Dose Finding Under Model Uncertainty with the MCP-Mod Approach

José Pinheiro
Janssen R&D

Joint work with **Frank Bretz** and **Björn Bornkamp** (Novartis AG)

BASS XXVIII – Virtual – October 25, 2021

Outline

- Motivation
- MCP-Mod approach
  - Independent and normally distributed data
  - More general data distributions
- Summary

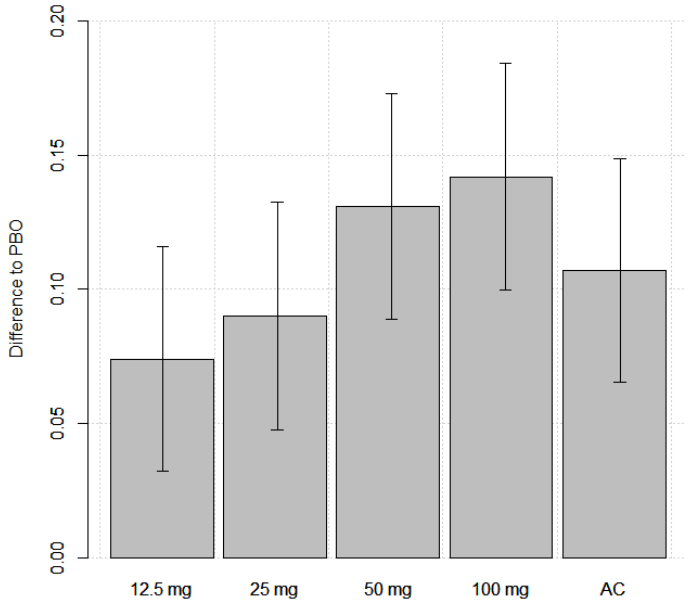
Outline

- Motivation
- MCP-Mod approach
- Summary

Need to Improve Dose Finding in Phase II

Pairwise comparisons

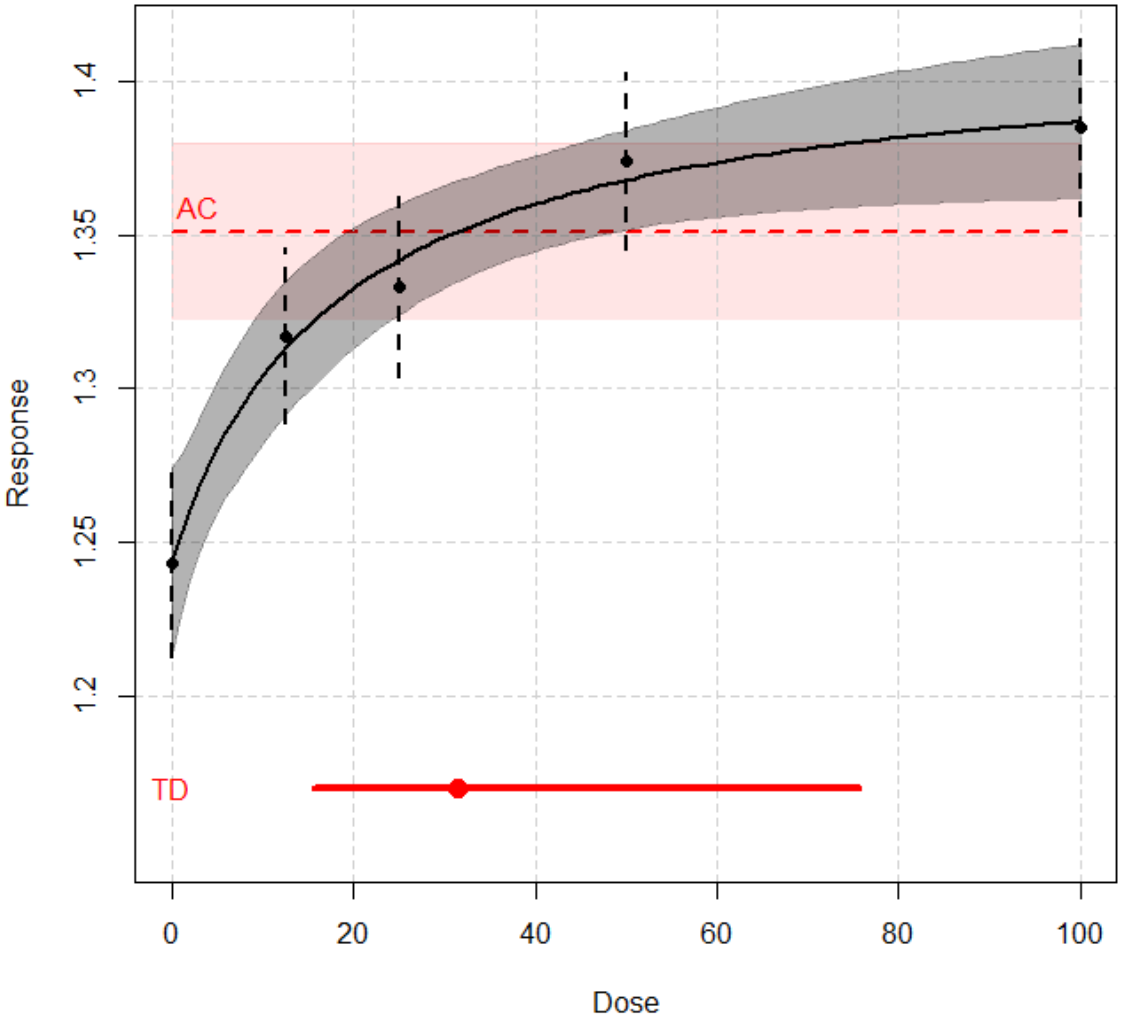
- Mismatch between real study objectives and objectives in protocol
  - Statistical objectives in protocol
    - Testing hypotheses: control versus active doses
    - Study design determined by this objective (sample size, number of doses, ...)
  - Output of a pairwise analysis



- Conclusion
  - All active doses (and the active comparator, AC) are significantly different from placebo
- What happens inbetween observed doses? What is the shape of the dose-response curve?
- Which doses give similar efficacy as the AC?

