

# Package ‘MCPModPack’

August 3, 2020

**Type** Package

**Title** Simulation-Based Design and Analysis of Dose-Finding Trials

**Version** 0.3

**Date** 2020-08-01

**Depends** R (>= 3.4.1), mvtnorm

**Imports** shiny, shinydashboard, devEMF, officer, flextable, Rcpp,  
RcppNumerical

**Suggests** testthat, devtools, DoseFinding

**LinkingTo** Rcpp, RcppEigen, RcppNumerical

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**Description** An efficient implementation of the MCPMod (Multiple Comparisons and Modeling) method to support a simulation-based design and analysis of dose-finding trials with normally distributed, binary and count endpoints (Bretz et al. (2005) <doi:10.1111/j.1541-0420.2005.00344.x>).

**License** GPL-3

**LazyLoad** yes

**LazyData** true

**NeedsCompilation** yes

**Repository** CRAN

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**URL** <https://github.com/medianainc/MCPModPack>

**BugReports** <https://github.com/medianainc/MCPModPack/issues>

**Date/Publication** 2020-08-03 05:30:02 UTC

## R topics documented:

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MCPModPack-package	<i>Design and analysis of dose-finding trials</i>
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## Description

The MCPModPack package facilitates the design and analysis of dose-finding clinical trials with normally distributed, binary and count endpoints using the MCPMod methodology.

## Details

Package:	MCPModPack
Type:	Package
Version:	0.2
Date:	2020-06-27
License:	GPL-3

Key functions included in the package:

- [MCPModAnalysis](#): Analyze data from a dose-finding trial using MCPMod.
- [AnalysisReport](#): Generate a detailed summary of MCPMod analysis results in a Microsoft Word format.
- [AnalysisApp](#): Launch a Shiny-based graphical user interface to analyze data from a dose-finding trial.
- [MCPModSimulation](#): Perform a simulation-based evaluation of dose-finding trial designs using MCPMod.
- [SimulationReport](#): Generate a detailed summary of MCPMod simulation results in a Microsoft Word format.
- [SimulationApp](#): Launch a Shiny-based graphical user interface to perform a simulation-based evaluation of dose-finding trial designs.

The package comes with three example data sets:

- **normal**: Data set based on a dose-finding trial with a normally distributed endpoint.
- **binary**: Data set based on a dose-finding trial with a binary endpoint.
- **count**: Data set based on a dose-finding trial with a count endpoint.

### Author(s)

Alex Dmitrienko <admitrienko@medianainc.com>

### References

Bornkamp, B., Bezlyak, V., Bretz, F. (2015). Implementing the MCP-Mod procedure for dose-response testing and estimation. *Modern Approaches to Clinical Trials Using SAS*. Menon, S., Zink, R. (editors). SAS Press: Cary, NC.

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

Bretz, F., Tamhane, A.C., Pinheiro, J. (2009). Multiple testing in dose response problems. *Multiple Testing Problems in Pharmaceutical Statistics*. Dmitrienko, A., Tamhane, A.C., Bretz, F. (editors). New York: Chapman and Hall/CRC Press.

Nandakumar, S., Dmitrienko, A., Lipkovich, I. (2017). Dose-finding methods. *Analysis of Clinical Trials Using SAS: A Practical Guide* (Second Edition). Dmitrienko, A., Koch, G.G. (editors). SAS Press: Cary, NC.

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

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

### Examples

```
# MCPMod-based analysis of a dose-finding trial with a normally distributed endpoint

# Select the candidate dose-response models and initial values
# of the non-linear model parameters (linear, quadratic, exponential,
# emax, logistic and sigemax)
models = list(linear = NA,
              quadratic = -0.5,
              exponential = 0.3,
              emax = 0.3,
              logistic = c(0.5, 0.1),
              sigemax = c(0.5, 5))

# One-sided Type I error rate
alpha = 0.025

# Direction of the dose-response relationship
direction = "increasing"

# Model selection criterion
```

```
model_selection = "AIC"

# The treatment effect for identifying the target dose
# (this effect is defined relative to the placebo effect)
Delta = 0.5

# Perform an MCPMod-based analysis of the trial's data
# The data set normal is included in the package
results = MCPModAnalysis(endpoint_type = "Normal",
                          models = models,
                          dose = normal$dose,
                          resp = normal$resp,
                          alpha = alpha,
                          direction = direction,
                          model_selection = model_selection,
                          Delta = Delta)

# Simple summary of the MCPMod analysis results
results

# Detailed summary of the MCPMod analysis results
AnalysisReport(results,
               "MCPMod analysis summary (Normally distributed endpoint)",
               "MCPMod analysis summary (Normally distributed endpoint).docx")
```

