Part II

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

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Course Layout

- Slides Part I: Introduction, applications, and statistical properties
  - Coding Part I
- Lunch (12:00-1:00pm)
- Slides Part II: Equivalence tests and false discovery rates
  - Coding Part II
- Slides Part III: SGPV Variable Selection
  - Coding Part III
- Questions and Discussion

Outline

- Equivalence Tests
  - Two One-Sided Tests (TOST)
  - Comparison to SGPVs
- False Discovery Rates
  - R Packages
    - sgpv::fdrisk()
    - FDRestimation::p.fdr()

Equivalence Tests

- Establish bioequivalence between data and an established equivalence range or interval null
- 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
  - $H_0 = [\theta^-, \theta^+]$

TOST Test

- Most popular frequentist test is the Two One-Sided t-tests (TOST) (Schuirmann 1987)
  - Flips the null and alternative (be careful)
  - Uses the $(1-2\alpha)\%$ confidence interval (be careful)

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

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

TOST Test

- **Fail to reject the (original) null:** The confidence interval is outside of the indifference zone

$$H_0\colon (\theta < \theta^- \ or \ \theta > \theta^+)$$

- **Reject the (original) null:** The confidence interval is contained within the indifference zone

$$H_1\colon (\theta \geq \theta^- \ and \ \theta \leq \theta^+)$$

- Reported p-value is the p-value of largest magnitude from the two one-sided tests

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

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 $|I| > 2|H_0|$

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TOST vs. SGPV comparison

		SGPV Outcomes		
		Consistent with the alternative (SGPV near 0)	**Inconclusive** (SGPV near ½)	**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**

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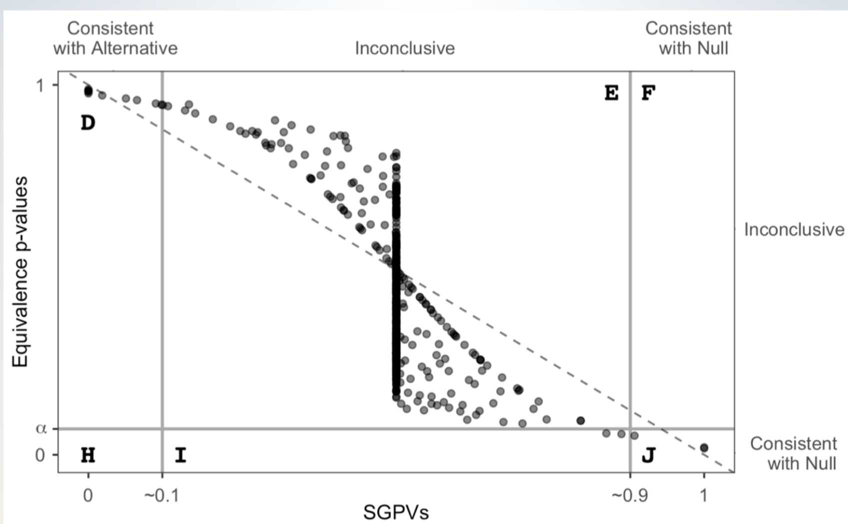
TOST v SGPV Simulation

- Simulate TOST and SGPV reported p-values
  - Data generated under the null, $N(0,1)$
  - Sample size of n=6
  - Yields 70% power for $\Delta = 1$ with 5% type 1 error
  - Indifference zone is $[\theta^-, \theta^+] = [-0.375, 0.375]$
  - Uncertainty interval is 95% confidence interval
  - 500 iterations (for illustration)

