

# Package ‘IsoGene’

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**Type** Package

**Title** Order-Restricted Inference for Microarray Experiments

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**Description** Offers framework for testing for monotonic relationship between gene expression and doses in a microarray experiment. Several testing procedures including the global likelihood-ratio test (Bartholomew, 1961), Williams (1971, 1972), Marcus (1976), M (Hu et al. 2005) and the modified M (Lin et al. 2007) are used to test for the monotonic trend in gene expression with respect to doses. BH (Benjamini and Hochberg 1995) and BY (Benjamini and Yekutieli 2004) FDR controlling procedures are applied to adjust the raw p-values obtained from the permutations.

**Depends** R (>= 2.10), Iso

**Imports** xtable, Biobase, affy, ff(>= 2.0.0), tcltk

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IsoGene-package	<i>IsoGene</i>
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## Description

Library IsoGene aims to identify for genes with a monotonic trend in the expression levels with respect to the increasing doses using several test statistics. They include the global likelihood ratio test ( $E^2$ , Bartholomew 1961, Barlow et al. 1972 and Robertson et al. 1988), Williams (1971, 1972), Marcus (1976), the M (Hu et al. 2005) and the modified M (Lin et al. 2007). The p-values of the five test statistics are obtained using permutation and they are adjusted using BH (Benjamini and Hochberg 1995) and BY (Benjamini and Yekutieli 2004) procedures are used for controlling the FDR.

## Details

Package:	IsoGene
Type:	Package
Version:	1.0
Date:	2007-05-02
License:	Free

## Value

The package includes the following functions:

<a href="#">IsoGene1</a>	calculates the five test statistics in testing both increasing and decreasing alternatives for a single gene
<a href="#">IsoGenem</a>	calculates the five test statistics in testing both increasing and decreasing alternatives for all the genes in the data set

<a href="#">IsoRawp</a>	obtains the raw (one-sided and two-sided) p-values using permutations
<a href="#">IsoTestBH</a>	BH or BY procedure to adjust p-values while controlling FDR
<a href="#">IsoGenemSAM</a>	calculates the SAM test statistic
<a href="#">Isofudge</a>	calculates the fudge factor in the SAM test statistic
<a href="#">Isoqqstat</a>	calculates the SAM test statistic using permutations
<a href="#">Isoallfdr</a>	obtains the delta table in the SAM procedure
<a href="#">Isoqval</a>	the SAM procedure to obtain q-values
<a href="#">IsoTestSAM</a>	the SAM procedure to obtain a list of significant genes
<a href="#">IsoSAMPlot</a>	SAM plot
<a href="#">IsoBHPlot</a>	plot of adjusted BH and BY p-values
<a href="#">IsoPlot</a>	plot of data, sample means, and a fitted isotonic regression curve with a likely direction
<a href="#">IsopvaluePlot</a>	plot of p-values obtained using permutation under increasing or decreasing alternatives

**Author(s)**

Lin et al.

Maintainer: Martin Otava <martin.otava@uhasselt.be>

**References**

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**See Also**

[mt.rawp2adjp](#), [IsoGene1](#), [IsoGenem](#), [IsoRawp](#), [IsoTestBH](#), [IsoGenemSAM](#), [Isofudge](#), [Isoqqstat](#), [Isoallfdr](#), [Isoqval](#), [IsoSAMPlot](#), [IsoBHPlot](#), [IsoPlot](#).

---

dopamine

*Dose-response microarray example data*

---

### Description

This dose-response microarray data contains 1000 genes and 6 doses (0=control, 0.01, 0.04, 0.16, 0.63, 2.5mg/kg) with 4-5 arrays at each dose level.

### Usage

```
data(dopamine)
```

### Format

An ExpressionSet object, the assayData has 1000 features and 26 samples, and in phenoData contains information of sample names and dose levels.

For the gene expression matrix obtained using the `express` function, the column names are (X1, X2, ..., X26). These correspond to the dose levels (obtained using `pData` function): 0, 0, 0.01, 0.01, 0.04, 0.04, 0.16, 0.16, 0.63, 0.63, 2.50, 2.50, 0, 0, 0, 0.01, 0.01, 0.01, 0.04, 0.04, 0.16, 0.16, 0.63, 0.63, 2.50, 2.50.

