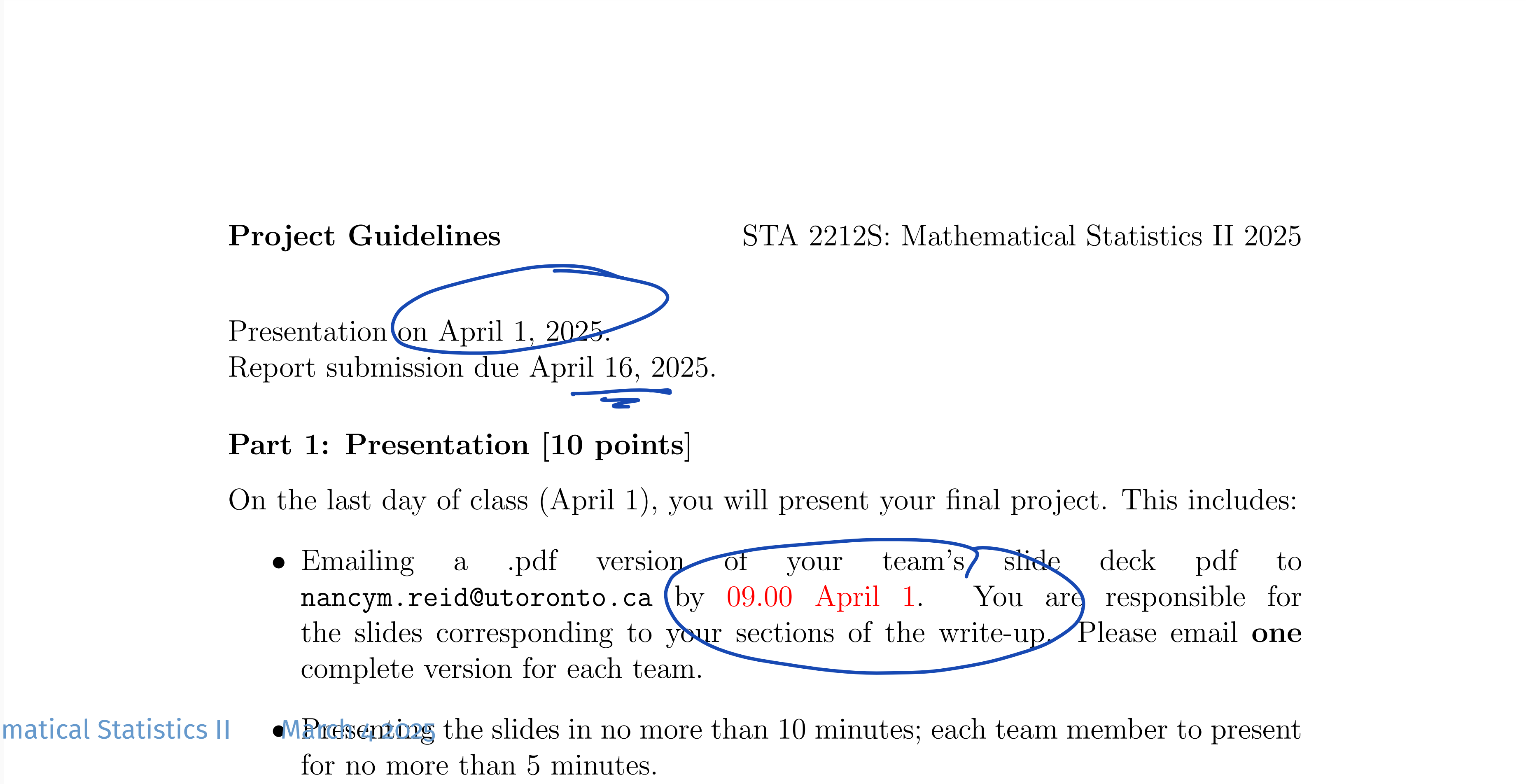
STATISTICS
COLLOQUIUM

Conformal Selection for Multivariate Data

Selecting high-quality candidates is crucial in drug discovery and precision medicine. While Conformal Selection (CS) ensures uncertainty quantification, it is limited to univariate responses. We propose Multivariate Conformal Selection (mCS), extending CS to multivariate settings using regional monotonicity and multivariate nonconformity scores for conformal p-values, ensuring finite-sample False Discovery Rate (FDR) control. We introduce two variants: one using distance-based scores and another optimizing scores via differentiable learning. Experiments on simulated and real-world data show mCS enhances selection power while maintaining FDR control, making it a robust tool for multivariate selection.

Project Guidelines

link



Project Guidelines STA 2212S: Mathematical Statistics II 2025

Presentation on April 1, 2025.
Report submission due April 16, 2025.

Part 1: Presentation [10 points]

On the last day of class (April 1), you will present your final project. This includes:

- Emailing a .pdf version of your team's slide deck pdf to `nancym.reid@utoronto.ca` by 09.00 April 1. You are responsible for the slides corresponding to your sections of the write-up. Please email **one** complete version for each team.
- Presenting the slides in no more than 10 minutes; each team member to present for no more than 5 minutes.

Recap: hypothesis testing

MS 7.3, AoS Ch 10

$X_1, \ldots, X_n \sim f(\boldsymbol{x}; \theta), \theta \in \Theta \subset \mathbb{R}^p$

in principle Θ inf.-dim.

- Null and alternative hypotheses $H_0: \theta \in \Theta_0 \subset \Theta$ $\quad H_1: \theta \in \Theta_1$ $\quad \Theta_0 \cup \Theta_1 = \Theta$

  composite null $\quad$ composite alt.

- Size and power α , β

  .05 $\alpha = \overset{\Pr}{}\{\text{type 1 error}\} = \Pr_{H_0}\{\text{reject } H_0\}$

  .8 $\beta = \Pr_{H_1}\{\text{reject } H_0\}$ power

- Test statistic $T = t(\boldsymbol{X})$

  testing function

  MS

- Rejection region $\{\boldsymbol{x} : T \geq c_\alpha\}$: if $x \in R$ then reject H_0

  AoS

  o.w. do not reject

- P-value $\mathrm{pr}_{H_0}(T \geq t^{obs})$ "as or more extreme" than obs.

  $\geq$

Recap: Neyman-Pearson lemma

MS Thm 7.2; AoS Thm 10.30

composite is still MP

- for testing $\underline{\underline{\text{simple } H_0}}$ against $\underline{\underline{\text{simple } H_1}}$

$H_0: \underset{\sim}{\theta} = \underset{\sim}{\theta}_0 \quad H_1: \underset{\sim}{\theta} = \underset{\sim}{\theta}_1$

- test statistic

$$T = \frac{L(\theta_1; \boldsymbol{x})}{L(\theta_0; \boldsymbol{s})} = \frac{f(\boldsymbol{x}; \theta_1)}{f(\boldsymbol{x}; \theta_0)}$$

- critical region

$$R = \underline{\{\boldsymbol{x} : t(\boldsymbol{x}) \geq k\}}$$

- Choose $k = k_\alpha$ to satisfy

$$\underline{\mathrm{pr}_{H_0}(T \geq k_\alpha) \overset{\leq}{=} \alpha}$$

- This test is a most powerful test of H_0 against H_1 at level α.

mid-p

$\frac{1}{2} P_1(T = t^0\}$

$+ P_1(T > t^0)$

A neatly-typed proof (from MS)

$$1 \qquad \frac{f_1}{f_0} > k_\alpha$$

Let $\phi(\boldsymbol{x})$ be the test function for the test based on T.
Let $\psi(\boldsymbol{x})$ be any other function that maps $\boldsymbol{x}$ to $[0, 1]$.
If

$$\boxed{\mathrm{E}_{H_0}\{\psi(\boldsymbol{X})\} \le \mathrm{E}_{H_0}\{\phi(\boldsymbol{X})\} = \alpha}$$

then it must follow that

$$\underset{= \text{power}}{\mathrm{E}_{H_1}\{\psi(\boldsymbol{X})\}} \boxed{\le} \underset{= \text{power}}{\mathrm{E}_{H_1}\{\phi(\boldsymbol{X})\}}$$

Proof: $\forall\ \boldsymbol{x}$,

$$\underbrace{\psi(\boldsymbol{x})\{f_1(\boldsymbol{x}) - kf_0(\boldsymbol{x})\}}_{} \le \phi(\boldsymbol{x})\{f_1(\boldsymbol{x}) - kf_0(\boldsymbol{x})\}$$

Integrate and re-arrange terms to get the result

A neatly-typed proof (from SM 7.3)

Let R be the rejection region for the test based on

$$R = \{\boldsymbol{x} : T(\boldsymbol{x}) \geq k_\alpha\}$$

$T = f_1(\boldsymbol{x})/f_0(\boldsymbol{x})$

Let R' be some other rejection region also of size α

$\leq \alpha$

$$\alpha = \int_R f_0(\boldsymbol{x})d\boldsymbol{x} = \int_{R'} f_0(\boldsymbol{x})d\boldsymbol{x}$$

$$\int_{R-R'} f_0(\boldsymbol{x})d\boldsymbol{x} = \int_{R'-R} f_0(\boldsymbol{x})d\boldsymbol{x}$$

$A - B$

$= A \cap B^c$

On LHS $f_1(\boldsymbol{x}) \geq k_\alpha f_0(\boldsymbol{x})$.

On RHS $f_1(\boldsymbol{x}) < k_\alpha f_0(\boldsymbol{x})$.

