Package 'ThresholdROC'

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Type Package

Title Optimum Threshold Estimation

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Description
Functions that provide point and interval estimations of optimum thresholds for continuous diagnostic tests. The methodology used is based on minimizing an overall cost function in the two- and three-state settings. We also provide functions for sample size determination and estimation of diagnostic accuracy measures. We also include graphical tools. The statistical methodology used here can be found in Perez-Jaume et al (2017) <doi:10.18637/jss.v082.i04>.

License GPL (>= 2)

Depends R (>= 3.1)

Imports MASS, numDeriv, pROC, ks

LazyData TRUE

NeedsCompilation no

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R topics documented:

AD   *Alzheimer's disease data*

Description

This dataset, obtained by Konstantina Skaltsa from Kapaki et al. 2003, contains measurements from the tau protein located in the cerebrospinal fluid (Tau variable) of 49 control subjects (Status==0) and 49 patients with Alzheimer's disease (Status==1). A column indicating the identifier of the subject is also included (id variable).

Usage

```
data("AD")
```

References

Kapaki E, Paraskevas G, Zalonis I, Zournas C. (2003). CSF Tau Protein and beta-amyloid (1-42) in Alzheimer's Disease diagnosis: Discrimination from Normal Ageing and the Other Dementias in the Greek Population. European Journal of Neurology, 10, 119-128.

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

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chemo   *Response to chemotherapy data set*

Description

This dataset contains Standardized Uptake Value (SUV) measurements (SUV variable) from 50 patients of breast cancer who underwent chemotherapy. After surgery, response to chemotherapy was evaluated using the pathology results in the surgical specimens, which was taken as gold standard by assigning one of the following three states: stable disease, partial remission and complete remission (resp variable). A column indicating the identifier of the patient is also included (id variable).

Usage

```
data("chemo")
```

References

Duch J, Fuster D, Munoz M, Fernandez P, Paredes P, Fontanillas M, Guzman F, Rubi S, Lomena F, Pons F. (2009). 18 F-FDG PET/CT for Early Prediction of Response to Neoadjuvant Chemotherapy in Breast Cancer. European Journal of Nuclear Molecular Imaging, 36, 1551-1557.

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

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diagnostic	*Diagnostic tests*

Description

This function calculates common measures of accuracy of diagnostic tests involving 2x2 contingency tables of classification results (usually, test outcome versus status tables).

Usage

```
diagnostic(tab, method = c("par", "exact"),
  casecontrol = FALSE, p = NULL, conf.level = 0.95)
```

Arguments

tab	an object of class `table` or `matrix` in the following form:
	TP FP
	FN TN
	where TP=number of true positives, FP=number of false positives, FN=number of false negatives and TN=number of true negatives; that is, a table where the first row corresponds to the positive tests and the second row to the negative tests; the first column corresponds to the diseased subjects and the second one to the healthy individuals. `dim(tab)` should be `c(2, 2)`.
method	method for calculating the confidence intervals for sensitivity, specificity, predictive values, accuracy and error rate. The user can choose between `"par"` (parametric) and `"exact"` (exact). The last one is recommended for small sample sizes. Default, `"par"`. The user can specify just the initial letters. See **Details**.
casecontrol	were data collected in a case-control study? Default, `FALSE`.
p	disease prevalence (only when `casecontrol = TRUE`; otherwise, this parameter is ignored).
conf.level	confidence level for the confidence intervals. Default, 0.95 (95%).

Details

For details about the expressions for the statistical measures calculated by this function, see **References**.

Since sensitivity, specificity, predictive values, accuracy and error rate are proportions, their confidence intervals are calculated using the functions prop.test (if method = "par") and binom.test (if method = "exact") from the stats package.

Confidence intervals for the likelihood ratios are calculated using the formulas proposed in Zhou et al (2002), Section 4.1.3. Furthermore, when likelihood ratios can not be calculated due to division by 0, the following correction is applied: 0.5 units are added to tab.

Confidence intervals for the odds ratio are calculated using the formulas proposed in Zhou et al (2002), Section 4.1.4. The same correction described before is applied when odds ratio can not be calculated due to division by 0.

Confidence intervals for the Youden index are calculated using the expression

$$CI(1 - \alpha) = (Y - z_{1-\alpha/2} * Var(Y), Y + z_{1-\alpha/2} * Var(Y)),$$

where Y is the Youden index estimate, $z_{1-\alpha/2}$ is the $1 - \alpha/2$ quantile of a $N(0, 1)$ distribution and $Var(Y)$ is the variance of the Youden index estimator, which is calculated as $Var(Sensitivity) + Var(Specificity)$.

Value

A data.frame with ten rows and three columns containing the point estimate and confidence intervals for the following statistical measures: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio, odds ratio, Youden index, accuracy and error rate.

Author(s)

Sara Perez-Jaume, Natalia Pallares

References

Youden, WJ. (1950). Index for rating diagnostic tests. Cancer 3:32-35.

Zhou XH, Obuchowski NA and McClish DK. (2002). Statistical methods in diagnostic medicine. John Wiley and sons.

