Correcting for Multiple Hypothesis Testing

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Introduction

Introduction – Structure

Today I'd like to talk about multiple hypothesis testing, its empirical implications, and solutions to avoid common pitfalls

- This is quite a practical talk
- For one particular reason I will focus this on implementations in Stata
- I have code that I will show from time-to-time along side (details below)
- But the points absolutely hold regardless of the computational tools one uses
- In terms of materials, plan is to arrive to quite modern simulation-based methods
- But hopeully give a good general overview too!

The State of Empirical Work

Consider a number of facts based on empirical work:

- Most studies consider more than a single dependent variable of interest
- Frequentist hypothesis testing is often quite centrally used (and indeed, comes as default in many methods and their computational implementations)
- These methods are designed to limit false rejection of a null hypothesis to some small value
- Such error rates are valid test-by-test, but accumulate if we consider multiple tests
- This can be problematic, especially if one views rejection of a single test in a class as 'confirmatory' of some general idea

A Simple Illustrative Simulation

We can try 5000 simulations of the following models in Stata varying K and examining rejection rates...

$$y_i^k = \alpha + \tau Treat_i + \varepsilon_i^k \qquad \forall k \in \{1, \ldots, K\}$$

Table: Error Rates, and Error Rates by Class

	Number of Dependent Variables									
	1	2	3	4	5	6	7	8	9	10
Total Tests Rejected	265	569	783	1077	1314	1552	1862	2163	2433	2638
Mean Tests Rejected	0.053	0.057	0.052	0.054	0.053	0.052	0.053	0.054	0.054	0.053
Proportion $\geq$ 1 Rejection	0.053	0.111	0.149	0.197	0.235	0.275	0.320	0.361	0.397	0.414
Proportion $\geq$ 2 Rejection	0.000	0.002	0.007	0.018	0.027	0.034	0.048	0.062	0.079	0.096

Refer to section (1) of the accompanying Stata code `multHyp.do`.

What to Do?

There are a number of ways forward to conduct valid inference in cases where multiple hypotheses are tested:

1. Dimension reduction
2. Familywise Error Rate Corrections
3. False Discovery Rate Corrections

This Talk

In this talk I plan to discuss each of these 3 methods and their Stata implementations.

- I *will not* delve too deeply into the math here. Many references for this information:
  - *Eg* text-book introductions: Lehmann and Romano (2005), Casella and Berger (2001), and Westfall and Young (1993)
  - Stata Journal papers with background: R. Newson and The ALSPAC Study Team (2003), R. B. Newson (2010), and Clarke, Romano, and Wolf (2020)
- I *will* however work through examples with code
- In the interests of controlling the DGP, this will all be based on simulated data
- This will be specifically tailored to modelling in social sciences: heavy reliance on regression based framework (OLS, IV, RDD, etc.)
- In general, I will point to papers *and* Stata routines throughout
- Code to follow along: `https://github.com/damiancclarke/multHypStata`

Brief Mathematical Background

Standard Definitions of Size and Power

Table: Outcomes of a single hypothesis test

		Null Hypothesis (H_0) is:	
		True	False
Decision about H_0:	Reject	Type I error, $Pr = \alpha$	Correct, $Pr = 1 - \beta$
	Don't Reject	Correct, $Pr = 1 - \alpha$	Type II error, $Pr = \beta$

- Generally we fix α to some arbitrary, small value, wishing to minimize the rate of type I errors
- Where H_0 is false, the *power* we have to detect an effect size $(1 - \beta)$ depends upon the value of the true parameter, the null, and the precision of the estimate
- There is generally a trade-off between size and power

Error Rates with Multiple Hypothesis Tests

Table: Classification of Multiple Hypothesis Tests

	Null Hypothesis (H_0) is true	Alternative hypothesis (H_1) is true	Total
Test is declared significant	V	S	R
Test is declared non-significant	U	T	$m - R$
Total	m_0	$m - m_0$	m

- V: Number of false positives (Type I error, or "False Discoveries")
- S: Number of true positives ("True Discoveries")
- T: Number of false negatives (Type II error)
- U: Number of true negatives
- $R = V + S$ is number of rejected null hypotheses ("Discoveries")

