

# Package ‘lilikoï’

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**Type** Package

**Title** Metabolomics Personalized Pathway Analysis Tool

**Version** 2.1.1

**Description** A comprehensive analysis tool for metabolomics data. It consists a variety of functional modules, including several new modules: a pre-processing module for normalization and imputation, an exploratory data analysis module for dimension reduction and source of variation analysis, a classification module with the new deep-learning method and other machine-learning methods, a prognosis module with cox-PH and neural-network based Cox-nnet methods, and pathway analysis module to visualize the pathway and interpret metabolite-pathway relationships. References: H. Paul Benton <<http://www.metabolomics-forum.com/index.php?topic=281.0>> Jeff Xia <[https://github.com/cangfengzhe/Metabo/blob/master/MetaboAnalyst/website/name\\_match.R](https://github.com/cangfengzhe/Metabo/blob/master/MetaboAnalyst/website/name_match.R)> Travers Ching, Xun Zhu, Lana X. Garmire (2018) <[doi:10.1371/journal.pcbi.1006076](https://doi.org/10.1371/journal.pcbi.1006076)>.

**biocViews**

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| lilikoi.explr | <i>Exploratory analysis</i> |
|---------------|-----------------------------|

---

### Description

Performs source of variation test and build PCA and t-SNE plots to visualize important information.

### Usage

```
lilikoi.explr(data, demo.data, pca = FALSE, tsne = FALSE)
```

### Arguments

|           |   |
|-----------|---|
| data      | is a input data frame for analysis with sample ids as row names and metabolite names or pathway names as column names.  |
| demo.data | is a demographic data frame with sample ids as row names, sample groups and demographic variable names as column names. |
| pca       | if TRUE, PCA plot will be out.  |
| tsne      | if TRUE, T-SNE plot will be out.  |

### Value

Source of variation test results and PCA and t-SNE plot

### Examples

```
# lilikoi.explr(data, demo.data, pca=TRUE, tsne=FALSE)
```

---

`lilikoï.featuresSelection`  
*A featuresSelection Function*

---

### Description

This function allows you to reduce the pathway diemnsion using xxxx

### Usage

```
lilikoï.featuresSelection(PDSmatrix, threshold = 0.5, method = "info")
```

### Arguments

|                        |  |
|------------------------|--|
| <code>PDSmatrix</code> | from PDSfun function                             |
| <code>threshold</code> | to select the top pathways                       |
| <code>method</code>    | information gain ("info") or gain ratio ("gain") |

### Value

A list of top metabolites or pathways.

### Examples

```
dt <- lilikoï.Loaddata(file=system.file("extdata",  
  "plasma_breast_cancer.csv", package = "lilikoï"))  
Metadata <- dt$Metadata  
dataSet <- dt$dataSet  
# Metabolite_pathway_table=lilikoï.MetaT0pathway('name')  
# PDSmatrix= lilikoï.PDSfun(Metabolite_pathway_table)  
# selected_Pathways_Weka= lilikoï.featuresSelection(PDSmatrix,threshold= 0.50,method="gain")
```

---

`lilikoï.KEGGplot`      *lilikoï.KEGGplot*

---

### Description

Visualizes selected pathways based on their metabolites expression data.

**Usage**

```
lilikoï.KEGGplot(
  metamat,
  sampleinfo,
  grouporder,
  pathid = "00250",
  specie = "hsa",
  filesuffix = "GSE16873",
  Metabolite_pathway_table = Metabolite_pathway_table
)
```

**Arguments**

|                          |  |
|--------------------------|--|
| metamat                  | metabolite expression data matrix  |
| sampleinfo               | is a vector of sample group, with element names as sample IDs.   |
| grouporder               | grouporder is a vector with 2 elements, the first element is the reference group name, like 'Normal', the second one is the experimental group name like 'Cancer'. |
| pathid                   | character variable, Pathway ID, usually 5 digits.  |
| specie                   | character, scientific name of the targeted species.  |
| filesuffix               | output file suffix   |
| Metabolite_pathway_table | Metabolites mapping table  |

