Testing Endpoints With Unknown Correlation

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Multiple testing procedures using joint distribution

EMA draft "Guideline on multiplicity issues in clinical trials":

> *"Controlling the type I error rate study-wise is frequently done by splitting the accepted and pre-specified type I error rate α and by then testing the various null hypotheses at fractions of α [...] Other test procedures are available, that can be* **more powerful if the correlation between the test statistics are taken into account***, e.g. the Dunnett's test on multiple comparisons to a single control."*

FDA draft guidance on "Multiple Endpoints in Clinical Trials":

> *"Because it is difficult to know the true correlation structure among different endpoints (not simply the observed correlations within the dataset of the particular study),* **it is generally not possible to statistically adjust (relax) the Type I error rate for such correlations***."*

Design setting

- **Interest**: Comparing two endpoints (1,2) between two groups (T,C)
- **Null hypotheses**:

$$\text{Endpoint 1: } H_1 : \mu_1^T \leq \mu_1^C \text{ vs. } H_1' : \mu_1^T > \mu_1^C$$
$$\text{Endpoint 2: } H_2 : \mu_2^T \leq \mu_2^C \text{ vs. } H_2' : \mu_2^T > \mu_2^C$$

- Control of **familywise error rate (FWER)** at $\alpha = 0.025$
- The observations $\boldsymbol{Y}_i^j = (Y_{i1}^j, Y_{i2}^j)$, $j \in \{T, C\}$, $i = 1, ..., n$, are independently standard **normally distributed** with mean $\begin{pmatrix} \mu_1^j \\ \mu_2^j \end{pmatrix}$ and covariance matrix $\boldsymbol{\Sigma} = \begin{pmatrix} 1 & \rho \\ \rho & 1 \end{pmatrix}$
- **Problem**: same but **unknown** correlation ρ between endpoints
- Distribution of the z statistics $\boldsymbol{Z} = (Z_1, Z_2) \sim N((\theta_1, \theta_2), \boldsymbol{\Sigma})$

Dealing with the unknown correlation

1. **Adjust for fixed assumed correlation**:
   The critical values are calculated for some assumed correlation. If ρ is misspecified, this may result in an inflation of the FWER above the pre-specified α level.

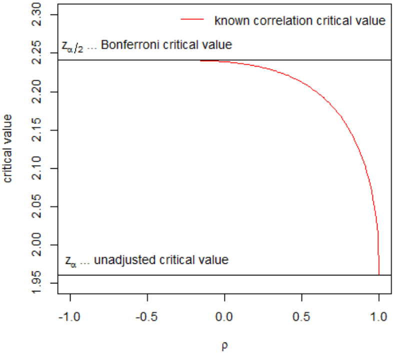
2. **Plug-in estimated correlation**:
   An estimate of the correlation between the endpoints can be used to derive the critical values. Depending on the distribution of the estimator, this may also inflate the α level. Asymptotically the method controls the FWER for a consistent estimator.

3. **Apply improved Berger and Boos method**:
   The type I error rate is maximized over a confidence interval of ρ. The significance level is adjusted for the coverage probability such that the overall type I error rate is controlled at level α.

Critical values for known true correlation ρ

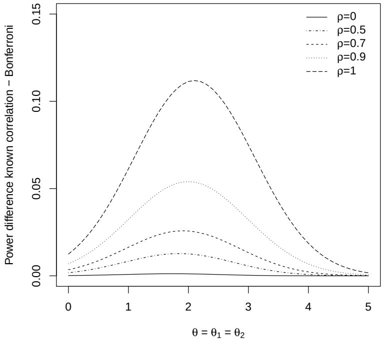
If the true correlation ρ between the test statistics is known (e.g. Dunnett test), the critical values can be calculated under the global point null hypothesis $H_0 : \delta_1 = \delta_2 = 0$:

$$
\begin{aligned}
&1 - P_{H_0,\rho}(Z_1 \leq c_1(\rho,\alpha), Z_2 \leq c_2(\rho,\alpha)) = \alpha \\
&\geq 1 - P_{\delta_1 \leq 0, \delta_2 \leq 0, \rho}(Z_1 \leq c_1(\rho,\alpha), Z_2 \leq c_2(\rho,\alpha))
\end{aligned}
$$



For equal critical values: $c_1(\rho,\alpha) = c_2(\rho,\alpha) = c(\rho,\alpha)$

Improvement due to correlation compared to Bonferroni



Disjunctive power, $\theta_1 = \theta_2 = \theta$

ρ	θ_{max}	power difference
0.5	1.8	0.013
0.7	1.9	0.026
0.9	2.0	0.054
1	2.1	0.112

Sample size for power=0.8

ρ	sample size improvement
0.5	2.2%
0.7	4.5%
0.9	9.0%
1	17.4%

Correlation between endpoints is usually unknown, but often assumed known: Tamhane (2010), Kunz (2015), Li (2017)

