Package 'SIMMS'

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Type Package

Title Subnetwork Integration for Multi-Modal Signatures

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License GPL-2

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`SIMMS-package` *SIMMS - Subnetwork Integration for Multi-Modal Signatures*

Description

Algorithms to create prognostic biomarkers using biological networks

Details

Package:	SIMMS
Type:	Package
License:	GPL-2
LazyLoad:	yes

Author(s)

Syed Haider, Michal Grzadkowski & Paul C. Boutros

Examples

```
options("warn" = -1);

# get data directory
```

```
data.directory <- get.program.defaults(networks.database = "test")[["test.data.dir"]];

# initialise params
output.directory  <- tempdir();
data.types <- c("mRNA");
feature.selection.datasets <- c("Breastdata1");
training.datasets <- c("Breastdata1");
validation.datasets <- c("Breastdata2");
feature.selection.p.thresholds <- c(0.5);
feature.selection.p.threshold <- 0.5;
learning.algorithms <- c("backward", "forward", "glm");
top.n.features <- 5;

# compute network HRs for all the subnet features
derive.network.features(
  data.directory = data.directory,
  output.directory = output.directory,
  data.types = data.types,
  feature.selection.datasets = feature.selection.datasets,
  feature.selection.p.thresholds = feature.selection.p.thresholds,
  networks.database = "test"
  );

# preparing training and validation datasets.
# Normalisation & patientwise subnet feature scores
prepare.training.validation.datasets(
  data.directory = data.directory,
  output.directory = output.directory,
  data.types = data.types,
  p.threshold = feature.selection.p.threshold,
  feature.selection.datasets = feature.selection.datasets,
  datasets = unique(c(training.datasets, validation.datasets)),
  networks.database = "test"
  );

# create classifier assessing univariate prognostic power of subnetwork modules (Train and Validate)
create.classifier.univariate(
  data.directory = data.directory,
  output.directory = output.directory,
  feature.selection.datasets = feature.selection.datasets,
  feature.selection.p.threshold = feature.selection.p.threshold,
  training.datasets = training.datasets,
  validation.datasets = validation.datasets,
  top.n.features = top.n.features
  );

# create a multivariate classifier (Train and Validate)
create.classifier.multivariate(
  data.directory = data.directory,
  output.directory = output.directory,
  feature.selection.datasets = feature.selection.datasets,
  feature.selection.p.threshold = feature.selection.p.threshold,
  training.datasets = training.datasets,
```

```
  validation.datasets = validation.datasets,
  learning.algorithms = learning.algorithms,
  top.n.features = top.n.features
  );

# (optional) plot Kaplan-Meier survival curves and perform senstivity analysis
if (FALSE){
  create.survivalplots(
    data.directory = data.directory,
    output.directory = output.directory,
    training.datasets = training.datasets,
    validation.datasets = validation.datasets,
    top.n.features = top.n.features,
    learning.algorithms = learning.algorithms,
    survtime.cutoffs = c(5),
    KM.plotting.fun = "create.KM.plot",
    resolution = 100
    );
  }
```

`calculate.meta.survival` *Fit a meta-analytic Cox proportional hazards model to a single feature*

Description

Takes a meta-analysis data object and fits a Cox proportional hazards model (possibly with adjustment for some specific covariates) by median-dichotomizing patients within each individual dataset.

Usage

```
calculate.meta.survival(
  feature.name,
  expression.data,
  survival.data,
  rounding = 3,
  other.data = NULL,
  data.type.ordinal = FALSE,
  centre.data = "median"
)
```

Arguments

`feature.name`	Character indicate what feature (gene/probe/etc.) should be extracted for analysis
`expression.data`	A list where each component is an expression matrix (patients = columns, genes = rows) for a different dataset

survival.data	A list where each component is an object of class Surv
rounding	How many digits after the decimal place to include
other.data	A list of other covariates to be passed to the Cox model (all elements in this list are used
data.type.ordinal	Logical indicating whether to treat this datatype as ordinal. Defaults to FALSE
centre.data	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'

Value

Returns a vector containing the HR, p-value, n, and 95% confidence limits of the HR (see fit.coxmodel() for details)

Author(s)

Paul C. Boutros

Examples

```
data.directory <- get.program.defaults()[["test.data.dir"]];
data.types <- c("mRNA");
x1 <- load.cancer.datasets(
  datasets.to.load = c('Breastdata1'),
  data.types = data.types,
  data.directory = data.directory
  );
x2 <- calculate.meta.survival(
  feature.name = "1000_at",
  expression.data = x1$all.data[[data.types[1]]],
  survival.data = x1$all.survobj
  );
```