Error Rates with Multiple Hypothesis Tests

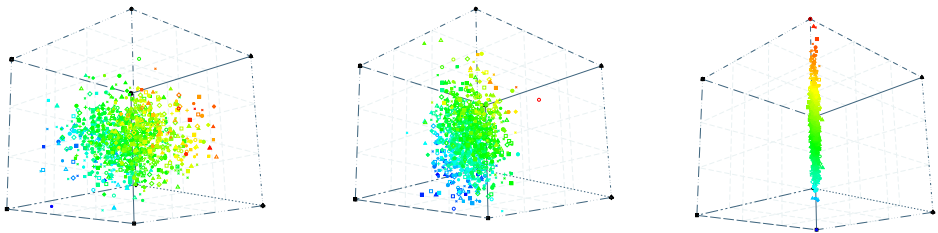
When testing multiple hypotheses, it is no longer clear that we can just (eg) minimize the rate of false rejections...

- **Family-Wise Error Rate** $FWER = Pr(V \geq 1)$
  - By assuring that $FWER \leq \alpha$, probability of making one or more type I errors in whole family is limited at α
  - Stringent control over false discoveries

- **False Discovery Rate** $FDR = E[V/R]$
  - To avoid division by zero, FDR is defined as 0 when $R = 0$.
  - Formally, $FDR = E[V/R|R > 0] \cdot P(R > 0)$
  - FDR control offers less control over false discoveries (more type I error), but often at greater power (less type II error)

Getting into some simulations...

Figure: Correlations (Y_1, Y_2, Y_3)



(a) $\rho = 0$ (b) $\rho = 0.5$ (c) $\rho = 0.99$

Multivariate normals simulated as per Gould (Undated). Stata visualization: Rostam-Afschar and Jessen (2014).

Refer to section (2) of the accompanying Stata code `multHyp.do`.

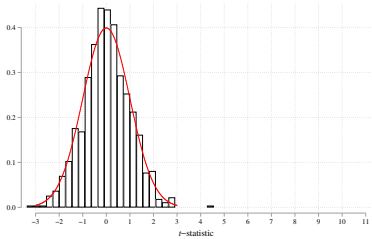
Indexes and Dimension Reduction

Indexes and Dimension Reduction

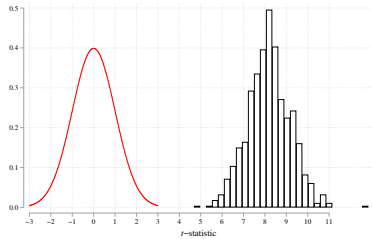
A simple option if one is concerned about multiple outcomes is to compress the information into a single dimension or index.

- How to go about generating the index and aggregating sources of information is an interesting problem
- Anderson (2008) is a tour of force here (in Stata: Schwab et al. (2020))
- Anderson (2008)'s proposal: "overweight" variables which bring more independent variation to the index
- This is very different to what a principal component analysis would draw out
- This decision is *not* innocuous
- One draw-back here: it pre-supposes some prior about relationships between independent and dependent variables

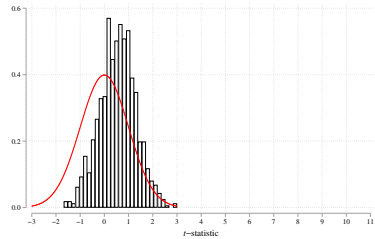
Figure: Behaviour of the Anderson Index



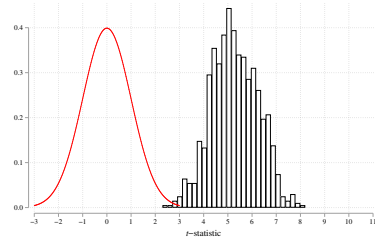
(a) All null effects



(b) All non-zero effects



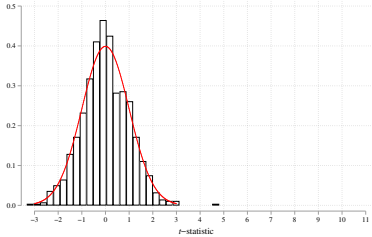
(c) 1 correlated non-zero effect



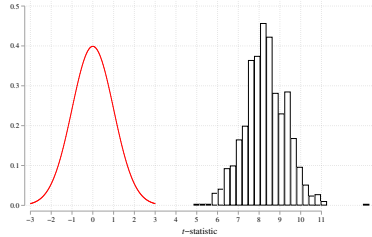
(d) 1 independent non-zero effect

Refer to section (3) of the accompanying Stata code `multHyp.do`.