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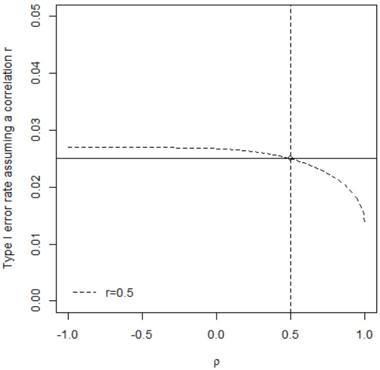
   The type I error rate is maximized over a confidence interval of ρ. The significance level is adjusted for the coverage probability such that the overall type I error rate is controlled at level α.

Type I error rate assuming certain correlation

r ... assumed correlation, ρ ... true correlation, $H_0: \delta_1 = \delta_2 = 0$

The inflation in type I error rate is maximal for equal critical values:
Calculation of critical values: $1 - P_{H_0,r}(Z_1 \leq c(r,\alpha), Z_2 \leq c(r,\alpha)) = \alpha$
Type I error rate: $FWER(\rho) = 1 - P_{H_0,\rho}(Z_1 \leq c(r,\alpha), Z_2 \leq c(r,\alpha))$



- The type I error rate decreases with the true correlation ρ, lies above $\alpha = 0.025$ for $\rho < r$ and is maximal for $\rho = -1$.
- The type I error rate increases with the assumed correlation r and is maximal for $r = 1$.

Type I error rate assuming certain correlation

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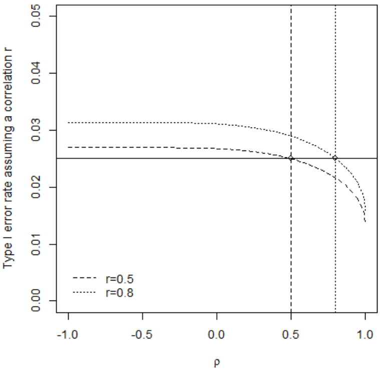

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$r \ldots$ assumed correlation, $\rho \ldots$ true correlation, $H_0 : \delta_1 = \delta_2 = 0$

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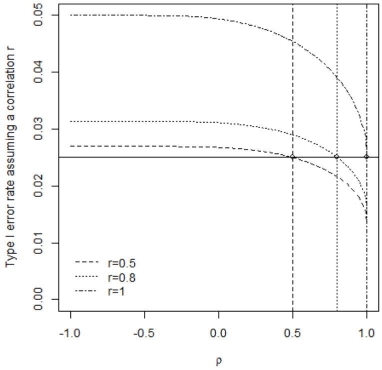

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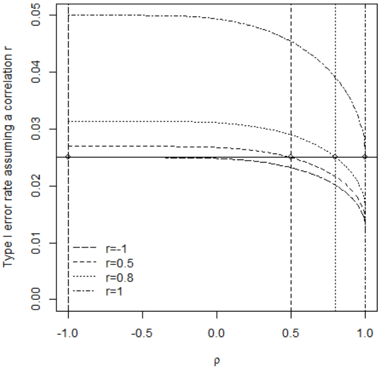

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Dealing with the unknown correlation

1. **Adjust for fixed assumed correlation**:
   The critical values are calculated for some assumed correlation. If ρ is misspecified, this may result in an inflation of the FWER above the pre-specified α level.

2. **Plug-in estimated correlation**:
   An estimate of the correlation between the endpoints can be used to derive the critical values. Depending on the distribution of the estimator, this may also inflate the α level. Asymptotically the method controls the FWER for a consistent estimator.

3. **Apply improved Berger and Boos method**:
   The type I error rate is maximized over a confidence interval of ρ. The significance level is adjusted for the coverage probability such that the overall type I error rate is controlled at level α.

Type I error rate plugging in estimated correlation

- If we plug in the estimate of the correlation between the endpoints the FWER would be:

$$FWER(\rho) = 1 - \int P_{H_0,\rho}(Z_1 \leq c(\hat{r}, \alpha), Z_2 \leq c(\hat{r}, \alpha)|\hat{r}) f_\rho(\hat{r}) d\hat{r}$$

with critical values calculated solving

$$1 - P_{H_0,\hat{r}}(Z_1 \leq c(\hat{r}, \alpha), Z_2 \leq c(\hat{r}, \alpha)) = \alpha$$

- When using a consistent estimator of ρ the FWER for large sample sizes is asymptotically controlled.

- For small sample sizes the inflation in type I error rate depends on the whole distribution of the estimator.

