Application of MCP-Mod to proof of concept studies

Training : Master MSID

Tarik Lahmiti

Supervisor : Franck Pellissier

Sanofi-Aventis R&D

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Summary

Motivations

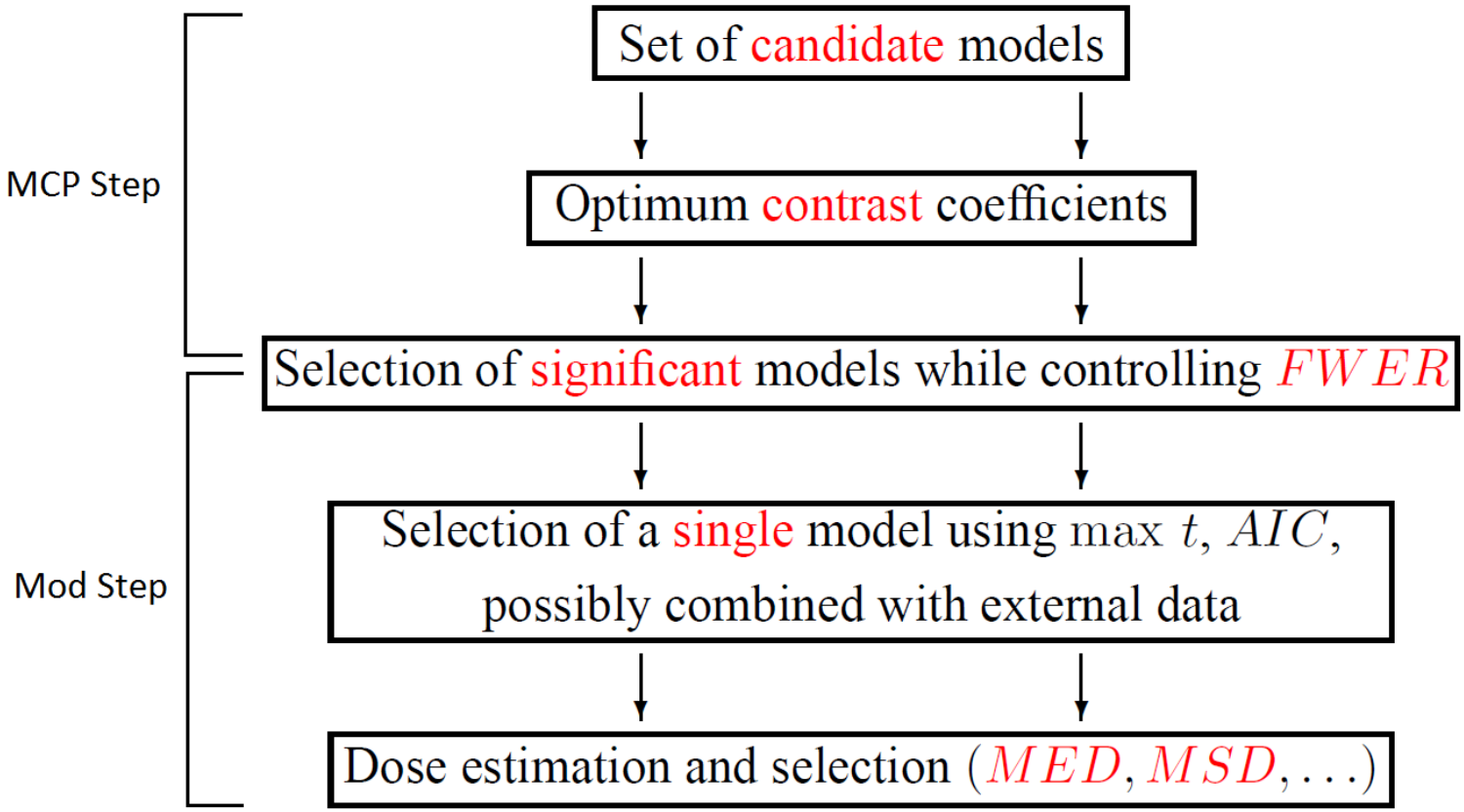
- Currently most of the PoC trials are designed as a two arms trials, placebo vs MTD
- One can think to include several doses in a PoC studies. There are two benefits :
  - provide valuable information for designing subsequent dose-finding studies, resulting in a more optimized development
  - avoid mis-selection of the unique dose of the PoC
- MCP-Mod allows to validate PoC studies without inflating too much the number of subjects or lowering the power too much.

