# Package 'adaptest'

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**Title** Data-Adaptive Statistics for High-Dimensional Multiple Testing

**Version** 1.6.1

**Description** Data-adaptive test statistics represent a general methodology for performing multiple hypothesis testing on effects sizes while maintaining honest statistical inference when operating in high-dimensional settings (<doi here>). The utilities provided here extend the use of this general methodology to many common data analytic challenges that arise in modern computational and genomic biology.

**Depends** R (>= 3.6.0)

**License** GPL-2

**URL** https://github.com/wilsoncai1992/adaptest

**BugReports** https://github.com/wilsoncai1992/adaptest/issues

**Encoding** UTF-8

**LazyData** true

**Imports** methods, graphics, stats, utils, calibrate, origami (>= 1.0.0), SummarizedExperiment, S4Vectors, tmle

**Suggests** Matrix, testthat, rmarkdown, knitr, BiocStyle, SuperLearner, earth, gam, nnls, airway

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# R topics documented:



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`adaptest` *Data-adaptive Statistics for High-Dimensional Multiple Testing*

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## Description

Computes marginal average treatment effects of a binary point treatment on multi-dimensional outcomes, adjusting for baseline covariates, using Targeted Minimum Loss-Based Estimation. A data-mining algorithm is used to perform biomarker selection before multiple testing to increase power.

## Usage

```
adaptest(Y, A, W = NULL, n_top, n_fold, parameter_wrapper = rank_DE,
  learning_library = c("SL.glm", "SL.step", "SL.glm.interaction",
  "SL.gam", "SL.earth"), absolute = FALSE, negative = FALSE,
  p_cutoff = 0.05, q_cutoff = 0.05)
```

## Arguments

| | |
|---|---|
| `Y` | (numeric vector) - A `data.frame` or `matrix` of binary or continuous biomarker measures (outcome variables). Alternatively, this will be an object of class `adapTMLE` if the wrapper `bioadaptest` is invoked (n.b., the wrapper is the preferred interface for standard data analytic use-cases arising in computational and genomic biology). |
| `A` | (numeric vector) - binary treatment indicator: `1` = treatment, `0` = control |
| `W` | (numeric vector, numeric matrix, or numeric data.frame) - matrix of baseline covariates where each column correspond to one baseline covariate and each row corresponds to one observation. |
| `n_top` | (integer vector) - value for the number of candidate covariates to generate using the data-adaptive estimation algorithm |
| `n_fold` | (integer vector) - number of cross-validation folds. |

parameter_wrapper
: (function) - user-defined function that takes input (Y, A, W, absolute, negative) and outputs a (integer vector) containing ranks of biomarkers (outcome variables). For details, please refer to the documentation for rank_DE

learning_library
: (character vector) - library of learning algorithms to be used in fitting the "Q" and "g" step of the standard TMLE procedure.

absolute
: (logical) - whether or not to test for absolute effect size. If FALSE, test for directional effect. This overrides argument negative.

negative
: (logical) - whether or not to test for negative effect size. If FALSE = test for positive effect size. This is effective only when absolute = FALSE.

p_cutoff
: (numeric) - p-value cutoff (default as 0.05) at and below which to be considered significant. Used in inference stage.

q_cutoff
: (numeric) - q-value cutoff (default as 0.05) at and below which to be considered significant. Used in multiple testing stage.

## Value

S4 object of class data_adapt, sub-classed from the container class SummarizedExperiment, with the following additional slots containing data-mining selected biomarkers and their TMLE-based differential expression and inference, as well as the original call to this function (for user reference), respectively.

top_index (integer vector) - indices for the data-mining selected biomarkers

top_colname (character vector) - names for the data-mining selected biomarkers

top_colname_significant_q (character vector) - names for the data-mining selected biomarkers, which are significant after multiple testing stage

DE (numeric vector) - differential expression effect sizes for the biomarkers in top_colname

p_value (numeric vector) - p-values for the biomarkers in top_colname

q_value (numeric vector) - q-values for the biomarkers in top_colname

significant_q (integer vector) - indices of top_colname which is significant after multiple testing stage.

mean_rank_top (numeric vector) - average ranking across folds of cross-validation folds for the biomarkers in top_colname

folds (origami::folds class) - cross validation object

## Examples

```
set.seed(1234)
data(simpleArray)
simulated_array <- simulated_array
simulated_treatment <- simulated_treatment

adaptest(Y = simulated_array,
         A = simulated_treatment,
         W = NULL,
         n_top = 5,
         n_fold = 3,
         learning_library = 'SL.glm',
         parameter_wrapper = adaptest::rank_DE,
         absolute = FALSE,
         negative = FALSE)
```

## adapTMLE-class *Constructor for class adaptmle*

### Description

Constructor for class adaptmle

### Value

class adaptmle object, sub-classed from SummarizedExperiment.

