Discussion PSI Webinar, Nov 11, 2019
Longitudinal modelling: Time to take the next step?

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Two talks: common findings

- Using longitudinal measurements increase power of test of treatment effect
  - results obtained through different simulation examples
  - two arms PoC studies with continuous measurement
- Björn Bornkamp (Novartis)
  - MMRM more power than cross-sectional
  - Influence of shape of response, ratio WSV/BSV
  - LMEM more power than MMRM (less parameters)
- Tobias Mielke (J&J)
  - Longitudinal modelling add substantial efficiency
  - Wrong model could lead to incorrect conclusions
    - Model selection: a good approach (BUT no problem in type I error here)
    - Model averaging: good alternative

Comparison of model averaging (MA) and model selection (MS) in dose finding trials analyzed by nonlinear mixed effect models (NLMEM)

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Citation: CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 418–429; doi:10.1002/psp4.12196

WHITE PAPER

Advanced Methods for Dose and Regimen Finding During Drug Development: Summary of the EMA/EFPIA Workshop on Dose Finding (London 4–5 December 2014)

FT Musuamba[1,2,3*], E Manolis[1,4], N Holford[5], SYA Cheung[6], LE Friberg[7], K Ogungbenro[8], M Posch[9], JWT Yates[6], S Berry[10], N Thomas[11], S Corriol-Rohou[6], B Bornkamp[12], F Bretz[9,12], AC Hooker[7], PH Van der Graaf[13,14], JF Standing[1,15], J Hay[1,16], S Cole[1,16], V Gigante[1,17], K Karlsson[1,18], T Dumortier[12], N Benda[1,19], F Serone[1,17], S Das[6], A Brochot[20], F Ehmann[4], R Hemmings[16] and I Skottheim Rusten[1,21]

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

MCP-MOD[1]

- Starting from a predefined set of dose-response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

PMX

1. Model building using multiple LRT on nonlinear mixed effect models (MS)

2. Estimate the dose-response curve using the selected model

Advantages vs PMX

- Models pre-specified
- Takes model uncertainty into account
- Control the type I error

Advantages vs MCP-MOD

- Longitudinal analysis of the data

Two projects

I. To compare predictive performances of model averaging (MA) and model selection (MS) based on a predefined set of NLMEMs with similar disease progression model and different dose-effect relationships

The AAPS Journal (2018) 20:56
DOI: 10.1208/s12248-018-0205-x

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Research Article

Comparison of Model Averaging and Model Selection in Dose Finding Trials Analyzed by Nonlinear Mixed Effect Models

Simon Buatois,[1,2,3,5] Sebastian Ueckert,[4] Nicolas Frey,[1] Sylvie Retout,[1,2] and France Mentré[3]

Two projects

I. To compare predictive performances of model averaging (MA) and model selection (MS) based on a predefined set of NLMEMs with similar disease progression model and different dose-effect relationships

II. To extend MCP-MOD to allow for NLMEM for both MCP and MOD step and to compare MS and MA for the MOD step

Statistics
in Medicine

Research Article

Received 30 April 2013, Accepted 1 November 2013 Published online 3 December 2013 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6052

Model-based dose finding under model uncertainty using general parametric models

José Pinheiro,[a] Björn Bornkamp,[b*†] Ekkehard Glimm[b] and Frank Bretz[b]

J Pharmacokinet Pharmacodyn (2017) 44:581–597
DOI 10.1007/s10928-017-9550-0

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ORIGINAL PAPER

Model selection and averaging of nonlinear mixed-effect models for robust phase III dose selection

Yasunori Aoki[1,2] · Daniel Röshammar[3,4] · Bengt Hamrén[3] · Andrew C. Hooker[1]

MCP-MOD[1]

- Starting from a predefined set of dc response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

Best of both worlds ?

PMX

1. Model building using multiple LRT on nonlinear mixed effect models (MS)

2. Estimate the dose-response curve using the selected model

Advantages vs PMX

- Models pre-specified
- Takes model uncertainty into account
- Control the type I error

Advantages vs MCP-MOD

- Longitudinal analysis of the data

MCP-MOD[1]

cLRT-MOD

Predefined set of dose-response candidate models:

1. **MCP-step:** Assessment of dose-response signal using contrast test on the best model (MS)

1. cLRT-step: Assessment of dose-response signal using a corrected-Likelihood Ratio Test[2]

2. **MOD-step:** Estimate the dose-response curve using either model selection (MS) or model averaging (MA)

[1] Bretz F . *et al*, Biometrics, 2005

[2] Dette H. et al, Biometrics, 2015

II. Weak drug effect & N=50

Type I error & Power

Simulation model

Test

		Linear	Log-linear	Emax	Sigmoid	No-DE
		Power (%)				Type-I error [3.2-7%]
LRT	Linear	75.8	72.4	79.6	89.4	4.8
	Log-linear	62.0	83.0	84.8	91.8	4.0
	Emax	65.2	81.6	84.4	91.2	5.6
	Sigmoid	67.8	40.4	47.2	57.2	5.8
	MS	79.0	86.6	89.6	93.6	7.6
cLRT		71.2	81.2	83.8	90.6	5.6
MCP		14.2	11.2	12.4	16.4	3.0

Conclusion of Simon Buatois' work

- This work extends the MCP-MOD methodology to use NLMEM in both MCP and MOD steps
- By deriving the reference distribution of the LRT under the null-hypothesis for all candidate models, the method maintains the nominal type-I error while using the full longitudinal information
- The work, furthermore, shows how model averaging provides substantially better coverage in the MOD step, and how the ignorance of model uncertainty leads to an under-estimation of the confidence intervals

Buatois S, Ueckert S, Frey N, Retout S, Mentré F. A pharmacometric extension of MCP-MOD in dose finding studies. *PAGE 27* (2018), ACOP9 (2018).

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Perspectives on longitudinal modelling in drug development

- What are the next steps before acceptance by regulatory authorities?
  - Other modelling scenario
  - Clear choice of a statistical approach
    - Looking at GOF?
  - Start by specific cases
    - Dose response (extension of MCP-MOD)
    - Bioequivalence (MBBE grants with FDA)
    - Rare diseases
    - Pediatrics
    - …
  - Role of the SxP ISoP/ASA SIG?

http://community.amstat.org/sxp/home

ASA AMERICAN STATISTICAL ASSOCIATION Promoting the Practice and Profession of Statistics® Statistics and Pharmacometrics Interest Group (SxP)

ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS