

# Package ‘metadeconfoundR’

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**Type** Package

**Title** Covariate-Sensitive Analysis of Cross-Sectional High-Dimensional Data

**Version** 1.0.5

**Maintainer** Till Birkner <metadeconf@till-birkner.de>

**Description** Using non-parametric tests, naive associations between omics features and metadata in cross-sectional data-sets are detected. In a second step, confounding effects between metadata associated to the same omics feature are detected and labeled using nested post-hoc model comparison tests, as first described in Forslund, Chakaroun, Zimmermann-Kogadeeva, et al. (2021) <doi:10.1038/s41586-021-04177-9>. The generated output can be graphically summarized using the built-in plotting function.

**License** GPL-2

**Encoding** UTF-8

**LazyData** true

**URL** <https://github.com/TillBirkner/metadeconfoundR>

**BugReports** <https://github.com/TillBirkner/metadeconfoundR/issues>

**Imports** lmtree, foreach, parallel, doParallel, stats, logger, lme4, ggplot2, reshape2, methods, rlang, circlize, dplyr, ggraph, igraph, magrittr, scales, stringr

**Depends** R (>= 3.5.0), detectseparation

**Suggests** pander, knitr, gridExtra, kableExtra, testthat (>= 3.0.0), covr

**VignetteBuilder** knitr

**RoxygenNote** 7.3.3

**Config/testthat/edition** 3

**NeedsCompilation** no

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BuildConfounderMap	<i>BuildConfounderMap</i>
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## Description

BuildConfounderMap summarizes confounder analysis of a [MetaDeconfound](#) output in a circle plot

## Usage

```
BuildConfounderMap(  
  metaDeconfOutput,  
  q_cutoff = 0.1,  
  featureColor = c("black"),  
  featureNames = NULL,  
  metaVariableNames = NULL,  
  d_col = c("blue", "white", "red"),  
  d_range = "full",  
  trusted = c("OK_sd", "OK_nc", "OK_d", "AD")  
)
```

## Arguments

metaDeconfOutput	output of a metadeconfound run
q_cutoff	optional FDR-value cutoff used to remove low-significance entries from data
featureColor	optional vector of colors named after each unique feature in metaDeconfOutput

featureNames	optional two-column-dataframe containing corresponding "human-readable" names to the "machine-readable" feature names used as row.names in metaDeconfOutput. These human readable names will be displayed in the final plot. First column: machine-readable, second column: human-readable.
metaVariableNames	optional two-column-dataframe containing corresponding "human-readable" names to the "machine-readable" metadata names used as column names in metaDeconfOutput. These human readable names will be displayed in the final plot. First column: machine-readable, second column: human-readable.
d_col	set color range for effect size as c(minimum, middle, maximum), default c("red", "white", "blue")
d_range	range of effect size colors shown; "full": (default) range from -1 to +1 (best for comparability between multiple plots); "fit": range reduced according to maximum and minimum effect size present in resulting plot (better color resolution for weaker effects)
trusted	character vector of confounding status labels to be treated as trustworthy, not-confounded signal. default = c("OK_sd", "OK_nc", "OK_d", "AD")

## Details

for more details and explanations please see the package vignette.

## Value

list of ggplot2 objects

## Author(s)

Kilian Dahm

## Examples

```
data(reduced_feature)
data(metaMatMetformin)

example_output <- MetaDeconfound(featureMat = reduced_feature,
                                 metaMat = metaMatMetformin,
                                 logLevel = "ERROR")

plotObject <- BuildConfounderMap(example_output)
library(ggraph)
plotObject$MMS0001
```

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 BuildHeatmap

*BuildHeatmap*


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### Description

BuildHeatmap summarizes [MetaDeconfound](#) output in a heatmap or cuneiform plot

### Usage

```
BuildHeatmap(
  metaDeconfOutput,
  q_cutoff = 0.1,
  d_cutoff = 0.01,
  cuneiform = FALSE,
  coloring = 0,
  showConfounded = TRUE,
  intermedData = FALSE,
  featureNames = NULL,
  metaVariableNames = NULL,
  d_range = "full",
  d_col = c("blue", "white", "red"),
  keepMeta = NULL,
  keepFeature = NULL,
  trusted = c("OK_sd", "OK_nc", "OK_d", "AD"),
  tileBordCol = "black",
  reOrder = "both",
  plotPartial = "Ds",
  starSize = 2,
  starNudge_y = 0
)
```

