Generalizing the MCPMod methodology beyond normal, independent data

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• Motivation: improving dose selection in clinical development
• Dose response (DR) estimation under model uncertainty: MCPMod
• Extending MCPMod: gMCPMod
• Concluding Remarks
Motivation

• Pharmaceutical industry **pipeline problem**: expiring patents in blockbusters, low number of new approved drugs

• Poor understanding of dose response and resulting inadequate dose selection for confirmatory studies identified as **key driver** of late stage failure

• Dose finding studies often designed as mini-confirmatory trials: focus on hypothesis testing, instead of estimation
Dose Selection

- Two main goals in Phase II studies:
  - proof-of-concept (PoC) – any evidence of treatment effect
  - dose-selection – which dose(s) to take into phase III?
    minimum effective dose (MED), maximum safe dose (MSD)

- ICH-E4: Purpose of dose-response information is to find the
  Smallest dose with a discernible useful effect

- Emphasis is placed on identifying or estimating the MED
  - Assurance that a desired effect size is plausible

- Analysis strategies categorized into two broad classes:
  multiple comparisons (MCP) of contrasts between doses and
  modeling of dose response relationship
Finding the MED – an illustration

- Either D2, D3 or any dose in-between could be estimated as MED
- Modeling is more flexible, but requires additional assumptions
Multiple Comparisons vs. Modeling

**Multiple comparison procedures (MCP):** emphasis on inference
- Dose treated as categorical variable
- Mostly pairwise comparisons against control
- Allows control of type I error (T1E)
- Little prior knowledge required: Less sensitive to assumptions

**Modeling (Mod):** emphasis on estimation
- Assumes a parametric dose-response model $y = f(d, \theta) + \epsilon$
- Dose is a continuous variable: Target dose can be any dose
- Estimation of MED and other target doses is done by inverse regression (with confidence intervals)
- Better understanding of dose-response relationship: useful for planning future studies and simulations
Impact of model uncertainty on dose estimation
Finding right dose is not simple

- True shape of dose-response model is typically unknown
- Choice of a working model may have a substantial impact on dose selection
- Model selection using observed data needs to account for statistical uncertainty and associated multiplicity issues → Useful to have a unified approach combining the advantages of MCP and modeling: this is the goal of MCP-Mod
MCPMod: a unified dose finding approach

- Set of candidate models
- Optimal contrast coefficients
- Establishing a dose response signal while controlling T1E
- Selection of a single model using max $t$, $AIC$, ... possibly combined with external data
- Dose estimation and selection ($MED, ED_x$, ...)

Design

Analysis
MCPMod: Software implementation

- DoseFinding package in R, freely available on CRAN covers,
  - multiple contrast tests (trend test, Dunnett test, etc.)
  - Nonlinear Regression
  - MCP-Mod methodology
  - Calculation of optimal and robust designs
  - Basic functionality for response-adaptive designs
  - Handling of non-normal endpoints (e.g. binary, count data)

- Note: MCPMod R package is an earlier, outdated version of the package, only available for backcompatibility

Developed and maintained by Björn Bornkamp
Extending the basic MCPMod

• MCPMod originally developed for parallel arm designs, normally distributed, homoscedastic response, with single measurement per patient

• DR models represent expected response; model contrasts applied to response means (or LSMEANS)

• Basic framework has had broad application, but does not cover important cases of practical interest

• Key ideas of MCPMod are not limited to original framework → can be extended to more general applications is key goal of presentation
Examples of applications not covered by MCPMod

- Non-normally distributed responses: binary, Poisson, negative binomial, etc
- Longitudinal data, repeated measures, and, more broadly, correlated data (e.g., crossover studies)
- Time-to-event, with potential censoring, (e.g., survival data)
- Combinations of the above, e.g., longitudinal binary responses, correlated time-to-event data

⇒ **Generalized** MCPMod can handle all of the above
Generalized MCPMod: Basic concepts

• Key idea is to decouple DR model from expected response, focusing instead on more general characteristic (parameter) of response distribution

• More concretely, assume dependency of response on dose occurs through parameter $\mu = \mu(d)$ of response distribution, i.e., $y \sim F(x, \eta, \mu(d))$, $x$ covariates, $\eta$ nuisance parameters

