The MCP-Mod methodology – A statistical methodology for dose-response

Björn Bornkamp

Acknowledgements: Frank Bretz & José Pinheiro

NOVARTIS

Overview

- MCP-Mod (***M***ultiple ***C***omparison ***P***rocedure – ***Mod***elling)
- Simulation based comparison: MCP-Mod vs ANOVA
- EMA qualification opinion on MCP-Mod (January 2014)

What is MCP-Mod?

Multiple Comparison Procedures – Modelling: Overview

- A method for model-based dose-response testing and estimation
  - MCP-step
    - Establish a dose-response signal (the dose-response curve is not flat) using multiple comparison procedures
  - Mod-step
    - Estimate the dose-response curve and target doses of interest (ED_{50}, ED_{90}, MED, etc) using modelling techniques
- What is novel about the approach?
  - Modelling pre-specified at design stage as primary analysis
    - Design (doses & sample size) tailored to the needs of the analysis method
  - Model uncertainty at design stage is addressed by using
    - a candidate set of models (for MCP and Mod step)
    - & a procedure on how to perform model selection (or model averaging)

What is MCP-Mod?

Multiple Comparison Procedures – Modelling: At Novartis

- Method developed Novartis internally in ~ 2004
- Since then used in > 15 completed studies with df element
  - often as primary analysis

Drug	Phase	Condition studied	Treatment groups
1	Phase IIb	Gout	5 doses, AC
2	Phase IIb	Diabetes	PBO, 4 doses
3	Phase III	Prevention of cardiovascular events	PBO, 3 doses
4	Phase IIb	Psoriasis	PBO, 3 od and 4 bid doses
5	Phase IIb	Multiple Sclerosis	PBO, 5 doses
6	Phase IIa/b	Epilepsy	PBO, 2 doses
7	Phase II	Hypertension	PBO, 3 od doses, 1 bid dose
8	Phase IIb	Diabetes	PBO, 5 doses, AC
9	Phase III	Familial Chylomicronemia Syndrome	PBO, 2 doses
10	Phase II	Hypertriglyceridemia	PBO, 3 doses, 2 AC
11	Phase IIb	Hypertension	PBO, 3 doses, 3 AC
12	Phase IIb	Diabetes	PBO, 7 doses
13	Phase IIb	COPD	PBO, 4 od doses, AC
14	Phase IIb	COPD	PBO, 3 bid doses, 4 od doses
15	Phase IIb	Asthma	PBO, 9 od doses, 4 bid doses, AC
16	Phase II	COPD	PBO, 4 doses
17	Phase IIa	Dental pain	PBO, 6 doses, AC
18	Phase II	Generalized anxiety disorder	PBO, 4 doses

MCP-Mod: Dose-response modelling under model uncertainty

*see **Bretz et al (2005)**, Biometrics, 61, 738-748 & **Pinheiro et al (2014)**, Statistics in Medicine, 33, 1646-1661*

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

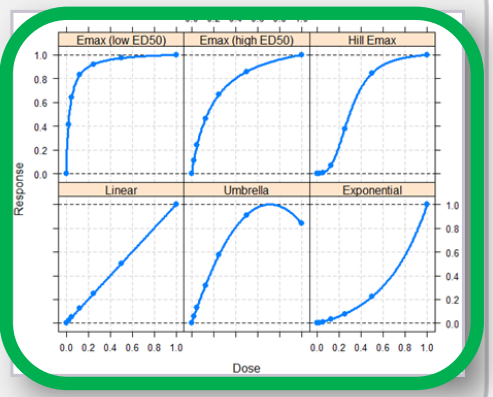
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



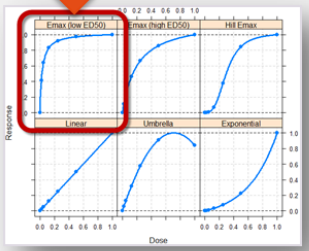
Trial conduct

$p < \alpha$?