$R - R' \subset R$

$R' - R \subset R^c$

$$\int_{R-R'} f_1(\boldsymbol{x})d\boldsymbol{x} \geq \int_{R'-R} f_1(\boldsymbol{x})d\boldsymbol{x}$$

Add integral over intersection $R \cap R'$

$$\int_R f_1 \geq \int_{R'} f_0$$

Choosing test statistics

$\theta \in \mathbb{R}$

$H_0: \theta = \theta_0 \quad H_1: \theta > \theta_0$

1. Optimal choice – Neyman-Pearson lemma

Might be UMP (HW 7) for $H_1': \theta = \theta_1$

R is free of

2. Pragmatic choice – likelihood-based test statistics

$(\underline{\hat{\theta}} - \underline{\theta})^T j(\hat{\theta})(\hat{\theta} - \theta) : \theta_1 > \theta_0$

$\underline{\ell}'(\theta)^T j^{-1}(\hat{\theta}) \underline{\ell}'(\theta)$

$2\{\ell(\hat{\theta}) - \ell(\tilde{\theta}_0)\}$

3. Pragmatic choice – nonparametric test statistics

control α

(a) Need to know distribution of test statistic under H_0

(b) Test statistic should be large when H_0 is not true

(c) Test statistic should have maximum power to detect departures from H_0

high

$\tilde{\theta}_0 = \arg\sup_{\theta \in \Theta_0} \ell(\theta)$

in probability

$\hat{\theta} = \arg\sup_{\theta \in \Theta} \ell(\theta)$

$(\text{not } \Theta_1)$

generalized LRT

Choosing test statistics

1. Optimal choice – Neyman-Pearson lemma

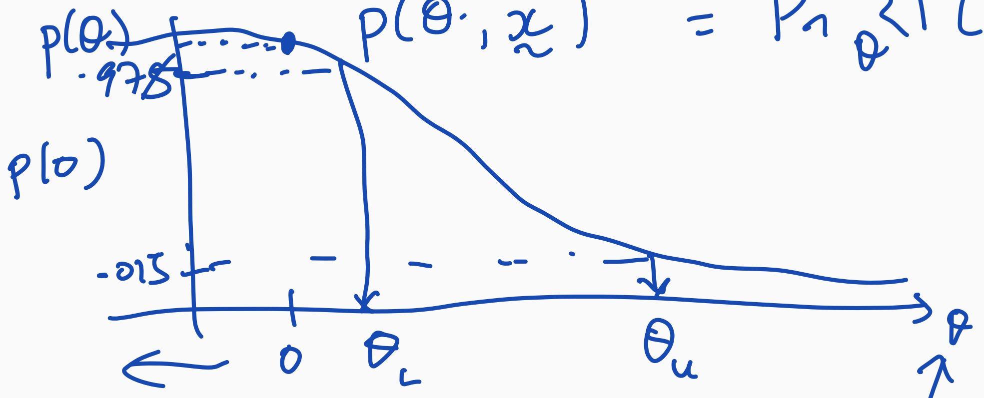
Might be UMP (HW 7)

2. Pragmatic choice – likelihood-based test statistics

Wald, score (Rao), LRT

3. Pragmatic choice – nonparametric test statistics

$$p(\theta, \underset{\sim}{x}) = \text{"}Pr_\theta\{T(\underset{\sim}{X}) \geq t^{obs}\}\text{"}$$



$p_{obs} = 1 - p(0)$

is the p-value for $H_0: \theta = 0$ vs $H_1: \theta < 0$

$$\theta = (\psi, \lambda) \longrightarrow \ell_{prof}$$

Choosing test statistics

1. Optimal choice – Neyman-Pearson lemma

Might be UMP (HW 7)

2. Pragmatic choice – likelihood-based test statistics
3. Pragmatic choice – nonparametric test statistics

Example: Sign test

SM Ex.7.26

- $X_1, \ldots, X_n$ i.i.d. $F(\cdot)$
- $H_0 : \mu = \mu_0$, $\mu = F^{-1}(1/2)$ median of distribution
- $H_1 : \mu \geq \mu_0$

both H composite

- test statistic

$$\underbrace{T = \sum_{i=1}^{n} 1\{X_i > \mu_0\}} \qquad (1)$$

- under H_0, (2)

$$\underline{T \sim Binom(n, 1/2)} \;\approx\; N\left(\frac{n}{2}, \sqrt{\frac{n}{\cancel{2}}\left(\frac{1}{2} \times \frac{1}{2}\right)}\right)$$

- p-value

$$p_{obs} = \underbrace{\mathrm{pr}_{H_0}(T \overset{\downarrow}{\geq} t_{obs})} = \underbrace{\sum_{r=t_{obs}}^{n} \binom{n}{r} \frac{1}{2^n}} \doteq \underbrace{1 - \Phi\left\{\frac{2(t_{obs} - n/2)}{n^{1/2}}\right\}}. \qquad \frac{t_{obs} - \frac{n}{2}}{\left(\frac{\sqrt{n}}{2}\right)}$$

normal cdf

Power of the sign test

SM Ex.7.30

- $H_0 : \mu = \mu_0 \qquad H_1 : \mu > \mu_0$
- Test statistic $T = \sum_{i=1}^{n} 1\{X_i > \mu_0\}$ ✓
- Rejection region $R = \{T \geq c_\alpha\}$ ✓
- $c_\alpha \approx \boxed{n/2 - n^{1/2} z_\alpha / 2}$ ✓ $\approx (\bar{x} - z_{\alpha/2} \hat{se})$
- Power = $\underline{\mathrm{pr}_{H_1}}(\underline{\text{reject } H_0}) = \underline{\mathrm{pr}_{H_1}}(\underline{T \geq c_\alpha})$
- to $\underline{\text{calculate power we}}$ need values for $\underline{\underline{\mu}}$ and for $\underline{\underline{F}}$

$\mu = F^{-1}(1/2)$

Normal approx

$\boxed{\text{Need distribution of } T \text{ under } H_1}$

Power of the sign test

SM Ex.7.30

$T = \frac{1}{n} \sum 1\{X_i \geq \mu_0\}$

- $H_0 : \mu = \mu_0 \qquad H_1 : \mu > \mu_0$
- Test statistic $T = \sum_{i=1}^{n} 1\{X_i > \mu_0\}$
- Rejection region $R = \{T \geq c_\alpha\}$
- $c_\alpha \approx n/2 - n^{1/2} z_\alpha / 2$

$\mu = F^{-1}(1/2)$

$\Pr_{\mu_1}(X_i \geq \mu_0) \leftarrow$ need

Normal approx

- Power = $\mathrm{pr}_{H_1}(\text{reject } H_0) = \mathrm{pr}_{H_1}(T \geq c_\alpha)$
- to calculate power we need values for μ and for F ← parameters need to be sp.

Need distribution of T under H_1

- SM assumes F is $N(\mu, \sigma^2)$, so (under H_1)

$\delta = n^{1/2}(\mu_1 - \mu_0)/\sigma$

pick μ_1

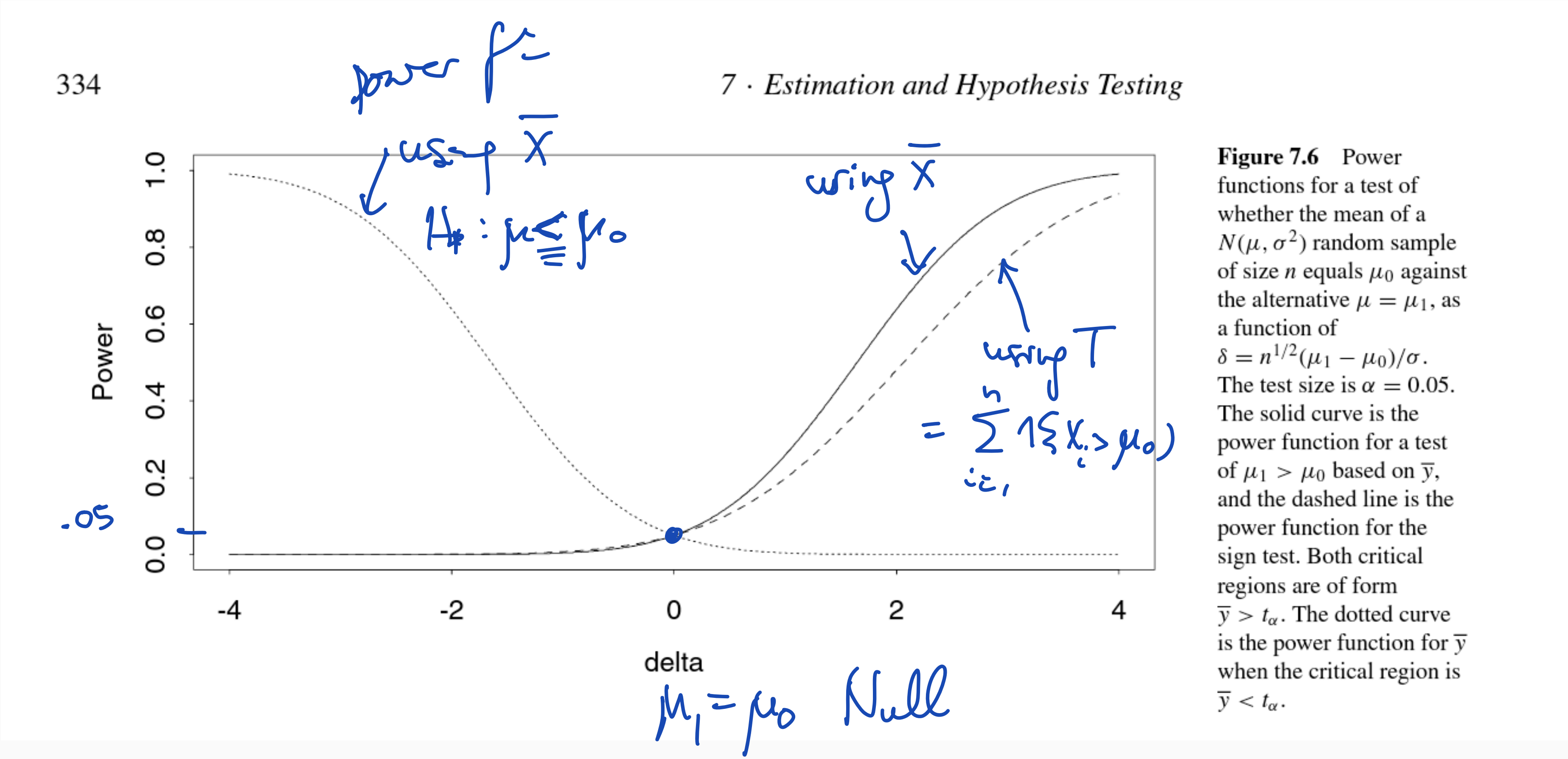
$$\underset{\sigma^2}{\mathrm{pr}_{\mu_1}}(T \geq c_\alpha) = \mathrm{pr}_{\mu_1}(T \geq n/2 - n^{1/2} z_\alpha/2) \doteq \Phi\left\{\frac{n\Phi(n^{-1/2}\delta) - n/2 + n^{1/2} z_\alpha}{[n\Phi(n^{-1/2}\delta)\{1 - \Phi(n^{-1/2}\}]}\right\}$$

