Clinical trials with multiple objectives – optimal rejection regions based on Neyman-Pearson tests

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General Framework

- Interested in testing two elementary null hypotheses $H_i : \mu_i \leq 0$ $(i = 1, 2)$
- Associated with two (correlated) bivariate normal Z-statistics

$$Z_1, Z_2 \sim N\left((\mu_1, \mu_2), \begin{bmatrix} 1 & \rho \\ \rho & 1 \end{bmatrix}\right)$$

- Directly applicable to common testing scenarios, e.g.:
    - Comparison of two treatment arms against a common control with equal sample sizes for all 3 groups gives $\rho = 0.5$, i.e "Dunnett Situation" (ρ will depend on the allocation ratio)
    - When testing the full population and a subgroup (ρ will depend on size of subgroup)
    - Correlated co-primary endpoints (here ρ usually is unknown)
- Type I error inflation when each hypothesis is tested naively at α

Objectives

- How can we test an elementary null hypothesis $H_i : \mu_i \leq 0$ ($i = 1, 2$)
  - while controlling Familywise Error Rate (FWER) at level α?
  - and maximising the power?

FWER: probability of incorrectly rejecting at least one null hypothesis

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- Use closed testing principle and define test for the intersection hypothesis
  - Reject H_i if $Z_i \geq z_{1-\alpha}$ and a test for the intersection H_{12} can be rejected at level α
  - Intersection point null $H_{12} : (\mu_1, \mu_2) = (0, 0)$
  - Maximising power at $(\mu_1, \mu_2) = (\theta_1', \theta_2')$
  - Controlling Type I Error Rate under the point null at level α

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- Apply Neyman-Pearson Lemma

FWER: probability of incorrectly rejecting at least one null hypothesis

Optimising The Intersection Hypothesis H_{12} Test

- According to Neyman-Pearson Lemma the most powerful test for testing H_{12} against point alternative has the rejection region in a Z_1 and Z_2 plane

$$R = \{(Z_1, Z_2) | w_1 Z_1 + w_2 Z_2 \geq c\},$$

where $w_1 = \frac{\theta_1' - \rho\theta_2'}{(1-\rho^2)}$, $w_2 = \frac{\theta_2' - \rho\theta_1'}{(1-\rho^2)}$, and

$c = \Phi^{-1}(1-\alpha)\sqrt{w_1^2 + w_2^2 + 2 w_1 w_2 \rho}$

- For a proof see Bittman et al (2009)

Optimal Rejection Regions

The rejection region boundary $w_1 Z_1 + w_2 Z_2 = c$ has a negative slope if

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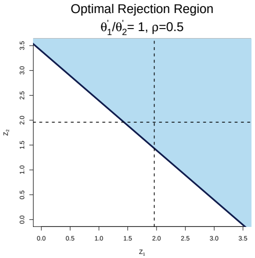

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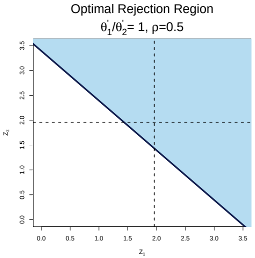

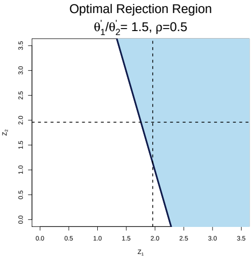

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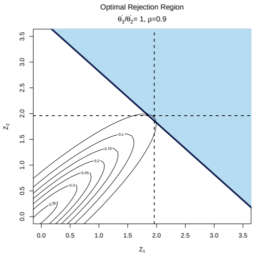

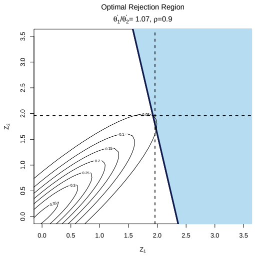

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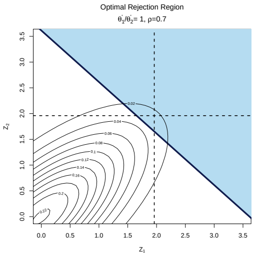

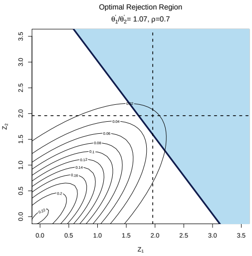

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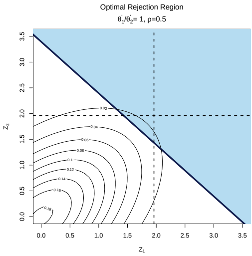

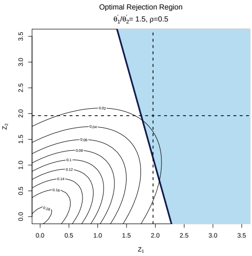

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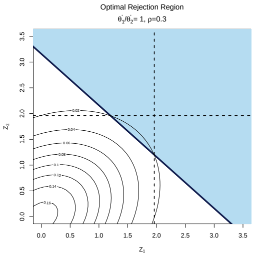