See Also

thres2

Examples

```
# example 1 (Zhou et al, 2002)
japan <- matrix(c(56, 23, 6, 78), ncol=2, byrow=TRUE)
colnames(japan) <- c("D", "nD")
rownames(japan) <- c("+", "-")
```

```
japan
p <- 0.196 # disease prevalence
diagnostic(japan, "par", casecontrol=TRUE, p=p)

# example 2
table <- matrix(c(22, 2, 3, 3), ncol=2, byrow=TRUE)
diagnostic(table, "par")
diagnostic(table, "exact")

# example 3
table2 <- matrix(c(22, 2, 0, 3), ncol=2, byrow=TRUE)
diagnostic(table2, "exact")

# example 4
# generate a random sample of diseased and non-diased subjects
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased
# threshold estimation
rho <- 0.2 # prevalence
thres <- thres2(k1, k2, rho, method="equal", ci.method="delta")$T$thres
# diagnostic test using the threshold estimate
marker <- c(k1, k2) # biomarker
condition <- c(rep("nD", length(k1)), rep("D", length(k2))) # condition
test <- ifelse(marker<thres, "-", "+") # test outcome according to thres
# build the table
table3 <- table(test, condition)[2:1, ]
# diagnostic test
round(diagnostic(table3), 3)
```

    `lines.thres2`   *Add threshold lines to a plot (two-state setting)*

Description

The function includes vertical lines for the threshold and confidence interval in a plot created with
`plot.thres2()`.

Usage

```
## S3 method for class 'thres2'
lines(x, ci = TRUE, which.boot = c("norm", "perc"),
  col = 1, lty = c(1, 2), lwd = 1, ...)
```

Arguments

x	an object of class `thres2`.
ci	should the confidence interval be plotted? Default, `TRUE`. No confidence interval will be plotted if x does not contain one (that is, x$CI is NULL).
which.boot	in case x contains confidence intervals calculated by bootstrapping, which one should be printed? The user can choose between `"norm"` (based on normal distribution) or `"perc"` (based on percentiles). Default, `"norm"`. This argument is ignored if the confidence intervals were calculated by the delta method.
col	color for the threshold and its corresponding confidence interval. Default, 1.
lty	a 2-dimensional vector containing:
	`lty[1]`: line type for the threshold
	`lty[2]`: line type for the confidence interval
	Default, `c(1, 2)`. If `length(lty)` is not 2, `lty` will be recycled.
lwd	line width for the threshold and its corresponding confidence interval. Default, 1.
...	further arguments to be passed to `abline()`.

Value

With a `plot.thres2` open, this function adds lines for the required threshold.

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

See Also

[thres2](), [plot.thres2]()

Examples

```
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.2
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased

thres <- thres2(k1, k2, rho, method="eq", ci.method="d")
plot(thres, col=c(1, 2, 4), lwd=c(2, 2, 1), leg.pos="topright")
thresunequal <- thres2(k1, k2, rho, method="unequal", ci=FALSE)
lines(thresunequal, col=3) # almost the same; no confidence interval
```

```
## Not run:
  thresboot <- thres2(k1, k2, rho, method="emp", ci.method="b")
  lines(thresboot, col=5, which.boot="norm")

## End(Not run)
```

---

lines.thres3   *Add threshold lines to a plot (three-state setting)*

Description

The function includes vertical lines for the thresholds and confidence intervals in a plot created with `plot.thres3()`.

Usage

```
## S3 method for class 'thres3'
lines(x, ci = TRUE, which.boot = c("norm", "perc"),
  col = 1, lty = c(1, 2), lwd = 1, ...)
```

Arguments

x	an object of class thres3.
ci	should the confidence intervals be plotted? Default, TRUE. No confidence intervals will be plotted if x does not contain one (that is, x$CI is NULL).
which.boot	in case x contains confidence intervals calculated by bootstrapping, which one should be printed? the user can choose between "norm" (based on normal distribution) or "perc" (based on percentiles). Default, "norm". This argument is ignored if parametric confidence intervals were calculated.
col	color for the thresholds and their corresponding confidence intervals. Default, 1.
lty	a 2-dimensional vector containing: lty[1]: line type for the thresholds lty[2]: line type for the confidence intervals Default, c(1, 2). If length(lty) is not 2, lty will be recycled.
lwd	line width for the thresholds and their corresponding confidence intervals. Default, 1.
...	further arguments to be passed to abline().

Value

With a `plot.thres3` open, this function adds lines for the required threshold estimates.

References

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

See Also

thres3, plot.thres3

Examples

```
set.seed(1234)
n <- 100
k1 <- rlnorm(n)
k2 <- rnorm(n, 3, 1)
k3 <- rnorm(n, 5, 1)
rho <- c(1/3, 1/3, 1/3)

# assuming trinormality
start <- c(mean(k1), mean(k3))
thres1 <- thres3(k1, k2, k3, rho, dist1="norm", dist2="norm",
                 dist3="norm", start=start, ci.method="param")

# not assuming trinormality
start2 <- c(0.05, 0.6, 0.5, 0.95)
set.seed(2014)
thres2 <- thres3(k1, k2, k3, rho, start=start2, B=1000,
                 ci.method="boot", dist1="lnorm", dist2="norm",
                 dist3="norm")
plot(thres2, leg.pos="topright", leg.cex=0.8, col=1:4)
lines(thres1, col=5)
```

---

plot.thres2   *Threshold and density plot (two-state setting)*

Description

This function provides a graph including the sample densities (diseased and non-diseased populations), the threshold and its confidence interval.

