**Package ‘IHW’**

March 27, 2024

**Title** Independent Hypothesis Weighting

**Version** 1.30.0

**Description** Independent hypothesis weighting (IHW) is a multiple testing procedure that increases power compared to the method of Benjamini and Hochberg by assigning data-driven weights to each hypothesis. The input to IHW is a two-column table of p-values and covariates. The covariate can be any continuous-valued or categorical variable that is thought to be informative on the statistical properties of each hypothesis test, while it is independent of the p-value under the null hypothesis.

**Depends** R (>= 3.3.0)

**License** Artistic-2.0

**LazyData** true

**Imports** methods, slam, lpsymphony, fdrtool, BiocGenerics

**Suggests** ggplot2, dplyr, gridExtra, scales, DESeq2, airway, testthat, Matrix, BiocStyle, knitr, rmarkdown, devtools

**VignetteBuilder** knitr

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Description

Given p-values and a nominal significance level alpha, this function returns the rejection threshold of the Benjamini-Hochberg procedure, i.e. a value $t_{BH}$ such that p-values with $p_i \leq t_{BH}$ get rejected by the procedure.

Usage

```
get_bh_threshold(pvals, alpha, mtests = length(pvals))
```

Arguments

- `pvals`: Numeric, vector of p-values
- `alpha`: Numeric in $[0,1]$, significance level of the multiple testing procedure
- `mtests`: Integer, total number of hypothesis tests; only set this (to non-default) when you know what you are doing!

Value

A numeric in $[0,1]$, threshold of the BH procedure

Examples

```
pvalues <- c(runif(1000), rbeta(1000, 0.5, 7)) # generate some p-values
adj_pvalues <- p.adjust(pvalues, method="BH") # calculate adjusted p-values
$ t_{BH} <- get_bh_threshold(pvalues, 0.1) # get rejection threshold at alpha=0.1
all((pvalues <= t_{BH}) == (adj_pvalues <= 0.1)) # equivalence of two formulations
```
groups_by_filter

Stratify hypotheses based on increasing value of the covariate

Description

Hypotheses are stratified into nbins different strata of (approximately) equal size based on increasing value of the covariate.

Usage

groups_by_filter(covariate, nbins, ties.method = "random", seed = NULL)

Arguments

covariate Numeric vector of ordinal covariates based on which the stratification will be done.
nbins Integer, number of groups/strata into which p-values will be split based on covariate.
ties.method Character specifying how ties are treated, see rank function.
seed Integer, specifies random seed to be used when ties.method=="random".

Value

A factor with nbins different levels, each entry corresponds to the stratum the i-th hypothesis was assigned to.

Examples

covariates <- runif(100)
groups <- groups_by_filter(covariates,10)
table(groups)

ihw.default

ihw: Main function for Independent Hypothesis Weighting

Description

Given a vector of p-values, a vector of covariates which are independent of the p-values under the null hypothesis and a nominal significance level alpha, IHW learns multiple testing weights and then applies the weighted Benjamin Hochberg (or Bonferroni) procedure.
## Default S3 method:

```r
iwh(
  pvalues,  # Numeric vector of unadjusted p-values.
covariates,  # Vector which contains the one-dimensional covariates (independent under the
  alpha,  # H0 of the p-value) for each test. Can be numeric or a factor. (If numeric it will
  covariate_type = "ordinal",  # be converted into factor by binning.)
nbins = "auto",  # Numeric, sets the nominal level for FDR control.
  m_groups = NULL,  # "ordinal" or "nominal" (i.e. whether covariates can be sorted in increasing order
  folds = NULL,  # or not)
  quiet = TRUE,  # Integer, number of groups into which p-values will be split based on covariate.
  nfolds = 5L,  # Use "auto" for automatic selection of the number of bins. Only applicable when
  nbins_internal = 5L,  # covariates is not a factor.
  nsplits_internal = 1L,  # Integer vector of length equal to the number of levels of the covariates (only to
  lambdas = "auto",  # be specified when the latter is a factor/categorical). Each entry corresponds to
  seed = 1L,  # the number of hypotheses to be tested in each group (stratum). This argument
  distrib_estimator = "grenander",  # needs to be given when the complete vector of p-values is not available, but only
  lp_solver = "lpsymphony",  # p-values below a given threshold, for example because of memory reasons. See
  adjustment_type = "BH",  # the vignette for additional details and an example of how this principle can be
  null_proportion = FALSE,  # applied with numerical covariates.
  null_proportion_level = 0.5,
  return_internal = FALSE,
  ...
)
```
folds Integer vector or NULL. Pre-specify assignment of hypotheses into folds.
quiet Boolean, if False a lot of messages are printed during the fitting stages.
nfolds Number of folds into which the p-values will be split for the pre-validation procedure
nfolds_internal Within each fold, a second (nested) layer of cross-validation can be conducted to choose a good regularization parameter. This parameter controls the number of nested folds.
nsplits_internal Integer, how many times to repeat the nfolds_internal splitting. Can lead to better regularization parameter selection but makes ihw a lot slower.
lambdas Numeric vector which defines the grid of possible regularization parameters. Use "auto" for automatic selection.
seed Integer or NULL. Split of hypotheses into folds is done randomly. To have the output of the function be reproducible, the seed of the random number generator is set to this value at the start of the function. Use NULL if you don’t want to set the seed.
distrib_estimator Character ("grenander" or "ECDF"). Only use this if you know what you are doing. ECDF with nfolds > 1 or lp_solver == "lpsymphony" will in general be excessively slow, except for very small problems.
lp_solver Character ("lpsymphony" or "gurobi"). Internally, IHW solves a sequence of linear programs, which can be solved with either of these solvers.
adjustment_type Character ("BH" or "bonferroni") depending on whether you want to control FDR or FWER.
null_proportion Boolean, if True (default is False), a modified version of Storey’s estimator is used within each bin to estimate the proportion of null hypotheses.
null_proportion_level Numeric, threshold for Storey’s pi0 estimation procedure, defaults to 0.5
return_internal Returns a lower level representation of the output (only useful for debugging purposes).
... Arguments passed to internal functions.
formula formula, specified in the form pvalue~covariate (only 1D covariate supported)
data data.frame from which the variables in formula should be taken