Need to Improve Dose Finding in Phase II

Model-based analyses



- Modelling provides more information
  - Smoothes dose estimates
  - Interpolation between doses
  - Confidence intervals for quantities of interest, e.g. target dose (TD) achieving same effect as AC
- Modelling often only done as supportive analysis
  - Studies not designed for this purpose
- Issues with modelling
  - Pre-specification

Need to Improve Dose Finding in Phase II

Finding the right dose is not that simple

- True underlying dose response profile is typically unknown before and even after completing a dose finding study uncertainty might remain
- Selecting a working model may have a substantial impact on the final dose estimate
- Model selection using observed data needs to account for the inherent uncertainty
  - ➔ Useful to have a unified approach combining the advantages of dose response signal testing and modeling
  - ➔ MCP-Mod: A structured approach to model-based design and analysis of Phase II dose finding studies under model uncertainty

MCP-Mod

Development over the past 14 years

- Selected methodological developments
  - Bretz et al. (2005): normal homoscedastic data, no covariates
  - Pinheiro et al. (2006a): Sample size calculation based on MCP step
  - Dette et al. (2008): Optimal designs for Mod step
  - Bornkamp et al. (2009): Detailed description of `MCP-Mod` package in R (later converted into `DoseFinding` package)
  - Bornkamp et al. (2011): Adaptive MCP-Mod with Bayesian elements
  - Pinheiro et al. (2014): General parametric models (non-normal endpoints, non-parallel designs)
  - König et al (2014): Extension of MCP-Mod to confirmatory studies
- Current software implementations
  - `DoseFinding` package available on CRAN and ADDPLAN DF module
- CHMP (2014) Qualification Opinion and FDA (2016) Fit-for-Purpose Determination of MCP-Mod

Outline

- Introduction
- MCP-Mod approach
  - Independent and normally distributed data
  - More general data distributions
- Summary

Example of a Phase IIb Study (`biom`)

Study design and summary results

- `biom` example data set from the `DoseFinding` R package on CRAN
- A randomized double-blind parallel groups trial
- 100 patients allocated equally to either placebo or one of four active doses coded as 0.05, 0.20, 0.60, and 1
- Normally distributed response variable
- Larger responses indicate better outcomes in efficacy

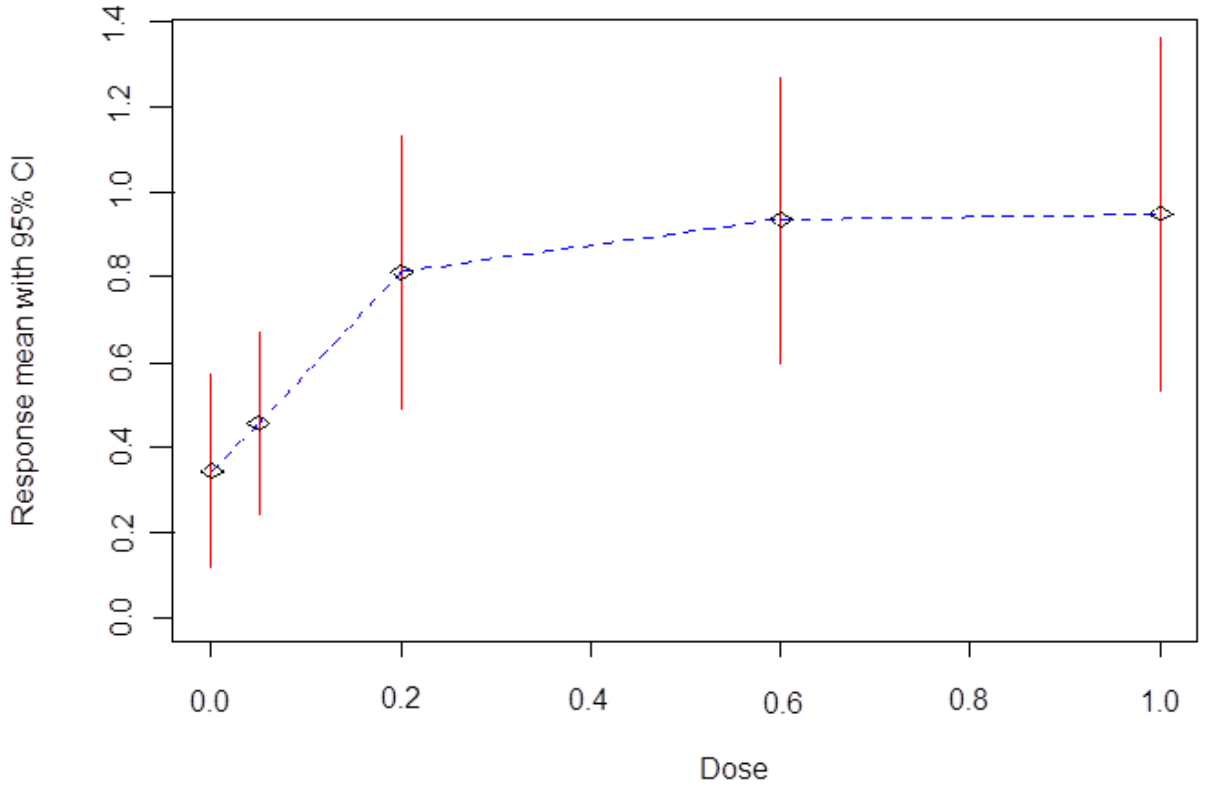
Dose	0	0.05	0.2	0.6	1
Mean	0.345	0.457	0.810	0.934	0.949
95% CI lower bound*	0.118	0.242	0.486	0.599	0.533
95% CI upper bound	0.571	0.672	1.134	1.270	1.364

* CI: confidence interval

Example of a Phase IIb Study (`biom`)

Mean plot

- Mean response at each dose with 95% CI



- Questions:
  - Is there a significant dose response signal?
  - What is the underlying dose response relationship?
  - What is the minimum effective dose with respect to a target effect?

MCP-Mod

A unified dose finding approach

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

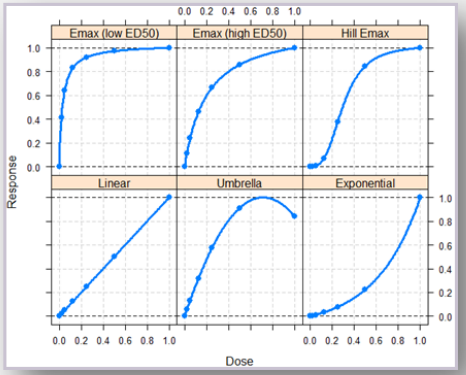
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



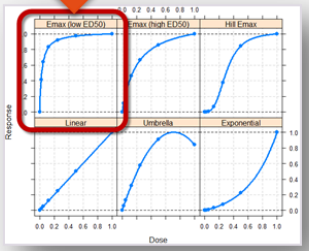
Trial conduct

$p < \alpha$?

Trial Analysis Stage

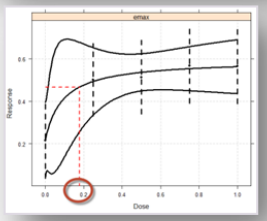
MCP step

- 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)



MCP-Mod

Candidate models

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)

- Identify a set of M parameterized candidate models

$$f_m(d, \boldsymbol{\theta}_m) = \theta_0 + \theta_1 f_m^0(d, \boldsymbol{\theta}_m^0)$$

together with pre-specified standardized model parameter values $\boldsymbol{\theta}_m^0$ for the standardized model $f_m^0(d, \boldsymbol{\theta}^0)$, where $i = 1, \ldots, k$ and $m = 1, \ldots, M$

- Each model will be tested using a contrast test with optimal contrast coefficients

