Hypothesis Testing, Power, Sample Size and Confidence Intervals (Part 1)

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Outline

Introduction

- Goal of hypothesis testing is to rule out chance as an explanation for an observed effect
- Example: Cholesterol lowering medications
  - 25 people treated with a statin and 25 with a placebo
  - Average cholesterol after treatment is 180 with statins and 200 with placebo.
- Do we have sufficient evidence to suggest that statins lower cholesterol?
- Can we be sure that statin use as opposed to a chance occurrence led to lower cholesterol levels?

Hypotheses

- Scientific Hypotheses
  - Often involve estimation of a quantity of interest
  - After amputation, to what extent does treatment with clonidine lead to lower rates of phantom limb pain than with standard therapy? (Difference or ratio in rates)
  - What is the average increase in alanine aminotransferase (ALT) one month after doubling the dose of medication X? (Difference in means)
- Statistical Hypothesis
  - A statement to be judged. Usually of the form: population parameter X is equal to a specified constant
  - Population mean potassium K, $\mu = 4.0$ mEq/L
  - Difference in population means, $\mu_1 - \mu_2 = 0.0$ mEq/L

Statistical Hypotheses

- Null Hypothesis: H_0
  - A straw man; something we hope to disprove
  - It is usually is a statement of no effects.
  - It can also be of the form $H_0: \mu =$constant, or H_0: probability of heads equal 1/2.
- Alternative Hypothesis: H_A
  - What you expect to favor over the null
- If H_0 : Mean K value = 3.5 mEq/L
  - One sided alternative hypothesis: H_A : Mean K $>$ 3.5 mEq/L
  - Two-sided alternative hypothesis: H_A : Mean K $\neq$ 3.5 mEq/L (values far away from the null)

Classical (Frequentist) Statistics

- Emphasizes hypothesis testing
- Begin by assuming H_0 is true
- Examines whether data are consistent with H_0
- Proof by contradiction
  - If, under H_0, the data are strange or extreme, then doubts are cast on the null.
- Evidence is summarized with a single statistic which captures the tendency of the data.
- The statistic is compared to the parameter value given by H_0

Classical (Frequentist) Statistics

- **p-value**: Under the assumption that H_0 is true, it is the probability of getting a statistic as or more in favor of H_A over H_0 than was observed in the data.
- Low p-values indicate that if H_0 is true, we have observed an improbable event.
- Mount evidence against the null, and when sufficient, reject H_0.
- **NOTE:** Failing to reject H_0 does not mean we have gathered evidence in favor of it (i.e., absence of evidence does not imply evidence of absence)
  - There are many reasons for not rejecting H_0 (e.g., small samples, inefficient designs, imprecise measurements, etc.)

Classical (Frequentist) Statistics

- Clinical significance is ignored.
- Parametric statistics: assumes the data arise from a certain distribution, often a normal or Gaussian.
- Non-parametric statistics: does not assume a distribution and usually looks at ranks rather than raw values.

Bayesian Statistics

- We can compute the probability that a statement, that is of clinical significance, is true
  - Given the data we observed, does medication X lower the mean cholesterol by more than 10 units?
- May be more natural than the frequentist approach, but it requires a lot more work.
- Supported by decision theory:
- Begin with a (prior) belief $\rightarrow$ learn from your data $\rightarrow$ Form a new (posterior) belief that combines the prior belief and the new data
- We can then formally integrate information accrued from other studies as well as from skeptics.
- Becoming more popular.

