Generalizing the MCPMod methodology beyond normal, independent data

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Outline

- 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

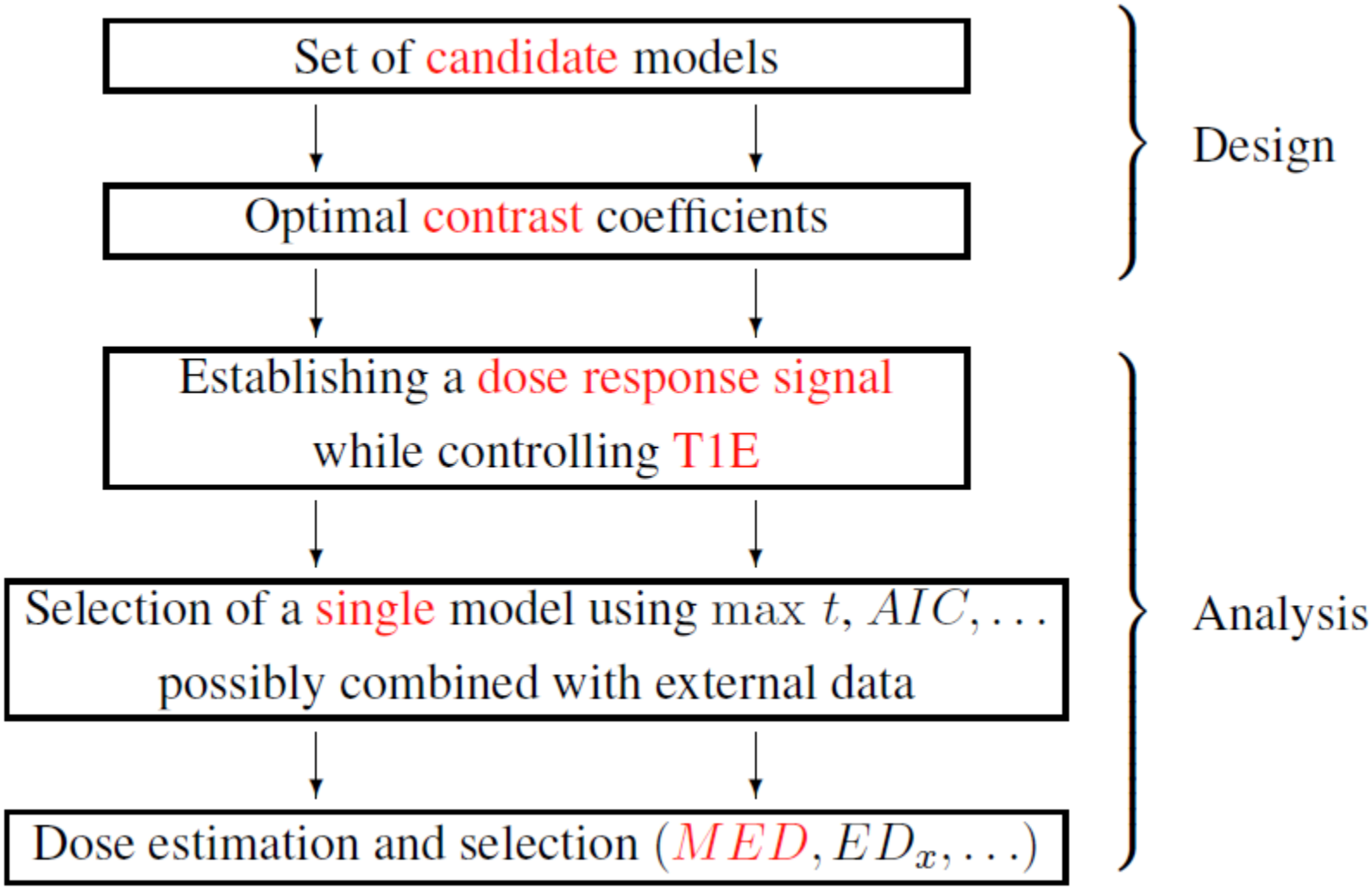
- Two main goals in Phase II studies:
  - proof-of-concept (PoC) – any evidence of treatment effect
  - dose-selection – which dose(s) to take into phase III?
    minimum effective dose (MED), maximum safe dose (MSD)
- ICH-E4: Purpose of dose-response information is to find the

  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 $\Longrightarrow$ 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