• MCPMod approach translated to $\mu(d)$:
  → Model uncertainty via candidate models
  → DR signal testing via model contrasts
  → Model selection via information criteria
  → DR estimation and dose selection via modeling
Representing and estimating DR

• All DR information is conveyed via $\mu(d)$ – interpretable parameterization is key: communication with clinical team, choice of candidate models (guesstimates), clinically relevant treatment effects

• Example: survival data modeled as Weibull($k, \lambda$) – using $\lambda$ as “DR parameter” would not be adequate; using median survival instead would be more meaningful (reparameterization would be needed)

• Second stage DR model: $\mu(d) = f(d, \theta) = \theta_0 + \theta_1 f_0(d, \theta^0)$, $f_0$ standardized model and $\theta^0$ its parameter vector

• DR estimate $\hat{\mu}(d)$ obtained via appropriate estimation method (e.g., LS, ML, etc)
• Similar steps as in original MCPMod, but focusing on DR parameter \( \mu(d) \) and its estimate \( \hat{\mu}(d) \)

• Set of candidate models to represent \( \mu(d) \): need guesstimates for standardized model parameters

• For DR signal test, utilize ANOVA parameterization for DR parameter: \( \mu_A(d_k) = \theta_k, k = 1, ..., K \)

• Let \( \mu_A(d) = (\theta_1, ..., \theta_K) \) and \( \hat{\mu}_A(d) = (\hat{\theta}_1, ..., \hat{\theta}_K) \) its corresponding estimate

• Key assumption: \( \hat{\mu}_A(d) \sim N(\mu_A(d), \Psi_A) \) under estimation method used

• Model contrasts are applied to \( \hat{\mu}_A(d) \)
gMCPMod implementation (cont.)

- Optimal model contrasts obtained using general result from Bornkamp (2006), applied to asymptotic distrib. of $\hat{\mu}_A(d)$

$$c_{opt,m} = \Psi_A^{-1} \left( \mu_m - \frac{1'\Psi_A^{-1}\mu_m}{1'\Psi_A^{-1}1} \right), \ m = 1, \ldots, M$$

In practice, need to replace $\Psi_A$ with estimate $\hat{\Psi}_A$

- At design phase, guesstimates may be needed for $\hat{\Psi}_A$

- Multiplicity adjusted critical values for DR signal test derived from joint (asymptotic) distribution of contrast tests

- Optimal contrasts and MCP critical values may be revised at analysis phase, with updated estimate $\hat{\Psi}_A$
gMCPMod implementation (cont.)

- Model selection, DR and target dose estimation can be implemented using two alternative approaches:
  - **direct incorporation** of parametric model in response distribution, \( y \sim F(x, \eta, f(d, \theta)) \), using appropriate method to estimate all parameters (including \( \theta \)) and produce information criteria, etc
  - focusing again on \( \hat{\mu}_A(d) \) and using **generalized LS**

\[
\hat{\theta} = \arg \min_{\theta} [\hat{\mu}_A(d) - f(d, \theta)]' \Psi_A^{-1} [\hat{\mu}_A(d) - f(d, \theta)]
\]

to estimate DR parameters and obtain information criteria

- First approach is more **accurate**; second is better suited for **general purpose software**
Application: MCPMod with longitudinal data

• Indication: neurodegenerative disease, measured by function scale that decreases linearly with time
• Goal of drug is to reduce the rate of worsening in the functional scale over time (i.e., increase slope)
• Trial design:
  → placebo + 4 doses (1, 3, 10, and 30 mg), balanced
  → one year duration
  → measurements at baseline and every 3 months thereafter
  → N = 50/arm
• Study goals: test DR signal (PoC), estimate DR, select dose
• Conventional MCPMod cannot be used
Linearity of functional scale

Loess smoother on historical placebo data
Mixed-effects model formulation

- Correlation among patients repeated measures need to be taken into account \( \Rightarrow \) **mixed-effects** model:
  \[
  y_{i,j} = (\beta_0 + b_{0i}) + (\mu(d) + b_{1i})t_j + \varepsilon_{ij},
  \]
  \[
  (b_{0i}, b_{1i}) \sim N(0, \Lambda), \varepsilon_{ij} \sim N(0, \sigma^2)
  \]

- DR parameter \( \mu(d) \) is expected time slope, which is expressed by **second-level** model, e.g., emax model
  \[
  \mu(d) = e_0 + e_M d / (ED_{50} + d)
  \]