Usage

```
## S3 method for class 'thres2'
plot(x, bw = c("nrd0", "nrd0"), ci = TRUE,
  which.boot = c("norm", "perc"), col = c(1, 2, 3),
  lty = c(1, 1, 1, 2), lwd = c(1, 1, 1),
  legend = TRUE, leg.pos = "topleft", leg.cex = 1,
  xlim = NULL, ylim = NULL,
  main = paste0("Threshold estimate ", ifelse(ci, "and CI ", ""),
  "(method ", x$T$method, ")"),
  xlab = "", ...)
```

Arguments

x	an object of class `thres2`.
bw	vector containing the bandwith for the non-diseased sample in the first position and the bandwith for the diseased sample in the second position (to be passed to `density()`). Default, `c("nrd0", "nrd0")`.
ci	should the confidence interval be plotted? Default, `TRUE`. No confidence interval will be plotted if x does not contain one (that is, `x$CI` is `NULL`).
which.boot	in case x contains confidence intervals calculated by bootstrapping, which one should be printed? The user can choose between `"norm"` (based on normal distribution) or `"perc"` (based on percentiles). Default, `"norm"`. This argument is ignored if the confidence intervals were calculated by the delta method.
col	a 3-dimensional vector containing:
	`col[1]`: color for the density of the non-diseased sample
	`col[2]`: color for the density of the diseased sample
	`col[3]`: color for the threshold and its corresponding confidence interval
	Default, `c(1, 2, 3)`. If `length(col)` is not 3, `col` will be recycled.
lty	a 4-dimensional vector containing:
	`lty[1]`: line type for the density of the non-diseased sample
	`lty[2]`: line type for the density of the diseased sample
	`lty[3]`: line type for the threshold
	`lty[4]`: line type for the confidence interval
	Default, `c(1, 1, 1, 2)`. If `length(lty)` is not 4, `lty` will be recycled.
lwd	a 3-dimensional vector containing:
	`lwd[1]`: line width for the density of the non-diseased sample
	`lwd[2]`: line width for the density of the diseased sample
	`lwd[3]`: line width for the threshold and its corresponding confidence interval
	Default, `c(1, 1, 1)`. If `length(lwd)` is not 3, `lwd` will be recycled.
legend	logical asking if an automatic legend should be added to the graph. Default, `TRUE`.
leg.pos	position of the legend. Default, `"topleft"`. Ignored if `legend=FALSE`.
leg.cex	number that reescales the size of the legend. Ignored if `legend=FALSE`. Default, 1.
xlim	2-dimensional vector indicating the lower and upper limits for x-axis. Default value (NULL) sets those limits automatically.
ylim	2-dimensional vector indicating the lower and upper limits for y-axis. Default value (NULL) sets those limits automatically.
main, xlab, ...	further arguments to be passed to `plot()`.

Value

Estimates of the density functions for both samples and vertical lines representing the threshold and its confidence limits are drawn.

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

See Also

thres2, lines.thres2

Examples

```
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.2
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased

thres <- thres2(k1, k2, rho, method="eq", ci.method="d")
plot(thres, col=c(1, 2, 4), lwd=c(2, 2, 1), leg.pos="topright")
```

---

plot.thres3   *Thresholds and density plot (three-state setting)*

Description

This function provides a graph including the three sample densities, the thresholds and their confidence intervals.

Usage

```
## S3 method for class 'thres3'
plot(x, bw = c("nrd0", "nrd0", "nrd0"), ci = TRUE,
  which.boot = c("norm", "perc"), col = c(1, 2, 3, 4),
  lty = c(1, 1, 1, 1, 2), lwd = c(1, 1, 1, 1),
  legend = TRUE, leg.pos = "topleft", leg.cex = 1,
  xlim = NULL, ylim = NULL,
  main = paste0("Threshold estimates", ifelse(ci, " and CIs", "")),
  xlab = "", ...)
```

Arguments

x   an object of class thres3.

bw	vector containing the bandwith for the first sample in the first position, the bandwith for the second sample in the second position and the bandwith for the third sample in the third position (to be passed to density()). Default, c("nrd0", "nrd0", "nrd0").
ci	should the confidence intervals be plotted? Default, TRUE. No confidence intervals will be plotted if x does not contain one (that is, x$CI is NULL).
which.boot	in case x contains confidence intervals calculated by bootstrapping, which one should be printed? The user can choose between "norm" (based on normal distribution) or "perc" (based on percentiles). Default, "norm". This argument is ignored if parametric confidence intervals were calculated.
col	a 4-dimensional vector containing:
	col[1]: color for the density of the first sample
	col[2]: color for the density of the second sample
	col[3]: color for the density of the third sample
	col[4]: color for the thresholds and their corresponding confidence intervals
	Default, c(1, 2, 3, 4). If length(col) is not 4, col will be recycled.
lty	a 5-dimensional vector containing:
	lty[1]: line type for the density of the first sample
	lty[2]: line type for the density of the second sample
	lty[3]: line type for the density of the third sample
	lty[4]: line type for the thresholds
	lty[5]: line type for the confidence intervals
	Default, c(1, 1, 1, 1, 2). If length(lty) is not 5, lty will be recycled.
lwd	a 4-dimensional vector containing:
	lwd[1]: line width for the density of the first sample
	lwd[2]: line width for the density of the second sample
	lwd[3]: line width for the density of the third sample
	lwd[4]: line width for the thresholds and their corresponding confidence intervals
	Default, c(1, 1, 1, 1). If length(lwd) is not 4, lwd will be recycled.
legend	logical asking if an automatic legend should be added to the graph. Default, TRUE.
leg.pos	position of the legend. Default, "topleft". Ignored if legend=FALSE.
leg.cex	number that reescales the size of the legend. Ignored if legend=FALSE. Default, 1.
xlim	2-dimensional vector indicating the lower and upper limits for x-axis. Default value (NULL) sets those limits automatically.
ylim	2-dimensional vector indicating the lower and upper limits for y-axis. Default value (NULL) sets those limits automatically.
main, xlab, ...	further arguments to be passed to plot().