MCP-Mod

`biom` *example revisited: Candidate models*

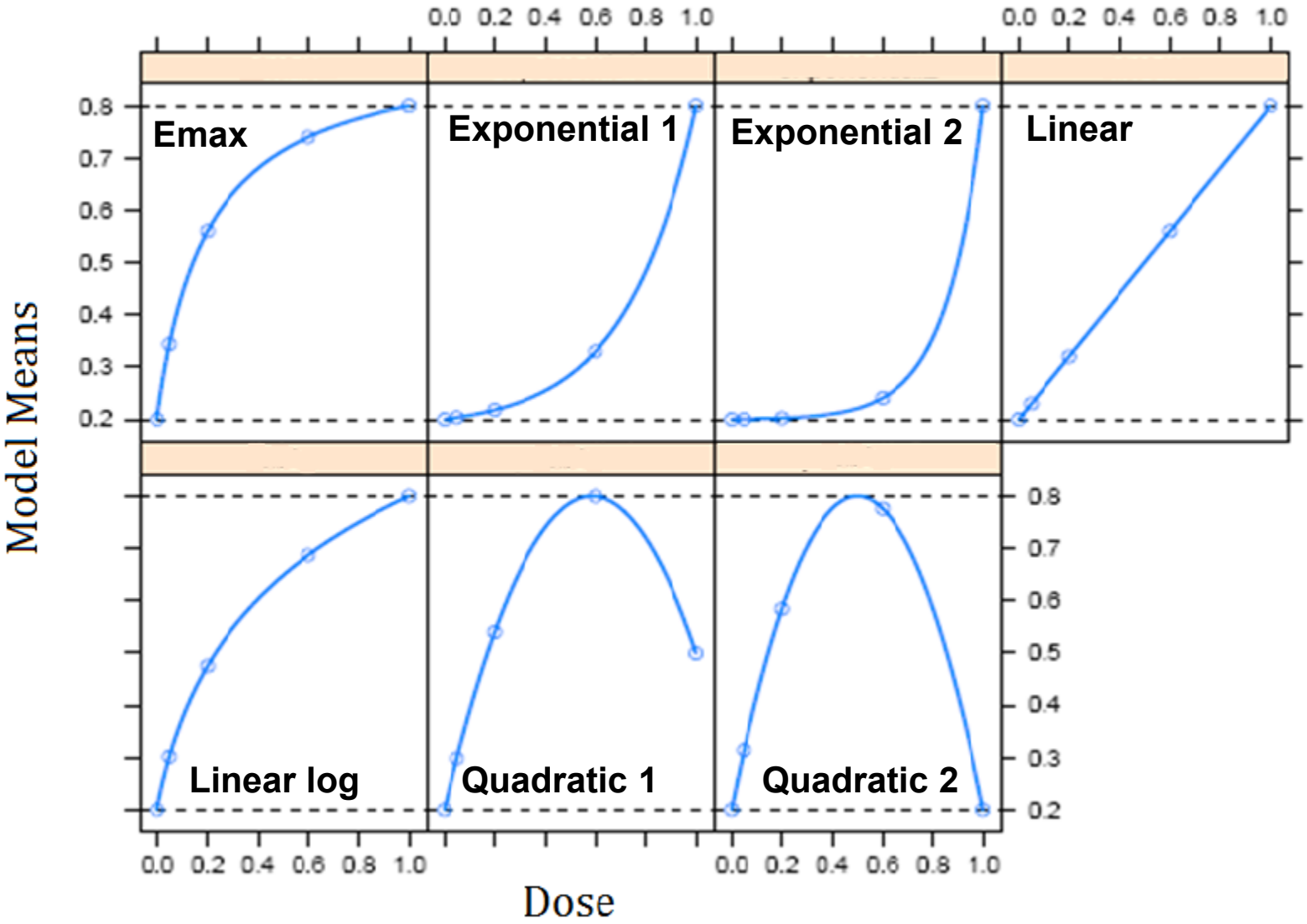
- Selected candidate models

Model	$f(d, \boldsymbol{\theta})$	$f^0(d, \boldsymbol{\theta}^0)$	Pre-specified $\boldsymbol{\theta}^0$
Linear	$E_0 + \delta d$	d	
Emax	$E_0 + E_{\max} d/(ED_{50} + d)$	$d/(ED_{50} + d)$	$ED_{50} = 0.2$
Linear log-dose	$E_0 + \delta \log(d + c)$	$\log(d + c)$	
Exponential 1	$E_0 + E_1(\exp(d/\delta) - 1)$	$\exp(d/\delta) - 1$	$\delta = 0.279$
Exponential 2	$E_0 + E_1(\exp(d/\delta) - 1)$	$\exp(d/\delta') - 1$	$\delta' = 0.15$
Quadratic 1	$E_0 + \beta_1 d + \beta_2 d^2$	$d + (\beta_2/\lvert\beta_1\rvert) d^2$	$\beta_2/\lvert\beta_1\rvert = -0.854$
Quadratic 2	$E_0 + \beta_1 d + \beta_2 d^2$	$d + (\beta_2'/\lvert\beta_1'\rvert) d^2$	$\beta_2'/\lvert\beta_1'\rvert = -1$

- The pre-specified standardized model parameters $\boldsymbol{\theta}^0$ are elicited from previous studies, the literature, or discussions with clinical teams

MCP-Mod

`biom` *example revisited: Model shapes*



MCP-Mod

Model contrast test statistics

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

- Construct multiple contrast tests to detect a positive dose effect using optimal coefficients $c_{m1}, \ldots c_{mk}$ to maximize the test power under model $m = 1, \ldots, M$
- In the balanced (equal allocation) case,

$$\begin{pmatrix} c_{m1} \\ \vdots \\ c_{mk} \end{pmatrix} \propto \begin{pmatrix} \mu_{m1} - \bar{\mu}_m \\ \vdots \\ \mu_{mk} - \bar{\mu}_m \end{pmatrix} \propto \begin{pmatrix} \mu_{m1}^0 - \bar{\mu}_m^0 \\ \vdots \\ \mu_{mk}^0 - \bar{\mu}_m^0 \end{pmatrix},$$

  where $\mu_{mi} = f_m\left(d_i, \boldsymbol{\theta}_m\right)$, $\bar{\mu}_m = N^{-1}\sum_{i=1}^k \mu_{mi}$, $\mu_{mi}^0 = f_m^0(d_i, \boldsymbol{\theta}_m^0)$, $\bar{\mu}_m^0 = N^{-1}\sum_{i=1}^k \mu_{mi}^0$, and N is the total sample size

- The optimal contrast coefficients depend only on the pre-specified standardized model $f_m^0(d, \boldsymbol{\theta}_m^0)$