Objectives

- Assess MCP-Mod as an alternative to other methods (ANOVA, Trend test) for PoC studies
- Application of generalized MCP-Mod (crossover, repeated measures, heterogeneity of variances)
- Package DoseFinding version 0.9-11, R version 3.0.3

Summary

Step approach MCP-Mod



- Classical approach :

$$Y_{ij} = \mu_i + \epsilon_{ij}, \quad \epsilon_{ij} \overset{iid}{\sim} \mathcal{N}(0, \sigma^2), \quad i = 1, \ldots, k, \quad j = 1, \ldots, n_i,$$

- All candidate models are of the form :

$$\mu(d, \theta) = \theta_0 + \theta_1 f^0(d, \theta_2)$$

with $f^0(d, \theta_2)$ standardized form of the dose d and parameters θ_2. Parameters θ_0 and θ_1 determine the location and scale of the function f

- θ_2 guesstimates could be find by a guessed dose response relationship.

Each model is tested using a contrast test :

- which maximizes the power to detect this model as the underlying one,
- based on guesstimates

Characteristics of the MCP step :

- FWER control
- If at least one model exhibits a significant contrast test, a dose-effect trend (PoC) is shown

- Optimal contrasts :

$$c_m^{opt} \propto S^{-1}\left(\mu_m^0 - \frac{\mu_m^{0\,\prime} S^{-1} 1}{1' S^{-1} 1} 1\right) \quad , \quad m = 1, \ldots, M$$

with S the variance-covariance of the estimated dose-response parameters $\widehat{\mu}$ obtained from an ANOVA

and μ_m^0 the mean response vector under model m.

- we normalize for convenience : $||c_m^{opt}|| = 1$

- Contrast Test for testing $H_0 : c_m^{opt\prime}\mu = 0$ vs. $H_1 : c_m^{opt\prime}\mu > 0$ is

$$Z_m = \frac{c_m^{opt\prime}\widehat{\mu}}{\left[\left(C^{opt\prime}\widehat{S}C^{opt}\right)\right]_{m,m}^{\frac{1}{2}}} \quad , \quad Z_m \rightsquigarrow \mathcal{N}(0,1) \text{ under } H_0$$

  where C^{opt} is determined by using the estimated var-cov matrix $\widehat{S}$ provided by the ANOVA

- In Stage Mod, only the models with a significant contrast test are selected and we choose the "best"(higher Z-statistic, AIC, BIC...) model (or model averaging). Estimation of the MED

Summary

Application of MCP-Mod method on a study previous

Study in 20 healthy subjects

Objective : To detect and quantify a dose-response effect

Design : Cross-over with

- five sequence,
- five period,
- five doses : placebo, $2.5, 5, 10, 20 \mu g$

TABLE : Guessed models

Model name	$f(d,\theta)$	Guesstimates
Linear	$E_0 + \delta d$	*NA*
E_{max1}	$E_0 + E_{max}\frac{d}{ED_{50}+d}$	$ED_{50} = 7.6$
E_{max2}	$E_0 + E_{max}\frac{d}{ED_{50}+d}$	$ED_{50} = 2.6$
$Logistic_1$	$E_0 + E_{max}\frac{1}{1+\exp\left(\frac{ED_{50}-d}{\delta}\right)}$	$ED_{50} = 6.9$, $\delta = 1.40$
$Logistic_2$	$E_0 + E_{max}\frac{1}{1+\exp\left(\frac{ED_{50}-d}{\delta}\right)}$	$ED_{50} = 8.0$, $\delta = 2.39$
$Logistic_3$	$E_0 + E_{max}\frac{1}{1+\exp\left(\frac{ED_{50}-d}{\delta}\right)}$	$ED_{50} = 2.0$, $\delta = 2.72$