### Examples

```
library(SummarizedExperiment)
library(airway)
data(airway)

example_adaptmle_class <- function(se, n_top = 20, n_fold = 10) {
    call <- match.call(expand.dots = TRUE)
    adaptmle <- .adaptmle(
         SummarizedExperiment::SummarizedExperiment(
            assays = SummarizedExperiment::assay(se),
            colData = SummarizedExperiment::colData(se)
         ),
         call = call,
         folds = list(),  # folds (from origami)
         plot_ingredients = list(),  # top_colname
         diff_exp = as.numeric(rep(NaN, n_top)),  # DE
         p_value = as.numeric(rep(NaN, n_top)),  # p_value
         q_value = as.numeric(rep(NaN, n_top)),  # q_value
         q_sig = as.numeric(rep(NaN, n_top)),  # significant_q
         q_sig_names = list(),  # top_colname_significant_q
         rank_mean = as.numeric(rep(NaN, n_top * n_fold)),  # mean_rank_top
         prob_top = as.numeric(rep(NaN, n_top * n_fold)),  # prob_in_top
         top_index = as.numeric(rep(NaN, n_top * n_fold))  # top_index
    )
    return(adaptmle)
}

example_class <- example_adaptmle_class(se = airway)
```

## bioadaptest *Data Adaptive Multiple Testing for Computational Biology*

### Description

A thin wrapper that implements the main data-adaptive multiple hypothesis testing strategy for data structures commonly found in computational biology experiments, using the popular SummarizedExperiment container class.

## Usage

```
bioadaptest(data_in, var_int, cntrl_set = NULL, n_top = 25,
  n_fold = 10, parameter_wrapper = rank_DE,
  learning_library = c("SL.mean", "SL.glm"), absolute = FALSE,
  negative = FALSE, p_cutoff = 0.05, q_cutoff = 0.05)
```

## Arguments

| | |
|---|---|
| data_in | An object of class SummarizedExperiment, a common container class for computational biology and bioinformatics. This object is used to construct the output object of class adaptmle. |
| var_int | A numeric vector of binary treatment assignment whose effect on the biological units is to be assessed. The data-adpative target parameter approach finds any biological sites strongly impacted by this quantity across the observed experimental units (subjects). |
| cntrl_set | A matrix of discrete variables representing baseline covariates that are controlled for in the estimation of the data-adaptive target parameter via targeted maximum likelihood estimation. If NULL, an identity vector is generated internally. |
| n_top | (integer vector) - value for the number of candidate covariates to generate using the data-adaptive estimation algorithm. |
| n_fold | (integer vector) - number of cross-validation folds. |
| parameter_wrapper | (function) - user-defined function that takes input (Y, A, W, absolute, negative) and outputs a (integer vector) containing ranks of biomarkers (outcome variables). For detail, please refer to the documentation for rank_DE. |
| learning_library | (character vector) - library of learning algorithms to be used in fitting the "Q" and "g" step of the standard TMLE procedure. |
| absolute | (logical) - whether or not to test for absolute effect size. If FALSE, test for directional effect. This overrides argument negative. |
| negative | (logical) - whether or not to test for negative effect size. If FALSE = test for positive effect size. This is effective only when absolute = FALSE. |
| p_cutoff | The minimum p-value required to evaluate a given biological unit (e.g., gene) as statistically significant. |
| q_cutoff | The minimum p-value required to evaluate a given biological unit (e.g., gene) as statistically significant after applying a correction for multiple hypothesis testing. |

## Value

An object of class adaptmle, sub-classed from the popular container class SummarizedExperiment, containing information about the experiment being analyzed as well as results from applying the TMLE for the data-adaptive target parameter as produced by adpatest.

## Examples

```
library(SummarizedExperiment)
library(airway)
set.seed(5678)
```

```
data(airway)
genes_sub <- order(sample(seq_len(100)))
air_reduced <- airway[genes_sub, ]
simple_air <- cbind(air_reduced, air_reduced)
dex_var = as.numeric(as.matrix(colData(simple_air))[, 3] - 1)
airway_out <- bioadaptest(data_in = simple_air,
                          var_int = dex_var,
                          cntrl_set = NULL,
                          n_top = 5,
                          n_fold = 2,
                          parameter_wrapper = rank_DE)
```

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`cv_param_est` *Compute data-adaptive parameter estimate for a single cross-validation fold*

---

## Description

Compute data-adaptive parameter estimate for a single cross-validation fold

## Usage

```
cv_param_est(fold, data, parameter_wrapper, absolute, negative, n_top,
  learning_library, Y_name, A_name, W_name)
```