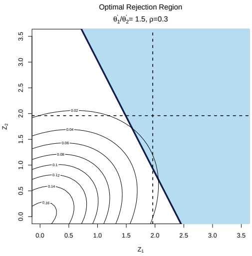

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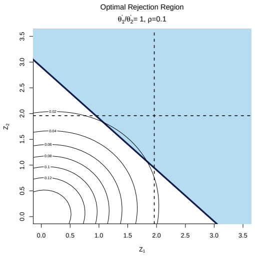

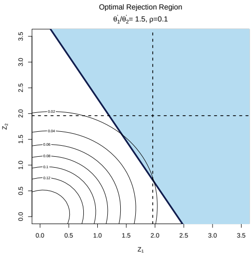

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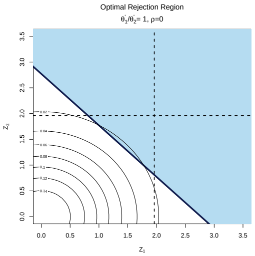

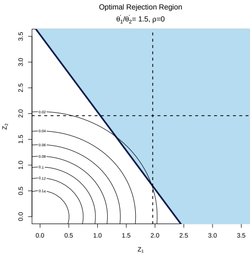

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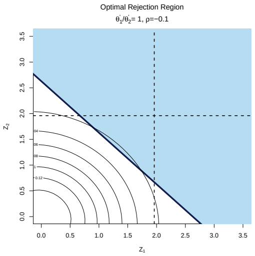

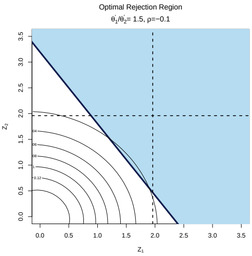

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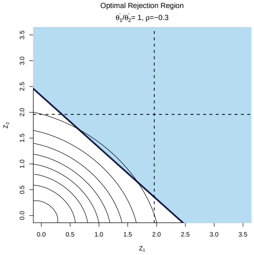

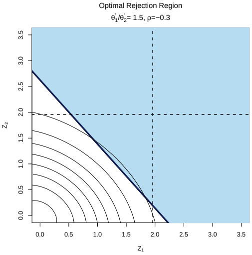

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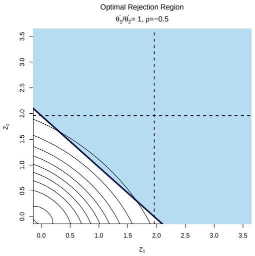

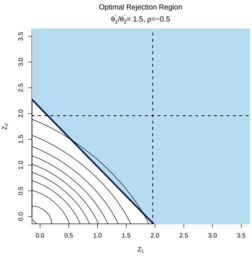

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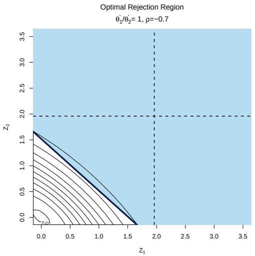

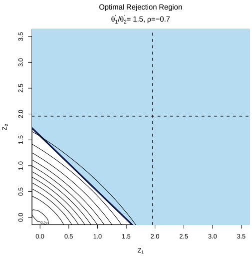

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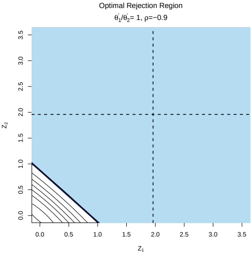

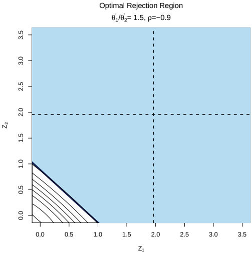

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- Is a vertical line if $\theta_1'/\theta_2' = 1/\rho$ for $\rho \geq 0$
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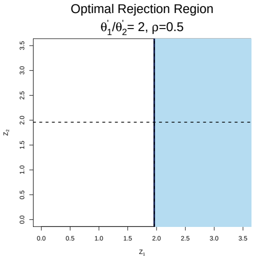

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- Is a horizontal line if $\theta_1'/\theta_2' = \rho$ for $\rho \geq 0$
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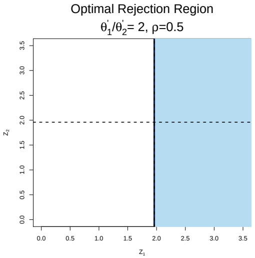

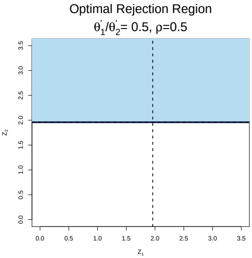

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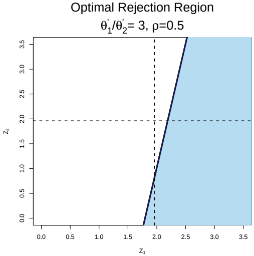

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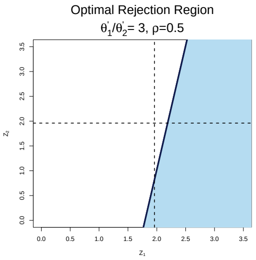

