

Package ‘fcdr’

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Title Flexible cFDR

Version 1.0.0

Description Provides functions to implement the Flexible cFDR (Hutchinson et al. (2021) <[doi:10.1371/journal.pgen.1009853](https://doi.org/10.1371/journal.pgen.1009853)>) and Binary cFDR (Hutchinson et al. (2021) <[doi:10.1101/2021.10.21.465274](https://doi.org/10.1101/2021.10.21.465274)>) methodologies to leverage auxiliary data from arbitrary distributions, for example functional genomic data, with GWAS p-values to generate re-weighted p-values.

Imports locfdr, MASS, ggplot2, cowplot, fields, dplyr, spatstat.geom, polyCub, hexbin, bigsplines, data.table, grDevices, Hmisc

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binary_cfd	<i>Perform cFDR leveraging binary auxiliary covariates</i>
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Description

Perform cFDR leveraging binary auxiliary covariates

Usage

```
binary_cfd(p, q, group)
```

Arguments

p	p-values for principal trait (vector of length n)
q	binary auxiliary data values (vector of length n)
group	group membership of each SNP for leave-one-out procedure (vector of length n) (e.g. chromosome number or LD block)

Value

data.frame of p, q and v values

Examples

```
# In this example, we generate some p-values (representing GWAS p-values)
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).
# We use the parameters_in_locfdr() function to extract the parameters estimated by
# the locfdr function.

# generate p
set.seed(2)
n <- 1000
n1p <- 50
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
p <- 2*pnorm(-abs(zp))

# generate q
q <- rbinom(n, 1, 0.1)
```

```
group <- c(rep("A", n/2), rep("B", n/2))  
binary_cfdR(p, q, group)
```

`corr_plot`*Violin plot of p-values for quantiles of q*

Description

Violin plot of p-values for quantiles of q

Usage

```
corr_plot(p, q, ylim = c(0, 1.5))
```

Arguments

p	p values for principal trait (vector of length n)
q	auxiliary data values (vector of length n)
ylim	y-axis limits (-log10)

Details

Can be used to investigate the relationship between p and q

If this shows a non-monotonic relationship then the cFDR framework should not be used (because e.g. cFDR cannot simultaneously shrink v-values for high p and low p)

Value

ggplot object

Examples

```
# In this example, we generate some p-values (representing GWAS p-values)  
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).  
# We use the corr_plot() function to visualise the relationship between p and q.  
  
# generate p  
set.seed(1)  
n <- 1000  
n1p <- 50  
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))  
p <- 2*pnorm(-abs(zp))  
  
# generate q  
mixture_comp1 <- function(x) rnorm(x, mean = -0.5, sd = 0.5)
```

```

mixture_comp2 <- function(x) rnorm(x, mean = 2, sd = 1)
q <- c(mixture_comp1(n1p), mixture_comp2(n-n1p))

corr_plot(p, q)

```

flexible_cfdr

*Perform Flexible cFDR***Description**

Performs Flexible cFDR for continuous auxiliary covariates

Usage

```

flexible_cfdr(
  p,
  q,
  indep_index,
  res_p = 300,
  res_q = 500,
  nxbin = 1000,
  gridp = 50,
  splinecorr = TRUE,
  dist_thr = 0.5,
  locfdr_df = 10,
  plot = TRUE,
  maf = NULL,
  check_indep_cor = TRUE,
  enforce_p_q_cor = TRUE
)

```

Arguments

p	p-values for principal trait (vector of length n)
q	continuous auxiliary data values (vector of length n)
indep_index	indices of independent SNPs
res_p	number of grid points in x-direction (p) for KDE estimation
res_q	number of grid points in y-direction (q) for KDE estimation
nxbin	number of bins in x-direction (p) for hex-binning
gridp	number of data points required in a KDE grid point for left-censoring
splinecorr	logical value for whether spline correction should be implemented
dist_thr	distance threshold for spline correction
locfdr_df	df parameter in locfdr function

plot	logical value for whether to produce plots to assess KDE fit
maf	minor allele frequencies for SNPs to which p and q relate (optional and used to perform MAF matching)
check_indep_cor	check that sign of the correlation between p and q is the same in the independent subset as in the whole
enforce_p_q_cor	if p and q are negatively correlated, flip the sign on q values

Details

If maf is specified, then the independent SNPs will be down-sampled to match the minor allele frequency distribution.

