Package 'MCPModPack'

May 30, 2023

Type Package

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

Version 0.5

Date 2023-05-23

Depends R (>= 3.4.1), mvtnorm

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

Suggests testthat, devtools, DoseFinding, covr

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

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Repository CRAN

URL https://github.com/medianasoft/MCPModPack

BugReports https://github.com/medianasoft/MCPModPack/issues

Date/Publication 2023-05-30 12:20:04 UTC

R topics documented:

`MCPModPack-package` *Design and analysis of dose-finding trials*

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:	0.3
Date:	2020-08-01
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@mediana.us>

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.

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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 (remove tempfile)
AnalysisReport(results,
  "MCPMod analysis summary (Normally distributed endpoint)",
 tempfile("MCPMod analysis summary (Normally distributed endpoint).docx", fileext=".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@mediana.us>

See Also

MCPModAnalysis, AnalysisReport

AnalysisReport *Generation of a Word-based summary of MCPMod analysis results*

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 MCPModAnalysis 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@mediana.us>

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 (remove tempfile)
AnalysisReport(results,
  "MCPMod analysis summary (Binary endpoint)",
  tempfile("MCPMod analysis summary (Binary endpoint).docx", fileext=".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` *Example data set with a count endpoint*

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.

`MCPModAnalysis` *MCPMod-based analysis of dose-finding clinical trials with normally distributed, binary and count endpoints*

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

`endpoint_type` Character value defining the primary endpoint's type. Possible values:

- `"Normal"`: Normally distributed primary endpoint.
- `"Binary"`: Binary primary endpoint.
- `"Count"`: Count-type primary endpoint.

`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.

`dose, resp` Numeric vectors of equal length specifying the dose and response values.

`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:

- `"Increasing"`: A larger value of the treatment difference corresponds to a beneficial treatment effect.
- `"Decreasing"`: A smaller value of the treatment difference indicates a beneficial treatment effect.

`model_selection`
Character value defining the criterion for selecting the best dose-response model. Possible values:

- `"AIC"`: Akaike information criterion (AIC).
- `"maxT"`: Most significant test statistic.
- `"aveAIC"`: Weighted AIC-based criterion.

`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).

Value

The function returns an object of class '`MCPModAnalysisResults`'. 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.

`descriptive_statistics`
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@mediana.us>

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 (remove tempfile)
AnalysisReport(results,
  "MCPMod analysis summary (Binary endpoint)",
  tempfile("MCPMod analysis summary (Binary endpoint).docx", fileext=".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: • `"Normal"`: Normally distributed primary endpoint. • `"Binary"`: Binary primary endpoint. • `"Count"`: Count-type primary endpoint.
`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:

- `"Increasing"`: A larger value of the treatment difference corresponds to a beneficial treatment effect.
- `"Decreasing"`: A smaller value of the treatment difference indicates a beneficial treatment effect.

`model_selection`

Character value defining the criterion for selecting the best dose-response model. Possible values:

- `"AIC"`: Akaike information criterion (AIC).
- `"maxT"`: Most significant test statistic.
- `"aveAIC"`: Weighted AIC-based criterion.

`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 nonlinear 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:

- `"placebo_effect"`: Numeric value defining the placebo effect in the assumed dose-response model.
- `"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.
- `"sd"`: Numeric vector defining the standard deviations of the response variable in each trial arm (required for normally distributed endpoints).

`sim_parameters` List defining the design and simulation parameters in the simulated trial. The following components are required:

- `"n"`: Integer vector defining the number of patients in each trial arm.
- `"doses"`: Numeric vector defining the dose levels in each trial arm.
- `"dropout_rate"`: Numeric value defining the dropout rate in the simulated trial (between 0 and 1).
- `"nsims"`: Integer value defining the number of simulation runs.
- `"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 predefined 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.

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)

Alex Dmitrienko <admitrienko@mediana.us>

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 (remove tempfile)
SimulationReport(results,
  "MCPMod simulation summary (Count endpoint)",
  tempfile("MCPMod simulation summary (Count endpoint).docx", fileext=".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 — *Creation of a Shiny-based interface to perform an MCPMod-based simulation of dose-finding trial designs*

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@mediana.us>

See Also

`MCPModSimulation`, `SimulationReport`

SimulationReport — *Generation of a Word-based summary of MCPMod simulation results*

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 `MCPModSimulation` 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@mediana.us>

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 (remove tempfile)
SimulationReport(results,
  "MCPMod simulation summary (Binary endpoint)",
  tempfile("MCPMod simulation summary (Binary endpoint).docx", fileext=".docx"))
```

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