Package 'Tweedieverse'

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Title Differential analysis of omics data based on the Tweedie distribution

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Description A toolkit for differential analysis of omics data. Implements a range of statistical methodology based on the Tweedie distribution. Unlike traditional single-omics tools, Tweedieverse is technology-agnostic and can be applied to both count and continuous measurements arising from diverse high-throughput technologies (e.g. transcript abundances from bulk and single-cell RNA-Seq studies in the form of UMI counts or non-UMI counts, microbiome taxonomic and functional profiles in the form of counts or relative abundances, and compound abundance levels or peak intensities from metabolomics and other mass spectrometry-based experiments, among others). The software includes multiple analysis methods (e.g. self-adaptive, zero-inflated, and non-zero-inflated statistical models) as well as multiple customization options such as the inclusion of random effects and multiple covariates along with several data exploration capabilities and visualization modules in a unified estimation umbrella.

Depends R (>= 3.6)

Imports cplm, statmod, glmmTMB, pbapply, logging, parallel, dplyr, tweedie, ggplot2, grid, pheatmap, bbmle, parameters

Suggests data.table, knitr

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LazyData TRUE

RoxygenNote 7.1.1

VignetteBuilder knitr

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`Tweedieverse` *Multi-omics Differential Analysis with Tweedie GLMs*

Description

Fit a per-feature Tweedie generalized linear model to omics features.

Usage

```
Tweedieverse(
  input_features,
  input_metadata,
  output,
  abd_threshold = 0,
  prev_threshold = 0.1,
  var_threshold = 0,
  base_model = "CPLM",
  link = "log",
  fixed_effects = NULL,
  random_effects = NULL,
  cutoff_ZSCP = 0.3,
  criteria_ZACP = "BIC",
  adjust_offset = TRUE,
  scale_factor = NULL,
  max_significance = 0.05,
  correction = "BH",
  standardize = TRUE,
  cores = 1,
  optimizer = "nlminb",
  na.action = na.exclude,
  plot_heatmap = FALSE,
  plot_scatter = FALSE,
  heatmap_first_n = 50
)
```

Arguments

`input_features`	A tab-delimited input file or an R data frame of features (rows/columns). Samples are expected to have matching sample names with `input_metadata`.
`input_metadata`	A tab-delimited input file or an R data frame of metadata (rows/columns). Samples are expected to have matching sample names with `input_features`.
`output`	The output folder to write results.
`abd_threshold`	If prevalence-abundance filtering is desired, only features that are present (or detected) in at least `prev_threshold` percent of samples at `abd_threshold` minimum abundance (read count or proportion) are retained. Default value for `abd_threshold` is `0.0`. To disable prevalence-abundance filtering, set `abd_threshold = -Inf`.
`prev_threshold`	If prevalence-abundance filtering is desired, only features that are present (or detected) in at least `prev_threshold` percent of samples at `abd_threshold` minimum abundance (read count or proportion) are retained. Default value for `prev_threshold` is `0.1`.
`var_threshold`	If variance filtering is desired, only features that have variances greater than `var_threshold` are retained. This step is done after the prevalence-abundance filtering. Default value for `var_threshold` is `0.0` (i.e. no variance filtering).
`base_model`	The per-feature base model. Default is "CPLM". Must be one of "CPLM", "ZICP", "ZSCP", or "ZACP".
`link`	A specification of the GLM link function. Default is "log". Must be one of "log", "identity", "sqrt", or "inverse".

fixed_effects	Metadata variable(s) describing the fixed effects coefficients.
random_effects	Metadata variable(s) describing the random effects part of the model.
cutoff_ZSCP	For base_model = "ZSCP", the cutoff to stratify features for adaptive ZI modeling based on sparsity (zero-inflation proportion). Default is 0.3. Must be between 0 and 1.
criteria_ZACP	For base_model = "ZACP", the criteria to select the best fitting model per feature. The possible options are 'AIC' and BIC' (default). More criteria will be supported in a future release.
adjust_offset	If TRUE (default), an offset term will be included as the logarithm of scale_factor.
scale_factor	Name of the numerical variable containing library size (for non-normalized data) or scale factor (for normalized data) across samples to be included as an offset in the base model (when adjust_offset = TRUE). If not found in metadata, defaults to the sample-wise total sums, unless adjust_offset = FALSE.
max_significance	The q-value threshold for significance. Default is 0.05.
correction	The correction method for computing the q-value (see p.adjust for options, default is 'BH').
standardize	Should continuous metadata be standardized? Default is TRUE. Bypassed for categorical variables.
cores	An integer that indicates the number of R processes to run in parallel. Default is 1.
optimizer	The optimization routine to be used for estimating the parameters of the Tweedie model. Possible choices are "nlminb" (the default, see nlminb), "bobyqa" (bobyqa), and "L-BFGS-B" (optim). Ignored for random effects modeling which uses an alternative Template Model Builder (TMB) approach (glmmTMB).
na.action	How to handle missing values? See na.action. Default is na.exclude.
plot_heatmap	Logical. If TRUE (default is FALSE), generate a heatmap of the (top heatmap_first_n) significant associations.
plot_scatter	Logical. If TRUE (default is FALSE), generate scatter/box plots of individual associations.
heatmap_first_n	In heatmap, plot top N features with significant associations (default is 50).

Value

A data frame containing coefficient estimates, p-values, and q-values (multiplicity-adjusted p-values) are returned.