Calculate a sample estimate of the correlation

Averaging across Pearson correlation estimates from two samples $\hat{r}_C$, $\hat{r}_T$:
$\hat{r}_j = \frac{1}{n-1}\sum_{i=1}^{n}(Y_{i1}^j - \bar{Y}_1^j)(Y_{i2}^j - \bar{Y}_2^j)$, $j \in \{C, T\}$ and $\bar{Y}_k^j = \frac{1}{n}\sum_{i=1}^{n} Y_{ik}^j$

Different estimators for correlation estimation

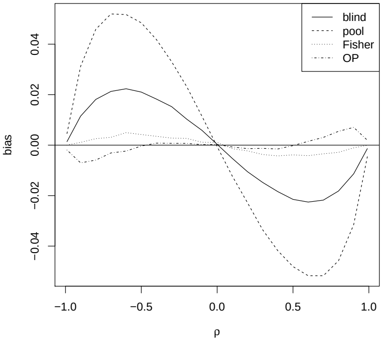
$\hat{r}_{pool}$	$\hat{r}_{pool} = \frac{\hat{r}_C + \hat{r}_T}{2}$	pooled
$\hat{r}_{blind}$	$\hat{r}_{blind} = \frac{1}{2n-1}\sum_{j\in\{C,T\}}\sum_{i=1}^{n}(Y_{i1}^j - \bar{Y}_1^j)(Y_{i2}^j - \bar{Y}_2^j)$	blinded
$\hat{r}_{Fisher}$	$z_j = \frac{1}{2} ln\left(\frac{1+\hat{r}_j}{1-\hat{r}_j}\right) \rightarrow \bar{z} = \frac{z_C + z_T}{2} \rightarrow \hat{r}_{Fisher} = \frac{e^{2\bar{z}}-1}{e^{2\bar{z}}+1}$	Fisher
$\hat{r}_{OP}$	$\hat{r}_{OP} = \frac{1}{2}\sum_{j\in\{C,T\}}\left(\hat{r}_j + \frac{\hat{r}_j(1-\hat{r}_j^2)}{2(n-3)}\right)$	Olkin Pratt

Alexander (1990)

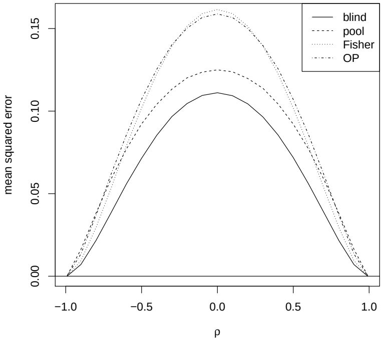
Distribution of estimators

n=5, $\delta_1 = \delta_2 = 0$, 10^5 simulation runs

Bias



Mean squared error

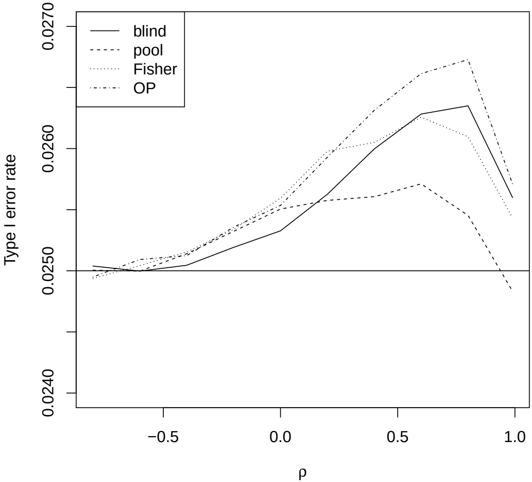


Which estimator should one choose?

Kunz (2017)

Type I error rate for different estimators

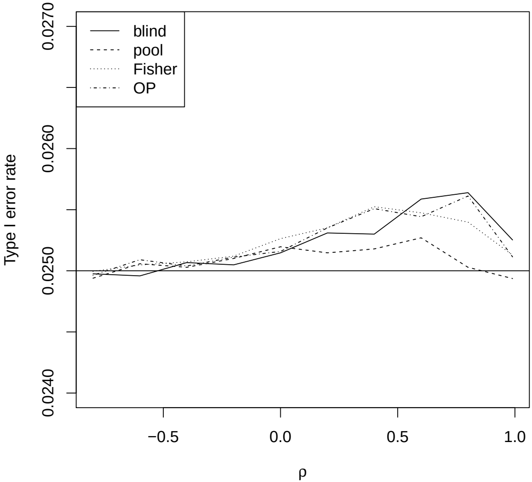
n=5, $\delta_1 = \delta_2 = 0$, 10^7 simulation runs, equal critical values



