

Power and sample size calculations for interaction analysis

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Treatment-by-subgroup interactions

Subgrouping factor in clinical trials:

- ▶ treatment-by-centre interaction in multi-centre trials
- ▶ inconsistency in multi-regional trials
- ▶ subgroup heterogeneity in trials with pre-defined subgroups
- ▶ biomarker-by-treatment interactions
- ▶ ...

Cell means model in a randomized two-way layout

$$y_{ijk} = \mu_{ij} + \epsilon_{ijk}, \quad \epsilon_{ijk} \sim N(0, \sigma^2) \quad (1)$$

with $i = 1, \dots, I$ (treatment factor)

$j = 1, \dots, J$ (sub-grouping factor)

$k = 1, \dots, N$, where $N = \sum_{i=1}^I \sum_{j=1}^J n_{ij}$

$$\boldsymbol{\mu} = (\mu_{11}, \mu_{21}, \dots, \mu_{1J}, \mu_{2J}) = (\mu_1, \dots, \mu_L)$$

Hypotheses to test for interactions

Product-type interaction contrasts:

$$H_0 : \quad \mathbf{C}^{Int} \boldsymbol{\mu} = \boldsymbol{\theta} \qquad H_A : \quad \mathbf{C}^{Int} \boldsymbol{\mu} \neq \boldsymbol{\theta}, \qquad (2)$$

where $\mathbf{C}^{Int} = \mathbf{C}^{Subgroup} \otimes \mathbf{C}^{Treat}$ defines the $M \times L$ product-type interaction contrast matrix

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Ratios of treatment differences:

$$H_0^m : \frac{\mathbf{h}_{m\boldsymbol{\mu}}}{\mathbf{d}_{m\boldsymbol{\mu}}} \geq \omega \quad H_A^m : \frac{\mathbf{h}_{m\boldsymbol{\mu}}}{\mathbf{d}_{m\boldsymbol{\mu}}} < \omega, \quad (3)$$

where $\mathbf{C}_{Numerator} = (\mathbf{h}_1, \dots, \mathbf{h}_m)$ and $\mathbf{C}_{Denominator} = (\mathbf{d}_1, \dots, \mathbf{d}_m)$ denote the numerator and denominator interaction contrast matrix.

Test - Product-type interaction contrasts

The test-statistic to test the m local null hypothesis in Eq. 2 is given by

$$T_m = \frac{\sum_{l=1}^L c_l \hat{\mu}_l - \theta_m}{s \sqrt{\sum_{l=1}^L c_l^2 / n_l}} = \frac{\mathbf{c}_m' \hat{\boldsymbol{\mu}} - \theta_m}{s \sqrt{\mathbf{c}_m' \mathbf{M} \mathbf{c}_m}},$$

where $\mathbf{M} = \text{diag} (n_1^{-1}, \dots, n_L^{-1})$ and $\mathbf{T} = (T_1, \dots, T_M)$.

Under H_0 \mathbf{T} follows a central multivariate t-distribution $Mt_{df=\nu, \mathbf{R}}$, with $\nu = \sum_{l=1}^L (n_l - 1)$ and correlation matrix $\mathbf{R} = [\rho_{mm'}]$ with elements:

$$\rho_{mm'} = \frac{\sum_{l=1}^L c_{ml} c_{m'l} / n_l}{\sqrt{\left(\sum_{l=1}^L c_{ml}^2 / n_l \right) \left(\sum_{l=1}^L c_{m'l}^2 / n_l \right)}}.$$

Power - Product type interaction contrasts

The m th non-centrality parameter is given by [Bretz et al., 2001]

$$\delta_m = \frac{\mathbf{c}_m \boldsymbol{\mu} - \theta_m}{\sigma \sqrt{\mathbf{c}_m' \mathbf{M} \mathbf{c}_m}}.$$

Under the global null hypothesis $H_0 : \mathbf{C}^{Int} \boldsymbol{\mu} = \boldsymbol{\theta}$, the non-centrality parameter vector $\boldsymbol{\delta} = \mathbf{0}$.

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The power of T_0 to detect H_A at significance level α is

$$\begin{aligned} P(T_0 \geq t_{1-\alpha, \nu, \mathbf{R}} | H_A) &= 1 - \beta \\ &= 1 - P(|T_1| \leq t_{1-\alpha, \nu, \mathbf{R}}, \dots, |T_M| \leq t_{1-\alpha, \nu, \mathbf{R}} | H_A), \end{aligned}$$

where $T_0 = \max(|T_1|, \dots, |T_M|)$.