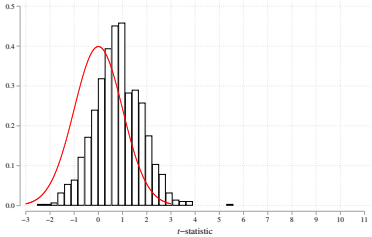
Figure: Behaviour of Principal Component



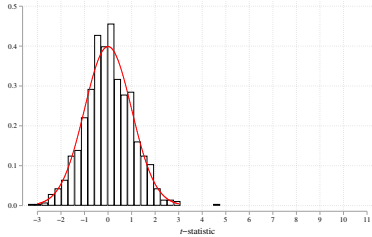
(a) All null effects



(b) All non-zero effects



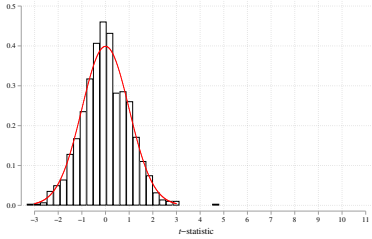
(c) 1 correlated non-zero effect



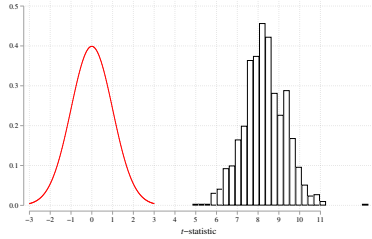
(d) 1 independent non-zero effect

Refer to section (3) of the accompanying Stata code `multHyp.do`.

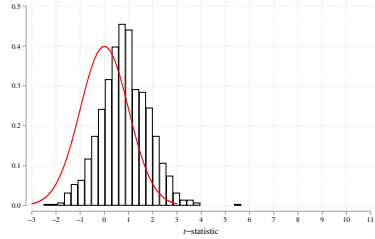
Figure: Behaviour of a Summary Index



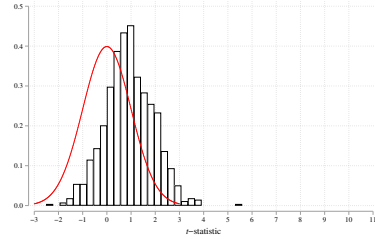
(a) All null effects



(b) All non-zero effects



(c) 1 correlated non-zero effect



(d) 1 independent non-zero effect

Refer to section (3) of the accompanying Stata code `multHyp.do`.

Familywise Error Rate Corrections

Familywise Error Rate Corrections

Alternative to aggregation is the consideration of the full family of hypotheses as separate tests: then correction for multiple testing just requires adjusting critical values

- This provides you with more information
- Familywise error rate (FWER) corrections seek to limit the probability of falsely rejecting *any* tests across the entire family to α
- Earliest and perhaps most well known of these is Bonferroni (1935)
- These procedures – in particular the early generation models – can be costly in terms of power
- This is a classic trade-off between size and power
- *But* much of the cost in early models comes from restrictive dependence assumptions
- Tremendous recent advances here using (a) step-down, and, especially (b) simulation-based methods

A Comparison: Bonferroni, Holm and Romano-Wolf

Part 1: Bonferroni (1935)

Consider null hypotheses $H_1, \ldots, H_m$, with p-values $p_1, \ldots, p_m$. Control of the FWER at $\leq \alpha$ is guaranteed if:

$$\text{Reject null hypotheses for each } p_i \leq \frac{\alpha}{m}$$

Part 2: Holm (1979)

Consider null hypotheses $H_1, \ldots, H_m$, with p-values $p_1, \ldots, p_m$ **ordered from lowest to highest**. Control of the FWER at $\leq \alpha$ is guaranteed if:

1. Start at p_1, if $p_1 < \frac{\alpha}{m}$, reject and continue, else end.
2. Move to p_2, if $p_2 < \frac{\alpha}{m-1}$, reject and continue, else end.
3. ...
4. Move to p_k, if $p_k < \frac{\alpha}{m+1-k}$, reject and continue, else end.