Trial Analysis Stage

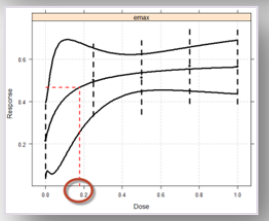
MCP step

- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models



Mod step

Dose-response and target dose estimation based on selected model(s)



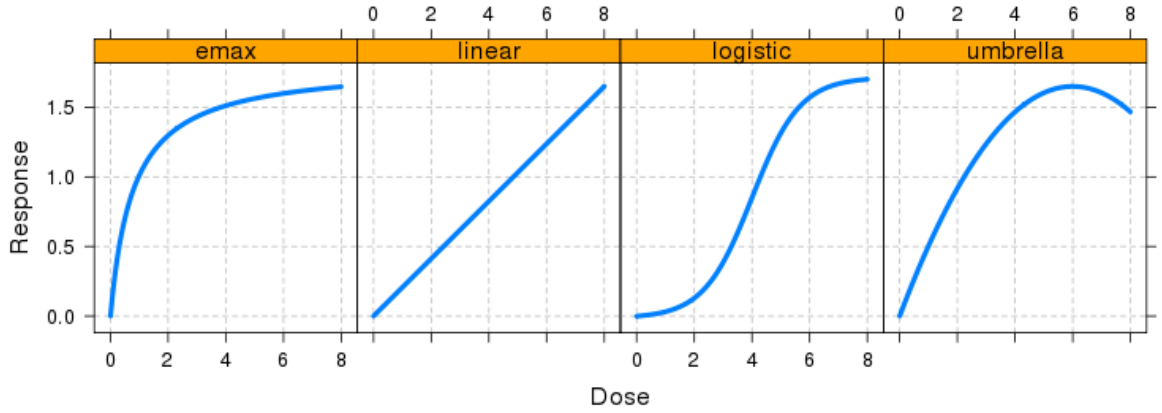
Scope of MCP-Mod

- Development Phase
  - Ph II dose-response studies to support dose selection for Phase III
- Dose-Response
  - Population dose-response (cross-sectional) *usually*
  - Response can be continuous, binary, count, time-to-event
- Number of doses, dose-range
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendations (rules of thumb): 4-7 active doses, >10-fold dose range
- Control
  - MCP-step makes most sense when there is a placebo control in the trial
- Basic MCP-Mod can be extended
  - regimen, random effects, longitudinal, ...

Simulation comparison to different ANOVA designs

Simulation scenarios as in: J. Biopharm. Statistics (2007), 17, 965-995.

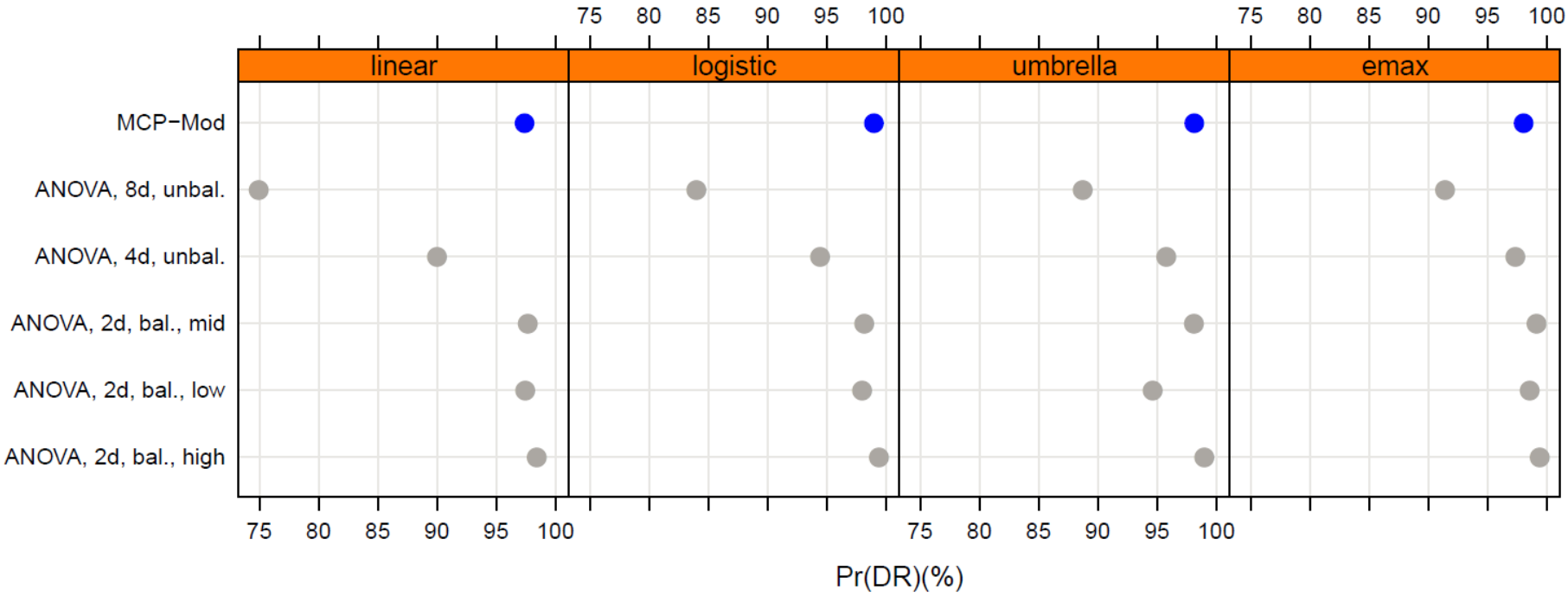
- Scenarios for mean (sample size, σ^2 realistic)



