Package 'aop'

December 5, 2016

Type Package

Title Adverse Outcome Pathway Analysis

Version 1.0.0

Date 2015-08-25

Author Lyle D. Burgoon <Lyle.D.Burgoon@usace.army.mil>

Maintainer Lyle D. Burgoon <Lyle.D.Burgoon@usace.army.mil>

Description Provides tools for analyzing adverse outcome pathways (AOPs) for pharmacological and toxicological research. Functionality includes the ability to perform causal network analysis of networks developed in and exported from Cytoscape or existing as R graph objects, and identifying the point of departure/screening/risk value from concentration-response data.

License CC0

Suggests RUnit, knitr, rmarkdown, BiocGenerics

Imports graph (>= 1.38.3), rjson (>= 0.2.14), igraph (>= 0.7.1), Rgraphviz (>= 2.10.0), methods, plyr (>= 1.8.3), ggplot2 (>= 1.0.1), splines

VignetteBuilder knitr

LazyData true

Collate 'aopCytoscape_Class.R' 'aop_cytoscape_methods.R' 'aop_graph_analysis.R' 'bmr_Class.R' 'pod_analysis.R'

NeedsCompilation no

Repository CRAN

Date/Publication 2016-12-05 18:28:47

R topics documented:

`aop_backdoor` *Backdoor Causal Network Analysis for AOPs*

Description

Performs a backdoor causal network analysis to idenitfy nodes/key events which are sufficient to infer causality.

Usage

```
aop_backdoor(aop_graph, ke_coord, ao_coord, measureable_nodes = NULL)
```

Arguments

`aop_graph`	a `graphNEL` object that encodes the AOP. Typically, this would be output from the `convert_aop_to_graph function`.
`ke_coord`	typically this is the molecular initiating event node, but really, this is any node that you want as the starting/source point. For instance, this is normally the point at which exposure to a stressor is going to enter the AOP.
`ao_coord`	typically this is the adverse outcome node.
`measureable_nodes`	this param is not used yet. In the future this node will be a `vector` of the nodes where an assay is available to measure the node. In a future release this param will focus the backdoor algorithm on finding only those nodes for which measurements can actually be taken, as opposed to causal nodes regardless of our ability to measure them. This allows for the assumption that AOP key events may or may not be measureable.

Details

This function performs Pearl's backdoor analysis. Whereas Pearl was interested in identifying nodes which need to be measured to make a causal statement, we are interested in identifying those nodes/key events which need to measured to say that an adverse outcome is likely to occur. It's essentially the same thing as Pearl, only a slightly different interpretation.

Value

causal_nodes `vector` a vector of the names of the causal nodes.

Examples

```
steatosis_json_file <- system.file("extdata", "steatosis_aop_json.cyjs",
package = "aop")
steatosis_aop <- convert_cytoscape_to_aop(steatosis_json_file)
steatosis_aop_graph <- convert_aop_to_graph(steatosis_aop)
aop_backdoor(steatosis_aop_graph, "391", "388")
```

---

aop_cytoscape-class *aop_cytoscape class*

Description

Creates an object of class aop_cytoscape

Slots

`name`: Object of class `"character"`, containing the name of the AOP.

`nodes`: Object of class `"list"`, containing the list of nodes.

`edges`: Object of class `"list"`, contianing the list of edges.

Author(s)

Lyle D. Burgoon

---

bmr-class *bmr class*

Description

Creates an object of class bmr (bootstrap metaregression)

Slots

`models`: Object of class `"list"`, containing the models.

`fits`: Object of class `"list"`, containing the model fit predictions.

`medians`: Object of class `"vector"`, containing the medians.

`confidence_envelope`: Object of class `"data.frame"`, containing the lower and upper confidence bounds.

Author(s)

Lyle D. Burgoon

`bootstrap_metaregression` *Perform Bootstrap Metaregression*

Description

Performs bootstrap metaregression on a concentration-response dataset.

Usage

```
bootstrap_metaregression(x, dataset_size, iterations = 1000)
```

Arguments

`x`	an object of class `data.frame`.
`dataset_size`	a numeric object with the size of an individual dataset in `x`.
`iterations`	the number of iterations to run; default is 1,000.

Details

This function performs bootstrap metaregression on a concentration-response dataset. The dataset must be a data.frame with two columns: 1) Activity and 2) Concentration.

Value

bmr_obj a `bmr` object that holds all of the bootstrap metaregression models produced.

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
```

`calculate_confidence_and_median` *Calculate the confidence envelope and the median for the bootstrap metaregression concentration response models.*

Description

Calculates the 95 concentration-response data.

Usage

```
calculate_confidence_and_median(bootstrap_metaregression_obj)
```

Arguments

bootstrap_metaregression_obj
: the object that contains the bootstrap metaregression models as a bmr object.

Details

This is an internal function that calculates the 95 the median for concentration-response data. It is called by the bootstrap_metaregression function.

Value

bmr_obj a bmr object that holds all of the bootstrap metaregression models produced.

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
```

---

convert_aop_to_graph *Convert AOP to Graph*

Description

Converts an AOP (encoded as aop_cytoscape object) to a graphNEL object.

