Package ‘CBEA’

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Title  Competitive Balances for Taxonomic Enrichment Analysis in R
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Description  This package implements CBEA, a method to perform set-based analysis for microbiome relative abundance data. This approach constructs a competitive balance between taxa within the set and remainder taxa per sample. More details can be found in the Nguyen et al. 2021+ manuscript. Additionally, this package adds support functions to help users perform taxa-set enrichment analyses using existing gene set analysis methods. In the future we hope to also provide curated knowledge driven taxa sets.

License  MIT + file LICENSE

URL  https://github.com/qpmnguyen/CBEA,
https://qpmnguyen.github.io/CBEA/

BugReports  https://github.com/qpmnguyen/CBEA//issues

Depends  R (>= 4.2.0)

Imports  BiocParallel, BiocSet, dplyr, lmom, fitdistrplus, magrittr, methods, mixtools, Rcpp (>= 1.0.7), stats, SummarizedExperiment, tibble, TreeSummarizedExperiment, tidyr, glue, generics, rlang, goftest

Suggests  phyloseq, BiocStyle, covr, knitr, RefManageR, rmarkdown, sessioninfo, testthat (>= 3.0.0), tidyverse, roxygen2, mia, purrr

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Description

See main function cbea documentation for more details.

Usage

```r
.cbea(
  ab_tab,
  set_list,
  output,
  distr,
  adj = FALSE,
  n_perm = 100,
  parametric = TRUE,
  thresh = 0.05,
  init = NULL,
  control = NULL,
  parallel_backend = NULL,
  ...
)
```

Arguments

- `ab_tab` (Matrix). Named n by p matrix. This is the OTU/ASV/Strain table where taxa are columns.
- `set_list` (List). List of length m. This is a list of set membership by column names.
- `output` See documentation `cbea`
- `distr` See documentation `cbea`
- `adj` See documentation `cbea`
- `n_perm` See documentation `cbea`
- `parametric` See documentation `cbea`
- `thresh` See documentation `cbea`
- `init` See documentation `cbea`
- `control` See documentation `cbea`
- `parallel_backend` See documentation `cbea`
- `...` See documentation `cbea`

Value

A `data.frame` of size n by m. n is the total number of samples and m is the total number of sets with elements represented in the data.
cbea

Enrichment analysis using competitive compositional balances (CBEA)

Description

cbea is used compute enrichment scores per sample for pre-defined sets using the CBEA (Competitive Balances for Enrichment Analysis).

Usage

cbea(
  obj,
  set,
  output,
  distr = NULL,
  adj = FALSE,
  n_perm = 100,
  parametric = TRUE,
  thresh = 0.05,
  init = NULL,
  control = NULL,
  parallel_backend = NULL,
  ...
)

## S4 method for signature 'TreeSummarizedExperiment'
cbea(
  obj,
  set,
  output,
  distr = NULL,
  abund_values,
  adj = FALSE,
  n_perm = 100,
  parametric = TRUE,
  thresh = 0.05,
  init = NULL,
  control = NULL,
  parallel_backend = NULL,
  ...
)

## S4 method for signature 'data.frame'
cbea(
  obj,
  set,
cbea

taxa_are_rows = FALSE,
    id_col = NULL,
  output,
   distr = NULL,
  adj = FALSE,
   n_perm = 100,
parametric = TRUE,
    thresh = 0.05,
    init = NULL,
control = NULL,
parallel_backend = NULL,
...
)

## S4 method for signature 'matrix'
cbea(
    obj,
    set,
    taxa_are_rows = FALSE,
  output,
   distr = NULL,
  adj = FALSE,
   n_perm = 100,
parametric = TRUE,
    thresh = 0.05,
    init = NULL,
control = NULL,
parallel_backend = NULL,
...
)

Arguments

obj The element of class TreeSummarizedExperiment, data.frame, or matrix.
phyloseq is not supported due to conflicting dependencies and TreeSummarizedExperiment
is much more compact.

