Proc MCPMod- A tool for Dose Finding using MCPMod

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Agenda

- Problem at hand: Bronchodilator case study
- The traditional approach
- Why use MCPMod?
- The Proc MCPMod
  - Necessity of a SAS based tool for dose finding
  - Why use Proc MCPMod?
- Case study analyzed using Proc MCPMod
  - Syntax and Output in SAS
- Features coming soon in Proc MCPMod

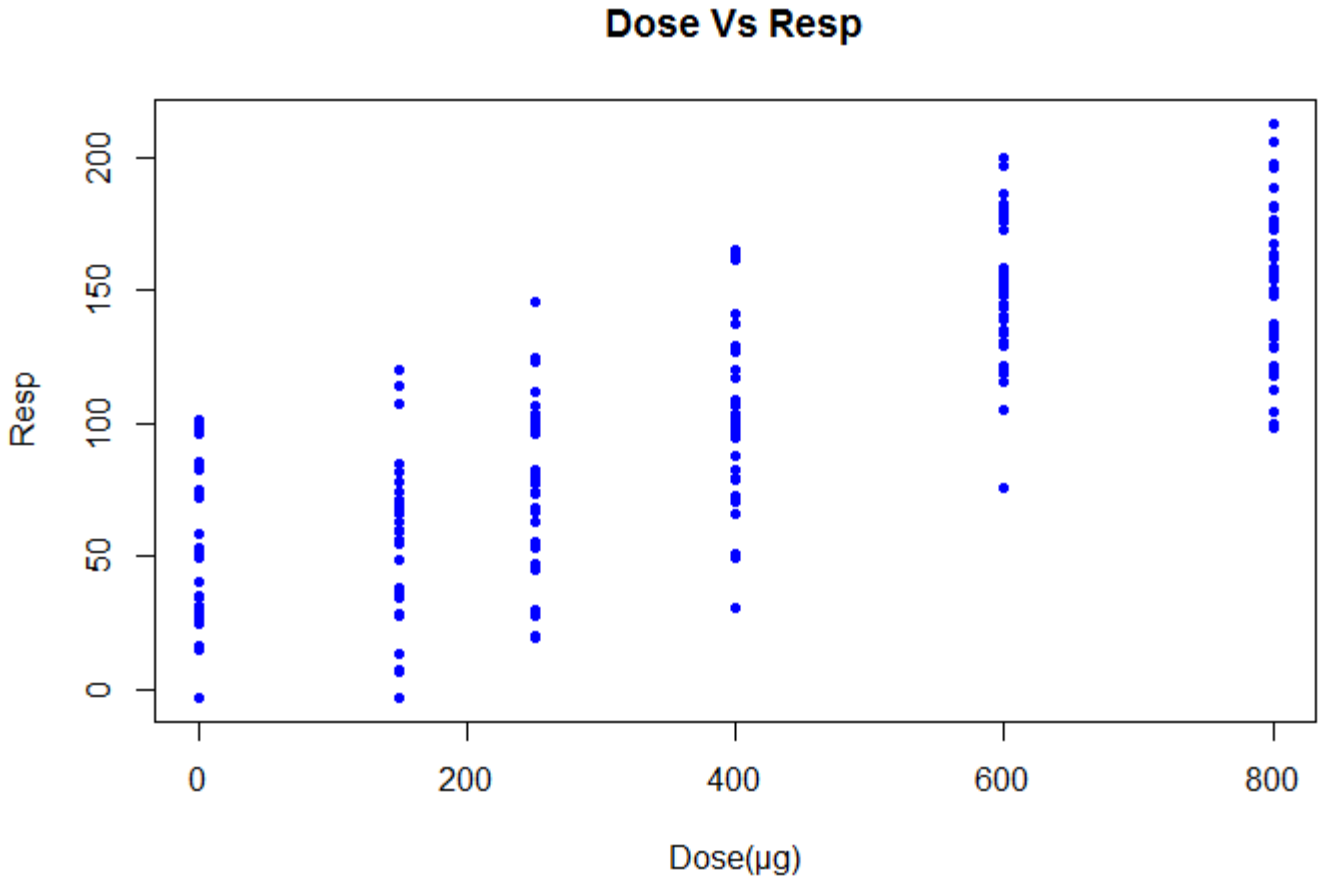
The Study- Background

- Study of Dose-response to Bronchodilator and Dose-Finding in Children aged 2.5 to 6 Years
- Condition: Asthma
- Background:
  - Bronchodilator (BD) dose-effect relationship is a part of the characteristics of asthma disease.
- Problem:
  - There are no data on BD dose-response relationship in wheezy **pre-school children** whose disease pathophysiology is poorly understood.
- Aim:
  - Estimate the bronchodilator dose-effect in pre-schoolers
  - Determine the minimum dose to be used in a bronchodilator test to demonstrate bronchial reversibility.

The Study- Background

- Endpoint:
  - Interrupter resistance (Rint) used to measure a BD effect
  - Response to BD depends on the dose used
  - Normally distributed
- Sample:
  - 200 children aged between 2 yrs 6months and 6 yrs 11 months
- Drug: Salbutamol
- Doses:
  - Placebo, 150 µg, 250 µg, 400 µg,
    600 µg, 800 µg

The Study- Problem



The Study- Problem

High uncertainty about the true dose-response relationship!

Traditional approach

- Goal
  - Establish Proof of Concept
  - Estimate target dose
- Multiple Comparison Procedure
  - Testing significance of contrasts between different doses while preserving FWER
- Modeling
  - Assuming a functional dose-response model, estimate dose required to achieve desired effect
- Limitations
  - MCP: Inference is restricted to doses under study
  - Modeling: Inference is highly dependent on the chosen model

A Novel Approach!

- MCP-Mod
  - Combines multiple comparison and model based approaches
  - Robust to model misspecification