MCP-Mod

`biom` *example revisited: Optimal contrast coefficients*

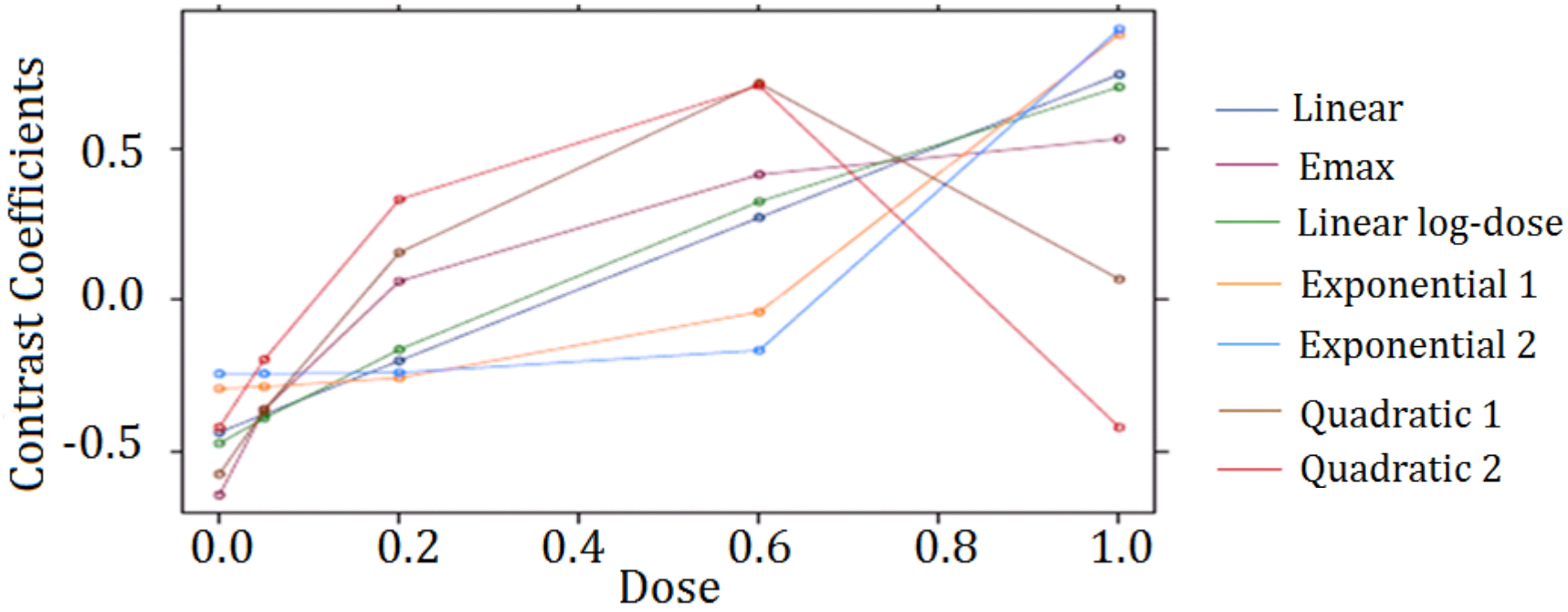
- Optimal coefficients calculated for each candidate model

	Dose				
Model	**0**	**0.05**	**0.2**	**0.6**	**1**
Linear	-0.44	-0.38	-0.20	0.27	0.74
Emax	-0.64	-0.36	0.06	0.41	0.53
Linear log-dose	-0.47	-0.39	-0.16	0.32	0.70
Exponential 1	-0.29	-0.29	-0.26	-0.04	0.87
Exponential 2	-0.24	-0.24	-0.24	-0.17	0.89
Quadratic 1	-0.57	-0.36	0.16	0.71	0.07
Quadratic 2	-0.42	-0.20	0.33	0.71	-0.42

MCP-Mod

`biom` *example revisited: Graphical display of contrast coefficients*

- Plot of optimal contrast coefficients



- The underlying dose response model shapes are well reflected by the optimal contrast shapes

MCP-Mod

Sample size calculation

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

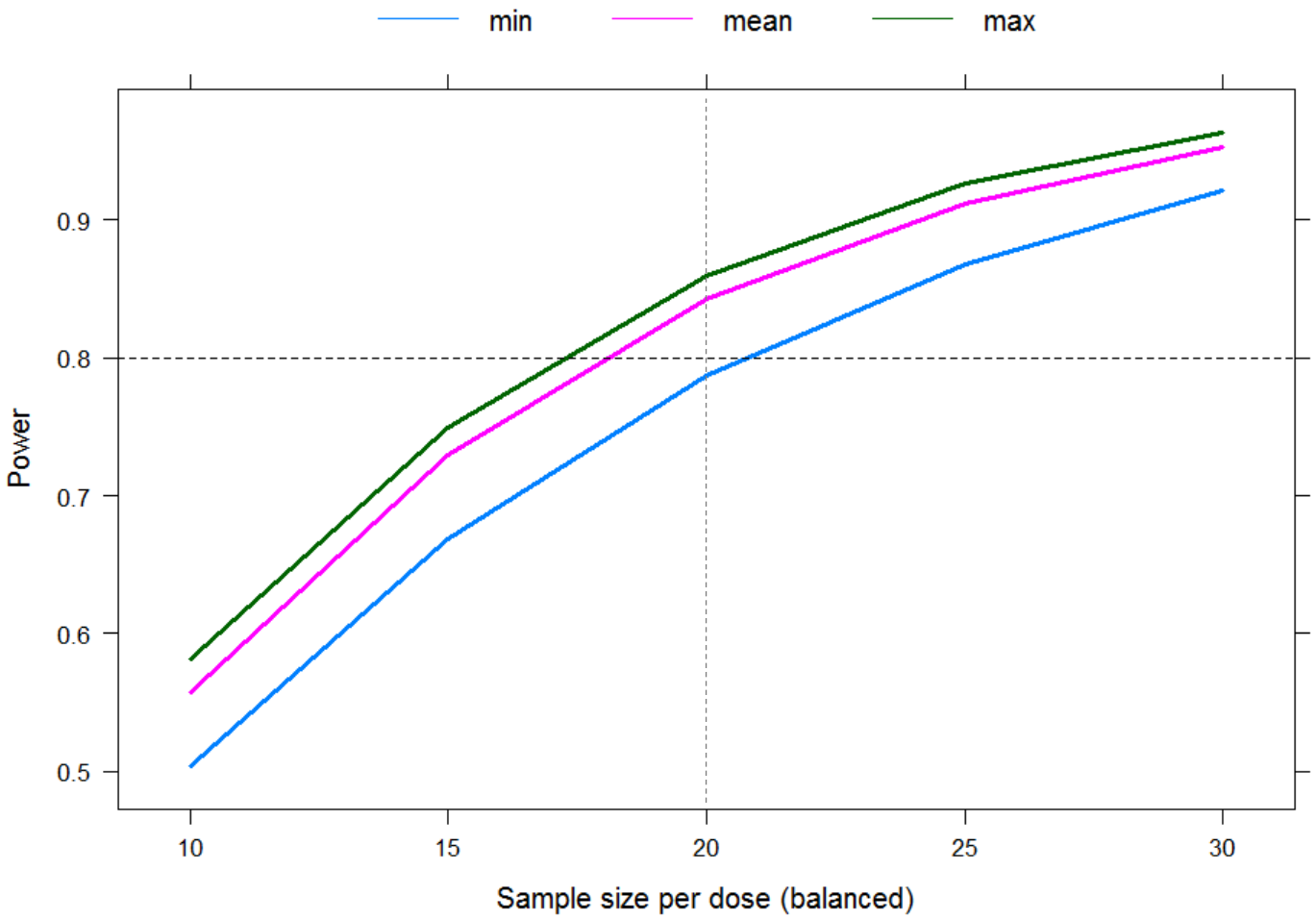
Dose determination and sample size calculation to achieve targeted performance characteristics