set BiocSet. Sets to be tested for enrichment in the BiocSet format. Taxa names
must be in the same format as elements in the set.

output (String). The form of the output of the model. Has to be either zscore, cdf,
    raw, pval, or sig.

distr (String). The choice of distribution for the null. Can be either mnorm (2 compo-
    nent mixture normal), norm (Normal distribution), or NULL if parametric is
    TRUE.

adj (Logical). Whether correlation adjustment procedure is utilized. Defaults to
    FALSE.

n_perm (Numeric). Add bootstrap resamples to both the permuted and unpermuted data
set. This might help with stabilizing the distribution fitting procedure, especially
if the sample size is low. Defaults to 1.
parametric  (Logical). Indicate whether a parametric distribution will be fitted to estimate z-scores, CDF values, and p-values. Defaults to TRUE
thresh  (Numeric). Threshold for significant p-values if sig is the output. Defaults to 0.05
init  (Named List). Initialization parameters for estimating the null distribution. Default is NULL.
control  (Named List). Additional arguments to be passed to fitdistr and normmixEM. Defaults to NULL.
parallel_backend
See documentation cbea
...  Additional arguments not used at the moment.
abund_values  (Character). Character value for selecting the assay to be the input to cbea
taxa_are_rows  (Logical). Indicate whether the data frame or matrix has taxa as rows
id_col  (Character Vector). Vector of character to indicate metadata columns to keep (for example, sample_id)

Details
This function support different formats of the OTU table, however for best results please use TreeSummarizedExperiment. phyloseq is supported, however CBEA will not explicitly import phyloseq package and will require users to install them separately. If use data.frame or matrix, users should specify whether taxa are rows using the taxa_are_rows option. Additionally, for data.frame, users can specify metadata columns to be kept via the id_col argument.
The output argument specifies what type of values will be returned in the final matrix. The options pval or sig returns either unadjusted p-values or dummy variables indicating whether a set is significantly enriched in that sample (based on unadjusted p-values thresholded at thresh). The option raw returns raw scores computed for each set without any distribution fitting or inference procedure. Users can use this option to examine the distribution of CBEA scores under the null.

Value
R An n by m matrix of enrichment scores at the sample level

Examples

data(hmp_gingival)
seq <- hmp_gingival$data
set <- hmp_gingival$set
# n_perm = 10 to reduce runtime
mod <- cbea(obj = seq, set = set, output = "zscore",
abund_values = "16S_rRNA",
distr = "norm", parametric = TRUE,
adj = TRUE, thresh = 0.05, n_perm = 10)
**check_args**

*Checking arguments of the function*

**Description**

This function extracts the parent environment (when called under the cbea function) and then check all the arguments.

**Usage**

```r
check_args()
```

**Value**

None

**check_distr_arg**

*This function checks for validity of arguments based on the parameters and the distribution of interest*

**Description**

This function checks for validity of arguments based on the parameters and the distribution of interest.

**Usage**

```r
check_distr_arg(param, distr, .note = NULL)
```

**Arguments**

- `param` (List): Named list of parameter values
- `distr` (String): String name of the distribution being evaluated
- `.note` (String): Any additional annotation to be put in front of error messages

**Value**

Returns 0 if there are no errors
**combine_distr**  
*Combining two distributions*

**Description**
Pass along handling of combining distributions to avoid clogging up the main function

**Usage**

```r
combine_distr(perm, unperm, distr, ...)
```

**Arguments**

- `perm` (List). A list of parameters for permuted distribution
- `unperm` (List). A list of parameters for the unpermuted distribution
- `distr` (String). Distribution of choice

**Value**
A list of the combined distribution form based on the initial distribution of choice

---

**dlst**  
*Definition for location-scale t distribution*

**Description**
Internal functions for defining the t-distribution in terms of location-scale.

**Usage**

```r
dlst(x, df = 1, mu = 0, sigma = 1, log = FALSE)
plst(q, df = 1, mu = 0, sigma = 1, log = FALSE)
```

**Arguments**

- `x`, `q` The data vector
- `df` Degrees of freedom
- `mu` The location parameter
- `sigma` The scale parameter
- `log` Indicate whether probabilities are return as log
Value

