

# Package ‘adSplit’

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**Title** Annotation-Driven Clustering

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**Description** This package implements clustering of microarray gene expression profiles according to functional annotations. For each term genes are annotated to, splits into two subclasses are computed and a significance of the supporting gene set is determined.

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**Depends** R (>= 2.1.0), methods (>= 2.1.0)

**Imports** AnnotationDbi, Biobase (>= 1.5.12), cluster (>= 1.9.1), GO.db (>= 1.8.1), graphics, grDevices, KEGGREST (>= 1.30.1), multtest (>= 1.6.0), stats (>= 2.1.0)

**Suggests** golubEsets (>= 1.0), vsn (>= 1.5.0), hu6800.db (>= 1.8.1)

**LazyLoad** yes

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**License** GPL (>= 2)

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|         |                                 |
|---------|---------------------------------|
| adSplit | <i>Annotation-Driven Splits</i> |
|---------|---------------------------------|

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## Description

This function searches for annotation-driven splits of patients in microarray data. A split is a partitioning of patients into two groups. In order to do so it refers to GO terms and KEGG pathways. In addition, a significance measure can be computed by simulating a random distribution of scores. DLD-scores are used to judge the quality of a split.

## Usage

```
adSplit(mydata, annotation.ids, chip.name,
        min.probes = 20, max.probes = NULL,
        B = NULL, min.group.size = 5, ngenes = 50,
        ignore.genes = 5)
```

## Arguments

|                |                                                                                                                                                                                                                              |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| mydata         | either an expression set as defined by the package Biobase or a matrix of expression levels (rows=genes, columns=samples).                                                                                                   |
| annotation.ids | a vector of GO or KEGG identifiers in the form "GO:..." or "KEGG:..." respectively. The prefix "KEGG:" is removed from the KEGG-identifiers before accessing the chip's "...PATH2PROBES" hash.                               |
| chip.name      | the name of the chip by which the expression set is measured. adSplit attempts to load a library of the same name and expects to find a hash called "<chip-name>GO2ALLPROBES" and one called "<chip-name>PATH2PROBES" there. |
| min.probes     | annotation identifiers with fewer than this associated genes are skipped.                                                                                                                                                    |
| max.probes     | annotation identifiers with more than this associated genes are skipped. The default is ten percent of the genes on the chip.                                                                                                |

|                |                                                                                                                                                                   |
|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| B              | the number of random gene set samplings to be performed to compute empirical p-values.                                                                            |
| min.group.size | filter criteria to avoid splits suggesting tiny groups. Splits where one of the two suggested groups are smaller than this number are removed from the split set. |
| ngenes         | number of genes used to compute DLD scores.                                                                                                                       |
| ignore.genes   | number of best scoring genes to be ignored when computing DLD scores.                                                                                             |

### Details

This function applies the same splitting procedure to all annotation identifiers provided. Firstly, the associated genes for one identifier are determined and extracted from the expression data. Then the `diana2means` function is applied to the restricted data and the different splits generated are collected into a single `splitSet` object.

As annotation identifiers vectors of identifiers of the KEGG: nnnnn and GO: nnnnnn are valid. In addition, the keywords "KEGG", "GO" and "all" are allowed, representing all terms in the corresponding ontology.

If B is set to a integer number this number of samplings are used to generate a null-distribution of DLD-scores. This distribution is used to compute empirical p-values for each split. If more than one valid split is found, multiple testing is corrected for by applying Benjamini-Hochbergs correction from the `multtest` package.

