Testing Errors, Power, and Multiple Comparisons

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Introduction

- Hypothesis testing is an important statistical tool, but it needs to be applied appropriately within the broader investigative process that underlies statistical thinking (and scientific inquiry more generally)
- In this lecture, we will cover a few important considerations, and the vocabulary associated with them, when using hypothesis testing as a decision making tool

Clofibrate

- In 1980, the *New England Journal of Medicine* published results from a randomized, placebo-controlled, double-blind experiment involving the cholesterol-lowering drug *clofibrate*
- Of the subjects randomly assigned to take clofibrate, adherers were defined as those who took more than 80% of their prescribed pills:

	Number	Deaths
Took at least 80%	708	15%
Took less than 80%	357	25%
Total	1103	20%

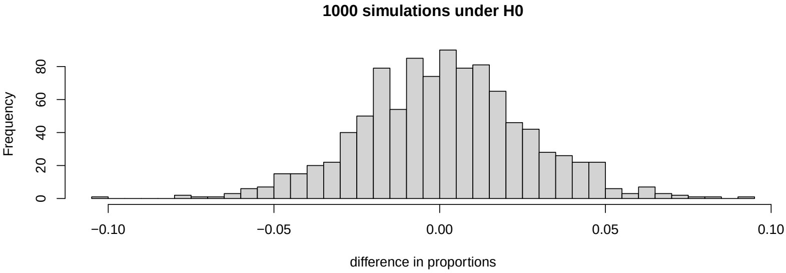
Clofibrate

Is clofibrate effective? We might evaluate the hypothesis:

$$H_0 : p_{\text{death}|\text{adherer}} - p_{\text{death}|\text{nonadherer}} = 0$$

The study observed:

$$\hat{p}_{\text{death}|\text{adherer}} - \hat{p}_{\text{death}|\text{nonadherer}} = 106/708 - 89/357 = -0.10$$



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	Clofibrate		Placebo	
	Number	Deaths	Number	Deaths
Adherers	708	15%	1813	15%
Nonadherers	357	25%	882	28%
Total	1103	20%	2789	21%

Once we consider the experiment's placebo group, clofibrate no longer appears to be effective.

Clofibrate

- This experiment should have been analyzed using the **intent-to-treat** principle:

$$\hat{p}_{\text{death}|\text{clofibrate}} - \hat{p}_{\text{death}|\text{placebo}} = -0.01$$

- The corresponding hypothesis test yields an unconvincing *p*-value of 0.51
  - Using a **significance level** (evidence threshold) of $\alpha = 0.05$, we don't have evidence to refute the null hypothesis that clofibrate and placebo are equally effective
  - But is it *possible* that prescribing clofibrate really is better than prescribing placebo?

Clofibrate

- Yes, clofibrate *could* be better (remember a high p-value doesn't *prove* the Null Hypothesis)
    - This would mean that our experiment/analysis resulted in a *decision error*
    - Put differently, we failed to reject H_0 because $p \geq \alpha$, but that was a mistake because H_0 was false and should've been rejected

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- A second type of error would be incorrectly rejecting a null hypothesis that is actually true
  - Any guesses on the *exciting names* statisticians have given these *two types of errors*?

Type I and Type II Errors

- A **type I error** occurs when the null hypothesis is *rejected*, but in reality it is *true*
- A **type II error** occurs when the null hypothesis *cannot be rejected*, but in reality it is *false*

	H0 is true	H0 is false
Don't Reject H0	Correct	Type II Error
Reject H0	Type I Error	Correct

Which type of error might have been made in the clofibrate study?

Practice

Describe (in words) what a Type I and Type II error would be for the following scnarios:

1. H_0 : Person A is not guilty of the crime vs. H_A : Person A is guilty of the crime
2. H_0 : Drug A doesn't cure disease B vs. H_A : Drug A cures disease B

Additionally, how do you think a data analyst could decrease the chances of making a Type I error? (Assuming the data have already been collected)

Practice (Solution)

1. A type I error would be deciding an innocent person is guilty, a type II error would be deciding a guilty person is innocent
2. A type I error would be deciding that an ineffective drug is beneficial, a type II error would be deciding a beneficial drug is not effective

We could reduce our chances of making a Type I error by lowering our significance threshold.

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  - Trivially, how could we guarantee we make zero type I errors?
- Type I error rates are *controllable*, as they depend entirely on the null distribution (namely the tail-areas defined by α)
  - Type II errors are not easily controlled, as they require you to know the *true* effect size (something you're usually trying to *estimate*!)

Power

Rather than fixating on controlling Type II errors, statisticians instead focus on a quantity known as **statistical power**:

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- Calculating the power of an experiment requires us to specify an *effect size* (usually based upon *clinical significance*)
  - Power also depends upon sample size and α
  - Trivially, how could we guarantee 100% power?