### References

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

Gene Expression Studies Using Affymetrix Microarrays, Goehlmann, H. and Talloen, W., Chapman & Hall/CRC, 2009

### Examples

```
data(dopamine)
require(Biobase)
express <- data.frame(exprs(dopamine))
dose <- unlist(pData(dopamine))
IsoPlot(dose, express[56,], type="continuous", add.curve=TRUE)
```

---

`exampleData`*Dose-response microarray example data*

---

**Description**

This dose-response microarray data contains 1000 genes and 4 doses (one control dose, i.e., zero dose, and three increasing doses) with 3 arrays at each dose level.

**Usage**

```
data(exampleData)
```

**Format**

A data frame with 1000 observations on the following 12 variables.

- X1 Sample one with zero dose
- X1.1 Sample two with zero dose
- X1.2 Sample three with zero dose
- X2 Sample one with second dose
- X2.1 Sample two with second dose
- X2.2 Sample three with second dose
- X3 Sample one with third dose
- X3.1 Sample two with third dose
- X3.2 Sample three with third dose
- X4 Sample one with fourth dose
- X4.1 Sample two with fourth dose
- X4.2 Sample three with fourth dose

**References**

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

**Examples**

```
data(exampleData)
x <- c(rep(1,3),rep(2,3),rep(3,3),rep(4,3))
gene1 <- as.numeric(exampleData[1,])
IsoPlot(x, gene1)
```

---

`Isoallfdr`*Obtaining the delta table in the SAM procedure*

---

**Description**

The function obtains the delta table in the SAM procedure for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M).

**Usage**

```
Isoallfdr(qqstat, ddelta, stat)
```

**Arguments**

<code>qqstat</code>	output from function <code>Isoqqstat</code> containing the test statistics of permutations
<code>ddelta</code>	give a list of values as cut-off to find the number of significant genes in the SAM procedure. If unspecified, the default value is assigned using the centiles of the absolute difference between the observed and expected test statistics.
<code>stat</code>	choose one of the five test statistics to use

**Value**

`dtable`: the delta table in the SAM procedure containing six columns. The first column is the cut-off value to find the number of significant genes, the second column is the median number of false positives, the third column is the 90% percentile number of false positives, the fourth column is the number of significant genes, the fifth column is the median FDR, and the last column is the 90% FDR.

**Note**

This function calculates the delta table in the SAM procedure for the five test statistics. To use the SAM procedure, the number of genes in the dataset is preferably larger than 500.

**Author(s)**

Lin et al.

**References**

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2(1).

**See Also**

[isoreg](#), [Isoqqstat](#), [Isoqval](#), [IsoTestSAM](#), [IsoSAMPlot](#)

## Examples

```
set.seed(1234)

x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
  rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
qqstat <- Isoqqstat(x, y, fudge="pooled",niter=50)
allfdr <- Isoallfdr(qqstat,,stat="E2")
```

---

IsoBHPlot

*Plot of adjusted p-values using BH or BY adjustment*

---

## Description

The function produces a plot with adjusted p-values using BH (Benjamini and Hochberg 1995) and BY (Benjamini and Yekutieli 2004) procedures controlling for FDR. The raw p-values and adjusted BH and BY p-values are plotted.

## Usage

```
IsoBHPlot(rp, FDR, stat = c("E2", "Williams", "Marcus",
  "M", "ModifM"))
```

## Arguments

rp	raw p-value matrix with each row for one gene and 6 columns, the first column contains the Probe.ID, the second to the sixth columns are raw p-values for the five test statistics
FDR	the desired FDR to control
stat	choose one of the five test statistic to use

## Value

A plot of adjusted p-values using BH and BY procedures will be produced.

## Author(s)

Lin et al.

## References

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

## See Also

[IsoTestBH](#), [IsoRawp](#)

## Examples

```
rp <- data.frame(paste("g", 1:100), matrix(runif(500,0,1), 100, 5))
IsoBHPlot(rp, FDR = 0.05, stat = "E2")
```

---

Isofudge

*Calculation of the fudge factor for the five SAM test statistics in the SAM procedure*

---

## Description

The function calculates the fudge factor for SAM test statistics for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M).

## Usage

```
Isofudge(x, y)
```

## Arguments

x indicates the dose levels  
y gene expression for all genes

## Value

A vector of five fudge factor values for the five SAM test statistics.

## Note

This function calculates the fudge factor for SAM test statistics for the five test statistics.