### Value

Returns an object of class `splitSet` with the following list elements:

|        |                                                                                                                                                                        |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| cuts   | a matrix of split attributions. One row per annotation identifier (GO term or KEGG pathway for which a split has been generated. One column per object in the dataset. |
| score  | one score per generated split.                                                                                                                                         |
| pvalue | one empirical p-value per generated split, or NULL                                                                                                                     |
| qvalue | one q-value computed according Benjamini-Hochberg's correction for multiple testing per generated split, or NULL                                                       |

### Author(s)

Claudio Lottaz, Joern Toedling

### See Also

[diana2means](#), [randomDiana2means](#), [image.splitSet](#)

### Examples

```
# prepare data
library(golubEsets)
data(Golub_Merge)

# generate annotation-driven splits for apoptosis and signal transduction
```

```

x <- adSplit(Golub_Merge, "GO:0006915", "hu6800")
x <- adSplit(Golub_Merge, c("GO:0007165", "GO:0006915"), "hu6800", max.probes=7000)

# generate a split for alanine, aspartate and glutamate metabolism including
# an empirical p-value
x <- adSplit(Golub_Merge, "KEGG:00250", "hu6800", B=100)

# generate splits for all KEGG pathways.
x <- adSplit(Golub_Merge, "KEGG", "hu6800")
image(x)

```

---

|                  |                                  |
|------------------|----------------------------------|
| adSplit-internal | <i>adSplit Internal Function</i> |
|------------------|----------------------------------|

---

### Description

Function for internal use only.

### Details

No details given. This function is subject to change without further notice.

### Author(s)

Claudio Lottaz

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|             |                                                 |
|-------------|-------------------------------------------------|
| diana2means | <i>2-Means with Hierarchical Initialization</i> |
|-------------|-------------------------------------------------|

---

### Description

Split a set of data points into two coherent groups using the k-means algorithm. Instead of random initialization, divisive hierarchical clustering is used to determine initial groups and the corresponding centroids.

### Usage

```

diana2means(mydata, mingroupsize = 5,
             ngenes = 50, ignore.genes = 5,
             return.cut = FALSE)

```

### Arguments

|              |                                                                                                                            |
|--------------|----------------------------------------------------------------------------------------------------------------------------|
| mydata       | either an expression set as defined by the package Biobase or a matrix of expression levels (rows=genes, columns=samples). |
| mingroupsize | report only splits where both groups are larger than this size.                                                            |
| ngenes       | number of genes used to compute cluster quality DLD-score.                                                                 |
| ignore.genes | number of best scoring genes to be ignored when computing DLD-scores.                                                      |
| return.cut   | logical, whether to return the attributions of samples to groups.                                                          |

### Details

This function uses divisive hierarchical clustering (diana) to generate a first split of the data. Thereby, each column of the data matrix is considered to represent a data element. From the thus generated tentative groups, centroids are deduced and used to initialize the k-means clustering algorithm.

For the split optimized by k-means the DLD-score is determined using the `ngenes` and `ignore.genes` arguments.

### Value

If the logical `return.cut` is set to `FALSE` (the default), a single number is representing the DLD-score for the generated split is returned. Otherwise an object of class `split` containing the following elements is returned:

|                    |                                                                                              |
|--------------------|----------------------------------------------------------------------------------------------|
| <code>cut</code>   | one number out of 0 and 1 per column in the original data, specifying the split attribution. |
| <code>score</code> | the DLD-score achieved by the split.                                                         |

### Author(s)

Joern Toedling, Claudio Lottaz

### See Also

[diana](#)

### Examples

```
# get golub data
library(vsn)
library(golubEsets)
data(Golub_Merge)

# use 10% most variable genes
e <- exprs(Golub_Merge)
vars <- apply(e, 1, var)
e <- e[vars > quantile(vars,0.9),]

# use diana2means to get splits and scores
diana2means(e)
diana2means(e, return.cut=TRUE)
```

---

drawRandomPS

*Draw sets of probe-sets*

---

### Description

This function draws a given number of probe-sets randomly, such that probe-sets referring to the same are either included or excluded as a whole.