Usage

```
convert_aop_to_graph(aop)
```

Arguments

aop
: an object of class aop_cytoscape.

Details

This function converts an aop_cytoscape object to a graphNEL object. This allows us to perform graph-based analyses of the AOP.

Value

aop_graph a graphNEL object representation of the AOP

Examples

```
library(graph)
steatosis_json_file <- system.file("extdata", "steatosis_aop_json.cyjs",
package = "aop")
steatosis_aop <- convert_cytoscape_to_aop(steatosis_json_file)
steatosis_aop_graph <- convert_aop_to_graph(steatosis_aop)
plot(steatosis_aop_graph)
```

convert_cytoscape_to_aop *Convert Cytoscape Graph to an AOP*

Description

Converts a cytoscape JSON file to an aop_cytoscape-class object.

Usage

```
convert_cytoscape_to_aop(file)
```

Arguments

file	a Cytoscape JSON file.

Details

This function converts a JSON file exported from Cytoscape into a aop_cytoscape-class object. Once an aop_cytoscape-class object, we can perform conversion to a graphNEL object, and then perform graph-based analyses.

Value

aop a aop_cytoscape-class object.

Examples

```
steatosis_json_file <- system.file("extdata", "steatosis_aop_json.cyjs",
package = "aop")
steatosis_aop <- convert_cytoscape_to_aop(steatosis_json_file)
```

getAOPNodeName *Get Node Name from ID*

Description

Given an id, this method returns an aop_cytoscape node name.

Usage

```
getAOPNodeName(theObject, id)

## S4 method for signature 'aop_cytoscape'
getAOPNodeName(theObject, id)
```

Arguments

theObject	is an AOP as an object of class aop_cytoscape.
id	an object of class character such as "389".

Value

the name of the node

Examples

```
library(graph)
steatosis_json_file <- system.file("extdata", "steatosis_aop_json.cyjs",
package = "aop")
steatosis_aop <- convert_cytoscape_to_aop(steatosis_json_file)
getAOPNodeName(steatosis_aop, "389")
```

---

internal_model_fits *An internal function for calculating interpolation values.*

Description

An internal function for calculating interpolation values.

Usage

```
internal_model_fits(bmr_model, interval)
```

Arguments

bmr_model	a model of class lm based on a bootstrap natural splin metaregression of concentration-response data.
interval	a numeric value that specifies how large the interval should be between each value used for interpolation.

Value

temp_df a data.frame consisting of concentration and activity columns that represent the interpolated model-based response/activity values.

oxybenzone — *High Throughput Screening Data (Tox21) for Assessing the Estrogenicity of Oxybenzone*

Description

A dataset containing the concentration-response data for analyzing the estrogenicity of oxybenzone from PubChem (Assay ID: 743075, Substance ID: 144209183, Chemical ID: 4632; Assay ID: 743079, Substance ID: 144203969 Chemical ID: 4632). 125 rows. 58 rows x 4 cols/variables.

Usage

```
data(oxybenzone)
```

Format

A data frame with 58 rows and 4 variables

Details

AssayDataset DatasetReplicate Concentration Activity

- AssayDataset. Coded value (1/2) that corresponds to an Assay ID
- DatasetReplicate. This is the "biological" replicate within an AssayDataset (1–3)
- Concentration. This is the concentration of the chemical in the assay (5.55694e-04–7.03500e+01)
- Activity. This is the assay activity. Percent response for these assays. (1.646933e-03–1.140800e+02)

plot_metaregression_confidence_envelope — *Plot the metaregression confidence envelope and median results from the bootstrap metaregression models.*

Description

A function to plot the metaregression confidence envelope and median results from the bootstrap metaregression models.

Usage

```
plot_metaregression_confidence_envelope(bootstrap_metaregression_obj,
  graph_pod = FALSE, pod, pod_threshold, median_line_color = "orange",
  pod_and_threshold_color = "green")
```

Arguments

bootstrap_metaregression_obj	the object that contains the bootstrap metaregression models as a bmr object.
graph_pod	a boolean that determines if the point of departure will be displayed on the graph.
pod	the chemical's point of departure as a numeric value
pod_threshold	the threshold value used to calculate the chemical's point of departure.
median_line_color	the color for the median line, default is "orange".
pod_and_threshold_color	the color of the POD and threshold "crosshairs" on the plot. The default is "green".