---

calculate.network.coefficients

Calculate Cox statistics for input dataset

Description

Function to compute hazard ratios for the genes in pathway-derived networks, by aggregating input datasets into one training cohort. The hazard ratios are computed for each pair by calculating the HR of each gene independently and as an interaction (i.e. y = HR(A) + HR(B) + HR(A:B)

Usage

```
calculate.network.coefficients(
  data.directory = ".",
  output.directory = ".",
  training.datasets = NULL,
  data.types = c("mRNA"),
  data.types.ordinal = c("cna"),
  centre.data = "median",
  subnets.file.flattened = NULL,
  truncate.survival = 100,
  subset = NULL
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `training.datasets`
`output.directory`	Path to the output folder where intermediate and results files will be saved
`training.datasets`	A vector containing names of training datasets
`data.types`	A vector of molecular datatypes to load. Defaults to c('mRNA')
`data.types.ordinal`	A vector of molecular datatypes to be treated as ordinal. Defaults to c('cna')
`centre.data`	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'
`subnets.file.flattened`	File containing all the binary ineractions derived from pathway-derived networks
`truncate.survival`	A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation
`subset`	A list with a Field and Entry component specifying a subset of patients to be selected whose annotation Field matches Entry

Value

Returns a list of matrices for each of the data types. Matrices contain nodes HR/P, edges HR and edges P.

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
options("warn" = -1);
program.data <- get.program.defaults(networks.database = "test");
data.directory <- program.data[["test.data.dir"]];
subnets.file.flattened <- program.data[["subnets.file.flattened"]];
output.directory = tempdir();
coef.nodes.edges <- calculate.network.coefficients(
  data.directory = data.directory,
  output.directory = output.directory,
  training.datasets = c("Breastdata1"),
  data.types = c("mRNA"),
  subnets.file.flattened = subnets.file.flattened
  );
```

---

calculate.sensitivity.stats

Computes sensitivity measures

Description

Computes sensitivity measures: TP, FP, TN, FN, Sensitivity, Specificity, Accuracy

Usage

```
calculate.sensitivity.stats(all.data = NULL)
```

Arguments

`all.data`	A data matrix containing predicted and real risk groups

Value

A vector containing TP, FP, TN, FN, Sensitivity, Specificity, Accuracy

Author(s)

Syed Haider

centre.scale.dataset *Centre and scale a data matrix*

Description

Centre and scale a data matrix. Scaling is done on each column separately

Usage

```
centre.scale.dataset(x = NULL, centre.data = "median")
```

Arguments

x	A sample by feature data matrix
centre.data	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'

Value

A centred and scaled data matrix

Author(s)

Syed Haider

Examples

```
tmp <- matrix(data = rnorm(100, 10, 2), nrow = 20);
tmp.scaled.median <- centre.scale.dataset(x = tmp);
tmp.scaled.mean <- centre.scale.dataset(x = tmp, centre.data = "mean");
tmp.scaled.custom <- centre.scale.dataset(x = tmp, centre.data = 0.3);
```

create.classifier.multivariate *Trains and tests a multivariate survival model*

Description

Trains a model on training datasets. Predicts the risk score for all the training & datasets, independently. This function also predicts the risk score for combined training datasets cohort and validation datasets cohort. The risk score estimation is done by multivariate models fit by `fit.survivalmodel`. The function also predicts risk scores for each of the `top.n.features` independently.

