Package: NMTox (via r-universe)

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Title Dose-Response Relationship Analysis of Nanomaterial Toxicity

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Description Perform an exploration and a preliminary analysis on the dose- response relationship of nanomaterial toxicity. Several functions are provided for data exploration, including functions for creating a subset of dataset, frequency tables and plots. Inference for order restricted dose- response data is performed by testing the significance of monotonic dose-response relationship, using Williams, Marcus, M, Modified M and Likelihood ratio tests. Several methods of multiplicity adjustment are also provided. Description of the methods can be found in <https://github.com/rahmasarina/dose-response-analysis/blob/main/Methodology.pdf>.

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`adjPlot` *Plot the adjusted p-values, raw p-values and FDR level*

Description

This function generates plots of adjusted p-values, raw p-values and selected FDR level

Usage

```
adjPlot(data.nm, data.control, id, nano, response, dose, end, end.cat,
  unit, unit.cat, stat=c("E2","Williams","Marcus","M","ModM"), niter,
  method=c("BH","BY"), control.opt=c("same","all"), set.seed, vars, FDR)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose

unit.cat	Specific unit of measurement of the dose
stat	Test statistics ("E2" for the global likelihood test, "Williams" for Williams test, "Marcus" for Marcus test, "M" for M test or "ModM" for modified M test)
niter	Number of permutations
method	Method used to adjust for the multiplicity
control.opt	Option for the control doses if unit and unit.cat are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "same" in the control.opt. If all control doses with any units of measurement are included, then specify "all".
set.seed	Specify seed
vars	Variable(s) used to subset the data
FDR	The desired FDR to control

Details

- This function calculates the p-values for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, data.control and id do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify "same" in control.opt.
- Plots can also be generated for subsets of data in each nanomaterial, by specifying the variables used to split the data in vars.

Value

This function generates plots of adjusted p-values, raw p-values and selected FDR for both directions (up and down) of the trend

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

Examples

```
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)
#
adjPlot(data.nm=invitrodata, data.control=controldata, id="experimentID",
nano="name", response="value", dose="concentration", end="endpoint",
end.cat="DNA STRAND BREAKS", unit="concentration_unit", unit.cat="ug/cm2",
stat="E2", niter=1000, method="BH", control.opt="same",
set.seed = 1234, FDR=0.05)
```

FrCtrl *Create a frequency table of the control values*

Description

This function provides a table containing the frequencies of the control values and the number of available data in the specified dataset. Since it is possible to have a dose with different units of measurement in one dataset, this function helps in showing how many control values are available for each nanomaterial for a specific unit of measurement of the dose.

Usage

```
FrCtrl(data.nm, data.control, id, nano, dose, end, end.cat, unit,
  unit.cat, vars)
```

Arguments

data.nm	Data containing the result of toxicity study
data.control	Data of control values
id	Identifier of the experiment
nano	Name of the nanomaterial
dose	Dose or concentration
end	Toxicity endpoint
end.cat	Specific toxicity endpoint of interest
unit	Unit of measurement of the dose
unit.cat	Specific unit of measurement of the dose
vars	Variables used to subset the data

Details

- This function performs data exploration for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, `data.control` and `id` do not need to be specified.
- The exploration can also be performed on the subsets of data by splitting the data of each nanomaterial according to the variable(s) specified in `vars`

Value

The value returned from `FrCtrl` is a table containing:

- `Freq(Dose=0.0).same`: frequency of control values with dose measured in `unit.cat`
- `Freq(obs).same`: number of observations with dose measured in `unit.cat`
- `Freq(Dose=0.0).all`: frequency of control values with dose measured `unit.cat` and in other units of measurement
- `Freq(obs).all`: number of observations with dose measured in `unit.cat` and control dose measured in any units,

for each nanomaterial or subset of data

Examples

```
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)

# Frequency of controls for each nanomaterial in geninvitro dataset
# with DNA STRAND BREAKS as the toxicity endpoint and concentration
# measured in "ug/cm2":
#
FrCtrl(data.nm=invitrodata, data.control=controldata, nano="name",
       end="endpoint", end.cat="DNA STRAND BREAKS", id="experimentID",
       dose="concentration", unit="concentration_unit", unit.cat="ug/cm2")