Author(s)

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Examples

```
## Not run:

##############################################################################
# Example 1 - Differential Abundance Analysis of Synthetic Microbiome Counts #
##############################################################################
```

```
#######################################
# Install and Load Required Libraries #
#######################################

library(devtools)
devtools::install_github('biobakery/sparseDOSSA@varyLibSize')
library(sparseDOSSA)
library(stringi)

######################
# Specify Parameters #
######################

n.microbes <- 200 # Number of Features
n.samples <- 100 # Number of Samples
spike.perc <- 0.02 # Percentage of Spiked-in Bugs
spikeStrength<-"20" # Effect Size

##########################
# Specify Binary Metadata #
##########################

n.metadata <- 1
UserMetadata<-as.matrix(rep(c(0,1), each=n.samples/2))
UserMetadata<-t(UserMetadata) # Transpose

#################################################
# Spiked-in Metadata (Which Metadata to Spike-in) #
#################################################

Metadatafrozenidx<-1
spikeCount<-as.character(length(Metadatafrozenidx))
significant_metadata<-paste('Metadata', Metadatafrozenidx, sep='')

############################################
# Generate SparseDOSSA Synthetic Abundances #
############################################

DD<-sparseDOSSA::sparseDOSSA(number_features = n.microbes,
number_samples = n.samples,
UserMetadata=UserMetadata,
Metadatafrozenidx=Metadatafrozenidx,
datasetCount = 1,
spikeCount = spikeCount,
spikeStrength = spikeStrength,
noZeroInflate=TRUE,
percent_spiked=spike.perc,
seed = 1234)

##############################
# Gather SparseDOSSA Outputs #
##############################

sparsedossa_results <- as.data.frame(DD$OTU_count)
rownames(sparsedossa_results)<-sparsedossa_results$X1
sparsedossa_results<-sparsedossa_results[-1,-1]
```

```
colnames(sparsedossa_results)<-paste('Sample', 1:ncol(sparsedossa_results), sep='')
data<-as.matrix(sparsedossa_results[-c((n.metadata+1):(2*n.microbes+n.metadata)),])
data<-data.matrix(data)
class(data) <- "numeric"
truth<-c(unlist(DD$truth))
truth<-truth[!stri_detect_fixed(truth,":")]
truth<-truth[(5+n.metadata):length(truth)]
truth<-as.data.frame(truth)
significant_features<-truth[seq(1,
(as.numeric(spikeCount)+1)*(n.microbes*spike.perc), (as.numeric(spikeCount)+1)),]
significant_features<-as.vector(significant_features)

####################
# Extract Features #
####################

features<-as.data.frame(t(data[-c(1:n.metadata),]))

####################
# Extract Metadata #
####################

metadata<-as.data.frame(data[1,])
colnames(metadata)<-rownames(data)[1]

##############################
# Mark True Positive Features #
##############################

wh.TP = colnames(features) %in% significant_features
colnames(features)<-paste("Feature", 1:n.microbes, sep = "")
newname = paste0(colnames(features)[wh.TP], "_TP")
colnames(features)[wh.TP] <- newname;
colnames(features)[grep('TP', colnames(features))]

####################
# Run Tweedieverse #
####################

##################
# Default options #
##################

CPLM <-Tweedieverse(
features,
metadata,
output = './demo_output/CPLM') # Assuming demo_output exists

##############################################
# User-defined prevalence-abundance filtering #
##############################################

ZICP<-Tweedieverse(
features,
metadata,
output = './demo_output/ZICP', # Assuming demo_output exists
base_model = 'ZICP',
```

```
abd_threshold = 0.0,
prev_threshold = 0.2)

###################################
# User-defined variance filtering  #
###################################

sds<-apply(features, 2, sd)
var_threshold = median(sds)/2
ZSCP<-Tweedieverse(
features,
metadata,
output = './demo_output/ZSCP', # Assuming demo_output exists
base_model = 'ZSCP',
var_threshold = var_threshold)

##################
# Multiple cores #
##################

ZACP<-Tweedieverse(
features,
metadata,
output = './demo_output/ZACP', # Assuming demo_output exists
base_model = 'ZACP',
cores = 4)

#############################################################################
# Example 2 - Multivariable Association on HMP2 Longitudinal Microbiomes #
#############################################################################

######################
# HMP2 Data Analysis #
######################

#############
# Load Data #
#############

library(data.table)
input_features <- fread("https://raw.githubusercontent.com/biobakery/Maaslin2/master/inst/extdata/HMP2_taxo
input_metadata <-fread("https://raw.githubusercontent.com/biobakery/Maaslin2/master/inst/extdata/HMP2_metac

###############
# Format data #
###############

library(tibble)
features<- column_to_rownames(features, 'ID')
metadata<- column_to_rownames(metadata, 'ID')

#############
# Fit Model #
#############

library(Tweedieverse)
HMP2 <- Tweedieverse(
```

```
    features,
    metadata,
    output = './demo_output/HMP2', # Assuming demo_output exists
    fixed_effects = c('diagnosis', 'dysbiosisnonIBD','dysbiosisUC','dysbiosisCD', 'antibiotics', 'age'),
    random_effects = c('site', 'subject'),
    base_model = 'CPLM',
    adjust_offset = FALSE, # No offset as the values are relative abundances
    cores = 8, # Make sure your computer has the capability
    standardize = FALSE)


    ## End(Not run)
```

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