# A multiple comparison procedure for dose-finding trials with subpopulations

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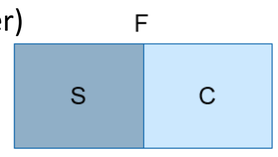
- MCP-Mod [1, 2] is a methodology for dose-response testing and dose estimation in Phase II dose-finding trials
- MCP-Mod takes uncertainty about the underlying dose-response shape into account by performing multiple contrast tests, which are optimal under different candidate dose-response models
- **We propose an extension of the MCP part of MCP-Mod to trials with multiple populations of interest, for example a subgroup and the full population**
- **Our proposed testing procedures control the family-wise error rate across all populations and candidate models**

## Setting

- Phase II randomized dose-finding trial with $k$ doses
- Prespecified subgroup (for example based on predictive biomarker)
- Three populations of interest:
  full population (F), subgroup (S) and complement (C)




- Aim: Establish significant dose-response signal in at least one of the populations
- Possible testing strategies:
  1. Single population [*SP*]: only test in F, standard MCP-Mod
  2. Multi-population I [*MP (F + S)*]: tests in F and S
  3. Multi-population II [*MP (F + S + C)*]: tests in all populations

## Multiple contrast tests in multiple populations

**Notation and model:**

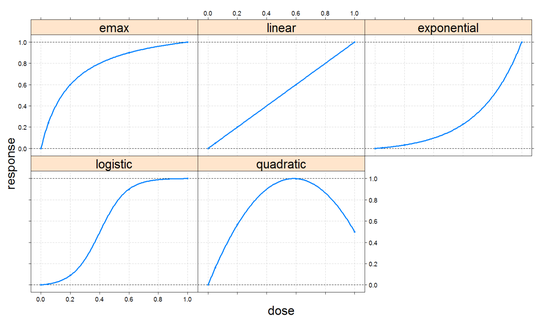
- In each population $\mathrm{P} \in \{\mathrm{F}, \mathrm{S}, \mathrm{C}\}$ we denote by
  - ${n_i}^{(P)}$ the number of patients in dose group $i$ (${n_i}^{(F)} = {n_i}^{(S)} + {n_i}^{(C)}$)
  - ${\bar{Y}_i}^{(P)}$ the sample mean in dose group $i$
  - $s^{(P)}$ the sample standard deviation in population P

- Model for a normally distributed response:

$$ {Y_{ij}}^{(P)} = {\mu_i}^{(P)} + {\epsilon_{ij}}^{(P)};\ {\epsilon_{ij}}^{(P)} \sim N(0, \sigma_P^2)\ iid, $$
$$ i = 1, \dots, k,\ \ j = 1, \dots, {n_i}^{(P)},\ \ P = S, C $$

**Multiple candidate models:**

- We consider M candidate models
- For each candidate model we can obtain contrast coefficients $c_{m1}, \dots, c_{mk}$ with optimal power




**Multiple contrast tests:**

- For each candidate model $m = 1, \dots, M$ and each considered population *P* we test

$$ {H_0}^{(P,m)}: \sum_{i=1}^{k} c_{mi}{\mu_i}^{(P)} = 0 \quad \text{vs.} \quad {H_1}^{(P,m)}: \sum_{i=1}^{k} c_{mi}{\mu_i}^{(P)} > 0, $$

using contrast test statistics

$$ {T_m}^{(P)} = \frac{\sum_{i=1}^{k} c_{mi}\ {\bar{Y}_i}^{(P)}}{s^{(P)}\sqrt{\sum_{i=1}^{k} c_{mi}^2\ /{n_i}^{(P)}}} $$

## Family-wise error rate control

- MCP-Mod uses the joint distribution of the test statistics to determine critical values (Max $t$-test)
- Here the joint distribution depends on assumptions we make for the variance in the populations S and C

**Under homoscedasticity (${\sigma_S}^2 = {\sigma_C}^2$):**

- $s^{(P)} = s$ is the pooled variance estimator (pooled over doses)
- ${T_1}^{(F)}, \dots, {T_M}^{(F)}, {T_1}^{(S)}, \dots, {T_M}^{(S)}, {T_1}^{(C)}, \dots, {T_M}^{(C)}$ jointly follow $MVT(0, R, \upsilon)$-distribution with $\upsilon = n - 3k$ degrees of freedom and correlation matrix

$$ R = \begin{pmatrix} R_F & R_{FS} & R_{FC} \\ {R_{FS}}' & R_S & R_{SC} \\ {R_{FC}}' & {R_{SC}}' & R_C \end{pmatrix} $$