### Arguments

metaDeconfOutput	output of a metadeconfound run
q_cutoff	optional FDR-value cutoff used to remove low-significance entries from data
d_cutoff	optional effect size cutoff used to remove low effect size entries from data
cuneiform	optional logical parameter, plot cuneiform instead of heatmap when cuneiform = TRUE
coloring	optional, can be 0,1,2; 0: color all tiles according to effectsize ; 1: don't color not significant tiles 2: like 1 but also don't color confounded signal tiles
showConfounded	optional logical parameter; set to FALSE to remove significance markers from confounded signals
intermedData	only return intermediate data for plotting, default = FALSE



```

logLevel = "ERROR")

plotObject <- BuildHeatmap(example_output)

alternativePlot <- BuildHeatmap(example_output, coloring = 2, showConfounded = FALSE)

```

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GetPartialEfSizes      *GetPartialEfSizes*

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### Description

GetPartialEfSizes takes [MetaDeconfound](#) output and generates partial effect sizes for all significant associations

### Usage

```

GetPartialEfSizes(
  featureMat,
  metaMat,
  metaDeconfOutput,
  doRanks = NA,
  randomVar = NA,
  fixedVar = NA
)

```

### Arguments

featureMat	a data frame with row(sample ID) and column(feature such as metabolite or microbial OTU ) names, listing features for all samples
metaMat	a data frame with row(sample ID) and column(meta data such as age,BMI and all possible confounders) names listing metadata for all samples. first column should be case status with case=1 and control=0. All binary variables need to be in 0/1 syntax!
metaDeconfOutput	long format output of the MetaDeconfound output created for the supplied featureMat and metaMat
doRanks	optional vector of metavariable names, that should be rank transformed when building linear models in the doconfounding step
randomVar	optional vector of metavariable names to be treated as random effect variables. These variables will not be tested for naive associations and will not be included as potential confounders, but will be added as random effects "+ (1 variable)" into any models being built. Any associations reducible to the supplied random effect(s) will be labeled as "NS". Note: Ps, Qs, Ds are computed independently and thereby not changed through inclusion of random effects.

`fixedVar` optional vector of metavariable names to be treated as fixed effect variables. These variables will not be tested for naive associations and will not be included as potential confounders, but will be added as fixed effects "+ variable" into any models being built. Any associations reducible to the supplied fixed effect(s) will be labeled as "NS". Note: Ps, Qs, Ds are computed independently and thereby not changed through inclusion of fixed effects.

## Details

for more details and explanations please see the package vignette.

## Value

long format data.frame similar to `Metadeconfound()` output

## Examples

```
data(reduced_feature)
data(metaMatMetformin)

example_output <- MetaDeconfound(featureMat = reduced_feature,
                                metaMat = metaMatMetformin,
                                logLevel = "ERROR",
                                returnLong = TRUE)

#
ex_out_partial <- GetPartialEfSizes(featureMat = reduced_feature,
                                    metaMat = metaMatMetformin,
                                    metaDeconfOutput = example_output)
```

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ImportLongPrior

*ImportLongPrior*

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## Description

ImportLongPrior imports prior knowledge of associations between individual features and metadata in form of a long-format dataframe.

## Usage

```
ImportLongPrior(longPrior, featureMat, metaMat)
```

**Arguments**

longPrior	long-format dataframe as generated by <code>Metadeconfound(returnLong = TRUE)</code> . Must contain at least one column containing feature names and one column containing associated metadata names, called "feature" and "metaVariable", respectively. Only associations between features and metadata present in featureMat and metaMat will be returned. Additionally, "Qs" and "status" (as produced by <a href="#">MetaDeconfound</a> ) columns can be supplied and will be parsed as well. If only "feature" and "metaVariable" columns are supplied, all listed associations are assumed to be significant. If "status" is supplied, only non-"NS" labeled associations will be kept.
featureMat	omics features to be analyzed by <a href="#">MetaDeconfound</a>
metaMat	metadata to be analyzed by <a href="#">MetaDeconfound</a>

**Details**

This function is meant to facilitate incorporation of prior knowledge about associations between measured omics features and available metadata both from earlier `metadeconfoundR` runs by supplying the long-format `Metadeconfound(returnLong = TRUE)` output directly or by supplying a simple list of known associations from other studies.