Numeric values representing the density and cumulative probability values of the location-scale t distribution

Functions

- `dlst`: Probability Density Function
- `plst`: Cumulative distribution function

Examples

```r
val <- rnorm(10)
dlst(val, df = 1, mu = 0, sigma = 1)
val <- rnorm(10)
plst(q = val, df = 1, mu = 0, sigma = 1)
```

---

**estimate_distr**  
Estimate distribution parameters from data

Description

This function takes a numeric vector input and attempts to find the most optimal solution for the parameters of the distribution of choice. Right now only `norm` and `mnorm` distributions are supported.

Usage

```r
estimate_distr(data, distr, init = NULL, args_list = NULL)
```

Arguments

- `data` (Numeric Vector). A vector of numbers that can be inputted to estimate the parameters of the distributional forms.
- `distr` (String). The distribution to be fitted. Right now only `norm` or `mnorm` is supported.
- `init` (List). Initialization parameters for each distribution. For mixtures, each named element in the list should be a vector with length equal to the number of components.
- `args_list` (List). Named list of additional arguments passed onto fitdist and normalmixEM
- `...` Other parameters passed to fitdistrplus or normalmixEM

Details

The package `fitdistrplus` is used to estimate parameters of the normal distribution while the package `normalmixEM` is used to estimate parameters of the mixture normal distribution. So far we suggest only estimating two components for the mixture normal distribution. For default options, we use mostly defaults from the packages themselves. The only difference was the mixture normal distribution where the convergence parameters were loosened and requiring more iterations to converge.
**Value**

A named list with all the parameter names and values

---

**fit_scores**  
*Function to compute CBEA scores for each set*

---

**Description**

Function to compute CBEA scores for each set

**Usage**

```r
fit_scores(
    index_vec,
    ab_tab,
    adj,
    distr,
    output,
    n_perm,
    parametric,
    thresh,
    init,
    control
)
```

**Arguments**

- `index_vec` (Character Vector). A character vector indicating the elements of the set of interest
- `ab_tab` (Matrix). Named n by p matrix. This is the OTU/ASV/Strain table where taxa are columns.
- `adj` (Logical). See documentation `cbea`
- `distr` (Character). See documentation `cbea`
- `output` (Character). See documentation `cbea`
- `n_perm` (Numeric). The total number of permutations.
- `parametric` (Logical). See documentation `cbea`
- `thresh` (Numeric). See documentation `cbea`
- `init` (List). See documentation `cbea`
- `control` (List). See documentation `cbea`

**Value**

This function returns a list containing output scores and other diagnostics (as sublists)
**get_adj_mnorm**

*Function to perform the adjustment for the mixture normal distribution*

**Description**

Function to perform the adjustment for the mixture normal distribution

**Usage**

```
get_adj_mnorm(perm, unperm, verbose = FALSE, fix_comp = "none")
```

**Arguments**

- `perm` (List): Parameter values of the distribution of scores
- `unperm` (List): Parameter values of the distribution of scores computed on unpermuted data
- `fix_comp` (Character): Which component to keep

**Value**

A List of parameters for the adjusted mixture normal.

---

**get_diagnostics**

*Get diagnostic values using parent environment.*

**Description**

This function is used internally inside fit_scores to grab the relevant objects from the previous parent environment (i.e. the environment from fit_scores) and compute relevant information. The role of this function is break diagnostic component into a different function for maintenance.

