

# Package ‘gep2pep’

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**Title** Creation and Analysis of Pathway Expression Profiles (PEPs)  
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**Author** Francesco Napolitano <franapoli@gmail.com>  
**Maintainer** Francesco Napolitano <franapoli@gmail.com>  
**Description** Pathway Expression Profiles (PEPs) are based on the expression of pathways (defined as sets of genes) as opposed to individual genes. This package converts gene expression profiles to PEPs and performs enrichment analysis of both pathways and experimental conditions, such as ``drug set enrichment analysis" and ``gene2drug" drug discovery analysis respectively.  
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gep2pep-package	<i>gep2pep: creation and analysis of Pathway Expression Profiles</i>
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## Description

Pathway Expression Profiles (PEPs) are based on the expression of pathways (or generic gene sets) belonging to a collection, as opposed to individual genes. `gep2pep` supports the conversion of gene expression profiles (GEPs) to PEPs and performs enrichment analysis of both pathways and conditions.

## Details

`gep2pep` creates a local repository of gene sets, which can also be imported from the MSigDB [1] database. The local repository is in the `repo` format. When a GEP, defined as a ranked list of genes, is passed to `buildPEPs`, the stored database of pathways is used to convert the GEP to a PEP and permanently store the latter.

One type of analysis that can be performed on PEPs and that is directly supported by `gep2pep` is the Drug-Set Enrichment Analysis (DSEA [2]). It finds pathways that are consistently dysregulated by a set of drugs, as opposed to a background of other drugs. Of course PEPs may refer to non-pharmacological conditions (genetic perturbations, disease states, cell types, etc.) for analogous analyses. See `CondSEA` function.

A complementary approach is that of finding conditions that consistently dysregulate a set of pathways. This is the pathway-based version of the Gene Set Enrichment Analysis (GSEA). As an application example, this approach can be used to find drugs mimicking the dysregulation of a gene

by looking for drugs dysregulating pathways involving the gene (this has been published as the gene2drug tool [3]). See [PathSEA](#).

Both DSEA and gene2drug analyses can be performed using preprocessed data from <http://dsea.tigem.it/downloads.php>. The data include Connectivity Map [4] GEPs (drug-induced gene expression profiles) converted to PEPs in the form of a gep2pep repository.

Naming conventions:

- pathway: any set of gene identifiers (not necessarily representing a molecular pathway).
- pathway collection: a set of pathways.
- pathway database: a set of pathway collections, like the MSigDB.
- Gene Expression Profile (GEP): a named vector where names are gene identifiers of the same type as those in the pathway database and elements are ranks ranging from 1 to the number of genes.
- Pathway Expression Profile (PEP): a ranked list of pathways, as converted from a GEP according to a pathway collection.
- condition: any transcriptomic-modelled biological state (drug treatment, gene knock-out, disease state, cell type, etc.) characterized by an induced GEP and therefore a PEP.
- gep2pep repository: a pathway database and possibly a related database of PEPs as created by the gep2pep package. It is implemented in repo format.

#### Author(s)

Francesco Napolitano <[franapoli@gmail.com](mailto:franapoli@gmail.com)>

#### References

- [1] Subramanian A. et al. Gene set enrichment analysis: A knowledge-based approach for interpreting genome-wide expression profiles. PNAS 102, 15545-15550 (2005).
- [2] Napolitano F. et al, Drug-set enrichment analysis: a novel tool to investigate drug mode of action. Bioinformatics 32, 235-241 (2016).
- [3] Napolitano, F. et al. gene2drug: a computational tool for pathway-based rational drug repositioning. Bioinformatics (2017). <https://doi.org/10.1093/bioinformatics/btx800>
- [4] Lamb, J. et al. The Connectivity Map: Using Gene-Expression Signatures to Connect Small Molecules, Genes, and Disease. Science 313, 1929-1935 (2006).

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addSingleGeneSets	<i>Adds a collection of single-gene psuedo-sets.</i>
-------------------	--

---

#### Description

This function can be used to add single-gene (as opposed to pathway) -based collections. Sets including a single gene don't need to go through normal Kolmogorov-Smirnov statistic computation and are treated differently for performance.

#### Usage

```
addSingleGeneSets(rp, genes, organism = "Homo Sapiens")
```

**Arguments**

rp	A repository created by <code>createRepository</code> .
genes	a character vector containing the gene names. For each of them a single-gene GeneSet will be created.
organism	Character vector used to annotate the created sets. "Homo Sapiens" by default.