Value

Estimates of the density functions for the three samples and vertical lines representing the thresholds and their confidence limits are drawn.

References

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

See Also

[thres3](), [lines.thres3]()

Examples

```
set.seed(1234)
n <- 100
k1 <- rlnorm(n)
k2 <- rnorm(n, 3, 1)
k3 <- rnorm(n, 5, 1)
rho <- c(1/3, 1/3, 1/3)

# assuming trinormality
start <- c(mean(k1), mean(k3))
thres <- thres3(k1, k2, k3, rho, dist1="norm", dist2="norm",
                dist3="norm", start=start, ci.method="param")
plot(thres, leg.pos="topright")

# not assuming trinormality
thres <- thres3(k1, k2, k3, rho, dist1="lnorm", dist2="norm",
                dist3="norm", ci.method="boot")
plot(thres, leg.pos="topright", which.boot="perc")
```

---

plotCostROC   *Plot ROC curve and cost function*

Description

This function plots the ROC curve and the cost function associated to the disease prevalence and costs.

Usage

```
plotCostROC(x, type = "l", ...)
```

Arguments

x	an object of class thres2 or thres3. See **Details**.
type	1-character string giving the type of plot desired. Default, "l". See **Details**.
...	other graphical parameters to be passed to plot().

Details

If the argument x was constructed with method="empirical", the argument extra.info should be switched to TRUE (this only applies when x is an object of class thres2).

For parameter type the following values are possible: ″p″ for points, ″l″ for lines, ″b″ for both points and lines, ″c″ for empty points joined by lines, ″o″ for overplotted points and lines, ″s″ and ″S″ for stair steps and ″h″ for histogram-like vertical lines. Finally, ″n″ does not produce any points or lines.

Value

When x is an object of class thres2, two plots are produced. The first one shows the cost function with the cost minimising threshold in red. The second one is the step ROC curve with the sensitivity and specificity achieved in red. If method = "empirical" is used when building x, empirical cost function and ROC curve are plotted. If method = "smooth" is used when building x, smooth cost function and ROC curve are plotted.

When x is an object of class thres3, two plots are produced. The first one shows the cost function C(T1) with the first cost minimising threshold in red. The second one shows the cost function C(T2) with the second cost minimising threshold in red.

Note

This function uses the plot() function and further arguments can be set to customise the resulting plot.

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

See Also

[thres2](#)

Examples

```
## Not run:
# example 1: x is an object of class 'thres2'
n1 <- 100
n2 <- 100
set.seed(19998)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.3
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased
```

```
x <- thres2(k1, k2, rho, method="emp", ci.method="boot", extra=TRUE)

par(mfrow=c(1,2))
plotCostROC(x)


# example 2: x is an object of class 'thres3'
set.seed(2015)
n <- 100
k1 <- rlnorm(n)
k2 <- rnorm(n, 3, 1)
k3 <- rnorm(n, 5, 1)
rho <- c(1/3, 1/3, 1/3)
y <- thres3(k1, k2, k3, rho, B=1000, ci.method="boot", dist1="lnorm", dist2="norm", dist3="norm")

par(mfrow=c(1,2))
plotCostROC(y)

## End(Not run)
```

---

secondDer2   *Second partial derivative of the cost function (two-state setting)*

Description

This function calculates the second partial derivative of the cost function at a given threshold.

Usage

```
secondDer2(x)
```

Arguments

x   an object of class thres2.

Details

This function evaluates the second derivative of the cost function at the threshold estimate so that the user can assess if this is positive (meaning that the estimation of the threshold leads to a minimum in the cost function) or close to zero and hence the minimum of the cost function does not exist. A closed formula is given when assuming binormality, otherwise the second derivative is evaluated numerically in the threshold estimate using functions from the package numDeriv.

Value

The value of the second derivative of the cost function at the given threshold.

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

See Also

thres2

Examples

```
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.2
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased
x <- thres2(k1, k2, rho, method="equal", ci.method="delta")
secondDer2(x)
```

---

secondDer3 *Second partial derivative of the cost function (three-state setting)*

Description

This function calculates the second partial derivatives of the cost function at a given pair of thresholds.

Usage

```
secondDer3(x)
```

Arguments

x   an object of class `thres3`.

Details

This function evaluates the second partial derivatives of the cost function at the threshold estimates so that the user can assess if these are positive (meaning that the estimation of the thresholds leads to a minimum in the cost function) or close to zero and hence the minimum of the cost function does not exist. A closed formula is given when assuming trinormality, otherwise the second derivatives are evaluated numerically in the threshold estimates using functions from the package `numDeriv`.

Value

The value of the second derivative of the cost function at the given thresholds.