# Frequency of controls for each cell type in each nanomaterial
# (in geninvitro dataset) with DNA STRAND BREAKS as the toxicity
# endpoint and concentration measured in "ug/cm2":
```

```
#
FrCtrl(data.nm=invitrodata, data.control=controldata, nano="name",
       end="endpoint", end.cat="DNA STRAND BREAKS", id="experimentID",
       dose="concentration", unit="concentration_unit", unit.cat="ug/cm2",
       vars="celltype")
```

`Frtab` *Generate the number of unique values, the list of unique values, or the number of observations of specified variable(s)*

Description

This function produces the number of unique values, the list of unique values, or the number of observations of certain variable(s) in the dataset

Usage

```
Frtab(data, x, cat, val, opt=c("un", "list", "obs", "ls.obs"),
  na.rm=FALSE)
```

Arguments

`data`	Dataset
`x`	Variable(s) to be explored
`cat`	Variable used to group or subset the data
`val`	Specific value of variable `cat`. If `val` is specified, then only result for this value will be shown.
`opt`	Options for the result: If `opt` is `un`, then the number of unique values of `x` will be counted. If `opt` is `list`, then the list of unique values of `x` will be generated. If `opt` is `obs`, then the number of observations of `x` will be counted. If `opt` is `ls.obs`, then the number of observations for each unique value will be generated.
`na.rm`	If `na.rm` is `FALSE` (the default), then missing values are not removed from the dataset. If `na.rm=TRUE`, then missing values are removed from the dataset

Value

This function generates the number of unique values, the list of unique values, or the number of observations of specified variable(s).

Examples

```
# List of nanomaterial in geninvitro dataset:
Frtab(data=geninvitro, x="name", opt="list")

# How many types of endpoint are measured in geninvitro data?
Frtab(data=geninvitro, x="endpoint", opt="un")
```

```
# How many observations are available for variable "unit"?
Frtab(data=geninvitro, x="unit", opt="obs")

# How many types of endpoint and nanomaterial are available in geninvitro data?
Frtab(data=geninvitro, x=c("name","endpoint"), opt="un")

# How many types of endpoint are available for each nanomaterial
# in geninvitro data?
Frtab(data=geninvitro, x="endpoint", cat="name", opt="un")

# How many observations are available for each endpoint in each nanomaterial?
Frtab(data=geninvitro, x=c("name","endpoint"), opt="ls.obs")

# How many observations with "DNA STRAND BREAKS" as the endpoint are available
# for each nanomaterial in geninvitro data?
Frtab(data=geninvitro, x="name", cat="endpoint", val="DNA STRAND BREAKS",
opt="ls.obs")
```

`Frtab.sub` *Count the number of observations for each unique value of a variable on a subset of data*

Description

This function counts the number of observations for each unique value of a variable on a subset of data. The subset of data is created according to the specified endpoint and unit of measurement of the dose.

Usage

```
Frtab.sub(data.nm, data.control, id, nano, dose, end, end.cat, unit,
  unit.cat, control.opt=c("same","all"), x)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose

unit.cat	Specific unit of measurement of the dose
control.opt	Option for the control doses. If only control doses with the same unit of measurement as the non-control ones are included, then specify "same" in the control.opt. If all control doses with any units of measurement are included, then specify "all".
x	Variable to be explored

Details

- This function counts for each nanomaterial in the dataset. The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, data.control and id do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify "same" in control.opt.

Value

This function generates a table containing the number of observations for each unique value of a variable on a subset of data

Examples

```
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control",
             "Control", "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control",
             "Control", "medium", "medium + BSA", "untreated"), include=FALSE)

# Frequency of each unique value of the dose for each nanomaterial
# in geninvitro dataset, with DNA STRAND BREAKS as the toxicity endpoint
# and only observations with concentration measured in "ug/cm2" are considered:
#
Frtab.sub(data.nm=invitrodata, data.control=controldata, nano="name",
           end="endpoint", end.cat="DNA STRAND BREAKS", id="experimentID",
           dose="concentration", unit="concentration_unit", unit.cat="ug/cm2",
           control.opt="same", x="concentration")
```

`geninvitro` *Genetic toxicity in vitro dataset*

Description

This dataset contains the result of genetic toxicity in vitro studies and variables related to the experiments for several different nanomaterials.