A Comparison: Bonferroni, Holm and Romano-Wolf

Part 3: Romano-Wolf (2005)

Consider null hypotheses $H_1, \ldots, H_m$, with p-values $p_1, \ldots, p_m$ **ordered from lowest to highest** and the corresponding studentized t-statistics $t_1, t_2, \ldots, t_m$. For each statistic, calculate B bootstrap replicates of a re-centred Studentized test statistic, $t_1^{*,b}, t_2^{*,b}, \ldots, t_m^{*,b}$. Control of the FWER at $\leq \alpha$ is guaranteed if:

1. For the B bootstrap replicates, calculate $max_{t,1}^{*,b} = max\{t_1^{*,b}, t_2^{*,b}, t_3^{*,b}, \ldots, t_m^{*,b}\}$. Define $\hat{c(0.95,1)}$ as the 95th quantile of this max. If $t_1 > \hat{c}(0.95, 1)$, reject and continue, else end.
2. Move to H_2 and calculate $max_{t,2}^{*,b} = max\{t_2^{*,b}, t_3^{*,b}, \ldots, t_m^{*,b}\}$. Define $\hat{c}(0.95, 2)$ as the 95th quantile of this max. If $t_2 > \hat{c}(0.95, 2)$, reject and continue, else end.
3. ...
4. Move to H_k and calculate $max_{t,k}^{*,b} = max\{t_k^{*,b}, \ldots, t_m^{*,b}\}$. Define $\hat{c}(0.95, k)$ as the 95th quantile of this max. If $t_k > \hat{c}(0.95, k)$, reject and continue, else end.

Familywise Error Rate Corrections

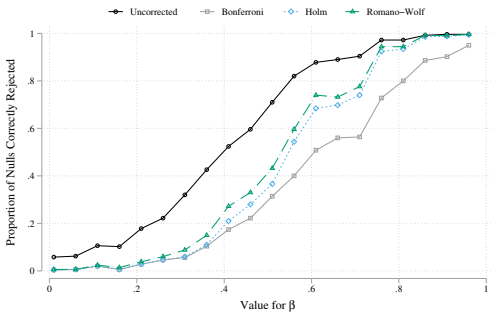
Table: Familywise Error Rate Corrections in Stata

Correction	Stata Implementation	Note
Bonferroni (1935)	R. B. Newson 2010	1st generation
Holm (1979)	R. B. Newson 2010	Step-down
Westfall and Young (1993)	Reif 2017; Jones, Molitor, and Reif 2019	Step-down, arbitrary dependence
Romano and Wolf (2005)	Clarke 2016; Clarke 2021	Step-down, arbitrary dependence
Method Specific		
List, A. Shaikh, and Xu (2019)	Seidel and Yang Xu 2016	Restricted R-W style implementation
List, A. Shaikh, and Xu (2019)	Steinmayr 2020	Restricted R-W style implementation

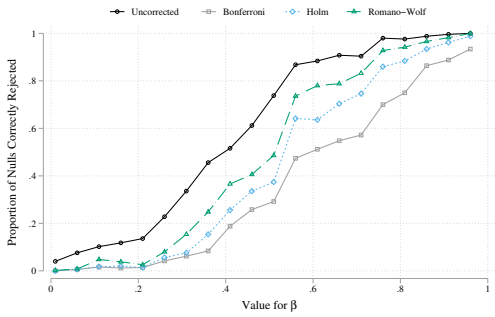
Notes: Full details of algorithms is provided in papers in left-hand column. Help files, github repos or Stata Journal papers (R. B. Newson 2010; Clarke, Romano, and Wolf 2020) provide computational background and Stata-specific syntax points. David McKenzie has an extremely useful blog post summary of this: `https://blogs.worldbank.org/impactevaluations/updated-overview-multiple-hypothesis-testing-commands-stata`