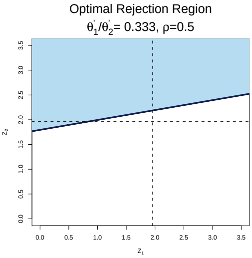

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Under these configurations Type I Error of point null hypothesis H_{12} is controlled, but NOT of the composite null hypothesis
$H_{12} = \{(\mu_1, \mu_2) | \mu_1 \leq 0 \wedge \mu_2 \leq 0\}$

- E.g. Type I Error when $(\mu_1 = 0, \mu_2 \to -\infty) = 1!$

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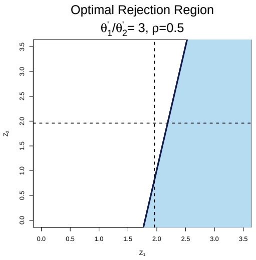
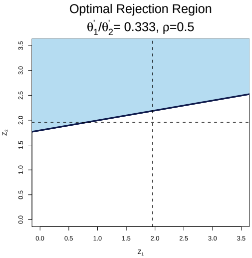
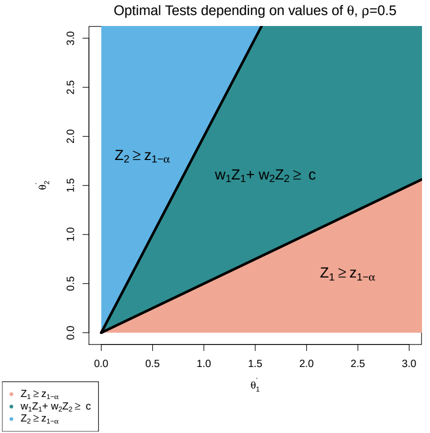




Testing Composite Intersection Null Hypothesis



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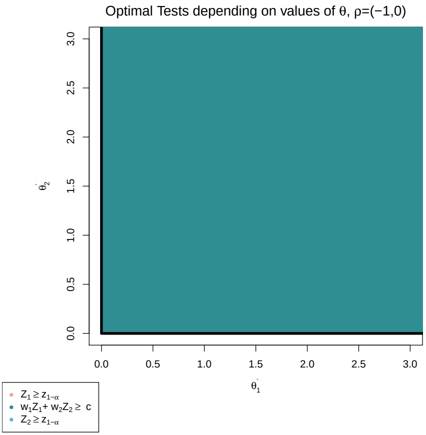

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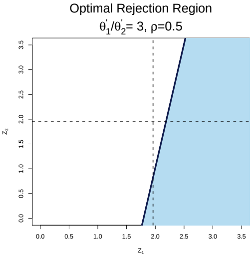
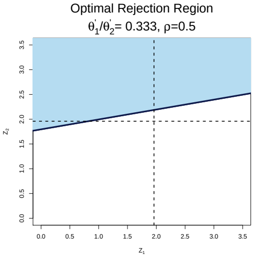


Rejection Region for The Point Null H_{12}



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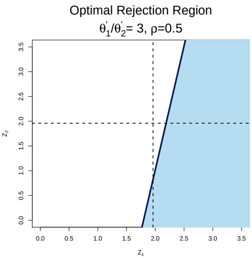

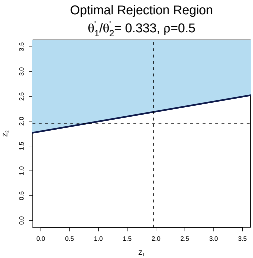

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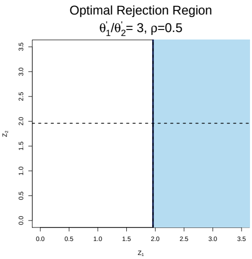
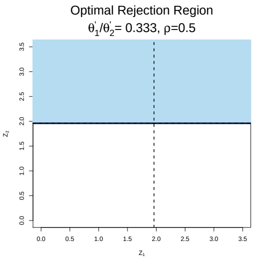
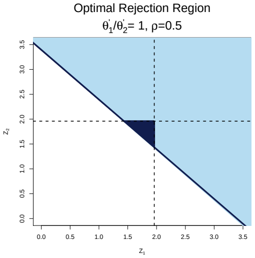


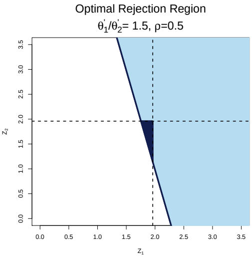


Rejection Region for The Composite Null H_{12}

Testing Elementary Hypotheses

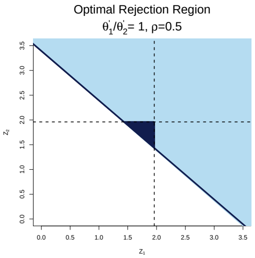
NON-CONSONANT TESTS

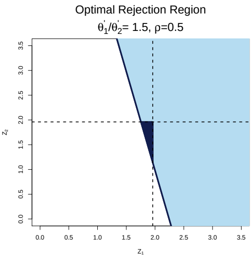




Consonant Rejection Regions

- If the rejection region boundary has a negative slope the test is non-consonant
  - For some outcomes the intersection hypothesis is rejected but none of the elementary hypotheses H_i $(i = 1, 2)$ can be rejected