Usage

```
data(geninvitro)
```

Format

A data frame with columns:

- name: Project-assigned name of the nanomaterial
- publicname: A widely accepted unique identifier
- supplier: Supplier/project where the data is originated from
- experimentID: Identifier of the experiment
- method: Method/assay used in the experiment
- studyprovider: Study provider
- endpoint: Toxicity endpoint measure
- value: Endpoint value
- unit: Unit of the endpoint
- celltype: Type of the cell used in the experiment
- treatment: Indicator of the treatment
- exptimeunit: Unit of measurement of the exposure time
- exptime: Exposure time
- concentration_unit: Unit of measurement of the concentration in variable *concentration*
- concentration: Concentration of the nanomaterial
- concentration_ml_unit: Unit of measurement of the concentration in variable *concentration_ml*
- concentration_ml: Concentration of the nanomaterial in amount per ml

Details

Since some of the controls in geninvitro dataset are not named according to the nanomaterial names, the experiment identifier (ID) can be used to identify which control values are related to which nanomaterial.

Source

This dataset was obtained from https://www.anses.fr/en/content/nanogenotox-project (NanoGenotox project) and it was extracted from eNanoMapper database https://search.data.enanomapper.net/

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Examples

```
data(geninvitro)
```

`Isoplot` *Create plot(s) of the observations, the sample means and the fitted isotonic regression curve*

Description

This function creates plot(s) of the observations, the sample means and the fitted isotonic regression curve for one or more nanomaterials simultaneously

Usage

```
Isoplot(data.nm, data.control, id, nano, response, dose, end, end.cat,
  unit, unit.cat, dose.type=c("dose","log"), type = c("continuous",
  "ordinal"), control.opt=c("same","all"), add.curve = TRUE, vars, nrow=1,
  ncol=1, xlabel="Dose", ylabel="Response")
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`dose.type`	Type of the dose to be plotted ("dose" for dose and "log" for log(dose))
`type`	Type of the dose (continuous or ordinal)

control.opt	Option for the control doses if unit and unit.cat are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "same" in the control.opt. If all control doses with any units of measurement are included, then specify "all".
add.curve	Adding curve to the plot
vars	Variable(s) used to subset the data
nrow	Number of row in the plotting space
ncol	Number of column in the plotting space
xlabel	Label for x-axis
ylabel	Label for y-axis

Details

- This function performs data exploration for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, data.control and id do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify "same" in control.opt.
- Dose-response plot can also be generated for subsets of data in each nanomaterial by specifying the variables used to split the data in vars.

Value

This function produces plot(s) consisting of observation data points, sample mean for each dose and fitted isotonic regression curve

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

Examples

```
# Example 1:
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
```

```
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)
#
# Generate dose-response plots for geninvitro, with DNA STRAND BREAKS
# as the endpoint, concentrations measured in "ug/cm2"
# and control doses measured in any units of measurement:
#
Isoplot(data.nm=invitrodata, data.control=controldata, id="experimentID",
        nano="name", response="value", dose="concentration", end="endpoint",
        end.cat="DNA STRAND BREAKS", unit="concentration_unit", unit.cat="ug/cm2",
        dose.type="dose", control.opt="all")

# Example 2:
# Split geninvitro data according to the cell type, method, study provider and
# unit of the concentration and generate dose-response plot for each subset
# of data with DNA STRAND BREAKS as the endpoint:
#
Isoplot(data.nm=invitrodata, data.control=controldata, id="experimentID",
        nano="name", response="value", dose="concentration", end="endpoint",
        end.cat="DNA STRAND BREAKS",  dose.type="dose",
        vars=c("celltype","method","studyprovider","concentration_unit"),
        nrow=2, ncol=2)
```

`IsoPlot.nm` *Create a plot of the observations, sample means and fitted isotonic regression curve for one nanomaterial*

Description

This function generates a dose-response plot (scatter plot) of the observations, sample means and fitted isotonic regression curve for one nanomaterial

Usage