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., $\mathbf{y} \sim F(\mathbf{x}, \boldsymbol{\eta}, \mu(d))$, x covariates, η 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, λ) – using λ as "DR parameter" would not be adequate; using median survival instead would be more meaningful (reparameterization would be needed)
- Second stage DR model: $\mu(d) = f(d, \boldsymbol{\theta}) = \theta_0 + \theta_1 f_0(d, \boldsymbol{\theta}^0)$, f_0 standardized model and θ^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: $\mu_A(d_k) = \theta_k, k = 1,\ldots,K$
- Let $\mu_A(\mathbf{d}) = (\theta_1,\ldots,\theta_K)$ and $\hat{\mu}_A(\mathbf{d}) = (\hat{\theta}_1,\ldots,\hat{\theta}_K)$ its corresponding estimate
- Key assumption: $\hat{\mu}_A(\mathbf{d}) \sim N(\mu_A(\mathbf{d}), \mathbf{\Psi}_A)$ under estimation method used
- Model contrasts are applied to $\hat{\mu}_A(\mathbf{d})$

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, $\mathbf{y} \sim F(\mathbf{x}, \boldsymbol{\eta}, f(d, \boldsymbol{\theta}))$, using appropriate method to estimate all parameters (including θ) and produce information criteria, etc.

  → focusing again on $\hat{\mu}_A(\mathbf{d})$ and using generalized LS

$$\widehat{\boldsymbol{\theta}} = \arg\min_{\boldsymbol{\theta}} [\widehat{\boldsymbol{\mu}}_A(\boldsymbol{d}) - f(\boldsymbol{d}, \boldsymbol{\theta})]' \boldsymbol{\Psi}_A^{-1} [\widehat{\boldsymbol{\mu}}_A(\boldsymbol{d}) - f(\boldsymbol{d}, \boldsymbol{\theta})]$$

  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

Mixed-effects model formulation

- Correlation among patients repeated measures need to be taken into account ⇨ mixed-effects model:

$$y_{i,j} = (\beta_0 + b_{0i}) + (\mu(d) + b_{1i})t_j + \varepsilon_{ij},$$

$$(b_{0i}, b_{1i}) \sim N(\mathbf{0}, \mathbf{\Lambda}), \varepsilon_{ij} \sim N(0, \sigma^2)$$

- 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

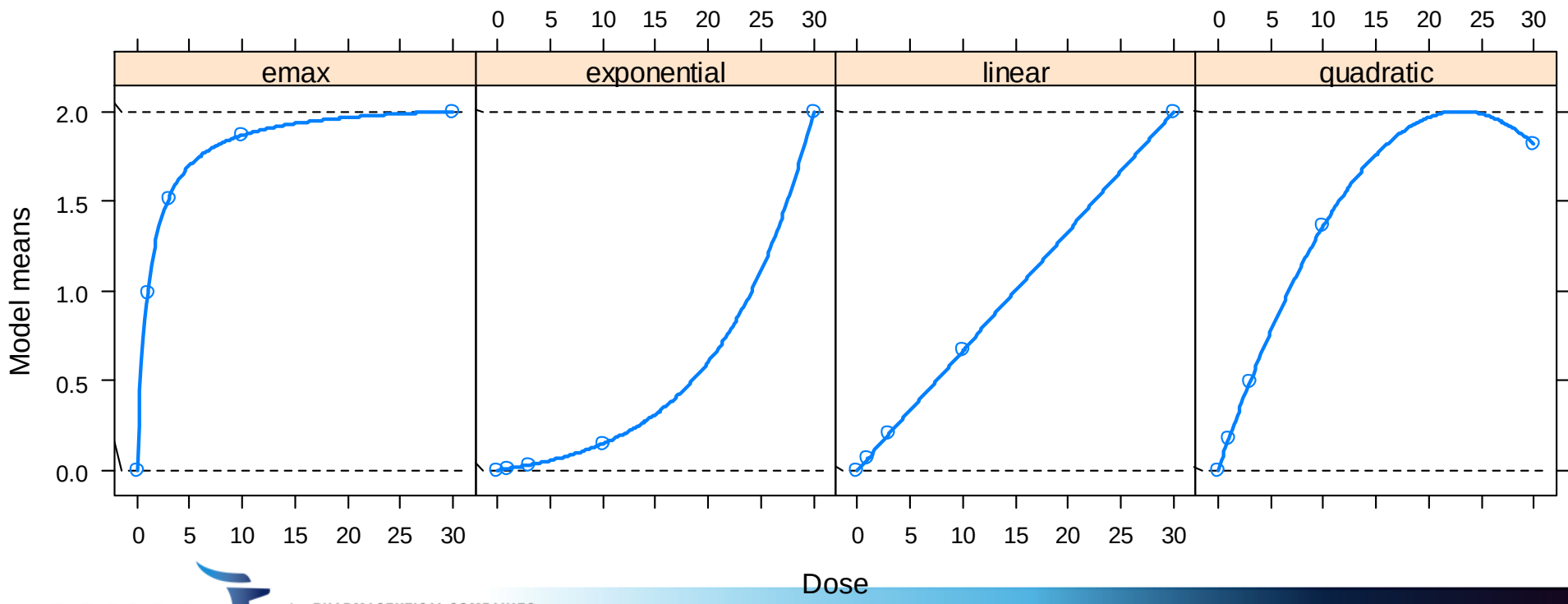
- Placebo effect: 0 increase in slope (natural progression)
- Maximum improvement over placebo for dose range: 2
- Target effect: 1.4
- From historical data, guesstimates for var-cov parameters:

