

# Package ‘pbcmc’

July 3, 2018

**Type** Package

**Title** Permutation-Based Confidence for Molecular Classification

**Version** 1.9.0

**Date** 2016-09-23

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**Description** The pbcmc package characterizes uncertainty assessment on gene expression classifiers, a. k. a. molecular signatures, based on a permutation test. In order to achieve this goal, synthetic simulated subjects are obtained by permutations of gene labels. Then, each synthetic subject is tested against the corresponding subtype classifier to build the null distribution. Thus, classification confidence measurement can be provided for each subject, to assist physician therapy choice. At present, it is only available for PAM50 implementation in genefu package but it can easily be extend to other molecular signatures.

**URL** <http://www.bdmg.com.ar/>

**License** GPL (>=2)

**Depends** R (>= 3.4), genefu

**Imports** Biobase, BiocGenerics, BiocParallel (>= 1.3.13), parallel, reshape2, grid, utils, cowplot, methods, limma, ggplot2, gridExtra, grDevices, stats

**Suggests** breastCancerUPP, breastCancerNKI, breastCancerVDX, breastCancerTRANSBIG, breastCancerMAINZ, breastCancerUNT

**biocViews** Classification, GeneExpression, Microarray, MultipleComparison, QualityControl, Normalization, Clustering, mRNAMicroarray, OneChannel, TwoChannel, RNASeq, KEGG, DifferentialExpression

**Collate** 'pbcmcPackage.R' 'MolecularPermutationClassifierClass.R'  
'MolecularPermutationClassifierConstructor.R'  
'MolecularPermutationClassifierGenerics.R'  
'MolecularPermutationClassifierGetseters.R'  
'MolecularPermutationClassifierShow.R' 'PAM50Class.R'  
'PAM50Classify.R' 'PAM50Constructor.R' 'PAM50Filter.R'

```
'PAM50Permutate.R' 'PAM50Report.R' 'PAM50Subtype.R'
'pbcmcData.R'
```

**RoxygenNote** 5.0.1

**NeedsCompilation** no

**git\_url** <https://git.bioconductor.org/packages/pbcmc>

**git\_branch** master

**git\_last\_commit** 6db70fe

**git\_last\_commit\_date** 2018-04-30

**Date/Publication** 2018-07-02

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as	PAM50 <i>high level coerce functions</i>
----	--

---

### Description

These functions (setAs and as.PAM50) are intended to be used with limma [MAList-class](#) in order to coerce its structure into a compatible PAM50 class.

### Usage

```
as(object,Class,strict=TRUE,ext=possibleExtends(thisClass,Class))
```

```
as.PAM50(object)
```

```
## S4 method for signature 'MAList'
```

```
as.PAM50(object)
```

## Arguments

object           MAList object with at least M and genes items, optionally targets.  
 Class            character with the name of class "PAM50" to be coerced.  
 strict, ext      see [as](#) function.

## Details

Basically the \$M and \$genes items are copied into a MolecularPermutationClassifier's exprs and annotation slots respectively. In addition, if present, \$targets content is also copied to the same named slot.

## Value

a PAM50 object with the respective copied data.

## Author(s)

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## See Also

[PAM50](#) for a complete example.

Other PAM50: [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subjectReport](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

## Examples

```
##Example 1: Create a PAM50 object -----
##1) Just an empty object
object<-PAM50()
object

##2) Using Breast Cancer NKI database, if available.
if(requireNamespace("breastCancerNKI")){
  object<-loadBCDataset(Class=PAM50, libname="nki", verbose=TRUE)
  object
  ##Now we can inspect the object
  head(exprs(object))      ##The gene expression
  head(annotation(object)) ##The available annotation
  head(targets(object))   ##The clinical data present in the package
}

##Example 2: Build a PAM50 object with user data -----
##Option 1: using PAM50 constructor. The user will only need:
##a) The M gene expression object, i. e., gene in rows and sample in columns
##b) The annotation data.frame which must include the compulsory fields
## "probe", "NCBI.gene.symbol" and "EntrezGene.ID"
M<-pam50$centroids
genes<-pam50$centroids.map
names(genes)<-c("probe", "NCBI.gene.symbol", "EntrezGene.ID")
object<-PAM50(exprs=M, annotation=genes)
object
```

```

##Option 2: Two ways to build it from a MAlist (as or as.PAM50)-----
##Let's use PAM50 classifier's centroids toy example, i. e., the five subject
##subtypes, which must correctly classify all the subject.
M<-pam50$centroids
genes<-pam50$centroids.map
names(genes)<-c("probe", "NCBI.gene.symbol", "EntrezGene.ID")
maux<-new("MAlist", list(M=M, genes=genes))
##calling as function
object<-as(maux, "PAM50")
object
##same result with as.PAM50 function
object<-as.PAM50(maux)
object

```

---

classify,PAM50-method *classify subjects with PAM50 molecular signature*

---

### Description

Obtain PAM50 subtype using *genefu* centroid Spearman's correlation implementation. If `std=="median"` probes with the same mapping are averaged. Then, the complete database is center normalized using gene median expression. This is done in order to assure selecting the same "gene" to those in "genefu" library, instead of the most variant probe (default in *geneid.map*), when more than one probe match the same gene. This selection is based on probe population variance that could depend on the number of accounted genes.