  - Flexible dose estimation
- Result
  - More informative phase 2 designs, more solid basis for confirmatory study!
- Endorsed by EMA and FDA!
- Let's use it!

Introducing Proc MCPMod!

- SAS add-on for analyzing dose-response data using MCPMod methodology
- Analyze normal, binary, count, time-to-event endpoints
- Fully validated and tested software
- Wide choice of candidate models
- Various model selection criteria
- Flexible dose estimation criteria
- Incorporate data on covariates

Proc MCPMod Syntax

```
PROC MCPMOD DATA = Bddata OUT = bigdemo COMPMETHOD = pval
   ALPHA = 0.025;
RESPONSE Resp;
DOSE Dose;
MODELDOSES 0 150 250 400 600 800/ PLACEFF = 50 MAXEFF = 200;
Emax: MODEL SigEmaxS(300, 2);
Linear: MODEL LinearS;
Logistic: MODEL LogitS(300, 25);
Quadratic: MODEL QuadS(0.1);
DOSESEL TD (DELTA = 50);
SELMODEL AIC;
DOSSUMRY OUT =  DOSSUMRY_d;
OPTCONT OUT = OPTCONT_d ;
CORMAT OUT = CORMAT_d ;
run;
```

Proc MCPMod Output


```
Output from MCPMod 1.1
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-----------------------------------------------------------------
MCP Mod
-----------------------------------------------------------------

INPUTS:
Endpoint: Normal
Input Data File: <WORK.BDDATA>
Out Data File: <WORK.BIGDEMO>
Dose Summary file: <WORK.DOSSUMRY_D>
Optimal Contrast file: <WORK.OPTCONT_D>
Contrast Correlation file: <WORK.CORMAT_D>
Total Number of observations in DataSet: 200
Number of observations ignored:  0
Dose Variable: Dose
Response Variable: Resp
Hypothesis Test: One-sided
Direction: Increasing
Level of Significance:  0.0250
Computation Method: p-value
Model Doses:  0.0000  1.0000  2.0000  3.0000  4.0000  5.0000
Number of Candidate models:  4
Placebo Effect:  10.0000
Max Effect:  100.0000
Model Specification:

MODEL1 : EmaxS(Ed50 = 7.0000)
MODEL2 : LinearS
MODEL3 : LogitS(Ed50 = 7.0000,delta = 0.8000)
MODEL4 : QuadS(Ratbeta12 = 2.5000)

Model selection Criterion:  AIC
Dose selection Criterion:  TD (50.0000  )

-----------------------------------------------------------------
```