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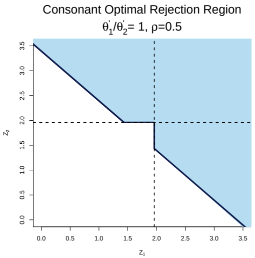
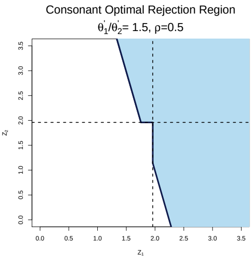
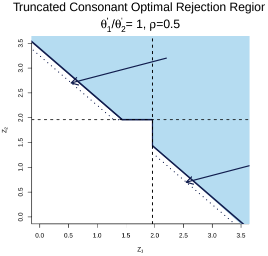
- Rejection regions and solutions for $\theta'_1 = \theta'_2$ already discussed in the literature (see e.g. Bittman et al (2009), Su et al (2012))
  - Exclusion of the region where H_1 and H_2 cannot be rejected

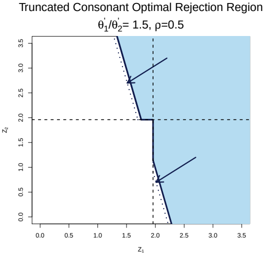




Consonant Rejection Regions

- If the rejection region boundary has a negative slope the test is non-consonant
  - For some outcomes the intersection hypothesis is rejected but none of the elementary hypotheses H_i $(i = 1, 2)$ can be rejected
- Rejection regions and solutions for $\theta'_1 = \theta'_2$ already discussed in the literature (see e.g. Bittman et al (2009), Su et al (2012))
  - Exclusion of the region where H_1 and H_2 cannot be rejected
  - Shift of the rejection line





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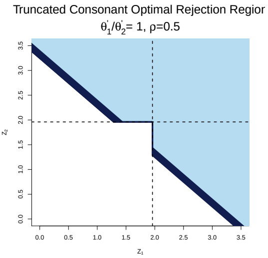
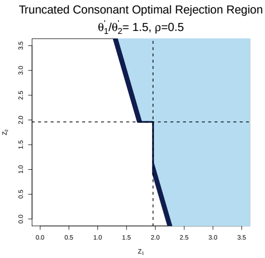
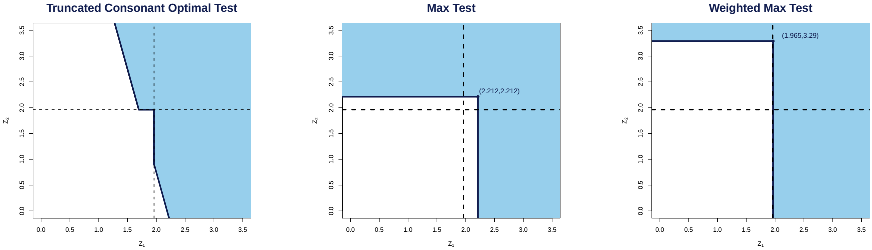




Power Considerations Within Closed Testing:

$\rho = 0.5,\ \theta'_1 = 3,\ \theta'_2 = 2$



True Effect	Disjunctive Power		
$\mu_1 = 3.0,\ \mu_2 = 2.0$	0.86151	0.81915	0.85117

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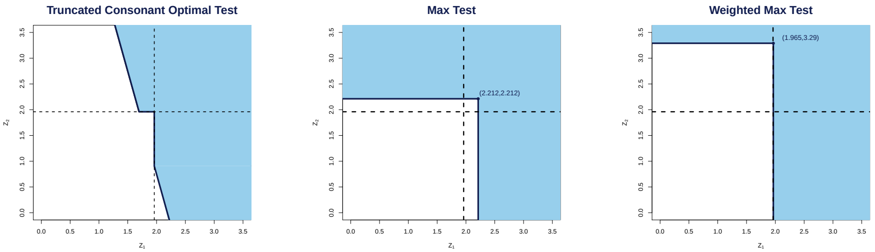
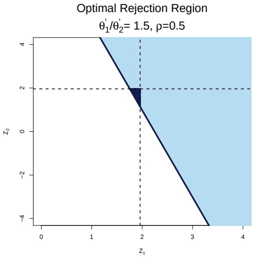


True Effect	Disjunctive Power		
$\mu_1 = 3.0$, $\mu_2 = 2.0$	0.86151	0.81915	0.85117
$\mu_1 = 1.5$, $\mu_2 = 3.0$	0.51703	0.79752	0.50952

How to make optimal tests more robust?