**Details**

Enrichment Scores and p-values for sets including a single gene are computed with dedicated (fast) routines. Although a statistic based on a single gene is not efficient per se, it is useful to have data in the same format as pathway-based profiles. `buildPEPs` internally calls single gene dedicated routines whenever a gene set collection is tagged (see `repo` function `tag`) with "SGE" ("Single Gene Expression"), which is done automatically by `addSingleGeneSets`. In that case, the `min_size` parameter is ignored.

**Value**

Nothing, used for side effects.

**See Also**

`buildPEPs`

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)

## The following will create PEPs in 2 separate files
geps <- loadSampleGEP()
addSingleGeneSets(rp, rownames(geps))

unlink(repo_path, TRUE)
```

---

as.CategorizedCollection

*Converts GeneSetCollection objects to CategorizedCollection objects.*

---

**Description**

Converts GeneSetCollection objects to CategorizedCollection objects.

**Usage**

```
as.CategorizedCollection(GScollection, category = "uncategorized",
  subCategory = "uncategorized")
```

**Arguments**

GScollection	An object of class GeneSetCollection.
category	The name of the category that all the gene sets will be assigned to (see details).
subCategory	The name of the subcategory that all the gene sets will be assigned to (see details).

**Details**

This function sets the `CollectionType` for each set in the collection to `CategorizedCollection`. If `GScollection` contains `BroadCollection` gene sets, their fields `category` and `subcategory` will be used. Otherwise the `category` and `subcategory` fields will be used.

**Value**

A `CategorizedCollection` object

**Examples**

```
## Not run:

## To run this example, first obtain the MSigDB database in XML
## format (see
## http://software.broadinstitute.org/gsea/downloads.jsp). It is
## assumed that the database is locally available as the file
## "msigdb_v6.0.xml".

The \code{importMSigDB.xml} function is just a shortcut to the
following:

db <- getBroadSets("msigdb_v6.1.xml")
db <- as.CategorizedCollection(db)

## The database is now in an acceptable format to create a local
## repository using createRepository

## End(Not run)

## A small sample of the MSigDB as imported by importMSigDB.xml is
## included in gep2pep. The following creates (and deletes) a
## gep2pep repository.

db_sample <- loadSamplePWS()

## The function \code{as.CategorizedCollection} can also be used to
## create arbitrary gene set collections specifying the categories
## and subcategories once for all the sets:

library(GSEABase)
mysets <- as.CategorizedCollection(
  GeneSetCollection(
    list(GeneSet(c("g1", "g2"), setName="set1"),
         GeneSet(c("g3", "g4"), setName="set2"))
    ),
  category="mycategory",
  subCategory="mysubcategory"
```

```

    )
newCollection <- GeneSetCollection(c(db_sample, mysets))

## The created repository will include both the sample gene sets
## and the two sets just created:

repo_path <- file.path(tempdir(), "gep2pepTemp")
rp <- createRepository(repo_path, newCollection)

## removing temporary repository
unlink(repo_path, TRUE)

```

---

buildPEPs

*Build PEPs from GEPs and stores them in the repository.*


---

### Description

Given a matrix of ranked lists of genes (GEPs) and a gep2pep repository, converts GEPs to PEPs and stores the latter in the repository.

### Usage