**Value**

Pathview visualization output

**Examples**

```
dt = lilikoï.Loaddata(file=system.file("extdata","plasma_breast_cancer.csv", package = "lilikoï"))
Metadata <- dt$Metadata
dataSet <- dt$dataSet
# convertResults=lilikoï.MetaT0pathway('name')
# Metabolite_pathway_table = convertResults$table

# data_dir=system.file("extdata", "plasma_breast_cancer.csv", package = "lilikoï")
# plasma_data <- read.csv(data_dir, check.names=FALSE, row.names=1, stringsAsFactors = FALSE)
# sampleinfo <- plasma_data$Label
# names(sampleinfo) <- row.names(plasma_data)

# metamat <- t(t(plasma_data[-1]))
# metamat <- log2(metamat)
# grouporder <- c('Normal', 'Cancer')
# make sure install pathview package first before running the following code.
# library(pathview)
# data("bods", package = "pathview")
```

```
# options(bitmapType='cairo')
#lilikoi.KEGGplot(metamat = metamat, sampleinfo = sampleinfo, grouporder = grouporder,
#pathid = '00250', specie = 'hsa',filesuffix = 'GSE16873',
#Metabolite_pathway_table = Metabolite_pathway_table)
```

---

lilikoi.Loaddata      *A Loaddata Function*

---

### Description

This function allows you to load your metabolomics data.

### Usage

```
lilikoi.Loaddata(filename)
```

### Arguments

filename      file name.

### Value

A data frame named Metadata.

### Examples

```
lilikoi.Loaddata(file=system.file("extdata", "plasma_breast_cancer.csv", package = "lilikoi"))
```

---

lilikoi.machine\_learning  
*A machine learning Function*

---

### Description

This function for classification using 8 different machine learning algorithms and it plots the ROC curves and the AUC, SEN, and specificity

**Usage**

```
lilikoimachine_learning(  
  MLmatrix = PDSmatrix,  
  measurementLabels = Label,  
  significantPathways = selected_Pathways_Weka,  
  trainportion = 0.8,  
  cvnum = 10,  
  dlround = 50,  
  nrun = 10,  
  Rpart = TRUE,  
  LDA = TRUE,  
  SVM = TRUE,  
  RF = TRUE,  
  GBM = TRUE,  
  PAM = TRUE,  
  LOG = TRUE,  
  DL = TRUE  
)
```

**Arguments**

|                     |   |
|---------------------|---|
| MLmatrix            | selected pathway deregulation score or metabolites expression matrix                      |
| measurementLabels   | measurement label for samples   |
| significantPathways | selected pathway names  |
| trainportion        | train percentage of the total sample size   |
| cvnum               | number of folds   |
| dlround             | epoch number for the deep learning method   |
| nrun                | denotes the total number of runs of each method to get their averaged performance metrics |
| Rpart               | TRUE if run Rpart method  |
| LDA                 | TRUE if run LDA method  |
| SVM                 | TRUE if run SVM method  |
| RF                  | TRUE if run random forest method  |
| GBM                 | TRUE if run GBM method  |
| PAM                 | TRUE if run PAM method  |
| LOG                 | TRUE if run LOG method  |
| DL                  | TRUE if run deep learning method  |

**Value**

Evaluation results and plots of all 8 machine learning algorithms, along with variable importance plots.

## Examples

```
dt = lilikoι.Loaddata(file=system.file("extdata","plasma_breast_cancer.csv", package = "lilikoι"))
Metadata <- dt$Metadata
# lilikoι.machine_learning(MLmatrix = Metadata, measurementLabels = Metadata$Label,
# significantPathways = 0,
# trainportion = 0.8, cvnum = 10, dlround=50,Rpart=TRUE,
# LDA=FALSE,SVM=FALSE,RF=FALSE,GBM=FALSE,PAM=FALSE,LOG=FALSE,DL=FALSE)
```