**Usage**

```
get_diagnostics(env = caller_env())
```

**Value**

This function returns a list of two components: diagnostic represent goodness-of-fit statistics for the distribution fitting itself while lmoment contains the l-moment comparisons between the computed raw scores, permuted scores, and other fitted distributions.
get_mean

Get the overall mean of a two component mixture distribution

**Description**

Get the overall mean of a two component mixture distribution

**Usage**

get_mean(mu, lambda)

**Arguments**

- **mu** (Vector). A two value vector of mean values.
- **lambda** (Vector). A two value vector of component mixing coefficients

**Value**

A numeric value representing the overall mean

get_raw_score

Get CBEA scores for a given matrix and a vector of column indices

**Description**

Get CBEA scores for a given matrix and a vector of column indices

**Usage**

get_raw_score(X, idx)

**Arguments**

- **X** (Matrix). OTU table of matrix format where taxa are columns and samples are rows
- **idx** (Integer vector). Vector of integers indicating the column ids of taxa in a set

**Value**

A matrix of size n by 1 where n is the total number of samples
get_sd

Examples

data(hmp_gingival)
seq <- hmp_gingival$data
seq_matrix <- SummarizedExperiment::assays(seq)[[1]]
seq_matrix <- t(seq_matrix) + 1
rand_set <- sample(seq_len(ncol(seq_matrix)), size = 10)
scores <- get_raw_score(X = seq_matrix, idx = rand_set)

get_sd  Get the overall standard deviation of a two component mixture distribution

Description

Get the overall standard deviation of a two component mixture distribution

Usage

get_sd(sigma, mu, mean, lambda)

Arguments

sigma  (Vector). A two value vector of component-wise variances
mu     (Vector). A two value vector of mean values.
mean   (Numeric Value). The overall mean.
lambda (Vector). A two value vector of component mixing coefficients

Value

A numeric value representing the overall standard deviation

---

glance.CBEAout  Glance at CBEAout object

Description

This function cleans up all diagnostics of the cbea method (from the CBEAout object) into a nice tibble::tibble()

Usage

## S3 method for class 'CBEAout'
glance(x, statistic, ...)

---
Arguments

x  An object of type CBEAout

statistic  What type of diagnostic to return. Users can choose to return fit_diagnostic which returns goodness of fit statistics for the different fitted distributions (e.g. log likelihoods) while fit_comparison returns comparisons across different distributions and raw values (and data) across the 4 l-moments.

...  Unused, kept for consistency with generics

Value  
A \texttt{tibble::tibble()} summarizing diagnostic fits per set (as row)

Examples

# load the data
data(hmp_gingival)
mod <- cbea(hmp_gingival$data, hmp_gingival$set, abund_values = "16SrRNA",
           output = "sig", distr = "norm", adj = FALSE, n_perm = 5, parametric = TRUE)
glance(mod, "fit_diagnostic")

---

\textbf{gmean}  \hspace{1cm} \textit{Geometric mean of a vector}

\textbf{Description}

Compute geometric mean of a vector using \(\exp(\text{mean}(\log(.x)))\) format

\textbf{Usage}

gmean(vec)

\textbf{Arguments}

vec  A vector of values with length \(n\)

\textbf{Value}

A numeric value of the geometric mean of the vector vec

\textbf{Examples}

ex <- abs(rnorm(10))
gmean(ex)
gmeanRow

Geometric mean of rows of a matrix

Description
This function computes the geometric mean by row of a numeric matrix

Usage
gmeanRow(X)

Arguments
X A numeric matrix with n rows and p columns

Value
A numeric vector of the geometric mean of the matrix X with length n

Examples
ex <- matrix(rnorm(100), nrow = 10, ncol = 10)
ex <- abs(ex)
gmeanRow(ex)

hmp_gingival
Gingival data set from the Human Microbiome Project

Description
Gingival data set from the Human Microbiome Project

Usage
data(hmp_gingival)

Format
A list with two elements

data The microbiome relative abundance data with relevant metadata obtained from the Human Microbiome Project via the HMP16SData package (snapshot: 11-15-2021). The data set is hosted the container of type phyloseq. Using the mia package users can convert it to the TreeSummarizedExperiment type.

set Sets of microbes based on their metabolism annotation at the Genera level. Annotations obtained via Calagar et al.’s repository on Zenodo (https://doi.org/10.5281/zenodo.3942108)
merge_lists

This function handles the ability to merge supplied and defaults

Description

This function handles the ability to merge supplied and defaults

Usage

merge_lists(defaults, supplied)

Arguments

defaults (List). Default options
supplied (List). Supplied options

Value

A merged list

References

Data can be downloaded directly from https://hmpdacc.org/hmp/
R interface of the data from https://doi.org/doi:10.18129/B9.bioc.HMP16SData


new_CBEAout

Creating an output object of type CBEAout

Description
This function takes a list of lists from each object and turns it into a CBEAout type object.