  $\longrightarrow$ $var(b_{0i}) \approx 64$; $var(b_{1i}) \approx 16$; $corr(b_{0i}, b_{1i}) \approx -0.2$; $var(\varepsilon_{ij}) \approx 4$

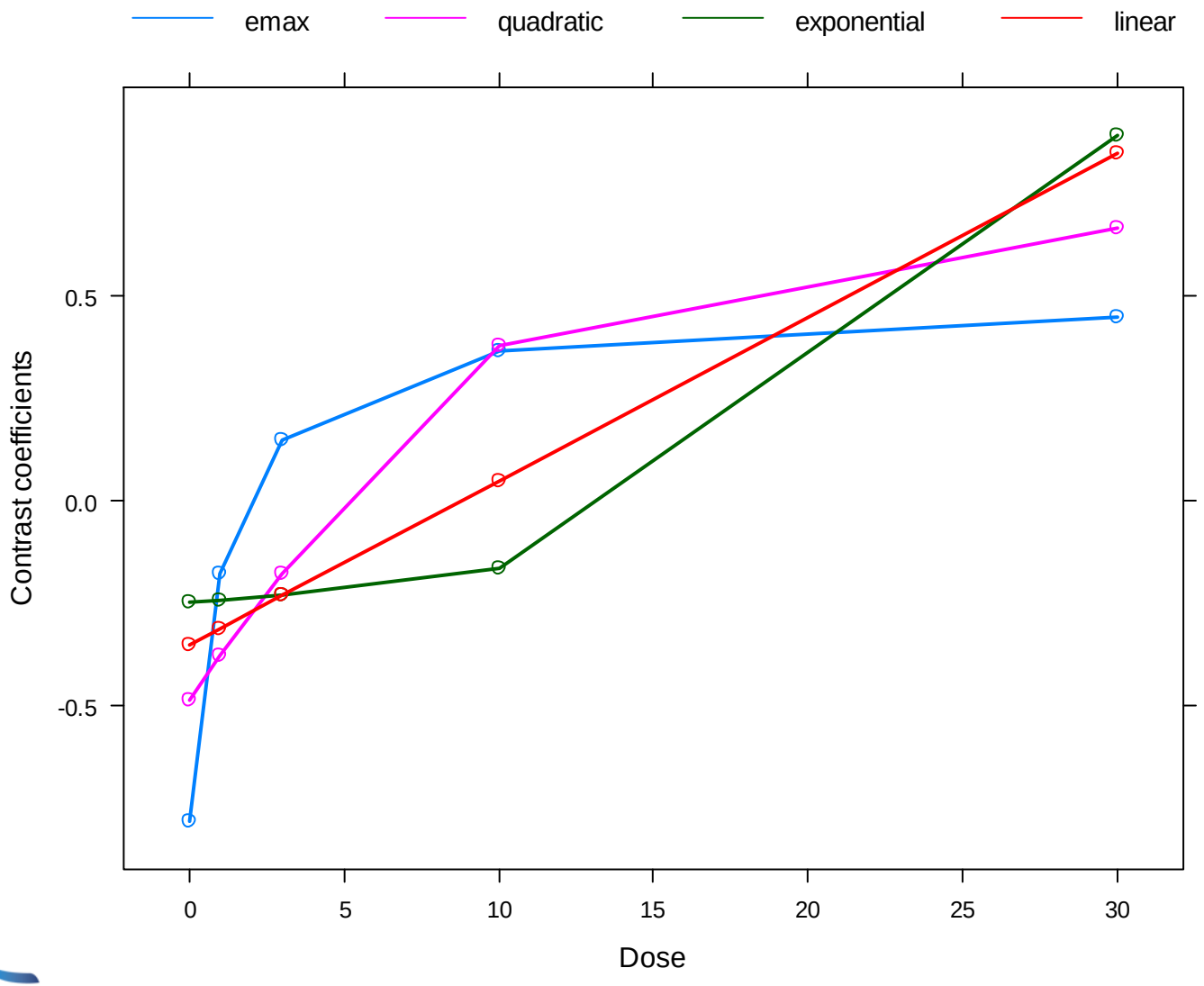
  $\rightarrow$ based on these and assumed design (N, visits, doses, etc), can derive guesstimate for var-cov matrix of ANOVA estimates: compound symmetric structure with var = 15.51 and cov = 0.134