```
IsoPlot.nm(data.nm, dose, response, type = c("continuous", "ordinal"),
  add.curve = TRUE, nano.cat = NULL, xlabel="Dose", ylabel="Response")
```

Arguments

`data.nm`	Dataset of a particular nanomaterial
`dose`	Dose or concentration (with the same unit of measurement)
`response`	Response (a certain endpoint value)
`type`	Type of the dose
`add.curve`	Adding curve to the plot

nano.cat	Title of the plot (referring to the name of the nanomaterial)
xlabel	label for the x-axis of the plot
ylabel	label for the y-axis of the plot

Details

This function is intended to be used inside the function Isoplot. However, it can also be used to generate a plot for one nanomaterial, with a particular unit of measurement of the dose and for a certain toxicity endpoint.

Value

This function produces a plot of the observations, sample means and fitted isotonic regression curve for one nanomaterial

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

Examples

```
#nm400 contains the result of genetic toxicity in vitro study of NM-400
#(Multi-walled carbon nanotubes) with associated controls
IsoPlot.nm(data.nm=nm400, dose="concentration", response="value",
           nano.cat="Multi-walled carbon nanotubes", xlabel="Concentration",
           ylabel="DNA STRAND BREAKS")
```

IsoPval.nm *Calculate p-values based on permutation for both increasing and decreasing ordered alternatives*

Description

This function calculates p-values based on permutation. The plots of the null distribution and the observed test statistic under increasing and decreasing ordered alternatives are also given.

Usage

```
IsoPval.nm(data.nm, dose, response, stat=c("E2", "Williams","Marcus",
  "M", "ModM"), niter, nano.cat=NULL)
```

Arguments

data.nm	Nanomaterial dataset
dose	Dose or concentration (with the same unit of measurement)
response	Response (a certain endpoint value)
stat	Test statistics ("E2" for the global likelihood test, "Williams" for Williams test, "Marcus" for Marcus test, "M" for M test or "ModM" for modified M test)
niter	Number of permutations
nano.cat	Name of the nanomaterial

Details

This function is intended to be used inside the function Isotest. However, it can also be used to calculate p-values and generate the plot for one nanomaterial, with a particular unit of measurement of the dose, for a certain toxicity endpoint.

Value

This value provides p-values based on the permutation, the plot of the null distribution and the observed test statistics.

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

See Also

Isotest

Examples

```
#nm400 contains the result of genetic toxicity in vitro study of NM-400
#(Multi-walled carbon nanotubes) with associated controls
IsoPval.nm(data.nm=nm400, dose="concentration", response="value",
           stat="E2", niter=1000)
```

`Isotest` *Calculate the test statistics and p-values for testing monotonic trend*

Description

This function provides the value of the test statistics, p-values, plot of the null distribution and the observed test statistics, and adjusted p-values according to the method chosen.

Usage

```
Isotest(data.nm, data.control, id, nano, response, dose, end, end.cat,
  unit, unit.cat, stat=c("E2","Williams","Marcus","M","ModM"), niter,
  method=p.adjust.methods, control.opt=c("same","all"), set.seed, vars)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`stat`	Test statistics ("`E2`" for the global likelihood test, "`Williams`" for Williams test, "`Marcus`" for Marcus test, "`M`" for M test or "`ModM`" for modified M test)
`niter`	Number of permutations
`method`	Method used to adjust for the multiplicity (see `p.adjust.methods`)
`control.opt`	Option for the control doses if `unit` and `unit.cat` are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "`same`" in the `control.opt`. If all control doses with any units of measurement are included, then specify "`all`".
`set.seed`	Specify seed
`vars`	Variable(s) used to subset the data

Details

- This function performs trend testing for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, `data.control` and `id` do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify `"same"` in `control.opt`.
- Trend testing can also be performed for subsets of data in each nanomaterial, by specifying the variables used to split the data in `vars`.

Value

This function calculates the value for the test statistics, the p-value (and its plot) based on the permutation, the adjusted p-value and the more likely direction of the monotonic trend.

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

Examples

```
# Example 1:
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)
#
# Perform test for the monotonic trend in geninvitro, with DNA STRAND BREAKS
# as the endpoint, concentrations measured in "ug/cm2" and control doses
# measured in any units of measurement:
#
Isotest(data.nm=invitrodata, data.control=controldata, id="experimentID",
        nano="name", response="value", dose="concentration", end="endpoint",
        end.cat="DNA STRAND BREAKS", unit="concentration_unit", unit.cat="ug/cm2",
        stat="E2", niter=1000, method="BH", control.opt="all", set.seed=1234)
```

```
#' # Example 2:
# Split geninvitro according to the endpoint and unit of the concentration
# and then perform test for the monotonic trend for each subset of data:
#
Isotest(data.nm=invitrodata, data.control=controldata,
        id="experimentID", nano="name", dose="concentration",
        response="value", stat="E2", niter=1000, method="BH", set.seed=1234,
        vars=c("endpoint","concentration_unit"))
```