  - MCP-Mod, optimal unbalanced design (PBO & 4 active doses)
    - 0, 0.54, 3.2, 4.8, 8 (D-optimal design), 1.5:1:1:1:1.5
  - ANOVA optimal unbalanced design on 4 & 8 doses & PBO
    - Allocation according to square-root rule (more patients on PBO)
  - ANOVA balanced allocation 2 doses & PBO
    - PBO & 2 active doses, vary the low dose (low (2), mid (4), high (6))

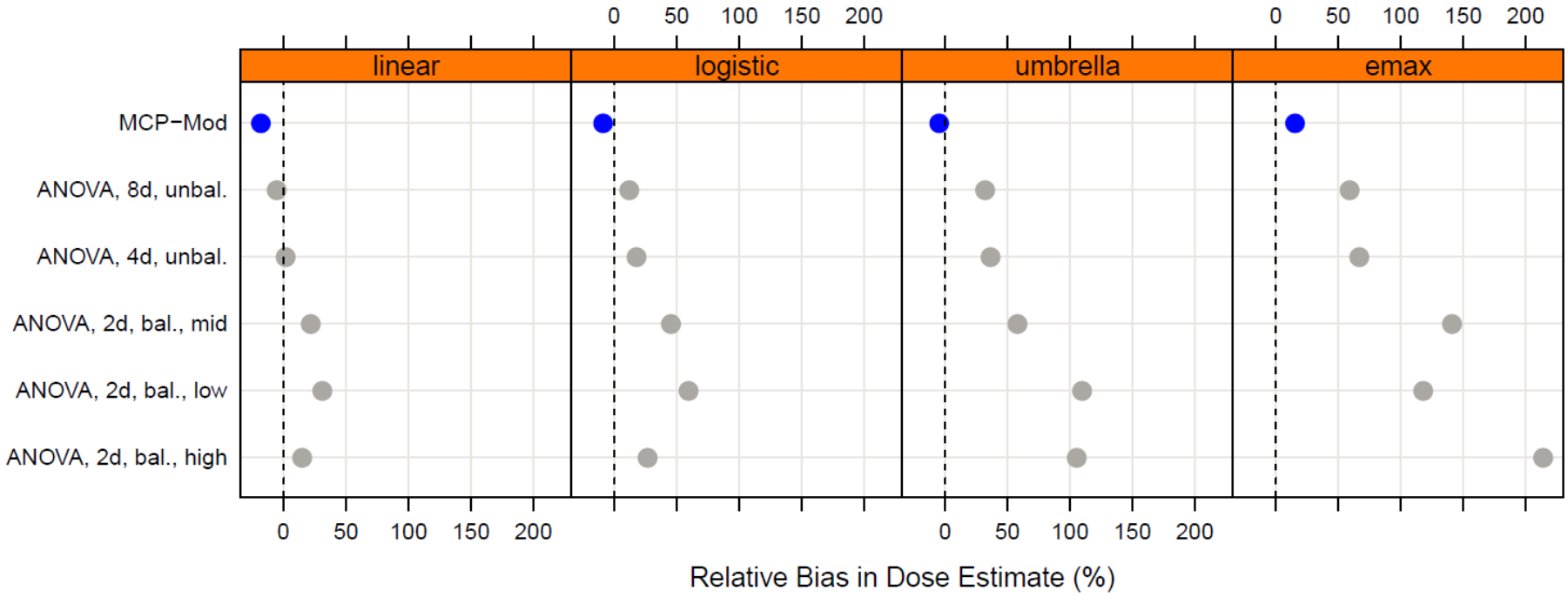
Simulation comparison to different ANOVA designs