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
slope_pod <- slope_pod_analysis(bmr_obj, 0.0001, 10, 0.1)
pod_and_threshold <- pod_envelope_analysis(bmr_obj, slope_pod, 10,
  min(oxybenzone$Concentration), max(oxybenzone$Concentration), 0.1)
plot_metaregression_confidence_envelope(bmr_obj, graph_pod = TRUE,
  pod = pod_and_threshold$pod, pod_threshold=pod_and_threshold$threshold)
```

---

plot_metaregression_spaghetti_plot

Make a spaghetti plot for the metaregression results

Description

Plots a subset of the metaregression results.

Usage

```
plot_metaregression_spaghetti_plot(bootstrap_metaregression_obj,
  number_to_plot = 100)
```

Arguments

bootstrap_metaregression_obj	the object that contains the bootstrap metaregression models as a bmr object.
number_to_plot	the number of bootstrap metaregression concentration-response models to plot. The default is 100 models.

Details

This function plots the concentration-response curves for a subset of the metaregression models generated.

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
plot_metaregression_spaghetti_plot(bmr_obj, number_to_plot=40)
```

---

plot_slope_analysis *Plot the median slope*

Description

This simply plots the slope as a function of concentration.

Usage

```
plot_slope_analysis(pod_slope_data, yaxis_limit = FALSE, yaxis_limit_values)
```

Arguments

pod_slope_data	the data.frame object that contains the concentration and slope data.
yaxis_limit	a boolean value (default is FALSE) that identifies if the user wants to specify y-axis limits.
yaxis_limit_values	a two-element vector that specifies the y-axis limits. For instance yaxis_limit_values = c(0, 20).

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
slope_pod <- slope_pod_analysis(bmr_obj, 0.0001, 10, 0.1)
plot_slope_analysis(slope_pod, TRUE, c(0,30))
```

---

pod_envelope_analysis *This function calculates the chemical's point of departure.*

Description

This function calculates the chemical's point of departure based on the concentration-response data.

Usage

```
pod_envelope_analysis(bmr_obj, slope_data, slope_threshold = 1,
  lower_interpolation_range, upper_interpolation_range, interval_size,
  agonist_assay = TRUE)
```

Arguments

bmr_obj	a bmr object that holds all of the bootstrap metaregression models produced.
slope_data	the data.frame object that contains the concentration and slope data.
slope_threshold	the numeric object that sets the threshold for the slope. This determines the upper bound on the concentration range that is determined to be the asymptote. In other words, the asymptote is defined as that region that has a slope less than the threshold at the lower end of the concentration-response curve.
lower_interpolation_range	a numeric value where the interpolation should be bounded on the lower end.
upper_interpolation_range	a numeric value where the interpolation should be bounded on the upper end.
interval_size	a numeric value that specifies how large the interval should be between each value used for interpolation between the lower and upper bounds.
agonist_assay	a boolean value that specifies if the assay is an agonist or antagonist assay.

Value

a two column data.frame that contains the chemical's point of departure and the threshold value.

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
slope_pod <- slope_pod_analysis(bmr_obj, 0.0001, 10, 0.1)
pod_and_threshold <- pod_envelope_analysis(bmr_obj, slope_pod,
  slope_threshold = 10, min(oxybenzone$Concentration),
  max(oxybenzone$Concentration), interval_size = 0.1)
```

---

pod_slope_analysis *This is intended as an internal function to facilitate the identification of the concentration where the asymptote is likely to end based on a slope threshold, so that the mean of the upper confidence limit for the asymptote can be calculated.*

Description

An internal function for calculating the boundary of the lower asymptote.

Usage

```
pod_slope_analysis(pod_slope_data, slope_threshold = 10)
```

Arguments

pod_slope_data	the data.frame object that contains the concentration and slope data.
slope_threshold	the numeric object that sets the threshold for the slope. This determines the upper bound on the concentration range that is determined to be the asymptote. In other words, the asymptote is defined as that region that has a slope less than the threshold at the lower end of the concentration-response curve.

---

slope_pod_analysis *Slope-based POD analysis*

Description

This requires lower and upper limits to be specified. This is the function that calculates the slope as part of the basis for the POD. The slope is used to identify the lower bound asymptote on the concentration-response curve.

Usage

```
slope_pod_analysis(bootstrap_metaregression_obj, lower_interpolation_range,
  upper_interpolation_range, interval_size)
```

Arguments

bootstrap_metaregression_obj	the object that contains the bootstrap metaregression models as a bmr object.
lower_interpolation_range	a numeric value where the interpolation should be bounded on the lower end.
upper_interpolation_range	a numeric value where the interpolation should be bounded on the upper end.
interval_size	a numeric value that specifies how large the interval should be between each value used for interpolation between the lower and upper bounds.

Value

slope_pod a two-column data.frame object that contains the concentration (column 1) and the median slope.

Examples

```
bmr_obj <- bootstrap_metaregression(oxybenzone, 15, 100)
slope_pod <- slope_pod_analysis(bmr_obj, 0.0001, 10, 0.1)
```

Index