

Package ‘oppti’

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Type Package

Title Outlier Protein and Phosphosite Target Identifier

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Description

The aim of oppti is to analyze protein (and phosphosite) expressions to find outlying markers for each sample in the given cohort(s) for the discovery of personalized actionable targets.

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Encoding UTF-8

LazyData true

Depends R (>= 3.5)

Imports limma, stats, reshape, ggplot2, grDevices, RColorBrewer, pheatmap, knitr, methods, devtools, parallelDist,

Suggests markdown

VignetteBuilder knitr

URL <https://github.com/Huang-lab/oppti>

BugReports <https://github.com/Huang-lab/oppti/issues>

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| artImpute | <i>Artificially miss and impute each data entry individually by ignoring outlying values</i> |
|-----------|--|

Description

Infers the normal-state expression of a marker based on its co-expression network, i.e., the weighted average of the marker's nearest neighbors in the data. The returned imputed data will later be used to elucidate dysregulated (protruding) events.

Usage

```
artImpute(dat, ku = 6, marker.proc.list = NULL, miss.pstat = 0.4,
  verbose = FALSE)
```

Arguments

| | |
|------------------|---|
| dat | an object of log ₂ -normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| ku | an integer in [1,num.markers], upper bound on the number of nearest neighbors of a marker. |
| marker.proc.list | character array, the row names of the data to be processed/imputed. |
| miss.pstat | the score threshold for ignoring potential outliers during imputation. miss.pstat = 1 ignores values outside of the density box (i.e., 1st-3rd quartiles). The algorithm ignores values lying at least (1/miss.pstat)-1 times IQR away from the box; e.g., use miss.pstat=1 to ignore all values lying outside of the box; use miss.pstat=0.4 to ignore values lying at least 1.5 x IQR away from the box; use miss.pstat=0 to employ all data during imputation. |
| verbose | logical, to show progress of the algorithm. |

Value

the imputed data that putatively represents the expressions of the markers in the (matched) normal states.

Examples

```
dat = setNames(as.data.frame(matrix(1:(5*10),5,10),
row.names = paste('marker',1:5,sep='')), paste('sample',1:10,sep=''))
imputed = artImpute(dat, ku = 2)
```

clusterData

Hierarchical cluster analysis

Description

Displays the hierarchically clustered data by the "pheatmap" package. The numbers of clusters along the markers/samples can be set by the user, then the cluster structures are estimated by pairwise analysis.

Usage

```
clusterData(data, annotation_row = NULL, annotation_col = NULL,
annotation_colors = NULL, main = NA, legend = TRUE,
clustering_distance_rows = "euclidean",
clustering_distance_cols = "euclidean", display_numbers = FALSE,
number_format = "%.0f", num_clusters_row = NULL,
num_clusters_col = NULL, cluster_rows = TRUE, cluster_cols = TRUE,
border_color = "gray60", annotate_new_clusters_col = FALSE,
zero_white = FALSE, color_low = '#006699', color_mid = 'white',
color_high = 'red', color_palette = NULL, show_rownames = FALSE,
show_colnames = FALSE, min_data = min(data, na.rm = TRUE),
max_data = max(data, na.rm = TRUE),
treeheight_row = ifelse(methods::is(cluster_rows, "hclust") ||
cluster_rows, 50, 0), treeheight_col = ifelse(methods::is(cluster_cols,
"hclust") || cluster_cols, 50, 0))
```

Arguments

- | | |
|----------------|---|
| data | an object of log2-normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| annotation_row | data frame that specifies the annotations shown on left side of the heat map. Each row defines the features for a specific row. The rows in the data and in the annotation are matched using corresponding row names. Note that color schemes takes into account if variable is continuous or discrete. |
| annotation_col | similar to annotation_row, but for columns. |