## Author(s)

Lin et al.



## References

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

## See Also

[isoreg](#), [Isoallfdr](#), [IsoGenemSAM](#), [Isoqqstat](#), [Isoqval](#), [IsoTestSAM](#), [IsoSAMPlot](#)

## Examples

```
set.seed(1234)
x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
  rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
fudge.factor <- Isofudge(x,y)
```

---

IsoGene1	<i>The five test statistics calculated for both the increasing and decreasing trends</i>
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---

## Description

The function calculates the values for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M) for testing increasing and decreasing alternatives.

## Usage

```
IsoGene1(x, y)
```

## Arguments

x	indicates the dose levels
y	is the gene expression for one gene

## Value

A list with components

E2.up	the test statistic of the global likelihood test for testing increasing alternative.
Williams.up	the test statistic of Williams for testing increasing alternative.
Marcus.up	the test statistic of Marcus for testing increasing alternative.
M.up	the M test statistic for testing increasing alternative.

ModM.up	the test statistic of the modified M for testing increasing alternative.
E2.dn	the test statistic of Williams for testing decreasing alternative.
Williams.dn	the test statistic of global likelihood test for testing decreasing alternative.
Marcus.dn	the test statistic of Williams for testing decreasing alternative.
M.dn	the test statistic of global likelihood test for testing decreasing alternative.
ModM.dn	the test statistic of Williams for testing increasing alternative.
direction	the direction with the higher likelihood of increasing (indicated by "u") or decreasing (indicated by "d") trend.

**Note**

This function calculates the five test statistics for both increasing and decreasing ordered alternatives for a single gene.

**Author(s)**

Lin et al.

**References**

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnsens, L. (editors), (2012), Springer.

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijnsens L. 2010, R Journal 2/1.

**See Also**

[isoreg](#)

**Examples**

```
x <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3))
y <- c(rnorm(3,1,1), rnorm(3,2,1), rnorm(3,3,1), rnorm(3,4,1))
stat <- IsoGene1(x,y)
stat
```

---

IsoGenem	<i>The five test statistics calculated for both the increasing and decreasing trends</i>
----------	--

---

**Description**

The function calculates the values for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M) for testing increasing and decreasing alternatives.

**Usage**

```
IsoGenem(x, y)
```

**Arguments**

x	indicates the dose levels
y	gene expression for all genes

**Value**

A list with components

E2.up	the test statistic of global likelihood test for testing increasing alternative.
Williams.up	the test statistic of Williams for testing increasing alternative.
Marcus.up	the test statistic of Marcus for testing increasing alternative.
M.up	the M test statistic for testing increasing alternative.
ModM.up	the test statistic of the modified M for testing increasing alternative.
E2.dn	the test statistic of Williams for testing increasing alternative.
Williams.dn	the test statistic of global likelihood test for testing increasing alternative.
Marcus.dn	the test statistic of Williams for testing increasing alternative.
M.dn	the test statistic of global likelihood test for testing increasing alternative.
ModM.dn	the test statistic of Williams for testing increasing alternative.
direction	the direction with the higher likelihood of increasing (indicated by "u") or decreasing (indicated by "d") trend.

**Note**

This function calculates the five test statistics for both increasing and decreasing ordered alternatives for all the genes (rows in the data set).

**Author(s)**

Lin et al.

## References

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

## See Also

[isoreg](#), [IsoGene1](#)

## Examples

```
## Not run:
set.seed(1234)
x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(90, 1,1),10,9) # 10 genes with no trends
y2 <- matrix(c(rnorm(30, 1,1), rnorm(30,2,1),
               rnorm(30,3,1)), 10, 9) # 10 genes with increasing trends
y <- data.frame(rbind(y1, y2)) # y needs to be a data frame
stat <- IsoGenem(x,y)
stat

## End(Not run)
```

---

IsoGenemSAM

*The five SAM test statistics calculated for both the increasing and decreasing trends*

---

## Description

The function calculates the values for the five SAM test statistics (the global likelihood test, Williams, Marcus, M, and the modified M) for the most likely direction.