`IsoTest.nm` *Calculate the value of the test statistics for testing monotonic trend*

Description

This function provides the value of the test statistics (the global likelihood test, Williams, Marcus, M or modified M test) for one nanomaterial

Usage

```
IsoTest.nm(data.nm, dose, response, stat=c("E2", "Williams","Marcus",
  "M", "ModM"))
```

Arguments

`data.nm`	Nanomaterial dataset
`dose`	Dose or concentration (with the same unit of measurement)
`response`	Response (a certain endpoint value)
`stat`	Test statistics ("`E2`" for the global likelihood test, "`Williams`" for Williams test, "`Marcus`" for Marcus test, "`M`" for M test or "`ModM`" for modified M test)

Details

This function is intended to be used inside the function `Isotest`. However, it can also be used to obtain the value of a specified test statistics for one nanomaterial, with a particular unit of measurement of the dose, for a certain toxicity endpoint.

Value

This function calculates the value of the specified test statistics for one nanomaterial

References

Lin D., Pramana, S., Verbeke, T., and Shkedy, Z. (2015). IsoGene: Order-Restricted Inference for Microarray Experiments. R package version 1.0-24. https://CRAN.R-project.org/package=IsoGene

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

See Also

Isotest

Examples

```
#nm400 contains the result of genetic toxicity in vitro study of NM-400
#(Multi-walled carbon nanotubes) with associated controls
IsoTest.nm(data.nm=nm400, dose="concentration", response="value", stat="E2")
```

---

nm400 *NM-400 in vitro dataset*

Description

This dataset contains the result of genetic toxicity in vitro study of NM-400 (Multi-walled carbon nanotubes) with associated controls and variables related to the experiments.

Usage

```
data(nm400)
```

Format

A data frame with columns:

- name: Project-assigned name of the nanomaterial
- publicname: A widely accepted unique identifier
- supplier: Supplier/project where the data is originated from
- experimentID: Identifier of the experiment
- method: Method/assay used in the experiment
- studyprovider: Study provider
- endpoint: Toxicity endpoint measure
- value: Endpoint value
- unit: Unit of the endpoint
- celltype: Type of the cell used in the experiment
- treatment: Indicator of the treatment
- exptimeunit: Unit of measurement of the exposure time
- exptime: Exposure time
- concentration_unit: Unit of measurement of the concentration in variable *concentration*
- concentration: Concentration of the nanomaterial
- concentration_ml_unit: Unit of measurement of the concentration in variable *concentration_ml*
- concentration_ml: Concentration of the nanomaterial in amount per ml

Source

This dataset was obtained from https://www.anses.fr/en/content/nanogenotox-project (NanoGenotox project) and it was extracted from eNanoMapper database https://search.data.enanomapper.net/

The NANOGENOTOX Joint Action received funding from the European Union, in the framework of the Health Programme under Grant Agreement n2009 21.

Supported by European Union's Horizon 2020 research and innovation programme under grant agreement No 814426 - NanoInformaTIX https://www.nanoinformatix.eu/

Examples

```
data(nm400)
```

`nmplot` *Create plots of the dose and the response for each nanomaterial in the dataset*

Description

This function generates scatter plots of the dose and the response for each nanomaterial in the dataset

Usage

```
nmplot(data.nm, data.control, id, nano, response, dose, end, end.cat,
  unit, unit.cat, type=c("dose","log"), control.opt=c("same","all"), vars,
  nrow=1, ncol=1)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`type`	Type of the dose to be plotted ("`dose`" for dose and "`log`" for log(dose))

control.opt	Option for the control doses if unit and unit.cat are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "same" in the control.opt. If all control doses with any units of measurement are included, then specify "all".
vars	Variables used to subset the data
nrow	Number of row in the plotting space (default is 1)
ncol	Number of column in the plotting space (default is 1)

Details

- This function generates plots for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, data.control and id do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify "same" in control.opt.
- Dose-response plot can also be generated for subsets of data in each nanomaterial, by specifying the variables used to split the data in vars.

Value

This function produces plots of the dose and the response for each nanomaterial in the dataset

Examples