Errors in Hypothesis Testing

- Type 1 error: Reject H_0 when it is true
  - Significance level (α) or Type 1 error rate: is the probability of making this type of error
  - This value is usually set to 0.05 for random reasons
- Type 2 error: Failing to reject H_0 when it is false
  - The value β is the probability of a type 2 error or type 2 error rate.
- Power: $1 - \beta$: probability of correctly rejecting H_0 when it is false

	State of H_0	
Decision	H_0 is true	H_0 is false
Do not reject H_0	Correct	Type 2 error (β)
Reject H_0	Type 1 error (α)	Correct

Notes Regarding Hypothesis Testing

- Two schools of thought
  - Neyman-Pearson: Fix Type 1 error rate (say $\alpha = 0.05$) and then make the binary decision, reject/do not reject
  - Fisher: Compute the p-value and quote the report in the publication.
  - We favor Fisher, but Neyman-Pearson is used all of the time.
- Fisher approach: discussion of p-values does not require discussion of type 1 and type 2 errors
  - Assume the sample was chosen randomly from a population whose parameter value is captured by H_0. The p-value is a measure of evidence against it.
- Neyman-Pearson approach: having to make a binary call (reject vs do not reject) regarding significance is arbitrary
  - There is nothing magical about 0.05
  - Statistical significance has nothing to do with clinical significance

One sample test for the mean

- Assumes the sample is drawn from a population where values are normally distributed (normality is actually not necessary)
- One sample tests for mean $\mu = \mu_0$ (constant) don't happen very often except when data are paired (to be discussed later)
- The t-test is based on the t-statistic

$$t = \frac{\text{estimated value - hypothesized value}}{\text{standard deviation of numerator}}$$

- Standard deviation of a summary statistic is called the **standard error** which is the square root of the variance of the statistic

One sample test for the mean

- Sample average: $\overline{x} = \frac{1}{n}\sum_{i=1}^{n} x_i$
  - The estimate of the population mean based on the observed sample
- Sample variance: $s^2 = \frac{1}{n-1}\sum_{i=1}^{n}(x_i - \overline{x})^2$
- Sample standard deviation: $s = \sqrt{s^2}$
- $H_0 : \ \mu = \mu_0$ vs. $H_A : \ \mu \neq \mu_0$
- One sample t-statistic

$$t = \frac{\overline{x} - \mu_0}{SE}$$

- Standard error of the mean, SE $= \frac{s}{\sqrt{n}}$

One sample t-test for the mean

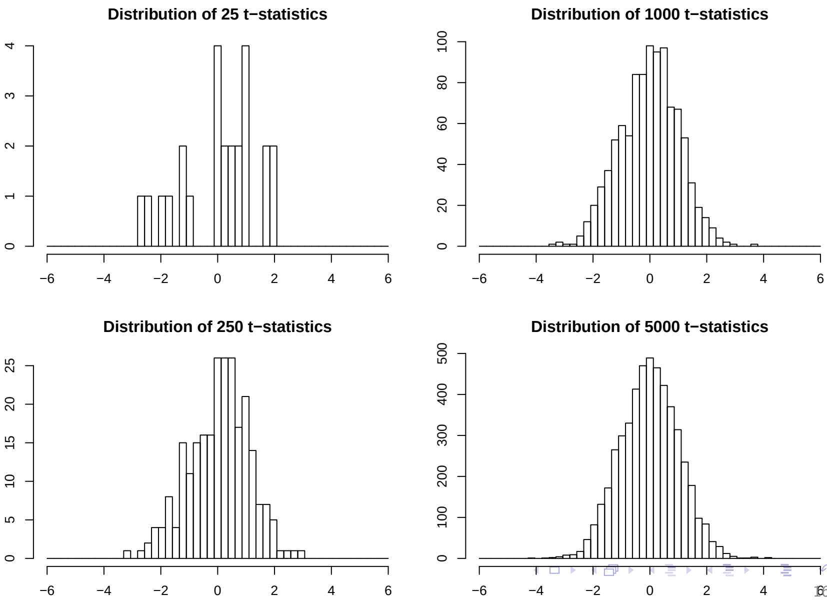
- When data come from a normal distribution and H_0 holds, the t ratio follows the $t-$ distribution. What does that mean?
- Draw a sample from the population, conduct the study and calculate the t-statistic.
- Do it again, and calculate the t-statistic again.
- Do it again and again.
- Now look at the distribution of all of those t-statistics.
- This tells us the relative probabilities of all t-statistics if H_0 is true.