## Usage

```
IsoGenemSAM(x, y, fudge.factor)
```

## Arguments

x	indicates the dose levels
y	gene expression for all genes
fudge.factor	the fudge factor values to be used in the SAM test statistics

**Value**

A list with components

E2	the SAM test statistic of global likelihood test for the likely direction of each gene.
Williams	the test statistic of Williams for the likely direction of each gene.
Marcus	the test statistic of Marcus for the likely direction of each gene.
M	the M test statistic for the likely direction of each gene.
ModM	the test statistic of the modified M for the likely direction of each gene.
direction	the direction with the higher likelihood of increasing (indicated by "u") or decreasing (indicated by "d") trend.

**Note**

This function calculates the five test statistics for both increasing and decreasing ordered alternatives for all the genes (rows in the data set).

**Author(s)**

Lin et al.

**References**

Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijnsens, L. (editors), (2012), Springer.

Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijnsens L. 2010, R Journal 2/1.

**See Also**

[isoreg](#), [IsoGene1](#), [Isorefudge](#)

---

IsomaxT

*The maxT procedure for order restricted inference*

---

**Description**

The function calculates the adjusted p-values for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M) using the maxT procedure.

**Usage**

```
IsomaxT(x, y, niter)
```

**Arguments**

x	indicates the dose levels
y	a data frame of the gene expression
niter	number of permutations to use

**Value**

A matrix with adjusted p-values for the five test statistics.

**Note**

This function calculates the five test statistics using the maxT procedure that is controlling the Family Wise Error Rate.

**Author(s)**

Lin et al.

**References**

Resampling based multiple testing, Westfall, P.H. and Young, S.S. 1993, Wiley.  
Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.

**See Also**

[IsoTestBH](#)

**Examples**

```
x.res <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(90, 1,1),10,9) # 10 genes with no trends
y2 <- matrix(c(rnorm(30, 1,1), rnorm(30,2,1),
              rnorm(30,3,1)), 10, 9) # 10 genes with increasing trends
dat.mat <- data.frame(rbind(y1, y2)) # y needs to be a data frame
niter=1000

set.seed(1234)
pval.maxT <- IsomaxT(x.res, dat.mat,niter)
```

---

IsoPlot

*IsoPlot*

---

**Description**

Plot of the data points and the sample means at each dose

**Usage**

```
IsoPlot(x, y, type=c("continuous", "ordinal"), add.curve = FALSE)
```

**Arguments**

x	indicates the dose levels
y	is the gene expression for one gene
type	specifies the dose levels to "continuous" or "ordinal". The default is "continuous".
add.curve	specifies whether a fitted isotonic regression curve with a likely direction is added or not. The default is FALSE.

**Value**

Plot of the data points, the sample means for each dose (either as continuous or ordinal), and a fitted isotonic regression curve (optional) is produced.

**Note**

This function produces a plot for a single gene.

**Author(s)**

Lin et al.

**References**

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**Examples**

```
x <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3))
y <- c(rnorm(3,1,1), rnorm(3,2,1), rnorm(3,3,1), rnorm(3,4,1))
IsoPlot(x, y)
IsoPlot(x, y, type="ordinal", add.curve=TRUE)
```

---

IsopvaluePlot	<i>Plot of p-values from permutations under increasing or decreasing alternatives</i>
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---

**Description**

The function calculates the p-values using permutations under increasing and decreasing ordered alternatives for one gene. The p-values ( $p^{up}$  and  $p^{down}$ ) are obtained from the plot of null distribution and observed statistics.

**Usage**

```
IsopvaluePlot(x, y, niter, stat = c("E2", "Williams", "Marcus", "M", "ModifM"))
```

**Arguments**

x	the dose levels
y	the gene expressions
niter	the number of permutations to use
stat	choose one of the five test statistics to use

**Value**

Plots of the null distribution and the observed test statistic under increasing and decreasing ordered alternatives.

**Note**

The function obtains the p-values under increasing and decreasing ordered alternatives for a single gene.

**Author(s)**

Lin et al.

**References**

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**See Also**

[IsoGene1](#)



**Examples**

```
x <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3))
y <- c(rnorm(3,1,1), rnorm(3,2,1), rnorm(3,3,1), rnorm(3,4,1))

IsoqvaluePlot(x, y, niter = 1000, stat = "Williams")
```

---

 Isoqqstat

*Implementation of five SAM test statistics in the SAM procedure*


---

**Description**

The function calculates SAM test statistics from permutations for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M).