```

buildPEPs(rp, gepts, min_size = 3, max_size = 500, parallel = FALSE,
  collections = "all", replace_existing = FALSE, donotstore = FALSE,
  progress_bar = TRUE, rawmode_id = NULL,
  rawmode_outdir = file.path(rp$root(), "raw"))

```

### Arguments

rp	A repository created by <a href="#">createRepository</a> .
gepts	A matrix of ranks where each row corresponds to a gene and each column to a condition. Each column must include all ranks from 1 to the number of rows. Row and column names must be defined. Row names will be matched against gene identifiers in the pathways collections, and unrecognized gene names will not be used.
min_size	An integer representing the minimum number of genes that must be included in a set before the KS statistic is computed. Smaller gene sets will get ES=NA and p=NA. Default is 3. Ignored for SGE mode (see <a href="#">addSingleGeneSets</a> ).
max_size	An integer representing the maximum number of genes that must be included in a set before the KS statistic is computed. Larger gene sets will get ES=NA and p=NA. Default is 500.
parallel	If TRUE, gene sets will be processed in parallel. Requires a parallel backend.
collections	A subset of the collection names returned by <a href="#">getCollections</a> . If set to "all" (default), all the collections in rp will be used.
replace_existing	What to do if PEPs, identified by column names of gepts are already present in the repository. If set to TRUE, they will be replaced, otherwise they will be skipped and only PEPs of new conditions will be computed and added. Either ways, will throw a warning.

donotstore	Just compute and return the pathway-based profiles without storing them in the repository. The repository is still required to load pathway data, however it will not be modified.
progress_bar	If set to TRUE (default) will show a progress bar updated after conversion of each column of geps.
rawmode_id	An integer to be appended to files produced in raw mode (see details). If set to NULL (default), raw mode is turned off.
rawmode_outdir	A character vector specifying the destination path for files produced in raw mode (by default it is ROOT/raw, where ROOT is the root of the repository). Ignored if rawmode_id is NULL.

## Details

By default, output is written to the repository as new items named using the collection name. However, it is possible to avoid the repository and write the output to regular files turning 'raw mode' on through the `rawmode_id` and `rawmode_outdir` parameters. This is particularly useful when dealing with very large corpora of GEPs, and conversions are split into independent jobs submitted to a scheduler. At the end, the data will need to be reconstructed and put into the repository using `importFromRawMode` in order to perform CondSEA or PathSEA analysis.

## Value

Nothing. The computed PEPs will be available in the repository.

## See Also

`buildPEPs`

## Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
## Repo root created.
## Repo created.
## [15:45:06] Storing pathway data for collection: c3_TFT
## [15:45:06] Storing pathway data for collection: c3_MIR
## [15:45:06] Storing pathway data for collection: c4_CGN

rp
##           ID   Dims   Size
## c3_TFT_sets  10  18.16 kB
## c3_MIR_sets  10  17.25 kB
## c4_CGN_sets  10   6.9 kB

## Loading sample gene expression profiles
geps <- loadSampleGEP()

geps[1:3,1:3]
##           (+)_chelidonine (+)_isoprenaline (+/_)_catechin
## AKT3                88             117             417
## MED6                357             410              34
## NR2E3               383             121             453
```

```

buildPEPs(rp, geps)

rp
##           ID Dims      Size
##  c3_TFT_sets 10 18.16 kB
##  c3_MIR_sets 10 17.25 kB
##  c4_CGN_sets 10  6.9 kB
##      c3_TFT  2  1.07 kB
##      c3_MIR  2  1.07 kB
##      c4_CGN  2  1.04 kB

unlink(repo_path, TRUE)

```

---

CategorizedCollection *Constructor method for objects of class CategorizedCollection.*

---

## Description

See CategorizedCollection-class.

## Usage

```

CategorizedCollection(category = "uncategorized",
  subCategory = "uncategorized")

```

## Arguments

category	A character defining the main category that the gene set belongs to.
subCategory	A character defining the secondary category that the gene set belongs to.

## Value

An object of class CategorizedCollection.

## Examples

```

library(GSEABase)
gs1 <- GeneSet(setName="set1", setIdentifier="101")
collectionType(gs1) <- CategorizedCollection()

```



---

CategorizedCollection-class

*A class to contain categorized gene set collection*


---

### Description

This class is a simple generalization of the BroadCollection function of GSEABase to store gene sets having assigned categories and subcategories that can be different from those of the MSigDB.

### Slots

category A character defining the main category that the gene set belongs to.

subCategory A character defining the secondary category that the gene set belongs to.

---

checkRepository

*Check an existyng repository for consistency*


---

### Description

Check both repository data consistency (see repo\_check from the repo package) and specific gep2pep data consistency.

### Usage

```
checkRepository(rp)
```

### Arguments

rp A repository created by [createRepository](#).

### Value

Nothing.

### Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
checkRepository(rp)

unlink(repo_path, TRUE)
```

---

clearCache	<i>Clear cached ranked matrices</i>
------------	-------------------------------------

---

## Description

Clear cached ranked matrices

## Usage

```
clearCache(rp_peps)
```

## Arguments

rp_peps	A repository created with <a href="#">createRepository</a> , and containing PEPs created with <a href="#">buildPEPs</a> .
---------	---

## Details

This will clear everything in the repository tagged with "stashed", which by default includes only matrices ranked by some gep2pep functions such as CondSEA.

## Value

Nothing, used for side effects

## See Also

[CondSEA](#)

## Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pgset <- c("(+)_chelidonine", "(+/_)_catechin")
psea <- CondSEA(rp, pgset, usecache=TRUE)

## the repository contains cached data
print(rp, all=TRUE)

clearCache(rp)

unlink(repo_path, TRUE)
```

CondSEA

*Performs Condition Set Enrichment Analysis***Description**

Condition Set Enrichment Analysis (CondSEA) can be seen as a Gene-SEA performed over rows (as opposed to columns) of a matrix of GEPs. It tells how much a pathway is consistently dysregulated under a set of conditions (such as a set of drug treatments, disease states, cell types, etc.) when compared to a statistical background of other conditions.