**Usage**

```
drawRandomPS(nps, EID2PSenv, allEIDs)
```

**Arguments**

|           |                                                             |
|-----------|-------------------------------------------------------------|
| nps       | number of probe-sets to be drawn.                           |
| EID2PSenv | a hash mapping EntrezGene to probe-set identifiers.         |
| allEIDs   | vector of all EntrezGene identifiers represented on a chip. |

**Value**

A named vector of probe-set identifiers. The names correspond to the EntrezGene identifiers.

**Author(s)**

Claudio Lottaz

**Examples**

```
# draw ten random probe-sets from hu6800
library(hu6800.db)
EID2PSenv <- makeEID2PROBESenv(hu6800ENTREZID)
drawRandomPS(10, EID2PSenv, ls(EID2PSenv))
```

---

|                 |                          |
|-----------------|--------------------------|
| golubKEGGSplits | <i>Exemplar splitSet</i> |
|-----------------|--------------------------|

---

**Description**

This is a data object precomputed by `adSplit` for illustration.

**Usage**

```
data(golubKEGGSplits)
```

**Format**

Annotation-driven split set holds 70 splits on 72 elements, scores range is: 3.382672 17.31385, empirical p-values range is: 0.005 0.955, q-value range is: 0.1633333 0.955.

**Details**

This object is generated by the following call:

```
golubKEGGSplits <- adSplit(golubNorm, "KEGG", "hu6800", B=1000)
```

where `golubNorm` is a normalized version of `Golub_Merge` from the `golubEsets` package.

**Examples**

```
data(golubKEGGSplits)
```

**Description**

Draws a histogram of empirical p-values and shows the corresponding q-values corrected for multiple testing.

**Usage**

```
## S3 method for class 'splitSet'
hist(x, main = "Distribution of p-Values",
      xlab = "p-values", col = "grey", xlim = c(0, 1), ...)
```

**Arguments**

|      |                                                                       |
|------|-----------------------------------------------------------------------|
| x    | object of type splitSet. Should hold a considerable number of splits. |
| main | main title of the histogram.                                          |
| xlab | legend for the x-axis.                                                |
| col  | color for the histogram bars.                                         |
| xlim | limits for the x-axis (p-values).                                     |
| ...  | further parameters passed on to the default hist function.            |

**Details**

This function draws a regular histogram of empirical p-values observed in the splitSet at hand. The corresponding q-values, corrected by the method suggested by Benjamini-Hochberg, are plotted into the same graph. The scale for the q-values is shown at the left hand side of the plot.

**Author(s)**

Claudio Lottaz

**See Also**

[adSplit](#)

**Examples**

```
data(golubKEGGSplits)
hist(golubKEGGSplits, col="red")
```

---

image.splitSet

*Illustrate Split Sets*


---

### Description

Draws an image of all splits, one per row, of a splitSet object. Each column corresponds to a patient.

### Usage

```
## S3 method for class 'splitSet'
image(x, filter.fdr = 1, main = "", max.label.length = 50,
      full.names = TRUE, xlab = NULL, sample.labels = FALSE,
      col = c("yellow", "red"), invert = FALSE,
      outfile = NULL, res = 72, pointsize = 7, ...)
```

### Arguments

|                  |                                                                                                                                          |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| x                | the object of class splitSet to be illustrated.                                                                                          |
| filter.fdr       | worst acceptable false discovery rate for the shown set of splits. All splits with q-values below this level are dropped from the image. |
| main             | a title for the image.                                                                                                                   |
| max.label.length | Maximal length of the annotations shown to the right of the image. Longer annotations are truncated.                                     |
| full.names       | Show full names for annotations instead of their identifiers only.                                                                       |
| xlab             | additional annotation on the x-axis.                                                                                                     |
| sample.labels    | whether names of samples are to be shown on the x-axis.                                                                                  |
| col              | two strings encoding the colors to be used to illustrate to which group a sample is attributed.                                          |
| invert           | whether to draw in white on black background.                                                                                            |
| outfile          | the filename on which to draw the image in postscript format. The default is NULL, meaning to produce the image interactively.           |
| res              | resolution for bitmap output on postscript.                                                                                              |
| pointsize        | size of font.                                                                                                                            |
| ...              | further arguments passed to image.                                                                                                       |

### Details

The set of splits given is illustrated as an image. Each row corresponds to an annotation, each column to a patient. In position (x,y), the association of patient x to a group with respect to annotation y is coded as colors (yellow and red by default). The image is ordered by hierarchical clustering such that similar patients and similar splits are brought closer together.