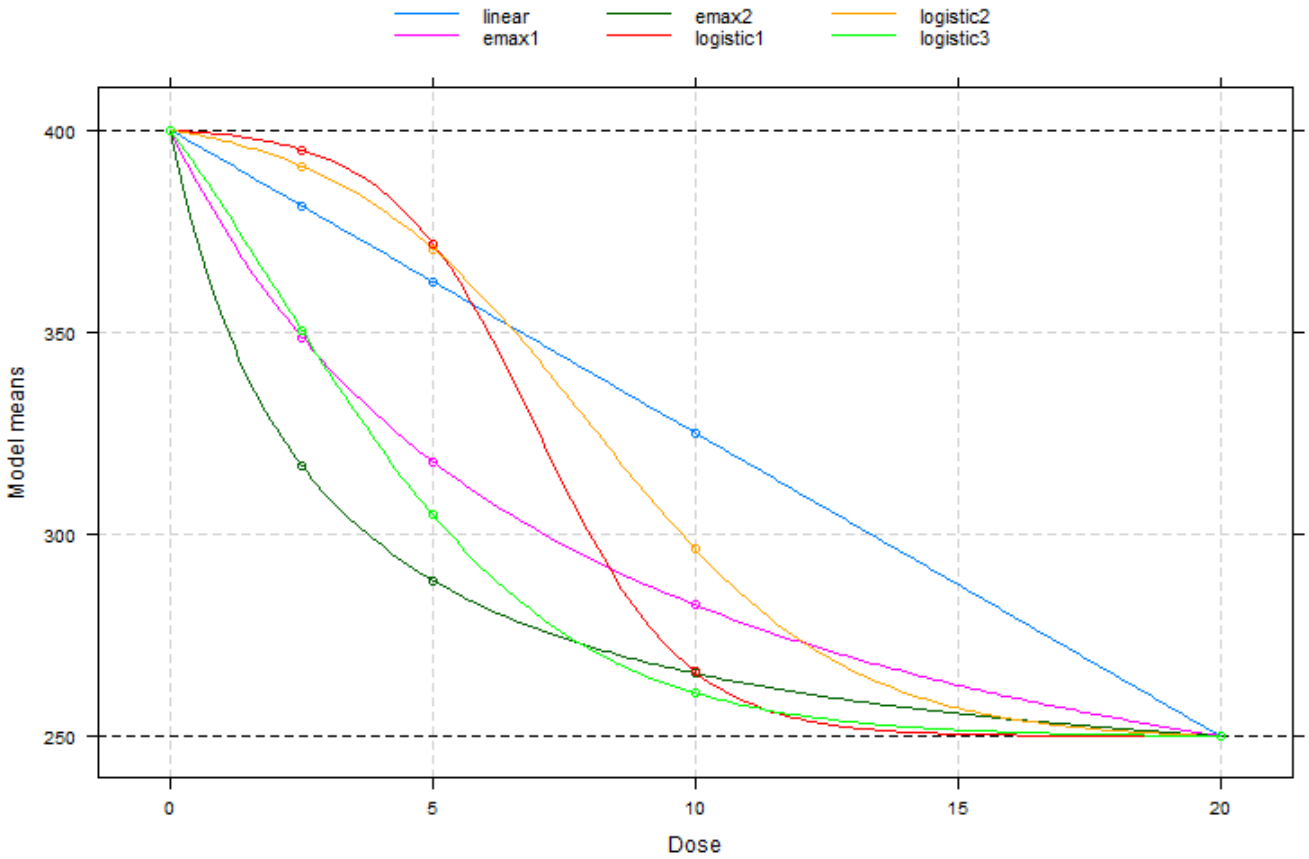


FIGURE : Candidate models

MCP-Mod analysis

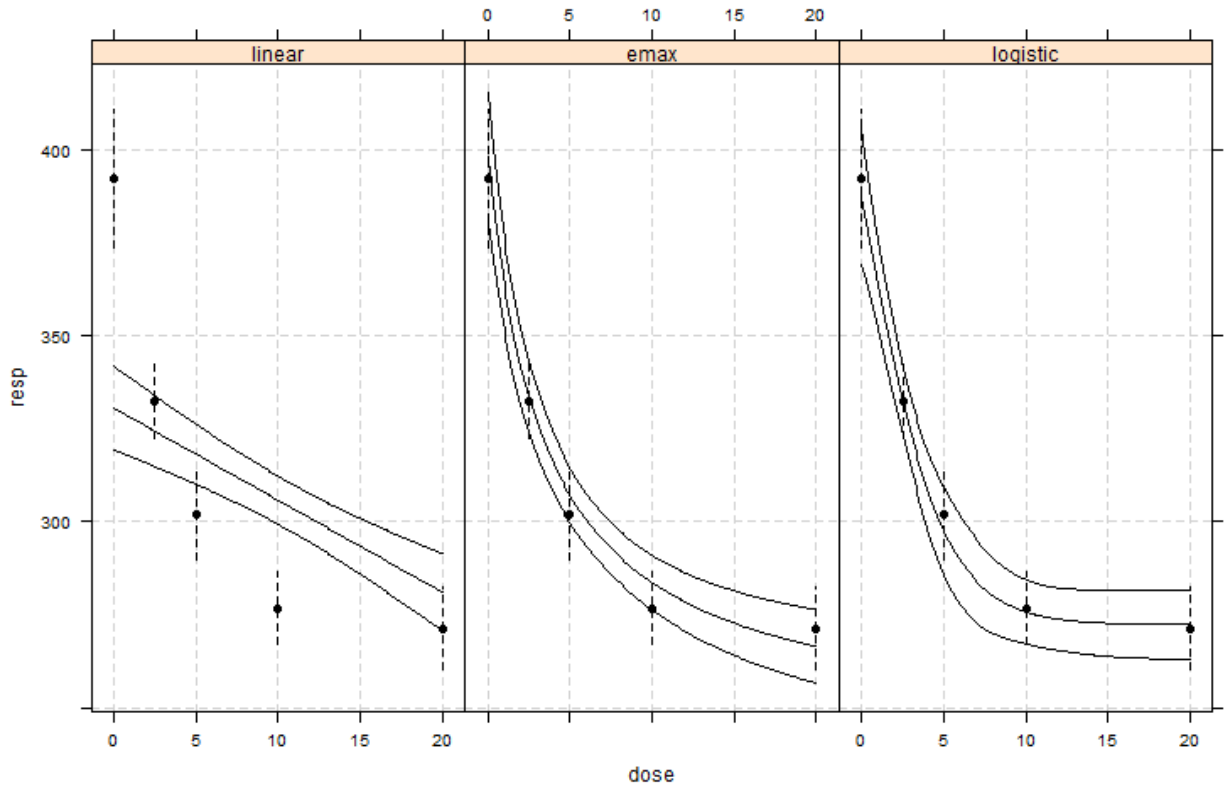


FIGURE : Graphic modeling of each candidate model

First conclusion from this example

- Appealing method,
- Technically easily implemented in R,
- Additional valuable information on the dose-response relationship,
- But operating characteristics of MCP part need to be properly assessed.

Summary

Presentation of simulation

- Parallel groups
- Single dose
- 6 subjects per dose
- 4 doses $(0, 0.25, 0.5, 1)$

- Simulations are based on :

$$\mu(d, \theta) = \theta_0 + \theta_1 f^0(d, \theta_2)$$

- Without loss of generality, $\theta_0 = 0$ and $\theta_1 = 1$
- 9 scenarios (Linear, Emax, Exponential, ...)
- 5000 simulated studies with $SD = 0.6$ and homoscedasticity (max effect size of $\frac{1}{0.6} = 1.67$)

Several analyses done : Trend test , ANOVA, MCP.

