Part II

Second-generation p-values: equivalence tests, statistical properties, and false discovery rates

---

Jeffrey D. Blume, and Megan H. Murray,

PhD almost PhD (July 6th defense)

School of Data Science   Department of Biostatistics

University of Virginia   Vanderbilt University

Course Layout

- Slides Part I: Introduction, applications, and statistical properties
  - Coding Part I
- Lunch (11:30-12:30)
- Slides Part II: Equivalence tests and false discovery rates
  - Coding Part II
- Slides Part III: SGPV Variable Selection
  - Coding Part III
- Questions and Discussion

ASA SGPV Short Course   Blume and Murray, 2022

Outline

→ Equivalence Tests

  → Two One-Sided Tests (TOST)

→ False Discovery Rates

  → R Packages

→ Code Part 2

ASA SGPV Short Course   Blume and Murray, 2022

Equivalence Tests

- Establish bioequivalence between data and an established range

- Example: A pharmaceutical company tests for drug approval by comparing new drug's performance to an approved drug's performance

- Uses an interval null or equivalence range
  - $H_0 = [\theta^-, \theta^+]$

- Most popular: TOST, Bayesian ROPE, test of Anderson and Hauck, and SGPV

ASA SGPV Short Course   Blume and Murray, 2022

TOST Test

- Two One-Sided Tests (Schuirmann 1987)

- Tests are ordinary, one-sided, α-level t-tests

- Flips the null and alternative hypotheses, and tests if the data $I_x = (I_x^-, I_x^+)$ are outside the equivalence range $[\theta^-, \theta^+]$

- $(H_{0_1}: \theta < \theta^-)$ and $(H_{0_2}: \theta > \theta^+)$

- If $both$ one-sided tests reject then conclude the evidence is contained in the equivalence range

- $p_T = max\{p_{T_1}, p_{T_2}\}$

ASA SGPV Short Course   Blume and Murray, 2022

SGPV Definition

**Second-generation
p-value (SGPV)**

$$p_\delta = \frac{|I \cap H_0|}{|I|} \times \max\left\{\frac{|I|}{2|H_0|}, 1\right\}$$

Proportion of data-supported hypotheses that are also null hypotheses

Small-sample correction factor

shrinks proportion to ½ when $|I|$ wide

when $|I| > 2|H_0|$

ASA SGPV Short Course   Blume and Murray, 2022
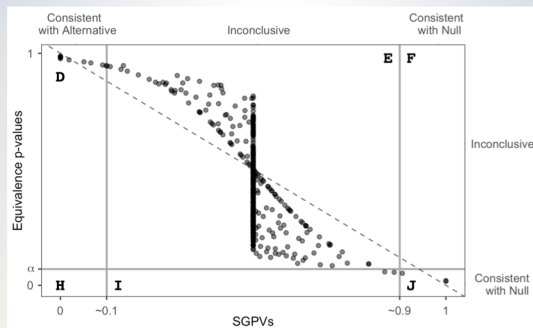
TOST vs. SGPV comparison

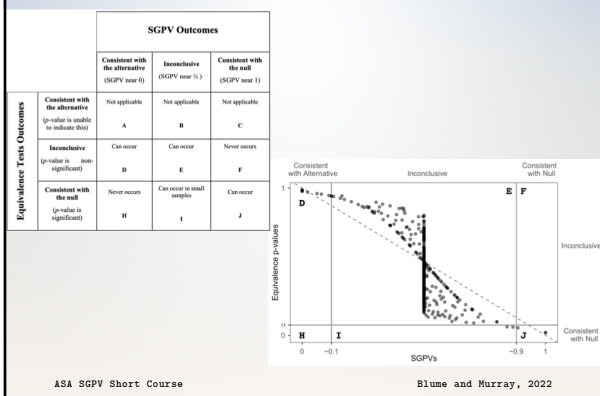|		SGPV Outcomes		
		Consistent with the alternative (SGPV near 0)	Inconclusive (SGPV near ⅓)	Consistent with the null (SGPV near 1)
Equivalence Tests Outcomes	Consistent with the alternative (*p*-value is unable to indicate this)	Not applicable A	Not applicable B	Not applicable C
	Inconclusive (*p*-value is non-significant)	Can occur D	Can occur E	Never occurs F
	Consistent with the null (*p*-value is significant)	Never occurs H	Can occur in small samples I	Can occur J

Blume and Murray, 2022

TOST vs. SGPV comparison

Blume and Murray, 2022

TOST vs. SGPV comparison

Blume and Murray, 2022

TOST vs. SGPV comparison

Equivalence Tests
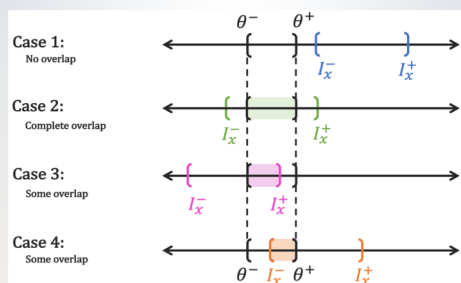
TOST vs. SGPV comparison

TOST	SGPV
2 inference outcomes	3 inference outcomes
Conclusions only about $(1-2\alpha)\%$ confidence interval	Any uncertainty data interval can be used
Type I Error is ultra-conservative (distribution of p_T is non-uniform)	Type I error is accurately assessed (limited by width of data interval)
Not uniformly most powerful	Has additional statistical properties explained in next section
No measure of overlap included in computation	Indicates when data agree with null or alternative without additional testing

Time for Code Part 2a!