---

AnalysisApp

*Creation of a Shiny-based interface to perform an MCPMod analysis  
of a dose-finding trial*

---

## Description

This function creates a Shiny-based graphical user interface to perform MCPMod-based analysis of a dose-finding trial. The application requires data sets with the dose and response information (comma-separated value file). The data set is required to include the dose and resp variables with a single record per patient. The first row of the file should contain the required variable names as follows: "dose","resp" (including the quotation marks and the comma). Subsequent rows should contain comma-separated values corresponding to the dose and response values for each patient (quotation marks are not required for the rows of data). See for example the [normal](#) data set.

## Usage

```
AnalysisApp()
```

## Author(s)

Alex Dmitrienko <admitrienko@medianainc.com>

**See Also**

[MCPModAnalysis](#), [AnalysisReport](#)

**Examples**

```
# Launch a Shiny-based interface to perform an MCPMod-based analysis
# of a dose-finding trial
AnalysisApp()
```

---

AnalysisReport	<i>Generation of a Word-based summary of MCPMod analysis results</i>
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**Description**

This function creates a detailed summary of MCPMod analysis results in a Microsoft Word format.

**Usage**

```
AnalysisReport(results, report_title, report_filename)
```

**Arguments**

results	Object of class ‘MCPModAnalysisResults’ created by the <a href="#">MCPModAnalysis</a> function.
report_title	Character value defining the report’s title.
report_filename	Character value defining the report’s filename. The report is saved in the current working directory.

**Author(s)**

Alex Dmitrienko <[admitrienko@medianainc.com](mailto:admitrienko@medianainc.com)>

**See Also**

[MCPModAnalysis](#), [SimulationReport](#)

**Examples**

```
# MCPMod-based analysis of a dose-finding trial with a
# binary endpoint

# Endpoint type
endpoint_type = "Binary"
```

```
# Select the candidate dose-response models and initial values
# of the non-linear model parameters (linear, quadratic, exponential,
# emax, logistic and sigemax)
models = list(linear = NA,
              quadratic = -0.5,
              exponential = 0.3,
              emax = 0.3,
              logistic = c(0.5, 0.1),
              sigemax = c(0.5, 5))

# One-sided Type I error rate
alpha = 0.025

# Direction of the dose-response relationship
direction = "increasing"

# Model selection criterion
model_selection = "AIC"

# The treatment effect for identifying the target dose
# (this effect is defined relative to the placebo effect)
Delta = 0.3

# Perform an MCPMod-based analysis of the trial's data
# The data set binary is included in the package
results = MCPModAnalysis(endpoint_type = endpoint_type,
                        models = models,
                        dose = binary$dose,
                        resp = binary$resp,
                        alpha = alpha,
                        direction = direction,
                        model_selection = model_selection,
                        Delta = Delta)

# Simple summary of the MCPMod analysis results
results

# Detailed summary of the MCPMod analysis results
AnalysisReport(results,
               "MCPMod analysis summary (Binary endpoint)",
               "MCPMod analysis summary (Binary endpoint).docx")
```

---

binary

*Example data set with a binary endpoint*

---

## Description

Example data set based on a trial with a binary primary endpoint.

**Usage**

```
data(binary)
```

**Format**

A data set with 100 observations and 2 variables:

dose Dose level (0 g, 0.05 g, 0.2 g, 0.6 g and 1 g).

resp Binary outcome variable (0 or 1). The value of 1 indicates a beneficial outcome.

---

count	<i>Example data set with a count endpoint</i>
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---

**Description**

Example data set based on a trial with a count primary endpoint.

**Usage**

```
data(count)
```

**Format**

A data set with 100 observations and 2 variables:

dose Dose level (0 g, 0.05 g, 0.2 g, 0.6 g and 1 g).

resp Count-type outcome variable (number of events for each patient). A higher value of this variable indicates a beneficial outcome.

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MCPModAnalysis	<i>MCPMod-based analysis of dose-finding clinical trials with normally distributed, binary and count endpoints</i>
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**Description**

This function implements the MCPMod-based analysis of dose-finding clinical trials with normally distributed, binary and count endpoints, including derivation of the optimal contrasts for the candidate dose-response models, evaluation of dose-response tests based on the optimal contrasts, selection of the significant dose-response models and estimation of the target dose. For more information, see the technical manual in the package's doc folder.