### Usage

```

## S4 method for signature 'PAM50'
classify(object, std = c("none", "scale", "robust",
  "median")[1], verbose = getOption("verbose", default = FALSE))

```

### Arguments

<code>object</code>	a <code>MolecularPermutationClassifier</code> subclass object.
<code>std</code>	character to select standardization alternative "none" (default), "scale" and "robust" as in <i>genefu</i> original implementation, plus the suggested "median" if many subjects are available.
<code>verbose</code>	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.

### Value

a PAM50 object with the updated slots:

<code>@exprs</code>	updated matrix with the used <code>std</code> parameter.
<code>@classification</code>	<b>\$subtype</b> subject named factor with all classifier possible levels, i.e, "Basal", "Her2", "LumA", "LumB" and "Normal".

**\$probability** numeric matrix with subtype class probability for each subject, as in `genefu`, obtained as the positive proportion of correlation explained by each subtype.

**\$correlation** numeric matrix with Spearman's rho correlation of each subject to the corresponding PAM50 subtypes.

### Author(s)

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### References

1. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, `genefu`: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer. R package version 1.16.0, [www.pmgenomics.ca/bhkLab/](http://www.pmgenomics.ca/bhkLab/)
2. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752.
3. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719.

### See Also

[PAM50](#) for a complete example.

Other PAM50: [as](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subjectReport](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

### Examples

```
##Using pam50centroids package example data
data(pam50centroids)

##Get the original PAM50 calls using genefu implementation
pam50centroids<-classify(pam50centroids, std="none", verbose=TRUE)
classification(pam50centroids)
```

---

filtrate

*Virtual functions for MolecularPermutationClassifier hierarchy*

---

### Description

The following functions establish an organized framework for `MolecularPermutationClassifier` subclasses data processing. In this context, the later are supposed to be implemented with respective responsibilities. In particular, once the class is created the user has to:

**filtrate:** Removes, from the `exprs` matrix, subjects not required by the classification algorithm.

**classify:** Generates subject classification according to subclass implementations (PAM50, etc.).

**permute:** Obtains subject classification based on the null correlation distribution by means permutation simulation.

**subtype:** Obtained the new classification using permutation results.

**subjectReport:** A friendly report for physician treatment decision support.

**databaseReport:** A pdf with all `subjectReports`, if a database is available.

**Usage**

```

filtrate(object, verbose = getOption("verbose", default = FALSE))

classify(object, ..., verbose = getOption("verbose", default = FALSE))

permutate(object, nPerm = 10000L, pCutoff = 0.01, where = "fdr",
  keep = FALSE, ..., seed = 1234567890, BPPARAM = bpparam(),
  verbose = getOption("verbose", default = TRUE))

subtypes(object, pCutoff = 0.01, ..., where = c("fdr", "pvalue")[1])

subjectReport(object, subject)

databaseReport(object, fileName, ..., verbose = getOption("verbose", default =
  TRUE))

```

**Arguments**

object	MolecularPermutationClassifier child class object
verbose	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.
...	additional parameters for future implementations.
nPerm	integer with number of permutations. Default: 1e4L.
pCutoff	numeric with p-value or fdr cutoff used, i.e., variable<pCutoff. Default: 0.01.
where	character with significant value used. Default value is "fdr".
keep	should null distribution simulation values be kept?. Default: FALSE
seed	integer to use as random seed. Default: 1234567890.
BPPARAM	an optional BiocParallelParam instance determining the parallel back-end to be used during evaluation, or a list of BiocParallelParam instances, to be applied in sequence for nested calls to bplapply. Default=bpparam().
subject	integer to select the appropriate subject to report.
fileName	character with the name of the pdf report file to save.

**Value**

A MolecularPermutationClassifier child according to the actual object class.

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**See Also**

[PAM50](#) for a complete example.

Other MolecularPermutationClassifier PAM50: [PAM50-class](#), [loadBCDataset](#)

**Examples**

```
##Using pam50centroids package example data
data(pam50centroids)
pam50centroids
pam50centroids<-filtrate(pam50centroids, verbose=TRUE)
pam50centroids<-classify(pam50centroids, std="none", verbose=TRUE)
##Let's run a quick example with 100 permutations. It is recommended at
##least 10.000
pam50centroids<-permutate(pam50centroids, nPerm=100, pCutoff=0.01,
corCutoff=0.1, verbose=TRUE)
pam50centroids
```

---

filtrate,PAM50-method    *filtrate centroid genes from PAM50 classification*

---

**Description**

Remove exprs rows not required by MolecularPermutationClassifier subclasses to classify samples, in this case PAM50. This means to only keep genes with valid EntrezGeneID, i. e., not NA and present in PAM50 signature centroids. In addition, annotation slot will only keep "probe", "EntrezGene.ID" and "NCBI.gene.symbol" fields required by genefu's intrinsic.cluster.predict function.

**Usage**

```
## S4 method for signature 'PAM50'
filtrate(object, verbose = getOption("verbose", default =
FALSE))
```

**Arguments**

object	a PAM50 object.
verbose	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.