FWER Corrections and Improvements in Power

Figure: Simulated Power to Reject False Null Hypotheses



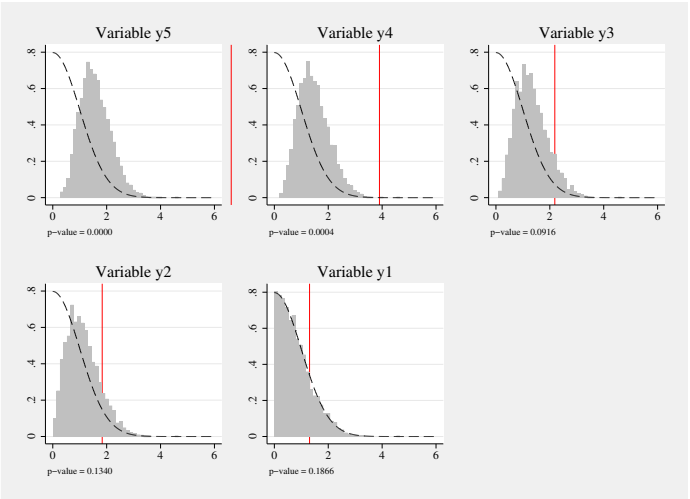
(a) $\rho = 0.25$



(b) $\rho = 0.75$

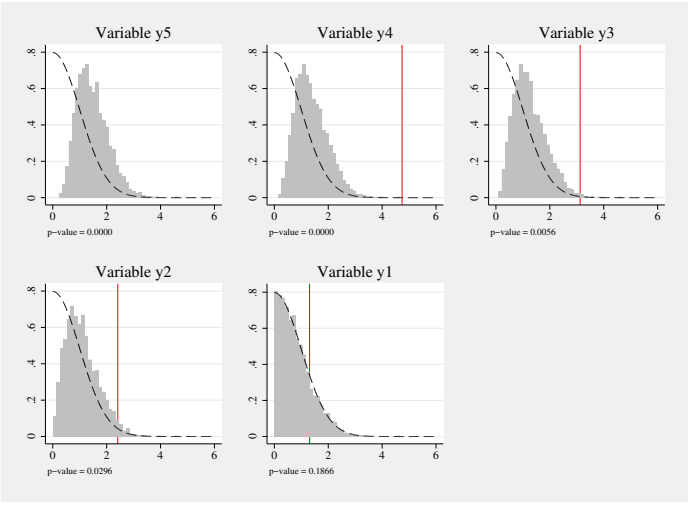
Refer to section (4) of the accompanying Stata code `multHyp.do`.

Figure: How Bootstrap Step-down Procedure Gains Power: $\rho = 0$



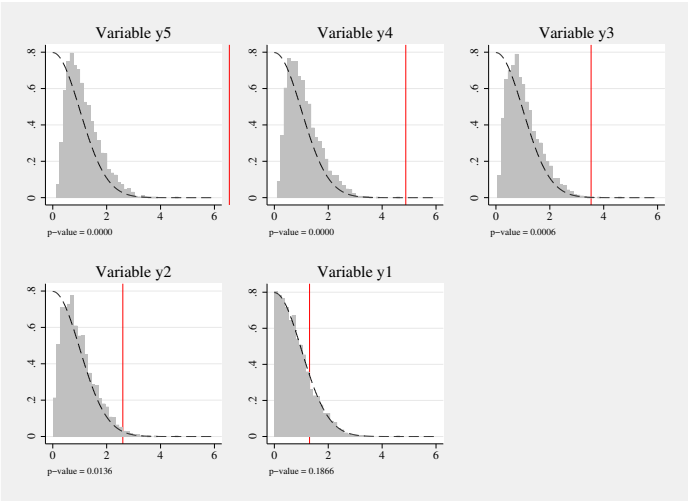
Refer to section (6) of the accompanying Stata code `multHyp.do`.