- Two different ways to calculate sample size
  - Estimation precision
    - Ensure the width of the confidence intervals for the quantities of interest (e.g., MED) are smaller than a pre-specified maximum value
  - Power analysis
    - Achieve a pre-specified power to detect a significant dose response signal
    - Considering the model uncertainty, one could
      - First, calculate the power for each of the candidate models
      - Then, aggregate the resulting values into a single combined measure of power, such as the minimum, mean, and maximum

MCP-Mod

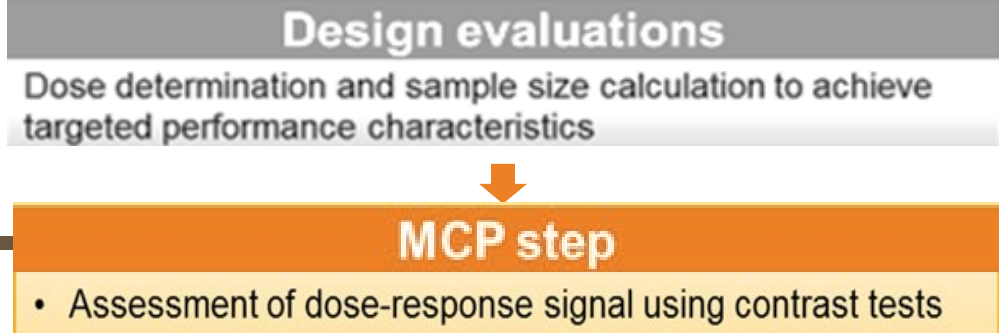
`biom` *example revisited: Sample size calculation*

- Power to detect a significant dose response signal for $\sigma = 1$



MCP-Mod

Dose response signal testing



- If observed maximum contrast test statistic

$$\max_m T_m > q_{1-\alpha}$$

then we declare a significant dose response signal

  - The critical value $q_{1-\alpha}$ is derived from the multivariate t distribution such that under the null hypothesis of no dose response

$$\Pr\left(\max_m T_m > q_{1-\alpha}\right) = \alpha$$

- All models with observed $T_m > q_{1-\alpha}$ are kept for possible use in dose response modelling

MCP-Mod

`biom` *example revisited: Dose response signal testing*

- The 5% one-sided critical value is $q_{0.95} = 2.15$

Model	Estimate	Standard error	T_m
Emax	0.55	0.159	3.46
Linear log-dose	0.49	0.159	3.11
Quadratic 1	0.49	0.159	3.10
Linear	0.47	0.159	2.97
Exponential 1	0.35	0.159	2.22
Exponential 2	0.30	0.159	1.90
Quadratic 2	0.29	0.159	1.85

- Conclusions:
  - Since $\max_m T_m = 3.46 > 2.15 = q_{1-\alpha}$, we conclude that there is a significant dose response signal
  - Models with $T_m > q_{0.95}$ are selected as significant models

MCP-Mod

Model selection

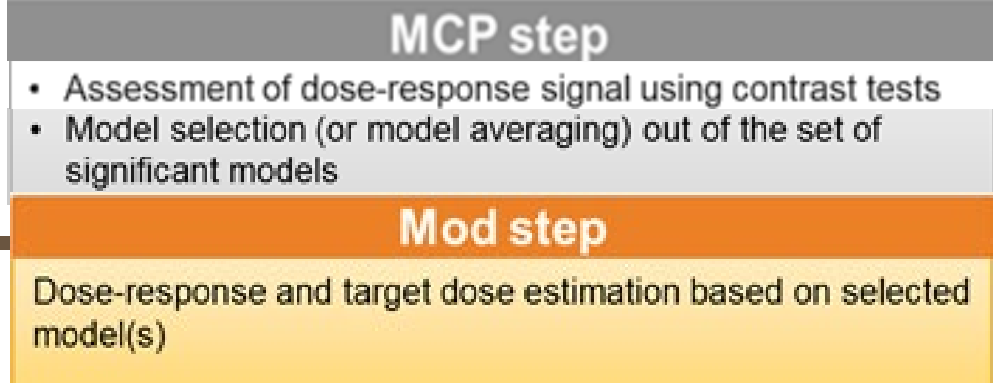
MCP step

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

- Either select a single model from the significant models
  - Existing model selection criteria can be used, such as
    - Akaike information criterion (AIC)
    - Bayesian information criterion (BIC)
    - maximum contrast test statistics (not recommended)
- Or apply model averaging techniques
  - Weighted estimates across all the significant models are produced for the quantities of interest (Buckland et al., 1997)

MCP-Mod

Dose estimation and selection



- Based on dose response modelling approaches, the selected model is used to fit the observed data and estimate a target dose (such as the MED or the ED_{90})

MCP-Mod

`biom` *example revisited: Dose response and MED estimation*

- Model selection, fitting and MED estimation via `MCPMod` function in `DoseFinding` R package
- Output (edited):

```
Selected model (AIC): emax

Estimated Dose Response Model:
emax model
    e0  eMax  ed50
0.322 0.746 0.142

Estimated MED, Delta=0.4
  emax
0.1642
```

- Emax model is selected from the candidate models and used for model parameter and MED estimation
  - Note that the Emax model above is the best fitting Emax model to the observed data and not the specific model shape included in the candidate set

Outline

- Introduction
- MCP-Mod approach
  - Independent and normally distributed data
  - More general data distributions
- Summary

Generalized MCP-Mod

Notation

- Assume patient responses $\boldsymbol{y}$ follow some distribution

$$\boldsymbol{y} \sim F\big(\boldsymbol{z}, \boldsymbol{\eta}, \mu(d)\big),$$

where

- $\mu(d)$ denotes the dose response information at dose d
- $\boldsymbol{\eta}$ nuisance parameters
- $\boldsymbol{z}$ covariates

- Main idea
  - Extract dose response parameters $\mu(d_i)$ from this model and perform contrast test and dose response model fitting on these parameters

- Concrete example to keep in mind
  - $\mu(d_i)$ coming from a normal model $N(\mu(d_i), \sigma^2)$

Generalized MCP-Mod

Applications

- Examples of application include
  - Binary data: $\mu(d)$ could be the probability or logit(probability)
  - Negative binomial data: $\mu(d)$ could be the log-mean of the distribution
  - Weibull: $\mu(d)$ could be the median of the survival distribution (using a re-parameterization of the Weibull model)
  - Cox PH: Requires working on control-adjusted data (not discussed here, but see Pinheiro et al. 2014)
  - Major restriction: $\mu(d)$ should be easily interpretable
    - need to formulate candidate models on this scale
- In each case: Fit an ANCOVA-type model (i.e. a model with dose as factor) and extract estimates $\hat{\boldsymbol{\mu}}$ and corresponding estimated covariance matrix $\boldsymbol{S}$
  - From there on, all cases are treated the same way