## Arguments

| | |
|---|---|
| `fold` | fold output from `origami` |
| `data` | entire training data |
| `parameter_wrapper` | user-defined function |
| `absolute` | boolean: `TRUE` = test for absolute effect size. This `FALSE` = test for directional effect. This overrides argument `negative`. |
| `negative` | boolean: `TRUE` = test for negative effect size, `FALSE` = test for positive effect size |
| `n_top` | integer value for the number of candidate covariates to generate using the data-adaptive estimation algorithm |
| `learning_library` | character of `SuperLearner` library |
| `Y_name` | (character) `colnames` of all biomarkers |
| `A_name` | (character) `colnames` of treatment |
| `W_name` | (character) `colnames` of all baseline covariates |

## Value

`data_adaptive_index` (integer vector) rank for each gene

`index_grid` (integer matrix) gene index from rank 1 to rank K

`psi_est` estimand of DE for rank 1 to rank K genes

`EIC_est` estimand of EIC for rank 1 to rank K genes

## data_adapt *S3-Style Constructor for Data Adaptive Parameter Class*

### Description

S3-Style Constructor for Data Adaptive Parameter Class

### Usage

```
data_adapt(Y, A, W = NULL, n_top, n_fold, absolute, negative,
  parameter_wrapper, learning_library)
```

### Arguments

| | |
|---|---|
| Y | (numeric vector) - continuous or binary biomarkers outcome variables |
| A | (numeric vector) - binary treatment indicator: 1 = treatment, 0 = control |
| W | (numeric vector, numeric matrix, or numeric data.frame) - matrix of baseline covariates where each column correspond to one baseline covariate. Each row correspond to one observation |
| n_top | (integer vector) - value for the number of candidate covariates to generate using the data-adaptive estimation algorithm. |
| n_fold | (integer vector) - number of cross-validation folds. |
| absolute | (logical) - whether or not to test for absolute effect size. If FALSE, test for directional effect. This overrides argument negative. |
| negative | (logical) - whether or not to test for negative effect size. If FALSE = test for positive effect size. This is effective only when absolute = FALSE. |
| parameter_wrapper | (function) - user-defined function that takes input (Y, A, W, absolute, negative) and outputs a (integer vector) containing ranks of biomarkers (outcome variables). For detail, please refer to the documentation for rank_DE. |
| learning_library | (character vector) - library of learning algorithms to be used in fitting the "Q" and "g" step of the standard TMLE procedure. |

### Value

S3 object of class "data_adapt" for data-adaptive multiple testing.

## get_composition *Decomposition tables of the data-adaptive parameter after data-mining*

### Description

Customized informative tables for examining data-adaptive statistics.

### Usage

```
get_composition(object, type = "small")
```

### Arguments

| | |
|---|---|
| object | (data_adapt) - object of class data_adapt as returned by adaptest |
| type | (character) - 'small' or 'big'. 'small' mode returns composition of data-adaptive parameters after multiple testing stage. 'big' mode returns composition of data-adaptive parameters before multiple testing stage. |

### Value

(numeric matrix) containing what fraction of the data-adaptive parameter comes from which biomarker in the original dataset.

### Examples

```
set.seed(1234)
data(simpleArray)
simulated_array <- simulated_array
simulated_treatment <- simulated_treatment

adaptest_out <- adaptest(Y = simulated_array,
                         A = simulated_treatment,
                         W = NULL,
                         n_top = 5,
                         n_fold = 3,
                         learning_library = 'SL.glm',
                         parameter_wrapper = adaptest::rank_DE,
                         absolute = FALSE,
                         negative = FALSE)
get_composition(adaptest_out, type = 'small')
```

---

## get_significant_biomarker

*Extract statistically significant biomarkers*

---

### Description

Extract statistically significant biomarkers

### Usage

```
get_significant_biomarker(object, cutoff = 0.5)
```

### Arguments

| | |
|---|---|
| object | data_adapt object |
| cutoff | cut-off value for composition percentage |

### Value

(integer vector) of significant gene index

## Examples

```
set.seed(1234)
data(simpleArray)
simulated_array <- simulated_array
simulated_treatment <- simulated_treatment

adaptest_out <- adaptest(Y = simulated_array,
                         A = simulated_treatment,
                         W = NULL,
                         n_top = 5,
                         n_fold = 3,
                         learning_library = 'SL.glm',
                         parameter_wrapper = adaptest::rank_DE,
                         absolute = FALSE,
                         negative = FALSE)
get_significant_biomarker(adaptest_out)
```

