



Model based dose-finding methods in Phase II clinical trials

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PSI Webinar

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Dose Finding Studies

The most important questions (Ruberg (1995))

- Proof-of-concept: Is there any evidence of a drug effect?
- What doses are (relevantly) different from control?
- What is the nature of the dose response relationship?
- Dose selection: Which doses should be considered for the next phases?

R code for MCP-Mod evaluation

```
library(DoseFinding)
data(biom)
models <- Mods(linear = NULL, linlog=NULL ,emax=0.2,exponential=0.7,
               doses=c(0,0.05,0.2,0.6,1))
## perform MCPMod procedure
mm_aic <- MCPMod(dose,resp,biom,models,Delta=0.4,alpha=0.05,
                 selModel="AIC")
```

R code for MCP-Mod evaluation

```
summary(mm_aic)
#Results
*****
MCP part
*****
Multiple Contrast Test

Contrasts:
      linear linlog   emax exponential
0    -0.437 -0.728 -0.643     -0.369
0.05 -0.378 -0.247 -0.361     -0.341
0.2  -0.201  0.089  0.061     -0.245
0.6   0.271  0.375  0.413      0.138
1     0.743  0.510  0.530      0.817

Contrast Correlation:
      linear linlog   emax exponential
linear   1.000  0.875  0.912      0.984
linlog   0.875  1.000  0.989      0.800
emax     0.912  0.989  1.000      0.836
exponential 0.984  0.800  0.836      1.000

Multiple Contrast Test:
      t-Stat adj-p
emax   3.464 < 0.001
linlog  3.411 0.00102
linear  2.972 0.00377
exponential 2.653 0.00809
```

R code for MCP-Mod evaluation

```
*****  
  Mod part  
*****  
  ** Fitted model 1  
Dose Response Model  
  
Model: linear  
Fit-type: normal  
  
Residuals:  
  Min      1Q  Median      3Q      Max  
-2.097 -0.445  0.136  0.512  2.164  
  
Coefficients with approx. stand. error:  
      Estimate Std. Error  
e0      0.492      0.0998  
delta   0.559      0.1885  
  
Residual standard error: 0.714  
Degrees of freedom: 98
```

R code for MCP-Mod evaluation

```

** Fitted model 2
Dose Response Model
Model: linlog
Fit-type: normal
Residuals:
  Min      1Q   Median      3Q      Max
-2.022 -0.406  0.143  0.430  2.089

Coefficients with approx. stand. error:
      Estimate Std. Error
e0      0.975      0.1065
delta   0.146      0.0422

Residual standard error: 0.704
Degrees of freedom: 98

** Fitted model 3
Dose Response Model
Model: emax
Fit-type: normal
Residuals:
  Min      1Q   Median      3Q      Max
-2.000 -0.442  0.130  0.429  2.088

Coefficients with approx. stand. error:
      Estimate Std. Error
e0      0.322      0.152
eMax    0.746      0.236
ed50    0.142      0.180

Residual standard error: 0.706
Degrees of freedom: 97

```

R code for MCP-Mod evaluation

```

** Fitted model 4
Dose Response Model

Model: exponential
Fit-type: normal

Residuals:
  Min      1Q   Median      3Q      Max
-2.122 -0.438  0.139  0.495  2.164

Coefficients with approx. stand. error:
           Estimate Std. Error
e0         0.511      0.116
e1         0.833      5.940
delta      2.000     11.231

Residual standard error: 0.72
Degrees of freedom: 97

*****
Model selection criteria (AIC):
*****
  linear      linlog      emax exponential
220.4986     217.6141     219.1383     223.1305

Selected model: linlog

*****
Estimated TD, Delta=0.4
*****
  linear      linlog      emax exponential
0.7161      0.1455      0.1642      0.7843

```

Model Selection

Dose Selection

Results from MCP-Mod evaluation

List of dose-response models:

Model	Formula	Adjusted p-value	AIC
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	< 0.001	219.138
Linear log-dose	$E_0 + \delta \log(d + 1)$	0.001	217.614
Linear	$E_0 + \delta d$	0.004	220.499
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	0.008	223.130

with ED_{50} the dose providing half of the maximum change and E_{max} the dose providing the maximum change.

The [Linear-log model is proposed for dose estimation](#), resulting in a Minimal Effective Dose (MED) of 0.15.



MCLRa and MCLRe

Proposed candidate set of models

Model	Formula	β
Linear	$E_0 + \delta d$	$\beta = \delta$
Linear log-dose	$E_0 + \delta \log(d + 1)$	$\beta = \delta$
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	$\beta = E_{max}$
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	$\beta = E_1$

MCLRa and MCLRe

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Linear log-dose	$E_0 + \delta \log(d + 1)$	$\beta = \delta$
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	$\beta = E_{max}$
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	$\beta = E_1$

Hypothesis Testing Step:

- For the l^{th} model they test : $H_{0,l} : \beta = 0$ against $H_{1,l} : \beta > 0$

MCLRa and MCLRe

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Model	Formula	β
Linear	$E_0 + \delta d$	$\beta = \delta$
Linear log-dose	$E_0 + \delta \log(d + 1)$	$\beta = \delta$
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	$\beta = E_{max}$
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	$\beta = E_1$

Hypothesis Testing Step:

- For the l^{th} model they test : $H_{0,l} : \beta = 0$ against $H_{1,l} : \beta > 0$

POC evaluation:

- There exist some model l for which we can reject $H_{0,l}$.