TOST vs. SGPV comparison



TOST vs. SGPV comparison

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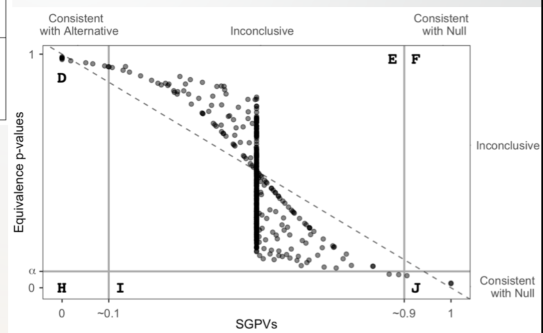
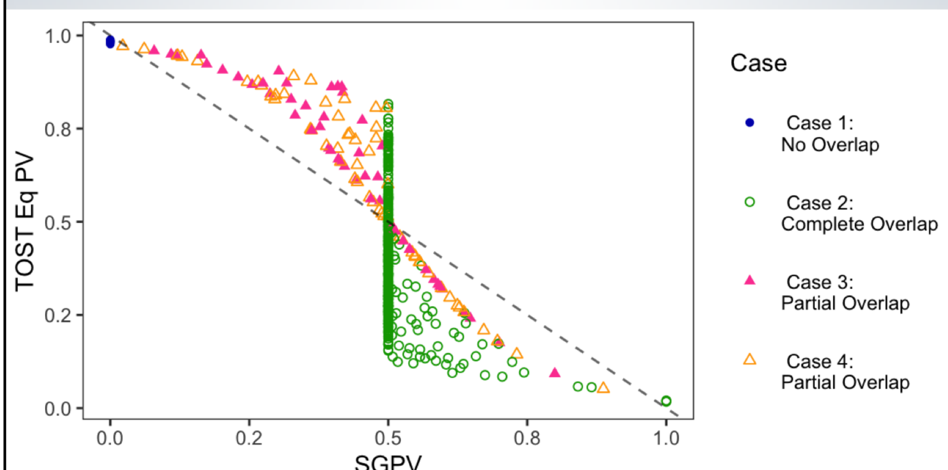
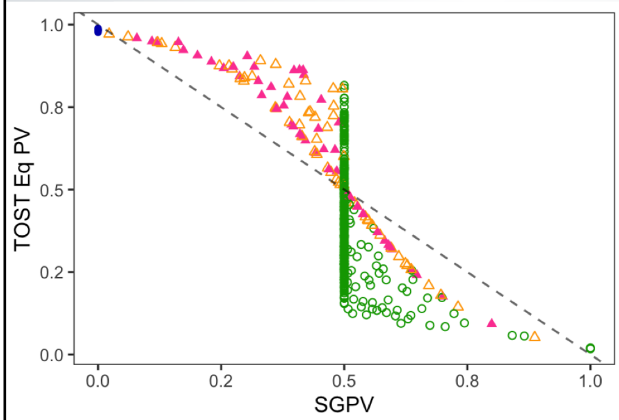
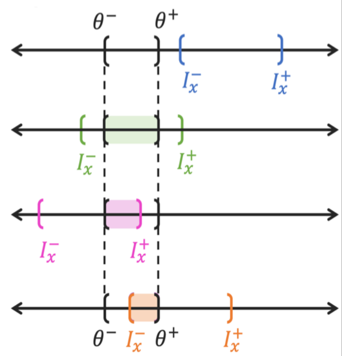


TOST vs. SGPV comparison



TOST vs. SGPV comparison





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Relationship

- Derived the mathematical relationship in all cases of overlap
- Case 3 and 4 of partial overlap:

$$p_\delta = \left[\left(\frac{1}{2c_\alpha}\right)\mathrm{F}_{\mathrm{n}}^{-1}(1-p_T) + \frac{1}{2}\right] \times max\left\{\frac{\frac{c_\alpha S}{\sqrt{n}}}{(\theta^+ - \theta^-)}, 1\right\}$$

- Limiting behavior under the null

$$P(Case\ 2) \to 1$$

$p_\delta \to 1$ (right)

$p_T \to 0$ (bottom)

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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	• Indicates when data agree with null or alternative without additional testing
• No measure of overlap included in computation	• Includes overlap in reported p-value

Comparison

- TOST and SGPV are not one-to-one unless the variance is known

- TOST has significant limitations
- *SGPV is more flexible and easier to interpret*

Time for Code Part 2a!