- Alternative approaches
  - Instead of shifting the line, bound the region with horizontal and vertical lines while fully exhausting α



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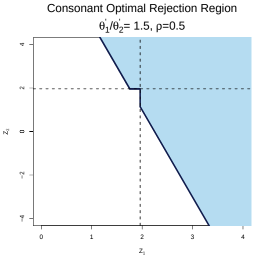

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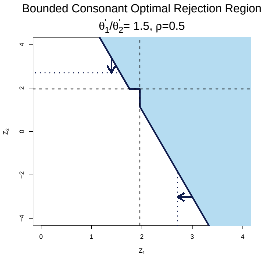

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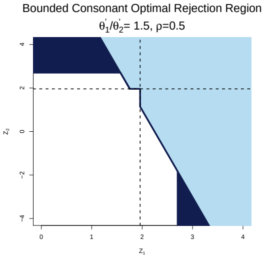

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- Alternative approaches
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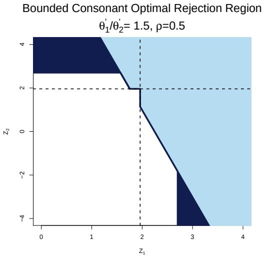
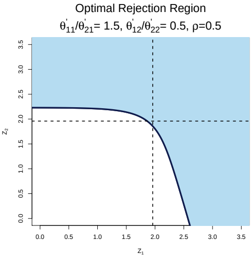
  - Use a two-point alternative, each with assigned probability





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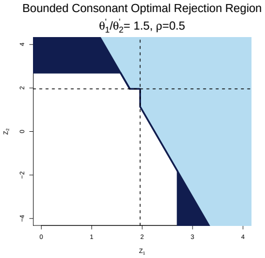

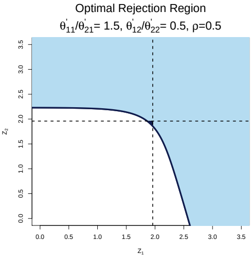

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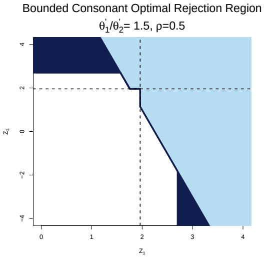
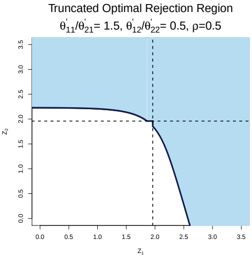
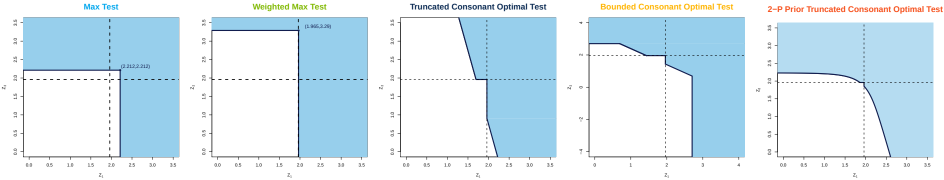




How to make optimal tests more robust?

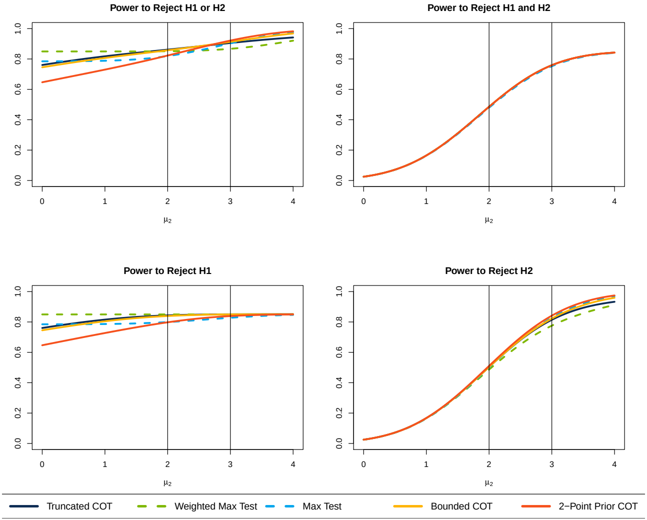
- Alternative approaches
  - Instead of shifting the line, bound the region with horizontal and vertical lines while fully exhausting α
  - Use a two-point alternative, each with assigned probability
- In the following we compare all 5 approaches:



Robustness of approaches when μ is different than θ'

Design parameters: $\theta'_1 = 3.0$, $\theta'_2 = 2.0$, $(\theta''_1 = 1.5$, $\theta''_2 = 3.0)$

True values: $\mu_1 = 3.0$, μ_2: shown on x-axis



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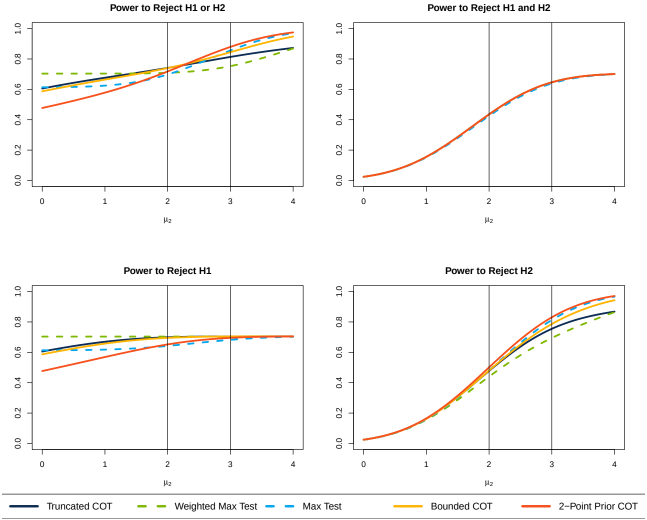
Design parameters: $\theta'_1 = 3.0$, $\theta'_2 = 2.0$, $(\theta''_1 = 1.5$, $\theta''_2 = 3.0)$