**Usage**

```
CondSEA(rp_peps, pgset, bgset = "all", collections = "all",
        details = TRUE, rankingFun = rankPEPsByRows.ES, usecache = FALSE,
        sortoutput = TRUE)
```

**Arguments**

rp_peps	A repository created with <a href="#">createRepository</a> , and containing PEPs created with <a href="#">buildPEPs</a> .
pgset	A vector of names of conditions. Corresponding PEPs must exist in all the pathway collections currently in rp.
bgset	The background against which to compare pgset. If set to all (default), all the remaining PEPs will be used. If provided, the corresponding PEPs must exist in all the pathway collections currently in rp.
collections	A subset of the collection names returned by <code>getCollections</code> . If set to "all" (default), all the collections in rp will be used.
details	If TRUE (default) rank details will be reported for each condition in pgset.
rankingFun	The function used to rank PEPs column-wise. By default <code>rankPEPsByRows.ES</code> is used, which ranks using gene set enrichment scores (see details).
usecache	If set to TRUE, the computed ranked matrix will be stored in the the repository (see details). FALSE by default.
sortoutput	If TRUE (default) the output gene sets will be sorted in order of increasing p-value.

**Details**

For each pathway, all conditions are ranked by how much they dysregulate it (from the most UP-regulating to the most DOWN-regulating). Then, a Kolmogorov-Smirnov (KS) test is performed to compare the ranks assigned to conditions in pgset against the ranks assigned to conditions in bgset. A positive (negative) Enrichment Score (ES) of the KS test indicates whether each pathway is UP- (DOWN-) regulated by pgset as compared to bgset. A p-value is associated to the ES.

When PEPs are obtained from drug-induced gene expression profiles, PathSEA is the Drug-Set Enrichment Analysis [1].

The `rankingFun` must take in input PEPs like those loaded from the repository and return a matrix of row-wise ranks. Each row must contains ranks from 1 to the number of PEPs minus the number of NAs in the row.

When usecache=TRUE, the ranked matrix is permanently stored in HDF5 format, and subsequent calls to CondSEA will load from the disk the necessary ranks (not the whole matrix). The correct cached data is identified by the alphabetically sorted set union(pgset, bgset), by the collection name, and by the ranking function. Additional calls to CondSEA with variations of these inputs will create additional cache. Cached data is hidden in the repository by default and can be printed with `rp_peps$print(all=TRUE)`, and cleared with `clearCache(rp_peps)`.

### Value

A list of 2, by names "CondSEA" and "details". The "CondSEA" entry is a 2-columns matrix including ESs and p-values (see details) for each pathway database and condition. The "details" entry reports the rank of each condition in pgset for each pathway.

### References

[1] Napolitano F. et al, Drug-set enrichment analysis: a novel tool to investigate drug mode of action. *Bioinformatics* 32, 235-241 (2016).

### See Also

`getResults`, `getDetails`, `clearCache`

### Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pgset <- c("(+)_chelidonine", "(+/-)_catechin")
psea <- CondSEA(rp, pgset)

res <- getResults(psea, "c3_TFT")

## getting the names of the top pathways

setId2setName(loadCollection(rp, "c3_TFT"), rownames(res))

unlink(repo_path, TRUE)
```

---

createMergedRepository

*Merge multiple PEPs to build a repository of consensus PEPs*

---

### Description

Merge multiple PEPs to build a repository of consensus PEPs

**Usage**

```
createMergedRepository(rpIn_path, rpOut_path, mergestr,
  progressBar = TRUE, collections = "all")
```

**Arguments**

rpIn_path	path to existing gep2pep repository
rpOut_path	path where the new merged repository will be created
mergestr	a named list of character vectors, each one including a set of PEP names. For each list entry, a consensus PEP will be created and assigned the entry name.
progressBar	if TRUE, show a progress bar
collections	A subset of the collection names returned by getCollections. If set to "all" (default), all the collections in rp will be used.

**Details**

The merging is performed as follows. Given N PEPs, the corresponding consensus PEP will get as enrichment score the average enrichment scores of the N PEPs, and as p-value the composition of the N PEP p-values by Fisher's method.

**Value**

Nothing, used for side effects.

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")
rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

mergestr <- list(
  che_iso = c("(+)_chelidonine", "(+)_isoprenaline"),
  cat_mk = c("(+)/_catechin", "(_)_mk_801")
)

merged_path <- file.path(tempdir(), "gep2pepTempMerged")

createMergedRepository(repo_path, merged_path, mergestr)

unlink(repo_path, TRUE)
unlink(merged_path, TRUE)
```

---

createRepository

*Creates a repository of pathway collections.*

---

**Description**

Given a database of collections, stores them in a local repository to be used by gep2pep functions.