Value

List of length two: (1) data.frame of p-values, q-values and v-values (2) data.frame of auxiliary data (q_low used for left censoring, how many data-points were left censored and/or spline corrected)

Examples

```
# this is a long running example

# In this example, we generate some p-values (representing GWAS p-values)
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).
# We use the flexible_cfd() function to generate v-values using default parameter values.

# generate p
set.seed(1)
n <- 1000
n1p <- 50
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
p <- 2*pnorm(-abs(zp))

# generate q
mixture_comp1 <- function(x) rnorm(x, mean = -0.5, sd = 0.5)
mixture_comp2 <- function(x) rnorm(x, mean = 2, sd = 1)
q <- c(mixture_comp1(n1p), mixture_comp2(n-n1p))

n_indep <- n

flexible_cfd(p, q, indep_index = 1:n_indep)
```

log10pv_plot

Plot $-\log_{10}(p)$ against $-\log_{10}(v)$ and colour by q **Description**

Plot $-\log_{10}(p)$ against $-\log_{10}(v)$ and colour by q

Usage

```
log10pv_plot(p, q, v, axis_lim = c(0, 20))
```

Arguments

<code>p</code>	<code>p</code> values for principal trait (vector of length <code>n</code>)
<code>q</code>	auxiliary data values (vector of length <code>n</code>)
<code>v</code>	<code>v</code> values from cFDR
<code>axis_lim</code>	Optional axis limits

Details

Can be used to visualise the results from Flexible cFDR

Value

ggplot object

Examples

```
# this is a long running example

# In this example, we generate some p-values (representing GWAS p-values)
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).
# We use the flexible_cfd_r() function to generate v-values and then the log10pv_plot() function
# to visualise the results.

# generate p
set.seed(1)
n <- 1000
n1p <- 50
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
p <- 2*pnorm(-abs(zp))

# generate q
mixture_comp1 <- function(x) rnorm(x, mean = -0.5, sd = 0.5)
mixture_comp2 <- function(x) rnorm(x, mean = 2, sd = 1)
q <- c(mixture_comp1(n1p), mixture_comp2(n-n1p))

n_indep <- n
```

```
res <- flexible_cfdr(p, q, indep_index = 1:n_indep)
log10pv_plot(p = res[[1]]$p, q = res[[1]]$q, v = res[[1]]$v)
```

match_ind_maf	<i>Function to downsample independent SNPs to match MAF distribution of whole set.</i>
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Description

Matches MAF distribution of independent set of SNPs to MAF distribution of whole set of SNPs to avoid MAF-based confounding.

Usage

```
match_ind_maf(maf, indep_index)
```

Arguments

maf	minor allele frequencies of (all) SNPs
indep_index	indices of independent SNPs

Details

Must supply maf values from the whole data set, not just the independent SNPs.

Value

indices of independent SNP in chosen in sample

parameters_in_locfdr	<i>parameters_in_locfdr</i>
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Description

parameters_in_locfdr

Usage

```
parameters_in_locfdr(
  p,
  q,
  indep_index,
  res_p = 300,
  res_q = 500,
  maf = NULL,
  check_indep_cor = TRUE,
  enforce_p_q_cor = TRUE
)
```

Arguments

p	p values for principal trait (vector of length n)
q	continuous auxiliary data values (vector of length n)
indep_index	indices of independent SNPs
res_p	resolution for p
res_q	resolution for q
maf	minor allele frequencies for SNPs to which p and q relate (optional and used to perform MAF matching)
check_indep_cor	check that sign of the correlation between p and q is the same in the independent subset as in the whole
enforce_p_q_cor	if p and q are negatively correlated, flip the sign on q values

Value

list of values used as input into `locfdr::locfdr` function intrinsically in `flexible_cfdp`