```
# Example 1:
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)
#
# Generate dose-response plot for geninvitro, with DNA STRAND BREAKS as the
# endpoint, concentrations measured in ug/cm2 and controls measured in any
# units of measurement:
#
nmplot(data.nm=invitrodata, data.control=controldata, id="experimentID",
       nano="name", response="value", dose="concentration", end="endpoint",
       end.cat="DNA STRAND BREAKS", unit="concentration_unit",
       unit.cat="ug/cm2", type="dose", control.opt="all")
```

```
# Example 2:
# Split geninvitro data according to the cell type and unit of the
# concentration and generate dose-response plot for each
# subset of data with DNA STRAND BREAKS as the endpoint:
#
nmplot(data.nm=invitrodata, data.control=controldata, id="experimentID",
       nano="name", response="value", dose="concentration", end="endpoint",
       end.cat="DNA STRAND BREAKS", type="dose", nrow=2, ncol=2,
       vars=c("celltype","concentration_unit"))
```

`nmplot.cat` *Create plots of the dose and the response grouped by a variable*

Description

This function generates scatter plots of the dose and the response, with the colour of the data points differentiated according to the value of a variable.

Usage

```
nmplot.cat(data.nm, data.control, id, nano, response, dose, end,
  end.cat, unit, unit.cat, x.cat, type = c("dose", "log"), control.opt =
  c("same", "all"), vars, nrow = 1, ncol = 1)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`x.cat`	Variable used to differentiate the colour of the data points in the plot(s)
`type`	Type of the dose to be plotted ("`dose`" for dose and "`log`" for log(dose))
`control.opt`	Option for the control doses if `unit` and `unit.cat` are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "`same`" in the `control.opt`. If all control doses with any units of measurement are included, then specify "`all`".
`vars`	Variable(s) used to subset the data
`nrow`	Number of rows in the plotting space (default is 1)
`ncol`	Number of columns in the plotting space (default is 1)

Details

- This function generates plots for each nanomaterial in the dataset (or for each subset of data). The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: `geninvitro` dataset and the `Examples`), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, `data.control` and `id` do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify `"same"` in `control.opt`.
- Dose-response plot can also be generated for subsets of data in each nanomaterial by specifying the variables used to split the data in `vars`.

Value

This function produces scatter plots of the dose and the response, grouped by a certain variable

Examples

```
# Example 1:
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)

# Generate dose-response plots for geninvitro, with DNA STRAND BREAKS as
# the endpoint, concentrations measured in "ug/cm2" and control doses
# measured in any units of measurement (different colours represent different
# study providers):
#
nmplot.cat(data.nm=invitrodata, data.control=controldata, id="experimentID",
           nano="name", response="value", dose="concentration", end="endpoint",
           end.cat="DNA STRAND BREAKS", unit="concentration_unit", unit.cat="ug/cm2",
           x.cat="studyprovider", type="dose", control.opt="all",
           nrow=1, ncol=1)

# Example 2:
# Split geninvitro data according to the method, study provider and unit of
# the concentration, and generate dose-response plot for each subset of data
# with DNA STRAND BREAKS as the endpoint (different colours represent
# different cell types):
#
nmplot.cat(data.nm=invitrodata, data.control=controldata, id="experimentID",
           nano="name", response="value", dose="concentration", end="endpoint",
```

```
end.cat="DNA STRAND BREAKS",  x.cat="celltype", type="dose",
vars=c("method","studyprovider","concentration_unit"),
nrow=2, ncol=2)
```

`nmplot.n` *Create plots of the dose and the response for every unique value of a certain variable*

Description

This function generates scatter plots of the dose and the response for every unique value of a specified variable

Usage

```
nmplot.n(data.nm, data.control, id, nano, response, dose, end,
  end.cat, unit, unit.cat, cat, type=c("dose","log"),
  control.opt=c("same","all"), nrow=1, ncol=1)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`cat`	Plot is generated for every unique value of `cat`
`type`	Type of the dose to be plotted ("`dose`" for dose and "`log`" for log(dose))
`control.opt`	Option for the control doses. If only control doses with the same unit of measurement as the non-control ones are included, then specify "`same`" in the `control.opt`. If all control doses with any units of measurement are included, then specify "`all`".
`nrow`	Number of rows in the plotting space (default is 1)
`ncol`	Number of columns in the plotting space (default is 1)

Details

- This function generates plots for each nanomaterial in the dataset. The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: geninvitro dataset and the Examples), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, `data.control` and `id` do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify `"same"` in `control.opt`.

Value

This function produces scatter plots of the dose and the response for every unique value of a specified variable

Examples