10 Minute Break!

Statistical Properties

Suppose interval I has coverage probability 1-α, then

Three 'Error' Rates

1. $P(p_\delta = 0|H_0) \le \alpha$ and $\rightarrow 0$ as $n \rightarrow \infty$
2. $P(p_\delta = 1|H_1) \le \alpha$ and $\rightarrow 0$ as $n \rightarrow \infty$
3. $P(0 < p_\delta < 1|H)$ controlled through sample size

Two False Discovery Rates

1. $P(H_0 \mid p_\delta = 0)$
2. $P(H_1 \mid p_\delta = 1)$

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%

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)

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

Error rates

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

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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)

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

Error Rates

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

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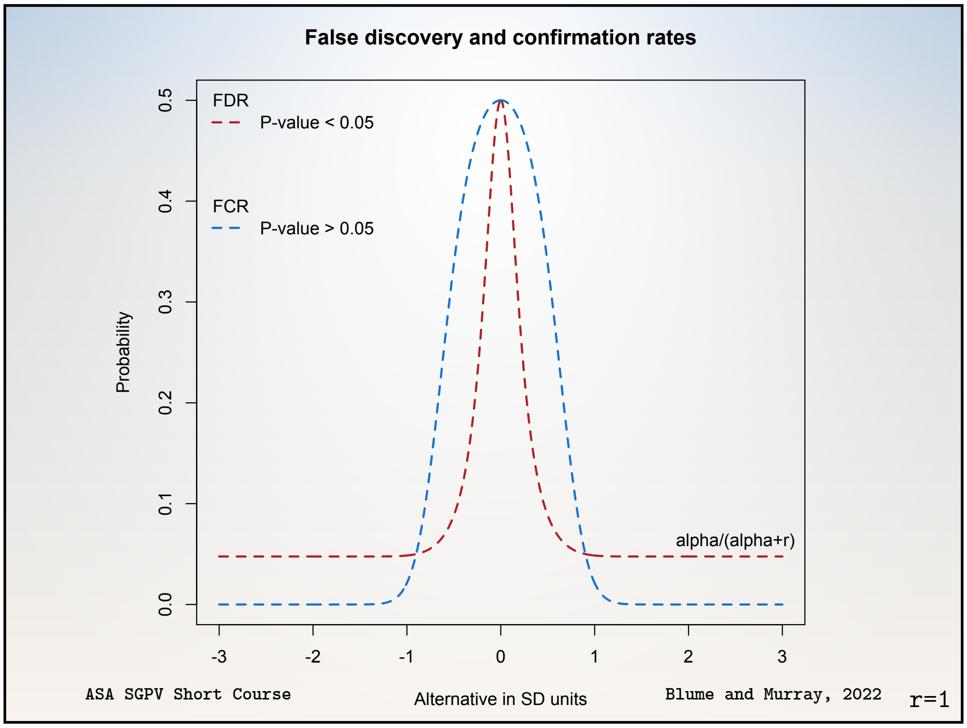
False discovery and confirmation rates
FDR
P-value < 0.05
FCR
P-value > 0.05
alpha/(alpha+r)
