

Package ‘phoenics’

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Title Pathways Longitudinal and Differential Analysis in Metabolomics

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Imports lme4, blme, tibble, FactoMineR, factoextra, tidyr, stats

Suggests KEGGREST

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Description Perform a differential analysis at pathway level based on metabolite quantifications and information on pathway metabolite composition.

The method is based on a Principal Component Analysis step and on a linear mixed model. Automatic query of metabolic pathways is also implemented.

License GPL-3

Repository CRAN

BugReports <https://forgemia.inra.fr/panoramics/phoenics/-/issues>

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from_ASICS_to_PHOENICS

Prepare quantification data from ASICS outputs

Description

Prepare quantification data from ASICS outputs for test_pathway. In short, it replaces metabolite names by metabolites KEGG codes and transposes the matrix to have samples in rows and metabolites in columns.

Usage

```
from_ASICS_to_PHOENICS(quantif)
```

Arguments

quantif output matrix of ASICS quantification

Value

A matrix of quantification with samples in rows and metabolites in columns, properly formatted for test_pathway

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References

Lefort G., Liaubet L., Canlet C., Tardivel P., Plère M.C., Quesnel H., Paris A., Iannuccelli N., Vialaneix N. Servien R. (2019). ASICS: an R package for a whole analysis workflow of 1D 1H NMR spectra. *Bioinformatics*, **35**(21): 4356–4363. doi:10.1093/bioinformatics/btz248

Tardivel P., Canlet C., Lefort G., Tremblay-Franco M., Debrauwer L., Concordet D., Servien R. (2017). ASICS: an automatic method for identification and quantification of metabolites in complex 1D 1H NMR spectra. *Metabolomics*, **13**(10): 109. doi:10.1007/s1130601712445

Examples

```
data("MTBLS422")
quantif <- from_ASICS_to_PHOENICS(quantif)
```

MTBLS422

Dataset "MTBLS422"

Description

Metabolites quantifications, associated metabolic pathways and experimental design to characterize the effects of two clinically important antibiotic treatments, ciprofloxacin and vancomycin-imipenem on mice.

Format

3 datasets are provided:

- `quantif`: a data frame with 10 rows (metabolites name) and 11 columns (samples id), which corresponds to the metabolites quantifications in the samples.
- `pathways`: a data frame with 11 rows and 4 columns, which contains informations about pathways and their metabolites.
- `design`: a data frame with 11 rows (samples id) and 4 columns (id and effects to be added in the model).

Details

The raw dataset have been made available on MetaboLights (with the id MTBLS422 <https://www.ebi.ac.uk/metabolights/editor/MTBLS422>) by [Choo *et al.*, 2017]. Metabolites quantifications were obtained based on the raw signal using ASICS package. Pathways were obtained using KEGGREST package. The datasets provided for the example are a subset of the original dataset.

References

- Choo J. M., Kanno T., Zain N. M. M., Leong L. E. X., Abell G. C. J., Keeble J. E., Bruce K. D., Mason A. J., Rogers G. B. (2017). Divergent relationships between fecal microbiota and metabolome following distinct antibiotic-induced disruptions. *mSphere*, **2**(1) doi:10.1128/msphere.0000517
- Lefort G., Liaubet L., Canlet C., Tardivel P., P'ere M.C., Quesnel H., Paris A., Iannuccelli N., Vialaneix N. Servien R. (2019). ASICS: an R package for a whole analysis workflow of 1D 1H NMR spectra. *Bioinformatics*, **35**(21): 4356–4363. doi:10.1093/bioinformatics/btz248
- Tardivel P., Canlet C., Lefort G., Tremblay-Franco M., Debrauwer L., Concordet D., Servien R. (2017). ASICS: an automatic method for identification and quantification of metabolites in complex 1D 1H NMR spectra. *Metabolomics*, **13**(10): 109. doi:10.1007/s1130601712445
- Tenenbaum D., Maintainer B. (2022). KEGGREST: Client-side REST access to the Kyoto Encyclopedia of Genes and Genomes (KEGG). R package version 1.38.0.