Example: one sample t-test for the mean

- The distribution of potassium concentrations in the target population are normally distributed with mean 4.3 and variance .1: N(4.3, .1).
- $H_0: \ \mu = 4.3$ vs. $H_A: \ \mu \neq 4.3$. Note that H_0 is true!
- Each time the study is done,
  - Sample 100 participants
  - Calculate:

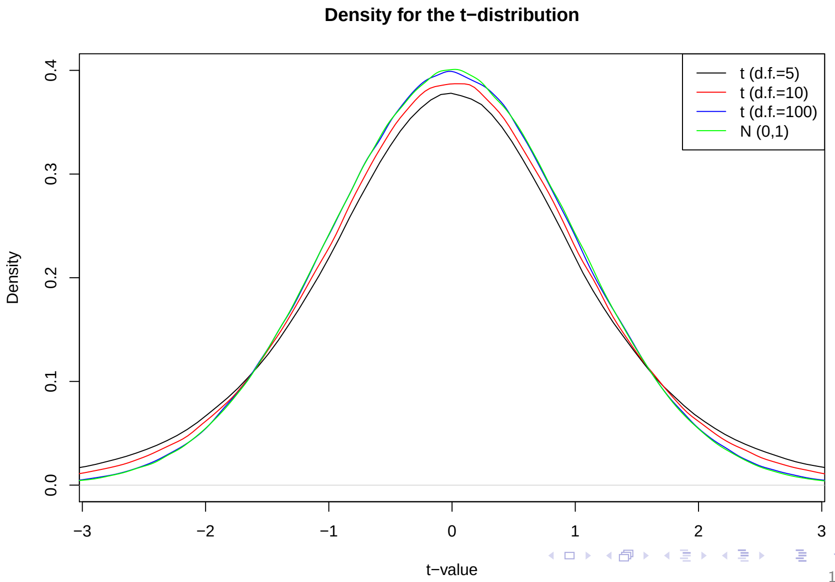
$$t = \frac{\overline{x} - 4.3}{SE}$$

- Conduct the study 25 times, 250 times, 1000 times, 5000 times


Distribution of 25 t−statistics
Distribution of 1000 t−statistics
Distribution of 250 t−statistics
Distribution of 5000 t−statistics
−6
−4
−2
0
2
4
6

One sample t-test for the mean

- With very small samples (n), the t statistic can be unstable because the sample standard deviation (s) is not a precise estimate of the population standard deviation (σ).
- So, the t-statistic has heavy tails for small n
- As n increases, the t-distribution converges to the normal distribution with mean equal to 0 and with standard deviation equal to one.
- The parameter defining the particular t-distribution we use (function of n) is called the degrees of freedom or d.f.
- d.f. $=$ n - number of means being estimated
- For the one-sample problem, d.f.=n-1
- Symbol is t_{n-1}