**Usage**

```
Isoqqstat(x, y, fudge, niter)
```

**Arguments**

x	indicates the dose levels
y	gene expression for all genes
fudge	the fudge factor value to be used in the SAM test statistics: either fudge="pooled" then it is calculated by the function, or fudge="none" then no fudge factor is used
niter	number of permutations used in the SAM procedure

**Value**

A list with components

aa1	the matrix of the observed test statistic values using the likelihood ratio test with 4 columns: the first column contains the observed test statistic values sorted in ascending order, the second contains the mean expected test statistic values obtained from permutations, the third column contains the difference between the first and the second column, and the last column gives the ranking of the genes in ascending order.
to1	the matrix of the test statistic values from permutations using the likelihood ratio test: each column of the matrix corresponds to the sorted test statistic from each permutation in an ascending order.
aa2	the matrix of the observed test statistic values using Williams' test with 4 columns: the first column is the sorted observed test statistic values in an ascending order, the second is the mean expected test statistic values obtained from permutations, the third column is the difference between the first and the second column, and the last column is the rankings of the genes in an ascending order.

to2	the matrix of the test statistic values from permutations using Williams' test: each column of the matrix corresponds to the sorted test statistic from each permutation in an ascending order.
aa3	the matrix of the observed test statistic values using Marcus' test with 4 columns: the first column is the sorted observed test statistic values in an ascending order, the second is the mean expected test statistic values obtained from permutations, the third column is the difference between the first and the second column, and the last column is the rankings of the genes in an ascending order.
to3	the matrix of the test statistic values from permutations using Marcus' test: each column of the matrix corresponds to the sorted test statistic from each permutation in an ascending order.
aa4	the matrix of the observed test statistic values using the M test with 4 columns: the first column is the sorted observed test statistic values in an ascending order, the second is the mean expected test statistic values obtained from permutations, the third column is the difference between the first and the second column, and the last column is the rankings of the genes in an ascending order.
to4	the matrix of the test statistic values from permutations using the M test: each column of the matrix corresponds to the sorted test statistic from each permutation in an ascending order.
aa5	the matrix of the observed test statistic values using the modified M test with 4 columns: the first column is the sorted observed test statistic values in an ascending order, the second is the mean expected test statistic values obtained from permutations, the third column is the difference between the first and the second column, and the last column is the rankings of the genes in an ascending order.
to5	the matrix of the test statistic values from permutations using the modified M test: each column of the matrix corresponds to the sorted test statistic from each permutation in an ascending order.

**Note**

This function calculates the SAM test statistics to be used in the SAM procedure for the five test statistics. To use the SAM procedure, the number of genes in the data set is preferably larger than 500.

**Author(s)**

Lin et al.

**References**

- Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.
- IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**See Also**

[isoreg](#), [Isoallfdr](#), [IsoGenemSAM](#) [Isoqval](#), [IsoTestSAM](#), [IsoSAMPlot](#)

**Examples**

```
set.seed(1234)

x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
  rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
qqstat <- Isoqqstat(x, y, fudge="pooled", niter = 50)
```

---

Isoqval

*Obtaining the list of significant genes using the SAM procedure*

---

**Description**

The function obtains the list of significant genes using the SAM procedure for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M).

**Usage**

```
Isoqval(delta, allfdr, qqstat, stat)
```

**Arguments**

delta	the delta value as cut-off to find the number of significant genes
allfdr	the delta table obtained from function Isoallfdr
qqstat	output from function Isoqqstat containing the test statistics of permutations
stat	choose one of the five test statistics to use

**Value**

A list of components

res	returns the list genes with descending q-values of the SAM procedure in three columns: the first column is the row number of the genes, the second column is the observed test statistic values, and the last column is the q-values
sign.list	returns the list of significant genes found by the defined delta value with descending p-values in three columns: the first column is the row number of the genes, the second column is the observed test statistic values, and the last column is the q-values

**Note**

This function obtains the list of significant genes using the SAM procedure for the five test statistics. To use the SAM procedure, the number of genes in the dataset is preferably larger than 500.

**Author(s)**

Lin et al.

**References**

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**See Also**

[isoreg](#), [Isoqqstat](#), [Isoallfdr](#), [IsoTestSAM](#), [IsoSAMPlot](#)

**Examples**

```
set.seed(1234)

x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
  rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
qqstat <- Isoqqstat(x, y, fudge="pooled", niter=50)
allfdr <- Isoallfdr(qqstat, ,stat="E2")
qval <- Isoqval(delta=0.2, allfdr, qqstat, stat="E2")
```

---

IsoRawp

*IsoRawp*

---

**Description**

The function calculates the raw one-sided and two-sided p-values for each test statistic using permutations.