**Value**

MolecularPermutationClassifier subclass with updated slots:

@exprs	only rows required by the classifier.
@annotation	consistent with exprs rows and only "probe", "EntrezGene.ID" and "NCBI.gene.symbol" annotation fields.

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**See Also**

[PAM50](#) for a complete example.

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subjectReport](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

**Examples**

```
##Using pam50centroids package example data
data(pam50centroids)
pam50centroids
pam50centroids<-filtrate(pam50centroids, verbose=TRUE)
pam50centroids

##Using Breast Cancer NKI database, if available.
if(requireNamespace("breastCancerNKI")){
  object<-loadBCDataset(Class=PAM50, libname="nki", verbose=TRUE)
  object
  object<-filtrate(object, verbose=TRUE)
  object
}
```

---

loadBCDataset

*MolecularPermutationClassifier high level constructor*


---

**Description**

High level constructor for MolecularPermutationClassifier subclasses using available Bioconductor's Breast Cancer example datasets.

**Usage**

```
loadBCDataset(Class, libname = c("upp", "nki", "vdx", "mainz", "transbig",
  "unt"), verbose = getOption("verbose", default = FALSE))

## S4 method for signature 'classGeneratorFunction'
loadBCDataset(Class, libname = c("upp",
  "nki", "vdx", "mainz", "transbig", "unt"), verbose = getOption("verbose",
  default = FALSE))
```

**Arguments**

Class	name of MolecularPermutationClassifier child class to use.
libname	lowercase character with the name of the breastCancerXXX database to be loaded. At present, XXX can be "upp", "nki", "vdx", "mainz", "transbig" or "unt". See reference for available breast cancer citations.
verbose	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.

**Value**

MolecularPermutationClassifier subclass object with exprs, annotation and targets slots taken from the libname used.

**Author(s)**

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## References

- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerUPP: Gene expression dataset published by Miller et al. [2005] (UPP).. R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.
- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerNKI: Genexpression dataset published by van't Veer et al. [2002] and van de Vijver et al. [2002] (NKI).. R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.
- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerVDX: Gene expression datasets published by Wang et al. [2005] and Minn et al. [2007] (VDX). R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.
- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerTRANSBIG: Gene expression dataset published by Desmedt et al. [2007] (TRANSBIG).. R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.
- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerMAINZ: Gene expression dataset published by Schmidt et al. [2008] (MAINZ).. R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.
- Schroeder M, Haibe-Kains B, Culhane A, Sotiriou C, Bontempi G and Quackenbush J (2011). breastCancerUNT: Gene expression dataset published by Sotiriou et al. [2007] (UNT).. R package version 1.3.1, <http://compbio.dfci.harvard.edu/>.

## See Also

[PAM50](#) for a complete example.

Other MolecularPermutationClassifier PAM50: [PAM50-class](#), [filtrate](#)

## Examples

```
##Using Breast Cancer NKI database, if available, to create a PAM50 class.
if(requireNamespace("breastCancerNKI")){
  object<-loadBCDataset(Class=PAM50, libname="nki", verbose=TRUE)
  object

  ##Now we can inspect the object
  head(exprs(object))      ##The gene expression
  head(annotation(object)) ##The available annotation
  head(targets(object))    ##The clinical data present in the package
}
```

---

MolecularPermutationClassifier-class

*Class MolecularPermutationClassifier S4 implementation in R*

---

## Description

Virtual class to represent gene-based molecular signature classification by means of permutation test.

**Slots**

parameters named list with at least the following fields:

**\$nPerm** integer with number of permutations. Default: 1e4L

**\$where** character with significant value used. Default value is "fdr".

**\$pCutoff** numeric with p-value or fdr cutoff used, i.e.,  $\text{variable} < \text{pCutoff}$ . Default: 0.01

**\$keep** should null distribution simulation values be kept?. Default: FALSE

exprs matrix with gene exprs profile, where genes are in rows and subjects as columns, a.k.a., M matrix.

annotation data.frame with individual annotations (genes, etc). Minimal compulsory fields are:

**\$probe** same characters as in `row.names(M)`.

**\$EntrezGene.ID** integer with NCBI Entrez Data Base.

**\$NCBI.gene.symbol** character with gene mnemonic, a.k.a. gene symbol.

targets data.frame with additional subject data (optional).

classification named list with at least the following fields:

**\$class** factor with all possible class levels.

permutation named list with at least the following fields:

**\$pvalues** numeric matrix with subjects in row and classes in columns.

**\$fdr** numeric matrix with False Discovery Rate correction of p-values by row.

**Superclasses**

None declared.

**Subclasses**

**PAM50** Peruo et al. (2000 and 2010) breast cancer subtypes, i. e., Luminal A, Luminal B, Basal, Her2 or Normal-like subtypes as implemented in `genefu` library (Haibe-Kains et al. 2014).