increasing sample size

Type I error rate for different estimators

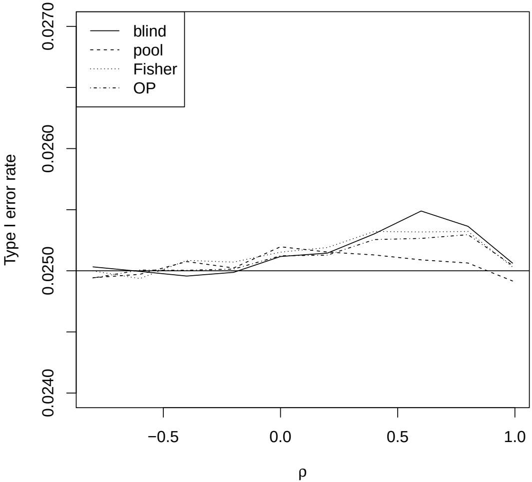
n=10, $\delta_1 = \delta_2 = 0$, 10^7 simulation runs, equal critical values



increasing sample size

Type I error rate for different estimators

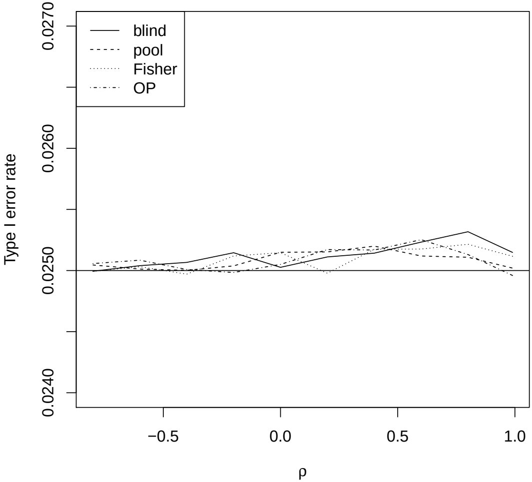
n=15, $\delta_1 = \delta_2 = 0$, 10^7 simulation runs, equal critical values



increasing sample size

Type I error rate for different estimators

$n{=}20$, $\delta_1 = \delta_2 = 0$, 10^7 simulation runs, equal critical values



Power of plug-in methods

equal critical values, n=5, n=20, $\theta_1 = \theta_2 = 2$, α'...adjusted level

method plug-in	α'	ρ = 0	0.2	0.4	0.6	0.8	0.9	0.99
$\hat{r}_{blind}$	0.0235	0.643	0.617	0.592	0.567	0.541	0.527	0.511
$\hat{r}_{pool}$	0.0241	0.641	0.614	0.588	0.561	0.535	0.520	0.508
$\hat{r}_{Fisher}$	0.0235	0.640	0.614	0.588	0.563	0.537	0.524	0.510
$\hat{r}_{OP}$	0.0233	0.638	0.612	0.587	0.563	0.539	0.526	0.504
$\hat{r}_{blind}$	0.0245	0.644	0.617	0.591	0.565	0.540	0.527	0.515
$\hat{r}_{pool}$	0.0247	0.645	0.617	0.590	0.564	0.538	0.526	0.511
$\hat{r}_{Fisher}$	0.0245	0.636	0.609	0.582	0.556	0.532	0.519	0.507
$\hat{r}_{OP}$	0.0247	0.645	0.617	0.590	0.565	0.539	0.527	0.515
Bonf.	0.025	0.645	0.615	0.583	0.548	0.504	0.474	0.405
known ρ	0.025	0.647	0.619	0.592	0.565	0.541	0.528	0.516

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2. **Plug-in estimated correlation**:
   An estimate of the correlation between the endpoints can be used to derive the critical values. Depending on the distribution of the estimator, this may also inflate the α level. Asymptotically the method controls the FWER for a consistent estimator.

3. **Apply improved Berger and Boos method**:
   The type I error rate is maximized over a confidence interval of ρ. The significance level is adjusted for the coverage probability such that the overall type I error rate is controlled at level α.

Improved Berger Boos method for unknown ρ

Algorithm for the improved Berger Boos procedure:

1. Choose a confidence width $1-\epsilon$.

2. Calculate the lower bound r^l of an $1-\epsilon$ confidence interval for the unknown correlation ρ, i.e. $P_{H_0,\rho}(\rho \geq r^l) \geq 1-\epsilon$.

3. Use this lower bound to calculate the critical boundaries by solving $1 - P_{H_0,r^l}(Z_1 \leq c(r^l,\alpha'), Z_2 \leq c(r^l,\alpha')) = \frac{\alpha}{1+\epsilon} =: \alpha'$

It can be shown that this procedure strongly controls the FWER:

$$
\begin{aligned}
FWER(\rho) &= \int_{-1}^{1} (1 - P_{H_0,\rho}(Z_1 \leq c(r^l,\alpha'), Z_2 \leq c(r^l,\alpha') | r^l)) f_\rho(r^l) dr^l \\
&\leq \alpha \quad \text{if} \quad \alpha' = \frac{\alpha}{1+\epsilon}
\end{aligned}
$$

Improved Berger Boos method for unknown ρ

- The **original Berger Boos method** also maximizes the type I error rate over a confidence interval, but chooses $\boldsymbol{\alpha' = \alpha - \epsilon}$. This corresponds to a less sharp inequality.
- The improvement is possible due to the fact that for the bivariate normal distribution **the sample mean and the sample correlation are independent**.
- The maximal type I error due to misspecification of ρ is $2\alpha'$ and the boundaries are decreasing respectively the **type I error rate is increasing with the assumed correlation**.
- The lower bound r^l of the confidence interval can e.g. be calculated for $\hat{r}_{blind}$ using **Fisher's arctan hyperbolic transformation**.