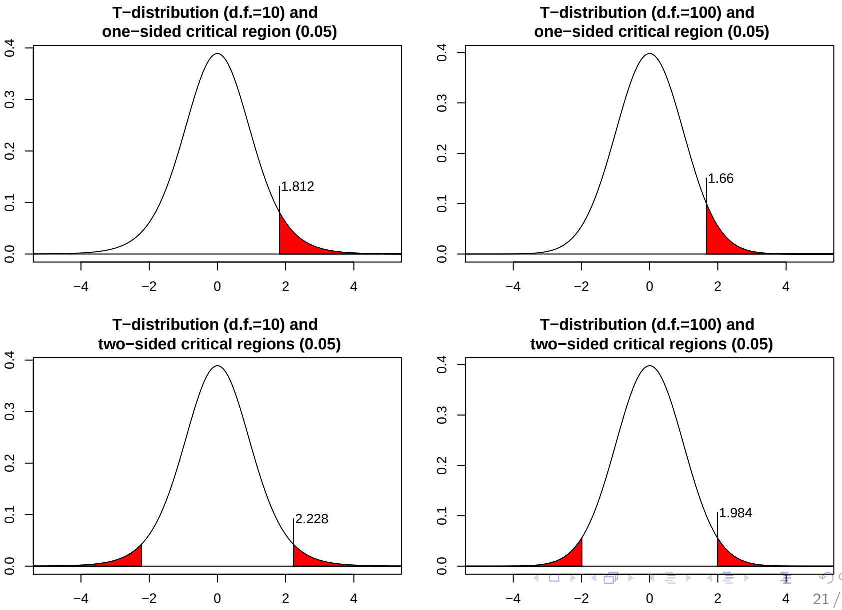

Density for the t−distribution
t (d.f.=5)
t (d.f.=10)
t (d.f.=100)
N (0,1)
Density
0.0
0.1
0.2
0.3
0.4
t−value
−3
−2
−1
0
1
2
3

One sample t-test for the mean

- One sided test: $H_0: \mu = \mu_0$ versus $H_A: \mu > \mu_0$
- One tailed p-value:
  - Probability of getting a value from the t_{n-1} distribution that is at least as much in favor of H_A over H_0 than what we had observed.
- Two-sided test: $H_0: \mu = \mu_0$ versus $H_A: \mu \neq \mu_0$
- Two-tailed p-value:
  - Probability of getting a value from the t_{n-1} distribution that is at least as big **in absolute value** as the one we observed.

One sample t-test for the mean

- Computer programs can compute the p-value for a given n and t-statistic
- Critical value
  - The value in the t (or any other) distribution that, if exceeded, yields a 'statistically significant' result for type 1 error rate equal to α
- Critical region
  - The set of all values that are considered statistically significantly different from H_0.


T−distribution (d.f.=10) and
one−sided critical region (0.05)
T−distribution (d.f.=100) and
one−sided critical region (0.05)
T−distribution (d.f.=10) and
two−sided critical regions (0.05)
T−distribution (d.f.=100) and
two−sided critical regions (0.05)
1.812
1.66
2.228
1.984
0.0
0.1
0.2
0.3
0.4
−4
−2
0
2
4

Power and Sample Size for a one sample test of means

- Power increases when
  - Type 1 error rate (α) increases: type 1 (α) versus type 2 (β) tradeoff
  - True μ is very far from μ_0
  - Variance or standard deviation (σ) decreases (decrease noise)
  - Sample size increases
- T-statistic

$$t = \frac{\overline{x} - \mu_0}{\sigma/\sqrt{n}}$$

- Power for a 2-tailed test is a function of the true mean μ, the hypothesized mean μ_0, and the standard deviation σ only through $|\mu - \mu_0|/\sigma$

Power and Sample Size for a one sample test of means

- Sample size to achieve $\alpha = 0.05$, power=0.90 is approximately

$$n = 10.51 \left(\frac{\sigma}{\mu - \mu_0} \right)^2$$

- Power calculators can be found at statpages.org/#Power
- PS is a very good power calculator (Dupont and Plummer): http://biostat.mc.vanderbilt.edu/PowerSampleSize

Example: Power and Sample Size

- The mean forced expiratory volume in 1 second in a population of asthmatics is 2.5 L/sec, and the standard deviation is assumed to be 1
- How many subjects are needed to reject $H_0 : \mu = 2.5$ in favor of $H_0 : \mu \neq 2.5$ if the new drug is expected to increase the FEV to 3 L/sec with $\alpha = 0.05$ and $\beta = 0.1$
- $\mu_0 = 2.5$, $\mu = 3.0$, $\sigma = 1$

$$n = 10.51 \left(\frac{1}{3.0 - 2.5} \right)^2 = 42.04$$

- We need 43 subjects to have 90 percent power to detect a 0.5 difference from 2.5.