```
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)

# Generate dose-response plots for geninvitro, with DNA STRAND BREAKS as
# the endpoint, concentrations measured in "ug/cm2" and control doses
# measured in any units of measurement (plot is generated for each study
# provider):
#
nmplot.n(data.nm=invitrodata, data.control=controldata, id="experimentID",
         nano="name", response="value", dose="concentration", end="endpoint",
         end.cat="DNA STRAND BREAKS", unit="concentration_unit",
         unit.cat="ug/cm2", cat="studyprovider", type="dose",
         control.opt ="all", nrow=1, ncol=1)
```

`nmplot.ncat` *Create plots of the dose and the response differentiated by specified variables*

Description

This function generates scatter plots of the dose and the response for every unique value of a certain variable, with the colour of the data points differentiated according to the value of another variable.

Usage

```
nmplot.ncat(data.nm, data.control, id, nano, response, dose, end,
  end.cat, unit, unit.cat,  cat, x.cat, type=c("dose","log"),
  control.opt=c("same","all"), nrow=1, ncol=1)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`response`	Response (endpoint value)
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose
`unit.cat`	Specific unit of measurement of the dose
`cat`	Plot is generated for every unique value of `cat`
`x.cat`	Variable used to differentiate the colour of the data points in the plot(s)
`type`	Type of the dose to be plotted ("`dose`" for dose and "`log`" for log(dose))
`control.opt`	Option for the control doses. If only control doses with the same unit of measurement as the non-control ones are included, then specify "`same`" in the `control.opt`. If all control doses with any units of measurement are included, then specify "`all`".
`nrow`	Number of rows in the plotting space (default is 1)
`ncol`	Number of columns in the plotting space (default is 1)

Details

- This function generates plots for each nanomaterial in the dataset. The different types of nanomaterials are identified by their names. Therefore, if some control values are named differently (see: `geninvitro` dataset and the `Examples`), a separate dataset containing only these values first needs to be created. Controls in the new dataset can be linked to the non-control observations belonging to the same experiment through the identifier of the experiment (the linking is performed inside this function). In this situation, it is necessary to have an indicator that can identify different experiments (such as experiment ID).
- If all controls in the dataset are named according to the related nanomaterial names, `data.control` and `id` do not need to be specified.
- If doses used in the experiment are all measured in the same unit of measurement, then specify "`same`" in `control.opt`.

Value

This function produces dose-response plots for every unique value of a certain variable, with different colours of data points based on the value of another variable

Examples

```
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)

# Generate dose-response plots for geninvitro, with DNA STRAND BREAKS as
# the endpoint and concentrations measured in "ug/cm2" (plot is generated for
# each study provider, with different colours represent different
# experiments):
#
nmplot.ncat(data.nm=invitrodata, data.control=controldata,
            id="experimentID", nano="name", response="value",
            dose="concentration", end="endpoint", end.cat="DNA STRAND BREAKS",
            unit="concentration_unit", unit.cat="ug/cm2", cat="studyprovider",
            x.cat="experimentID", type="dose", control.opt="same", nrow=1,
            ncol=1)
```

`SplitData` *Split the data of each nanomaterial into different subsets of data*

Description

This function splits the data of each nanomaterial into different subsets of data according to the unique values of selected variable(s)

Usage

```
SplitData(data.nm, data.control, id, nano, dose, end, end.cat, unit,
  unit.cat, control.opt=c("same","all"), vars)
```

Arguments

`data.nm`	Data containing the result of toxicity study
`data.control`	Data of control values
`id`	Identifier of the experiment
`nano`	Name of the nanomaterial
`dose`	Dose or concentration
`end`	Toxicity endpoint
`end.cat`	Specific toxicity endpoint of interest
`unit`	Unit of measurement of the dose

unit.cat	Specific unit of measurement of the dose
control.opt	Option for the control doses if unit and unit.cat are specified. If only control doses with the same unit of measurement as the non-control ones are included, then specify "same" in the control.opt. If all control doses with any units of measurement are included, then specify "all".
vars	Variables used to split the data