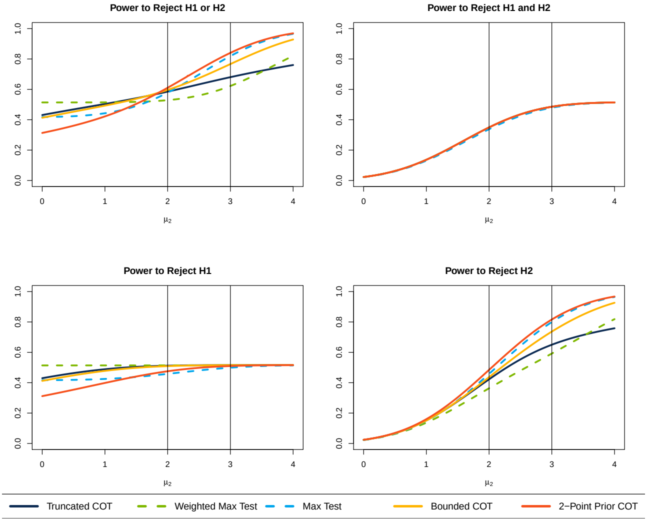
True values: $\mu_1 = 2.5$, μ_2: shown on x-axis



Robustness of approaches when μ is different than θ'

Design parameters: $\theta_1' = 3.0$, $\theta_2' = 2.0$, $(\theta_1'' = 1.5, \theta_2'' = 3.0)$

True values: $\mu_1 = 2.0$, μ_2: shown on x-axis



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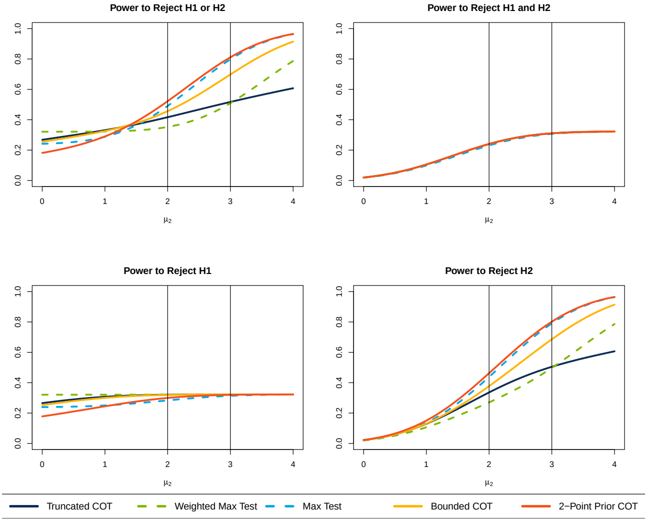
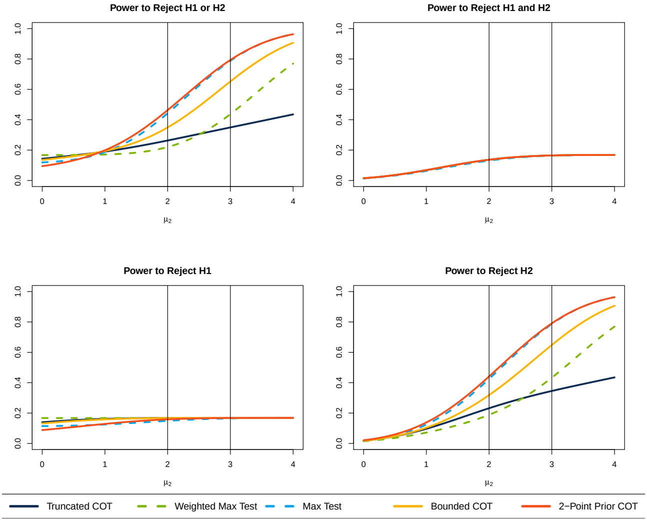
Design parameters: $\theta'_1 = 3.0$, $\theta'_2 = 2.0$, $(\theta''_1 = 1.5, \theta''_2 = 3.0)$
True values: $\mu_1 = 1.5$, μ_2: shown on x-axis



Robustness of approaches when μ is different than θ'

Design parameters: $\theta_1' = 3.0$, $\theta_2' = 2.0$, ($\theta_1'' = 1.5$, $\theta_2'' = 3.0$)

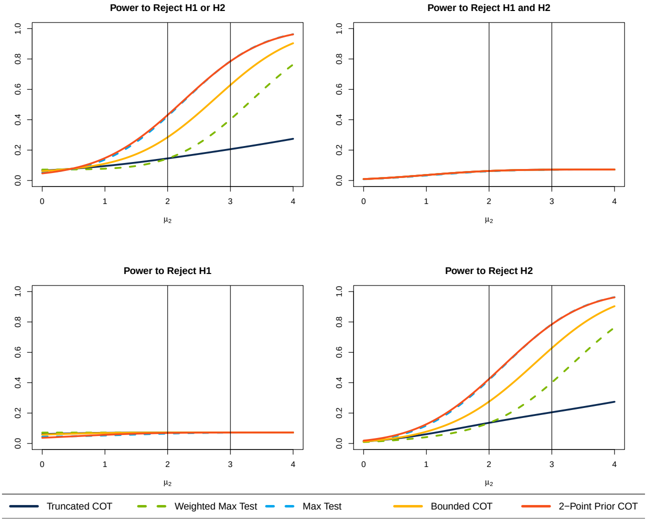
True values: $\mu_1 = 1.0$, μ_2: shown on x-axis