- Each submatrix is of dimension $MxM$, the correlation structure depends on candidate models and the overlap between populations

**Under heteroscedasticity (${\sigma_S}^2 \neq {\sigma_C}^2$):**

- Pooled variance estimation not appropriate, variance estimation marginal
- Joint distribution no longer multivariate $t$, approximations necessary
- Possible approximations for joint distribution:
  1. Multivariate normal distribution [*MP-Normal*]
  2. Multivariate *t*-distribution with minimum degrees of freedom [*MP-MinDF*]
  3. Multivariate *t*-distribution with multiple degrees of freedom [3]: For each test statistic obtain an adjusted *p*-value from a multivariate *t*-distribution with the degrees of freedom for that test statistic [*MP-MultDF*]

## FWER control and power for simulated trials

**Simulated trial design**:

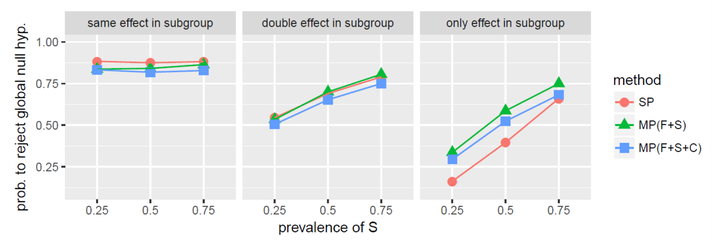
- 5 dose levels, 75 patients on each dose level
- Prevalence of S: 0.25, 0.5, 0.75 (on each dose level)
- Generate normally distributed data under the null hypothesis (constant model) and for different candidate shapes under the alternative

**Subgroup effect scenarios**:

1. Same treatment effect in S and C
2. Only a treatment effect in S, no treatment effect in C
3. Treatment effect in S is double the effect in C

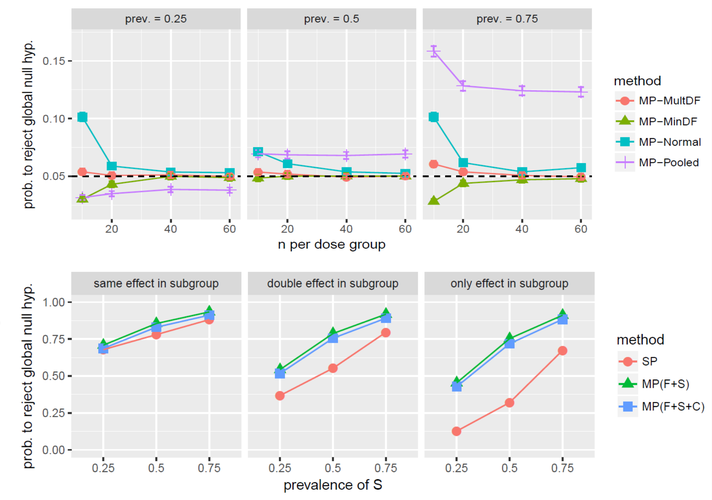
**Results for homoscedastic scenarios (${\sigma_S}^2 = {\sigma_C}^2$):**

- FWER control guaranteed (joint distribution is known)
- Multi-population testing increases power, when subgroup is large with a great effect (compared to complement)




**Results for heteroscedastic scenarios (${\sigma_S}^2 = 0.5{\sigma_C}^2$):**

- *MultDF* approximation less conservative than *MinDF* and controls FWER at close to nominal level even for small sample sizes
- With *MP-MultDF* clear increases in power over *SP* in all scenarios, even if the subgroup does not have an increased treatment effect




## Conclusions and discussion

- Proposed approaches control FWER under different assumptions for variances in the subpopulations
- Can increase power to detect a significant dose-response signal
- Model selection performance similar as for single population MCP
- Approach can also be used for multiple (overlapping) subgroups
- Extensions to generalized parametric models possible (using multivariate normal approximations)
- Extension of Mod part remains as an open problem

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[3] Hasler (2014). *The International Journal of Biostatistics*, **10**(1):17–28..