**Usage**

```
MCPModAnalysis(endpoint_type, models, dose, resp, alpha, direction,
                model_selection, Delta, theta)
```

**Arguments**

<code>endpoint_type</code>	Character value defining the primary endpoint's type. Possible values: <ul style="list-style-type: none"> <li>• "Normal": Normally distributed primary endpoint.</li> <li>• "Binary": Binary primary endpoint.</li> <li>• "Count": Count-type primary endpoint.</li> </ul>
<code>models</code>	List of candidate dose-response models with initial values of the non-linear model parameters. The package supports the following dose-response models: linear, quadratic, exponential, Emax, logistic and sigEmax. No initial value is required for the linear model, a single initial value is required for the quadratic, exponential and Emax models, and two initial values are required for the logistic and sigEmax models.
<code>dose, resp</code>	Numeric vectors of equal length specifying the dose and response values.
<code>alpha</code>	Numeric value defining the one-sided significance level (default value is 0.025).
<code>direction</code>	Character value defining the direction of the dose-response relationship. Possible values: <ul style="list-style-type: none"> <li>• "Increasing": A larger value of the treatment difference corresponds to a beneficial treatment effect.</li> <li>• "Decreasing": A smaller value of the treatment difference indicates a beneficial treatment effect.</li> </ul>
<code>model_selection</code>	Character value defining the criterion for selecting the best dose-response model. Possible values: <ul style="list-style-type: none"> <li>• "AIC": Akaike information criterion (AIC).</li> <li>• "maxT": Most significant test statistic.</li> <li>• "aveAIC": Weighted AIC-based criterion.</li> </ul>
<code>Delta</code>	Numeric value specifying the treatment effect for identifying the target dose. The treatment effect is defined relative to the placebo effect. A positive value is required if <code>direction = "Increasing"</code> and a negative value is required otherwise.
<code>theta</code>	Numeric vector defining the overdispersion parameter in each trial arm (required only with count-type primary endpoints).

**Value**

The function returns an object of class 'MCPModAnalysisResults'. This object is a list with the following components:

<code>input_parameters</code>	a list containing the user-specified parameters, e.g, endpoint type, model selection criteria, etc.
<code>selected_models</code>	a logical vector defining the candidate dose-response models.
<code>descriptive_statistics</code>	a list containing the descriptive statistics computed from the trial's data set.



`contrast_results` a list containing the contrast evaluation results for the candidate dose-response models, e.g., the model-specific optimal dose-response contrasts and contrast correlation matrix.

`mcp_results` a list containing the multiplicity adjustment results for the candidate dose-response models, e.g., the model-specific test statistics and adjusted p-values.

`mod_results` a list containing the modeling results for the candidate dose-response models, e.g., estimated model parameters, target dose estimate.

A detailed summary of the MCPMod analysis results can be generated using the `AnalysisReport` function.

### Author(s)

Alex Dmitrienko <admitrienko@medianainc.com>

### See Also

[MCPModSimulation](#)

### Examples

```
# MCPMod-based analysis of a dose-finding trial with a binary endpoint

# Endpoint type
endpoint_type = "Binary"

# Select the candidate dose-response models and initial values
# of the non-linear model parameters (linear, quadratic, exponential,
# emax, logistic and sigemax)
models = list(linear = NA,
              quadratic = -0.5,
              exponential = 0.3,
              emax = 0.3,
              logistic = c(0.5, 0.1),
              sigemax = c(0.5, 5))

# One-sided Type I error rate
alpha = 0.025

# Direction of the dose-response relationship
direction = "increasing"

# Model selection criterion
model_selection = "AIC"

# The treatment effect for identifying the target dose
# (this effect is defined relative to the placebo effect)
Delta = 0.3

# Perform an MCPMod-based analysis of the trial's data
```

```

# The data set binary is included in the package
results = MCPModAnalysis(endpoint_type = endpoint_type,
                          models = models,
                          dose = binary$dose,
                          resp = binary$resp,
                          alpha = alpha,
                          direction = direction,
                          model_selection = model_selection,
                          Delta = Delta)

# Simple summary of the MCPMod analysis results
results

# Detailed summary of the MCPMod analysis results
AnalysisReport(results,
               "MCPMod analysis summary (Binary endpoint)",
               "MCPMod analysis summary (Binary endpoint).docx")

```

---

MCPModSimulation

*MCPMod-based simulation of dose-finding trial designs*


---

## Description

This function implements the simulation-based analysis of dose-finding clinical trials with normally distributed, binary and count endpoints using the MCPMod methodology. For more information, see the technical manual in the package's doc folder.