$$\doteq \Phi\{z_\alpha + \delta(2/\pi)^{1/2}\}$$

- test based on $\bar{X}$ has power $\Phi(z_\alpha + \delta)$

$\left(\frac{\mu_1 - \mu_0}{\sigma}\right) = \delta$

… power of sign test



334 7 · *Estimation and Hypothesis Testing*

power f^n

using $\bar{X}$

$H_0 : \mu \leq \mu_0$

using $\bar{X}$

using T

$= \sum_{i=1}^{n} 1\{X_i > \mu_0)$

.05

$\mu_1 = \mu_0$ Null

Figure 7.6 Power functions for a test of whether the mean of a $N(\mu, \sigma^2)$ random sample of size n equals μ_0 against the alternative $\mu = \mu_1$, as a function of $\delta = n^{1/2}(\mu_1 - \mu_0)/\sigma$. The test size is $\alpha = 0.05$. The solid curve is the power function for a test of $\mu_1 > \mu_0$ based on $\bar{y}$, and the dashed line is the power function for the sign test. Both critical regions are of form $\bar{y} > t_\alpha$. The dotted curve is the power function for $\bar{y}$ when the critical region is $\bar{y} < t_\alpha$.

Permutation test

EH 4.4, AoS 10.5

leukemia data (EH): $X_1, \ldots, X_{47}$; $Y_1, \ldots, Y_{25}$

line 136

AoS Ex. 10.20

gs 1 . . - - - . . . . gs 2 . . . .

```
oneline
          ALL     ALL.1     ALL.2     ALL.3     ALL.4     ALL.5     ALL.6     ALL.7
136 0.9186952 1.634002 0.4595867 0.6379664 0.3440379 0.8614784 0.5132176 0.9790902
        ALL.8     ALL.9    ALL.10    ALL.11   ALL.12    ALL.13    ALL.14    ALL.15   ALL.16
136 0.2105782 0.8016072 0.6006949 0.3614374 1.04632 0.9697635 0.4873159 0.4976364 1.101717
       ALL.17    ALL.18    ALL.19       AML     AML.1     AML.2    AML.3     AML.4     AML.5
136 0.8563937 0.661415 0.817711 0.7671718 0.9793741 1.425479 1.074389 0.9839282 0.9859271
        AML.6     AML.7    AML.8     AML.9   AML.10    AML.11    AML.12   AML.13    ALL.20
136 0.3247027 0.7110302 1.09625 0.9675151 0.975123 0.7775957 0.9472205 1.261352 0.5679544
       ALL.21    ALL.22    ALL.23    ALL.24    ALL.25    ALL.26   ALL.27    ALL.28
136 0.8462901 0.8838616 0.7239931 0.7327029 0.7823618 0.5435396 0.832537 0.5527333
       ALL.29    ALL.30    ALL.31    ALL.32   ALL.33    ALL.34    ALL.35    ALL.36
136 0.7327029 0.5510955 0.8214005 0.6418498 0.720798 0.5830999 0.7657568 0.5262976
      ALL.37    ALL.38    ALL.39   ALL.40    ALL.41    ALL.42    ALL.43    ALL.44
136 1.466999 0.5445589 0.5725049 1.362768 0.8533535 0.8132982 0.8538596 0.5689876
       ALL.45   ALL.46    AML.14    AML.15   AML.16   AML.17    AML.18    AML.19   AML.20
136 0.6930355 1.067526 0.9677959 0.9338141 1.138926 1.161753 0.6242354 0.6590103 1.215186
       AML.21   AML.22   AML.23    AML.24
136 0.9340861 1.310376 0.771426 0.7556606
```

$\binom{72}{45}$ possible perm's

72 people

47 ALL

25 AML

one gene

$H_0 : F_X = F_Y$ $\quad$ H_1 $\quad$ $T = T(\boldsymbol{X}, \boldsymbol{Y}) =$

$F_X \neq F_Y$

$$\frac{\bar{y} - \bar{x}}{s_p \sqrt{\frac{1}{47} + \frac{1}{25}}} \sim t_{70}$$

H_0,

normal

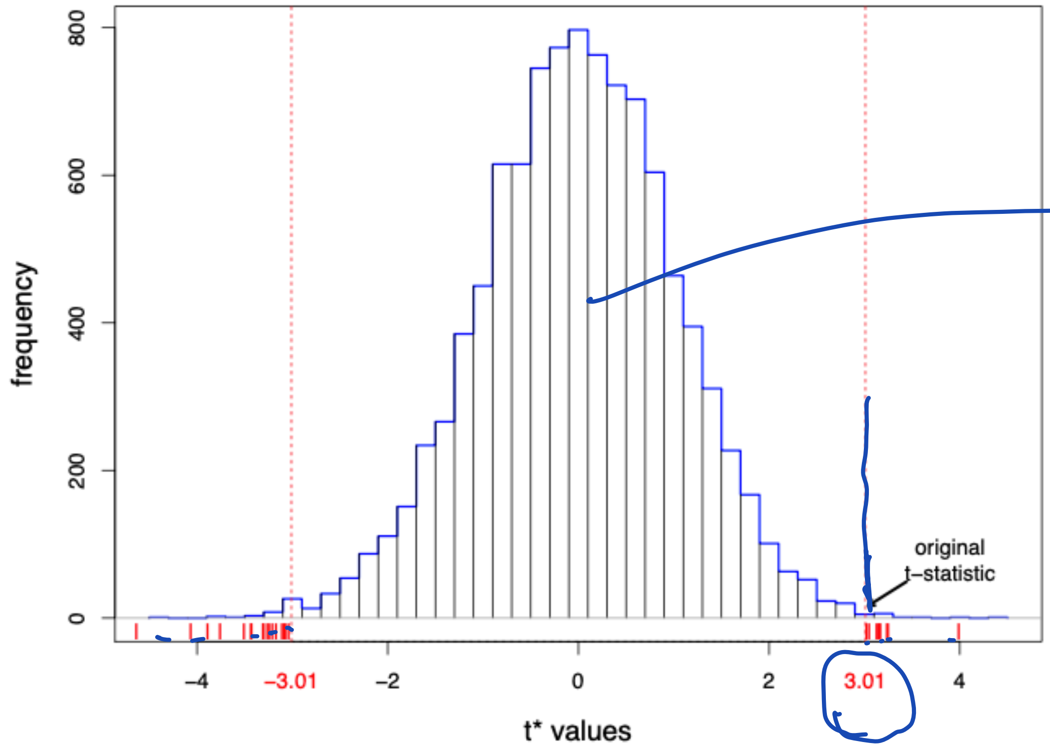


Figure 4.3 10,000 permutation t^*-values for testing ALL vs AML, for gene 136 in the **leukemia** data of Figure 1.3. Of these, 26 t^*-values (red ticks) exceeded in absolute value the observed t-statistic 3.01, giving permutation significance level 0.0026.

dist^{n} of

obs'd ~~null of~~ t, T_1

$$= (\bar{x} - \bar{y}) / s_p \left(\frac{1}{n_1} + \frac{1}{n_2}\right)^{1/2}$$

under $H_0 : F_X = F_Y$

$T_2 = \text{median}(x_i\text{'s}) - \text{med}(Y_i)$

$$\Pr(T \geq 3.01)$$

$$= \sum_{t^*} 1\{t^* \geq 3.01\}$$

AoS 10.20 uses median

Hypothesis tests and significance tests

- Hypothesis tests typically means:
  - H_0, H_1
  - critical/rejection region $R \subset \mathcal{X}$,
  - level α, power $1 - \beta$
  - conclusion: “reject H_0 at level α” or “do not reject H_0 at level α”
  - planning: maximize power for some relevant alternative

minimize type II error

Hypothesis tests and significance tests

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  - level α, power $1 - \beta$
  - conclusion: "reject H_0 at level α" or "do not reject H_0 at level α"
  - planning: maximize power for some relevant alternative

minimize type II error

- Significance tests typically means:
  - H_0,
  - test statistic T
  - observed value t^{obs},
  - p-value $p^{obs} = \Pr(T \geq t^{obs}; H_0)$ ← exact or approx.
  - alternative hypothesis often only implicit

large T points to alternative

Diagnostic testing

Wikipedia

1. Hypothesis testing

AoS Table 10.1

		H_0 not rejected	H_0 rejected
truth	H_0 true		type 1 error
	H_1 true	type 2 error $1-\beta$	—