**Usage**

```
IsoRawp(x, y, niter, progressBar=TRUE)
```

**Arguments**

x	numeric vector containing the dose levels
y	a data frame of the gene expression with Probe IDs as row names
niter	number of permutations to use
progressBar	to enable or disable progress bar; default is TRUE and setting it as FALSE, when problems with tcltk package dependency occurs, solves the problem

**Details**

The number of permutations to use can be chosen based on the number of possible permutations of samples. If the possible number is too big, usually >5000 permutations can be sufficient.

**Value**

A list of components

raw.p.one	returns the one-sided p-value matrix for the five test statistics in 6 columns: the first column is the probe ID, the second to the last columns contain the raw p-values for each test statistic
raw.p.two	returns the two-sided p-value matrix for the five test statistics in 6 columns: the first column is the probe ID, the second to the last columns contain the raw p-values for each test statistic
rawp.up	returns the one-sided p-value matrix testing increasing alternative for the five test statistics in 6 columns: the first column is the probe ID, the second to the last columns contain the raw p-values for each test statistic
rawp.dn	returns the one-sided p-value matrix testing decreasing alternative for the five test statistics in 6 columns: the first column is the probe ID, the second to the last columns contain the raw p-values for each test statistic

**Note**

For each gene, the one-sided p-values are calculated from  $\min(p^{Up}, p^{Down})$  and the two sided p-values are calculated from  $\min\{2 * \min(p^{Up}, p^{Down}), 1\}$ , where  $p^{Up}$  and  $p^{Down}$  are the p-values calculated for each ordered alternative.

**Author(s)**

Lin et al.

**References**

- Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R, Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors), (2012), Springer.
- Testing for Trend in Dose-Response Microarray Experiments: a Comparison of Testing Procedures, Multiplicity, and Resampling-Based Inference, Lin et al. 2007, Stat. App. in Gen. & Mol. Bio., 6(1), article 26.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijnsens L. 2010, R Journal 2/1.

### See Also

[IsoTestBH](#)

### Examples

```
## Not run:
set.seed(1234)
x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(90, 1,1),10,9) # 10 genes with no trends
y2 <- matrix(c(rnorm(30, 1,1), rnorm(30,2,1),
               rnorm(30,3,1)), 10, 9) # 10 genes with increasing trends
y <- data.frame(rbind(y1, y2)) # y needs to be a data frame
rp <- IsoRawp(x, y, niter = 1000)
rp

## End(Not run)
```

---

IsoSAMPlot

*Plots produced using the SAM procedure*

---

### Description

The function produces four plots using the SAM procedure for one of the five test statistics (the likelihood ratio test, Williams, Marcus, the M and modified M tests): FDR vs. delta, number of significant genes vs. delta, number of false positives vs. delta, and the observed vs. expected SAM test statistics obtained from permutations.

### Usage

```
IsoSAMPlot(qqstat, allfdr, FDR, stat)
```

### Arguments

qqstat	output from function Isoqqstat containing the test statistics of permutations
allfdr	the delta table obtained from function Isoallfdr
FDR	choose the desired FDR to control
stat	choose one of the five test statistics to use

### Value

returns four plots produced using the SAM procedure.

**Note**

This function produces four plots using the SAM procedure for the five test statistics. To use the SAM procedure, the number of genes in the dataset is preferably larger than 500.

**Author(s)**

Lin et al.

**References**

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

**See Also**

[isoreg](#), [Isoqqstat](#), [Isoallfdr](#), [Isoqval](#), [IsoTestSAM](#)

**Examples**

```
set.seed(1234)

x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
  rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
qqstat <- Isoqqstat(x, y, fudge="pooled", niter=50)
allfdr <- Isoallfdr(qqstat, , stat = "E2")
IsoSAMPlot(qqstat, allfdr, FDR = 0.1, stat = "E2")
```

---

IsoTestBH

*Test of monotonic trends using the five test statistics with BH or BY adjustment*

---

**Description**

The function adjusts for the raw p-values of the five test statistics using BH or BY procedure.