**Value**

Always returns NULL.

**Author(s)**

Claudio Lottaz

**See Also**

[adSplit](#)

**Examples**

```
data(golubKEGGSplits)
image(golubKEGGSplits, filter.fdr=0.5)
```

---

makeEID2PROBESenv

*Generate EID2PROBES environment*

---

**Description**

Make hash containing probe-sets per EntrezGene identifier.

**Usage**

```
makeEID2PROBESenv(EIDenv)
```

**Arguments**

EIDenv            an environment containing one entry per probe-set holding all corresponding EntrezGene identifiers.

**Value**

An environment containing one entry per EntrezGene identifier holding all corresponding probe-sets.

**Author(s)**

Joern Toedling, Claudio Lottaz

**Examples**

```
library(hu6800.db)
makeEID2PROBESenv(hu6800ENTREZID)
```

---

|             |                                           |
|-------------|-------------------------------------------|
| print.split | <i>Print Information on Single Splits</i> |
|-------------|-------------------------------------------|

---

**Description**

Print information on a single split.

**Usage**

```
## S3 method for class 'split'  
print(x, ...)
```

**Arguments**

|     |                                   |
|-----|-----------------------------------|
| x   | the split-object to be described. |
| ... | not used.                         |

**Author(s)**

Claudio Lottaz

**See Also**

[diana2means](#)

---

|                |                                      |
|----------------|--------------------------------------|
| print.splitSet | <i>Print Summaries for splitSets</i> |
|----------------|--------------------------------------|

---

**Description**

Prints information of splitSets.

**Usage**

```
## S3 method for class 'splitSet'  
print(x, ...)
```

**Arguments**

|     |                                      |
|-----|--------------------------------------|
| x   | the splitSet-object to be described. |
| ... | not used.                            |

**Author(s)**

Claudio Lottaz

**See Also**[adSplit](#)**Examples**

```
data(golubKEGGSplits)
print(golubKEGGSplits)
```

---

|                   |                                                  |
|-------------------|--------------------------------------------------|
| randomDiana2means | <i>Generate null-distributions of DLD-scores</i> |
|-------------------|--------------------------------------------------|

---

**Description**

Draws a number of random sets of probe-sets consisting of the needed size and applies diana2means to compute DLD scores.

**Usage**

```
randomDiana2means(nprobes, data, chip, ndraws = 10000,
                  ngenes = 50, ignore.genes = 5)
```

**Arguments**

|              |                                                                                                  |
|--------------|--------------------------------------------------------------------------------------------------|
| nprobes      | the size of gene sets.                                                                           |
| data         | a matrix of expression data, rows correspond to genes, columns to samples.                       |
| chip         | the name of the used chip.                                                                       |
| ndraws       | the number of DLD scores computed.                                                               |
| ngenes       | the number of genes used to compute DLD scores (passed to diana2means).                          |
| ignore.genes | the number of best scoring genes to be ignored when computing DLD scores (passed to diana2means) |

**Details**

This function uses drawRandomPS to draw ndraws gene sets. On these it applies diana2means to determine a null-distribution of DLD-scores.

**Value**

A vector of DLD-scores.

**Author(s)**

Joern Toedling, Claudio Lottaz

**See Also**[drawRandomPS](#), [diana2means](#)

**Examples**

```
# prepare data
library(vsn)
library(golubEsets)
data(Golub_Merge)

# generate DLD scores
scores <- randomDiana2means(20, exprs(Golub_Merge), "hu6800", ndraws = 500)
```

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