Robustness of approaches when μ is different than θ'

Design parameters: $\theta'_1 = 3.0$, $\theta'_2 = 2.0$, ($\theta''_1 = 1.5$, $\theta''_2 = 3.0$)

True values: $\mu_1 = 0.5$, μ_2: shown on x-axis



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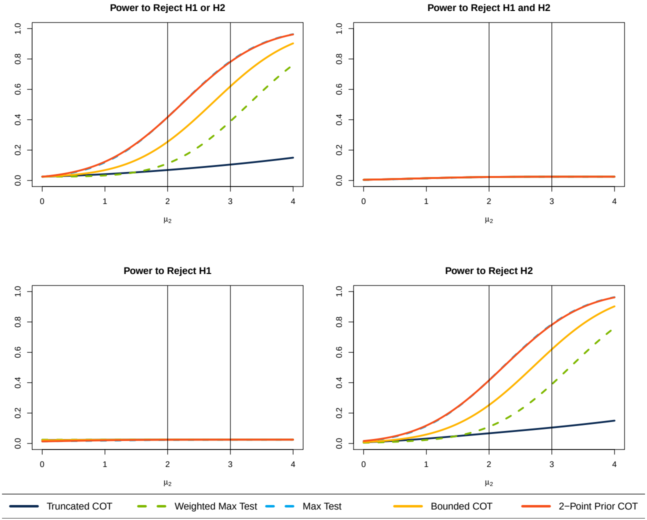

Remarks on correlation

- (Consonant) Optimal test directly applicable if ρ is known. This is the case if correlation is induced by design (e.g., for many-one comparisons or subgroup testing)
- More problematic if ρ is unknown, e.g., for different endpoints.
    - good knowledge and/or conservative assumption on ρ
    - plug-in observed correlation
    - plug-in boundary of an confidence interval for observed correlation (Berger and Boos, 1994)

Conclusions

- We found optimal test for intersection hypothesis H_{12} with a composite null
- In a Dunnett Situation the Consonant Optimal Test achieves higher power that the (Weighted) Max Test under the target effects
- However, there might be a power loss if the true effect size differs from the pre-specified alternative
- More robust approaches such as Bounded Consonant Optimal Test or use of two-point alternatives can improve the power results
- Use of utility functions (e.g. more weight on one hypothesis, number of rejected hypotheses ...) can be another approach for finding optimal rejection regions (not discussed here)

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Are there any questions?

BACK-UP

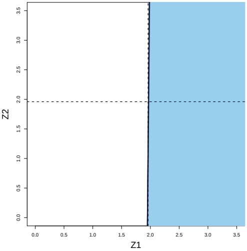
Optimal Rejection Regions

The rejection region boundary has a positive slope if

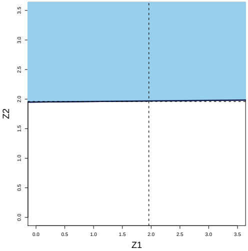
- $\theta_1'/\theta_2' > 1/\rho$ for $\rho > 0$
- $\theta_1'/\theta_2' < \rho$ for $\rho > 0$

$\rho = 0.1$:

$\theta_1'/\theta_2' = 11$



$\theta_1'/\theta_2' = 1/11$



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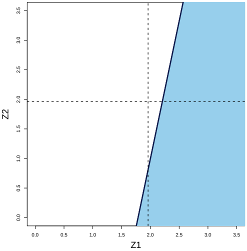
- $\theta_1'/\theta_2' > 1/\rho$ for $\rho > 0$
- $\theta_1'/\theta_2' < \rho$ for $\rho > 0$

$\rho = 0.3$:

$\theta_1'/\theta_2' = 11$



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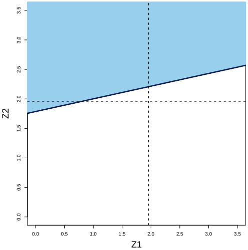

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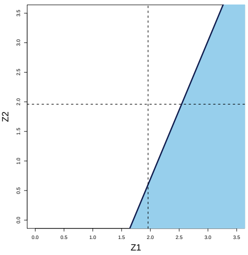
- $\theta_1'/\theta_2' > 1/\rho$ for $\rho > 0$
- $\theta_1'/\theta_2' < \rho$ for $\rho > 0$

$\rho = 0.5$:

$\theta_1'/\theta_2' = 11$



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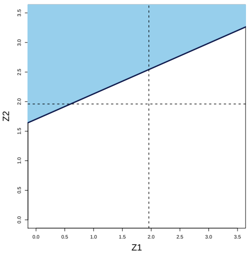