Value
A ihwResult object.

See Also
ihwResult, plot,ihwResult-method, ihw.DESeqResults
**Examples**

```r
save.seed <- .Random.seed; set.seed(1)
X <- runif(20000, min=0, max=2.5)  # covariate
H <- rbinom(20000,1,0.1)  # hypothesis true or false
Z <- rnorm(20000, H*X)  # Z-score
.Random.seed <- save.seed
pvalue <- 1-pnorm(Z)  # pvalue

ihw_fdr <- ihw(pvalue, X, .1)  # Standard IHW for FDR control
ihw_fwer <- ihw(pvalue, X, .1, adjustment_type = "bonferroni")  # FWER control
table(H[adj_pvalues(ihw_fdr) <= 0.1] == 0)  #how many false rejections?
table(H[adj_pvalues(ihw_fwer) <= 0.1] == 0)
```

---

**ihw.DESeqResults**

**ihw.DESeqResults: IHW method dispatching on DESeqResults objects**

**Description**

ihw.DESeqResults: IHW method dispatching on DESeqResults objects

**Usage**

```r
## S3 method for class 'DESeqResults'
ihw(deseq_res, filter = "baseMean", alpha = 0.1, adjustment_type = "BH", ...)
```

**Arguments**

- `deseq_res`: "DESeqResults" object
- `filter`: Vector of length equal to number of rows of deseq_res object. This is used for the covariates in the call to ihw. Can also be a character, in which case deseq_res[[filter]] is used as the covariate
- `alpha`: Numeric, sets the nominal level for FDR control.
- `adjustment_type`: Character ("BH" or "bonferroni") depending on whether you want to control FDR or FWER.
- `...`: Other optional keyword arguments passed to ihw.

**Value**

A "DESeqResults" object, which includes weights and adjusted p-values returned by IHW. In addition, includes a metadata slot with an "ihwResult" object.

**See Also**

ihw, ihwResult
Examples

```r
## Not run:
library("DESeq2")
library("airway")
data("airway")
dds <- DESeqDataSet(se = airway, design = ~ cell + dex)
dds <- DESeq(dds)
deseq_res <- results(dds)
deseq_res <- ihw(deseq_res, alpha=0.1)
  #equivalent: deseq_res2 <- results(dds, filterFun = ihw)

## End(Not run)
```

---

### ihwResult-class

An S4 class to represent the ihw output.

#### Description

An S4 class to represent the ihw output.

#### Usage

- `adj_pvalues(object)`
- `weights(object, levels_only = FALSE)`
- `thresholds(object, ...)`
- `pvalues(object)`
- `weighted_pvalues(object)`
- `covariates(object)`
## S4 method for signature 'ihwResult'
covariates(object)

covariate_type(object)

## S4 method for signature 'ihwResult'
covariate_type(object)

groups_factor(object)

## S4 method for signature 'ihwResult'
groups_factor(object)

nfolds(object)

## S4 method for signature 'ihwResult'
nfolds(object)

nbins(object)

## S4 method for signature 'ihwResult'
nbins(object)

alpha(object)

## S4 method for signature 'ihwResult'
alpha(object)

rejections(object, ...)

## S4 method for signature 'ihwResult'
rejections(object)

rejected_hypotheses(object, ...)

## S4 method for signature 'ihwResult'
rejected_hypotheses(object)

regularization_term(object)

## S4 method for signature 'ihwResult'
regularization_term(object)

m_groups(object)

## S4 method for signature 'ihwResult'
m_groups(object)
as.data.frame_ihwResult(x, row.names = NULL, optional = FALSE, ...)