**Functions**

MolecularPermutationClassifier S4 class includes the following functions:

- Integrity check:
  - validity** will check appropriate annotation data.frame minimal required columns, all named parameters and if exprs and annotation dimension matches.
  - prototype** just for an empty class with default values: `nPerm=1e4L`, `where="fdr"`, `pCutoff=0.01`, `corCutoff=0.1` and `keep=FALSE`.
- Generics:
  - `show,print` basic class display wrappers.
  - `summary` classifier statistics.
- Constructors (as this class is virtual see subclass' 'documentation).
  - `setAs` MAList to `PAM50`
  - `as.PAM50` wrapper for `PAM50` setAs from MAList.
  - `loadBCDataset` wrapper to load BreastCancerXX data (Class, exprs, annotation, clinical data).
- Getters for the corresponding slots (`parameters`, `exprs`, `annotation`, `targets`, `classification` and `permutation`).

- Setters for the corresponding slots (`parameters<-`, `annotation<-` and `targets<-`).
- Particular (virtual) functions:
  - `filtrate` remove from the `exprs` matrix subjects not required by the classification algorithm.
  - `classify` generate subject classification according to subclasses implementation (PAM50, etc.).
  - `permutate` obtain subject classification based on the null correlation distribution by means permutation simulation.
  - `subtypes` obtain the new classification using permutation results.
  - `subjectReport` a friendly report for Physician treatment decision support.
  - `databaseReport` a pdf with all subjectReports, if a database is available.

### Author(s)

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### References

1. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, `genefu`: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer. R package version 1.16.0, [www.pmgenomics.ca/bhklab/](http://www.pmgenomics.ca/bhklab/)
2. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752
3. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719

### See Also

`PAM50` for a complete example, `loadBCDataset` to load BreastCancerXX dataset, `filtrate`, `classify` and `permutate` to get corresponding Breast Cancer subtype. Getters/Setters for this class are `parameters`, `exprs`, `annotation`, `targets`, `classification` and `permutation`.

Other MolecularPermutationClassifier: `parameters`, `show`

---

PAM50-class

*PAM50 S4 implementation in R*

---

### Description

This is a concrete MolecularPermutationClassifier based on Perou et al. (2000 & 2010) PAM50 molecular signature, using `genefu` package implementation (Haibe-Kains et al. 2014).

### Slots

`parameters` named list with at least the following fields:

**\$nPerm** integer with number of permutations. Default: 1e4L

**\$where** character with significant value used. Default value is "fdr".

**\$pCutoff** numeric with p-value or fdr cutoff used, i.e., `variable<pCutoff`. Default: 0.01

**\$keep** should null distribution simulation values be kept?. Default: FALSE

**corCutoff** PAM50 additional numeric parameter with the correlation difference between classes cutoff used, i.e.,  $|\rho(\text{profile}, \text{class}_A) - \rho(\text{profile}, \text{class}_B)| > \text{corCutoff}$

**exprs** matrix with gene exprs profile, where genes are in rows and subjects as columns, a.k.a., M matrix.

**annotation** data.frame with individual annotations (genes, etc). Minimal compulsory fields are:

- \$probe** same characters as in row.names(M).
- \$EntrezGene.ID** integer with NCBI Entrez Data Base.
- \$NCBI.gene.symbol** character with gene mnemonic, a.k.a. gene symbol.

**targets** data.frame with additional subject data (optional).

**classification** named list with at least the following fields:

- \$subtype** factor with PAM50 subtype of each sample.
- \$probability** matrix with the subtype probability of each subtype per sample, as in `genefu` library.
- \$correlation** matrix with the observed correlation of each subtype per sample.

**permutation** named list with at least the following fields:

- \$correlation** Only if `keep==TRUE` is a list of the five subtypes containing a matrix with the permuted null distribution correlations.
- \$pvalues** matrix with the subject's p-values of the permutation test per subject.
- \$fdr** matrix with the corresponding adjusted p-values.
- \$subtype** data.frame where each subject has the reported "PAM50" subtype, the "Permuted" test result i.e. "Assigned", "Not Assigned" or "Ambiguous"; "Classes" whether is a single PAM50 subtype or more than one if Ambiguous case; "Class" if it is needed to assign just one i.e., a single PAM50 subtype or Not Assigned.

### Superclasses

Direct descendant from [MolecularPermutationClassifier-class](#).

### Subclasses

None declared.

### Function

Redefinition from `MolecularPermutationClassifier`: `filtrate`, `classify`, `permute`, `subjectReport` and `databaseReport`.

### Author(s)

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### References

1. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, `genefu`: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer. R package version 1.16.0, [www.pmgenomics.ca/bhklab/](http://www.pmgenomics.ca/bhklab/)
2. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752.
3. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719

**See Also**

Other MolecularPermutationClassifier PAM50: [filtrate](#), [loadBCDataset](#)