References

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

See Also

thres3

Examples

```
## Not run:
set.seed(1234)
n <- 100
k1 <- rlnorm(n)
k2 <- rnorm(n, 3, 1)
k3 <- rnorm(n, 5, 1)
rho <- c(1/3, 1/3, 1/3)
start <- c(mean(k1), mean(k3))
x <- thres3(k1, k2, k3, rho, dist1="norm", dist2="norm",
            dist3="norm", start=start, ci.method="param")

secondDer3(x)

## End(Not run)
```

SS   *Sample size estimation (two-state setting)*

Description

Estimates the sample size and the optimum sample size ratio needed for a given width, costs, disease prevalence and significance level under the assumption of binormality.

Usage

```
SS(par1.1, par1.2, par2.1, par2.2=NULL, rho, width,
   costs=matrix(c(0, 0, 1, (1-rho)/rho), 2, 2, byrow=TRUE),
   R=NULL, var.equal=FALSE, alpha=0.05)
```

Arguments

`par1.1`	healthy population mean.
`par1.2`	healthy population standard deviation.
`par2.1`	diseased population mean.
`par2.2`	diseased population standard deviation. It can be omitted when assuming equal variances (that is, when `var.equal=TRUE`) and in this situation the common variance is assumed to be equal to `par1.2`.
`rho`	disease prevalence.
`width`	desired interval width.
`costs`	cost matrix. Costs should be entered as a 2x2 matrix, where the first row corresponds to the true positive and true negative costs and the second row to the false positive and false negative costs. Default cost values are a combination of costs that yields R=1, which is equivalent to the Youden index method (for details about this concept, see **References**). It must be set to NULL if the user prefers to set R (see next argument).
`R`	if the cost matrix `costs` is not set, R desired (the algorithm will choose a suitable combination of costs that leads to R). Default, NULL (which leads to R=1 using the default `costs`).
`var.equal`	a logical variable indicating whether to use equal variances. Default, `FALSE`.
`alpha`	significance level for the confidence interval. Default, 0.05.

Value

an object of class `SS` which is a list with eight components:

`ss2`	sample size for the diseased group
`ss1`	sample size for the healthy group
`epsilon`	sample size ratio between non-diseased and diseased subjects
`width`	width of the confidence interval provided by the user
`alpha`	significance level provided by the user
`costs`	cost matrix provided by the user
`R`	R term, the product of the non-disease odds and the cost ratio (for further details about this concept, see **References**)
`prev`	disease prevalence provided by the user

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

Examples

```
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.3
width <- 0.5
SS(par1.1, par1.2, par2.1, par2.2, rho, width, var.equal=TRUE)
```

---

thres2   *Threshold point estimation and confidence intervals (two-state setting)*

Description

This function calculates the threshold estimate and its corresponding confidence interval in a two-state setting.

Usage

```
thres2(k1, k2, rho,
    costs = matrix(c(0, 0, 1, (1 - rho)/rho), 2, 2, byrow = TRUE),
    R=NULL,
    method = c("equal", "unequal", "empirical", "smooth", "parametric"),
    dist1 = NULL, dist2 = NULL, ci = TRUE, ci.method = c("delta", "boot"),
    B = 1000, alpha = 0.05, extra.info = FALSE, na.rm = FALSE, q1=0.05, q2=0.95)
```

Arguments

k1	vector containing the healthy sample values.
k2	vector containing the diseased sample values.
rho	disease prevalence.
costs	cost matrix. Costs should be entered as a 2x2 matrix, where the first row corresponds to the true positive and true negative costs and the second row to the false positive and false negative costs. Default cost values are a combination of costs that yields R=1, which is equivalent to the Youden index method (for details about this concept, see **References**). It must be set to NULL if the user prefers to set R (see next argument).
R	if the cost matrix costs is not set, R desired (the algorithm will choose a suitable combination of costs that leads to R). Default, NULL (which leads to R=1 using the default costs).
method	method used in the estimation. The user can specify just the initial letters. Default, "equal". See **Details** for more information about the methods available.
dist1	distribution to be assumed for the healthy population. See **Details**.
dist2	distribution to be assumed for the diseased population. See **Details**.

ci	should a confidence interval be calculated? Default, TRUE. The user can set it to FALSE to supress the calculation of any confidence interval (in that case, arguments ci.method, B and alpha are ignored).
ci.method	method to be used for the confidence intervals calculation. The user can specify just the initial letters. Default, "delta". See **Details** for more information about the methods available.
B	number of bootstrap resamples when ci.method = "boot". Otherwise, ignored. Default, 1000.
alpha	significance level for the confidence interval. Default, 0.05.
extra.info	when using method="empirical", if set to TRUE the function returns extra information about the calculation of the threshold. Ignored when method is not "empirical". Default, FALSE.
na.rm	a logical value indicating whether NA values in k1 and k2 should be stripped before the computation proceeds. Default, FALSE.
q1	probability of the left distribution in order to determine a low quantile when method="parametric" (ignored otherwise). Default, 0.05.
q2	probability of the right distribution in order to determine a high quantile when method="parametric" (ignored otherwise). Default, 0.95.

Details

For parameter method the user can choose between "equal" (assumes binormality and equal variances), "unequal" (assumes binormality and unequal variances), "empirical" (leaves out any distributional assumption), "smooth" (leaves out any distributional assumption, but uses a kernel to estimate the densities) or "parametric" (based on the distribution assumed for the two populations).