Proc MCPMod Output

Output from MCPMod 1.1

DOSE-WISE SUMMARY

Dose	Subject Allocation	Mean Response	Median Response	SD Response
0.0000	30	11.0930	11.1916	2.1526
1.0000	34	24.2273	23.7936	2.0942
2.0000	34	55.2006	55.2551	2.0374
3.0000	34	85.9163	85.8311	1.7210
4.0000	34	100.0130	99.7342	2.5230
5.0000	34	104.2674	103.5949	1.8509

Output from MCPMod 1.1

OPTIMAL CONTRAST COEFFICIENTS

Dose	MODEL1	MODEL2	MODEL3	MODEL4
0.0000	-0.6507	-0.5612	-0.2450	0.3997
1.0000	-0.3576	-0.3866	-0.2717	0.3918
2.0000	-0.0622	-0.1372	-0.2507	0.2433
3.0000	0.1742	0.1122	-0.1781	0.0074
4.0000	0.3675	0.3617	0.0700	-0.3158
5.0000	0.5287	0.6111	0.8756	-0.7264

Proc MCPMod Output

Output from MCPMod 1.1

CONTRAST CORRELATION MATRIX

Model	MODEL1	MODEL2	MODEL3	MODEL4
MODEL1	1.0000	0.9875	0.7278	-0.9134
MODEL2	0.9875	1.0000	0.8153	-0.9658
MODEL3	0.7278	0.8153	1.0000	-0.9244
MODEL4	-0.9134	-0.9658	-0.9244	1.0000

Output from MCPMod 1.1

MULTIPLE CONTRAST TEST

	t-Stat	Raw p-value	Adj. p-value
MODEL1	239.0832	0.0000	0.0000
MODEL2	237.5153	0.0000	0.0000
MODEL3	167.3437	0.0000	0.0000
MODEL4	-220.3824	1.0000	1.0000

Proc MCPMod Output


```
Output from MCPMod 1.1
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DOSE RESPONSE MODEL FITTING

Fitted Model 1:
Model family: EMax

Parameter Estimates:
                Estimate      Std. Error
          E0      3.7891          1.2314
        Emax    262.2605         19.1370
        ED50      7.5000          0.9050

Residuals:
         Min           1Q       Median           3Q          Max
    -11.7007      -6.4102       0.8422       5.5526      13.9261


Residual standard error: 7.0871
Degrees of freedom: 197

--------------------------------------------------------------------------------
Fitted Model 2:
Model family: Linear

Parameter Estimates:
                Estimate      Std. Error
          E0     11.7852          1.0524
       Delta     20.6725          0.3442

Residuals:
         Min           1Q       Median           3Q          Max
    -16.6186      -5.5131      -0.8508       7.9301      14.0911


Residual standard error: 8.2134
Degrees of freedom: 198
```

Proc MCPMod Output


```
Output from MCPMod 1.1
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DOSE RESPONSE MODEL FITTING (contd...)

Fitted Model 3:
Model family: Logistic

Parameter Estimates:
                Estimate      Std. Error
          E0       5.8391          0.6438
        Emax      99.6426          0.8792
        ED50       2.0185          0.0138
       Delta       0.6925          0.0136

Residuals:
         Min          1Q      Median          3Q         Max
     -5.8374     -1.2916      0.2630      1.3439      4.7585


Residual standard error: 2.0725
Degrees of freedom: 196

------------------------------------------------------------------------
Fitted Model 4:
Model family: Quadratic

Parameter Estimates:
                Estimate      Std. Error
          E0       4.4384          1.0506
       Beta1      31.1371          0.9680
       Beta2      -2.0682          0.1838

Residuals:
         Min          1Q      Median          3Q         Max
    -11.1856     -5.8319      0.4219      5.2600     12.7901


Residual standard error: 6.4241
Degrees of freedom: 197
```