**Examples**

```
##Example 1: Create a PAM50 object -----
##1) Just an empty object
object<-PAM50()
object

##2) Using Breast Cancer NKI database, if available.
if(requireNamespace("breastCancerNKI")){
  object<-loadBCDataset(Class=PAM50, libname="nki", verbose=TRUE)
  object
  ##Now we can inspect the object
  head(exprs(object))    ##The gene expression
  head(annotation(object)) ##The available annotation
  head(targets(object))  ##The clinical data present in the package
}

##Example 2: Build a PAM50 object with user data -----
##Option 1: using PAM50 constructor. The user will only need:
##a) The M gene expression object, i. e., gene in rows and sample in columns
##b) The annotation data.frame which must include the compulsory fields
## "probe", "NCBI.gene.symbol" and "EntrezGene.ID"
M<-pam50$centroids
genes<-pam50$centroids.map
names(genes)<-c("probe", "NCBI.gene.symbol", "EntrezGene.ID")
object<-PAM50(exprs=M, annotation=genes)
object

##Option 2: Two ways to build it from a MAList (as or as.PAM50)-----
##Let's use PAM50 classifier's centroids toy example, i. e., the five subject
##subtypes, which must correctly classify all the subject.
M<-pam50$centroids
genes<-pam50$centroids.map
names(genes)<-c("probe", "NCBI.gene.symbol", "EntrezGene.ID")
maux<-new("MAList", list(M=M, genes=genes))
##calling as function
object<-as(maux, "PAM50")
object
##same result with as.PAM50 function
object<-as.PAM50(maux)
object

##Example3: Work with PAM50 object: filtrate, classify and permutate-----
##1)Keep only annotated genes presentes in PAM50 centroids
object<-filtrate(object, verbose=TRUE)

##2)Get PAM50 subtypes without any normalization
object<-classify(object, std="none", verbose=TRUE)
##Now we can inspect the how the calssification went
head(classification(object))

##3)Obtain the permutation subtype
##Let's run a quick example with 100 permutations. It is recommended at
```

```

##least 10.000
object<-permutate(object, nPerm=100, pCutoff=0.01, corCutoff=0.1,
  keep=TRUE, seed=1234567890, verbose=TRUE)
object
##Now we can inspect the how the permutation went
head(permutation(object))
##Which parameters were used?
parameters(object)

##Example 4: Obtain summary statistics and reports-----
##1) Let's check if we have a diagonal contingency matrix, i. e., no mistake
##is made in subtype assesment.
summary(object)

##2)Let's take a look at the how the patient genes behave according
## to PAM50
subjectReport(object, subject=1)
##3)Just get a pdf with all the used subjects (PAM50 centroids in this
##example).
#databaseReport(object, fileName="PAM50.pdf", verbose=TRUE)

```

---

pam50centroids

*Example PAM50 objects for pbcmc package*


---

## Description

The dataset corresponds to the Permutation-Based Confidence for Molecular Classification package [PAM50](#) example objects, that was [filtrated](#), [classified](#) and [permuted](#) using the following parameters:

**Permutations** 10000

**fdr** 0.01

**corCutoff** 0.1

**keep** TRUE

## Usage

```
data(pam50centroids)
```

## Format

pam50centroids corresponds with **pam50\$centroids** dataset available in [genefu](#) package.

## Value

a PAM50 object with the results obtained for pam50centroids simulations under the given parameters (see Detail section.)

## Author(s)

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## References

1. Bioscience data mining group <http://www.bdmg.com.ar>
2. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, *genefu: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer*. R package version 1.16.0, [www.pmgenomics.ca/bhklab/](http://www.pmgenomics.ca/bhklab/)
3. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752.
4. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719.

## See Also

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [permuate](#), [PAM50-method](#), [subjectReport](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

---

parameters

*Accessors for MolecularPermutationClassifier child class slots*

---

## Description

Slot setters/getters for MolecularPermutationClassifier hierarchy classes

## Usage

```
parameters(object)

## S4 method for signature 'MolecularPermutationClassifier'
parameters(object)

parameters(object) <- value

## S4 replacement method for signature 'MolecularPermutationClassifier'
parameters(object) <- value

## S4 method for signature 'MolecularPermutationClassifier'
exprs(object)

## S4 replacement method for signature 'MolecularPermutationClassifier,ANY'
exprs(object) <- value

## S4 method for signature 'MolecularPermutationClassifier'
annotation(object, ...)

## S4 replacement method for signature 'MolecularPermutationClassifier,ANY'
annotation(object) <- value

targets(object)

## S4 method for signature 'MolecularPermutationClassifier'
targets(object)
```

```

targets(object) <- value

## S4 replacement method for signature 'MolecularPermutationClassifier'
targets(object) <- value

classification(object)

## S4 method for signature 'MolecularPermutationClassifier'
classification(object)

permutation(object)

## S4 method for signature 'MolecularPermutationClassifier'
permutation(object)

```

### Arguments

object	MolecularPermutationClassifier subclass object
value	according to the function call: <ul style="list-style-type: none"> <li>parameters: named list with at least the following fields: <ul style="list-style-type: none"> <li><b>\$nPerm</b> integer with number of permutations. Default: 1e4L</li> <li><b>\$where</b> character with significant value used. Default value is "fdr".</li> <li><b>\$pCutoff</b> numeric with p-value or fdr cutoff used, i.e., <math>\text{variable} &lt; \text{pCutoff}</math>. Default: 0.01</li> <li><b>\$corCutoff</b> numeric with correlation difference between classes cutoff used, i.e., <math> \rho(\text{profile}, \text{class}_A) - \rho(\text{profile}, \text{class}_B)  &gt; \text{corCutoff}</math></li> <li><b>\$keep</b> should null distribution simulation values be kept?. Default: FALSE</li> </ul> </li> <li>annotation: data.frame with individual annotations (genes, etc). Minimal compulsory fields are: <ul style="list-style-type: none"> <li><b>\$probe</b> same characters as in row.names(M).</li> <li><b>\$EntrezGene.ID</b> integer with NCBI Entrez Data Base.</li> <li><b>\$NCBI.gene.symbol</b> character with gene mnemonic, a.k.a. gene symbol.</li> </ul> </li> <li>exprs: matrix with gene exprs profile, where genes are in rows and subjects as columns, a.k.a., <b>M matrix</b>.</li> <li>targets: data.frame with additional subject data.</li> </ul>
...	additional parameters according to function call.