Usage

```
create.classifier.multivariate(
  data.directory = ".",
  output.directory = ".",
  feature.selection.datasets = NULL,
  feature.selection.p.threshold = 0.05,
  training.datasets = NULL,
  validation.datasets = NULL,
  top.n.features = 25,
  models = c("1", "2", "3"),
  learning.algorithms = c("backward", "forward"),
  alpha.glm = c(1),
  k.fold.glm = 10,
  seed.value = 51214,
  cores.glm = 1,
  rf.ntree = 1000,
  rf.mtry = NULL,
  rf.nodesize = 15,
  rf.samptype = "swor",
  rf.sampsize = function(x) {     x * 0.66 },
  ...
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `feature.selection.datasets`, `training.datasets`, `validation.datasets`
`output.directory`	Path to the output folder where intermediate and results files will be saved
`feature.selection.datasets`	A vector containing names of datasets used for feature selection in function `derive.network.features()`
`feature.selection.p.threshold`	One of the P values that were used for feature selection in function `derive.network.features()`. This function does not support vector of P values as used in `derive.network.features()` for performance reasons
`training.datasets`	A vector containing names of training datasets
`validation.datasets`	A vector containing names of validation datasets
`top.n.features`	A numeric value specifying how many top ranked features will be used for univariate survival modelling
`models`	A character vector specifying which of the models ('1' = N+E, '2' = N, '3' = E) to run
`learning.algorithms`	A character vector specifying which learning algorithm to be used for model fitting and feature selection. Defaults to c('backward', 'forward'). Available options are: c('backward', 'forward', 'glm', 'randomforest')

alpha.glm	A numeric vector specifying elastic-net mixing parameter alpha, with range alpha raning from [0,1]. 1 for LASSO (default) and 0 for ridge. For multiple values of alpha, most optimal value is selected through cross validation on training set
k.fold.glm	A numeric value specifying k-fold cross validation if glm was chosen in learning.algorithms
seed.value	A numeric value specifying seed for glm k-fold cross or random forest validation if glm was chosen in learning.algorithms
cores.glm	An integer value specifying number of cores to be used for glm if it was chosen in learning.algorithms
rf.ntree	An integer value specifying the number of trees in random forest. Defaults to 1000. This should be tuned after starting with a large forest such as 1000 in the initial run and assessing the results in output\/OOB_error__TRAINING_* to see where the OOB error rate stablises, and then rerunning with the stablised rf.ntree parameter
rf.mtry	An integer value specifying the number of variables randomly selected for splitting a node. Defaults to sqrt(features), which is the same as in the underlying R package random survival forest randomForestSRC::rfsrc
rf.nodesize	An integer value specifying number of unique cases in a terminal node. Defaults to 15, which is the same as in the underlying R package random survival forest randomForestSRC::rfsrc
rf.samptype	An character string specifying name of sampling. Defaults to sampling without replacement 'swor'. Available options are: c('swor', 'swr')
rf.sampsize	A function specifying sampling size when rf.samptype is set to sampling without replacement ('swor'). Defaults to 66%: function(x){x * .66}
...	other params to be passed on to the random forest call to the underlying R package random survival forest randomForestSRC::rfsrc

Value

The output files are stored under output.directory/output/

Author(s)

Syed Haider & Vincent Stimper

Examples

```
# see package's main documentation
```

`create.classifier.univariate` *Trains and tests a univariate (per subnetwork module) survival model*

Description

Trains a model on training datasets. Predicts the risk score for all the training & datasets, independently. This function also predicts the risk score for combined training datasets cohort and validation datasets cohort. The risk score estimation is done by multivariate models fit by `fit.survivalmodel`. The function also predicts risk scores for each of the `top.n.features` independently.

Usage

```
create.classifier.univariate(
  data.directory = ".",
  output.directory = ".",
  feature.selection.datasets = NULL,
  feature.selection.p.threshold = 0.05,
  training.datasets = NULL,
  validation.datasets = NULL,
  top.n.features = 25,
  models = c("1", "2", "3")
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `feature.selection.datasets`, `training.datasets`, `validation.datasets`
`output.directory`	Path to the output folder where intermediate and results files will be saved
`feature.selection.datasets`	A vector containing names of datasets used for feature selection in function `derive.network.features()`
`feature.selection.p.threshold`	One of the P values that were used for feature selection in function `derive.network.features()`. This function does not support vector of P values as used in `derive.network.features()` for performance reasons
`training.datasets`	A vector containing names of training datasets
`validation.datasets`	A vector containing names of validation datasets
`top.n.features`	A numeric value specifying how many top ranked features will be used for univariate survival modelling
`models`	A character vector specifying which of the models ('1' = N+E, '2' = N, '3' = E) to run

Value

The output files are stored under `output.directory`/output/

Author(s)

Syed Haider

Examples

```
# see package's main documentation
```

`create.KM.plot` *Plots Kaplan-meier survival curve for a given risk grouping & survival params*

Description

A generic method to plot KM curves

Usage

```
create.KM.plot(
  riskgroup = NULL,
  survtime = NULL,
  survstat = NULL,
  file.name = NULL,
  main.title = "",
  resolution = 100
)
```

Arguments

`riskgroup`	A vector containing dichotomized risk groups
`survtime`	A vector containing survival time of the samples
`survstat`	A vector containing survival status of the samples
`file.name`	A string containing full qualified path of the output tiff file
`main.title`	A string specifying main title of the image
`resolution`	A numeric value specifying resolution of the tiff image of KM survival curves. Defaults to 100