Usage
new_CBEAout(out, call)

Arguments
out A list containing scores for each set
call A list containing all important arguments for printing

Value
A new CBEAout object (which is a cleaner list of lists)

pmnorm
The Two Component Mixture Normal Distribution

Description
The Two Component Mixture Normal Distribution.

Usage
pmnorm(q, mu, sigma, lambda, log = FALSE, verbose = FALSE)
dmnorm(x, mu, sigma, lambda, log = FALSE, verbose = FALSE)

Arguments
q, x (Vector). Values to calculate distributional values of.
mu (Vector). A two value vector of mean values.
sigma (Vector). A two value vector of component-wise variances
lambda (Vector). A two value vector of component mixing coefficients
log (Boolean). Whether returning probabilities are in log format
verbose (Boolean). Whether to return component values.

Value
A numeric value representing the probability density value of a two-component mixture distribution.
Functions

- pmnorm: Cumulative Distribution Function
- dmnorm: Probability Density Function

Examples

```r
library(mixtools)
lambda <- c(0.7, 0.3)
mu <- c(1, 2)
sigma <- c(1, 1)
v <- rnormmix(100, lambda=lambda, mu=mu, sigma=sigma)
pmnorm(v, lambda=lambda, mu=mu, sigma=sigma)
dmnorm(v, lambda=lambda, mu=mu, sigma=sigma)
```

Description

Print dispatch for `CBEAout` objects

Usage

```r
## S3 method for class 'CBEAout'
print(x, ...)
```

Arguments

- `x` The `CBEAout` object
- `...` Undefined arguments, keeping consistency for generics

Value

Text for printing

Description

Objects exported from other packages

These objects are imported from other packages. Follow the links below to see their documentation.

 generics `glance`, `tidy`
scale_scores

Scaling scores based on estimated null distribution

Description

Scaling scores based on estimated null distribution

Usage

scale_scores(scores, method, param, distr, thresh = 0.05)

Arguments

scores  (Numeric Vector). Raw CBEA scores generated without permutations
method  (String). The final form that the user want to return. Options include cdf, zscore, pval and sig.
param   (List). The parameters of the estimated null distribution. Names must match distribution.
thresh  (Numeric). The threshold to decide whether a set is significantly enriched. Only available if method is sig

Value

A vector of size n where n is the sample size

tidy.CBEAout

Tidy a CBEAout object

Description

This function takes in a CBEA type object and collects all values across all sets and samples that were evaluated.

Usage

## S3 method for class 'CBEAout'
tidy(x, ...)

Arguments

x  A CBEAout object.
... Unused, included for generic consistency only.
Value

A tidy `tibble::tibble()` summarizing scores per sample per set.

Examples

```r
# load the data
data(hmp_gingival)
mod <- cbea(hmp_gingival$data, hmp_gingival$set, abund_values = "16SrRNA",
output = "sig", distr = "norm", adj = FALSE, n_perm = 5, parametric = TRUE)
tidy(mod)
```

Description

Setting up parameter arrays for vectorized call to `d/pnorm` functions for multi-component mixture distributions

Usage

`var_setup(mu, sigma, lambda, vlen)`

Arguments

- `mu` See `pmnorm` documentation
- `sigma` See `pmnorm` documentation
- `lambda` See `pmnorm` documentation
- `vlen` (Integer). Length of the `x` or `p` vector to be evaluated

Value

A list containing `lambda`, `mu`, and `sigma`
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