**Usage**

```
createRepository(path, sets, name = NULL, description = NULL)
```

**Arguments**

path	Path to a non-existing directory where the repository will be created.
sets	An object of class CategorizedCollection.
name	Name of the repository. Defaults to NULL (a generic name will be given).
description	Description of the repository. If NULL (default), a generic description will be given.

**Details**

sets can be created by [importMSigDB.xml](#) or using GSEABase GeneSetCollection class and then converting it to CategorizedCollection. See examples.

**Value**

An object of class repo that can be passed to gep2pep functions.

**See Also**

buildPEPs

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
## Repo root created.
## Repo created.
## [15:45:06] Storing pathway data for collection: c3_TFT
## [15:45:06] Storing pathway data for collection: c3_MIR
## [15:45:06] Storing pathway data for collection: c4_CGN

rp
##           ID      Dims    Size
## c3_TFT_sets  10 18.16 kB
## c3_MIR_sets  10 17.25 kB
## c4_CGN_sets  10   6.9 kB

unlink(repo_path, TRUE)
```

---

exportSEA

*Export CondSEA or PathSEA results to XLS format*

---

**Description**

The XLS output includes the full CondSEA or PathSEA results, together with additional gene set information for the CondSEA. If the PathSEA or CondSEA analysis was performed with details=TRUE, details will be reported in the XLS file. This function requires the WriteXLS library.

**Usage**

```
exportSEA(rp, results, outname = NULL)
```

**Arguments**

rp	A repository created by <a href="#">createRepository</a> .
results	The output of CondSEA or PathSEA.
outname	Name of the XLS file to be created.

**Value**

Nothing.

**See Also**

CondSEA, PathSEA

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pgset <- c("(+)_chelidone", "(+/-)_catechin")
psea <- CondSEA(rp, pgset)

## Not run:
exportSEA(rp, psea)

## End(Not run)

unlink(repo_path, TRUE)
```

---

gene2pathways

*Finds pathways including a given gene.*

---

**Description**

Given a gene, find the set of pathways that involve it in each collection of the repository. This can be used to define a set of pathways for the [PathSEA](#).

**Usage**

```
gene2pathways(rp, genes, and = TRUE)
```

**Arguments**

rp	A repository created by <a href="#">createRepository</a> .
genes	A vector of gene identifiers of the same type as that used to create the repository.
and	If set to TRUE (default), will return sets containing all of genes. Otherwise will return the sets containing any of genes.

**Value**

A database of pathways suitable as input to [PathSEA](#).

**See Also**

[createRepository](#), [PathSEA](#)

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)

## Finding all pathways containing "FAM126A":
subpw <- gene2pathways(rp, "FAM126A")

print(names(subpw))

unlink(repo_path, TRUE)
```

---

getCollections	<i>Returns the names of the pathway collections in a repository.</i>
----------------	--

---

**Description**

Given a gep2pep repository, returns the names of the stored collections by looking at appropriate repository item names.

**Usage**

```
getCollections(rp)
```

**Arguments**

rp	A repository created by <a href="#">createRepository</a> .
----	--

**Details**

Each collection in a database has a "category" and a "subcategory" assigned, which are used to build the collection identifier as "category\_subcategory". This function obtains the identifiers by looking at data stored in the repository rp (entries that are tagged with "sets").



**Value**

Vector of collection names (see details).

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
## Repo root created.
## Repo created.
## [15:45:06] Storing pathway data for collection: c3_TFT
## [15:45:06] Storing pathway data for collection: c3_MIR
## [15:45:06] Storing pathway data for collection: c4_CGN

getCollections(rp)
## [1] "c3_TFT" "c3_MIR" "c4_CGN"

unlink(repo_path, TRUE)
```

---

getDetails

*Extracts the details matrix from CondSEA or PathSEA output*

---

**Description**

Extracts the details matrix from CondSEA or PathSEA output

**Usage**

```
getDetails(analysis, collection)
```

**Arguments**

analysis	The output of either CondSEA or PathSEA.
collection	One of the names returned by getCollections.