| | |
|--|--|
| <code>annotation_colors</code> | list for specifying <code>annotation_row</code> and <code>annotation_col</code> track colors manually. It is possible to define the colors for only some of the features. |
| <code>main</code> | character string, an overall title for the plot. |
| <code>legend</code> | logical, to determine if legend should be drawn or not. |
| <code>clustering_distance_rows</code> | distance measure used in clustering rows. Possible values are "correlation" for Pearson correlation and all the distances supported by <code>dist</code> , such as "euclidean", etc. If the value is none of the above it is assumed that a distance matrix is provided. |
| <code>clustering_distance_cols</code> | distance measure used in clustering columns. Possible values the same as for <code>clustering_distance_rows</code> . |
| <code>display_numbers</code> | logical, determining if the numeric values are also printed to the cells. If this is a matrix (with same dimensions as original matrix), the contents of the matrix are shown instead of original values. |
| <code>number_format</code> | format strings (C printf style) of the numbers shown in cells. For example "%.2f" shows 2 decimal places and "%.1e" shows exponential notation (see more in <code>sprintf</code>). |
| <code>num_clusters_row</code> | number of clusters the rows are divided into, based on the hierarchical clustering (using <code>cutree</code>), if rows are not clustered, the argument is ignored. |
| <code>num_clusters_col</code> | similar to <code>num_clusters_row</code> , but for columns. |
| <code>cluster_rows</code> | logical, determining if the rows should be clustered; or a <code>hclust</code> object. |
| <code>cluster_cols</code> | similar to <code>cluster_rows</code> , but for columns. |
| <code>border_color</code> | color of cell borders on heatmap, use <code>NA</code> if no border should be drawn. |
| <code>annotate_new_clusters_col</code> | logical, to annotate cluster IDs (column) that will be identified. |
| <code>zero_white</code> | logical, to display 0 values as white in the colormap. |
| <code>color_low</code> | color code for the low intensity values in the colormap. |
| <code>color_mid</code> | color code for the medium intensity values in the colormap. |
| <code>color_high</code> | color code for the high intensity values in the colormap. |
| <code>color_palette</code> | vector of colors used in heatmap. |
| <code>show_rownames</code> | boolean, specifying if row names are be shown. |
| <code>show_colnames</code> | boolean, specifying if column names are be shown. |
| <code>min_data</code> | numeric, data value corresponding to minimum intensity in the <code>color_palette</code> |
| <code>max_data</code> | numeric, data value corresponding to maximum intensity in the <code>color_palette</code> |
| <code>treeheight_row</code> | the height of a tree for rows, if these are clustered. Default value is 50 points. |
| <code>treeheight_col</code> | the height of a tree for columns, if these are clustered. Default value is 50 points. |

Value

tree, the hierarchical tree structure.

cluster_IDs_row, the (row) cluster identities of the markers.

cluster_IDs_col, the (column) cluster identities of the samples.

Examples

```
set.seed(1)
dat = setNames(as.data.frame(matrix(runif(10*10),10,10)),
row.names = paste('marker',1:10,sep=''), paste('sample',1:10,sep=''))
result = clusterData(dat)
```

dropMarkers

Filter out markers

Description

Filters out markers based on the percentage of missing values, low-expression and low-variability rates.

Usage

```
dropMarkers(dat, percent_NA = 0.2, low_mean_and_std = 0.05,
q_low_var = 0.25, force_drop = NULL)
```

Arguments

| | |
|------------------|---|
| dat | an object of log2-normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| percent_NA | a constant in [0,1], the percentage of missing values that will be tolerated in the filtered data. |
| low_mean_and_std | a constant in [0,inf], the lower-bound of the mean or standard deviation of a marker in the filtered data. |
| q_low_var | a constant in [0,1], the quantile of marker variances which serves as a lower-bound of the marker variances in the filtered data. |
| force_drop | character array containing the marker names that user specifically wants to filter out. |

Value

filtered data with the same format as the input data.

the row names (markers) of the data that are filtered out due to low-expression or low-variability.

Examples

```

dat = setNames(as.data.frame(matrix(1:(5*10),5,10),
row.names = paste('marker',1:5,sep='')), paste('sample',1:10,sep=''))
dat[1,1:2] = NA # marker1 have 20% missing values
dropMarkers(dat, percent_NA = .2) # marker1 is filtered out

```

dysReg

Analyze dysregulated (protruding) events

Description

For each marker processed, draws a scatter plot of matching values of observed vs imputed expressions.

Usage

```
dysReg(dat, dat.imp, marker.proc.list = NULL, verbose = FALSE)
```

Arguments

| | |
|------------------|---|
| dat | an object of log ₂ -normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| dat.imp | the imputed data that putatively represents the expressions of the markers in the (matched) normal states. |
| marker.proc.list | character array, the row names of the data to be processed for dysregulation. |
| verbose | logical, to show progress of the algorithm |

Value

samples' distances to regression line (i.e., dysregulation) on the scatter plots.
the scatter plots.