Power to detect dose-response trend (larger is better)



Simulation comparison to different ANOVA designs

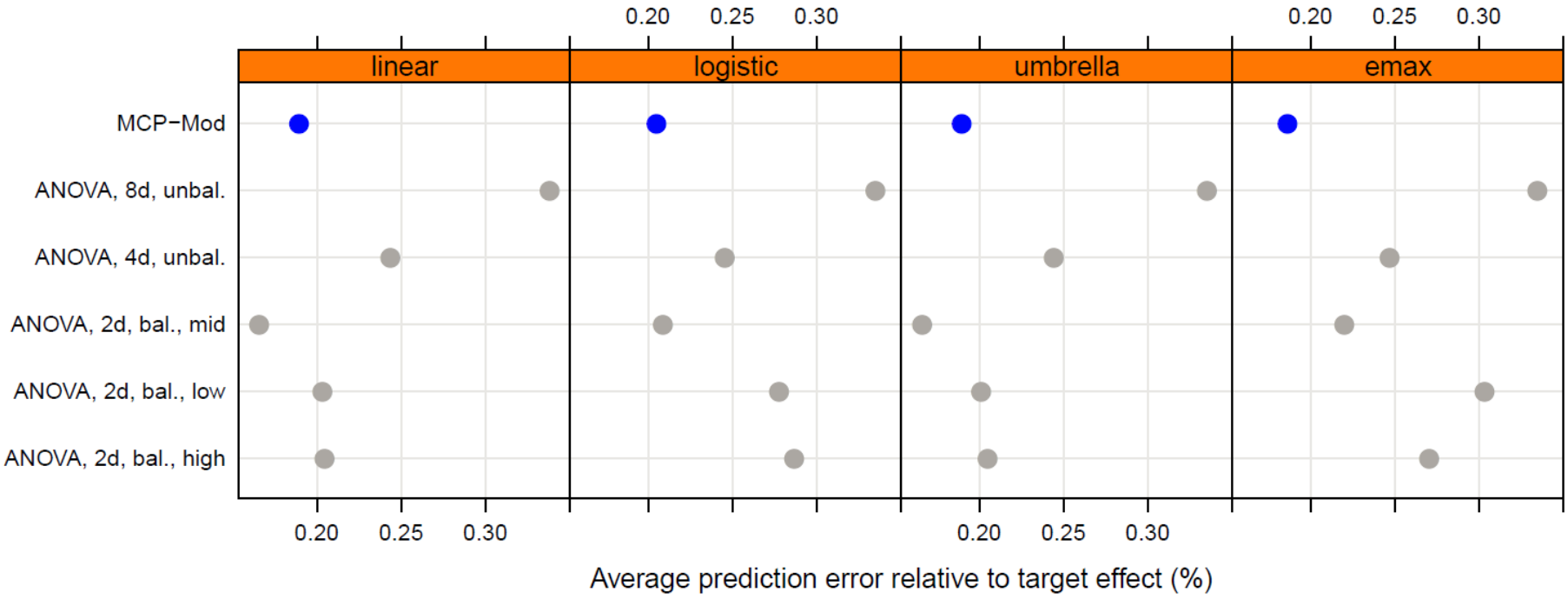
Bias in target dose estimate (closer to zero is better)*