**Value**

A matrix including the ranks of each pathway (over rows) and each condition (over columns) used as input to CondSEA or PathSEA.

**See Also**

CondSEA, PathSEA

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pgset <- c("(+)_chelidonine", "(+/_)_catechin")
psea <- CondSEA(rp, pgset)

getDetails(psea, "c3_TFT")

unlink(repo_path, TRUE)
```

---

**getResults***Extracts the results matrix from CondSEA or PathSEA output*

---

**Description**

Extracts the results matrix from CondSEA or PathSEA output

**Usage**

```
getResults(analysis, collection)
```

**Arguments**

analysis	The output of either CondSEA or PathSEA.
collection	One of the names returned by getCollections.

**Value**

A 2-columns matrix including ESs and p-values (see details) for each pathway database and condition.

**See Also**

CondSEA, PathSEA

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pgset <- c("(+)_chelidonine", "(+/_)_catechin")
psea <- CondSEA(rp, pgset)
```

```

getResults(psea, "c3_TFT")

unlink(repo_path, TRUE)

```

---

importFromRawMode	<i>Imports PEPs created in raw mode</i>
-------------------	---

---

## Description

Raw mode is meant to deal with large collections of PEPs (like hundreds of thousands). In this case, problems may arise while trying to convert GEPs by loading all of them in memory at once. Raw mode is meant to be used with HDF5 format, which allows to load subsets of GEPs from the disk. buildPEPs, when used in raw mode, can create the corresponding subsets of PEPs, so that the job can be distributed on a computer cluster. importFromRawMode is meant to join the chunks into HDF5 matrices, which are then stored into the repository. The .loadPEPs function can seamlessly load PEPs stored in normal (RDS) or HDF5 format.

## Usage

```

importFromRawMode(rp, path = file.path(rp$root(), "raw"),
  collections = "all")

```

## Arguments

rp	A repository created by <a href="#">createRepository</a> .
path	Path where raw PEPs are stored (default is a "raw" directory under the repository root folder).
collections	A subset of the collection names returned by getCollections. If set to "all" (default), all the collections in rp will be used.

## Details

PEPs are expected to be found at the specified path and follow the naming convention as generated by buildPEPs. According to such convention, each file is named using the format category\_subcategory#chunknumber.RDS. All non-alphanumeric characters from the original category and subcategory names are replaced with an underscore (in rare cases this could create ambiguity that should be manually prevented). All chunks for the same subcategory are joined together following the chunk numbers into a single HDF5 matrix and stored in the repository as an "attachment" (see repo documentation).

Note that raw PEPs (by default everything at repository\_root/raw) can be safely removed once they have been imported.

## Value

Nothing, used for side effects.

## See Also

buildPEPs

**Examples**

```

db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)

## The following will create PEPs in 2 separate files
geps <- loadSampleGEP()
buildPEPs(rp, geps[,1:2], progress_bar=FALSE,
  rawmode_id=1)
buildPEPs(rp, geps[,3:5], progress_bar=FALSE,
  rawmode_id=2)

## The separate files are then merged into one (possibly big) file
## in HDF5 format

importFromRawMode(rp)

## Now most operations (excluding the addition of new PEPs to
## existing collections) will be available as usual.

unlink(repo_path, TRUE)

```

---

importMSigDB.xml	<i>Imports pathways data from an MSigDB XML file.</i>
------------------	---

---

**Description**

Creates a `GeneSetCollection` object using the XML distribution of the MSigDB (see references). The returned object can be passed to `createRepository`.

**Usage**

```
importMSigDB.xml(fname, organism = "Homo Sapiens")
```

**Arguments**

fname	Path to an XML file downloaded from MSigDB.
organism	Select only gene sets for a given organism. Default is "Homo Sapiens".

**Details**

This function now just calls `getBroadSets(fname)` from the `GSEABase` package. However, it is left for backward compatibility and as an entry point to package functionalities.