Examples

```

dat = setNames(as.data.frame(matrix(1:(5*10),5,10),
row.names = paste('marker',1:5,sep='')), paste('sample',1:10,sep=''))
dat.imp = artImpute(dat, ku=2)
result = dysReg(dat, dat.imp)

```

markOut *Display outlying expressions*

Description

Mark outlying expressions on the scatter plot of a given marker

Usage

```
markOut(dat, dat.imp, dat.imp.test, dat.dys, dys.sig.thr.upp,
marker.proc.list = NULL, dataset = "", num.omit.fit = NULL,
draw.sc = TRUE, draw.vi = TRUE, conf.int = 0.95,
ylab = "Observed", xlab = "Inferred")
```

Arguments

| | |
|------------------|--|
| dat | an object of log ₂ -normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| dat.imp | the imputed data that putatively represents the expressions of the markers in the (matched) normal states. |
| dat.imp.test | marker's p-value of the statistical significance between its observed vs imputed values computed by the Kolmogorov-Smirnov test. |
| dat.dys | samples' distances to regression line (i.e., dysregulation) on the scatter plots. |
| dys.sig.thr.upp | the dysregulation score threshold to elucidate/mark significantly dysregulated outlier events. |
| marker.proc.list | character array, the row names of the data to be processed for outlier analyses and for plotting. |
| dataset | the cohort name to be used in the output files. |
| num.omit.fit | number of outlying events to ignore when fitting a marker's observed expressions to the imputed ones. |
| draw.sc | logical, to draw a scatter plot for every marker in marker.proc.list in a separate PDF file. |
| draw.vi | logical, to draw a violin plot for every marker in marker.proc.list in a separate PDF file. |
| conf.int | confidence interval to display around the regression line |
| ylab | a title for the y axis |
| xlab | a title for the x axis |

Value

the scatter plots of the markers where the outlier dysregulation events are highlighted by red mark.

Examples

```
set.seed(1)
dat = setNames(as.data.frame(matrix(runif(10*10),10,10),
row.names = paste('marker',1:10,sep=' '), paste('sample',1:10,sep=' ')))
dat.imp = artImpute(dat, ku=6)
dat.imp.test = statTest(dat, dat.imp)[[1]]
dat.dys = dysReg(dat, dat.imp)[[1]]
plots = markOut(dat, dat.imp, dat.imp.test, dat.dys, dys.sig.thr.upp = .25)
```

oppti

Outlier protein and phosphosite target identification

Description

Find outlying markers and events across cancer types.

Usage

```
oppti(data, mad.norm = FALSE, cohort.names = NULL, panel = "global",
panel.markers = NULL, tol.nas = 20, ku = 6, miss.pstat = 0.4,
demo.panels = FALSE, save.data = FALSE, draw.sc.plots = FALSE,
draw.vi.plots = FALSE, draw.sc.markers = NULL,
draw.ou.plots = FALSE, draw.ou.markers = NULL, verbose = FALSE)
```

Arguments

| | |
|----------------------------|---|
| <code>data</code> | a list object where each element contains a proteomics data for a different cohort (markers in the rows, samples in the columns) or a character string defining the path to such data (in .RDS format). |
| <code>mad.norm</code> | logical, to normalize the proteomes to have a unit Median Absolute Deviation. |
| <code>cohort.names</code> | character array. |
| <code>panel</code> | a character string describing marker panel, e.g., 'kinases'. Use 'global' to analyze all markers quantified across cohorts (default). Use 'pancan' to analyze the markers commonly quantified across the cohorts. |
| <code>panel.markers</code> | a character array containing the set of marker names that user wants to analyze, e.g., <code>panel.markers = c("AAK1", "AATK", "ABL1", "ABL2", ...)</code> . |
| <code>tol.nas</code> | a constant in [0,100], tolerance for the percentage of NAs in a marker, e.g., <code>tol.nas = 20</code> will filter out markers containing 20% or more NAs across samples. |
| <code>ku</code> | an integer in [1,num.markers], upper bound on the number of nearest neighbors of a marker. |
| <code>miss.pstat</code> | a constant in [0,1], statistic to estimate potential outliers. See 'artImpute()'. |
| <code>demo.panels</code> | logical, to draw demographics of the panel in each cohort. |
| <code>save.data</code> | logical, to save intermediate data (background inference and dysregulation measures). |

| | |
|-----------------|---|
| draw.sc.plots | logical, to draw each marker's qqplot of observed vs inferred (imputed) expressions. |
| draw.vi.plots | logical, to draw each marker's violin plot of observed vs imputed expressions. |
| draw.sc.markers | character array, marker list to draw scatter plots |
| draw.ou.plots | logical, to draw each marker's outlier prevalence (by the percentage of outlying samples) across the cohorts. |
| draw.ou.markers | character array, marker list to draw pan-cancer outlier percentage plots |
| verbose | logical, to show progress of the algorithm. |

Value

dysregulation scores of every marker for each sample.

the imputed data that putatively represents the expressions of the markers in the (matched) normal states.

the result of Kolmogorov-Smirnov tests that evaluates the statistical significance of each marker's outlier samples.

a data list containing, for each cohort, the percentage of outlier samples for every marker.

a data list containing, for each cohort, the outlier significance threshold.