Examples

```
data(MTBLS422)

design[1:5, ]
pathways[1:5, ]
```

```
quantif[1:5, 1:5]
```

overlap_coefficient *Calculate overlap coefficient between pathways*

Description

Calculate overlap coefficient between pathways

Usage

```
overlap_coefficient(pathwayA, pathwayB, pathways = NULL, organism = NULL)
```

Arguments

pathwayA	a character string of pathway name or pathway code or a character vector of metabolite names or metabolite codes
pathwayB	a character string of pathway name or pathway code or a character vector of metabolite names or metabolite codes
pathways	data.frame or matrix with metabolites in rows and the following information in columns: <ul style="list-style-type: none">• metabolite_code metabolite code• metabolite_name metabolite name• pathway_code pathway code (identifier)• pathway_name name of the pathway Used if pathwayA and pathwayB are pathway names or pathway codes.
organism	organism code in KEGG database. Required if pathways = NULL and pathwayA and pathwayB are pathway names and ignored otherwise.

Value

A value between 0 and 1 calculated with the formula:

$$OC(A, B) = \frac{|A \cap B|}{\min(|A|, |B|)}$$

An overlap coefficient of 1 means that one pathway is included in the other. An overlap coefficient of 0 means that there is no overlap between the pathways.

References

Wieder C., Lai R.P.J., Ebbels T.M.D. (2022). Single sample pathway analysis in metabolomics: performance evaluation and application. *BMC Bioinformatics*, **23**, 481. doi:10.1186/s12859022-050051

Examples

```
data("MTBLS422")
pathwayA <- "Galactose metabolism"
pathwayB <- "Vitamin digestion and absorption"
overlap_coefficient(pathwayA, pathwayB, pathways)

if (requireNamespace("KEGGREST", quietly = TRUE)) {
  pathwayA <- "Galactose metabolism"
  pathwayB <- "Vitamin digestion and absorption"

  overlap_coefficient(pathwayA, pathwayB, organism = "mmu")
}

pathwayA <- "mmu00052"
pathwayB <- "mmu00562"
overlap_coefficient(pathwayA, pathwayB, pathways)

pathwayA <- c("C00029", "C00116", "C00137", "C00794", "C00984", "C01697")
pathwayB <- c("C00191", "C00092", "C00137")
overlap_coefficient(pathwayA, pathwayB)
```

pathwayRes

Class pathwayRes

Description

S3 class for pathway differential analysis results

Usage

```
## S3 method for class 'pathwayRes'
summary(object, ...)

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

## S3 method for class 'pathwayRes'
plot(
  x,
  ...,
  pathway_id = NULL,
  plot = c("eig", "var", "ind"),
  habillage = "none"
)

head(object)
```

```
extract(object, pathway_id)
```

```
adjust_pval(object, method = p.adjust.methods, n = length(object))
```

Arguments

object, x	object of class pathwayRes
...	not used
pathway_id	a character string or vector of pathway codes or names
plot	a character string indicating the type of plot to return. Default to "eig" (the screegraph of the PCA is displayed)
habillage	a character string indicating the column of the design used to color the individuals. Only used when plot = "ind". Default to "none" (no color)
method	a character string indicating the correction method to be used for multiple testing correction (authorized values are those of p.adjust.methods)
n	number of comparisons for multiple testing correction

Details

Methods for the class pathwayRes

Value

The function `extract` returns an object of class `pathwayRes` which is a list of pathway results, containing only the pathways in `pathway_id`.

The function `adjust_pval` returns a data.frame with pathways in rows and the following information in columns:

pathway_name	name of the pathway
pathway_code	pathway code (identifier)
Fixed_effect	tested effect
pval	raw p-value of the pathway
adjusted_pval	adjusted p-value of the pathway

Examples

```
data("MTBLS422")
quantif <- from_ASICS_to_PHOENICS(quantif)
out_test <- test_pathway(quantif, design, pathways,
                        fixed = c("Age", "Treatment"), random = "Mouse",
                        npc = 2, model = "blmer")

summary(out_test)
print(out_test)
plot(out_test)
plot(out_test, "mmu00052", plot = "var")
plot(out_test, "mmu00052", plot = "ind", habillage = "Age")
```

```
head(out_test)
extract(out_test, "mmu00562")
adj_pval <- adjust_pval(out_test)
```

pathway_search	<i>Query KEGG pathways for a given set of metabolites</i>
----------------	---