Value

The KM survival curves are stored under `output.dir`/graphs/

Author(s)

Syed Haider

`create.sensitivity.plot` *Plots sensitivity analysis for class label dichotomization at supplied survtime cutoffs*

Description

A method to computer sensitivity, specificity and accuracy at all the survtime cutoff steps provided

Usage

```
create.sensitivity.plot(
  riskscore = NULL,
  riskgroup = NULL,
  survtime = NULL,
  survstat = NULL,
  survtime.cutoffs = c(seq(5, 10, 1)),
  output.directory = ".",
  file.stem = NULL,
  main.title = "",
  resolution = 100
)
```

Arguments

`riskscore`	A vector containing predicted risk scores
`riskgroup`	A vector containing dichotomized risk groups
`survtime`	A vector containing survival time of the samples
`survstat`	A vector containing survival status of the samples
`survtime.cutoffs`	A vector containing cutoff time points used to dichotomize patients into low- and high-risk groups
`output.directory`	Path to the output folder where intermediate and results files will be saved
`file.stem`	A string containing base name for image and text files produced by this method
`main.title`	A string specifying main title of the image
`resolution`	A numeric value specifying resolution of the tiff image of KM survival curves. Defaults to 100

Value

The sensitivity analysis plots are stored under `output.directory`/graphs/. The sensitivity analysis results are stored under `output.directory`/output/

Author(s)

Syed Haider

`create.survivalplots` *Plots Kaplan-meier survival curves*

Description

Plots Kaplan-meier survival curves for all the training & datasets, independently as well as combined training datasets cohort and validation datasets cohort. The function also plots KM survival curves for each of the `top.n.features` independently.

Usage

```
create.survivalplots(
  data.directory = ".",
  output.directory = ".",
  training.datasets = NULL,
  validation.datasets = NULL,
  top.n.features = 25,
  learning.algorithms = c("backward", "forward"),
  truncate.survival = 100,
  survtime.cutoffs = c(seq(5, 10, 1)),
  main.title = FALSE,
  KM.plotting.fun = "create.KM.plot",
  plot.univariate.data = FALSE,
  plot.multivariate.data = TRUE,
  resolution = 100
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `training.datasets`, `validation.datasets`
`output.directory`	Path to the output folder where intermediate and results files were saved
`training.datasets`	A vector containing names of training datasets
`validation.datasets`	A vector containing names of validation datasets
`top.n.features`	A numeric value specifying how many top ranked features will be used for univariate survival modelling
`learning.algorithms`	A character vector specifying which learning algorithm to be used for model fitting and feature selection. Defaults to c('backward', 'forward'). Available options are: c('backward', 'forward', 'glm', 'randomforest')

`truncate.survival`
: A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation

`survtime.cutoffs`
: A vector containing survival cutoff time points to be used for dichotomization of patients into risk groups for senstivity analysis

`main.title`
: A logical to specify plot's main title. Defaults to FASLE

`KM.plotting.fun`
: A string containing the name of the method to use for plotting KM curves. Defaults to `create.KM.plot`

`plot.univariate.data`
: Logical to indicate whether to plot univariate results for all subnetworks. Default to FALSE

`plot.multivariate.data`
: Logical to indicate whether to plot multivariate results for all subnetworks. Defaults to TRUE

`resolution`
: A numeric value specifying resolution of the png images of KM survival curves. Defaults to 100

Value

The KM survival curves are stored under `output.directory`/graphs/

Author(s)

Syed Haider

Examples

```
# see package's main documentation
```

`create.survobj` *Utility function for loading meta-analysis lists*

Description

Create Surv objects from an annotation-matrix with handling for different time units.

Usage

```
create.survobj(annotation = NULL, truncate.survival = 100)
```

Arguments

annotation	A patient annotation matrix (patients = rows) with (at least) columns for survtime, survstat, and survtime.unit
truncate.survival	A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation

Value

Returns an object of class Surv

Author(s)

Paul C. Boutros

Examples

```
annotation.file <- paste(
  get.program.defaults()[["test.data.dir"]],
  "/Breastdata2/patient_annotation.txt", sep = ""
  );
annotation <- read.table(
  annotation.file,
  header = TRUE,
  row.names = 1,
  sep = "\t"
  );

# select the appropriate survtime and survstat variable for this dataset
annotation$survstat      <- annotation[,'e.dfs'];
annotation$survtime      <- annotation[,'t.dfs'];
annotation$survtime.unit <- annotation[,'t.dfs.unit'];