Confidence Intervals

- Two-sided, $100(1-\alpha)\%$ CI for the mean μ is given by

$$(\overline{x} - t_{n-1,1-\alpha/2} \cdot SE, \overline{x} + t_{n-1,1-\alpha/2} \cdot SE)$$

- $t_{n-1,1-\alpha/2}$ is the critical value from the t-distribution with d.f.=n-1
- For large n, $t_{n-1,1-\alpha/2}$ is equal to 1.96 for $\alpha = 0.05$
- $1-\alpha$ is called the confidence level or confidence coefficient

Confidence Intervals

- $100(1-\alpha)\%$ confidence interval (CI)
  - If we were able to repeat a study a large number of times, then $100 \cdot (1-\alpha)$ percent of CIs would contain the true value.
- Two-sided $100(1-\alpha)\%$ CI
  - Includes the null hypothesis μ_0 if and only if a hypothesis test $H_0: \ \mu = \mu_0$ is not rejected for a 2-sided α significance level test.
  - If a 95% CI does not contain μ_0, we can reject $H_0 : \mu = \mu_0$ at the $\alpha = 0.05$ significance level

n	$\overline{x}$	σ	p-value	95% CI
20	27.31	54.23	0.036	(1.930, 52.690)
20	27.31	59.23	0.053	(-0.410, 55.030)
20	25.31	54.23	0.051	(-0.070, 50.690)
17	27.31	54.23	0.054	(-0.572, 55.192)

  - CIs provide more information than p-values

Special case: Paired data and one-sample tests

- Assume we want to study whether furosemide (or lasix) has an impact on potassium concentrations among hospitalized patients.
- That is, we would like to test $H_0: \ \mu_{on-furo} - \mu_{off-furo} = 0$ versus $H_A: \ \mu_{on-furo} - \mu_{off-furo} \neq 0$
- In theory, we could sample n_1 participants not on furosemide and compare them to n_2 participants on furosemide
- However, a very robust and efficient design to test this hypothesis is with a paired sample approach
- On n patients, measure K concentrations just prior to and 12 hours following furosemide administration.

Special case: Paired data and one-sample tests

- The effect measure to test H_0 versus H_A, is the mean, within person difference between pre and post- administration K concentrations.
- $W_i = Y_{on-furo,i} - Y_{off-furo,i}$
- Note that $\overline{W} = \overline{Y}_{on-furo} - \overline{Y}_{off-furo}$
  - The average of the differences is equal to the difference between the averages
- $H_0: \ \mu_w = 0$ versus $H_A: \ \mu_w \neq 0$ is equivalent to the above H_0 and H_A
- $\overline{W} = -0.075$ mEq/L and $s = 0.08$

$$t_{99} = \frac{-0.075 - 0}{0.08/\sqrt{100}} = 9.375$$

- The p-value is less than 0.0001 $\rightarrow$ a highly (!!!!) statistically significant reduction

One Sample Methods for a Probability

- Y is binary (0/1): Its distribution is bernoulli(p) (p is the probability that $Y = 1$).
- p is also the mean of Y and $p(1-p)$ is the variance.
- We want to test $H_0 : p = p_0$ versus $H_A : p \neq p_0$
- Estimate the population probability p with the sample proportion or sample average $\hat{p}$

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

One Sample Methods for a Probability

- A z-test is an approximate test that assumes the test statistic has a normal distribution i.e., it is a t-statistic with the d.f. very large

$$z = \frac{\hat{p} - p_0}{\sqrt{p_0(1-p_0)/n}}$$

- The z-statistic has the same form as the t-statistic

$$z = \frac{\text{estimated value - hypothesized value}}{\text{standard deviation of numerator}}$$