Power Calculations

- Statisticians are often asked to perform *power calculations* to help plan future studies, addressing the question:
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- This link is an example of a power calculator for difference in proportions tests
- If the death rates observed in the clofibrate study (0.20 and 0.21) are true at the population level, sample sizes of ~ 25000 in each group are needed to have an 80% chance of rejecting the null hypothesis and detecting this difference!
  - If we're willing to accept a 10% type I error rate, the requirement drops to ~ 20000

Takeaways

- Statisticians use significance thresholds (ie: α) to limit the probability of making a *type I error*
  - These thresholds control the long-run rate of “false positives” in scientific experiments
- *Type II errors* are more complicated, and statisticians usually focus on *power* instead
  - Power depends upon n, α, and the effect size
  - Planning an experiment usually involves calculating the necessary sample size(s) to achieve reasonable power to detect a clinically significant effect without compromising type I error control

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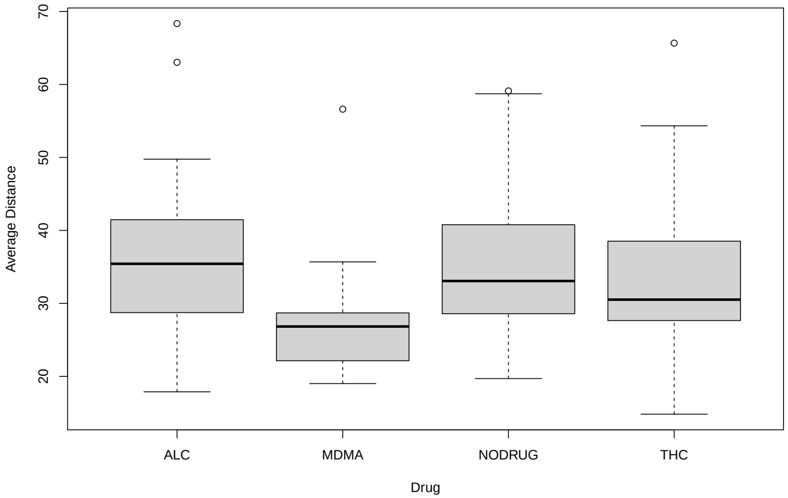
- In a driving simulator, subjects were told to follow a lead vehicle that was programmed to vary its speed unpredictably
  - As the lead vehicle erratically changed speed, more cautious drivers follow at a larger distance, while riskier drivers tailgate the vehicle
- The study's outcome variable was the average following distance of each participant
- The study's explanatory variable was the participant's drug use group: Alcohol, MDMA, THC, or no drugs used
  - Participants who used multiple drugs were classified according to the "hardest" drug they used (MDMA $>$ THC $>$ Alcohol)

Drug Use and Tailgating

After removing a couple of outliers, here's what the data look like:



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1. ALC vs NODRUG, p-value $= 0.5102$
2. ALC vs MDMA, p-value $= 0.00417$
3. ALC vs THC, p-value $= 0.8959$
4. THC vs NODRUG, p-value $= 0.4782$
5. THC vs MDMA, p-value $= 0.01383$
6. MDMA vs NODRUG, p-value $= 0.00216$

If we use the results of all 6 tests (evaluated vs. $\alpha = 0.05$), does this experiment still have a 5% chance of making a Type I error?

The Bonferroni Adjustment

The Type I error rate for this *family of tests* is inflated, if the null hypothesis is true for all 6 tests in the tailgating study (and if the tests are independent); Then, using $\alpha = 0.05$:

$$\begin{aligned} Pr(\text{At least one type I error}) &= 1 - Pr(\text{No type I errors}) \\ &= 1 - (1 - 0.05)^6 = 26.5\% \end{aligned}$$

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This suggests a simple *correction* to significance threshold: $\alpha^* = \alpha/h$, where h is the number of hypothesis tests being performed. Now:

$$\begin{aligned} Pr(\text{At least one type I error}) &= 1 - Pr(\text{No type I errors}) \\ &= 1 - (1 - 0.05/6)^6 \approx 5\% \end{aligned}$$

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Setting $\alpha^* = \alpha/h$ is known as the **Bonferroni Adjustment** (or *Bonferroni Correction*). Now, how many of the six hypotheses can be rejected while still achieving a *family-wise Type I error rate* of 5%?

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Since $\alpha^* = 0.05/6 = 0.0083$, only two of six tests are now considered “statistically significant”; but we've controlled the likelihood of our *entire analysis* making a Type I error at 5%

Bonferroni Adjusted *p*-values

- Occasionally you'll see **adjusted p-values** get reported (rather than an explanation of how to compare the original *p*-values to an adjusted significance threshold)
    - For the Bonferroni adjustment, this simply entails multiplying each of the original *p*-values by h (the number of tests)
- "Bonferroni Adjusted *p*-values" can then be compared directly with a significance threshold describing the desired Type I error rate
    - For example, you could compare the adjusted *p*-values to 0.05 to achieve a 5% family-wise Type I error rate

Practice

A genetic association study tested for differences in gene expression between two types of leukemia. The study tested 7129 genes.

1) If all 7129 tests were done using $\alpha = 0.01$, and there are no genetic differences between these two types of leukemia, how many "statistically significant" results would you expect?
2) Suppose 783 genes had *p*-values less than 0.01, do you believe there is some association between genes and type of leukemia
3) Suppose you wanted to use the Bonferroni adjustment to ensure a Type I error rate no larger than 5%. What would your adjusted significance threshold be?
4) Suppose the "most significant" gene had a *p*-value of 0.000001, what is its *Bonferroni Adjusted p-value*?

Practice - Solution

1) You'd expect $7129 * 0.01 = 71$ Type I errors
2) Yes, there were over 10 times (712) more significant results than expected
3) $\alpha^* = 0.05/7129 = 0.000007$
4) The adjusted *p*-value is $0.000001 * 7129$, or $p^* = 0.007$

Conclusion

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  - There is an inherent trade-off between Type I and Type II errors that must be managed by the data analyst

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- Hypothesis testing can be considered a decision making tool, but this can lead to errors
    - There is an inherent trade-off between Type I and Type II errors that must be managed by the data analyst
- Performing multiple hypothesis tests within the same experiment can be problematic
    - Taken to the extreme (like genetic association example), it's possible that "significant findings" are more likely to be Type I errors than real discoveries
    - Approaches like the Bonferroni correction can be used to control the *family-wise* Type I error rate of an experiment