Disjunctive power of the Berger Boos method I

equal critical values, $\theta_1 = \theta_2 = 2$, $\hat{r}_{blind}$, $n = 5 \rightarrow \delta_1 = \delta_2 = 1.26$

$1-\epsilon$	ρ						
	0	0.2	0.4	0.6	0.8	0.9	0.99
1	**0.645**	**0.615**	**0.583**	0.548	0.504	0.474	0.426
0.99	0.644	0.614	**0.583**	**0.550**	0.514	0.497	0.498
0.98	0.642	0.613	0.582	**0.550**	0.515	0.500	0.499
0.97	0.641	0.611	0.581	0.549	**0.516**	0.501	**0.500**
0.96	0.639	0.610	0.579	0.548	**0.516**	**0.502**	0.499
0.95	0.638	0.608	0.579	0.547	**0.516**	**0.502**	0.499
0.94	0.636	0.607	0.577	0.547	**0.516**	**0.502**	0.498
0.93	0.634	0.606	0.576	0.546	**0.516**	**0.502**	0.498
0.92	0.633	0.604	0.575	0.545	0.515	**0.502**	0.497
0.91	0.632	0.603	0.574	0.544	0.514	0.501	0.496
0.90	0.630	0.601	0.573	0.543	0.514	0.501	0.495
Bonferroni	0.646	0.615	0.583	0.548	0.504	0.474	0.427
known ρ	0.647	0.619	0.592	0.565	0.541	0.528	0.517

Disjunctive power of the Berger Boos method II

equal critical values, $\hat{r}_{blind}$, $\theta_1 = \theta_2 = 2$, $n = 20 \rightarrow \delta_1 = \delta_2 = 0.63$

$1-\epsilon$	ρ						
	0	0.2	0.4	0.6	0.8	0.9	0.99
1	**0.645**	**0.615**	0.583	0.548	0.504	0.474	0.427
0.99	0.644	0.614	**0.584**	**0.553**	**0.524**	**0.511**	**0.507**
0.98	0.642	0.613	0.583	**0.553**	**0.524**	**0.511**	**0.507**
0.97	0.641	0.611	0.582	0.552	0.523	**0.511**	0.506
0.96	0.639	0.610	0.580	0.551	0.523	**0.511**	0.505
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0.92	0.633	0.604	0.575	0.546	0.519	0.507	0.500
0.91	0.631	0.602	0.574	0.545	0.518	0.506	0.499
0.90	0.629	0.601	0.572	0.544	0.517	0.505	0.498
Bonferroni	0.646	0.615	0.583	0.548	0.504	0.474	0.427
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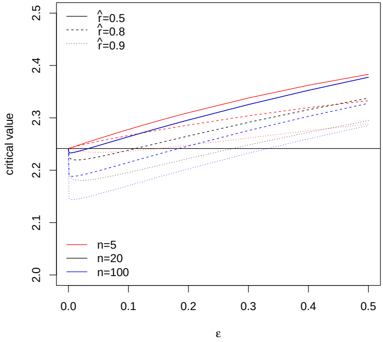
How to choose the width $1-\epsilon$ of the confidence interval



- A small choice of ϵ would be reasonable to improve the power for moderate and high correlations.

- The lower ϵ the larger the confidence interval over which the supremum must be taken, but the higher the significance level for which to calculate c.

- For $\epsilon = 0$ the lower bound is $r^l = -1$ and the boundaries would be Bonferroni boundaries.

- Choosing ϵ after observing the data such that the critical value is minimized may lead to an alpha inflation.

Summary and Extensions

- **Assuming a certain correlation:**
  The type I error rate can double and the improvement in power compared to Bonferroni lies below 11.2 percentage points.

- **Plugging-in an estimate for the correlation:**
  There is a marginal inflation in type I error rate, which decreases for higher sample sizes. An adjusted significance level could be used to exactly control the FWER.

- **Applying the improved Berger Boos method:**
  The type I error rate can be controlled, but the improvement in power is less than when the correlation is known and depends on the chosen width $1 - \epsilon$ of the confidence interval.