---

# plot.data_adapt *Plot method for data_adapt objects*

---

## Description

Customized plotting method for easily examining data-adaptive statistics

## Usage

```
## S3 method for class 'data_adapt'
plot(x, ..., plot_type = c("biomarker",
  "adapt_param"))
```

## Arguments

| | |
|---|---|
| x | (data_adapt) - object of class data_adapt as returned by adaptest |
| ... | additional arguments passed to plot as necessary |
| plot_type | character vector specifying which of the two types of plots to generate: "biomarker" for a plot sorted average CV-rank, or "adapt_param" for a plot sorted by q-values with labels corresponding to indices |

## Value

plot of model statistics

## print.data_adapt *Print method for data_adapt objects*

### Description

Customized informative print method for examining data-adaptive statistics

### Usage

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

### Arguments

| | |
|---|---|
| x | (data_adapt) - object of class data_adapt as returned by adaptest |
| ... | additional arguments passed to print as necessary |

### Value

strings into stdout; containing information of the fitted model

## rank_DE *Compute ranking of biomarkers by sorting effect sizes*

### Description

Computes ranking of biomarkers based effect sizes, which are computed by Targeted Minimum Loss-Based Estimation. This function is designed to be called inside adaptest; it should not be run by itself outside of that context.

### Usage

```
rank_DE(Y, A, W, absolute = FALSE, negative = FALSE,
  learning_library = c("SL.glm", "SL.step", "SL.glm.interaction",
  "SL.gam"))
```

### Arguments

| | |
|---|---|
| Y | (numeric vector) - continuous or binary biomarkers outcome variables |
| A | (numeric vector) - binary treatment indicator: 1 = treatment, 0 = control |
| W | (numeric vector, numeric matrix, or numeric data.frame) - matrix of baseline covariates where each column corrspond to one baseline covariate. Each row correspond to one observation |
| absolute | (logical) - whether or not to test for absolute effect size. If FALSE, test for directional effect. This overrides argument negative. |
| negative | (logical) - whether or not to test for negative effect size. If FALSE = test for positive effect size. This is effective only when absolute = FALSE. |
| learning_library | (character vector) - library of learning algorithms to be used in fitting the "Q" and "g" step of the standard TMLE procedure. |

## Value

an integer vector containing ranks of biomarkers.

## Examples

```
set.seed(1234)
data(simpleArray)
simulated_array <- simulated_array
simulated_treatment <- simulated_treatment
rank_DE(Y = simulated_array,
        A = simulated_treatment,
        W = rep(1, length(simulated_treatment)),
        absolute = FALSE,
        negative = FALSE)
```

---

# rank_ttest *Compute ranking of biomarkers by sorting t-test p-values*

---

## Description

Compute ranking of biomarkers by sorting t-test p-values

## Usage

```
rank_ttest(Y, A, W)
```

## Arguments

| | |
|---|---|
| Y | (numeric vector) - continuous or binary biomarkers outcome variables |
| A | (numeric vector) - binary treatment indicator: 1 = treatment, 0 = control |
| W | (numeric vector, numeric matrix, or numeric data.frame) - matrix of baseline covariates where each column corrspond to one baseline covariate and each row correspond to one observation. |

## Value

an integer vector containing ranks of biomarkers.

## Examples

```
set.seed(1234)
data(simpleArray)
rank_ttest(Y = simulated_array,
           A = simulated_treatment,
           W = rep(1, length(A)))
```

## simulated_array *Simulated differential expression data with one exposure*

### Description

A dataset containing 1e4 biomarkers and one exposure

### Usage

```
simulated_array
```

### Format

A numeric matrix containing 1e4 biomarkers of 1e2 subjects.

This is example data to be used in testing the `adaptest` procedure. Consult the vignettes for how to use this data.

### Value

A matrix `simulated_array`

## simulated_treatment *Simulated differential expression data with one exposure*

### Description

A dataset containing 1e4 biomarkers and one exposure

### Usage

```
simulated_treatment
```

### Format

A numeric vector containing binary exposures

This is example data to be used in testing the `adaptest` procedure. Consult the vignettes for how to use this data.

### Value

A numeric vector `simulated_treatment`.

summary.data_adapt *Summary tables for data_adapt objects*

## Description

Summary tables for data_adapt objects

## Usage

```
## S3 method for class 'data_adapt'
summary(object, type = "adapt_param", ...)
```

## Arguments

| | |
|---|---|
| object | (data_adapt) object as returned by adaptest |
| type | (character) - 'adapt_param' or 'biomarker'. 'adapt_param' mode summarizes the data-adaptive target parameter. 'biomarker' mode summarizes chracteristics of the biomarkers from the original data |
| ... | not implemented |

## Value

(data.frame) of the summary statistics

type = 'adapt_param' wtih columns: 'data-adaptive parameters', 'Differential expression', 'p-values', 'q-values'

type = 'biomarker' wtih columns: 'biomakers', 'mean rank', ' appear in top'

# Index