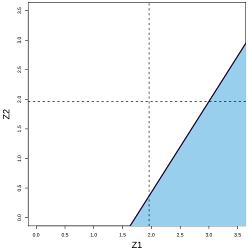
Optimal Rejection Regions

The rejection region boundary has a positive slope if

- $\theta_1'/\theta_2' > 1/\rho$ for $\rho > 0$
- $\theta_1'/\theta_2' < \rho$ for $\rho > 0$

$\rho = 0.7$:

$\theta_1'/\theta_2' = 11$



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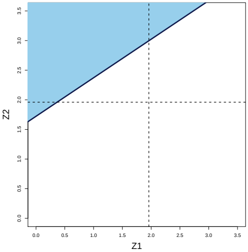


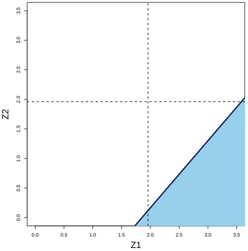
Optimal Rejection Regions

The rejection region boundary has a positive slope if

- $\theta_1'/\theta_2' > 1/\rho$ for $\rho > 0$
- $\theta_1'/\theta_2' < \rho$ for $\rho > 0$

$\rho = 0.9$:

$\theta_1'/\theta_2' = 11$



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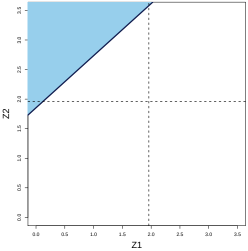
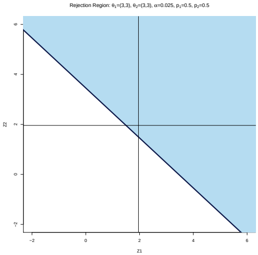


Two-point alternative

Two sets of alternatives considered such that:

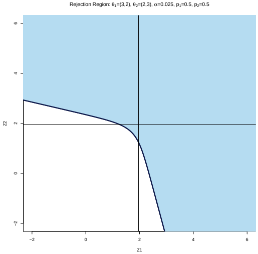
- $ALR = \frac{f_{H'}(Z_1,Z_2)}{f_H(Z_1,Z_2)} = \frac{\sum_{i=1}^{2} p_i f_{H'_i}(Z_1,Z_2)}{f_H(Z_1,Z_2)}$
- Rejection region cannot be found analytically. Numerical approximation instead
- Rejection regions change depending on $\theta'_{1i}/\theta'_{2i}$

Two-point Alternative Rejection Regions



- Rejection regions change depending on $\theta'_{1i}/\theta'_{2i}$
  - If none of the alternatives has $\theta'_1/\theta'_2 > 1/\rho$, then the shape does not cross the lines $Z_{1-\alpha}$

Two-point Alternative Rejection Regions



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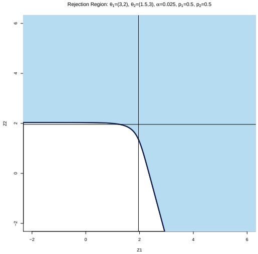

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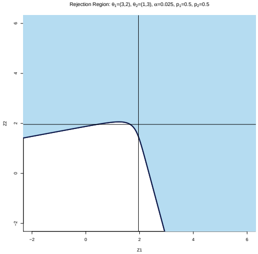

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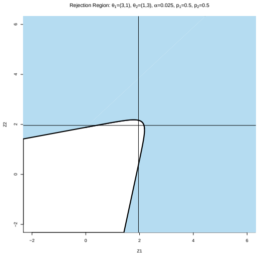
Two-point Alternative Rejection Regions



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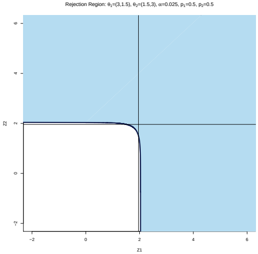
  - If none of the alternatives has $\theta'_1/\theta'_2 > 1/\rho$, then the shape does not cross the lines $Z_{1-\alpha}$
  - If one of the alternatives has $\theta'_1/\theta'_2 > 1/\rho$, then the rejection region boundary crosses $Z_{1-\alpha}$
  - If the alternatives have $\theta'_1/\theta'_2 > 1/\rho$ and $\theta'_2/\theta'_1 > 1/\rho$, then the rejection region boundary crosses the lines $Z_i = Z_{1-\alpha}$

Two-point Alternative Rejection Regions



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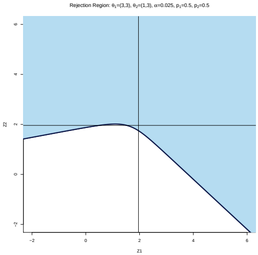
Two-point Alternative Rejection Regions



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  - If the alternatives have $\theta'_1/\theta'_2 > 1/\rho$ and $\theta'_2/\theta'_1 > 1/\rho$, then the rejection region boundary crosses the lines $Z_i = Z_{1-\alpha}$

Two- and N-Point Priors

- Conjecture that rejection boundary of optimal test is concave for any prior
- For consonant test, truncation has to be performed
- For smaller values of z-statistics, the rejection region would be bounded by $z_{1-\alpha}$.

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