*Target dose: Smallest dose achieving a clinically relevant effect of 1.3 over placebo

Simulation comparison to different ANOVA designs

Estimation error for dose means (smaller is better)



Simulation comparison to different ANOVA designs

Conclusions

- Dose-response modelling typically as good as the best of 5 ANOVA approaches
  - no single ANOVA approach similarly robust
  - Examples:
    - ANOVA 8d performs well for estimating the target dose, but worse in terms of power and dose-response estimation
    - ANOVA 2d high performs well if the true dose-response is linear, but very bad if the true dose response is of Emax type
- Performance of ANOVA is sensitive to underlying shape
  - in particular if the number of doses is small
  - if the number of doses (within an ANOVA approach) is larger the power detoriates

CHMP Qualification Opinion

- The European Medicines Agency (via the CHMP) offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.
  - Examples: novel methodology, imaging method or biomarker.
- First opinion issued in 2009, since then 8 qualification opinions (5 biomarkers, 1 MRI techn., 1 simulation tool)
  - MCP-Mod first methodology qualified

CHMP Qualification Opinion

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/SAWP/757052/2013
Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

Quotes from qualification opinion

Summary

- *"...The MCP-Mod approach is efficient in the sense that it uses the available data better than the commonly applied pairwise comparisons..."*
- *"... the methodological approach will promote better trial designs incorporating a wider dose range and increased number of dose levels..."*
- *"... Properly implemented however, the benefits include not only efficient data collection and more precise answers to important questions [...] but should also serve to enhance discussions with stakeholders in advance of the trial comparing different strategies and explaining risks and limitations of potential designs. ..."*

Quotes from qualification opinion

Other Modelling Approaches

- *"... It is fully appreciated that certain benefits that may be derived from an MCP-Mod approach would also be derived from other model-based approaches and that modelling approaches are not restricted to those based on dose-response. MCP-Mod represents one tool in the toolbox of the well-informed drug developer. In that sense, this opinion does not preclude any other statistical methodology for model-based design and analysis of exploratory dose finding studies from being used...."*

Quotes from qualification opinion

On type I error control in Phase II

- *"...Designing an experiment that permits conclusions to be drawn with control of false-positive error rate is clearly desirable for the study sponsor. It is mandated by regulators in the confirmatory phase of development, though not in the exploratory phase that is under discussion here, where factors other than strict type I error control may influence decisions regarding future clinical development. The choice of 5% used by the Applicant in their illustrations is arbitrary and could be varied based on the certainty that the Applicant wish to have for their decision-making..."*

Quotes from qualification opinion

Other messages

- *"... many of the 'best-practice' approaches described by the authors, for example the inclusion of multiple dose levels and attempting to quantify dose-response curves are explicit in this regulatory document [ICH E4 guidance on dose-response] and despite not being widely practiced, are welcomed and regarded as uncontroversial..."*
- *"...it is arguable therefore that to qualify MCP-Mod as an improvement over the commonly used approach is uncontroversial from a regulatory perspective. [...] yet the use of this type of approach in regulatory submissions remains rare and hence, the fact that these sub-optimal approaches persist makes this a relevant topic for a CHMP opinion..."*

Comments

- Positive CHMP qualification opinion on MCP-Mod
  - Emphasizes importance of well designed dose-finding studies
  - Illustrates openness towards model-based approaches
    - one among a few ongoing EMA initiatives in this direction
      - concept paper on extrapolation
      - EFPIA/EMA workshops (Manolis et al. (2013) doi:10.1038/psp.2013.7)
- MCP-Mod
  - In terms of complexity of the modelling: Getting close to the boundary of what can be pre-specified
  - MCP-Mod does not alleviate the need for additional analyses to better understand the drug, leading to better decision making
    - e.g. longitudinal dose-exposure-response modelling