- **Extensions:**
  - T-distributed test statistics for unknown variance
  - More than two endpoints with different covariance structures

References

[1] R. A. Alexander. A note on averaging correlations. *Bulletin of the Psychonomic Society*, 28(4):335–336, 1990.

[2] R. L. Berger and D. D. Boos. P values maximized over a confidence set for the nuisance parameter. *Journal of the American Statistical Association*, 89(427):1012–1016, 1994.

[3] C. U. Kunz, T. Friede, N. Parsons, S. Todd, and N. Stallard. A comparison of methods for treatment selection in seamless phase II/III clinical trials incorporating information on short-term endpoints. *Journal of Biopharmaceutical Statistics*, 25(1):170–189, 2015.

[4] C. U. Kunz, N. Stallard, N. Parsons, S. Todd, and T. Friede. Blinded versus unblinded estimation of a correlation coefficient to inform interim design adaptations. *Biometrical Journal*, 59(2):344–357, 2017.

[5] X. Li, M. S. Wulfsohn, and G. G. Koch. Considerations on testing secondary endpoints in group sequential design. *Statistics in Biopharmaceutical Research*, 9(4):333–337, 2017.

[6] A. C. Tamhane, Y. Wu, and C. R. Mehta. Adaptive extensions of a two-stage group sequential procedure for testing primary and secondary endpoints (i): unknown correlation between the endpoints. *Statistics in Medicine*, 31(19):2027–2040, 2012.

MinP permutation test

- Conditionally and unconditionally controls the type I error rate:

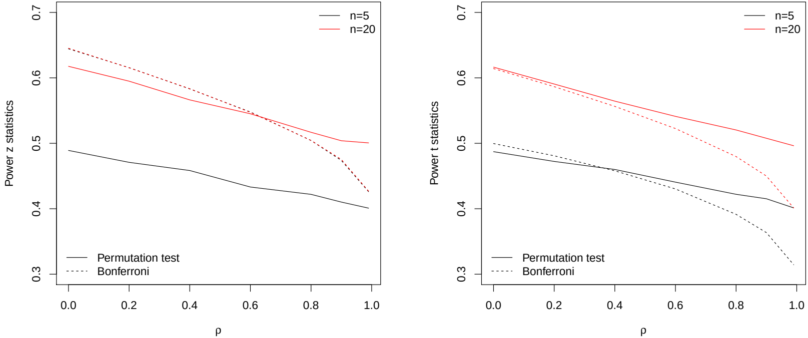
$$P(p \leq \alpha | \hat{F}(y)) = \alpha$$
$$FWER = \int P(p \leq \alpha | \hat{F}(y)) f(y) dy = \alpha$$

- With large sample sizes the permutation distribution must be randomly sampled out of all possible permutations and therefore, the permutation test is then only exact up to simulation error which can be made arbitrarily small by sufficient sampling.

- Re-sampling based testing procedures always test the strong null hypothesis of $H_0 : F^T = F^C$ with F^j, $j = T, C$, being the joint distribution of the test statistics in the treatment respectively the control group.

Power of the MinP permutation test

- Due to the discreteness of the permutation distribution the actual type I error rate can be a bit less than the nominal significance level which negatively affects the power.
- As the z statistics are not pivotal, the empirical distribution of the t statistics is a better approximation of the true distribution than for the z statistics.



Improved Berger Boos method for nuisance parameter ρ

Theorem (Improved Berger Boos method)

Let r^l be the lower bound of an $1-\epsilon$ confidence interval for ρ under the null hypothesis, i.e. $P_{0,\rho}(\rho \geq r^l) \geq 1-\epsilon$ and let $f_\rho(r^l)$ be its probability density function. If the critical value $c(r^l)$ is chosen according to $1 - P_{0,r^l}(\boldsymbol{Z} \leq c(r^l)) \leq \alpha' = \frac{\alpha}{1+\epsilon}$ then $FWER(\rho) = \int_{-1}^{1}(1-P_{0,\rho}(\boldsymbol{Z} \leq c(r^l)))f_\rho(r^l)dr^l \leq \alpha$.

$$FWER(\rho) = \int_{-1}^{1}(1-P_{0,\rho}(\boldsymbol{Z} \leq c(r^l)))f_\rho(r^l)dr^l =$$

$$\int_{-1}^{\rho}(1-P_{0,\rho}(\boldsymbol{Z} \leq c(r^l)))f_\rho(r^l)dr^l + \int_{\rho}^{1}(1-P_{0,\rho}(\boldsymbol{Z} \leq c(r^l)))f_\rho(r^l)dr^l \leq$$

$$(1-P_{0,\rho}(\boldsymbol{Z} \leq c(\rho)))\int_{-1}^{\rho} f_\rho(r^l)dr^l + (1-P_{0,\rho}(\boldsymbol{Z} \leq c(1)))\int_{\rho}^{1} f_\rho(r^l)dr^l$$