Description

Query KEGG pathways for a given set of metabolites

Usage

```
pathway_search(metab, organism, min_size = 2)
```

Arguments

metab	vector of metabolite KEGG codes
organism	organism code in KEGG database
min_size	minimal number of metabolites required for a pathway to be returned

Value

a data.frame with metabolites in rows and the following information in columns:

- metabolite_code metabolite code
- metabolite_name metabolite name
- pathway_code pathway code (identifier)
- pathway_name name of the pathway

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References

Kanehisa M., Goto S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes, *Nucleic Acids Research*, Volume 28, Issue 1, Pages 27–30, doi:[10.1093/nar/28.1.27](https://doi.org/10.1093/nar/28.1.27)

Tenenbaum D., Maintainer B. (2022). KEGGREST: Client-side REST access to the Kyoto Encyclopedia of Genes and Genomes (KEGG). R package version 1.38.0.

Examples

```

if (requireNamespace("KEGGREST", quietly = TRUE)) {
  data("MTBLS422")
  quantif <- from_ASICS_to_PHOENICS(quantif)

  pathways <- pathway_search(metab = colnames(quantif), organism = "mmu")
}

```

test_pathway	<i>Pathway differential analysis based on longitudinal metabolomics data</i>
--------------	--

Description

Perform a differential analysis at pathway level based on metabolite quantifications and information on pathway metabolite composition. The method relies on a PCA step.

Usage

```

test_pathway(
  quantif,
  design,
  pathways = "auto",
  fixed,
  random,
  npc = 1L,
  model = c("lmer", "blmer"),
  organism = NULL,
  min_size = 2
)

```

Arguments

quantif	data.frame or matrix of the metabolite quantification with samples in rows (sample identifiers must be row names) and metabolites in columns (metabolite codes must be column names)
design	data.frame or matrix with samples in rows (sample identifiers must be row names) and the different effects to be included in the model in columns. Column names must be provided and are used as arguments for fixed and random
pathways	data.frame or matrix with metabolites in rows (all metabolites in columns of quantif must have a row in this input) and the following information in columns: <ul style="list-style-type: none"> • metabolite_code metabolite code • metabolite_name metabolite name • pathway_code pathway code (identifier)

	<ul style="list-style-type: none"> • pathway_name name of the pathway
fixed	character vector of fixed effects to be included in the model. They must correspond to column names of design
random	character vector of random effects to be included in the model. They must correspond to column names of design
npc	number of PCs for the PCA step
model	a character string indicating if the model has to be fitted using lmer or blmer . Default to "lmer"
organism	organism code in KEGG database. Required if pathways = "auto" and ignored otherwise
min_size	minimal number of metabolites in a pathway. Required if pathways = "auto" and ignored otherwise. Default to 2

Details

If pathways = "auto", information on pathways in which metabolites are present is automatically obtained by the function [pathway_search](#) using KEGGREST that queries KEGG database. Results are specific to a given organism (passed in organism). Pathways containing less than min_size metabolites are filtered out.

Value

an object of class pathwayRes which is a list of pathway results. Each element of the list contain the following entries:

pathway_name	a character corresponding to the pathway name
pathway_code	a character corresponding to the pathway code
metabolites	a data.frame with the names and codes of the quantified metabolites in the pathway
PCA	the result of the pathway PCA (a PCA object as obtained from PCA)
model	the output of the mixed model fit
test_pathway	a data.frame with the p-values for each tested fixed effect

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See Also

[pathway_search](#) for the automatic annotation of metabolites in KEGG pathways.

Examples

```
data("MTBLS422")
quantif <- from_ASICS_to_PHOENICS(quantif)
out_test <- test_pathway(quantif, design, pathways,
                        fixed = c("Age", "Treatment"), random = "Mouse",
                        npc = 2, model = "blmer")

out_test

if (requireNamespace("KEGGREST", quietly = TRUE)) {

  out_test2 <- test_pathway(quantif, design, pathways = "auto",
                          fixed = c("Age", "Treatment"), random = "Mouse",
                          npc = 2, model = "blmer", organism = "mmu")

  out_test2

}
```

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