MCLRa and MCLRe

Proposed candidate set of models

Model	Formula	β
Linear	$E_0 + \delta d$	$\beta = \delta$
Linear log-dose	$E_0 + \delta \log(d + 1)$	$\beta = \delta$
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	$\beta = E_{max}$
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	$\beta = E_1$

Hypothesis Testing Step:

- For the l^{th} model they test : $H_{0,l} : \beta = 0$ against $H_{1,l} : \beta > 0$

POC evaluation:

- There exist some model l for which we can reject $H_{0,l}$.

Test statistics:

- Both uses likelihood ratio tests: MCLRe: Exact
MCLRa: Asymptotic

R code for MCLRa

```
library(LRcontrast)
pValue_LR<-pLRcontrast(dose = biom$dose, resp = biom$resp,
  models = c("linear", "emax","exponential", "linlog"),
  nsim = 10000,info=FALSE)#Runtime: 131.31secs
sValue_LR<-sLRcontrast(dose = biom$dose, resp = biom$resp,
  models = c("linear", "emax","exponential", "linlog"))
#qValue_LR<-qLRcontrast(dose = biom$dose,
#  models = c("linear", "emax","exponential", "linlog"),
#  nsim=10000)
```

R code for MCLRa

```

library(LRcontrast)
pValue_LR<-pLRcontrast(dose = biom$dose, resp = biom$resp,
                      models = c("linear", "emax","exponential", "linlog"),
                      nsim = 10000,info=FALSE)#Runtime: 131.31secs
sValue_LR<-sLRcontrast(dose = biom$dose, resp = biom$resp,
                      models = c("linear", "emax","exponential", "linlog"))
#qValue_LR<-qLRcontrast(dose = biom$dose,
#                       models = c("linear", "emax","exponential", "linlog"),
#                       nsim=10000)

```

```

#Result
#pValue_LR
#
#      unadj-p  adj-p
#linear      0.0018 0.0053
#emax        0.0003 0.0003
#exponential 0.0038 0.0076
#linlog      0.0003 0.0005

#sValue_LR
#
#      statistic
#linear      8.5806
#emax       11.9410
#exponential 7.9487
#linlog     11.4651
#max        11.9410

```

Results from MCLRa evaluation

List of dose-response models:

Model	Formula	Adj p-value (MCP-Mod)	Adj p-value (MCLRa)
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	< 0.001	0.0003
Linear log-dose	$E_0 + \delta \log(d + 1)$	0.001	0.0005
Linear	$E_0 + \delta d$	0.004	0.0053
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	0.008	0.0076

The **Linear-log model** is proposed for dose estimation based on AIC criterion, resulting in a Minimal Effective Dose (MED) of 0.15.

R code for MCLRe

```
install.packages("fftw")
install.packages("~/R-code/chebsample_1.0.tar.gz", repos = NULL,
                 type = "source")
install.packages("~/Downloads/R-code/mnll_1.0.tar.gz", repos = NULL,
                 type = "source")
library(chebsample)
library(mnll)
library(DoseFinding)
source("MCLRe_Evaluation.R")
data(biom)
pMCLRe<-pMCLRe(data=biom,doses=c(0,0.05,0.2,0.6,1))
print(pMCLRe)
```

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R code for MCLRe

```
install.packages("fftw")
install.packages("~/R-code/chebsample_1.0.tar.gz", repos = NULL,
                 type = "source")
install.packages("~/Downloads/R-code/mnll_1.0.tar.gz", repos = NULL,
                 type = "source")
library(chebsample)
library(mnll)
library(DoseFinding)
source("MCLRe_Evaluation.R")
data(biom)
pMCLRe<-pMCLRe(data=biom,doses=c(0,0.05,0.2,0.6,1))
print(pMCLRe)
```

```
#Result
#      Model      Parameter estimates      test-statistic adj p-value p-value
#1    Emax    alpha=0.32, beta=0.75, gamma=0.14      0.335      0.001      0.001
#2  Linlog    alpha=0.97, beta=0.15      0.329      0.002      0.003
#3   Linear    alpha=0.49, beta=0.56      0.287      0.006      0.002
#4 Exponential alpha=0.51, beta=0.83, gamma=2.00      0.276      0.009      0.004
```

Results from MCLRe evaluation

List of dose-response models:

Model	Formula	Adj p-value (MCP-Mod)	Adj p-value (MCLRa)	Adj p-value (MCLRe)
E _{max}	$E_0 + E_{max} \frac{d}{ED_{50} + d}$	< 0.001	0.0003	0.001
Linear log-dose	$E_0 + \delta \log(d + 1)$	0.001	0.0005	0.002
Linear	$E_0 + \delta d$	0.004	0.0053	0.006
Exponential	$E_0 + E_1 [\exp(\frac{d}{\delta})]$	0.008	0.0076	0.009

The **Linear-log model** is proposed for dose estimation based on AIC criterion, resulting in a Minimal Effective Dose (MED) of 0.15.