See Also

[artImpute()] for how to set 'miss.pstat' and 'ku'

Examples

```
set.seed(1)
dat = setNames(as.data.frame(matrix(runif(10*10),10,10),
row.names = paste('marker',1:10,sep='')), paste('sample',1:10,sep=''))
result = oppti(dat)
```

| | |
|-----------|----------------------------------|
| outScores | <i>Analyze putative outliers</i> |
|-----------|----------------------------------|

Description

Calculates a statistical measure of each data entry being a putative outlier

Usage

```
outScores(dat)
```

Arguments

dat an object of log2-normalized protein (or gene) expressions, containing markers in rows and samples in columns.

Value

outlier p-statistics

Examples

```
dat = setNames(as.data.frame(matrix(1:(5*10),5,10),
row.names = paste('marker',1:5,sep='')), paste('sample',1:10,sep=''))
result = outScores(dat)
```

plotDen

Draw densities

Description

Draw column densities of an object over multiple plots by using `limma::plotDensities()` function.

Usage

```
plotDen(dat, name = "", per.plot = 8, main = NULL, group = NULL,
legend = TRUE)
```

Arguments

| | |
|-----------------------|--|
| <code>dat</code> | an object of log2-normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| <code>name</code> | name tag for the output file. |
| <code>per.plot</code> | number of densities to be drawn on a single plot. If NULL, <code>ncol(object)</code> will be used. |
| <code>main</code> | character string, an overall title for the plot. |
| <code>group</code> | vector or factor classifying the arrays into groups. Should be same length as <code>ncol(object)</code> . |
| <code>legend</code> | character string giving position to place legend. See ‘legend’ for possible values. Can also be logical, with FALSE meaning no legend. |

Value

pdf plot(s).

Examples

```
dat = setNames(as.data.frame(matrix(1:(5*10),5,10),
row.names = paste('marker',1:5,sep='')), paste('sample',1:10,sep=''))
plotDen(dat, name = 'myresults')
```

| | |
|------------|--|
| rankPerOut | <i>Rank markers by the percentage of outlying events</i> |
|------------|--|

Description

Ranks markers in the order of decreasing percentage of outlying events.

Usage

```
rankPerOut(dat.dys, marker.proc.list = NULL, dys.sig.thr.upp)
```

Arguments

`dat.dys` samples' distances to regression line (i.e., dysregulation) on the scatter plots.
`marker.proc.list` character array, the row names of the data to be processed for outlier analyses.
`dys.sig.thr.upp` the dysregulation score threshold to elucidate/mark significantly dysregulated outlier events.

Value

markers rank-ordered by the percentage of outliers over the samples.
the percentages of outliers corresponding to ranked markers.

Examples

```
set.seed(1)
dat = setNames(as.data.frame(matrix(runif(10*10),10,10),
row.names = paste('marker',1:10,sep='')), paste('sample',1:10,sep=''))
dat.imp = artImpute(dat, ku=6)
dat.dys = dysReg(dat, dat.imp)[[1]]
result = rankPerOut(dat.dys, dys.sig.thr.upp = .25)
```

| | |
|----------|---|
| statTest | <i>Analyze dysregulation significance</i> |
|----------|---|

Description

Rank-order markers by the significance of deviation of the observed expressions from the (matched) imputed expressions based on the Kolmogorov-Smirnov (KS) test.

Usage

```
statTest(dat, dat.imp, marker.proc.list = NULL, pval.insig = 0.2)
```

Arguments

| | |
|-------------------------------|---|
| <code>dat</code> | an object of log ₂ -normalized protein (or gene) expressions, containing markers in rows and samples in columns. |
| <code>dat.imp</code> | the imputed data that putatively represents the expressions of the markers in the (matched) normal states. |
| <code>marker.proc.list</code> | character array, the row names of the data to be processed for dysregulation significance. |
| <code>pval.insig</code> | p-value threshold to determine spurious (null) dysregulation events. |

Value

each marker's p-value of the statistical significance between its observed vs imputed values computed by the KS test.

ranked p-values (KS test) of the significant markers, which are lower than `pval.insig`.

ranked significantly dysregulated markers with p-values lower than `pval.insig`.

ranked p-values (KS test) of the insignificant markers, which are greater than `pval.insig`.

ranked insignificantly dysregulated markers (spurious dysregulations) with p-values greater than `pval.insig`.

Examples

```
set.seed(1)
dat = setNames(as.data.frame(matrix(runif(10*10),10,10),
row.names = paste('marker',1:10,sep='')), paste('sample',1:10,sep=''))
dat.imp = artImpute(dat, ku=6)
result = statTest(dat, dat.imp) # the dysregulations on marker4 is
# statistically significant with p-value 0.05244755.
```

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