## Usage

```

MCPModSimulation(endpoint_type, models, alpha, direction,
                 model_selection, Delta, theta, sim_models, sim_parameters)

```

## Arguments

endpoint_type	Character value defining the primary endpoint's type. Possible values: <ul style="list-style-type: none"> <li>• "Normal": Normally distributed primary endpoint.</li> <li>• "Binary": Binary primary endpoint.</li> <li>• "Count": Count-type primary endpoint.</li> </ul>
models	List of candidate dose-response models with initial values of the non-linear model parameters. The package supports the following dose-response models: linear, quadratic, exponential, emax, logistic and sigemax. No initial value is required for the linear model, a single initial value is required for the quadratic, exponential and Emax models, and two initial values are required for the logistic and sigEmax models.
alpha	Numeric value defining the one-sided significance level (default value is 0.025).

direction	Character value defining the direction of the dose-response relationship. Possible values: <ul style="list-style-type: none"> <li>• "Increasing": A larger value of the treatment difference corresponds to a beneficial treatment effect.</li> <li>• "Decreasing": A smaller value of the treatment difference indicates a beneficial treatment effect.</li> </ul>
model_selection	Character value defining the criterion for selecting the best dose-response model. Possible values: <ul style="list-style-type: none"> <li>• "AIC": Akaike information criterion (AIC).</li> <li>• "maxT": Most significant test statistic.</li> <li>• "aveAIC": Weighted AIC-based criterion.</li> </ul>
Delta	Numeric value specifying the treatment effect for identifying the target dose. The treatment effect is defined relative to the placebo effect. A positive value is required if direction = "Increasing" and a negative value is required otherwise.
theta	Numeric vector defining the overdispersion parameter in each trial arm (required only with count-type primary endpoints).
sim_models	List defining the assumed dose-response model and initial values of the non-linear parameters in the simulated trial. The package supports the following dose-response models: linear, quadratic, exponential, Emax, logistic and sigEmax. No initial value is required for the linear model, a single initial value is required for the quadratic, exponential and Emax models, and two initial values are required for the logistic and sigEmax models. The following components are required: <ul style="list-style-type: none"> <li>• "placebo_effect": Numeric value defining the placebo effect in the assumed dose-response model.</li> <li>• "max_effect": Numeric vector defining the effects at the maximum dose in the assumed dose-response model. These effects are defined relative to the placebo effect. Positive values are required if direction = "Increasing" and negative values are required otherwise.</li> <li>• "sd": Numeric vector defining the standard deviations of the response variable in each trial arm (required for normally distributed endpoints).</li> </ul>
sim_parameters	List defining the design and simulation parameters in the simulated trial. The following components are required: <ul style="list-style-type: none"> <li>• "n": Integer vector defining the number of patients in each trial arm.</li> <li>• "doses": Numeric vector defining the dose levels in each trial arm.</li> <li>• "dropout_rate": Numeric value defining the dropout rate in the simulated trial (between 0 and 1).</li> <li>• "nsims": Integer value defining the number of simulation runs.</li> <li>• "go_threshold": Numeric value specifying the threshold for computing go probabilities, i.e., probabilities that the maximum effect for the best dose-response model corresponding to a significant contrast exceeds a pre-defined value. The threshold is defined relative to the placebo effect. A positive value is required if direction = "Increasing" and a negative value is required otherwise.</li> </ul>

**Value**

The function returns an object of class 'MCPModSimulationResults'. This object is a list with the following components:

```
input_parameters      a list containing the user-specified parameters, e.g, endpoint type, model selection criteria, etc.
selected_models      a logical vector defining the candidate dose-response models.
sim_results          a list containing the simulation results based on the assumed dose-response model, e.g., power, target dose estimates, etc.
```

A detailed summary of the simulation results can be generated using the SimulationReport function.

**Author(s)**

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**See Also**

[MCPModAnalysis](#)