Figure: How Bootstrap Step-down Procedure Gains Power: $\rho = 0.5$



Refer to section (6) of the accompanying Stata code `multHyp.do`.

Figure: How Bootstrap Step-down Procedure Gains Power: $\rho = 0.9$



Refer to section (6) of the accompanying Stata code `multHyp.do`.

False Discovery Rate Corrections

False Discovery Rate Corrections

FWER corrections provide a clear framework for controlling error rates across multiple hypotheses, but in the limit, clearly become too demanding...

- While it is reasonable to aspire to *no* false rejection when K=10, it seems less reasonable when K=100 (or more)
- False discovery rate corrections seek to limit "false discoveries": proportion of null hypotheses rejected that are actually true
- More recent developments, in line with bio-statistic applications with many many tests
- FDR corrections imply that $\alpha\%$ of "discoveries" will actually be false
- Typically, FDR corrections have greater power than FWER procedures, at the cost of more false rejections
- In the specific case that all null hypotheses are true, $FDR = FWER$
- Suitability of one or other also depends on subjective considerations of type I vs type II

False Discovery Rate Corrections

Table: False Discovery Rate Corrections in Stata

Correction	Stata Implementation	Note
Benjamini and Hochberg 1995	R. B. Newson 2010	Provides decision rule (accept/reject) for input values of α
Benjamini and Yekutieli 2001	R. B. Newson 2010	Provides decision rule (accept/reject) for input values of α
Benjamini and Yekutieli 2001	Anderson 2008	Directly provides a p-value

Notes: Full details of algorithms are provided in papers in left-hand column. Stata Journal papers (R. B. Newson 2010) or do file documentation provide computational background and Stata-specific syntax points. David McKenzie has an extremely useful blog post summary of this: `https://blogs.worldbank.org/impactevaluations/updated-overview-multiple-hypothesis-testing-commands-stata`

False Discovery Rate Corrections

Table: Performance of FDR and FWER Routines

	$\rho = 0$			$\rho = 0.33$			$\rho = 0.67$		
	Pr(A)	Pr(B)	Pr(C)	Pr(A)	Pr(B)	Pr(C)	Pr(A)	Pr(B)	Pr(C)
Naïve	0.294	0.115	0.258	0.264	0.117	0.258	0.174	0.116	0.262
FDR									
Benjamini-Hochberg	0.084	0.042	0.168	0.078	0.046	0.163	0.046	0.043	0.164
Benjamini-Yekutieli	0.018	0.013	0.105	0.022	0.016	0.109	0.020	0.022	0.104
FWER									
Bonferroni	0.028	0.020	0.131	0.024	0.023	0.132	0.024	0.028	0.128
Holm	0.030	0.020	0.135	0.032	0.026	0.135	0.028	0.030	0.132
Westfall-Young	0.032	0.022	0.130	0.032	0.028	0.132	0.040	0.041	0.153
Romano-Wolf	0.030	0.023	0.129	0.036	0.029	0.137	0.038	0.038	0.156

$Pr(A) \equiv Pr$(Reject at least 1 true null). A "Familywise error"

$Pr(B) \equiv Pr$(Rejected null is actually true|null is rejected). Rate of "false discoveries".

$Pr(C) \equiv Pr$(Reject null|null is false). "Power" to detect real effect.

Refer to section (5) of the accompanying Stata code `multHyp.do`.

Discussion and Conclusion

Discussion and Conclusion

There is a growing, though incomplete, movement towards correctly adjusting for multiple hypothesis testing

- A very small selection of empirical papers implementing these sort of things are:
  - Lee and A. M. Shaikh 2014
  - Gertler et al. 2014
  - Attanasio et al. 2014
- However, this is certainly not universal
- Non-comprehensively, it seems to me like these are quite widely used in pre-specified projects (some values in Viviano, Wuthrich, and Niehaus (2021))
- But much less so in designs where power is an issue: IV, RDD
  - Presumably adaptive designs like RDD could define bandwidths optimally to account for multiple hypothesis correction
- More generally, relates to interesting work on the file drawer problem

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