Proc MCPMod Output

Output from MCPMod 1.1

MODEL SELECTION

Model family	AIC
Emax	1355.9452
Linear	1413.9513
Logistic	865.1108

Selected Model: Logistic

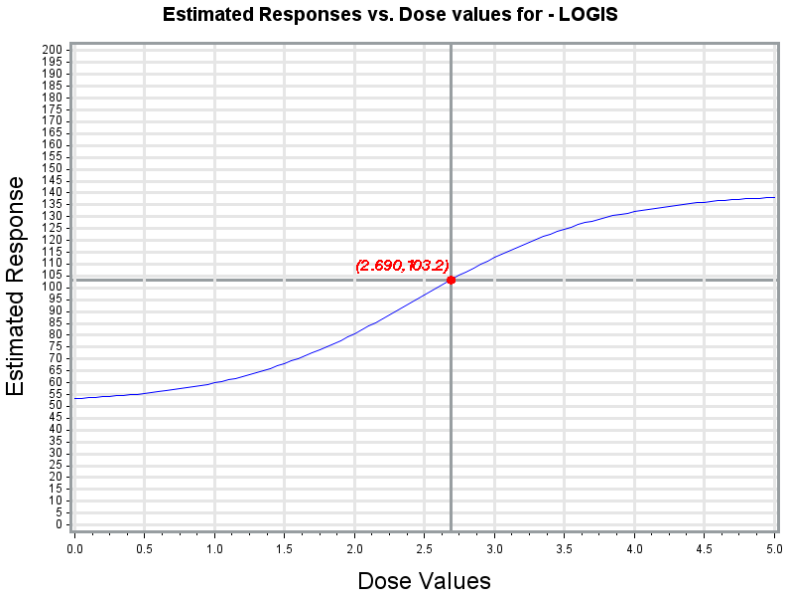
Output from MCPMod 1.1

DOSE ESTIMATION

Table 1: For Delta = 50.0000

Model family	Estimated TD (cont)	Estimated TD (disc)
EMax	1.7667	2.0000
Linear	2.4187	3.0000
Logistic	2.1665	3.0000

Additional Plots and Tables



	Dose	Sub_Alloc	Mean_Resp	Median_Resp	SD_Resp
1	0	30	51.768877977	50.786702785	30.440771893
2	1	34	62.512804716	61.10143553	30.35489329
3	2	34	78.448335334	75.313424905	33.529846699
4	3	34	115.06847731	113.5327478	25.072594065
5	4	34	129.75291144	126.21865695	33.643627009
6	5	34	139.32473576	141.0898789	28.304399797

	Est_Param1	Est_Param2	Est_Param3	Est_Param4	SE_Param1	SE_Param2	SE_Param3	SE_Param4
1	41.161355305	241.35767826	7.5	.	5.4220987904	84.265869585	4.3302965457	.
2	47.59451198	19.387864585	.	.	3.9360755021	1.2872343341	.	.
3	51.142934481	88.87795196	2.459162775	0.6613536237	6.7873110421	10.890586834	0.1961393126	0.1955960059
4	46.716820037	20.638022551	-0.247081395	.	5.0353763321	4.6396929134	0.8808195461	.

Why Proc MCPMod?

- SAS environment:
  - Most preferred clinical data management and reporting tool
  - PROC MCPMod: Only SAS tool for MCPMod analysis
  - Can be used seamlessly with other/ existing SAS procedures
- Easy to learn and implement
  - Simple, intuitive syntax
  - Data stored and managed in SAS, no overheads for data porting, reviewing and retrieving
- Available on Linux OS!

Coming soon in the Proc…

- More options for contrast computations
  - Dunnett, Williams and Marcus methods
- Different alternative hypotheses
  - One- sided and two- sided alternatives

Custom PROC development

- SAS/ Toolkit
  - Supports creation of customized PROCs
  - Lets you enhance the power of SAS with your own customization
  - Write “engines” in languages such as C, C++ etc.
  - “Wrap” your compiled code into a brand new PROC than can integrate into the SAS system

Thank You!

Questions?