### Value

according to function call one of the following objects:

parameters	named list see value parameter
exprs	matrix with gene exprs profile, where genes are in rows and subjects as columns, a.k.a., <b>M matrix</b> .
annotation	data.frame see value parameter
classification	named list with at least the following fields:

**\$class** factor with with all possible class levels.



permutation      named list with at least the following fields:

**pvalues** numeric matrix with subjects in row and classes in columns.

**\$fdr** numeric matrix with False Discovery Rate correction of pvalues by row.

parameters<-    MolecularPermutationClassifier object with parameters updated slot.

exprs<-          MolecularPermutationClassifier object with exprs updated slot.

annotation<-    MolecularPermutationClassifier object with annotation updated slot.

targets<-        MolecularPermutationClassifier object with targets updated slot.

### Author(s)

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### See Also

[PAM50](#) for a complete example.

Other MolecularPermutationClassifier: [MolecularPermutationClassifier-class](#), [show](#)

### Examples

```
##Using pam50centroids package example data
data(pam50centroids)

##Now we can inspect pam50centroids object
head(exprs(pam50centroids))      ##The gene expression
head(annotation(pam50centroids)) ##The available annotation
head(targets(pam50centroids))   ##The clinical data present in the package

##Work with the parameters
parameters(pam50centroids)      ##Display them
aux<-parameters(pam50centroids)
aux$keep<-TRUE                   ##Set keep to FALSE
parameters(pam50centroids)<-aux
parameters(pam50centroids)

##Also exprs<-, annotation<- and targets<- available functions to update
##the respective slots
```

### Description

Gene expression-based classifiers, known as molecular signatures (MS), are a set of genes coordinately expressed and an algorithm that use these data to predict disease subtypes, response to therapy, disease risk or clinical outcome (Andre et al. 2006). They are especially important in breast cancer (BC) where several MS are currently on the market like PAM50 (Perou et al. 2000 & 2010), Prosigna [www.prosigna.com](http://www.prosigna.com), Oncotype DX [www.oncotypedx.com](http://www.oncotypedx.com), MammaPrint [www.agendia.com](http://www.agendia.com), etc. As far as the authors know, these classifiers do not give a real uncertainty of the classification at all. This package characterizes MS classification uncertainty. In order to

achieve this goal, synthetic simulated subjects are obtained by permutations of gene labels. Then, each synthetic subject is tested against the classifier corresponding subtype to build the null distribution, thus, classification confidence measurement can be provided for each subject. In this context, subjects belonging to the null distribution (random or noisy individuals) are not assigned (NA) to any class. On the contrary, if reliable results are obtained, subjects could be either assigned (A) to the more reliably subtype or marked as ambiguous (AMB) if proximal to two or more reliable subtypes. In the later, the combinations of classes are given. At present, it is only implemented for *genefu*'s PAM50 package (Haibe-Kains et al. 2014) but it can easily be extended to other MS. This package includes the following features:

- Implemented classifier:
  1. PAM50.
- Single subject classification:
  1. No pilot study needs to be carried out to obtain classification uncertainty.
  2. No normalization is required. If required, external database normalization, *genefu* normalization alternatives (scale/robust) or even gene median can be applied before simulations.
- Classification:
  1. The original PAM50 calls obtained by *genefu*.
  2. The proposed classification scheme: Assigned (PAM50 call), Not Assigned (NA) or Ambiguous (reliable PAM50 class combinations).
  3. Classification significance p-value or False Discovery Rate (FDR).
  4. Observed subject Spearman's correlation for each breast cancer subtype.
- Physician treatment decision support:
  1. A friendly subject report is provided which includes summary data such as subtype centroid Spearman's correlation, p-value and FDR for each subtype, original PAM50 classification and the recommended strategy (assigned, not assigned or ambiguous classes).
  2. Scatter plot of the observed gene-expression (subject) versus PAM50 centroids panel, plus the corresponding linear regression fit.
  3. Null distribution boxplot, plus observed (subject) value.

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#### References

1. Andre F, Pusztai L, 2006, Molecular classification of breast cancer: implications for selection of adjuvant chemotherapy. *Nature Clinical Practice Oncology* 3(11), 621-632.
2. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, *genefu*: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer. R package version 1.16.0, [www.pngenomics.ca/bhklab/](http://www.pngenomics.ca/bhklab/)
3. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752
4. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719

---

permutate,PAM50-method

permutate *subject gene-expression for PAM50 confidence*


---

## Description

Calculate the null Spearman's  $\rho$  distribution of each subtype by means of gene label permutation, in order to evaluate if the observed values could be obtained by random change.