# only keep samples with survival data
annotation <- annotation[!is.na(annotation$survstat) & !is.na(annotation$survstat),];

surv.obj <- create.survobj(annotation = annotation);
```

---

derive.network.features

Derive univariate features from pathway-derived networks

Description

This function fits Cox model to features as well as interaction between features. The coefficients of features are subsequently used to compute impact score of each of the pathway-derived networks.

Usage

```
derive.network.features(
  data.directory = ".",
  output.directory = ".",
  data.types = c("mRNA"),
  data.types.ordinal = c("cna"),
  centre.data = "median",
  feature.selection.fun = "calculate.network.coefficients",
  feature.selection.datasets = NULL,
  feature.selection.p.thresholds = c(0.05),
  truncate.survival = 100,
  networks.database = "default",
  subset = NULL,
  ...
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `feature.selection.datasets`
`output.directory`	Path to the output folder where intermediate and results files will be saved
`data.types`	A vector of molecular datatypes to load. Defaults to c('mRNA')
`data.types.ordinal`	A vector of molecular datatypes to be treated as ordinal. Defaults to c('cna')
`centre.data`	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'
`feature.selection.fun`	Name of the function to be used to estimate network coefficients. Defaults to 'calculate.network.coefficients'
`feature.selection.datasets`	A vector containing names of training datasets to be used to compute cox statistics
`feature.selection.p.thresholds`	A vector containing P values to be used as threshold for including features into overall impact score of a network
`truncate.survival`	A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation
`networks.database`	Name of the pathway networks database. Default to NCI PID/Reactome/Biocarta i-e "default"
`subset`	A list with a Field and Entry component specifying a subset of patients to be selected from each dataset whose annotation Field matches Entry

... other params to be passed on to user-defined method for estimating coefficients of network features

Value

The output files are stored under `data.directory`/output/

Author(s)

Syed Haider

Examples

```
options("warn" = -1);

# get data directory
data.directory <- get.program.defaults(networks.database = "test")[["test.data.dir"]];

# initialise params
output.directory <- tempdir();
data.types <- c("mRNA");
feature.selection.datasets <- c("Breastdata1");
feature.selection.p.thresholds <- c(0.05);

# estimate network coefficients for all the subnet features
derive.network.features(
  data.directory = data.directory,
  output.directory = output.directory,
  data.types = data.types,
  feature.selection.fun = "calculate.network.coefficients",
  feature.selection.datasets = feature.selection.datasets,
  feature.selection.p.thresholds = feature.selection.p.thresholds,
  networks.database = "test"
  );
```

`dichotomize.dataset` *Dichotomize a single dataset*

Description

Split a dataset into two groups by median-dichotomization

Usage

```
dichotomize.dataset(x, split.at = "median")
```

Arguments

x	A vector of values to be dichotomized
split.at	An character string or a numeric value that is be used to dichotomize. Valid values are: 'median', 'mean', or a user defined numeric threshold. Defaults to 'median'

Value

A vector of the data dichotomized onto a 0/1 (low/high) scale.

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
tmp <- rnorm(100);
tmp.groups.median <- dichotomize.dataset(tmp);
tmp.groups.mean <- dichotomize.dataset(tmp, split.at = "mean");
tmp.groups.custom <- dichotomize.dataset(tmp, split.at = 0.3);
```

---

dichotomize.meta.dataset

Dichotomize and unlist a meta-analysis list

Description

Takes a meta-analysis list (and possibly extra data) and dichotomizes based on a specific gene, then returns the unlisted data to the caller.

Usage

```
dichotomize.meta.dataset(
  feature.name,
  expression.data,
  survival.data,
  other.data = NULL,
  data.type.ordinal = FALSE,
  centre.data = "median"
)
```

Arguments

feature.name	Character indicate what feature (gene/probe/etc.) should be extracted for analysis
expression.data	A list where each component is an expression matrix (patients = columns, genes = rows) for a different dataset
survival.data	A list where each component is an object of class Surv
other.data	A list of other covariates to be unlisted in the final output (all elements in this list are used)
data.type.ordinal	Logical indicating whether to treat this datatype as ordinal. Defaults to FALSE
centre.data	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'

Details

NB: other.data handling of missing components (i.e. those present in only some datasets) has not been debugged (but may work regardless).

Value

Returns a list containing components groups (after dichotomization), survtime (in the units of the input data), and survstat. Additional vectors are unlisted from other.data if that parameter is not NULL.

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
data.directory <- get.program.defaults()[["test.data.dir"]];
data.types <- c("mRNA");
x1 <- load.cancer.datasets(
  datasets.to.load = c('Breastdata1'),
  data.types = data.types,
  data.directory = data.directory
  );
x2 <- dichotomize.meta.dataset(
  feature.name = "1000_at",
  expression.data = x1$all.data[[data.types[1]]],
  survival.data = x1$all.survobj
  );
```

`fit.coxmodel` *Fit a Cox proportional hazards model*

Description

Fit a Cox model (possibly with some linear adjustments) and return key statistics about the fit.