$\Pr = \beta\ \alpha$

$\Pr = \underline{\underline{\beta}} = \text{power}$

2. Diagnostic testing

link

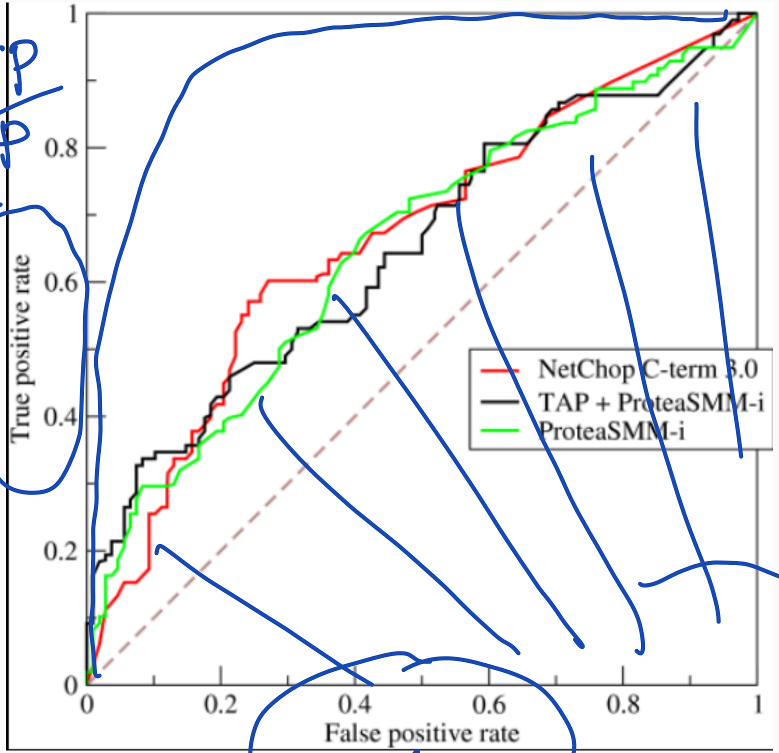
		test negative	test positive	
truth	C19 neg	TN	X FP	N
	C19 pos	FN X	TP	P

FP false pos.

TN true neg.

Diagnostic testing and ROC

$\frac{TP}{P}$



AUC

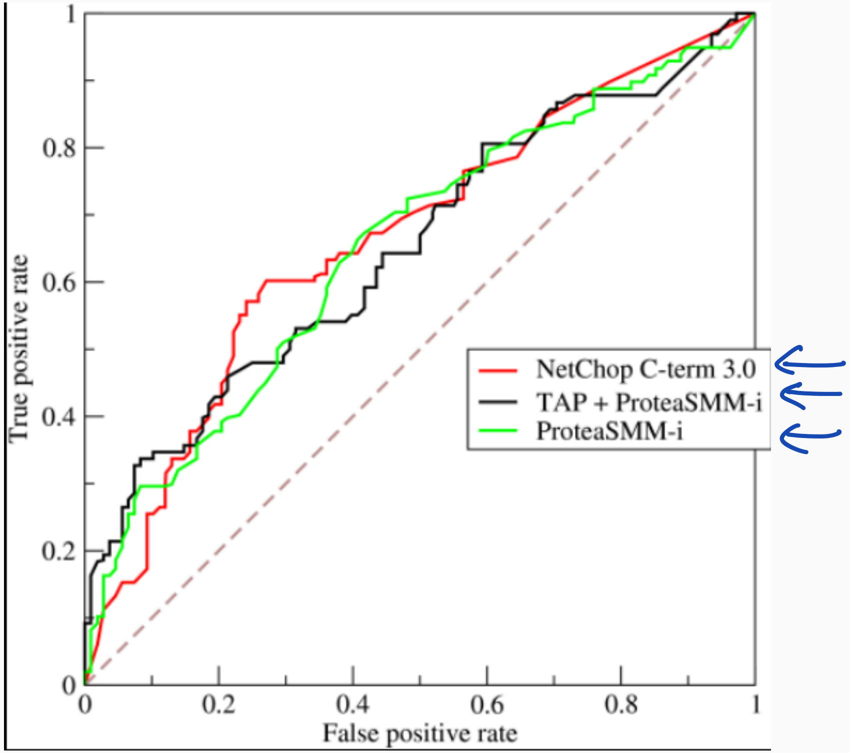
small

True positive rate = sensitivity = TP/P

False positive rate = 1− specificity = $1 - TN/N$

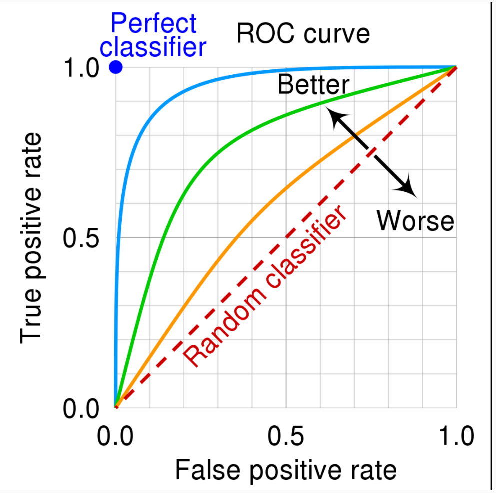
$\frac{N-TN}{N} = \frac{FP}{N}$

Diagnostic testing and ROC



True positive rate =
sensitivity =
TP/P

False positive rate =
1− specificity =
$1 - TN/N$



Covid testing

Cochrane Library, PLoS One

Rapid flow test, care home link

rapid flow

PCR

		test negative	test positive	
"truth"	C19 neg	114,993	X 101	115,094 N
	C19 pos	371 X	128	499 P

Sensitivity = TP/P = 128/499 = 0.257   26%

Specificity = TN/N = 114,993/115094 =0.999

Cochrane review

meta-analysis

“consistently high specificities”

“sensitivity varied widely: average sensitivities by brand ranged from 34.3% to 91.3% ”

Multiple testing

AoS Table 10.2

1. Hypothesis testing

AoS Table 10.1

		H_0 not rejected	H_0 rejected
truth	H_0 true		type 1 error
	H_1 true	type 2 error	

F D Rate $= E\left(\frac{V}{R}\right)$

alse

iscovery

3. Multiple testing

AoS Table 10.2

for each

		H_0 not rejected	H_0 rejected	
truth	H_0 true	U	V	m_0
	H_1 true	T	S	m_1
		$m-R$	R	m

many tests

?

large # ~1000

of all rejections how many were false

FDP, FDR

proportion

$\frac{V}{R}$

Multiple testing

EH 15.2, AoS 10.7

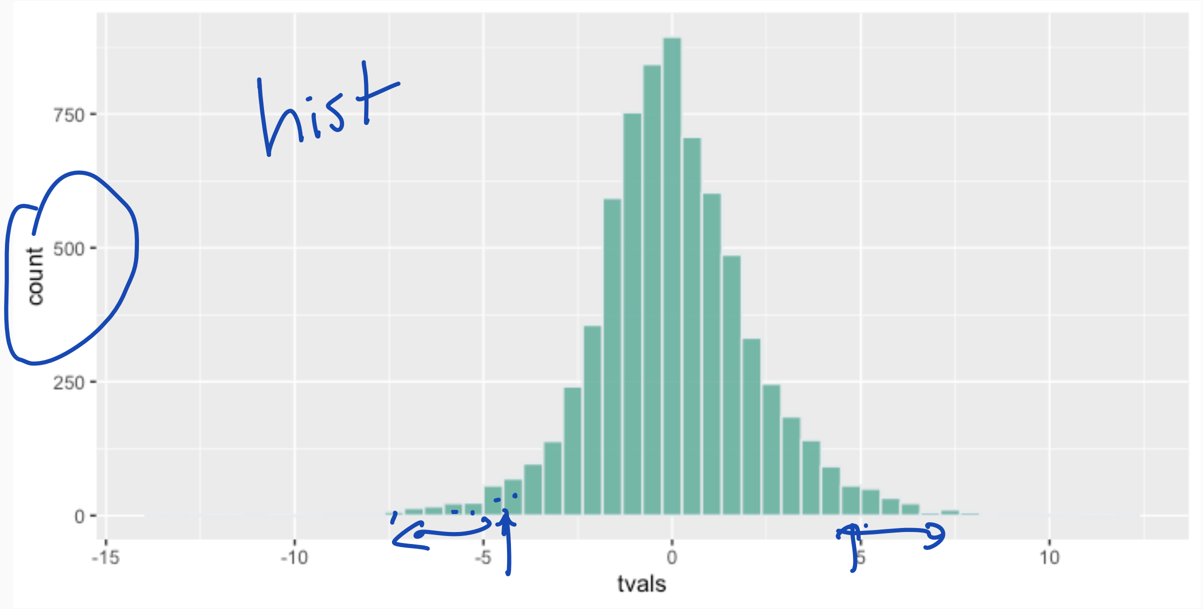
```
leukemia_big <- read.csv
  ("http://web.stanford.edu/~hastie/CASI_files/DATA/leukemia_big.csv")
  dim(leukemia_big)
  [1] 7128   72
```

- each row is a different gene; 47 AML responses and 25 ALL responses
- we could compute 7128 *t*-statistics for the mean difference between AML and ALL

```
tvals <- rep(0,7128)
for (i in 1:7128){
  leukemia_big[i,] %>% select(starts_with("ALL")) %>% as.numeric() -> x
  leukemia_big[i,] %>% select(starts_with("AML")) %>% as.numeric() -> y
  tvals[i] <- t.test(x,y,var.equal=T)$statistic
  }
```