Probability
0.0
0.1
0.2
0.3
0.4
0.5
-3
-2
-1
0
1
2
3
Alternative in SD units
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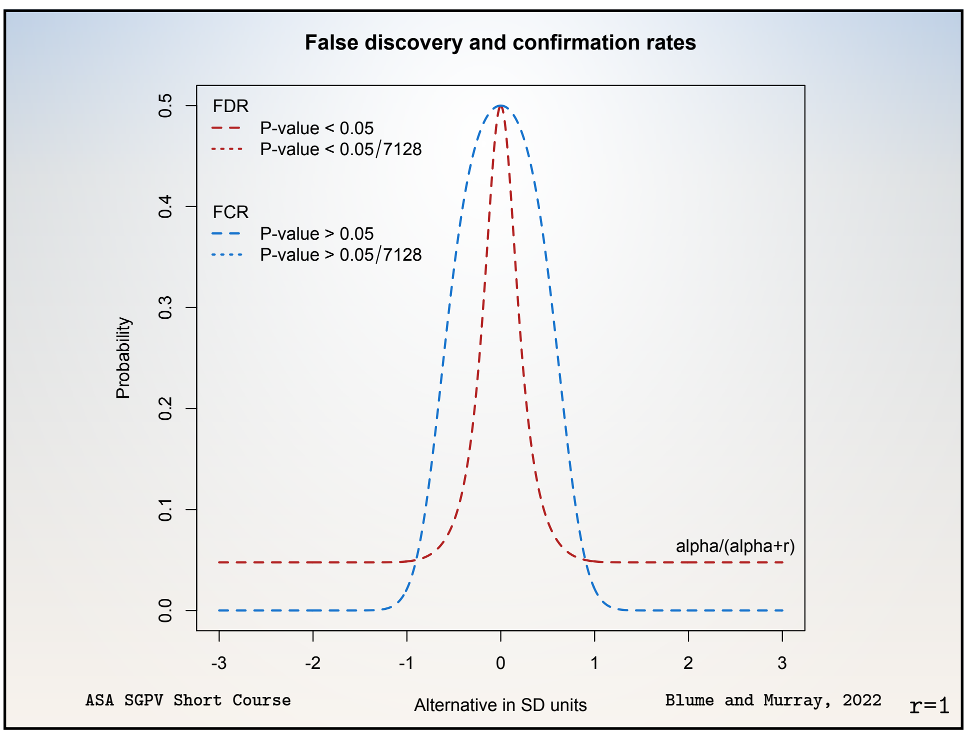
r=1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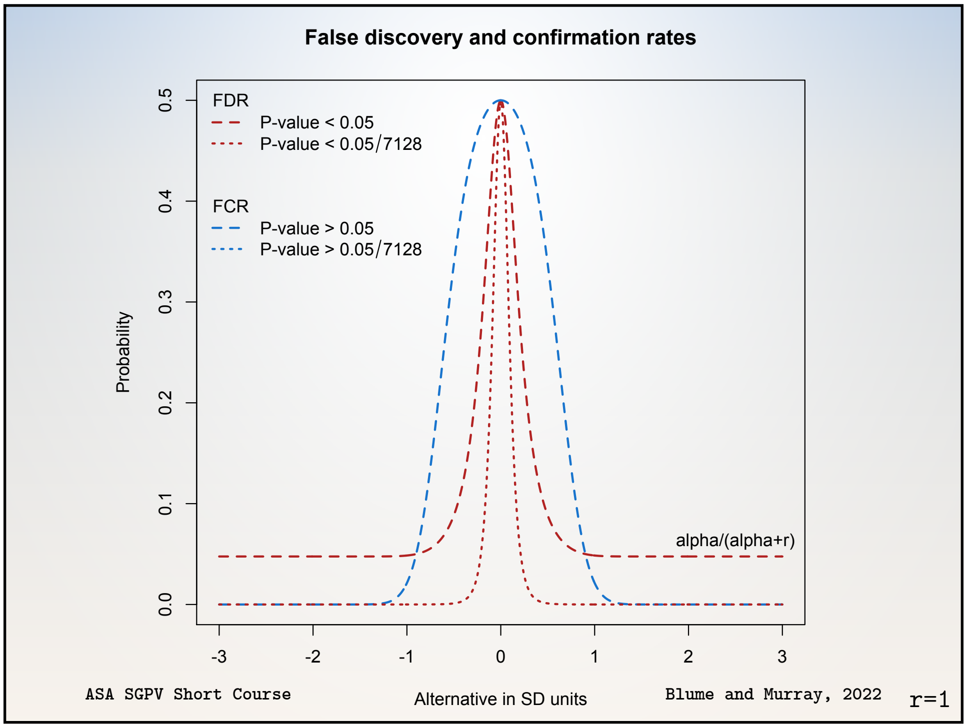
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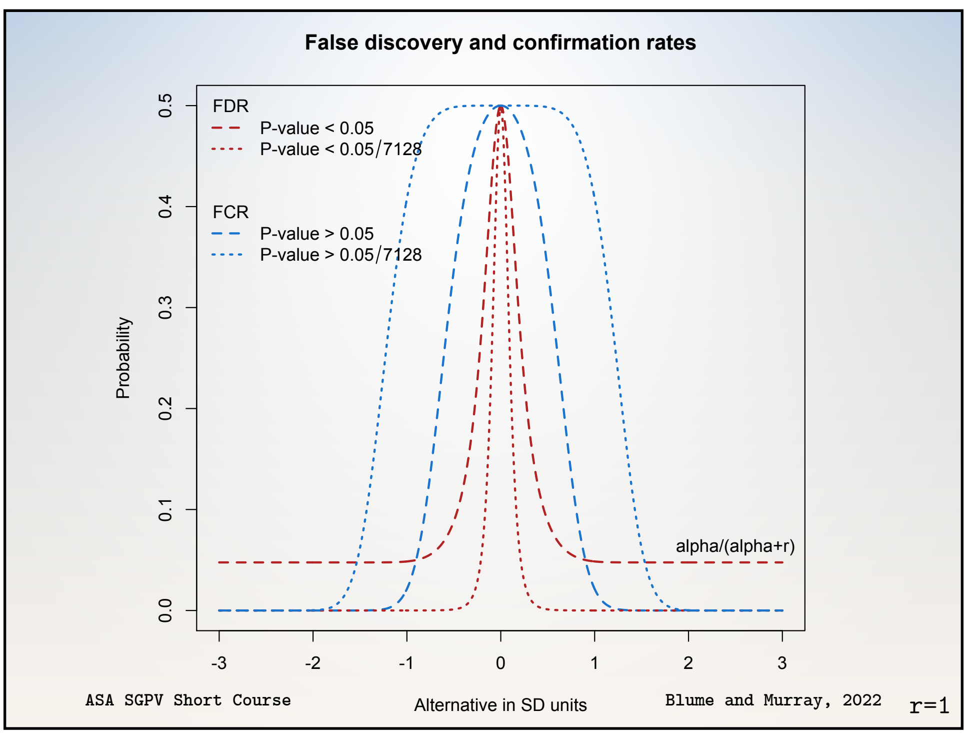
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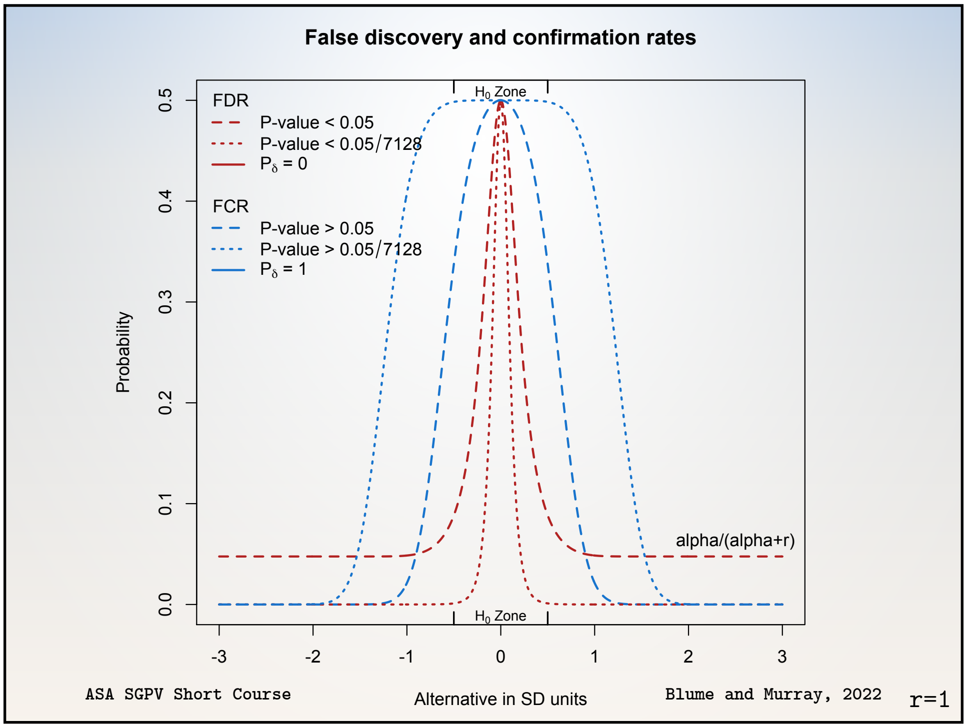
False discovery and confirmation rates
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$P_\delta = 0$