Generalized MCP-Mod

MCP step

- At design stage
  - Specify multiple candidate dose-response shapes $\boldsymbol{\mu}_1, \ldots, \boldsymbol{\mu}_M$
  - Derive optimal contrasts $\boldsymbol{c}_1^{opt}, \ldots, \boldsymbol{c}_M^{opt}$ for these shapes
- At analysis stage:
  - Derive $\hat{\boldsymbol{\mu}}$ and $\boldsymbol{S}$ based on the observed data and the contrast test statistics

$$z_m = \left(\boldsymbol{c}_m^{opt}\right)' \hat{\boldsymbol{\mu}} \Big/ \sqrt{\left(\boldsymbol{c}_m^{opt}\right)' \boldsymbol{S} \left(\boldsymbol{c}_m^{opt}\right)}, \qquad m = 1, \ldots, M$$

  - Calculation of p-values can be done via the joint distribution of $z_1, \ldots, z_M$ under the null hypothesis of no dose response

Generalized MCP-Mod

MCP step – derivation of optimal contrasts

- Assume a particular dose-response mean vector

$$\boldsymbol{\mu}_m = \left(\mu(d_1), \ldots, \mu(d_k)\right)$$

for k active doses $d_1, \ldots, d_k$, including placebo

- Maximizing power of the single contrast test is the same as maximizing the non-centrality parameter $\boldsymbol{c}'\boldsymbol{\mu}_m / \sqrt{\boldsymbol{c}' S \boldsymbol{c}}$

- Optimization leads to

$$\boldsymbol{c}_m^{opt} \propto \boldsymbol{S}^{-1}\left(\boldsymbol{\mu}_m - \frac{\boldsymbol{\mu}_m{}'\boldsymbol{S}^{-1}\mathbf{1}}{\mathbf{1}'\boldsymbol{S}^{-1}\mathbf{1}}\right)$$

Generalized MCP-Mod

MCP step

- If the asymptotic distribution of $\hat{\boldsymbol{\mu}}$ is multivariate normal, then the distribution of the contrast statistics is also multivariate normal
  - In the case of normal data the exact distribution is multivariate *t*
- Multiple models ⇒ multiple test problem
  - Using $z_{max} = \max z_m$ with an appropriate critical value $q_{1-\alpha}$ ensures overall Type I error rate control at pre-specified level $\alpha \in (0,1)$

Generalized MCP-Mod

Mod step

- All models with significant contrast test statistic are fitted
- For normally distributed data, minimize least squares
- For generalized approach, assume $\hat{\boldsymbol{\mu}}$ is available that is multivariate normal distributed with covariance matrix $\boldsymbol{S}$
  - Use generalized least squares

$$\left(\hat{\boldsymbol{\mu}} - \boldsymbol{\mu}(d)\right)' \boldsymbol{S}^{-1} \left(\hat{\boldsymbol{\mu}} - \boldsymbol{\mu}(d)\right)$$

  - Advantages
    - Applicable to non-normal and/or correlated data
    - Asymptotic approximations available (similar asymptotic distribution as MLE)
    - Often numerically similar to „traditional“ ML estimates
    - Only one software implementation needed for all parametric models with estimation methods leading to parameter estimates with asymptotic multivariate normal distribution

Generalized MCP-Mod

Mod step

- Model-based analysis
  - Either select one model (AIC, BIC, ...)
  - Or perform model averaging, e.g.
    - by using weights determined by AIC, BIC
      - i.e. using weights proportional to $exp(-AIC_m/2)$ or $exp(-BIC_m/2)$
    - or by bootstrapping the model selection itself and using bootstrap estimates
- Perform inference on quantities of interest using the selected dose response model(s)

Example

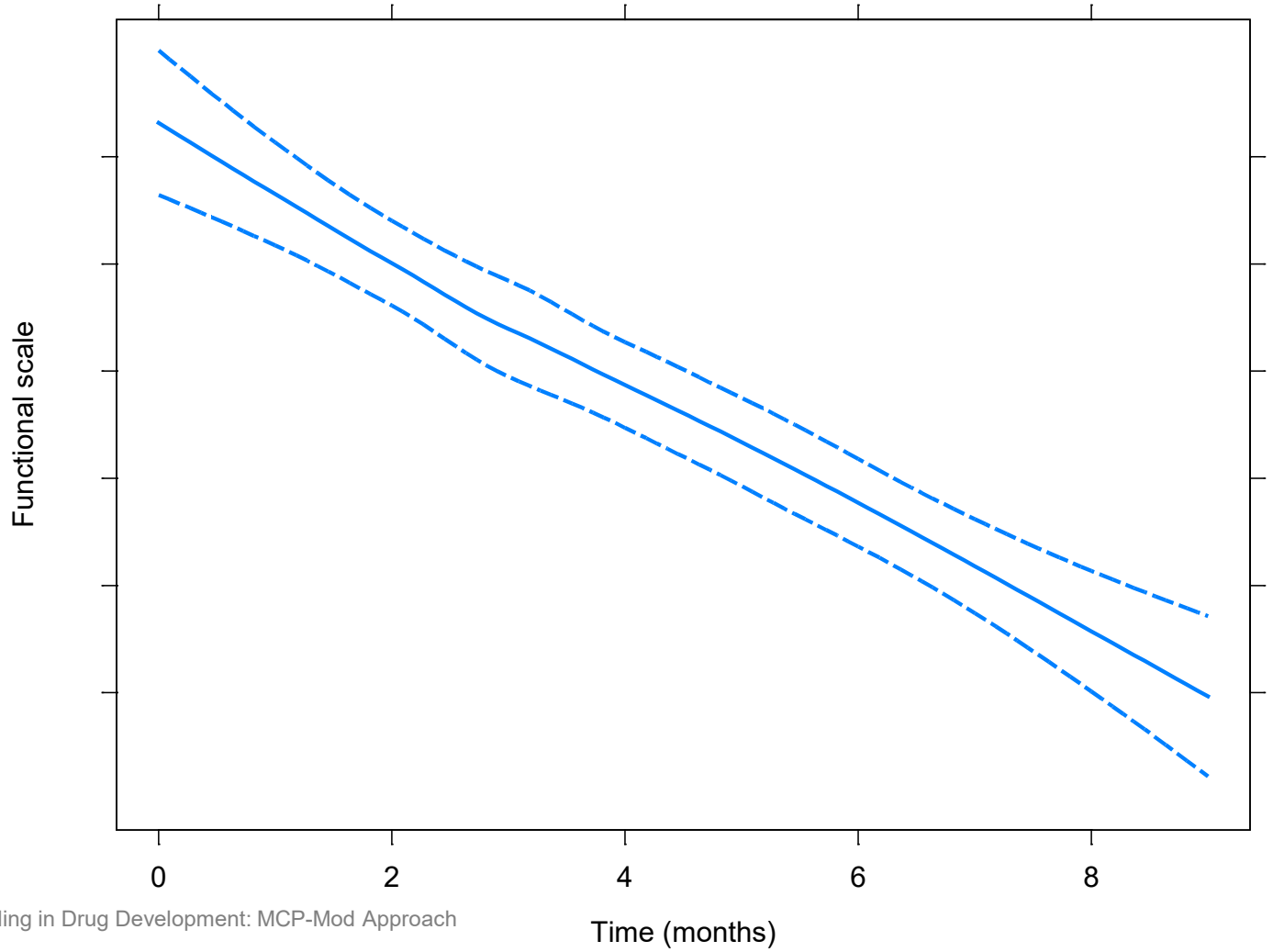
Background

- Disease progression measured by functional scale that decreases linearly with time
- Objective is to reduce, or stop, rate of worsening over time (i.e., impact slope)
- Trial design:
  - Placebo and 4 doses (1, 3, 10, 30 mg), balanced with 50 patients/arm
  - one year duration with measurements at baseline and every 3 months thereafter
- Study objective: test dose response signal, and estimate dose-time response