Multiple testing

EH 1.2, 15.2



across 7128 genes

" $\overset{\cdot}{\sim} t_{70}$ "

```
summary(tvals)
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
-13.52611  -1.20672  -0.08406   0.02308   1.20886  12.26065
```

Multiple testing

- H_{0i} versus H_{1i}, $\quad i = 1, \ldots, m = 7128$
- p-values $p_1, \ldots, p_m$ ←
- Bonferroni method: reject H_{0i} if $p_i < \alpha/m$ $\qquad \frac{.05}{7128} = 7 \times 10^{-6}$ FWER
- pr(any H_0 falsely rejected) $\leq \alpha$ very conservative

Multiple testing

EH 15.2, AoS 10.7

- H_{0i} versus $H_{1i}, \quad i = 1, \dots, m$
- p-values $p_1, \dots, p_m$
- Bonferroni method: reject H_{0i} if $p_i < \alpha/m$
- $\mathrm{pr}(\text{any } H_0 \text{ falsely rejected }) \leq \alpha$

FWER

very conservative

- FDR method controls the number of rejections that are false

FDP = V/R

		H_0 not rejected	H_0 rejected	
truth	H_0 true	U	V	m_0
	H_1 true	T	S	m_1
		$m - R$	R	m

$FDR = \mathrm{E}(FDP)$

Benjamini-Hochberg

AoS 10.7; EH 15.2

- order the p-values $p_{(1)}, \ldots, p_{(m)}$
- find i_{max}, the largest index for which

$$p_{(\underline{i})} \leq \frac{i}{m}q$$

“type 1 error”

- Let BH_q be the rule that rejects $\underline{H_{0i} \text{ for } i \leq i_{max}}$, not rejecting otherwise

Benjamini-Hochberg

AoS 10.7; EH 15.2

- order the p-values $p_{(1)}, \ldots, p_{(m)}$
- find i_{max}, the largest index for which

$$p_{(i)} \leq \frac{i}{m} q$$

- Let BH_q be the rule that rejects $\underline{H_{0i} \text{ for } i \leq i_{max}}$, not rejecting otherwise
- **Theorem**: If the p-values corresponding to valid null hypotheses are independent of each other, then

$$FDR(BH_q) = \pi_0 q \leq q, \qquad \text{where } \pi_0 = \overset{\text{true null}}{m_0} / m \text{ \# tests}$$

π_0 unknown but close to 1

- $\underline{\text{change the bound under dependence}}$

$$p_{(i)} \leq \frac{i}{mC_m} q \qquad C_m = \sum_{i=1}^{m} \frac{1}{i}$$

Example

index	1	2	3	4	5	6	7	8	9	10
pval	0.00017	0.00448	0.00671	0.00907	0.01220	0.33626	0.3934	0.5388	0.5813	0.9862
cut1	0.00500	0.01000	0.01500	0.02000	0.02500	0.03000	0.0350	0.0400	0.0450	0.0500
cut2	0.00171	0.00341	0.00512	0.00683	0.00854	0.01024	0.0119	0.0137	0.0154	0.0171

$\frac{\alpha k}{10}$

Bonfer.

FDR cutoff.

$\leq .01$

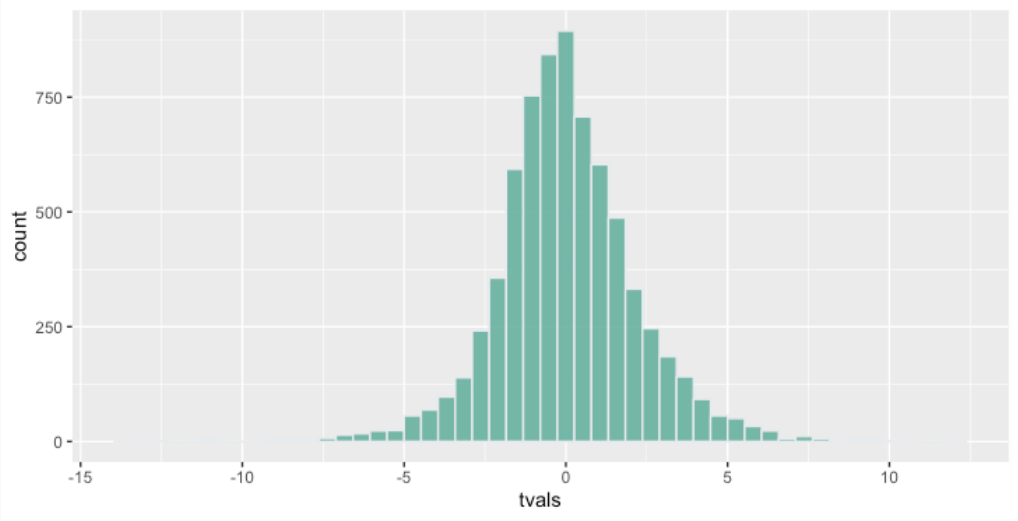
$> .01$

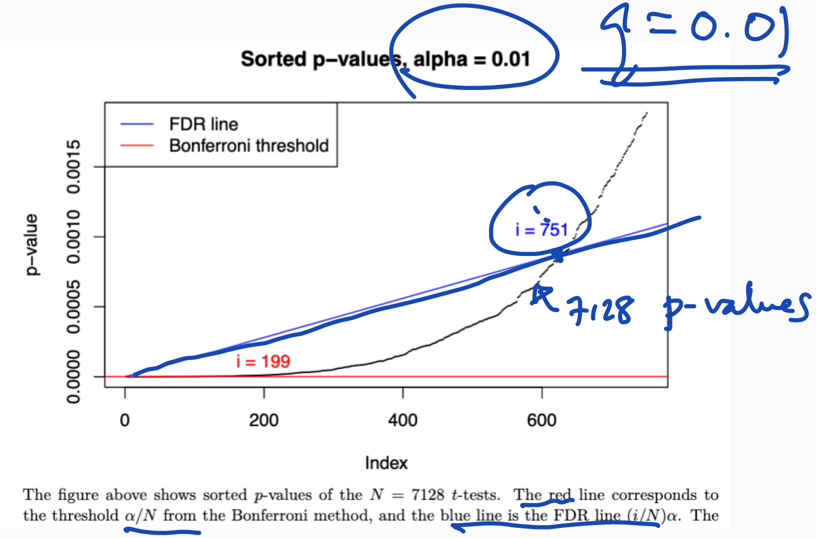
1st 5 tests are "signif" using FDR of .01

$\frac{\alpha}{m}$ Bonferroni

Multiple testing

EH 1.2, 15.2





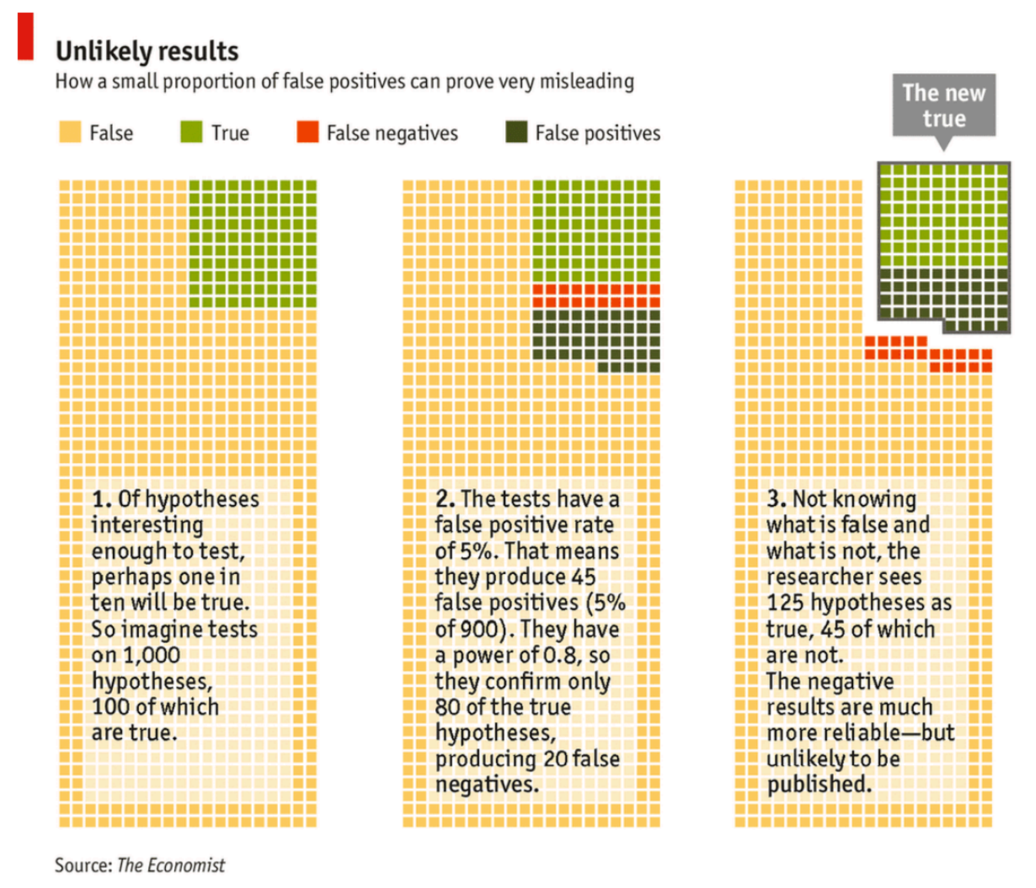
q = 0.01

7128 p-values

The figure above shows sorted p-values of the $N = 7128$ t-tests. The red line corresponds to the threshold α/N from the Bonferroni method, and the blue line is the FDR line $(i/N)\alpha$. The

```
> summary(ttest)
     Min.   1st Qu.    Median      Mean   3rd Qu.      Max.
-13.52611  -1.20672  -0.08406   0.02308   1.20886  12.26065
```

Multiple testing



Unlikely results

How a small proportion of false positives can prove very misleading

1. Of hypotheses interesting enough to test, perhaps one in ten will be true. So imagine tests on 1,000 hypotheses, 100 of which are true.