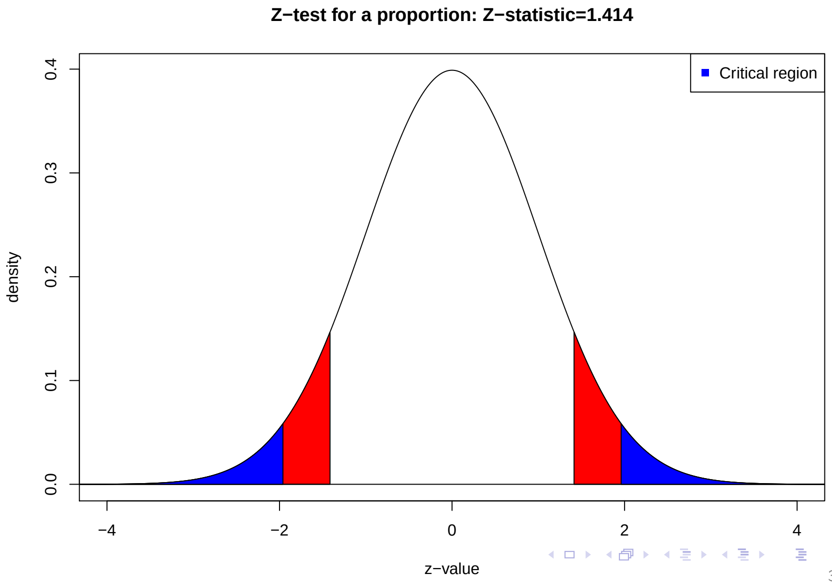
  where $\sqrt{p_0(1-p_0)/n}$ is the standard deviation of the numerator which is the standard error assuming the H_0 is true.
- (see t-statistic distributions)

One Sample test for a probability: Is our coin fair?

- $Y \sim bernoulli(p)$: $H_0 : p = 0.5$ versus $H_A : p \neq 0.5$
- Flip the coin 50 times. Heads (Y=1) shows up 30 times ($\hat{p} = 0.6$).

$$z = \frac{0.6 - 0.5}{\sqrt{(0.5)(0.5)/50}} = 1.414$$

- The p-value associated with Z is 2 $\times$ the area under the normal curve to the right of z=1.414 (e.g. the area to the right of 1.414 plus the area to the left of -1.414)
- The critical value for a 2-sided $\alpha = 0.05$ significance level test is 1.96
- The p-value associated with this test is approximately 0.16
- Note that if p is very small or very large or if n is small, use exact methods (e.g. Fishers exact test or permutation test)


Z−test for a proportion: Z−statistic=1.414
Critical region
density
0.0
0.1
0.2
0.3
0.4
−4
−2
0
2
4
z−value

Power and confidence intervals

- Power increases when
  - n increases
  - p departs from p_0
  - p_0 departs from 0.5

$$z = \frac{\hat{p} - p_0}{\sqrt{p_0(1-p_0)/n}}$$

- Confidence interval
  - 95%CI: $(\hat{p} - 1.96 \cdot \sqrt{\hat{p}(1-\hat{p}/n}, \hat{p} - 1.96 \cdot \sqrt{\hat{p}(1-\hat{p}/n})$
- For the coin flipping example: $\hat{p} = 0.6$ and the 95% CI is given by

$$0.6 \pm 1.96 \cdot \sqrt{0.6 \times 0.4/50} = (0.464,\ 0.736)$$

which is consistent with the 0.16 p-value that we had observed for $H_0: \ p = 0.5$.

Two sample test for means

- Two groups of patients (not paired)
- These are much more common than 1 sample tests
- We assume data come from a normal distribution (although this is not completely necessary)
- For now, assume the two groups have equal variability in response distribution
- Test whether population means are equal
- Example: All patient in population 1 are treated with clonidine after limb amputation and all patients in population 2 are treated with standard therapy.
- Scientific question:
  - What is the difference in the mean pain scale scores at 6 months following the amputation?