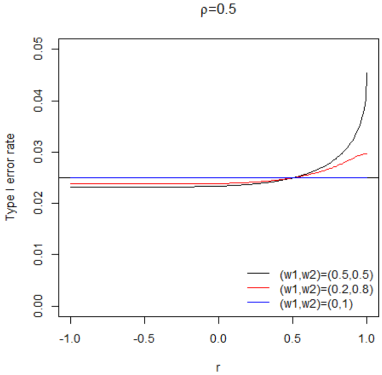
$$\leq \alpha'(1-\epsilon) + (1-P_{0,-1}(\boldsymbol{Z} \leq c(1)))\epsilon$$

$$\leq \alpha'(1-\epsilon) + 2\alpha'\epsilon = \alpha$$

Type I error rate assuming certain correlation II

General formulation of type I error rate:
$1 - P_{H_0,r}(Z_1 \leq c_1(r,\alpha), Z_2 \leq c_2(r,\alpha)) = \alpha$ with

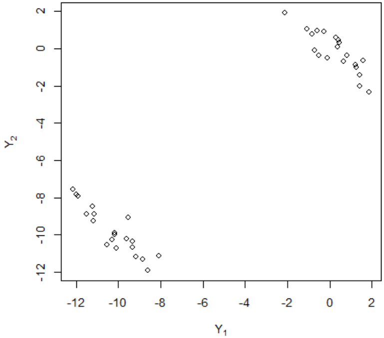
$$\begin{pmatrix} c_1(r,\alpha) \\ c_2(r,\alpha) \end{pmatrix} = \Phi^{-1}_{0,1}\left(1 - x(r)\alpha \begin{pmatrix} w_1 \\ w_2 \end{pmatrix}\right)$$



- The alpha inflation is maximal for equal critical values $(w_1, w_2) = (0.5, 0.5)$.
- For $(w_1, w_2) = (0,1) \vee (1,0)$, the correlation does not influence the critical value and therefore there is no inflation in type I error rate.

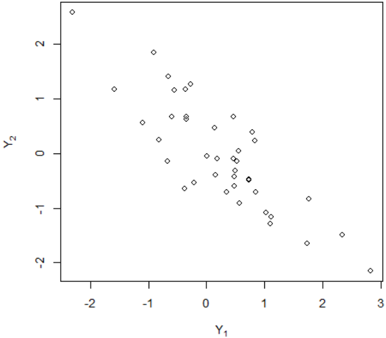
Example: n=20, $\rho = -0.8$

$\delta_1 = \delta_2 = -10$



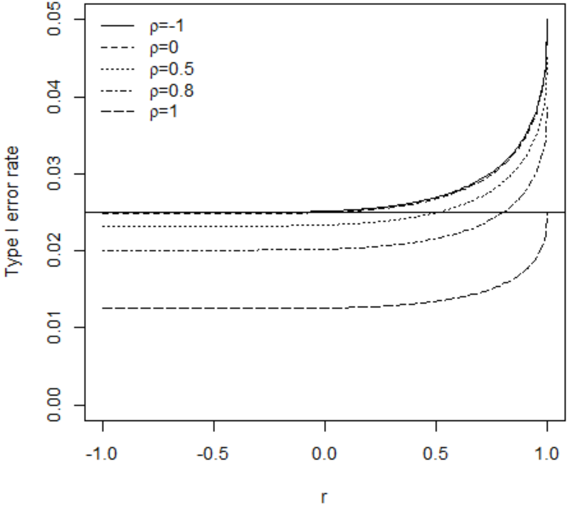
$$\hat{r}_{pool} = -0.79$$
$$\hat{r}_{Fisher} = -0.8$$
$$\hat{r}_{OP} = -0.8$$
$$\hat{r}_{blind} = 0.91$$

$\delta_1 = \delta_2 = 0$



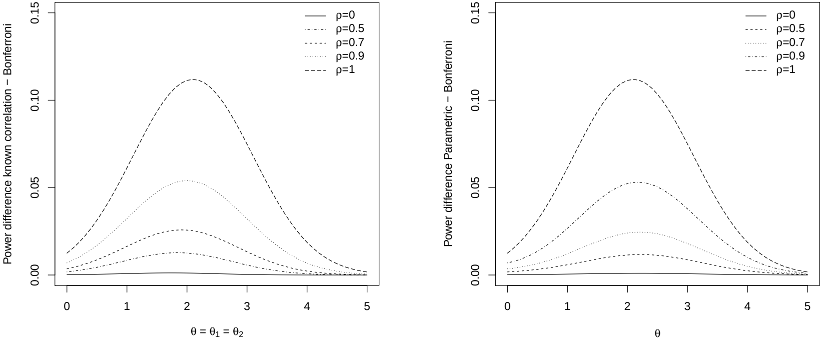
$$\hat{r}_{pool} = -0.79$$
$$\hat{r}_{Fisher} = -0.8$$
$$\hat{r}_{OP} = -0.8$$
$$\hat{r}_{blind} = -0.8$$