Parameters dist1 and dist2 can be chosen between the following 2-parameter distributions: "beta", "cauchy", "chisq" (chi-squared), "gamma", "lnorm" (lognormal), "logis" (logistic), "norm" (normal) and "weibull". Notice that dist1 and dist2 are only needed when method = "parametric".

For parameter ci.method the user can choose between "delta" (delta method is used to estimate the threshold standard error assuming a binormal underlying model) or "boot" (the confidence interval is calculated by bootstrap).

Value

An object of class thres2, which is a list with two components:

T	a list of at least seven components:
	thres threshold estimate.
	prev disease prevalence provided by the user.
	costs cost matrix provided by the user.
	R R term, the product of the non-disease odds and the cost ratio (for further details about this concept, see **References**).
	method method used in the estimation.
	k1 vector containing the healthy sample values provided by the user.
	k2 vector containing the diseased sample values provided by the user.

When method = "empirical", T also contains:

sens sensitivity obtained.

spec specificity obtained.

cost the minimum cost associated with T$thres.

tot.thres vector of possible thresholds. Only if extra.info = TRUE.

tot.cost vector of empirical costs. Only if extra.info = TRUE.

tot.spec.c complementary of the vector of empirical specificities (1-spec). Only if extra.info = T.

tot.sens vector of empirical sensitivities. Only if extra.info = TRUE.

When method = "parametric", T also contains:

dist1 distribution assumed for the healthy population.

dist2 distribution assumed for the diseased population.

pars1 a numeric vector containing the estimation of the parameters of dist1.

pars2 a numeric vector containing the estimation of the parameters of dist2.

CI   When ci.method = "delta", a list of five components:

lower the lower limit of the confidence interval.

upper the upper limit of the confidence interval.

se the standard error used in the calculation of the confidence interval.

alpha significance level provided by the user.

ci.method method used for the confidence intervals calculation.

When ci.method = "boot", a list of eight components:

low.norm the lower limit of the bootstrap confidence interval based on the normal distribution.

up.norm the upper limit of the bootstrap confidence interval based on the normal distribution.

se the bootstrap standard error used in the calculation of the confidence interval based on the normal distribution.

low.perc the lower limit of the bootstrap confidence interval based on percentiles.

up.perc the upper limit of the bootstrap confidence interval based on percentiles.

alpha significance level provided by the user.

B number of bootstrap resamples used.

ci.method method used for the confidence intervals calculation.

When ci = FALSE, NULL.

Note

It is assumed that k1 is the sample with lower values. If that is not the case, k1 and k2 (and the corresponding parameters) are exchanged.

References

Efron B, Tibshirani RJ. (1993). An introduction to the bootstrap, Chapman & Hall.

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

See Also

thresTH2, plot.thres2, lines.thres2

Examples

```
# example 1
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.2
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased

thres2(k1, k2, rho, method="eq", ci.method="d")
thres2(k1, k2, rho, method="uneq", ci.method="d")
# specify R instead of (default) costs
thres2(k1, k2, rho, costs=NULL, R=2, method="uneq", ci.method="d")
## Not run:
thres2(k1, k2, rho, method="empirical", ci.method="b")

# example 2
set.seed(1234)
k1 <- rnorm(50, 10, 3)
k2 <- rlnorm(55)
rho <- 0.3
thres2(k1, k2, rho, method="param", ci.method="boot", dist1="norm", dist2="lnorm")

## End(Not run)

# supress confidence intervals calculation
thres2(k1, k2, rho, method="equal", ci=FALSE)
thres2(k1, k2, rho, method="empirical", ci=FALSE)

# example 3
n1 <- 100
n2 <- 100
set.seed(1234)
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.2
k1 <- rnorm(n1, par1.1, par1.2) # non-diseased
k2 <- rnorm(n2, par2.1, par2.2) # diseased
## Not run:
thres2(k1, k2, rho, method="smooth", ci.method="b")

## End(Not run)
```

---

thres3	*Threshold point estimation and confidence intervals (three-state setting)*

Description

This function calculates the threshold estimates and their corresponding confidence intervals in a three-state setting.

Usage

```
thres3(k1, k2, k3, rho,
  costs = matrix(c(0, 1, 1, rho[1]/rho[2], 0, rho[3]/rho[2], 1, 1, 0),
  3, 3, byrow = TRUE), dist1 = "norm", dist2 = "norm",
  dist3 = "norm", start = NULL, ci = TRUE, ci.method = c("param", "boot"),
  B = 1000, alpha = 0.05, na.rm = FALSE)
```

Arguments

k1	vector containing the first sample values.
k2	vector containing the second sample values.
k3	vector containing the third sample values.
rho	3-dimensional vector of prevalences.
costs	cost matrix. Costs should be entered as a 3x3 matrix, where the first row corresponds to the costs associated with the classification of subjects in state 1 (C11, C12 and C13), second row corresponds to the costs associated with the classification of subjects in state 2 (C21, C22 and C23) and the third row corresponds to the costs associated with classification of subjects in state 3 (C31, C32, C33), where Cij is the cost of classifying an individual of class i as class j. Default cost values are a combination of costs that leads to the same thresholds as the Youden index method (see **References** for details).
dist1	distribution to be assumed for the first population. Default, "norm". See **Details**.
dist2	distribution to be assumed for the second population. Default, "norm". See **Details**.
dist3	distribution to be assumed for the third population. Default, "norm". See **Details**.
start	when the three distributions dist1, dist2 and dist3 are "norm", a 2-dimensional vector containing starting values for the thresholds. The authors recommend to use the mean of the distribution with lower values and the mean of the distribution with higher values. If any distribution is not "norm", this parameter is ignored. See **Details**.