Two sample test for means

- $H_0: \ \mu_1 = \mu_2$ which can be generalized to $H_0: \ \mu_1 - \mu_2 = 0$ or $H_0: \ \mu_1 - \mu_2 = \delta$
- The quantity of interest (QOI) is $\mu_1 - \mu_2$
- If we want to test $H_0: \ \mu_1 - \mu_2 = 0$ and if we assume the two populations have equal variances, then the t- statistic is given by:

$$t = \frac{\text{point estimate of the QOI} - 0}{\text{standard error of the numerator}}$$

- The estimate of the QOI: $\overline{x}_1 - \overline{x}_2$

Two sample test for means

- For two independent samples variance of the sum or of differences in means is equal to the sum of the variances
- The variance of the QOI is then given by $\frac{\sigma^2}{n_1} + \frac{\sigma^2}{n_2}$
- We need to estimate a single σ^2 from the two samples
- We use a weighted average of the two sample variances

$$s^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}$$

- The true standard error of the difference in sample means: $\sigma\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$
- Estimate with $s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}$

Two sample test for means

- The t-statistic is given by,

$$t = \frac{\overline{x}_1 - \overline{x}_2}{s\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

- Under H_0 t, has a t-distribution with $n_1 + n_2 - 2$ degrees of freedom.
- The -2 comes from the fact that we had to estimate the center of 2 distributions

Example: two sample test for means

- $n_1 = 8$, $n_2 = 21$, $s_1 = 15.34$, $s_2 = 18.23$, $\overline{x}_1 = 132.86$, $\overline{x}_2 = 127.44$

$$
\begin{aligned}
s^2 &= \frac{7(15.34)^2 + 20(18.23)^2}{7+20} = 307.18 \\
s &= \sqrt{307.18} = 17.527 \\
se &= 17.527\sqrt{\frac{1}{8} + \frac{1}{21}} = 7.282 \\
t &= \frac{5.42}{7.282} = 0.74
\end{aligned}
$$

on 27 d.f.

Example: two sample test for means

- The two-sided p-value is 0.466
  - You many verify with the surfstat.org t-distribution calculator
- The chance of getting a difference in means as large or larger than 5.42 if the two populations have the same mean in 0.466.
- No evidence to suggest that the population means are different.

Power and sample size: two sample test for means

- Power increases when
  - $\Delta = \mid \mu_1 - \mu_2 \mid$ increases
  - n_1 or n_2 increases
  - n_1 and n_2 are close
  - σ decreases
  - α increases
- Power depends on n_1, n_2, μ_1, μ_2, and σ approximately through

$$\frac{\Delta}{\sigma\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$$

- When using software to calculate power you can put in 0 for μ_1 and Δ for μ_2 since all that matters is their difference
- σ is often estimated from pilot data

Power and sample size: two sample test for means

- Example
  - From available data, ascertain a best guess of σ : assume it is 16.847.
  - Assume Δ=5, $n_1 = 100$, $n_2 = 100$, $\alpha = 0.05$
  - The surfstat software computes a power of 0.555
- The required sample size decreases with
  - $k = \frac{n_2}{n_1} \to 1$
  - Δ large
  - σ small
  - α large
  - Lower power requirements

Power and sample size: two sample test for means

- An approximate formula for required sample sizes to achieve power=0.9 with $\alpha = 0.05$ is

$$n_1 = \frac{10.51\sigma^2(1 + \frac{1}{k})}{\Delta^2}$$
$$n_2 = \frac{10.51\sigma^2(1 + k)}{\Delta^2}$$

σ	Δ	K	n_1	n_2	n
16.847	5	1.0	239	239	478
16.847	5	1.5	199	299	498
16.847	5	2.0	177	358	537
16.847	5	3.0	160	478	638

- Usually, websites are recommended for these calculations.

Confidence interval: two sample test for means

- Confidence interval

$$[(\overline{x}_1 - \overline{x}_2) - t_{n_1+n_2-2,1-\alpha/2} \times s \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}},$$

$$(\overline{x}_1 - \overline{x}_2) + t_{n_1+n_2-2,1-\alpha/2} \times s \times \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}]$$

Δ	s	n_1	n_2	LCI	UCI
5	16.847	100	100	3.01	6.99
5	16.847	75	125	2.95	7.05
5	16.847	50	150	2.70	7.30

Summary

- Hypothesis testing, power, sample size, and confidence intervals
  - One sample test for the mean
  - One sample test for a probability
  - Two sample test for the mean