Example

Linearity of functional scale

- Loess smoother on historical placebo data



Example

Two-stage approach

- Initial dose-time response model with an ANOVA-type parameterization for the functional scale measurement y_{it} on patient i at time t,

$$y_{it} = (\beta_0 + b_{0i}) + (\mu(d) + b_{1i})t + \varepsilon_{ij}$$

where

- $\mu(d)$ is the parameter of interest (linear slope of disease progression)
- b_{0i}, b_{1i} are patient specific random effects (intercept and slope)
- $(b_{0i}, b_{1i}) \sim N(\mathbf{0}, \mathbf{\Lambda})$ and $\varepsilon_{ij} \sim N(0, \sigma^2)$

Example

Two-stage approach

- The dose-response parameter $\mu(d)$ is expected time slope, which is expressed by a second-level model,
  - For example, for the Emax model

$$\mu(d) = E_0 + E_{max}\frac{d}{ED_{50}+d}$$

- Under ANOVA parameterization for $\mu(d)$, LME model is used to fit data; parametric models for $\mu(d)$ require NLME modeling

Example

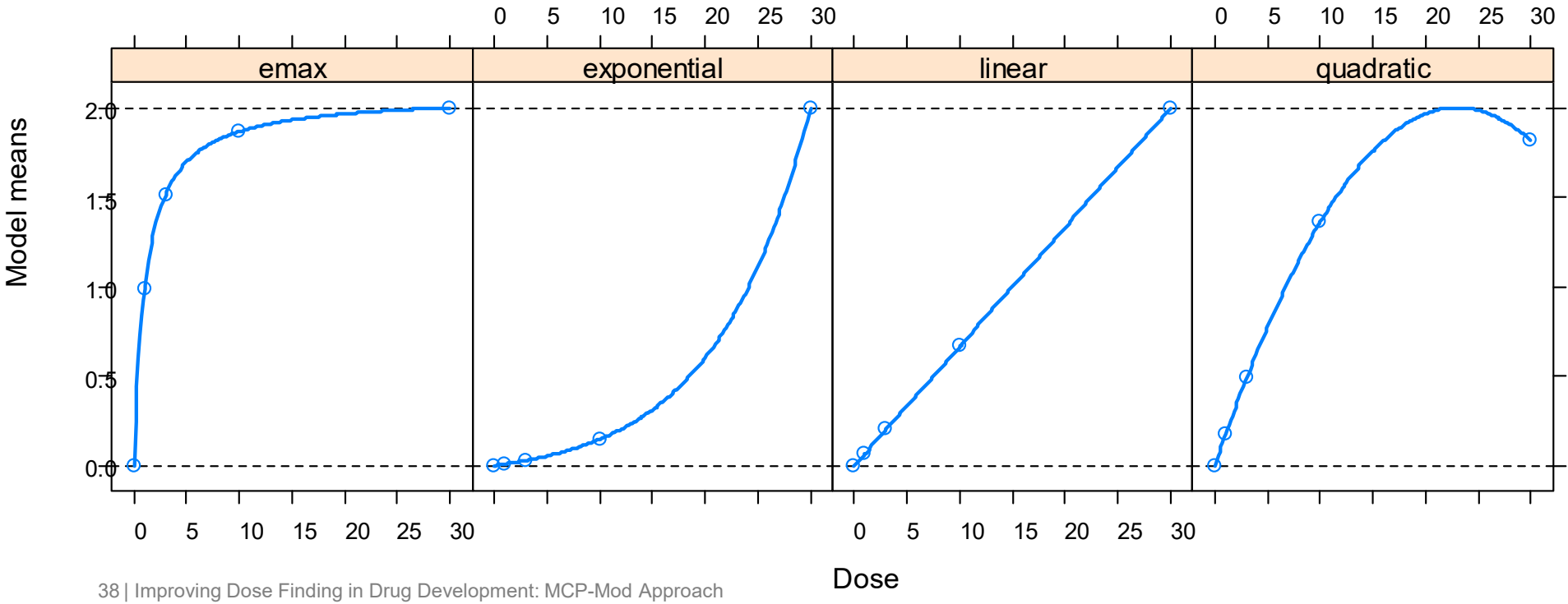
Assumptions

- Placebo effect: 0 change in slope (natural progression)
- Maximum improvement over placebo for dose range: 2
- Target effect: 1.4
- From historical data, estimates for variance-covariance parameters
  - $var(b_{0i}) \approx 64;\ var(b_{1i}) \approx 16;\ corr(b_{0i}, b_{1i}) \approx -0.2; var(\varepsilon_{ij}) = 4$
- Based on these and assumed design (sample size, visits, doses, etc.), can derive estimate for covariance matrix of ANOVA estimates
  - Compound symmetry with variance 0.1451 and covariance 0.0092