## S4 method for signature 'ihwResult'
as.data.frame(x, row.names = NULL, optional = FALSE, ...)

## S4 method for signature 'ihwResult'
nrow(x)

## S4 method for signature 'ihwResult'
show(object)

### Arguments

- **object, x**
  A ihwResult object as returned by a call to ihw(...)

- **levels_only**
  Logical, if FALSE, return a vector of weights (thresholds) with one weight (threshold) for each hypothesis, otherwise return a nfolds x nbins matrix of weights (thresholds)

- **...**
  Parameters passed in to individual methods

- **row.names, optional**
  See ?base::as.data.frame for a description of these arguments.

### Value

The different methods applied to an ihwResult object can return the following:

1) A vector of length equal to the number of hypotheses tested (e.g. the adjusted p-value or the weight of each hypothesis).

2) A matrix of dimension equal to nfolds x nbins (e.g. the weight of each stratum, fold combination, set by specifying levels_only=TRUE).

3) A vector of length 1 (usually a parameter of the ihwResult object such as nfolds or the total number of rejections).

4) A data.frame (as.data.frame) or just console output (show) for the extended Base generics.

See section below for the individual methods.

### Methods (by generic)

- adj_pvalues: Extract adjusted pvalues
- weights: Extract weights
- thresholds: Calculate ihw thresholds
- pvalues: Extract pvalues
- weighted_pvalues: Extract weighted pvalues
- covariates: Extract covariates
- covariate_type: Extract type of covariate ("ordinal" or "nominal")
- groups_factor: Extract factor of stratification (grouping) variable
ihwResult-class

- `nfold`: Extract number of folds
- `nbin`: Extract number of bins
- `alpha`: Extract nominal significance (alpha) level
- `rejections`: Total number of rejected hypotheses by ihw procedure
- `rejected_hypotheses`: Get a boolean vector of the rejected hypotheses
- `regularization_term`: Extract vector of regularization parameters used for each stratum
- `m_groups`: Extract total number of hypotheses within each stratum
- `as.data.frame`: Coerce ihwResult to data frame
- `nrow`: Return number of p-values
- `show`: Convenience method to show ihwResult object

Slots

- `df`: A data.frame that collects the input data, including the vector of p values and the covariate, the group assignment, as well as outputs (weighted p-values, adjusted p-values)
- `weights`: A (nbins X nfold) matrix of the weight assigned to each stratum
- `alpha`: Numeric, the nominal significance level at which the FDR is to be controlled
- `nbins`: Integer, number of distinct levels into which the hypotheses were stratified
- `nfold`: Integer, number of folds for pre-validation procedure
- `regularization_term`: Numeric vector, the final value of the regularization parameter within each fold
- `m_groups`: Integer vector, number of hypotheses tested in each stratum
- `penalty`: Character, "uniform deviation" or "total variation"
- `covariate_type`: Character, "ordinal" or "nominal"
- `adjustment_type`: Character, "BH" or "bonferroni"
- `reg_path_information`: A data.frame, information about the whole regularization path. (Currently not used, thus empty)
- `solver_information`: A list, solver specific output, e.g. were all subproblems solved to optimality? (Currently empty list)

See Also

ihw, plot, ihwResult-method

Examples

```r
save.seed <- .Random.seed; set.seed(1)
X <- runif(n = 20000, min = 0.5, max = 4.5) # Covariate
# Is the null hypothesis (mean=0) true or false?
H <- rbinom(n = length(X), size = 1, prob = 0.1)
Z <- rnorm(n = length(X), mean = H * X) # Z-score
.Random.seed <- save.seed

pvalue <- 1 - pnorm(Z) # pvalue
```
ihw_res <- ihw(pvalue, covariates = X, alpha = 0.1)
rejections(ihw_res)
colnames(as.data.frame(ihw_res))

plot(ihwResult-method  Plot functions for IHW

Description
See the vignette for usage examples.

Usage
## S4 method for signature 'ihwResult'
plot(
x,
x_axis = c(weights = "group", decisionboundary = "covariate")[what],
what = "weights",
scale = covariate_type(x)
)

Arguments
x Object of class ihwResult
x_axis Character: "group" or "covariate". Default is "group" if "what" is "weights", and "covariate" if "what" is "decisionboundary".
what Character: "weights" or "decisionboundary"
scale Character: "ordinal" or "nominal"

Value
A ggplot2 object.

Examples
save.seed <- .Random.seed; set.seed(1)
X <- runif(20000, min = 0.5, max = 4.5) # covariate
H <- rbinom(20000, 1, 0.1) # hypothesis true or false
Z <- rnorm(20000, H*X) # z-score
.Random.seed <- save.seed
pvalue <- 1-pnorm(Z) # pvalue
ihw_res <- ihw(pvalue, X, .1)
plot(ihw_res)
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