**Value**

wide-format dataframe that can be used as `minQValues` parameter in [MetaDeconfound](#)

**Examples**

```
data(reduced_feature)
data(metaMatMetformin)

# note that this example is only to demonstrate the process of integrating
# prior knowledge into a MetaDeconfound() analysis. Using the output of a
# MetaDeconfound() run as minQValues input for a second run with the exact
# same features and metadata will not lead to any new insights since the set
# of QValues calculated by MetaDeconfound() and the set supplied using the
# minQValues parameter are identical in this case.

example_output <- MetaDeconfound(featureMat = reduced_feature,
                                metaMat = metaMatMetformin,
                                returnLong = TRUE,
                                logLevel = "ERROR")

minQValues <- ImportLongPrior(longPrior = example_output,
                              featureMat = reduced_feature,
                              metaMat = metaMatMetformin)

example_output2 <- MetaDeconfound(featureMat = reduced_feature,
                                  metaMat = metaMatMetformin,
                                  minQValues = minQValues,
                                  logLevel = "ERROR")
```

---

MetaDeconfound	<i>MetaDeconfound</i>
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## Description

MetaDeconfound checks all feature <-> covariate combinations for confounding effects of covariates on feature <-> effect correlation

## Usage

```
MetaDeconfound(  
  featureMat,  
  metaMat,  
  nnodes = 1,  
  adjustMethod = "fdr",  
  adjustLevel = NULL,  
  robustCutoff = 5,  
  QCutoff = 0.1,  
  DCutoff = 0,  
  PHS_cutoff = 0.05,  
  logfile = NULL,  
  logLevel = "INFO",  
  startStop = NA,  
  QValues = NA,  
  DValues = NA,  
  minQValues = NULL,  
  deconfT = NULL,  
  deconfF = NULL,  
  doConfs = 2,  
  doRanks = NA,  
  randomVar = NA,  
  fixedVar = NA,  
  robustCutoffRho = NULL,  
  typeCategorical = NULL,  
  typeContinuous = NULL,  
  logistic = FALSE,  
  rawCounts = FALSE,  
  returnLong = FALSE,  
  collectMods = FALSE,  
  mediationMat = NULL,  
  noConfConfs = TRUE,  
  ...  
)
```

**Arguments**

featureMat	a data frame with row(sample ID) and column(feature such as metabolite or microbial OTU ) names, listing features for all samples
metaMat	a data frame with row(sample ID) and column(meta data such as age,BMI and all possible confounders) names listing metadata for all samples. The first column should be a binary status/outcome variable (e.g. case=1 and control=0). All other binary variables need to be in 0/1 syntax as well.
nnodes	number of nodes/cores to be used for parallel processing
adjustMethod	multiple testing p-value correction using one of the methods of <a href="#">p.adjust.methods</a>
adjustLevel	1 = correction for number of features (default); 2 = correction for number of features AND number of metavariables; 3 = correction for number of features AND number of variables in mediationMat (default when mediationMat is supplied)
robustCutoff	minimal number of sample size for each covariate in order to have sufficient power for association testing
QCutoff	significance cutoff for q-value, DEFAULT = 0.1
DCutoff	effect size cutoff (either Cliff's Delta or Spearman's rho), DEFAULT = 0
PHS_cutoff	PostHoc Significance cutoff
logfile	name of optional logging file.
logLevel	logging verbosity, possible levels: TRACE, DEBUG, INFO, WARN, ERROR, FATAL, OFF, DEFAULT = INFO
startStop	vector of optional strings controlling which parts of the pipeline should be executed. ("naiveStop": only naive associations will be computed, no confounder analysis is done)
QValues	optional data.frame containing pre-computed multiple-testing corrected p-values for naive associations
DValues	optional data.frame containing pre-computed effect sizes for naive associations
minQValues	pessimistic qvalues, can be generated by <a href="#">ImportLongPrior</a> . This dataframe of QValues is used to incorporate prior knowledge of potential associations between individual features and metadata by supplying QValues < QCutoff for these associations. All significant associations thus reported will be treated as potentially confounding influences.
deconfT	vector of metavariable names <i>*always*</i> to be included as potential confounder
deconfF	vector of metavariable names <i>*never*</i> to be included as potential confounder
doConfs	optional parameter for additional computation of confidence interval of linear models in the deconfounding step. level: (0 = no , 1 = logging, 2 = strict (default))
doRanks	optional vector of metavariable names, that should be rank transformed when building linear models in the doconfounding step
randomVar	optional vector of metavariable names to be treated as random effect variables. These variables will not be tested for naive associations and will not be included as potential confounders, but will be added as random effects "+ (1 variable)" into any models being built. Any associations reducible to the supplied random effect(s) will be labeled as "NS". Note: Ps, Qs, Ds are computed independently and thereby not changed through inclusion of random effects.