**Usage**

```
IsoTestBH(rp, FDR, type = c("BH", "BY"), stat = c("E2",
  "Williams", "Marcus", "M", "ModifM"))
```

**Arguments**

rp	raw p-value matrix with each row for one gene and 6 columns, the first column contains the Probe.ID, the second to the sixth columns are raw p-values for the five test statistics
FDR	the desired FDR to control
type	choose BH or BY procedure to control FDR
stat	choose one of the five test statistics to use

**Details**

The input raw p-values to this function can be the one sided or the two sided ones which are obtained using function `raw.p`. The results using one sided p-values and FDR controlling at  $\alpha/2$  is equivalent to that using two sided p-values and FDR controlling at  $\alpha$ .

**Value**

sign.genes	A list of significant genes while controlling FDR is obtained, with 4 columns: the first column is the probe ID, the second column is the row id, the third column is the raw p-values of the significant genes and the last column is the adjusted p-values of significant genes using BH or BY procedure
------------	--

**Note**

This function only allows one type of FDR adjustment, either BH or BY. For other type of adjustment, see function `mt.rawp2adjp` in package `multtest`.

**Author(s)**

Lin et al.

**References**

package `multtest`

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmans, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmans L. 2010, R Journal 2/1.

**See Also**

`'mt.rawp2adjp'`, [IsoRawp](#)

**Examples**

```
set.seed(1234)
rp <- data.frame(paste("g",1:100), matrix(runif(500,0,0.1), 100, 5))
sign <- IsoTestBH(rp, FDR = 0.05, type = "BH", stat = "E2")
```



---

`IsoTestSAM`*Obtaining the list of significant genes using the SAM procedure*

---

**Description**

The function obtains the list of significant genes using the SAM procedure for the five test statistics (the global likelihood test, Williams, Marcus, M, and the modified M).

**Usage**

```
IsoTestSAM(x, y, fudge, niter, FDR, stat)
```

**Arguments**

<code>x</code>	numeric vector containing the dose levels
<code>y</code>	data frame of the gene expression with Probe ID as row names
<code>fudge</code>	option used for calculating the fudge factor in the SAM test statistic, either "pooled" (fudge factor will be automatically computed in the function), or "none" if no fudge factor is used
<code>niter</code>	number of permutations to use
<code>FDR</code>	choose the desired FDR to control
<code>stat</code>	choose one of the five test statistics to use

**Value**

A list with components

<code>sign.genes1</code>	a list of genes declared significant using the SAM procedure in a matrix of 5 columns. The first column is the probe id, the second column is the corresponding row number of the probe in the dataset, and the third column is the ordered test statistic values, and the fourth column is the q-values of the SAM procedure. The last two columns are raw p-values based on permutations and BH adjusted p-values.
<code>qqstat</code>	output of Isoqqstat
<code>allfdr</code>	output of Isoallfdr

**Note**

This function obtains the list of significant genes using the SAM procedure for the five test statistics. To use the SAM procedure, the number of genes in the dataset is preferably larger than 500.

**Author(s)**

Lin et al.

## References

Lin D., Shkedy Z., Yekutieli D., Amaratunga D., and Bijmens, L. (editors). (2012) Modeling Dose-response Microarray Data in Early Drug Development Experiments Using R. Springer.

IsoGene: An R Package for Analyzing Dose-response Studies in Microarray Experiments, Pramana S., Lin D., Haldermans P., Shkedy Z., Verbeke T., De Bondt A., Talloen W., Goehlmann H., Bijmens L. 2010, R Journal 2/1.

## See Also

[isoreg](#), [Isorfudge](#), [IsoGenemSAM](#), [Isoqqstat](#), [Isoallfdr](#), [Isoqval](#), [IsoSAMplot](#)

## Examples

```
set.seed(1234)

x <- c(rep(1,3),rep(2,3),rep(3,3))
y1 <- matrix(rnorm(4500, 1,1),500,9) ## 500 genes with no trends
y2 <- matrix(c(rnorm(1500, 1,1),rnorm(1500,2,1),
              rnorm(1500,3,1)),500,9) ## 500 genes with increasing trends
y <- data.frame(rbind(y1, y2)) ##y needs to be a data frame
SAM.obj <- IsoTestSAM(x, y, fudge="pooled", niter=50, FDR=0.05, stat="E2")
```

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