One-sided testing with $\alpha = 5\%$

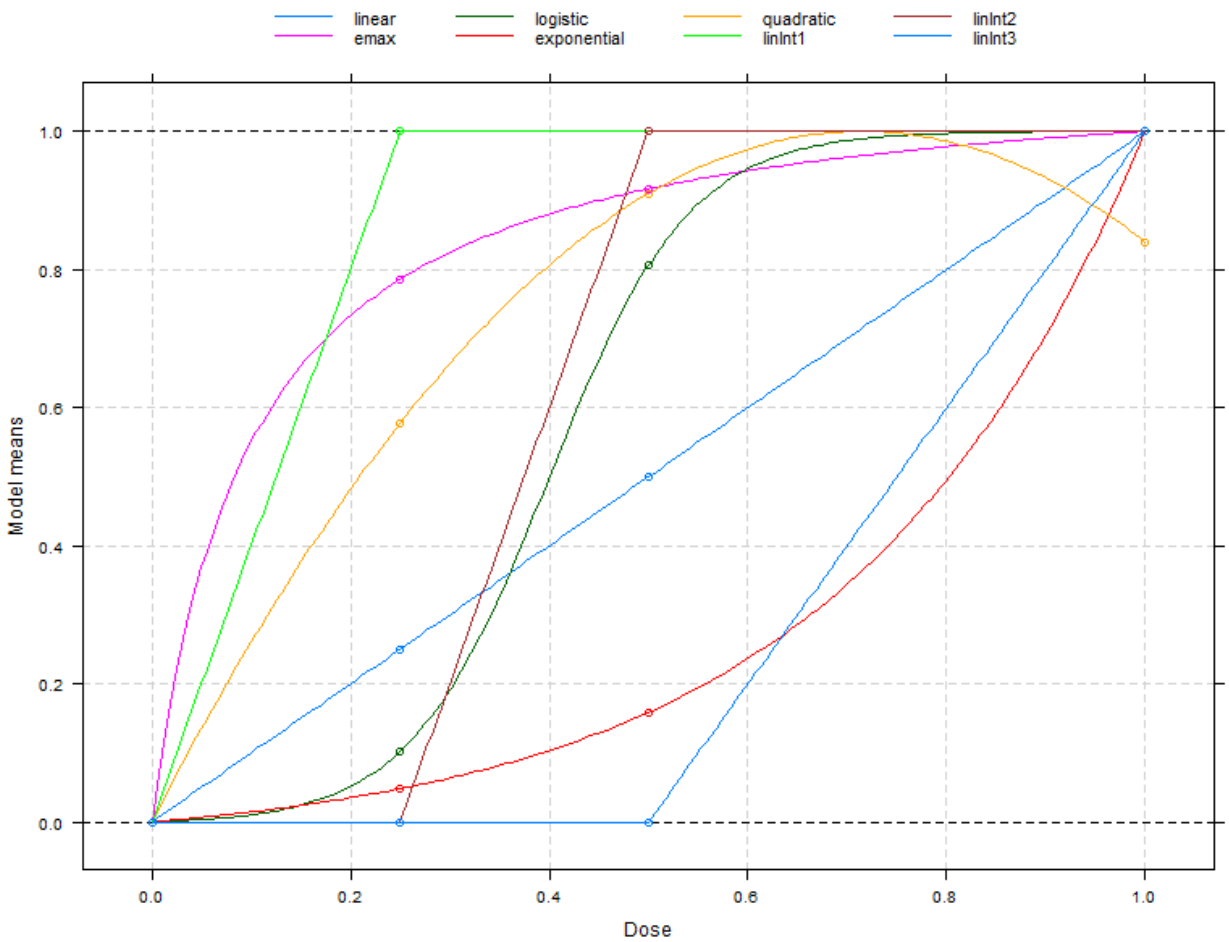


FIGURE : Overview of the simulation scenarios

Results

TABLE : Power (%) for each simulation

	Simulated models					
Analysis	Null	Linear	Emax	Expo.	Logi.	Quad.
Linear	4.7	89.5	80.4	90.8	93.2	72.4
Emax	5.0	75.3	92.9	57.0	83.7	86.3
Exponential	4.7	85.5	54.4	93.8	84.6	43.8
Logistique	4.9	85.1	77.1	80.7	95.4	76.1
Quadratic	5.2	74.3	91.6	52.8	88.9	87.9
MCP	4.7	84.9	88.1	89.0	92.9	81.7
ANOVA F-Test	5.0	74.8	80.7	82.3	86.1	71.9
ANOVA dose 1-0	4.6	84.4	84.4	84.4	84.4	72.5
ANOVA Holm	3.8	69.0	81.4	66.5	74.4	72.0
ANOVA Hochberg	3.9	69.5	83.3	66.7	75.1	73.4
ANOVA Hommel	4.0	70.0	84.1	66.8	75.9	74.7

Note : For a t-test with 12 subjects in each of 2 parallel groups : 98.9 % max. power

Power and sample size functions

- *sampSizeMCP()* : determines the required sample size to achieve a given power
- *powN()* : determines the power achieved for a given sample size