FCR
P-value > 0.05
P-value > 0.05/7128
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H_0 Zone
H_0 Zone
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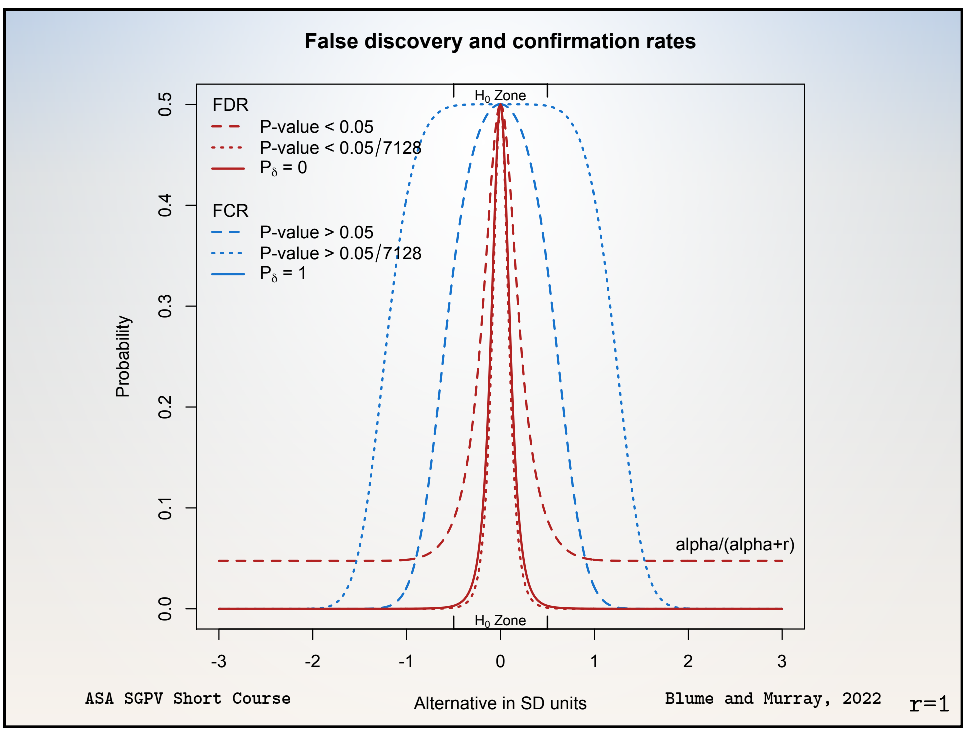
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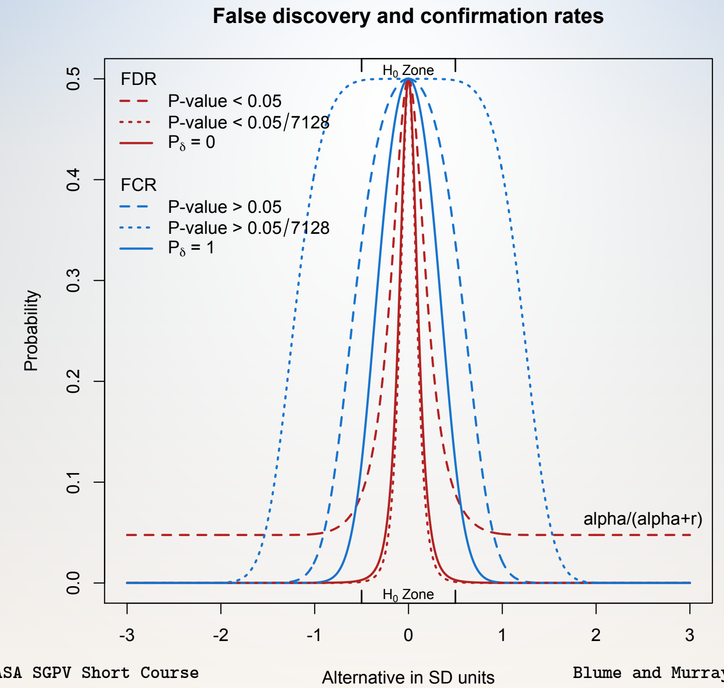

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FDR R Packages

- 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.

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Time for Code Part 2b!

10 Minute Break!