ci	should a confidence interval be calculated? Default, TRUE. The user can set it to FALSE to supress the calculation of any confidence interval (in that case, arguments ci.method, B and alpha are ignored).
ci.method	method to be used for the confidence intervals calculation. The user can specify just the initial letters. Default, "param". See **Details**.
B	number of bootstrap resamples when ci.method = "boot". Otherwise, ignored. Default, 1000.
alpha	significance level for the confidence interval. Default, 0.05.
na.rm	a logical value indicating whether NA values in k1, k2 and k3 should be stripped before the computation proceeds. Default, FALSE.

Details

Parameters dist1, dist2 and dist3 can be chosen between the following 2-parameter distributions: "beta", "cauchy", "chisq" (chi-squared), "gamma", "lnorm" (lognormal), "logis" (logistic), "norm" (normal) and "weibull".

For parameter ci.method the user can choose between "param" (parametric confidence intervals are calculated when assuming a trinormal underlying model) and "boot" (the confidence intervals are calculated by bootstrap).

When at least one of the distributions is not "norm", the function internally uses the thresTH3() function, which requires two intervals in which the two thresholds are expected to be found. These intervals are determined by the default values of thresTH3(). When all the distributions are "norm", the function uses the nlm() function, which requires two starting values (passed through the argument start).

Value

An object of class thres3, which is a list with two components:

T	a list of at least ten components:
	thres1 first threshold estimate.
	thres2 second threshold estimate.
	prev prevalences provided by the user.
	costs cost matrix provided by the user.
	k1 vector containing the first sample values provided by the user.
	k2 vector containing the second sample values provided by the user.
	k3 vector containing the third sample values provided by the user.
	dist1 distribution assumed for the first population.
	dist2 distribution assumed for the second population.
	dist3 distribution assumed for the third population.
	When not all distributions are normal, T also contains:
	pars1 a numeric vector containing the estimation of the parameters of dist1.
	pars2 a numeric vector containing the estimation of the parameters of dist2.
	pars3 a numeric vector containing the estimation of the parameters of dist3.

CI   When `ci.method = "param"`, a list of six components:

                                 `lower1` the lower limit of the confidence interval for the first threshold.

                                 `upper1` the upper limit of the confidence interval for the first threshold.

                                 `lower2` the lower limit of the confidence interval for the second threshold.

                                 `upper2` the upper limit of the confidence interval for the second threshold.

                                 `alpha` significance level provided by the user.

                                 `ci.method` method used for the confidence intervals calculation.

                                 When `ci.method = "boot"`, a list of eleven components:

                                 `low.norm1` the lower limit of the bootstrap confidence interval for the first threshold based on the normal distribution.

                                 `up.norm1` the upper limit of the bootstrap confidence interval for the first threshold based on the normal distribution.

                                 `low.norm2` the lower limit of the bootstrap confidence interval for the second threshold based on the normal distribution.

                                 `up.norm2` the upper limit of the bootstrap confidence interval for the second threshold based on the normal distribution.

                                 `low.perc1` the lower limit of the bootstrap confidence interval for the first threshold based on percentiles.

                                 `up.perc1` the upper limit of the bootstrap confidence interval for the first threshold based on percentiles.

                                 `low.perc2` the lower limit of the bootstrap confidence interval for the second threshold based on percentiles.

                                 `up.perc2` the upper limit of the bootstrap confidence interval for the second threshold based on percentiles.

                                 `alpha` significance level.

                                 `B` number of bootstrap resamples.

                                 `ci.method` method used for the confidence intervals calculation.

                                 When `ci = FALSE`, `NULL`.

Note

It is assumed that `k1` is the sample with lower values and `k3` is the one taking higher values. If that is not the case, `k1`, `k2` and `k3` (and the corresponding parameters) are re-ordered as needed.

References

Efron B, Tibshirani RJ. (1993). An introduction to the bootstrap, Chapman & Hall.

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

See Also

[thresTH3](), [plot.thres3](), [lines.thres3]()

Examples

```
set.seed(1234)
n <- 100
k1 <- rlnorm(n)
k2 <- rnorm(n, 3, 1)
k3 <- rnorm(n, 5, 1)
rho <- c(1/3, 1/3, 1/3)

# assuming trinormality
start <- c(mean(k1), mean(k3))
thres3(k1, k2, k3, rho, dist1="norm", dist2="norm", dist3="norm", start=start, ci.method="param")

# not assuming trinormality
thres3(k1, k2, k3, rho, B=1000, ci.method="boot", dist1="lnorm", dist2="norm", dist3="norm")

# supress confidence intervals calculation
thres3(k1, k2, k3, rho, ci=FALSE, dist1="lnorm", dist2="norm", dist3="norm")
```

ThresholdROC   *Optimum threshold estimation based on cost function in a two- and three- state settings*

Description

The ThresholdROC package provides point and interval estimations of the optimum threshold as well as graphical tools for continuous diagnostic tests (two- and three- state settings). The point estimation is based on the definition of a cost function which we opt to minimise. An analytical estimator is available for the binormal and trinormal model and the empirical one is used for all settings. The interval estimation is based on the Delta method variance estimator in a binormal parametric setting and on methods on non-linear equations for the trinormal setting. Bootstrap methods are also provided for the confidence intervals.