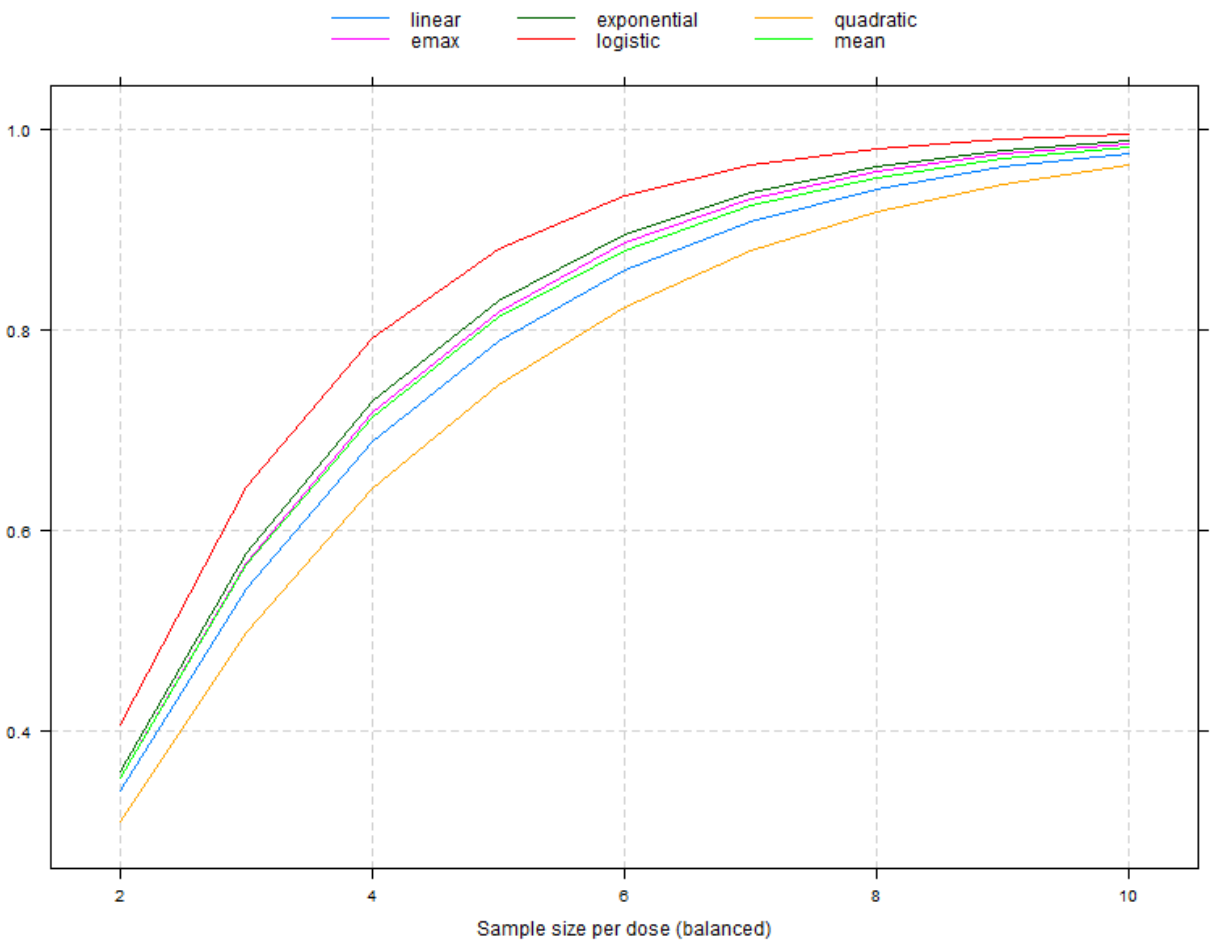


FIGURE : Power vs Sample size per dose

Unbalanced groups

TABLE : Power (%) with unbalanced groups

	Balanced groups $(1, 1, 1, 1)$	Unbalanced groups 1 $(2, 1, 1, 2)$	Unbalanced groups 2 $(3, 1, 1, 3)$
Min	82.3	85.0	87.4
Mean	87.9	92.0	92.5
Max	93.2	95.4	95.6

Same total number of subjects N=24

Assuming heteroscedasticity

- Allow for heterogeneity of variances when estimating S variance-covariance matrix (using *lme()*)
- Using same simulations as earlier (6 subjects per dose)

Methods	Linear	Emax	Expo.	Logi.	Quad.	MCP
FWER	7.5	6.9	7.1	8.2	7.4	9.6

- MCP, as well as any trend test, shows an α inflation

When increasing the sample size per dose :

TABLE : FWER (%) for different study sizes

	Subjects per dose		
Analysis	$n = 6$	$n = 12$	$n = 18$
Linear	7.5	5.5	4.5
Emax	6.9	5.7	4.8
Exponential	7.1	5.6	4.0
Logistique	8.2	5.9	5.0
Quadratic	7.4	5.9	4.9
MCP	9.6	6.8	6.0

Summary

Presentation of the simulations in crossover

- 6 subjects per study
- 4 doses by subject
- Between and within-subject variability assumed independent of the dose
- $SD_W = SD_B = 0.6$ and homoscedasticity, (max effect size $\frac{1}{0.6} = 1.67$)

Results

TABLE : Power (%) for each simulation

	Simulated models					
Analysis	Null	Linear	Emax	Expo.	Logi.	Quad.
Linear	5.7	90.1	81.3	91.7	93.4	72.8
Emax	6.2	75.8	93.2	57.2	84.3	86.8
Exponential	5.5	86.2	55.5	94.3	85.3	44.7
Logistique	5.4	84.9	77.5	80.9	96.2	76.5
Quadratic	5.9	75.5	92.0	53.0	88.9	87.9
MCP	7.3	88.1	90.6	91.3	94.6	85.1

Note : Slight α increase

Assuming heteroscedasticity

- Heterogeneous variances
- Homogeneous correlations

Methods	Linear	Emax	Expo.	Logi.	Quad.	MCP
FWER	12.24	10.74	11.20	12.82	11.58	14.42

- Serious α increase

Assuming homoscedasticity

When increasing the sample size per dose (assuming homoscedasticity) :

TABLE : FWER (%) for different study sizes

	Total Subjects			
Analysis	$n = 6$	$n = 12$	$n = 18$	$n = 24$
Linear	5.2	4.0	5.0	4.5
Emax	7.6	5.1	4.7	4.9
Exponential	4.7	3.8	4.3	4.4
Logistique	4.5	4.4	4.7	4.7
Quadratic	7.4	5.4	4.9	5.1
MCP	7.8	6.2	5.8	5.4