## Usage

```
## S4 method for signature 'PAM50'
permutate(object, nPerm = 10000, pCutoff = 0.01,
  where = "fdr", keep = FALSE, corCutoff = 0.1, seed = 1234567890,
  BPPARAM = bpparam(), verbose = getOption("verbose", default = TRUE))
```

## Arguments

object	a MolecularPermutationClassifier subclass object.
nPerm	integer with number of permutations. Default: 1e4L
pCutoff	numeric with p-value or fdr cutoff used, i.e., variable<pCutoff. Default: 0.01
where	character with significant value used. Default value is "fdr".
keep	should null distribution simulation values be kept?. Default: FALSE
corCutoff	numeric with correlation difference between classes cutoff used, i.e., $ \rho(profile, class_A) - \rho(profile, class_B)  > corCutoff$ . Default 0.1
seed	integer to use as random seed. Default: 1234567890.
BPPARAM	an optional BiocParallelParam instance determining the parallel back-end to be used during evaluation, or a list of BiocParallelParam instances, to be applied in sequence for nested calls to bplapply. Default=bpparam().
verbose	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.

## Value

a PAM50 object with the following updated slots:

@permutation	<b>\$pvalues</b> numeric matrix with subtype pvalues obtained as the number of times the permuted correlation is greater or equal the observed correlation divided the number of permutations.
	<b>\$fdr</b> subtype adjusted pvalues for each subject with False Discovery Rate.
	<b>\$correlations</b> list with subject matrix correlation of each permutation simulation.
	<b>\$subtype</b> data.frame with classification results obtained by subtype function.
@parameters	\$nPerm, \$pCutoff, \$where and \$keep updated accordingly.

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## References

1. Haibe-Kains B, Schroeder M, Bontempi G, Sotiriou C and Quackenbush J, 2014, *geneFu: Relevant Functions for Gene Expression Analysis, Especially in Breast Cancer*. R package version 1.16.0, [www.pmgenomics.ca/bhklab/](http://www.pmgenomics.ca/bhklab/)
2. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752.
3. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719.

## See Also

[PAM50](#) for a complete example.

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [subjectReport](#), [PAM50-me](#)  
[subtypes](#), [PAM50-method](#)

## Examples

```
##Using pam50centroids package example data
data(pam50centroids)
pam50centroids
pam50centroids<-filtrate(pam50centroids, verbose=TRUE)
pam50centroids<-classify(pam50centroids, std="none", verbose=TRUE)

##Let's run a quick example with 100 permutations. It is recommended at
##least 10.000
pam50centroids<-permutate(pam50centroids, nPerm=100, pCutoff=0.01,
corCutoff=0.1, verbose=TRUE)
pam50centroids
```

---

show

Show a *MolecularPermutationClassifier* subclass object

---

## Description

Basic *MolecularPermutationClassifier* class information display function (slots, dimensions, etc).

## Usage

```
## S4 method for signature 'MolecularPermutationClassifier'
show(object)
```

## Arguments

`object` an object of *MolecularPermutationClassifier* class hierarchy

## Value

console messages displaying the class content

**Author(s)**

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**See Also**

[PAM50](#) for a complete example.

Other MolecularPermutationClassifier: [MolecularPermutationClassifier-class](#), [parameters](#)

**Examples**

```
##For an empty object
object<-PAM50()
object

##Using pam50centroids package example data
data(pam50centroids)
pam50centroids
```

---

subjectReport,PAM50-method

*PAM50 permutation test results reports*

---

**Description**

subjectReport is basically a grid.arrange object which basically consists of three main parts: a summary table, a two row ggplot2 facet\_wrap with scatter ggplots (Wickham 2009) of subject expression and PAM50 centroids (Perou et al. 2000 & 2010) and a textGrob with the simulation parameter used. Particularly:

**tableGrob** with the following fields:

**\$Summary** subject name, PAM50 and Permuted subtype

**\$Fields** for the five PAM50 subtypes:

- Correlation: PAM50 centroid correlation with observed subject exprs.
- p-value: permutation p-value obtained using the simulation.
- FDR: adjusted p-value using False Discovery Rate.

**ggplot facet\_wrap** two rows to display scatter subject exprs vs PAM50 centroids, in addition to a the linear regression fit. If subject, has an unique subtype, then the graph is in red. In addition, if simulated permutations were run with keep=TRUE option, then null distribution boxplots are plotted with observed correlations as a big round point.

**textGrob** the permutation @parameter slot used in the simulation.

**Usage**

```
## S4 method for signature 'PAM50'
subjectReport(object, subject)

## S4 method for signature 'PAM50'
databaseReport(object, fileName, ...,
```

```

    verbose = getOption("verbose", default = TRUE))

## S4 method for signature 'PAM50'
summary(object, ...)

```

### Arguments

object	a PAM50 object.
subject	integer to select the appropriate subject to report.
fileName	character with the name of the pdf report file to save.
...	additional parameters for pdf function call.
verbose	should the user feedback be displayed? By default value is "verbose" global option parameter, if present, or FALSE otherwise.