<code>fixedVar</code>	optional vector of metavariable names to be treated as fixed effect variables. These variables will not be tested for naive associations and will not be included as potential confounders, but will be added as fixed effects "+ variable" into any models being built. Any associations reducible to the supplied fixed effect(s) will be labeled as "NS". Note: Ps, Qs, Ds are computed independently and thereby not changed through inclusion of fixed effects.
<code>robustCutoffRho</code>	optional robustness cutoff for continuous variables
<code>typeCategorical</code>	optional character vector of metavariable names to always be treated as categorical
<code>typeContinuous</code>	optional character vector of metavariable names to always be treated as continuous
<code>logistic</code>	optional logical parameter; DEFAULT = FALSE; Set TRUE to treat supplied features as binary instead of continuous
<code>rawCounts</code>	optional logical parameter; DEFAULT = FALSE; Set TRUE to treat supplied features as not normalized/rarefied counts; <code>metadeconfoundR</code> will compute total read count per sample and include this information in the modelling steps. WARNING: naive associations in first part of <code>metadeconfoundR</code> are computed on TSS-transformed version of input data.
<code>returnLong</code>	DEFAULT = FALSE; Set TRUE to get output in one long format data.frame instead of list of four wide format data.frames
<code>collectMods</code>	DEFAULT = FALSE; Set TRUE to collect all model objects generated by <code>Metadeconfound</code> and return them in a nested list alongside the standard Ps/Qs/Ds/status output.
<code>mediationMat</code>	optional additional data frame for mediation analysis with row(sample ID) and column(feature such as metabolite or microbial OTU) names. Features supplied here will be tested for associations in <code>featureMat</code> , and confounder controlled for variables in <code>metaMat</code> .
<code>noConfConfs</code>	DEFAULT = TRUE; Set FALSE if confounders that are themselves confounded by other variables should be kept in the list of confounders in the status label of affected associations.
<code>...</code>	for additional arguments used internally (development/debugging)

### Details

for more details and explanations please see the vignette.

### Value

list with elements (or data.frame with columns, when `returnLong = TRUE`) Ds = effectsize, Ps = uncorrected p-value for naive association, Qs = multiple testing corrected p-value/fdr, and status = confounding status for all feature <=> covariate combinations with following categories: (NS = not significant, OK\_sd = strictly deconfounded, OK\_nc = no covariates, OK\_d = doubtful, AD = ambiguously deconfounded, C: followed by comma separated covariate names = confounded by

listed covariates)

Can be plotted using [BuildHeatmap](#).

### Examples

```
data(reduced_feature)
data(metaMatMetformin)

example_output <- MetaDeconfound(featureMat = reduced_feature,
                                  metaMat = metaMatMetformin,
                                  logLevel = "ERROR")
```

---

metaMatMetformin      *Documentation for the metaMatMetformin RData in /data*

---

### Description

set of features from the metformin dataset (Forslund et al. (2015), DOI: <https://doi.org/10.1038/nature15766>), containing status for 5 different properties for 753 samples

---

reduced\_feature      *Documentation for the reduced\_feature RData in /data*

---

### Description

reduced set of features from the metformin dataset (Forslund et al. (2015), DOI: <https://doi.org/10.1038/nature15766>), containing feature measurements for 753 samples

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