Assuming heteroscedasticity

When increasing the sample size per dose (assuming heteroscedasticity) :

TABLE : FWER (%) for different study sizes

	Total Subjects			
Analysis	$n = 6$	$n = 12$	$n = 18$	$n = 24$
Linear	11.1	8.0	8.4	6.8
Emax	9.7	7.1	6.3	6.2
Exponential	10.8	7.0	7.6	6.6
Logistique	11.5	8.6	8.4	7.2
Quadratic	10.2	8.2	6.5	6.2
MCP	13.3	11.0	9.4	8.1

Summary

Conclusion

- MCP-mod method mainly developped for Dose-finding studies,
- It may be valuable for PoC studies too,
- MCP-Mod in the framework of PoC studies :
  - Pros : get preliminary valuable information about the dose-response relationship and safe approach in case of non-monotonic dose-response relationship (e.g. quadratic)
  - Cons : more dose levels requiring higher sample size or lower power

- Recommendation

	Assumption	
	Homogeneity of variance	Heterogeneity of variance
Parallel Groups	No trouble	Not recommended (unless very large N, e.g. $N \geq 20$)
Crossover	No trouble (as soon as N not too small, e.g. $N \geq 15$)	Not recommended (unless very large N, e.g. $N \geq 40$)

Bibliography


Branson M., Pinheiro J., Bretz F. (2003), *Searching for an adequate dose : Combining multiple comparisons and modeling techniques in dose-response studies.* Novartis Biometrics Technical Report No. 2003-08-20.


Bretz F., Pinheiro J., Branson M. (2005). *Combining multiple comparisons and modeling tecniques in dose responses studies.* Biometrics 61, 738-748.


Pinheiro J., Bornkamp B., Bretz F. (2006), *Design and analsis of dose finding studies combining multiple comparisons and modeling procedures.* Journal of Biopharmaceutical Statistic 16, 639-656


Bornkamp B., Pinheiro J., Bretz F. (2009), *MCPMod : An R Package for the Design and Analysis od Dose-Finding Studies.* Journal of Statistical Software, Volume29, Issue 7.


Pinheiro J., Bornkamp B., Glimm E., Bretz F. (2013), *Model-based dose finding under model uncertainty using general parametric models.* Statistic in Medecine 2014, 33 1646-1661.

Back-up Slides

Outputs R

```
MCPMod

Multiple Contrast Test:
          t-Stat  adj-p
emax2     11.441 <0.001
logistic3 10.914 <0.001
emax1     10.592 <0.001
logistic1  6.257 <0.001
logistic2  6.091 <0.001
linear     5.611 <0.001

Critical value: 2.385 (alpha=0.025, one-sided)
```

```
Estimated Dose Response Models:
linear model
     e0   delta
330.491  -2.469

emax model
      e0     eMax     ed50
 397.911 -154.480    3.523

logistic model
      e0     eMax     ed50    delta
 501.710 -229.369    0.020    2.388

*************************************
Model selection criteria (aveAIC):
*************************************
    linear       emax   logistic
112.404295  10.517273   8.822283

Model weights (AIC):
  linear     emax logistic
     0.0      0.3      0.7
```

TABLE : Models selection [1] rate with MCP-Mod

Candidate models	Linear	Emax	Expo.	Logi.	Quad.	No model used
Sim 1 (Linear)	30.7	8.0	22.3	18.5	5.4	15.1
Sim 2 (Emax)	8.1	48.5	1.1	40.3	26.2	11.9
Sim 3 (Expo.)	17.7	1.6	62.7	6.5	0.5	11.0
Sim 4 (Logistic)	15.0	2.8	5.9	58.1	11.1	7.1
Sim 5 (Quadratic)	6.5	24.5	0.8	11.0	38.9	18.3
Sim 6 (Linear Intp. #1)	2.5	64.9	0.2	0.8	21.1	9.5
Sim 7 (Linear Intp. #2)	4.0	0.5	1.6	79.8	3.4	10.7
Sim 8 (Linear Intp. #3)	10.3	0.7	77.5	2.7	0.2	8.7

[1] Best model selected (T_{max} criterion)

TABLE : Models selection [2] rate with MCP-Mod (Parallel groups)