2. The tests have a false positive rate of 5%. That means they produce 45 false positives (5% of 900). They have a power of 0.8, so they confirm only 80 of the true hypotheses, producing 20 false negatives.

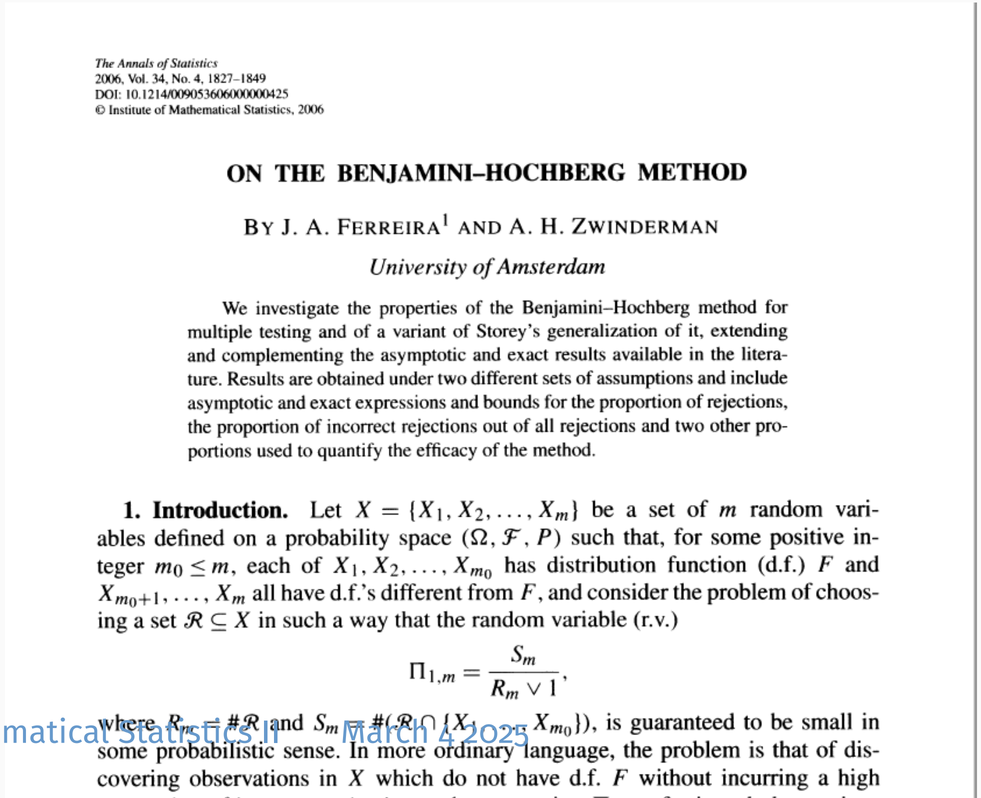
3. Not knowing what is false and what is not, the researcher sees 125 hypotheses as true, 45 of which are not. The negative results are much more reliable—but unlikely to be published.

Source: *The Economist*

Benjamini-Hochberg proof →1985

Theorem: If the p-values corresponding to valid null hypotheses are independent of each other, then

$$FDR(BH_q) = \pi_0 q \leq q, \qquad \text{where } \pi_0 = m_0/m$$



The Annals of Statistics
2006, Vol. 34, No. 4, 1827–1849
DOI: 10.1214/009053606000000425

ON THE BENJAMINI–HOCHBERG METHOD

By J. A. Ferreira[1] and A. H. Zwinderman

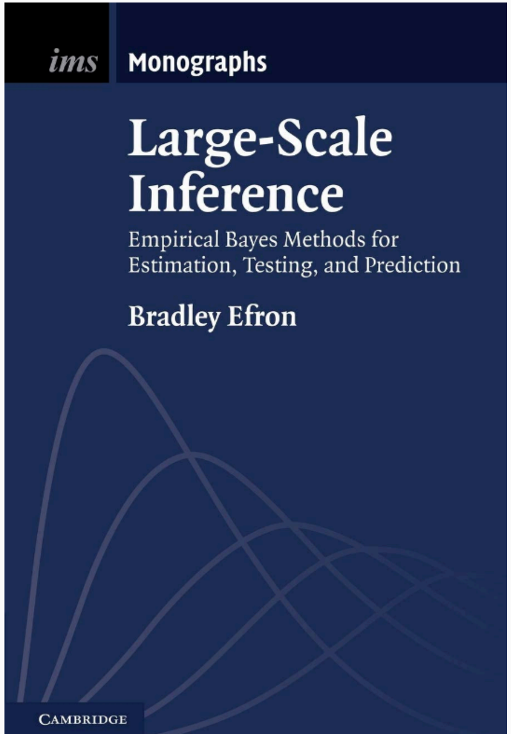
University of Amsterdam

We investigate the properties of the Benjamini–Hochberg method for multiple testing and of a variant of Storey's generalization of it, extending and complementing the asymptotic and exact results available in the literature. Results are obtained under two different sets of assumptions and include asymptotic and exact expressions and bounds for the proportion of rejections, the proportion of incorrect rejections out of all rejections and two other proportions used to quantify the efficacy of the method.

1. Introduction. Let $X = \{X_1, X_2, \ldots, X_m\}$ be a set of m random variables defined on a probability space $(\Omega, \mathcal{F}, P)$ such that, for some positive integer $m_0 \leq m$, each of $X_1, X_2, \ldots, X_{m_0}$ has distribution function (d.f.) F and $X_{m_0+1}, \ldots, X_m$ all have d.f.'s different from F, and consider the problem of choosing a set $\mathcal{R} \subseteq X$ in such a way that the random variable (r.v.)

$$\Pi_{1,m} = \frac{S_m}{R_m \vee 1},$$

where $R_m = \#\mathcal{R}$ and $S_m = \#(\mathcal{R} \cap \{X_1, \ldots, X_{m_0}\})$, is guaranteed to be small in some probabilistic sense. In more ordinary language, the problem is that of discovering observations in X which do not have d.f. F without incurring a high



ims Monographs

Large-Scale Inference

Empirical Bayes Methods for Estimation, Testing, and Prediction

Bradley Efron

Cambridge

Multinomial goodness of fit tests

MS 9.2; AoS 10.8

- $X_1, \dots, X_n$ i.i.d.
- $H_0 : X_i \sim f(x; \theta)$; $\quad H_1 : X_i$ arbitrary distribution
- Define k sets $A_1, \dots, A_k$ s.t.

$$\mathrm{pr}(X_i \in \cup_{j=1}^{k} A_j\} = 1$$

- Define

$$Y_j = \sum_{i=1}^{n} 1\{X_i \in A_j\}$$

number of obs in category j

Multinomial goodness of fit tests

- $X_1, \ldots, X_n$ i.i.d.
- $H_0 : X_i \sim f(x; \theta)$; $\quad H_1 : X_i$ arbitrary distribution
- Define k sets $A_1, \ldots, A_k$ s.t.

$$\mathrm{pr}(X_i \in \cup_{j=1}^{k} A_j\} = 1$$

- Define

$$Y_j = \sum_{i=1}^{n} 1\{X_i \in A_j\}$$

number of obs in category j

- $Y = (Y_1, \ldots, Y_k) \sim Mult_k(n; p)$
- $\mathrm{pr}(Y_1 = y_1, \ldots, Y_k = y_k; p) =$
- $H_0 : p = p(\theta)$; $\quad H_1 : p$ arbitrary

Multinomial goodness of fit tests

MS 9.2, AoS 10.8

- log-likelihood function

- generalized likelihood ratio test

Multinomial goodness of fit tests

- log-likelihood function

- generalized likelihood ratio test

- Theorem 9.1 (MS): Under H_0

$p = \dim(\theta)$

$$W = 2\sum_{j=1}^{k} Y_j \log\left(\frac{Y_j}{np_j(\tilde{\theta})}\right) \xrightarrow{d} \chi^2_{k-1-p}$$

Multinomial goodness of fit tests

- log-likelihood function

- generalized likelihood ratio test

- Theorem 9.1 (MS): Under H_0

$p = \dim(\theta)$

$$W = 2\sum_{j=1}^{k} Y_j \log\left(\frac{Y_j}{np_j(\tilde{\theta})}\right) \xrightarrow{d} \chi^2_{k-1-p}$$

- Theorem 92. (MS): Under H_0

$$Q = \sum_{j=1}^{k} \frac{\{Y_j - np_j(\hat{\theta})\}^2}{np_j(\hat{\theta})} \xrightarrow{d} \chi^2_{k-1-p}$$