Type I error rate of assumed correlation

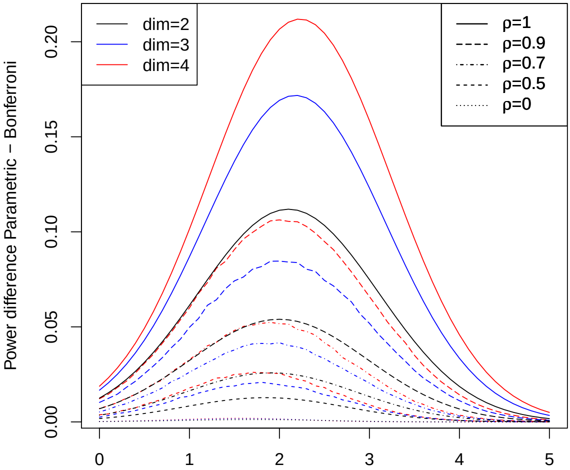


Improvement using the correlation

$\theta_1 = \theta_2 = \theta$ $\quad\quad$ $\theta_1 = \theta,\ \theta_2 = 0$



Improvement for higher dimensions



Berger Boos for power values around 0.9

equal critical values, $\theta_1 = \theta_2 = 3.1$, $n = 20 \rightarrow \delta_1 = \delta_2 = 0.98$

ϵ	ρ					
	0	0.2	0.4	0.6	0.8	0.9
0	0.9619	0.9459	0.9267	0.9037	0.8752	0.8537
0.01	0.9618	0.9453	0.9266	0.9049	0.8832	0.8733
0.02	0.9611	0.9443	0.9266	0.9056	0.8836	0.8734
0.03	0.9607	0.9442	0.9258	0.9049	0.8840	0.8730
0.04	0.9601	0.9437	0.9256	0.9049	0.8829	0.8728
0.05	0.9598	0.9429	0.9246	0.9042	0.8829	0.8725
0.06	0.9594	0.9430	0.9244	0.9041	0.8827	0.8719
0.07	0.9593	0.9421	0.9235	0.9034	0.8816	0.8715
0.08	0.9585	0.9419	0.9235	0.9024	0.8814	0.8709
0.09	0.9580	0.9412	0.9229	0.9020	0.8807	0.8695
0.1	0.9578	0.9407	0.9219	0.9021	0.8799	0.8701
Bonferroni	0.9619	0.9459	0.9267	0.9037	0.8752	0.8537
known ρ	0.9621	0.9465	0.9296	0.9116	0.8927	0.8829

Disjunctive power for plugging in $\hat{r}_{blind}$

equal critical values, $\theta_1 = \theta_2 = 2$

rho	Bonferroni	known correlation	$\hat{r}_{blind}$ for n=20		$\hat{r}_{blind}$ for n=5	
-1	0.809	0.809	0.804	-0.81	0.805	-0.34
-0.8	0.776	0.776	0.771	-0.62	0.774	-0.21
-0.6	0.739	0.739	0.735	-0.45	0.737	-0.08
-0.4	0.706	0.706	0.702	-0.27	0.709	0.05
-0.2	0.676	0.676	0.674	-0.09	0.675	0.18
0	0.646	0.647	0.645	0.09	0.651	0.30
0.2	0.615	0.619	0.616	0.27	0.623	0.43
0.4	0.583	0.592	0.594	0.45	0.599	0.57
0.6	0.548	0.565	0.567	0.63	0.572	0.71
0.8	0.504	0.541	0.542	0.82	0.545	0.85
1	0.405	0.516	0.512	0.91	0.514	1

Disjunctive power for plugging in $\hat{r}_{blind}$

equal critical values, $\theta_1 = \theta_2 = 3.1$

rho	Bonferroni	known correlation	$\hat{r}_{blind}$ for n=20	$\hat{r}_{blind}$ for n=5
-1	1	1	1	1
-0.8	0.9997	0.9997	0.9997	0.9997
-0.6	0.9959	0.9959	0.9960	0.9961
-0.4	0.9876	0.9876	0.9883	0.9884
-0.2	0.9760	0.9760	0.9763	0.9770
0	0.9619	0.9621	0.9622	0.9652
0.2	0.9459	0.9465	0.9463	0.9492
0.4	0.9267	0.9296	0.9326	0.9345
0.6	0.9037	0.9116	0.9117	0.9174
0.8	0.8752	0.8927	0.8924	0.8983
1	0.8537	0.8829	0.8731	0.8718