Usage

```
fit.coxmodel(
  groups,
  survobj,
  stages = NA,
  rounding = 3,
  other.data = NULL,
  data.type.ordinal = FALSE
)
```

Arguments

`groups`	Grouping of patients (passed directly to coxph, so factors & continuous variables are okay)
`survobj`	An object of class Surv (from the survival package) – patient ordering needs to be identical as for groups
`stages`	DEPRECATED! Use other.data instead.
`rounding`	How many digits of precision should be returned?
`other.data`	A data-frame (or matrix?) of variables to be controlled in the Cox model. If null, no adjustment is done. No interactions are fit.
`data.type.ordinal`	Logical indicating whether to treat this datatype as ordinal. Defaults to FALSE

Value

A list containing two elements. `cox.stats` containing a vector or matrix: HR, lower 95% CI of HR, upper 95% CI of HR, P-value (for groups), number of samples (total with group assignments, although some may not be included in fit for other reasons so this is an upper-limit). `cox.obj` containing coxph model object

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
survtime <- sample(seq(0.1,10,0.1), 100, replace = TRUE);
survstat <- sample(c(0,1), 100, replace = TRUE);
survobj <- Surv(survtime, survstat);
groups <- sample(c('A','B'), 100, replace = TRUE);
fit.coxmodel(
  groups = as.factor(groups),
  survobj = survobj
  );
```

`fit.interaction.model` *Cox model two features separately and together*

Description

Using a meta-analysis dataset take two features and Cox model them separately and together and extract HRs and p-values.

Usage

```
fit.interaction.model(
  feature1,
  feature2,
  expression.data,
  survival.data,
  data.type.ordinal = FALSE,
  centre.data = "median"
)
```

Arguments

`feature1`	String indicate what feature (gene/probe/etc.) should be extracted for analysis
`feature2`	String indicate what feature (gene/probe/etc.) should be extracted for analysis
`expression.data`	A list where each component is an expression matrix (patients = columns, features = rows) for a different dataset
`survival.data`	A list where each component is an object of class Surv
`data.type.ordinal`	Logical indicating whether to treat this datatype as ordinal. Defaults to FALSE
`centre.data`	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'

Details

The interaction model compares cases where feature1 and feature2 concord (both high or both low) to those where they do not. That is, the model is y = x1 + x2 + (x1 == x2) and not the typical y = x1 + x2 + x1:x2

Value

Returns a vector of six elements containing (HR,P) pairs for feature1, feature2, and the interaction

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
data.dir <- get.program.defaults()[["test.data.dir"]];
data.types <- c("mRNA");
x1 <- load.cancer.datasets(
  datasets.to.load = c('Breastdata1'),
  data.types = data.types,
  data.directory = data.dir
  );
x2 <- fit.interaction.model(
  feature1 = "1000_at",
  feature2 = "2549_at",
  expression.data = x1$all.data[[data.types[1]]],
  survival.data = x1$all.survobj
  );
```

---

fit.survivalmodel *Trains a multivariate survival model*

Description

Trains a multivariate survival model and conducts feature selection using both backward elimination and forward selection, independently. TO BE DEPRECATED AND HAS BEEN REPLACED BY `create.classifier.multivariate`

Usage

```
fit.survivalmodel(
  data.directory = ".",
  output.directory = ".",
  feature.selection.datasets = NULL,
  feature.selection.p.threshold = 0.05,
  training.datasets = NULL,
```

```
  top.n.features = 25,
  models = c("1", "2", "3")
)
```

Arguments

data.directory	Path to the directory containing datasets as specified by feature.selection.datasets, training.datasets
output.directory	Path to the output folder where intermediate and results files will be saved
feature.selection.datasets	A vector containing names of datasets used for feature selection in function derive.network.features()
feature.selection.p.threshold	One of the P values that were used for feature selection in function derive.network.features(). This function does not support vector of P values as used in derive.network.features() for performance reasons
training.datasets	A vector containing names of training datasets to be used to train multivariate survival model
top.n.features	A numeric value specifying how many top ranked features will be used to train the multivariate survival model
models	A character vector specifying which models ('1' = N+E, '2' = N, '3' = E) to run