**Value**

A `CategorizedCollection` object

**References**

<http://software.broadinstitute.org/gsea/downloads.jsp>

## Examples

```
## Not run:

## To run this example, first obtain the MSigDB database in XML
## format (see
## http://software.broadinstitute.org/gsea/downloads.jsp). It is
## assumed that the database is locally available as the file
## "msigdb_v6.0.xml".

db <- importMSigDB.xml("msigdb_v6.0.xml")

## The database is now in an acceptable format to create a local
## repository using createRepository

## End(Not run)

## A small excerpt from the MSigDB is included in gep2pep. The
## following creates (and then deletes) a gep2pep repository.

db_sample <- loadSamplePWS()

repo_path <- file.path(tempdir(), "gep2pepTemp")
rp <- createRepository(repo_path, db_sample)

## removing temporary repository
unlink(repo_path, TRUE)
```

---

loadCollection	<i>Loads a collection of pathways from the repository</i>
----------------	---

---

## Description

Loads a collection of pathways from the repository

## Usage

```
loadCollection(rp, collection)
```

## Arguments

rp	A repository created by <a href="#">createRepository</a> .
collection	One of the names returned by <a href="#">getCollections</a> .

## Value

a GeneSetCollection object loaded from the repository rp.

## Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
```

```
geps <- loadSampleGEP()
loadCollection(rp, "c3_TFT")
unlink(repo_path, TRUE)
```

---

loadESmatrix	<i>Loads the matrix of Enrichment Scores for a collection</i>
--------------	---

---

### Description

Loads the matrix of Enrichment Scores for a collection

### Usage

```
loadESmatrix(rp, collection)
```

### Arguments

rp	A repository created by <a href="#">createRepository</a> .
collection	One of the names returned by <code>getCollections</code> .

### Value

The matrix of Enrichment Scores (ES) of the Kolmogorov-Smirnov statistic for the pathway collection, if previously computed with `buildPEPs`. The entry  $i, j$  reports the ES for the pathway  $i$ , condition  $j$ . If `buildPEPs` was not run, throws an error.

### Examples

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

loadESmatrix(rp, "c3_TFT")[1:5, 1:2]

unlink(repo_path, TRUE)
```

---

loadPVmatrix	<i>Loads the matrix of p-values for a collection</i>
--------------	--

---

**Description**

Loads the matrix of p-values for a collection

**Usage**

```
loadPVmatrix(rp, collection)
```

**Arguments**

rp	A repository created by <a href="#">createRepository</a> .
collection	One of the names returned by <a href="#">getCollections</a> .

**Value**

The matrix of p-values (PV) of the Kolmogorov-Smirnov statistic for the pathway collection, if previously computed with [buildPEPs](#). The entry *i, j* reports the PV for the pathway *i*, condition *j*. If [buildPEPs](#) was not run, throws an error.

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

loadPVmatrix(rp, "c3_TFT")

unlink(repo_path, TRUE)
```

---

loadSampleGEP	<i>Loads sample Gene Expression Profiles</i>
---------------	--

---

**Description**

Loads sample Gene Expression Profiles

**Usage**

```
loadSampleGEP()
```

**Value**

Sample gene expression data

**Examples**

```
geps <- loadSampleGEP()
```

---

loadSamplePWS	<i>Loads sample pathway collections</i>
---------------	---

---

**Description**

Loads sample pathway collections

**Usage**

```
loadSamplePWS()
```

**Value**

Sample pathway collections in GeneSetCollection format

**Examples**

```
geps <- loadSampleGEP()
```

---

makeCollectionIDs	<i>Creates a collection label for each pathway.</i>
-------------------	---

---

**Description**

Given a database, uses "category" and "subcategory" entries to create a vector of collection identifiers. Useful to extract a collection from a database.

**Usage**

```
makeCollectionIDs(sets)
```

**Arguments**

sets	A pathway database in the same format as output by importMSigDB.xml.
------	--

**Value**

A vector of identifiers, one per pathway, with the format: "category\_subcategory".

**See Also**

```
importMSigDB.xml
```



**Examples**

```
db <- loadSamplePWS()
ids <- makeCollectionIDs(db)

unique(ids)
## [1] "c3_TFT" "c3_MIR" "c4_CGN"

db <- db[ids=="c3_MIR"]

length(db)
## [1] 10
```

---

openRepository	<i>Opens an existing repository of pathway collections.</i>
----------------	---

---

**Description**

The repository must have been created by [createRepository](#). Provides an R object to interact with the repository.

**Usage**

```
openRepository(path)
```

**Arguments**

path                      Path to a directory where the repository has been created with [createRepository](#).

**Details**

This function only calls the `repo_open` function from the `repo` package on `path`. It is meant to allow users not to explicitly load the `repo` library, unless they want to access advanced features.

**Value**

An object of class `repo` that can be passed to `gep2pep` functions.

**See Also**

[createRepository](#)

**Examples**

```
db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
rp2 <- openRepository(repo_path)