Multinomial goodness-of-fit tests

AoS 10.8; MS 9.2

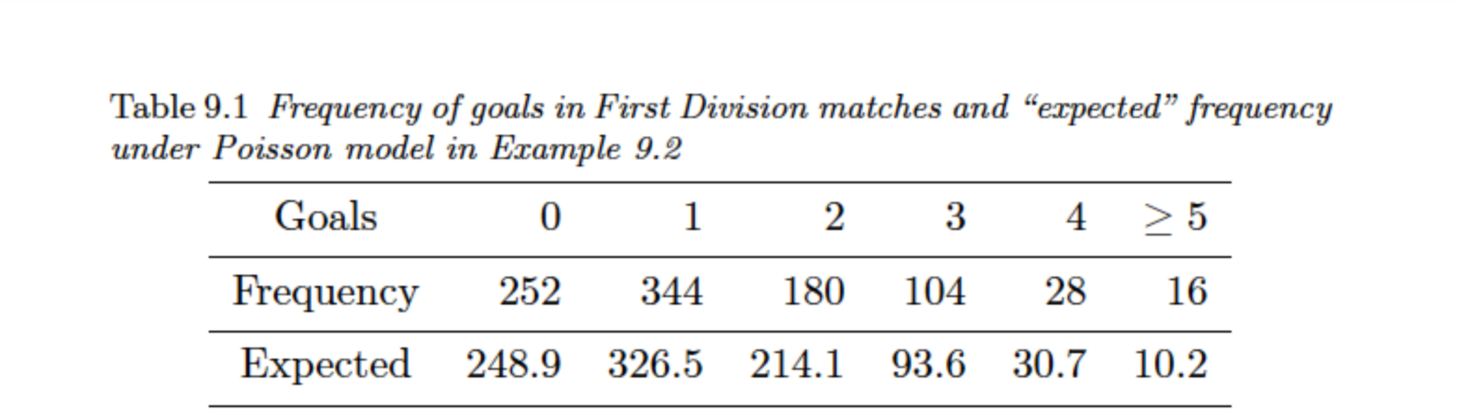


Table 9.1 *Frequency of goals in First Division matches and "expected" frequency under Poisson model in Example 9.2*

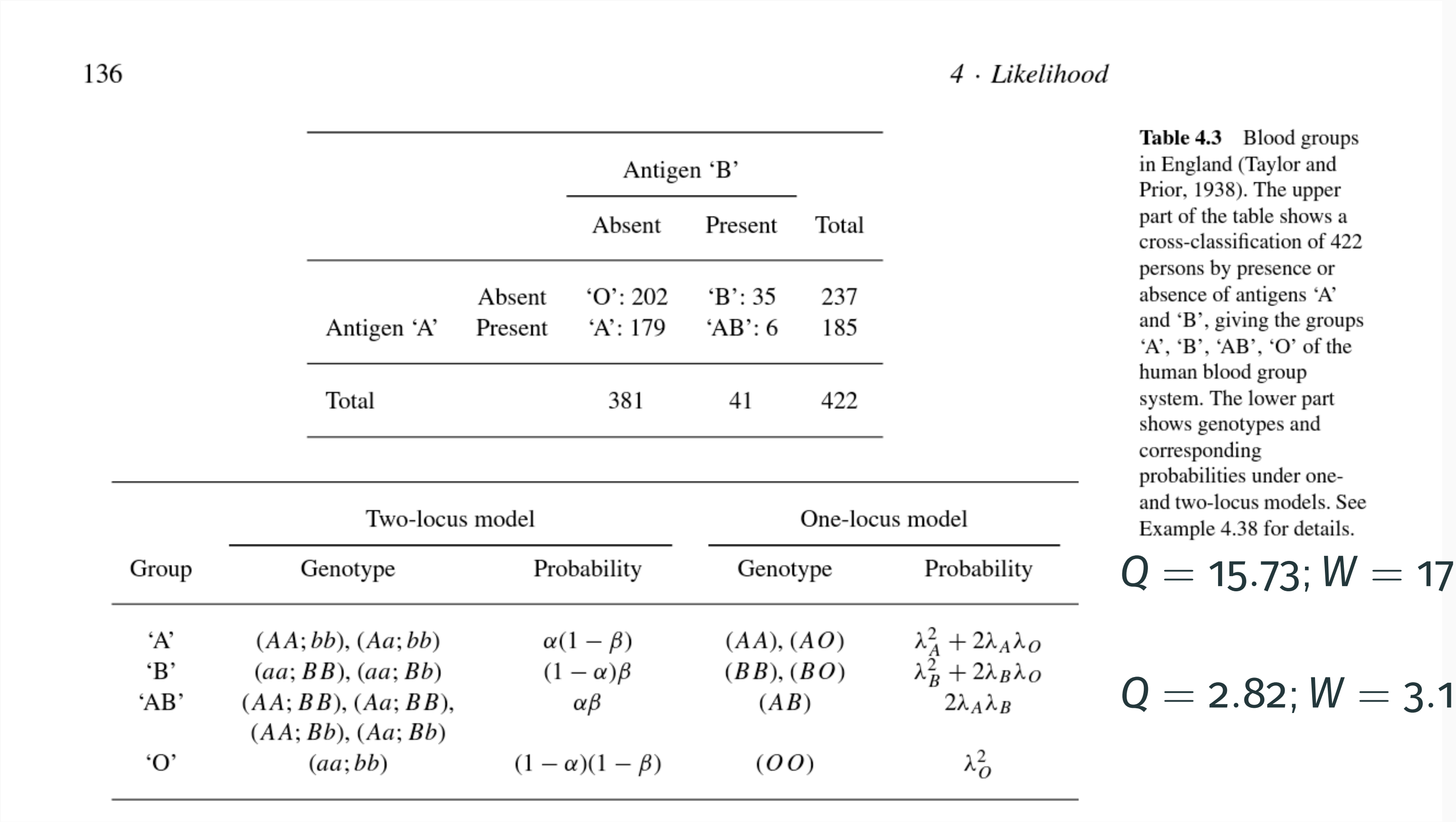
Goals	0	1	2	3	4	≥ 5
Frequency	252	344	180	104	28	16
Expected	248.9	326.5	214.1	93.6	30.7	10.2

$$p_0(\lambda) = 1 - \sum_{j=0}^{4} p_j(\lambda); \quad p_j(\lambda) = e^{-\lambda}\lambda^j/j!, \quad \tilde{\lambda} = 1.3118$$

$$Q = 11.09; \quad W = 10.87; \quad \mathrm{pr}(\chi_4^2 > [11.09, 10.87]) = [0.026, 0.028]$$

Multinomial goodness-of-fit tests

SM Ex 4.38



136 4 · *Likelihood*

		Antigen 'B'		
		Absent	Present	Total
	Absent	'O': 202	'B': 35	237
Antigen 'A'	Present	'A': 179	'AB': 6	185
Total		381	41	422

	Two-locus model		One-locus model	
Group	Genotype	Probability	Genotype	Probability
'A'	$(AA; bb)$, $(Aa; bb)$	$\alpha(1-\beta)$	(AA), (AO)	$\lambda_A^2 + 2\lambda_A\lambda_O$
'B'	$(aa; BB)$, $(aa; Bb)$	$(1-\alpha)\beta$	(BB), (BO)	$\lambda_B^2 + 2\lambda_B\lambda_O$
'AB'	$(AA; BB)$, $(Aa; BB)$, $(AA; Bb)$, $(Aa; Bb)$	$\alpha\beta$	(AB)	$2\lambda_A\lambda_B$
'O'	$(aa; bb)$	$(1-\alpha)(1-\beta)$	(OO)	λ_O^2

Table 4.3 Blood groups in England (Taylor and Prior, 1938). The upper part of the table shows a cross-classification of 422 persons by presence or absence of antigens 'A' and 'B', giving the groups 'A', 'B', 'AB', 'O' of the human blood group system. The lower part shows genotypes and corresponding probabilities under one- and two-locus models. See Example 4.38 for details.

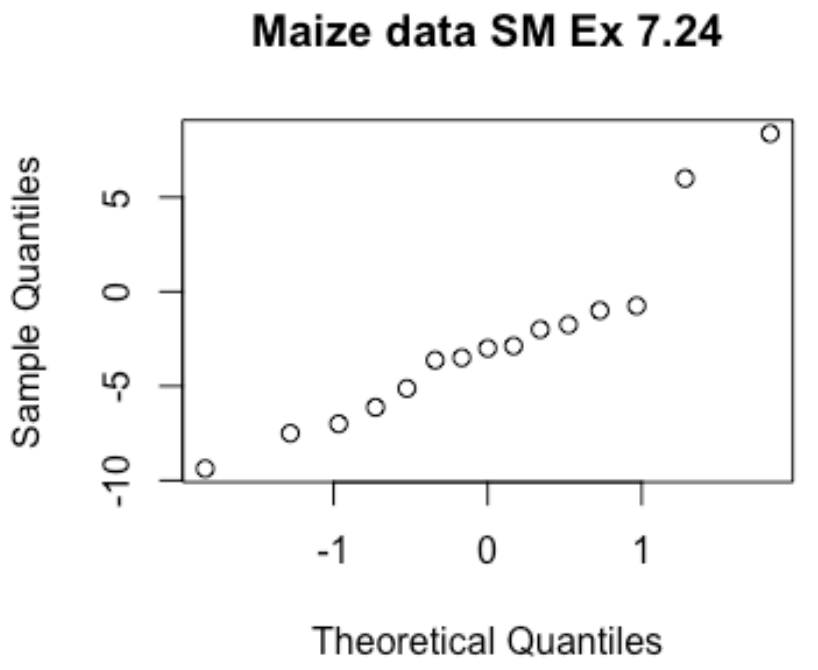
$Q = 15.73$; $W = 17.66$ (two-locus)

$p < 10^{-5}$

$Q = 2.82$; $W = 3.17$ (single locus)