Example

Candidate models

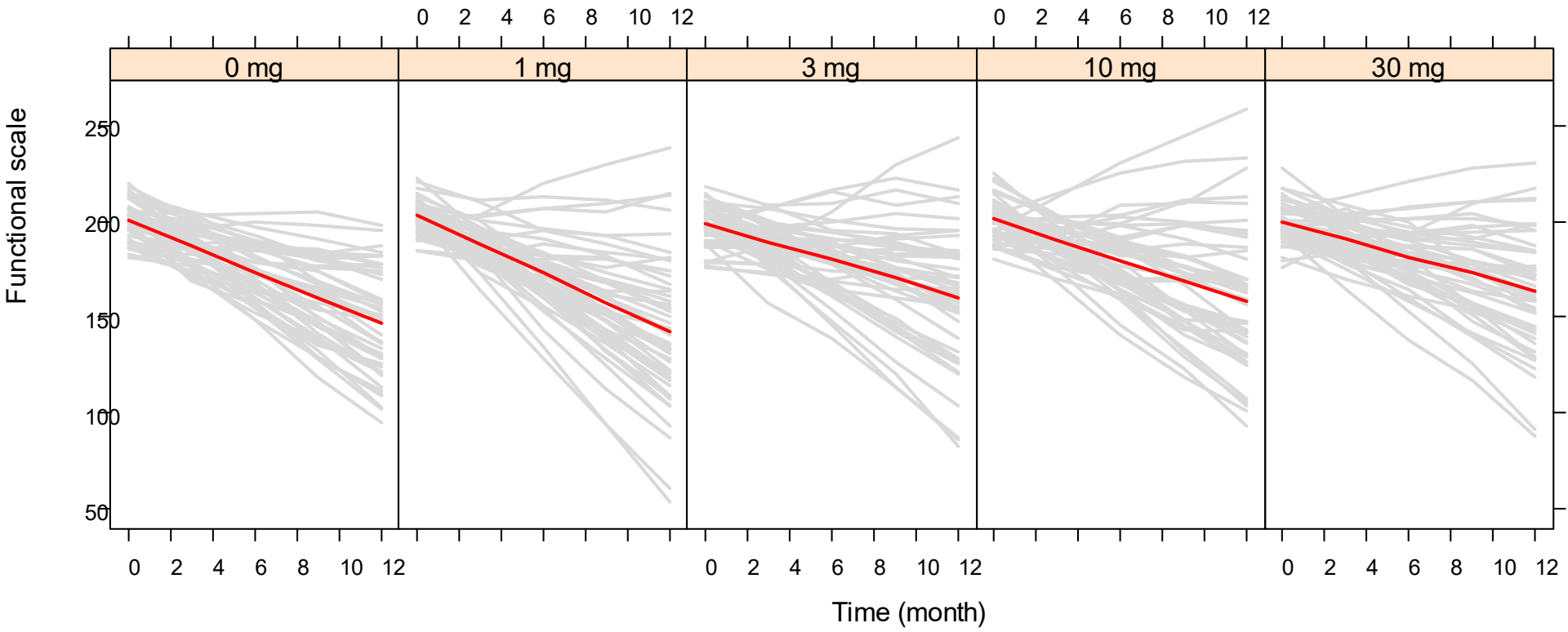
- Plausible dose response shapes for slope: linear, Emax, exponential, and quadratic
- Estimates of model parameters obtained from discussions with clinical team



Example

Simulated data for illustration

- Longitudinal data simulated according to Emax candidate model (and previous assumptions)



Example

DoseFinding *package – LME fit with ANOVA parameterization*

```
> library(nlme)
> fm   <- lme(resp ~ dose:time, dat, ~time|id)
>
> muH  <- fixef(fm)[-1]                          # extract d-r estimates to work with
> muH
 dose0:time dose1:time  dose3:time dose10:time  dose30:time
     -5.099     -4.581      -3.220      -2.879       -3.520
>
> covH <- vcov(fm)[-1,-1]                        # and their covariance matrix
> covH
            dose0:time dose1:time dose3:time dose10:time dose30:time
dose0:time      0.1490     0.0094     0.0094      0.0094      0.0094
dose1:time      0.0094     0.1490     0.0094      0.0094      0.0094
dose3:time      0.0094     0.0094     0.1490      0.0094      0.0094
dose10:time     0.0094     0.0094     0.0094      0.1490      0.0094
dose30:time     0.0094     0.0094     0.0094      0.0094      0.1490
```

Example

`DoseFinding` *package – Testing and modelling*

```
> MCTtest(doses, muH, S=covH, type = "general", critV = T, contMat=contMat)
. . .
Multiple Contrast Test:
            t-Stat     adj-p
emax        4.5606   < 1e-04
quadratic   3.6795 0.0002323
linear      2.2739 0.0252661
exponential 1.2767 0.1822576

Critical value: 2.2768 (alpha = 0.025, one-sided)

> fitMod(doses, muH, S=covH, model="emax", type = "general", bnds=c(0.1, 10))
Dose Response Model

Model: emax
Fit-type: general

Coefficients dose-response model
     e0    eMax    ed50
-5.1808  2.1802  1.1873
```

Example

NLME model fit of dose time response model

```
## emax
> fmE <- nlme(resp ~ b0 + (e0 + eM * dose/(ed50 + dose))*time, dat,
            fixed = b0 + e0 + eM + ed50 ~ 1, random = b0 + e0 ~ 1 | id,
            start = c(200, -4.6, 1.6, 3.2))
## quadratic
> fmQ <- nlme(resp ~ b0+(e0 + e1 * dose + e2 * dose * dose)*time, dat,
            fixed = b0 + e0 + e1 + e2 ~ 1, random = b0 + e0 ~ 1 | id,
            start = c(200, -4.5, 0.144, -0.033))
> fmE
. . .
  Log-likelihood: -4180.254
  Fixed: b0 + e0 + eM + ed50 ~ 1
        b0         e0         eM       ed50
200.451303  -5.178739   2.181037   1.198791
```

- Parameter estimates from NLME fit are very close to the ones from second-level model fit

Outline

- Introduction
- MCP-Mod approach
- Summary

MCP-Mod

In-scope: When to use MCP-Mod

- Drug development stage
  - Phase II dose finding studies to support dose selection for Phase III
- Response
  - Univariate (efficacy or safety) measurement (could be a binary, count, continuous or time-to-event endpoint). Observations typically cross-sectional (i.e. from a single time point)
- Dose
  - Or any other univariate, continuous, quantitative measurement
- Rules of thumb:
  - $4 - 7$ active doses
  - > 10-fold dose-range, logarithmic dose-spacing
  - include placebo and/or active control

MCP-Mod

Out-of-scope: When not to use MCP-Mod

- Titration designs and dose escalation studies
- Vaccines and regimen finding for biologics where there is no steady state
- Exposure-response analyses or pharmacokinetic-pharmacodynamic (PK-PD) models
  - similar principles could/should be applied
  - MCP-Mod is focused on dose response modelling only
- Predictions from a surrogate / biomarker or short term readout to a clinical Phase III endpoint

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

FDA Fit-for-Purpose Determination of MCP-Mod

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

May 26, 2016

Janssen Research & Development, LLC
Attention: Purve Patel, RPh
Director, Global Regulatory Affairs
920 Highway 202, South
Raritan, NJ 088969

Dear Ms. Patel:

Please refer to the submission by Janssen Pharmaceuticals and Novartis Pharmaceuticals intended to support the use of MCP-Mod[1, 2] as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. We have completed our review of your submission and have determined it is fit-for-purpose in the context outlined in this letter.

MCP-Mod: CHMP (2014) Qualification Opinion and (2016) FDA Fit-for-Purpose Determination

- Both emphasize the importance of conducting proper dose-finding studies before going to Phase III
- MCP-Mod will encourage better study designs (with more dose levels and broader dose-range)
  - MCP-Mod is only one method among several others
- Acceptance of model-based techniques often subject to discussion
  - EMA/CHMP and FDA are positive on MCP-Mod
- Difference of MCP-Mod to other model-based approaches
  - Modelling activity is pre-specified at design stage (less „cherry-picking“)
  - Acknowledges model uncertainty

Dose Finding

Take home messages

- Precise estimation of dose response provides the strongest basis supporting dose selection for Phase III / submissions
- Traditional dose ranging designs do not provide explicit dose response characterization, and often lack precision to differentiate active doses
- Model-based dose response assessment requires careful consideration of trial design
  - Essential to ensure inclusion of sufficient doses to cover both the steep part of the curve and the plateau
- Dose response relationships exist for both efficacy and safety, and it is necessary to estimate the therapeutic window
- Adaptive designs, in which dose allocation changes based on observed responses, should routinely be considered

Q&A

Questions?