Candidate Models	Linear	Emax	Exponential	Logistic	Quadratic
Simulation 1 (Linear)	79.9	61.0	74.1	73.5	60.2
Simulation 2 (Emax)	67.6	85.7	39.1	64.7	83.6
Simulation 3 (Exponential)	82.0	41.4	86.9	68.7	37.7
Simulation 4 (Logistic)	85.9	71.5	73.0	90.4	78.7
Simulation 5 (Quadratic)	57.2	75.7	29.5	63.4	76.9

[2] Best model selected (T_{max} criterion)

Assuming homoscedasticity

```
models <- Mods(linear = NULL, emax= c(0.1), exponential= c(0.3),
               logistic = c(0.4,0.07), quadratic = -0.7, doses = c(0,0.25,0.5,1))


fm <- lme(resp ~ as.factor(dose)-1, data = data2, random = ~1|Ind )


muHat <- fm$coefficient$fixed
covH     <- vcov(fm)
contMat <- optContr(models, S=covH)
dfe <- MCTtest(doses, muHat, S=covH, type = "general", critV = TRUE, pVal=TRUE, contMat = contMat,
                alpha=0.05, alternative="one.sided")
```

Assuming heteroscedasticity

```
models <- Mods(linear = NULL, emax= c(0.1), exponential= c(0.3),
               logistic = c(0.4,0.07), quadratic = -0.7, doses = c(0,0.25,0.5,1))
```

```
fm <- lme(resp ~ as.factor(dose)-1, data = data2, random = ~1|Ind,
   weights=varIdent(form=~1|as.factor(dose)))
```

```
muHat <- fm$coefficient$fixed
covH     <- vcov(fm)
contMat <- optContr(models, S=covH)
dfe <- MCTtest(doses, muHat, S=covH, type = "general", critV = TRUE, pVal=TRUE, contMat = contMat,
                alpha=0.05, alternative="one.sided")
```

sampSizeMCT() function

```
> n=6
> dose <- rep(c(0,0.25,0.5,1), c(n,n,n,n))
> models <- Mods(linear = NULL, emax= c(0.1), exponential= c(0.3),
+                logistic = c(0.4,0.07), quadratic = -0.7, doses = c(0,0.25,0.5,1),
+                placEff = 0, maxEff = 1)
> contMat <- optContr(models, w=1)
> size <- sampSizeMCT(upperN=40, lowerN=10, sigma=0.6, alpha=0.05 , contMat= contMat,
+                     altModels = models, power=0.8, sumFct=min,  alRatio= c(1,1,1,1),
+                     verbose = TRUE, Ntype = "total" )
Upper N: 40 Upper value 0.9639
Lower N: 10 Lower value 0.311

Iter: 1, N = 25, current value = 0.8221
Iter: 2, N = 18, current value = 0.6384
Iter: 3, N = 22, current value = 0.8226
Iter: 4, N = 20, current value = 0.7448
Iter: 5, N = 21, current value = 0.7438
>
> size
Sample size calculation

alRatio: 1 1 1 1
Total sample size: 24
Sample size per arm: 6 6 6 6
targFunc: 0.8207
```

powN() function

```
> Pow <- powN(upperN = 10, lowerN=2, step = 1, contMat = contMat, sumFct = c("mean", "min", "max"),
+             sigma = 0.6, altModels = models, alpha = 0.05, alRatio = c(1,1,1,1))
>
> Pow
      linear      emax exponential  logistic quadratic      mean       min       max
2  0.3401852 0.3535486   0.3579222 0.4062934 0.3097248 0.3535348 0.3097248 0.4062934
3  0.5425135 0.5673474   0.5764720 0.6425046 0.4974074 0.5652490 0.4974074 0.6425046
4  0.6852051 0.7156064   0.7264101 0.7892778 0.6380056 0.7109010 0.6380056 0.7892778
5  0.7879910 0.8179557   0.8287310 0.8797857 0.7449282 0.8118783 0.7449282 0.8797857
6  0.8597043 0.8864072   0.8953970 0.9331671 0.8231707 0.8795692 0.8231707 0.9331671
7  0.9078883 0.9299185   0.9369636 0.9634577 0.8785644 0.9233585 0.8785644 0.9634577
8  0.9408012 0.9577757   0.9630140 0.9804805 0.9181160 0.9520375 0.9181160 0.9804805
9  0.9617462 0.9747675   0.9784864 0.9896654 0.9451969 0.9699725 0.9451969 0.9896654
10 0.9759740 0.9851750   0.9877129 0.9946677 0.9638340 0.9814727 0.9638340 0.9946677
attr(,"alRatio")
[1] 1 1 1 1
attr(,"sumFct")
[1] "mean" "min"  "max"
attr(,"Ntype")
[1] "arm"
attr(,"class")
[1] "targN"
```