MHMC:

Proposed candidate set of models

- Define a nested candidate set of increasingly complex parametric dose-response models $M_0 \subset M_1 \subset \dots \subset M_m$ with M_0 the constant model:

	Model	Formula
M_0	No effect	E_0
M_1	Linear	$E_0 + \delta d$
M_2	Power	$E_0 + \delta d^h$
M_3	Four Parameter Logistic	$E_0 + E_{max} \frac{d^{\theta_3}}{ED_{50}^{\theta_3} + (de^{-\theta_2})^{\theta_3}}$

MHMC:

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	Model	Formula
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M_1	Linear	$E_0 + \delta d$
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M_3	Four Parameter Logistic	$E_0 + E_{max} \frac{d^{\theta_3}}{ED_{50}^{\theta_3} + (d e^{-\theta_2})^{\theta_3}}$

Hypothesis Testing Step and Model Selection Step:

- Test sequentially starting with constant model ($s = 0$) and proceed with more complex model (till $s = m - 1$):

$$H_{s0} : f(d, \theta) = M_s$$

$$H_{sa} : f(d, \theta) = M_r \quad \text{for any } r \in s + 1, \dots, m$$

MHMC:

Proposed candidate set of models

- Define a nested candidate set of increasingly complex parametric dose-response models $M_0 \subset M_1 \subset \dots \subset M_m$ with M_0 the constant model:

	Model	Formula
M_0	No effect	E_0
M_1	Linear	$E_0 + \delta d$
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Hypothesis Testing Step and Model Selection Step:

- Test sequentially starting with constant model($s = 0$) and proceed with more complex model(till $s = m - 1$):

$$H_{s0} : f(d, \theta) = M_s$$

$$H_{sa} : f(d, \theta) = M_r \quad \text{for any } r \in s + 1, \dots, m$$

Test Statistics:

$$T_s = \max_{s+1 \leq r \leq m} 2(L_r - L_s) / (df_r - df_s),$$

R code for MHMC

```
library(DoseFinding)
source("DRevaluation.R")

result <- Modsel(biom,estMED=TRUE)

#Result
#$T
#[1] 8.580597e+00 2.546418e+00 1.127270e+00 1.387041e-06

#$selmod
#[1] "power"

#$med
#[1] 0.23

#$coefs
#[1] 0.33 0.68 0.35
```

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Performance of the methods

Simulation studies comparing:

- MCP-Mod
- MCLRa
- MCLRe
- MHMC

In terms of

- Type I error
- Power to establish PoC
- Power to select the correct model
- Ability to estimate the MED

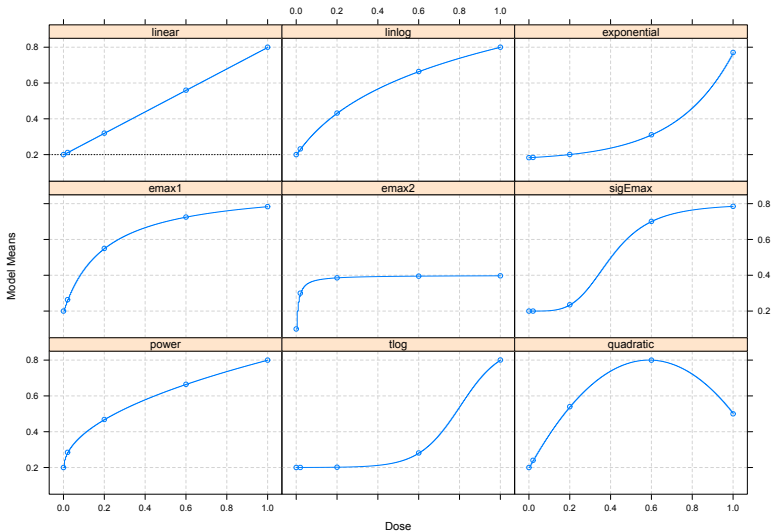
Simulation set up:

Design:

- Doses 0, 0.05, 0.2, 0.6 and 1.
- Sample sizes per dose group: 10, 25, 50, 75, 100.
- Candidate set same as used in the real data example.
- One-sided PoC test with $\alpha = 0.05$.
- 10 data generating dose-response shapes.
- Non-linear parameters estimates for MCP-Mod were chosen equal to population parameters.
- 10,000 simulations per shape x sample size combination.



Data Generating Shapes



Discussion

- The performance of MCP-Mod is highly influenced by its candidate set.
- MHMC methods performs uniformly better for monotone dose-response across all simulation scenarios.
- MCLRa method shows outstanding performance when the dose-response shape deviate drastically from the candidate set like the second emax (emax2) model.
- MCLRa and MCLRe approach shows similar performance but the MCLRe approach is computationally more intensive.
- The methods are highly comparable and for most of the scenarios the model selection probability or the dose-selection power differed only by 3–4%.
- Further details related to the methods can be found in Saha and Brannath (2019).



Reference

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