### Details

summary it basically prints descriptive data of PAM50 dataset, the test parameters used, a frequency table of PAM50 Subtypes and a contingency table with Classes vs PAM50 Subtypes.

databaseReport basically is a pdf report where the first page is a global summary of the database, i.e., a summary contingency table of permutation test classes against original PAM50 subtypes results. The following pages are the database respective subjectReport outputs.

### Value

depending on function call:

subjectReport	a grid.arrange object.
databaseReport	a pdf file with database summary and subjectReports.
summary	Console summary statistics plus a data.frame

### Author(s)

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### References

1. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. Nature 406:747-752.
2. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, The Lancet Oncology 11(8):718-719.
3. Wickham H, ggplot2: elegant graphics for data analysis. Springer New York, 2009.

### See Also

[PAM50](#) for a complete example.

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permutate](#), [PAM50-method](#), [subtypes](#), [PAM50-method](#)

**Examples**

```
##Using pam50centroids package example data
data(pam50centroids)
pam50centroids

##This object has already run filtrate, classify and permutate. So, now
##we can obtain some reports:
##1) database summary
summary(pam50centroids)

##2)Individual subject report. If keep=FALSE boxplot panel is not available
subjectReport(pam50centroids, subject=1)##Basal subtype
subjectReport(pam50centroids, subject=1)##Her2 subtype

##3) complete database report
#databaseReport(pam50centroids, fileName="PAM50.pdf", verbose=TRUE)
```

---

subtypes,PAM50-method *Subject subtypes for PAM50 adaptation with permuted results.*

---

**Description**

PAM50 subtypes are obtained using permuted test results. The idea is to give confidence in PAM50 subtype assessment (Perou et al. 2000 & 2010). In this context, the observed Spearman's  $\rho$  correlation is tested against the null distribution obtained for each subtype. Then, only significant correlations are used in according to the following scheme:

**Not assigned** all subtype have  $\text{fdr} > \text{pcutoff}$ . Hence, there is evidence that the observed  $\rho$  can be obtained by random chance.

**Assigned** only one  $\text{fdr} \leq \text{pcutoff}$ . There is not enough evidence to say that the observed  $\rho$  does not belong to the null distribution.

**Ambiguous** more than one have  $\text{fdr} \leq \text{pcutoff}$ . Then, one of the following alternatives holds given the result of  $|\rho(\text{profile}, \text{class}_A) - \rho(\text{profile}, \text{class}_B)| > \text{corCutoff}$ .

**Assigned** If the statement is TRUE.

**Ambiguous** If the statement is FALSE.

Under the above scheme, the physician has an objective measurement to support the patient treatment decision. Both, with the given permuted subtype and by interpreting the p-value or fdr of each subtype null distribution test.

**Usage**

```
## S4 method for signature 'PAM50'
subtypes(object, pCutoff = 0.01, corCutoff = 0.1,
  where = c("fdr", "pvalue")[1])
```

**Arguments**

object	a MolecularPermutationClassifier subclass object.
pCutoff	numeric with p-value/fdr cutoff used depending on "where" selection. Default: 0.01.

`corCutoff` numeric with correlation difference between classes cutoff used, i.e.,  $|\rho(\text{profile}, \text{class}_A) - \rho(\text{profile}, \text{class}_B)| > \text{corCutoff}$ . Default 0.1

where character with significant value used. Default value is "fdr".

### Value

a PAM50 object with the updated slots:

`@permutation` **\$subtype** data.frame with the following fields  
**\$PAM50** the original PAM50 subtype  
**\$Permuted** factor with the following levels:

- "Not assigned": all subtype have  $\text{fdr} > \text{pcutoff}$
- "Assigned": only one  $\text{fdr} \leq \text{pcutoff}$
- "Ambiguous": more than one  $\text{fdr} \leq \text{pcutoff}$

**\$Classes** a character according to "Permuted" field:

- the unique PAM50 subtype if "Assigned"
- a combination for "Ambiguous" or
- NA if "Not assigned".

**\$Class** idem as Classes but "Ambiguous" is set to PAM50 calls  
**\$Subtype** Classes but "Ambiguous" is kept as "Ambiguous" string.

`@parameters` `$pCutoff`, `$corCutoff` and `$where` are updated accordingly.

### Author(s)

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### References

1. Perou CM, Sorlie T, Eisen MB, et al., 2000, Molecular portraits of human breast tumors. *Nature* 406:747-752.
2. Perou CM, Parker JS, Prat A, Ellis MJ, Bernard PB., 2010, Clinical implementation of the intrinsic subtypes of breast cancer, *The Lancet Oncology* 11(8):718-719.

### See Also

[PAM50](#) for a complete example.

Other PAM50: [as](#), [classify](#), [PAM50-method](#), [filtrate](#), [PAM50-method](#), [pam50centroids](#), [permute](#), [PAM50-method](#), [subjectReport](#), [PAM50-method](#)

### Examples

```
##Using pam50centroids package example data, which already had been
##filtrated, classified and permutated.
data(pam50centroids)
summary(pam50centroids)

##Now, let's change pCutoff and corCutoff without the need to run pemutate
##again
pam50centroids<-subtypes(pam50centroids, pCutoff=0.01, corCutoff=Inf,
  where="fdr")
pam50centroids
summary(pam50centroids)##Note that only Basal is not Ambiguos
```



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