**Examples**

```
# Simulation-based evaluation of dose-finding trials with a count endpoint

# Endpoint type
endpoint_type = "Count"

# Select the candidate dose-response models and initial values
# of the non-linear model parameters (linear, quadratic, exponential,
# emax, logistic and sigemax)
models = list(linear = NA,
              quadratic = -0.5,
              exponential = 0.3,
              emax = 0.3,
              logistic = c(0.5, 0.1),
              sigemax = c(0.5, 5))

# One-sided Type I error rate
alpha = 0.025

# Direction of the dose-response relationship
direction = "increasing"

# Model selection criterion
model_selection = "AIC"

# The treatment effect for identifying the target dose
# (this effect is defined relative to the placebo effect)
```

```
Delta = 2

# Vector of overdispersion parameters
theta = c(2, 2, 2, 2, 2)

# Select the assumed dose-response model and values of the non-linear model parameters
sim_models = list(emax = 1,
                 placebo_effect = 3,
                 max_effect = seq(from = 0, to = 3, by = 1))

# Simulation parameters
# (go threshold is defined relative to the placebo effect)
sim_parameters = list(n = c(50, 50, 50, 50, 50),
                    doses = c(0, 0.05, 0.2, 0.6, 1),
                    dropout_rate = 0.05,
                    nsims = 1000,
                    go_threshold = 2)

# Perform an MCPMod-based simulation
results = MCPModSimulation(endpoint_type = endpoint_type,
                          models = models,
                          alpha = alpha,
                          direction = direction,
                          model_selection = model_selection,
                          Delta = Delta,
                          theta = theta,
                          sim_models = sim_models,
                          sim_parameters = sim_parameters)

# Simple summary of the MCPMod simulation results
results

# Detailed summary of the MCPMod simulation results
SimulationReport(results,
                "MCPMod simulation summary (Count endpoint)",
                "MCPMod simulation summary (Count endpoint).docx")
```

---

normal

*Example data set with a continuous endpoint*

---

## Description

Example data set based on a trial with a continuous (normally distributed) primary endpoint.

## Usage

```
data(normal)
```

**Format**

A data set with 100 observations and 2 variables:

dose Dose level (0 g, 0.05 g, 0.2 g, 0.6 g and 1 g).

resp Continuous outcome variable. A higher value of this variable indicates a beneficial outcome.

---

SimulationApp	<i>Creation of a Shiny-based interface to perform an MCPMod-based simulation of dose-finding trial designs</i>
---------------	--

---

**Description**

This function creates a Shiny-based graphical user interface to perform a simulation-based evaluation of dose-finding trial designs using MCPMod.

**Usage**

```
SimulationApp()
```

**Author(s)**

Alex Dmitrienko <admitrienko@medianainc.com>

**See Also**

[MCPModSimulation](#), [SimulationReport](#)

**Examples**

```
# Launch a Shiny-based interface to perform a simulation-based evaluation  
# of dose-finding trial designs  
SimulationApp()
```

---

SimulationReport	<i>Generation of a Word-based summary of MCPMod simulation results</i>
------------------	--

---

### Description

This function creates a detailed summary of MCPMod simulation results in a Microsoft Word format.

### Usage

```
SimulationReport(results, report_title, report_filename)
```

### Arguments

results	Object of class ‘MCPModSimulationResults’ created by the <a href="#">MCPModSimulation</a> function.
report_title	Character value defining the report’s title.
report_filename	Character value defining the report’s filename. The report is saved in the current working directory.

### Author(s)

Alex Dmitrienko <admitrienko@medianainc.com>

### See Also

[MCPModSimulation](#), [AnalysisReport](#)

### Examples

```
# Simulation-based evaluation of dose-finding trials with a binary endpoint

# Endpoint type
endpoint_type = "Binary"

# Select the candidate dose-response models and initial values
# of the non-linear model parameters (linear, quadratic, exponential,
# emax, logistic and sigemax)
models = list(linear = NA,
              quadratic = -0.5,
              exponential = 0.3,
              emax = 0.3,
              logistic = c(0.5, 0.1),
              sigemax = c(0.5, 5))

# One-sided Type I error rate
```

```
alpha = 0.025

# Direction of the dose-response relationship
direction = "increasing"

# Model selection criterion
model_selection = "AIC"

# The treatment effect for identifying the target dose
# (this effect is defined relative to the placebo effect)
Delta = 0.3

# Select the assumed dose-response model and values of the non-linear model parameters
sim_models = list(linear = NA,
                  placebo_effect = 0.2,
                  max_effect = seq(from = 0, to = 0.5, by = 0.1))

# Simulation parameters
sim_parameters = list(n = rep(40, 5),
                     doses = c(0, 0.05, 0.2, 0.6, 1),
                     dropout_rate = 0.05,
                     nsims = 1000,
                     go_threshold = 0.3)

# Perform an MCPMod-based simulation
results = MCPModSimulation(endpoint_type = endpoint_type,
                          models = models,
                          alpha = alpha,
                          direction = direction,
                          model_selection = model_selection,
                          Delta = Delta,
                          sim_models = sim_models,
                          sim_parameters = sim_parameters)

# Simple summary of the MCPMod simulation results
results

# Detailed summary of the MCPMod simulation results
SimulationReport(results,
                 "MCPMod simulation summary (Binary endpoint)",
                 "MCPMod simulation summary (Binary endpoint).docx")
```



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