---

`lilikoι.MetaTopathway` *A MetaTopathway Function*

---

## Description

This function allows you to convert your metabolites id such as names, kegg ids, pubchem ids. into pathways. Metabolites which have not pathways will be excluded from any downstream analysis make sure that you have three database files which are used for exact and fuzzy matching: `cmpd_db.rda`, `syn_nms_db.rda` and `Sijia_pathway.rda` This function was modified version of the `name.match` function in the below link: [https://github.com/cangfengzhe/Metabo/blob/master/MetaboAnalyst/website/name\\_1](https://github.com/cangfengzhe/Metabo/blob/master/MetaboAnalyst/website/name_1)

## Usage

```
lilikoι.MetaTopathway(
  q.type,
  hmdb = TRUE,
  pubchem = TRUE,
  chebi = FALSE,
  kegg = TRUE,
  metlin = FALSE
)
```

## Arguments

|                      |  |
|----------------------|--|
| <code>q.type</code>  | The type of the metabolites id such as 'name', 'kegg', 'hmdb', 'pubchem' |
| <code>hmdb</code>    | if TRUE, match metabolites id to the HMDB database.                      |
| <code>pubchem</code> | if TRUE, match metabolites id to the PubChem database.                   |
| <code>chebi</code>   | if TRUE, match metabolites id to the ChEBI database.                     |
| <code>kegg</code>    | if TRUE, match metabolites id to the KEGG database.                      |
| <code>metlin</code>  | if TRUE, match metabolites id to the METLIN database.                    |

## Value

A table showing the conversion results from metabolites ids to ids in different metabolomics databases and pathway ids and names.

## Examples

```
dt <- lilikoi.Loaddata(file=system.file("extdata",
  "plasma_breast_cancer.csv", package = "lilikoi"))
Metadata <- dt$Metadata
dataSet <- dt$dataSet
# Metabolite_pathway_table=lilikoi.MetaTOPathway('name')
```

---

|                   |                                      |
|-------------------|--------------------------------------|
| lilikoi.meta_path | <i>Metabolite-pathway regression</i> |
|-------------------|--------------------------------------|

---

## Description

Performs single variate linear regression between selected pathways and each of their metabolites. Output the network plot between pathways and metabolites.

## Usage

```
lilikoi.meta_path(  
  PDSmatrix,  
  selected_Pathways_Weka,  
  Metabolite_pathway_table,  
  pathway = "Pyruvate Metabolism"  
)
```

## Arguments

|                          |  |
|--------------------------|--|
| PDSmatrix                | Pathway deregulation score matrix                        |
| selected_Pathways_Weka   | Selected top pathways from the featureSelection function |
| Metabolite_pathway_table | Metabolites mapping table                                |
| pathway                  | interested pathway name                                  |

## Value

A bipartite graph of the relationships between pathways and their corresponding metabolites.



---

lilikoi.PDSfun      *A PDSfun Function*

---

**Description**

This function allows you to compute Pathway Desregulation Score deriving make sure that you have the below database for the metabolites and pathway list: meta\_path.RData

**Usage**

```
lilikoi.PDSfun(qvec)
```

**Arguments**

qvec                      This is the Metabolite\_pathway\_table from MetaTOpathway function. This table includes the metabolites ids and the its corrsponding hmdb ids

**Value**

A large matrix of the pathway deregulation scores for each pathway in different samples.

**References**

Nygård, S., Lingjærde, O.C., Caldas, C. et al. PathTracer: High-sensitivity detection of differential pathway activity in tumours. *Sci Rep* 9, 16332 (2019). <https://doi.org/10.1038/s41598-019-52529-3>

**Examples**

```
dt <- lilikoi.Loaddata(file=system.file("extdata",
  "plasma_breast_cancer.csv", package = "lilikoi"))
Metadata <- dt$Metadata
dataSet <- dt$dataSet
convertResults=lilikoi.MetaTOpathway('name')
Metabolite_pathway_table = convertResults$table
# PDSmatrix= lilikoi.PDSfun(Metabolite_pathway_table)
```

---

lilikoi.preproc\_knn      *An imputation function.*

---

**Description**

This function is used to preprocess data via knn imputation.

