Package ‘IHW’

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**Title** Independent Hypothesis Weighting

**Version** 1.2.0

**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

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**biocViews** MultipleComparison, RNASeq

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**R topics documented:**

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get_bh_threshold  Data-driven threshold of Benjamini Hochberg Procedure

Description
Given pvalues 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 <= 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".
ihw.default

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 Benjamini Hochberg (or Bonferroni) procedure.

Usage

## Default S3 method:
ihw(pvalues, covariates, alpha, covariate_type = "ordinal",
   nbins = "auto", m_groups = NULL, quiet = TRUE, nfolds = 5L,
   nfolds_internal = 5L, nsplits_internal = 1L, lambdas = "auto",
   seed = 1L, distrib_estimator = "grenander", lp_solver = "lpsymphony",
   adjustment_type = "BH", return_internal = FALSE, ...)

## S3 method for class 'formula'
ihw(formula, data = parent.frame(), ...)

Arguments

pvalues Numeric vector of unadjusted p-values.
covariates Vector which contains the one-dimensional covariates (independent under the H0 of the p-value) for each test. Can be numeric or a factor. (If numeric it will be converted into factor by binning.)
alpha Numeric, sets the nominal level for FDR control.
covariate_type "ordinal" or "nominal" (i.e. whether covariates can be sorted in increasing order or not)
nbins Integer, number of groups into which p-values will be split based on covariate. Use "auto" for automatic selection of the number of bins. Only applicable when covariates is not a factor.
m_groups Integer vector of length equal to the number of levels of the covariates (only to be specified when the latter is a factor/categorical). Each entry corresponds to the number of hypotheses to be tested in each group (stratum). This argument needs to be given when the complete vector of p-values is not available, but only p-values below a given threshold, for example because of memory reasons. See the vignette for additional details and an example of how this principle can be applied with numerical covariates.
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 output of the function be reproducible, we set a seed. Use NULL if you don’t want a 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.

return_internal

Returns a lower level representation of the output (only useful for debugging purposes).

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
```
ihw.DESeqResults

```
table(H[adj_pvalues(ihw_fdr) <= 0.1] == 0) #how many false rejections?
table(H[adj_pvalues(ihw_fwer) <= 0.1] == 0)
```

---

### Description

ihw.DESeqResults: IHW method dispatching on DESeqResults objects

### Usage

```
## 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

```
## 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)
## S4 method for signature 'ihwResult'
adj_pvalues(object)

weights(object, levels_only = FALSE)
thresholds(object, ...)
## S4 method for signature 'ihwResult'
thresholds(object, levels_only = FALSE)
pvalues(object)
## S4 method for signature 'ihwResult'
pvalues(object)

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

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

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

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

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

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

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.
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
- `nfolds`: Extract number of folds
- `nbins`: 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 nfolds) 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
- `nfolds`: 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
H <- rbinom(n = length(X), size = 1, prob = 0.1) # Is the null hypothesis (mean=0) true or false?
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

```r
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
ihow_res <- ihow(pvalue, X, .1)
plot(ihow_res)
```
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