- Under ANOVA parameterization for \( \mu(d) \), linear mixed-effects (**LME**) model used to fit data; parametric models for \( \mu(d) \) will require nonlinear mixed-effects (**NLME**) model
Assumptions

• Placebo effect: 0 increase in slope (natural progression)
• Maximum improvement over placebo for dose range: 2
• Target effect: 1.4

• From historical data, guesstimates for var-cov parameters:

  \[ \text{var}(b_0i) \approx 64; \text{var}(b_1i) \approx 16; \text{corr}(b_{0i}, b_{1i}) \approx -0.2; \]

  \[ \text{var}(\varepsilon_{ij}) \approx 4 \]

→ based on these and assumed design (N, visits, doses, etc), can derive guesstimate for var-cov matrix of ANOVA estimates: compound symmetric structure with var = 15.51 and cov = 0.134
Guesstimates and candidate models

- Plausible DR shapes: linear, emax, exponential, & quadratic

- Guesstimates for model parameters obtained from discussions with clinical team

- Functions in DoseFinding package:

```r
## 90% of max effect at 10 mg
> emx <- guesst(d = 10, p = 0.9, model = "emax")
> ed50
1.111111
## max effect at 23 mg
> quad <- guesst(d = 23, p = 1, model="quadratic")
> quad
delta
-0.02173913
```
Candidate models

![Graph showing model means for different dose levels for emax, exponential, linear, and quadratic models.](image)
Optimal contrasts

![Graph showing optimal contrasts with dose on the x-axis and contrast coefficients on the y-axis. The graph includes lines for emax, quadratic, exponential, and linear models.](image)
Applying gMCPMod

- Longitudinal data simulated according to emax candidate model (and previous assumptions)
LME model fit with ANOVA parameterization

> library(nlme)
> fm <- lme(resp ~ dose:time, dat, ~time|id)
> muH <- fixef(fm)[-1]
> muH
dose0:time  dose1:time  dose3:time  dose10:time  dose30:time
-4.485       -4.693       -3.431       -3.531       -3.159
> covH <- vcov(fm)[[-1,-1]
> covH
dose0:time  dose1:time  dose3:time  dose10:time  dose30:time  dose0:time
  dose0:time  0.1518       0.0079       0.0079       0.0079       0.0079       0.1518
dose1:time  0.0079       0.1518       0.0079       0.0079       0.0079       0.0079
dose3:time  0.0079       0.0079       0.1518       0.0079       0.0079       0.0079
dose10:time 0.0079       0.0079       0.0079       0.1518       0.0079       0.0079
dose30:time 0.0079       0.0079       0.0079       0.0079       0.1518       0.1518
gMCPMod: Testing DR signal and fitting DR model

> MCTtest(doses, muH, S=covH, type = "general", critV = T, contMat=contMat)

Multiple Contrast Test:

<table>
<thead>
<tr>
<th>t-Stat</th>
<th>adj-p</th>
</tr>
</thead>
<tbody>
<tr>
<td>emax</td>
<td>4.5606</td>
</tr>
<tr>
<td>quadratic</td>
<td>3.6795</td>
</tr>
<tr>
<td>linear</td>
<td>2.2739</td>
</tr>
<tr>
<td>exponential</td>
<td>1.2767</td>
</tr>
</tbody>
</table>

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
**NLME model fit of dose-time response model**

## emax

```r
> 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

```r
> 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))
```

```r
> 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 ones from second-level model fit
MED estimate

• Under emax model, MED for clinical effect $\delta < e_M$ is

$$MED(\delta) = \delta \cdot ED_{50}/(e_M - \delta)$$

• MED estimates from gMCPMod and NLME fits are very similar

→ gMCPMod: $M\hat{E}D(1.4) = 2.13$

→ NLME: $M\hat{E}D(1.4) = 2.15$
Concluding remarks

• Dose finding remains critical problem in clin. development

• Model-based approaches offer advantages over traditional MCP methods, but need to account for model uncertainty

• MCPMod provides a framework for model-based DR estimation and dose selection, under model uncertainty

• gMCPMod greatly expands application scope of MCPMod

• Focuses on estimated DR parameters, assumed asymptotically normal – any model/method satisfying this can in principle be used with gMCPMod

• Similar ideas as proposed by Hothorn et al. (2008) in the context of MCP testing
References