Value

The output files are stored under output.directory/output/

Author(s)

Syed Haider

See Also

create.classifier.multivariate

Examples

```
# see package's main documentation
```

get.adjacency.matrix *A utility function to convert tab delimited networks file into adjacency matrices*

Description

A utility function to convert tab-delimited networks file into adjacency matrices

Usage

```
get.adjacency.matrix(subnets.file = NULL)
```

Arguments

subnets.file	A tab-delimited file containing networks. New networks start with a new line with '#' at the begining of network name and subsequent lines contain a binary interaction per line

Value

A list of adjacency matrices

Author(s)

Syed Haider

Examples

```
subnets.file <- get.program.defaults()[["subnets.file"]];
all.adjacency.matrices <- get.adjacency.matrix(subnets.file);
```

get.chisq.stats *Applies survdiff function*

Description

Applies survdiff on different prognoses groups and computes Logrank P using chisquare statistics.

Usage

```
get.chisq.stats(groups, survobj)
```

Arguments

groups	Grouping of patients (passed directly to survdiff, so factors & continuous variables are okay)
survobj	An object of class Surv (from the survival package) – patient ordering needs to be identical as for groups

Value

A vector containing: Chisq, degrees of freedom (DOF) and Logrank P-value.

Author(s)

Syed Haider

Examples

```
survtime <- sample(seq(0.1,10,0.1), 100, replace = TRUE);
survstat <- sample(c(0,1), 100, replace = TRUE);
survobj <- Surv(survtime, survstat);
groups <- sample(c('A','B'), 100, replace = TRUE);
get.chisq.stats(
  groups = as.factor(groups),
  survobj = survobj
  );
```

---

get.program.defaults *A utility function to return the inst/ directory of the installed package and other default settings*

Description

A utility function to return the inst/ directory of the installed package to get the test datasets and other program related data contents

Usage

```
get.program.defaults(networks.database = "default")
```

Arguments

networks.database	Name of the pathway networks database. Default to NCI PID/Reactome/Biocarta i-e "default"

Value

Returns a list of paths to the input directories/files where the contents of this package are installed

Author(s)

Syed Haider

Examples

```
program.data <- get.program.defaults();
```

`load.cancer.datasets` *Load all cancer meta-analysis datasets*

Description

Returns a list of lists containing all cancer meta-analysis datasets

Usage

```
load.cancer.datasets(
  tumour.only = TRUE,
  with.survival.only = TRUE,
  truncate.survival = 100,
  datasets.to.load = "all",
  data.types = c("mRNA"),
  datasets.file = "datasets.txt",
  data.directory = ".",
  verbose = FALSE,
  subset = NULL
)
```

Arguments

`tumour.only`	Logical indicating if we should only load tumour samples (TRUE, the default)
`with.survival.only`	Logical indicating if we should only load samples with survival data (TRUE, the default)
`truncate.survival`	A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation
`datasets.to.load`	A vector of datasets to be loaded. If 'all', then all available datasets are loaded
`data.types`	A vector of molecular datatypes to load. Defaults to c('mRNA')
`datasets.file`	A file in data.directory containing a listing of all usable datasets
`data.directory`	A directory containing all data-files to be loaded
`verbose`	Logical indicating whether or not status messages should be given
`subset`	A list with a Field and Entry component specifying a subset of patients to be selected whose annotation Field matches Entry

Value

Returns a meta-analysis list of lists

Author(s)

Syed Haider & Paul C. Boutros

Examples

```
data.dir <- get.program.defaults()[["test.data.dir"]];
x1 <- load.cancer.datasets(
  datasets.to.load = c('Breastdata1'),
  data.types = c("mRNA"),
  data.directory = data.dir
  );
```

---

make.matrix *Utility function used by* get.adjacency.matrix()

Description

Utility function used by get.adjacency.matrix()

Usage

```
make.matrix(vertices, interactions)
```

Arguments

vertices	Comma separated list of nodes
interactions	Comma separated list of edges

Value

Returns adjacency matrix

Author(s)

Syed Haider

Examples

```
x1 <- make.matrix("a,b,c", "a:b,b:c");
```

`pred.survivalmodel` *Apply a multivariate survival model to validation datasets*