Examples

```
# In this example, we generate some p-values (representing GWAS p-values)
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).
# We use the parameters_in_locfdr() function to extract the parameters estimated by
# the locfdr function.

# generate p
set.seed(1)
n <- 1000
n1p <- 50
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
p <- 2*pnorm(-abs(zp))

# generate q
mixture_comp1 <- function(x) rnorm(x, mean = -0.5, sd = 0.5)
mixture_comp2 <- function(x) rnorm(x, mean = 2, sd = 1)
```

```
q <- c(mixture_comp1(n1p), mixture_comp2(n-n1p))  
n_indep <- n  
parameters_in_locfdr(p, q, indep_index = 1:n_indep)
```

pv_plot

Plot p against v and colour by q

Description

Plot p against v and colour by q

Usage

```
pv_plot(p, q, v, axis_lim = c(0, 1))
```

Arguments

p	p values for principal trait (vector of length n)
q	auxiliary data values (vector of length n)
v	v values from cFDR
axis_lim	Optional axis limits

Details

Can be used to visualise the results from Flexible cFDR

Value

ggplot object

Examples

```
# this is a long running example  
  
# In this example, we generate some p-values (representing GWAS p-values)  
# and some arbitrary auxiliary data values (e.g. representing functional genomic data).  
# We use the flexible_cfd_r() function to generate v-values and then the pv_plot() function  
# to visualise the results.  
  
# generate p  
set.seed(1)  
n <- 1000  
n1p <- 50  
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
```

```
p <- 2*pnorm(-abs(zp))

# generate q
mixture_comp1 <- function(x) rnorm(x, mean = -0.5, sd = 0.5)
mixture_comp2 <- function(x) rnorm(x, mean = 2, sd = 1)
q <- c(mixture_comp1(n1p), mixture_comp2(n-n1p))

n_indep <- n

res <- flexible_cfdr(p, q, indep_index = 1:n_indep)

pv_plot(p = res[[1]]$p, q = res[[1]]$q, v = res[[1]]$v)
```

stratified_qqplot *Stratified Q-Q plot.*

Description

Stratified Q-Q plot.

Usage

```
stratified_qqplot(
  data_frame,
  prin_value_label,
  cond_value_label = NULL,
  thresholds = c(1, 0.1, 0.01, 0.001, 1e-04)
)
```

Arguments

`data_frame` data.frame containing p-values and auxiliary data values
`prin_value_label`
 label of principal p-value column in `data_frame`
`cond_value_label`
 label of conditional trait column in `data_frame`
`thresholds` threshold values to define strata

Details

Can be used to investigate the relationship between p and q

Note that this function does not do the heavy lifting of styling the plot's aesthetics.

Value

ggplot object

Examples

```
# In this example, we generate some p-values (representing GWAS p-values)
# and some arbitrary auxiliary data values (e.g. representing GWAS p-values for a related trait).
# We use the stratified_qqplot() function to examine the relationship between p and q

# generate p
set.seed(1)
n <- 1000
n1p <- 50
zp <- c(rnorm(n1p, sd=5), rnorm(n-n1p, sd=1))
p <- 2*pnorm(-abs(zp))

# generate q
zq <- c(rnorm(n1p, sd=4), rnorm(n-n1p, sd=1.2))
q <- 2*pnorm(-abs(zq))

df <- data.frame(p, q)

stratified_qqplot(data_frame = df, prin_value_label = "p", cond_value_label = "q")
```

T1D_application_data *Data for T1D application*

Description

A data.frame containing the rsID, chromosome (CHR19) and base pair position (BP19) in hg19, reference allele (REF), alternative allele (ALLT), type 1 diabetes GWAS p-value (T1D_pval), minor allele frequency (MAF), LDAK weight (LDAK_weight), rheumatoid arthritis GWAS p-value (RA_pval), binary regulatory factor binding site overlap (DGF), average H3K27ac fold change value in T1D-relevant cell types (H3K27ac) for 113,543 SNPs in the T1D GWAS (<https://www.nature.com/articles/ng.3245>)

Usage

```
T1D_application_data
```

Format

A data frame with 113543 rows and 11 variables:

Details

Minor allele frequencies estimated from the CEU sub-population samples in the 1000 Genomes Project Phase 3 data set. Missing values were replaced by drawing samples from the empirical distribution of MAFs

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