ASA SGPV Short Course   Blume and Murray, 2022

---

10 Minute Break!

ASA SGPV Short Course   Blume and Murray, 2022

False Discovery Rates

- FDR for 5 SGPV=0 findings; computed under various null and alternative configurations (w/ flat prior).

SNP ID	SGPV rank	p-value rank	OR	1/8 SI lower limit	1/8 SI upper limit	FDR_1	FDR_2	FDR_3
kgp4568244_C	1	133	0.10	0.03	0.37	2.9%	17.1%	3.3%
kgp8051290_G	13	2002	15.58	1.95	124.68	4.3%	30.3%	4.9%
kgp4497498_A	28	255	4.37	1.80	10.64	2.5%	8.6%	3.1%
rs3123636_G	423	1	1.39	1.26	1.55	0.01%	0.1%	0.4%
kgp7460928_G	1443	3310	1.78	1.11	2.87	2.4%	2.0%	3.0%

ASA SGPV Short Course   Blume and Murray, 2022

False discovery rates

- Impact of α=0.05 vs α=0.05/7128   (7128 comparisons)

- False Discovery Rate (FDR)

Error rates

$$P(H_0|p < \alpha) = \left[1 + \frac{(1-\beta)}{\alpha}r\right]^{-1}$$

- False Confirmation Rate (FCR)

$$P(H_1|p > \alpha) = \left[1 + \frac{(1-\alpha)}{\beta}\frac{1}{r}\right]^{-1}$$

$r = P(H_1)/P(H_0)$

Error rates

ASA SGPV Short Course   Blume and Murray, 2022

False discovery rates

- Second-generation p-values
- False Discovery Rate (FDR)

Error Rates

$$P(H_0|p_\delta = 0) = \left[1 + \frac{P(p_\delta = 0|H_1)}{P(p_\delta = 0|H_0)}r\right]^{-1}$$

- False Confirmation Rate (FCR)

$$P(H_1|p_\delta = 1) = \left[1 + \frac{P(p_\delta = 1|H_0)}{P(p_\delta = 1|H_1)}\frac{1}{r}\right]^{-1}$$
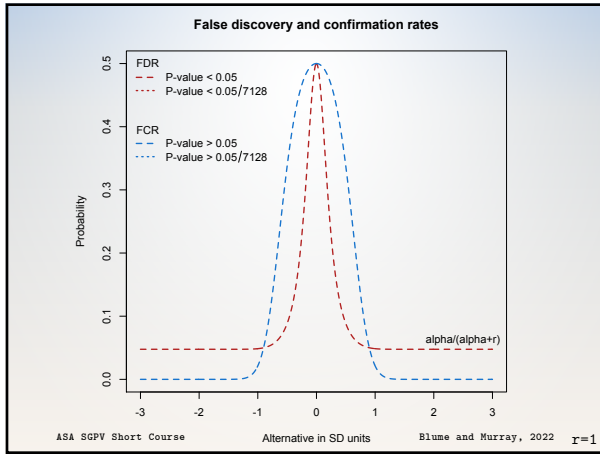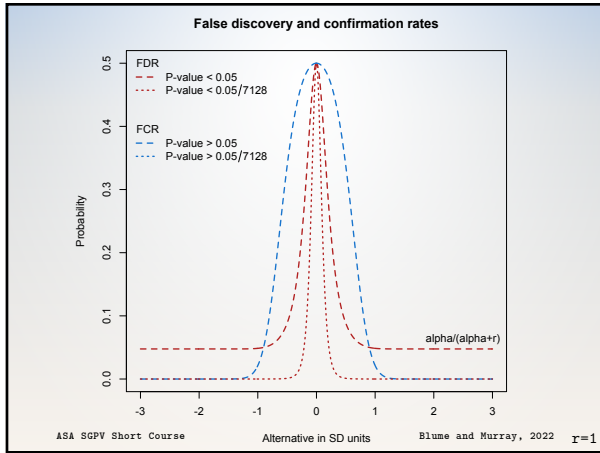
$r = P(H_1)/P(H_0)$

Error Rates

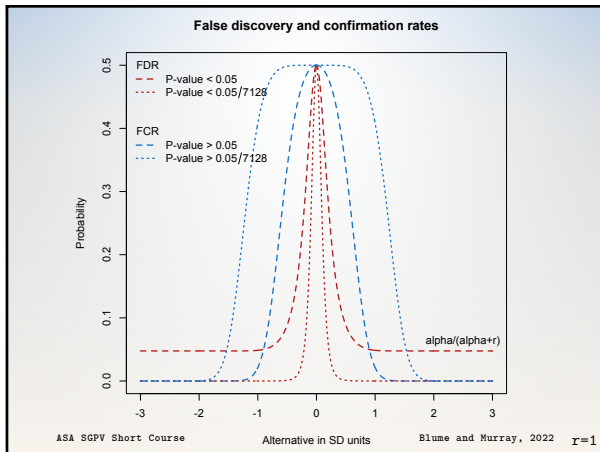ASA SGPV Short Course   Blume and Murray, 2022