Guesstimates and candidate models

- Plausible DR shapes: linear, emax, exponential, and quadratic
- Guesstimates for model parameters obtained from discussions with clinical team

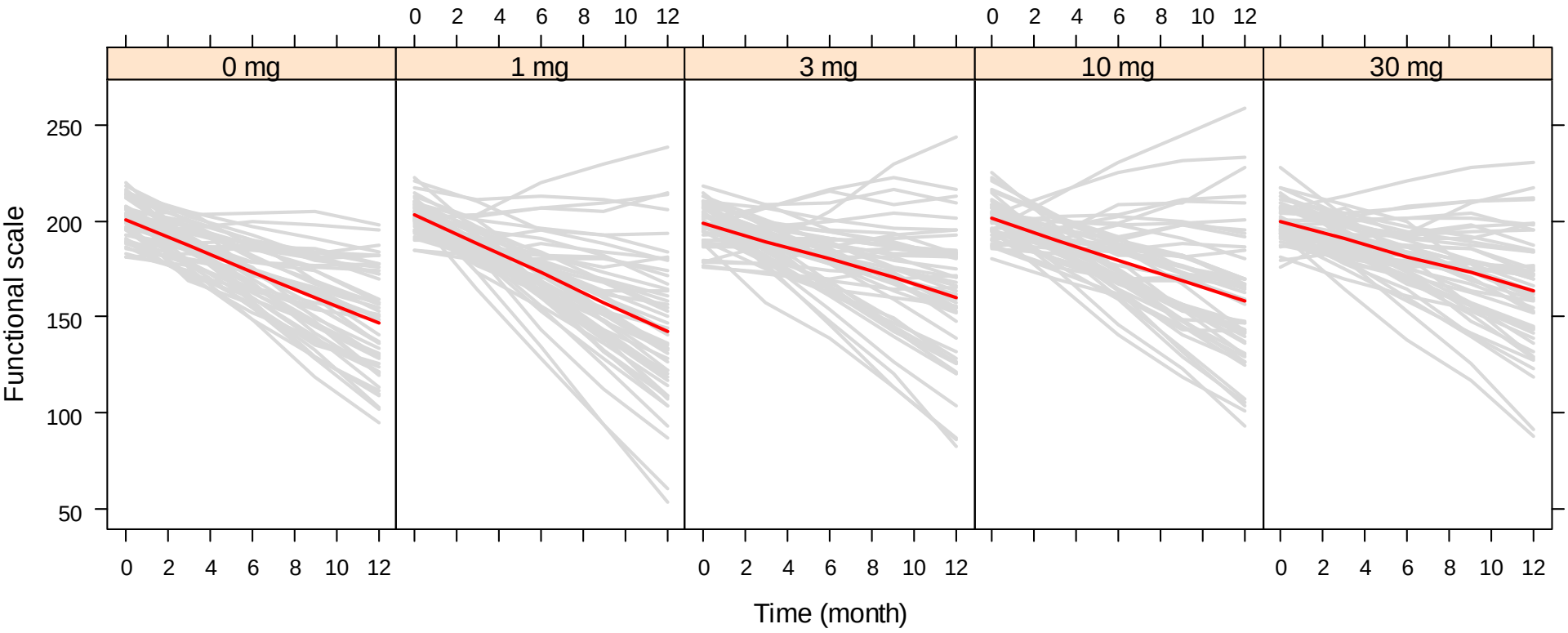


Optimal contrasts



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

  → NLME: $\hat{MED}(1.4) = 2.15$

Concluding remarks

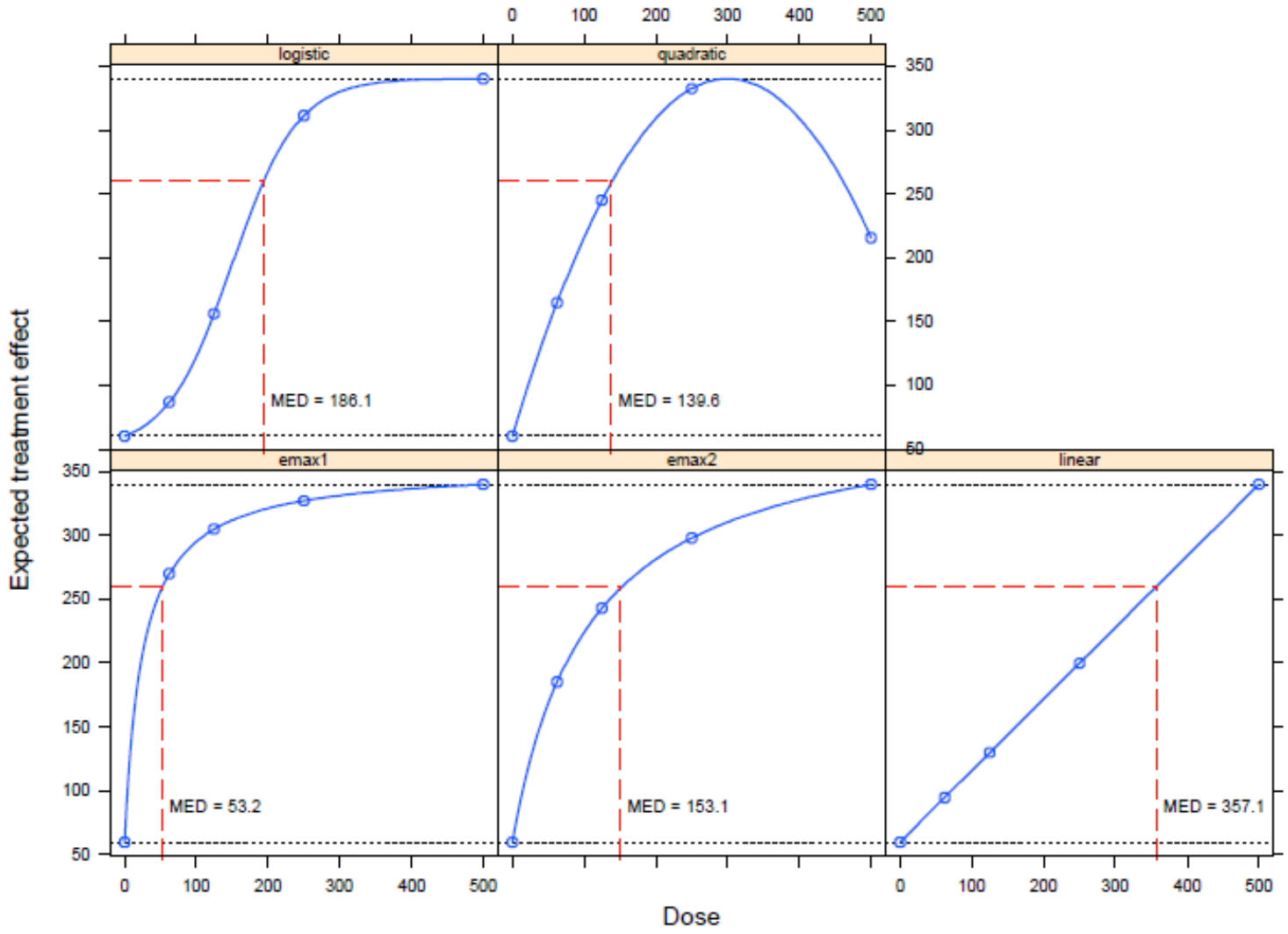
- Dose finding remains critical problem in clin. development
- Model-based approaches offer advantages over traditional MCP methods, but need to account for model uncertainty
- MCPMod provides a framework for model-based DR estimation and dose selection, under model uncertainty
- gMCPMod greatly expands 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

- Pinheiro, J., Bornkamp, B., Glimm, E. and Bretz, F. (2014) Model-based dose finding under model uncertainty using general parametric models. *Statistics in Medicine*, 33(10): 1646–1661
- Bornkamp, B. (2006) Comparison of model-based and model-free approaches for the analysis of dose response studies. Diploma thesis, University of Dortmund
- Bretz, F., Pinheiro, J.C., and Branson, M. (2005) Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*, **61**(3), 738–748.
- Hothorn, T., Bretz, F., and Westfall, P. (2008) Simultaneous inference in general parametric models. *Biometrical Journal*, **50**(3), 346–363

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 $\hat{\mu}_A(\mathbf{d})$

$$\boldsymbol{c}_{opt,m} = \boldsymbol{\Psi}_A^{-1}\left(\boldsymbol{\mu}_m - \frac{\mathbf{1}'\boldsymbol{\Psi}_A^{-1}\boldsymbol{\mu}_m}{\mathbf{1}'\boldsymbol{\Psi}_A^{-1}\mathbf{1}}\right),\ m = 1, \ldots, M$$

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

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