**Usage**

```
lilikoi.preproc_knn(inputdata = Metadata, method = c("knn"))
```

**Arguments**

|           |   |
|-----------|---|
| inputdata | An expression data frame with samples in the rows, metabolites in the columns |
| method    | The method to be used to process data, including                              |

**Value**

A KNN imputed dataset with samples in the rows, metabolites in the columns.

**Examples**

```
dt <- lilikoi.Loaddata(file=system.file("extdata",  
  "plasma_breast_cancer.csv", package = "lilikoi"))  
Metadata <- dt$Metadata  
dataSet <- dt$dataSet  
lilikoi.preproc_knn(inputdata=Metadata, method="knn")
```

---

lilikoi.preproc\_norm *A Normalization function.*

---

**Description**

This function is used to preprocess data via normalization. It provides three normalization methods: standard normalization, quantile normalization and median fold normalization. The median fold normalization is adapted from <http://www.metabolomics-forum.com/index.php?topic=281.0>.

**Usage**

```
lilikoi.preproc_norm(  
  inputdata = Metadata,  
  method = c("standard", "quantile", "median")  
)
```

**Arguments**

|           |   |
|-----------|---|
| inputdata | An expression data frame with samples in the rows, metabolites in the columns   |
| method    | The method to be used to process data, including standard normalization (standard), quantile normalization (quantile) and median fold normalization (median). |

**Value**

A normalized dataset with samples in the rows, metabolites in the columns.

**Examples**

```
dt <- lilikoiprognosis(file=system.file("extdata",
  "plasma_breast_cancer.csv", package = "lilikoiprognosis"))
Metadata <- dt$Metadata
dataSet <- dt$dataSet
lilikoiprognosis(inputdata=Metadata, method="standard")
```

---

lilikoiprognosis      *Pathway-based prognosis model*

---

**Description**

Fits a Cox proportional hazards regression model or a Cox neural network model to predict survival results.

**Usage**

```
lilikoiprognosis(
  event,
  time,
  exprdata,
  percent = NULL,
  alpha = 1,
  nfold = 5,
  method = "median",
  cvlambda = "lambda.1se",
  python.path = NULL,
  path = NULL,
  coxnnet = FALSE,
  coxnnet_method = "gradient"
)
```

**Arguments**

|          |   |
|----------|---|
| event    | survival event  |
| time     | survival time   |
| exprdata | dataset for penalization, with id in the rownames and pathway or metabolites names in the column names. |
| percent  | train-test separation percentage  |
| alpha    | denote which penalization method to use.  |
| nfold    | fold number for cross validation  |
| method   | determine the prognosis index, "quantile", "quantile" or "ratio".                                       |
| cvlambda | determine the lambda for prediction, "lambda.min" or "lambda.1se".                                      |

|                             |   |
|-----------------------------|---|
| <code>python.path</code>    | saved path for python3  |
| <code>path</code>           | saved path for the <code>L2cross_nopercent.py</code> and <code>L2cross.py</code> files in <code>lilikoiprognosis</code>   |
| <code>coxnnet</code>        | if TRUE, <code>coxnnet</code> will be used.   |
| <code>coxnnet_method</code> | the algorithm for gradient descent. Includes standard gradient descent ("gradient"), Nesterov accelerated gradient "nesterov" and momentum gradient descent ("momentum"). |

**Value**

A list of components:

|                        |  |
|------------------------|--|
| <code>c_index</code>   | C-index of the Cox-PH model                        |
| <code>diffptest</code> | Test results of the survival curve difference test |
| <code>survp</code>     | Kaplan Meier plot                                  |

**Examples**

```
# inst.path = path.package('lilikoiprognosis', quiet = FALSE) # path = "lilikoiprognosis/inst/", use R to run
# inst.path = file.path(inst.path, 'inst')
# python.path = "/Library/Frameworks/Python.framework/Versions/3.8/bin/python3"
# Prepare survival event, survival time and exprdata from your dataset.
# lilikoiprognosis(event, time, exprdata, percent=NULL, alpha=0, nfold=5, method="median",
#   cvlambda=NULL,python.path=NULL, path=inst.path, python.path=python.path,
#   coxnnet=FALSE,coxnnet_method="gradient")
```

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