Value

This function splits the data of each nanomaterial into different subsets of data according to the unique values of selected variable(s)

Examples

```
# Example 1:
# Create a dataset containing controls (which are named differently)
# from geninvitro dataset:
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"))

# Exclude controls (which are named differently) from geninvitro dataset:
invitrodata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
             "medium", "medium + BSA", "untreated"), include=FALSE)
#
# Split geninvitro data according to the cell type, method, study provider,
# unit of the concentration and the type of the endpoint:
datasub<-SplitData(data.nm=invitrodata, data.control=controldata,
                   id="experimentID", nano="name", dose="concentration",
                   vars=c("celltype", "method","studyprovider",
                   "concentration_unit","endpoint"))

# Example 2:
# Split geninvitro data with DNA STRAND BREAKS as the endpoint, according
# to the cell type, method, study provider, and unit of the concentration:
datasub2<-SplitData(data.nm=invitrodata, data.control=controldata,
                    id="experimentID", nano="name", dose="concentration",
                    end="endpoint", end.cat="DNA STRAND BREAKS",
                    vars=c("celltype","method","studyprovider",
                    "concentration_unit"))

# Example 3:
# Split geninvitro data with DNA STRAND BREAKS as the endpoint and
# concentration measured in ug/cm2, according to the cell type:
datasub3<-SplitData(data.nm=invitrodata, data.control=controldata,
                    id="experimentID", nano="name", dose="concentration",
                    end="endpoint", end.cat="DNA STRAND BREAKS",
                    unit="concentration_unit", unit.cat="ug/cm2",
                    control.opt="same", vars="celltype")
```

SubsetData *Create a subset of data*

Description

This function creates a subset of dataset according to specified criteria.

Usage

```
SubsetData(data, x, x.cat, include = TRUE)
```

Arguments

data	Data, structured in a dataframe
x	Variable(s) used to subset the data
x.cat	Specific criteria (value(s)) of x used to subset the data
include	Include/exclude value specified in x.cat. If include = TRUE (default value), then observations with x = x.cat are selected. If include = FALSE, then observations with value specified in x.cat will be omitted from the subset of the data.

Details

- If there are several variable x used as criteria to subset the data, x.cat can be written as list(... , ...)
- Values in x.cat should be specified in the same order as the x's

Value

This function returns a subset of data

Examples

```
# Create data of NM-400 (Multi-walled carbon nanotubes) from geninvitro dataset
data.sub<-SubsetData(data=geninvitro, x="name",
x.cat="NM-400 (Multi-walled carbon nanotubes)", include = TRUE)

# Create data of NM-400 (Multi-walled carbon nanotubes)
# with DNA STRAND BREAKS as the endpoint from geninvitro dataset
data.sub<-SubsetData(data=geninvitro, x=c("name","endpoint"),
x.cat=list("NM-400 (Multi-walled carbon nanotubes)","DNA STRAND BREAKS"),
include=TRUE)

# Exclude NM-400 (Multi-walled carbon nanotubes) from geninvitro dataset
data.sub<-SubsetData(data=geninvitro, x="name",
x.cat="NM-400 (Multi-walled carbon nanotubes)", include = FALSE)

# Create data of NM-400 (Multi-walled carbon nanotubes)
```

```
# and NM-110 (Zinc Oxide, uncoated) from geninvitro dataset
data.sub<-SubsetData(data=geninvitro, x="name",
x.cat=c("NM-400 (Multi-walled carbon nanotubes)",
"NM-110 (Zinc Oxide, uncoated)"), include = TRUE)

# Create data of NM-400 (Multi-walled carbon nanotubes)
# and NM-110 (Zinc Oxide, uncoated), with DNA STRAND BREAKS as the endpoint
data.sub<-SubsetData(data=geninvitro, x=c("name","endpoint"),
x.cat=list(c("NM-400 (Multi-walled carbon nanotubes)",
"NM-110 (Zinc Oxide, uncoated)"),"DNA STRAND BREAKS"),include = TRUE)

# Create a new dataset containing only control values from geninvitro dataset
controldata<-SubsetData(data=geninvitro, x="name", x.cat=c("control", "Control",
"medium", "medium + BSA", "untreated"))
```

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