Description

Predicts the risk score for all the training & validation datasets, independently. This function also predicts the risk score for combined training datasets cohort and validation datasets cohort. The risk score estimation is done by multivariate models fit by `fit.survivalmodel`. The function also predicts risk scores for each of the `top.n.features` independently. TO BE DEPRECATED AND HAS BEEN REPLACED BY `create.classifier.multivariate`

Usage

```
pred.survivalmodel(
  data.directory = ".",
  output.directory = ".",
  feature.selection.datasets = NULL,
  feature.selection.p.threshold = 0.05,
  training.datasets = NULL,
  validation.datasets = NULL,
  top.n.features = 25,
  models = c("1", "2", "3"),
  write.risk.data = TRUE
)
```

Arguments

`data.directory`	Path to the directory containing datasets as specified by `feature.selection.datasets`, `training.datasets`, `validation.datasets`
`output.directory`	Path to the output folder where intermediate and results files will be saved
`feature.selection.datasets`	A vector containing names of datasets used for feature selection in function `derive.network.features()`
`feature.selection.p.threshold`	One of the P values that were used for feature selection in function `derive.network.features()`. This function does not support vector of P values as used in `derive.network.features()` for performance reasons
`training.datasets`	A vector containing names of training datasets
`validation.datasets`	A vector containing names of validation datasets
`top.n.features`	A numeric value specifying how many top ranked features will be used for univariate survival modelling
`models`	A character vector specifying which of the models ('1' = N+E, '2' = N, '3' = E) to run

write.risk.data
: A toggle to control whether risk scores and patient risk groups should be written to file

Value

The output files are stored under output.directory/output/

Author(s)

Syed Haider

See Also

create.classifier.multivariate

Examples

```
# see package's main documentation
```

---

prepare.training.validation.datasets

Prepare training and validation datasets

Description

Computes per-patient pathway-derived network impact scores across all input datasets, independently

Usage

```
prepare.training.validation.datasets(
  data.directory = ".",
  output.directory = ".",
  data.types = c("mRNA"),
  data.types.ordinal = c("cna"),
  min.ordinal.threshold = c(cna = 3),
  centre.data = "median",
  p.threshold = 0.5,
  feature.selection.datasets = NULL,
  datasets = NULL,
  truncate.survival = 100,
  networks.database = "default",
  write.normed.datasets = TRUE,
  subset = NULL
)
```

Arguments

data.directory	Path to the directory containing datasets as specified by datasets
output.directory	Path to the output folder where intermediate and results files will be saved
data.types	A vector of molecular datatypes to load. Defaults to c('mRNA')
data.types.ordinal	A vector of molecular datatypes to be treated as ordinal. Defaults to c('cna')
min.ordinal.threshold	A named vector specifying minimum percent threshold for each ordinal data type to be used prior to estimating coefficients. Coefficient for features not satisfying minimum threshold will not be estimated, and set to 0. Defaults to cna threshold as 3 percent
centre.data	A character string specifying the centre value to be used for scaling data. Valid values are: 'median', 'mean', or a user defined numeric threshold e.g. '0.3' when modelling methylation beta values. This value is used for both scaling as well as for dichotomising data for estimating univariate betas from Cox model. Defaults to 'median'
p.threshold	Cox P value threshold to be applied for selecting features (e.g. genes) which will contribute to patient risk score estimation. Defaults to 0.5
feature.selection.datasets	A vector containing names of datasets used for feature selection in function derive.network.features()
datasets	A vector containing names of all the datasets to be later used for training and validation purposes
truncate.survival	A numeric value specifying survival truncation in years. Defaults to 100 years which effectively means no truncation
networks.database	Name of the pathway networks database. Default to NCI PID/Reactome/Biocarta i-e "default"
write.normed.datasets	A toggle to control whether processed mRNA and survival data should be written to file
subset	A list with a Field and Entry component specifying a subset of patients to be selected whose annotation Field matches Entry

Value

The output files are stored under output.directory/output/

Author(s)

Syed Haider

Examples

```
# get data directory
data.directory <- get.program.defaults()[["test.data.dir"]];

# initialise params
output.directory <- tempdir();
data.types <- c("mRNA");
feature.selection.datasets <- c("Breastdata1");
training.datasets <- c("Breastdata1");
validation.datasets <- c("Breastdata1", "Breastdata2");

# preparing training and validation datasets.
# Normalisation & patientwise subnet feature scores
prepare.training.validation.datasets(
  data.directory = data.directory,
  output.directory = output.directory,
  data.types =  data.types,
  feature.selection.datasets = feature.selection.datasets,
  datasets = unique(c(training.datasets, validation.datasets)),
  networks.database = "test"
  );
```

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