Software - Power for product-type interaction contrasts

R add-on package [R Core Team, 2013] MCPAN
[Schaarschmidt et al., 2013] with its function `powermcpt`

```
#CTukey <- matrix(c( 1,-1, 0,  
#                   1, 0,-1,  
#                   0, 1,-1),nrow=3,byrow=TRUE)  
#C <- kronecker(CTukey, t(c(-1,1)))  
C <- matrix(c(-1, 1, 1,-1, 0, 0,  
              -1, 1, 0, 0, 1,-1,  
              0, 0,-1, 1, 1,-1),nrow=3,byrow=TRUE)  
powermcpt(mu=c(10,15,10,15,10,20),  
          n=rep(10,6), sd=sqrt(5), cmat=C, rhs=0,  
          alternative="two.sided", alpha=0.05, ptype="anypair")
```

Test - Ratios of treatment differences

The test-statistic to test the m local null hypothesis in Eq. 2 is given by

$$T_m^{\text{ratio}} = \frac{(\mathbf{h}_m - \omega \mathbf{d}_m) \hat{\mu}}{s \sqrt{(\mathbf{h}_m - \omega \mathbf{d}_m) \mathbf{M} (\mathbf{h}_m - \omega \mathbf{d}_m)}}.$$

According to Dilba et al. [Dilba et al., 2006] under H_0 the vector of test statistics $\mathbf{T}^{\text{Ratio}} = (T_1^{\text{Ratio}}, \dots, T_M^{\text{Ratio}})$ follows a central multivariate t-distribution with ν degrees of freedom and a correlation matrix $\mathbf{R} = [\varsigma_{mm'}]$ with elements:

$$\varsigma_{mm'} = \frac{(\mathbf{h}_m - \omega \mathbf{d}_m) \mathbf{M} (\mathbf{h}_{m'} - \omega \mathbf{d}_{m'})}{\sqrt{(\mathbf{h}_m - \omega \mathbf{d}_m) \mathbf{M} (\mathbf{h}_m - \omega \mathbf{d}_m)} \sqrt{(\mathbf{h}_{m'} - \omega \mathbf{d}_{m'}) \mathbf{M} (\mathbf{h}_{m'} - \omega \mathbf{d}_{m'})}}.$$

Power - Ratios of treatment differences

The non-centrality parameters are given by

$$\tau_m = \frac{(\mathbf{h}_m - \omega \mathbf{d}_m) \boldsymbol{\mu}}{\sigma \sqrt{(\mathbf{h}_m - \omega \mathbf{d}_m) \mathbf{M} (\mathbf{h}_m - \omega \mathbf{d}_m)}}.$$

Under the global null hypothesis H_0 the non-centrality parameter vector $\boldsymbol{\tau} = \mathbf{0}$ and \mathbf{T} follows a central M variate t-distribution.

Power - Ratios of treatment differences

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Under the global null hypothesis H_0 the non-centrality parameter vector $\boldsymbol{\tau} = \mathbf{0}$ and \mathbf{T} follows a central M variate t-distribution. The power of T_0^{Ratio} to detect H_A at significance level α is

$$\begin{aligned} P\left(T_0^{\text{ratio}} > t_{1-\alpha, \nu, \mathbf{R}^{\text{ratio}}} | H_A\right) &= 1 - \beta \\ &= 1 - P\left(|T_1^{\text{ratio}}| \leq t_{1-\alpha, \nu, \mathbf{R}^{\text{ratio}}}, \dots, |T_M^{\text{ratio}}| \leq t_{1-\alpha, \nu, \mathbf{R}^{\text{ratio}}} | H_A\right) \end{aligned}$$

where $T_0^{\text{ratio}} = \max(|T_1^{\text{ratio}}|, \dots, |T_M^{\text{ratio}}|)$.

Software - Power ratios of treatment effects

```
#install.packages("devtools")
#library(devtools)
#install_github(username="AKitsche", repo="poco")
library(poco) #Power Consistency
PowCon(mu=c(10,15,10,15,10,20),
        n=10, sd=sqrt(5), n.sub=3,
        TreatMat="Tukey", SubMat="Tukey",
        thetas=1, alternative="two.sided", alpha=0.05)
#iterative procedure for sample size determination
?nPowCon
```

Rest siehe Hilfeseite ?PowCon

References I



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