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 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 $\max t, AIC, \ldots$, possibly combined with external data
- Dose estimation and selection ($MED, ED_x, \ldots$)
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).
gMCPMod implementation

• 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 $\hat{\mu}_A(d)$
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
• 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.
Mixed-effects model formulation

• Correlation among patients repeated measures need to be taken into account ⇒ **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 \[ \text{var} = 15.51 \text{ and } \text{cov} = 0.134 \]
Guesstimates and candidate models

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

- Guesstimates for model parameters obtained from discussions with clinical team
Optimal contrasts

Contrast coefficients vs. Dose

- emax
- quadratic
- exponential
- linear

Contrast coefficients

Dose

-0.5  0.0  0.5
0   5   10  15  20  25  30

emax quadratic exponential linear
Applying gMCPMod

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

```r
> 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  0.1518   0.0079    0.0079    0.0079    0.0079
dose1:time  0.0079   0.1518    0.0079    0.0079    0.0079
dose3:time  0.0079   0.0079   0.1518    0.0079    0.0079
dose10:time 0.0079   0.0079   0.0079  0.1518    0.0079
dose30:time 0.0079   0.0079   0.0079   0.0079  0.1518
```
gMCPMod: Testing DR signal and fitting DR model

```
> 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
```
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))
```

> fmE

...  
Log-likelihood: -4180.254  
Fixed: b0 + e0 + eM + ed50 ~ 1  
\[
\begin{align*}
  & \text{b0} & \text{e0} & \text{eM} & \text{ed50} \\
  & 200.451303 & -5.178739 & 2.181037 & 1.198791 \\
\end{align*}
\]

⇒ 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

  $\rightarrow$ gMCPMod: $\hat{MED}(1.4) = 2.13$

  $\rightarrow$ NLME: $\hat{MED}(1.4) = 2.15$
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


Back up
Impact of model uncertainty on dose estimation
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 $\hat{\Psi}_A$