## rp and rp2 point to the same data:
identical(rp$entries(), rp2$entries())
## > [1] TRUE

unlink(repo_path, TRUE)
```

PathSEA

*Performs Pathway Set Enrichment Analysis (PSEA)***Description**

PathSEA is analogous to the Gene Set Enrichment Analysis (GSEA), but for pathways instead of single genes. It can therefore be used to look for conditions under which a given set of pathways is consistently UP- or DOWN-regulated.

**Usage**

```
PathSEA(rp_peps, pathways, bgsets = "all", collections = "all",
        subset = "all", details = TRUE, rankingFun = rankPEPsByCols.SPV)
```

**Arguments**

rp_peps	A repository created with <a href="#">createRepository</a> , and containing PEPs created with <a href="#">buildPEPs</a> .
pathways	A database of pathways in the same format as input to <a href="#">createRepository</a> . PSEA will be performed for each database separately.
bgsets	Another list like pathways, representing the statistical background for each database. If set to "all" (the default), all pathways that are in the repository and not in pathways will be used.
collections	A subset of the collection names returned by <code>getCollections</code> . If set to "all" (default), all the collections in rp will be used.
subset	Character vector including PEP names to be considered (all by default, which may take time).
details	If TRUE (default) details will be reported for each condition in pgset.
rankingFun	The function used to rank PEPs column-wise. By default <code>rankPEPsByCols.ES</code> is used, which uses gene set enrichment scores (see details).

**Details**

For each condition, all pathways are ranked by how much they are dysregulated by it (from the most UP-regulated to the most DOWN-regulated, according to the corresponding p-values). Then, a Kolmogorov-Smirnov (KS) test is performed to compare the ranks assigned to pathways in pathways against the ranks assigned to pathways in bgsets. A positive (negative) Enrichment Score (ES) of the KS test indicates whether each pathway is UP- (DOWN-) regulated by pgset as compared to bgset. A p-value is associated to the ES.

When PEPs are obtained from drug-induced gene expression profiles, PathSEA can be used together with `gene2pathways` to perform `gene2drug [1]` analysis, which predicts which drugs may target a gene of interest (or mimick such effect).

The `rankingFun` must take in input PEPs like those loaded from the repository and return a matrix of column-wise ranks. Each column must contain ranks from 1 to the number of gene sets minus the number of NAs in the column.

**Value**

A list of 2, by names "PathSEA" and "details". The "PathSEA" entry is a 2-columns matrix including ESs and p-values for each collection and condition. The "details" entry reports the rank of each pathway in pathways for each condition.

**References**

[1] Napolitano, F. et al. gene2drug: a computational tool for pathway-based rational drug repositioning. *Bioinformatics* (2017). <https://doi.org/10.1093/bioinformatics/btx800>

**See Also**

getResults, getDetails

**Examples**

```
library(GSEABase)

db <- loadSamplePWS()
repo_path <- file.path(tempdir(), "gep2pepTemp")

rp <- createRepository(repo_path, db)
geps <- loadSampleGEP()
buildPEPs(rp, geps)

pathways <- c("M11607", "M10817", "M16694",          ## from c3_TFT
              "M19723", "M5038", "M13419", "M1094") ## from c4_CGN
w <- sapply(db, setIdentifier) %in% pathways

psea <- PathSEA(rp, db[w])
## [15:35:29] Working on collection: c3_TFT
## [15:35:29] Common pathway sets removed from bgset.
## [15:35:29] Column-ranking collection...
## [15:35:29] Computing enrichments...
## [15:35:29] done.
## [15:35:29] Working on collection: C4_CGN
## [15:35:29] Common pathway sets removed from bgset.
## [15:35:29] Column-ranking collection...
## [15:35:29] Computing enrichments...
## [15:35:29] done.

getResults(psea, "c3_TFT")
##              ES      PV
## ( )_mk_801    0.7142857 0.1666667
## ( )_atenolol  0.7142857 0.1666667
## (+)_isoprenaline 0.5714286 0.4000000
## (+/_)_catechin 0.5714286 0.4000000
## (+)_chelidone 0.3333333 0.9333333

unlink(repo_path, TRUE)
```

---

setId2setName	<i>Converts gene set IDs to gene set names</i>
---------------	--

---

**Description**

Converts gene set IDs to gene set names

**Usage**

```
setId2setName(sets, ids)
```

**Arguments**

sets	An object of class GeneSetCollection
ids	character vector of gene set IDs to be converted to set names

**Value**

A vector of gene set names

**See Also**

CondSEA, PathSEA

**Examples**

```
collection <- loadSamplePWS()
setId2setName(collection, c("M3128", "M11607"))
```

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