$p = 0.09; 0.07$

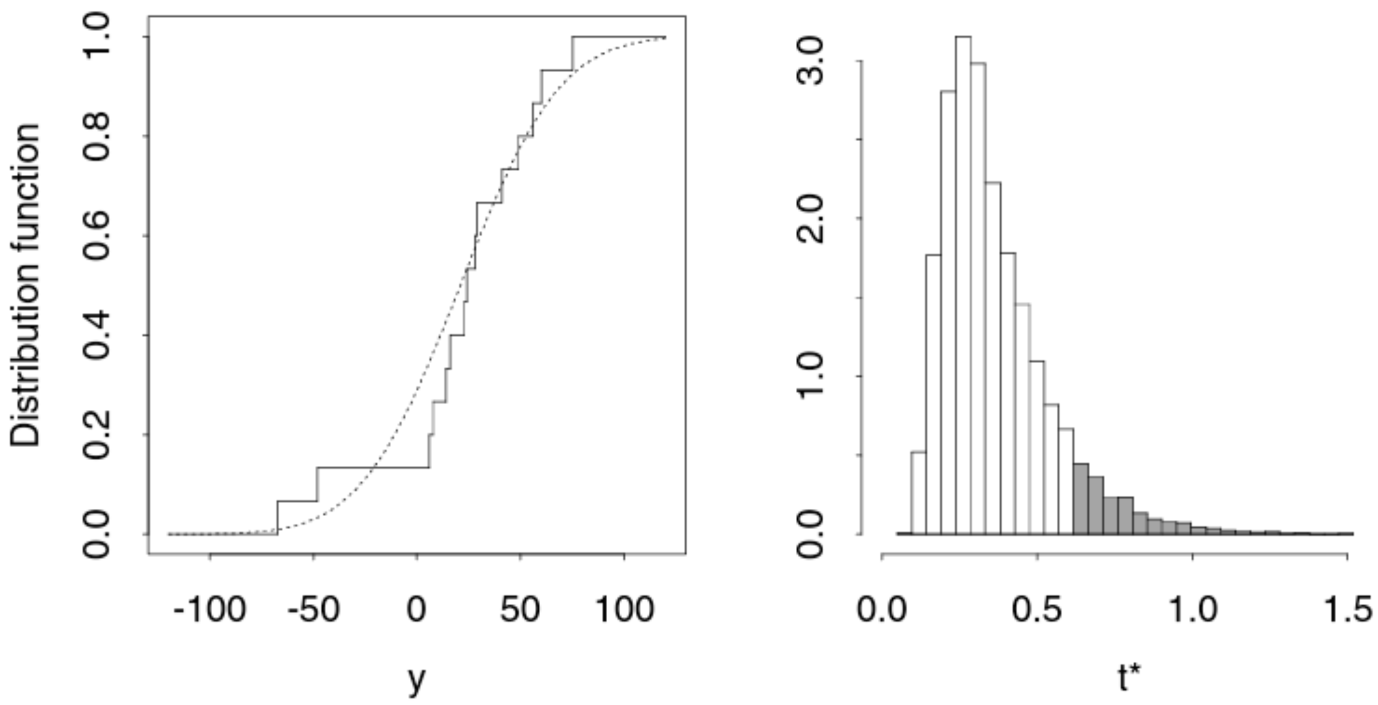
Smooth goodness-of-fit tests



```
library(SMPracticals)
data(darwin)
cross <- seq(1,30,by=2)
self <- cross+1
diffs <- darwin[self,4]-darwin[cross,4]
qqnorm(diffs)
```

Smooth goodness-of-fit tests

Figure 7.5 Analysis of maize data. Left: empirical distribution function for height differences, with fitted normal distribution (dots). Right: null density of Anderson–Darling statistic T for normal samples of size $n = 15$ with location and scale estimated. The shaded part of the histogram shows values of T^* in excess of the observed value t_{obs}.



SM Example 7.24 testing $N(\mu, \sigma^2)$ distribution

Smooth goodness-of-fit tests

MS 9.3, SM p.327-9

- $X_1, \ldots, X_n \quad i.i.d. \quad F(\cdot); \quad H_0 : F = F_0$

cumulative d.f.

- $\widehat{F}_n(t) = \frac{1}{n}\sum_{i=1}^{n} 1\{X_i \leq t\}$

- three test statistics:
  1. $\sup_t |\widehat{F}_n(t) - F_0(t)|$
  2. $\int \{\widehat{F}_n(t) - F_0(t)\}^2 dF_0(t)$
  3. $\displaystyle\int \frac{\{\widehat{F}_n(t) - F_0(t)\}^2}{F_0(t)\{1 - F_0(t)\}} dF_0(t)$

- SM Example 7.24 testing $N(\mu, \sigma^2)$ distribution
- SM Example 7.23; 6.14 testing $U(0, 1)$ distribution

Smooth goodness-of-fit tests

- Special case $H_0 : F(t) = F_0(t) = t$ $X_i \sim U(0,1)$
- Recall

$$E_0\{\widehat{F}_n(t)\} = F_0(t) = t, \quad \text{var}\{\widehat{F}_n(t)\} = t(1-t)/n$$

- What about distribution of

$$\sup_t |\widehat{F}_n(t) - t| \qquad \int \{\widehat{F}_n(t) - t\}^2 dt \qquad \int \frac{\{\widehat{F}_n(t) - t\}^2}{F_0(t)\{1-t\}} dt$$

- need joint density of $\widehat{F}_n(t)\ \forall\ t$

Smooth goodness-of-fit tests

MS 9.3

- Special case $H_0 : F(t) = F_0(t) = t$ $X_i \sim U(0,1)$
- Recall

$$E_0\{\widehat{F}_n(t)\} = F_0(t) = t, \quad \text{var}\{\widehat{F}_n(t)\} = t(1-t)/n$$

- What about distribution of

$$\sup_t |\widehat{F}_n(t) - t| \qquad \int\{\widehat{F}_n(t) - t\}^2 dt \qquad \int \frac{\{\widehat{F}_n(t) - t\}^2}{F_0(t)\{1-t\}} dt$$

- need joint density of $\widehat{F}_n(t) \,\forall\, t$
- define stochastic process $B_n(t) = \sqrt{n}(\widehat{F}_n(t) - t)$
- vector $(B_n(t_1), \dots, B_n(t_k)) \xrightarrow{d} N_k(0, C), \quad C_{ij} = \min(t_i, t_j) - t_i t_j$ MS 9.3
- a Brownian bridge is a continuous function on $(0,1)$

  with all finite-dimensional distributions as above

Smooth goodness-of-fit tests

- Kolmogorov-Smirnov test

$$K_n = \sup_{0 \leq t \leq 1} |B_n(t)|$$

- Cramer-vonMises test

$$W_n^2 = \int_0^1 B_n^2(t) dt$$

- Anderson-Darling test

$$A_n^2 = \int_0^1 \frac{B_n^2(t)}{t(1-t)} dt$$

Smooth goodness-of-fit tests

- Kolmogorov-Smirnov test

$$K_n = \sup_{0 \le t \le 1} |B_n(t)|$$

- Cramer-vonMises test

$$W_n^2 = \int_0^1 B_n^2(t) dt$$

- Anderson-Darling test

$$A_n^2 = \int_0^1 \frac{B_n^2(t)}{t(1-t)} dt$$

- limit theorems

$$K_n \xrightarrow{d} K, \qquad W_n^2 \xrightarrow{d} \sum_{j=1}^{\infty} \frac{Z_j^2}{j^2\pi^2}, \qquad A_n^2 \xrightarrow{d} \sum_{j=1}^{\infty} \frac{Z_j^2}{j(j+1)}$$

$\mathrm{pr}(K > x) = 2\sum_{j=1}^{\infty}(-1)^{j+1}\exp(-2j^2x^2)$

Smooth goodness-of-fit tests

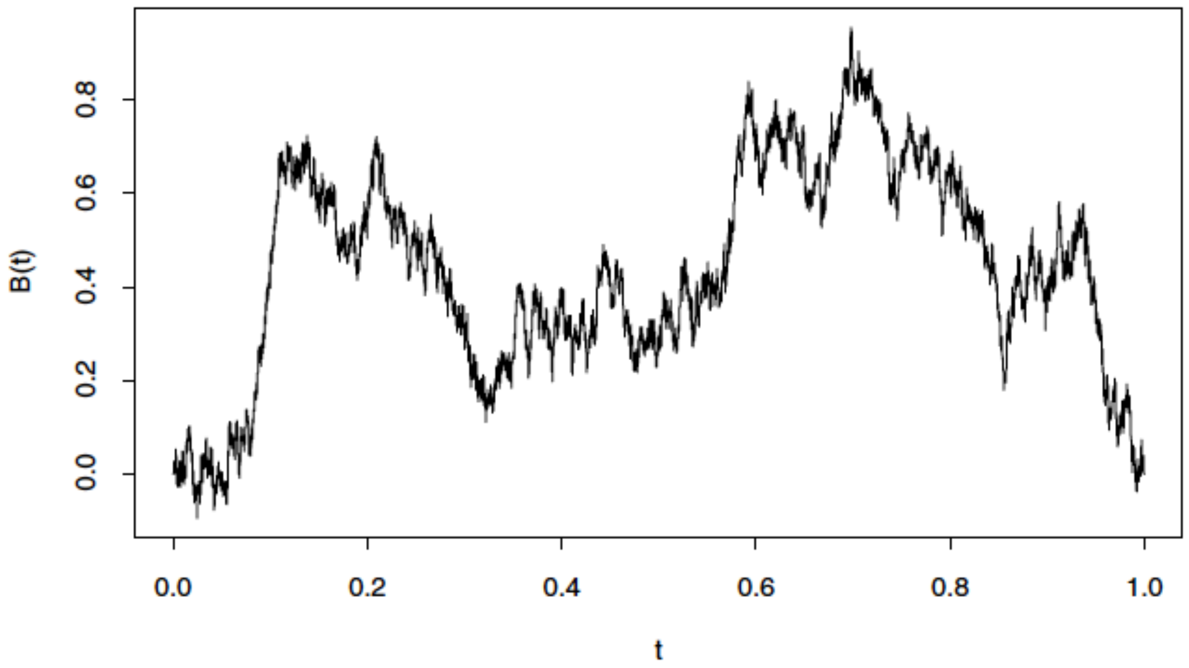


Figure 9.1 *A simulated realization of a Brownian bridge process.*