False discovery and confirmation rates
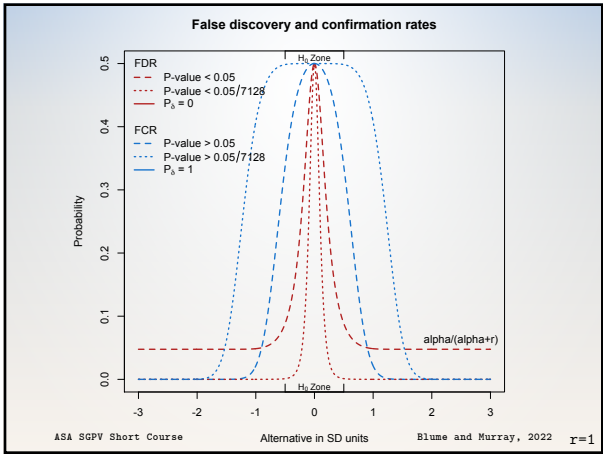
6
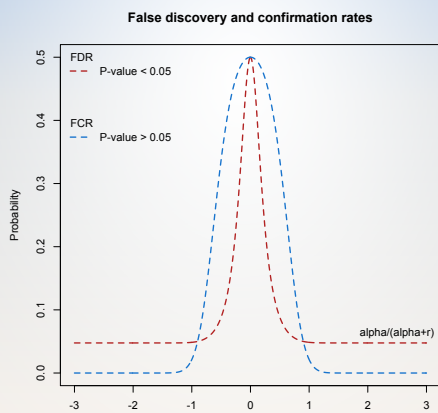
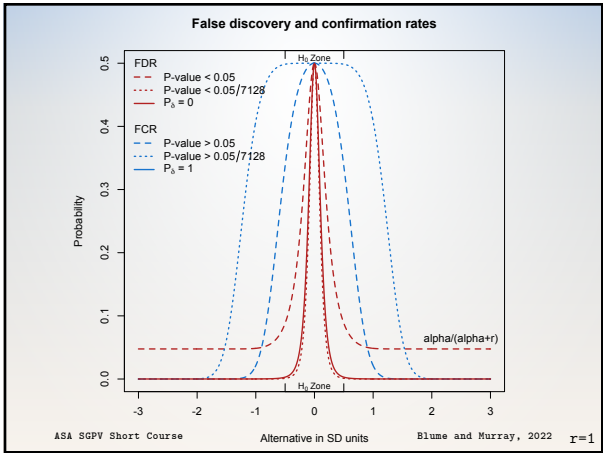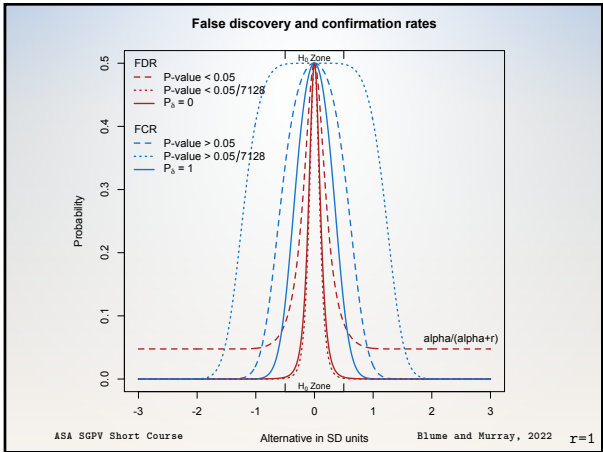## Remarks

- Second-generation *p*-values…
  - Has three "Error" rates
  - Allows Type I and II rate to converge to zero
  - Control changes of inconclusive results
  - Controls error rate using *science*
  - Reduces the false discovery rate

- Anchoring the scale of the effect size…
  - Eliminates most Type I Errors
  - Improves scientific translation of statistical model

ASA SGPV Short Course   Blume and Murray, 2022

FDR R Packages

- SGPVs
  - Valerie Welty
  - sgpv::fdrisk()
  - This function computes the false discovery risk (sometimes called the "empirical bayes FDR") for a second-generation *p*-value of 0, or the false confirmation risk for a second-generation *p*-value of 1.

- Raw p-values
  - FDRestimation::p.fdr()
  - This function computes FDRs and Method Adjusted p-values.
  - Methods include: Benjamini-Hochberg, Benjamini-Yeukateli, Bonferroni, Holm, Hochberg, and Sidak.

ASA SGPV Short Course   Blume and Murray, 2022

Time for Code Part 2b!

ASA SGPV Short Course   Blume and Murray, 2022

10 Minute Break!

ASA SGPV Short Course   Blume and Murray, 2022