Details

Package:	ThresholdROC
Type:	Package
Version:	2.9.0
Date:	2021-07-30
License:	GPL (>= 2)

The most important functions are thres2 and thres3. They offer a wide range of options for threshold estimation and inference in two and three state settings. We also include the function diagnostic, which calculates common measures of the accuracy of diagnostic tests involving 2x2 contingency tables of classification results.

Author(s)

Sara Perez-Jaume, Natalia Pallares, Konstantina Skaltsa

Maintainer: Sara Perez-Jaume <spjaume@gmail.com>

References

Efron B, Tibshirani RJ. (1993). An introduction to the bootstrap, Chapman & Hall.

Perez-Jaume S, Skaltsa K, Pallares N, Carrasco JL. (2017). ThresholdROC: Optimum Threshold Estimation Tools for Continuous Diagnostic Tests in R. Journal of Statistical Software 82(4):1-21. doi: 10.18637/jss.v082.i04.

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

Zhou XH, Obuchowski NA and McClish DK. (2002). Statistical methods in diagnostic medicine. John Wiley and sons.

---

thresTH2   *Population-based threshold calculation (two-state setting)*

Description

This function estimates the theoretical optimum threshold for the specific distribution parameters, decision costs and disease prevalence in a two-state setting.

Usage

```
thresTH2(dist1, dist2, par1.1, par1.2, par2.1, par2.2, rho,
  costs = matrix(c(0, 0, 1, (1 - rho)/rho), 2, 2, byrow = TRUE),
  R=NULL, q1 = 0.05, q2 = 0.95, tol = 10^(-8))
```

Arguments

dist1	distribution to be assumed for the healthy population. See **Details**.
dist2	distribution to be assumed for the diseased population. See **Details**.
par1.1	first parameter of the distribution chosen for the healthy population.
par1.2	second parameter of the distribution chosen for the healthy population.
par2.1	first parameter of the distribution chosen for the diseased population.
par2.2	second parameter of the distribution chosen for the diseased population.
rho	disease prevalence.

costs	cost matrix. Costs should be entered as a 2x2 matrix, where the first row corresponds to the true positive and true negative costs and the second row to the false positive and false negative costs. Default cost values are a combination of costs that yields R=1, which is equivalent to the Youden index method (for details about this concept, see **References**). It must be set to NULL if the user prefers to set R (see next argument).
R	if the cost matrix costs is not set, R desired (the algorithm will choose a suitable combination of costs that leads to R). Default, NULL (which leads to R=1 using the default costs).
q1	probability of the left distribution in order to determine a low quantile. Default, 0.05.
q2	probability of the right distribution in order to determine a high quantile. Default, 0.95.
tol	tolerance to be used in function uniroot. Default, 10^(-8).

Details

Parameters dist1 and dist2 can be chosen between the following 2-parameter distributions: "beta", "cauchy", "chisq" (chi-squared), "gamma", "lnorm" (lognormal), "logis" (logistic), "norm" (normal) and "weibull".

Value

An object of class thresTH2, which is a list with five components:

thres	threshold estimate.
prev	disease prevalence provided by the user.
costs	cost matrix provided by the user.
R	R term, the product of the non-disease odds and the cost ratio (for further details about this concept, see **References**).
method	method used in the estimation. For an object of class thresTH2 it is always equal to "theoretical" (meaning that the population-based method has been used).

Note

It is assumed that dist1 is the distribution with lower values. If not, dist1 and dist2 (and the corresponding parameters) are exchanged.

References

Skaltsa K, Jover L, Carrasco JL. (2010). Estimation of the diagnostic threshold accounting for decision costs and sampling uncertainty. Biometrical Journal 52(5):676-697.

Examples

```
# example 1
dist1 <- "norm"
dist2 <- "norm"
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
rho <- 0.1

thresTH2(dist1, dist2, par1.1, par1.2, par2.1, par2.2, rho)


# example 2
dist1 <- "norm"
dist2 <- "lnorm"
par1.1 <- 0
par1.2 <- 1
par2.1 <- 1
par2.2 <- 0.5
rho <- 0.3

thresTH2(dist1, dist2, par1.1, par1.2, par2.1, par2.2, rho)
```

---

thresTH3 *Population-based threshold calculation (three-state setting)*

Description

This function estimates the theoretical optimum thresholds for the specific distribution parameters, decision costs and prevalences in a three-state setting.

Usage

```
thresTH3(dist1, dist2, dist3, par1.1, par1.2,
  par2.1, par2.2, par3.1, par3.2, rho,
  costs = matrix(c(0, 1, 1, rho[1]/rho[2], 0, rho[3]/rho[2], 1, 1, 0),
  3, 3, byrow = TRUE), q1=0.05, q2=0.5, q3=0.95, tol = 10^(-8))
```

Arguments

dist1	distribution to be assumed for the first population. See **Details**.
dist2	distribution to be assumed for the second population. See **Details**.
dist3	distribution to be assumed for the third population. See **Details**.
par1.1	first parameter of the first distribution.
par1.2	second parameter of the first distribution.
par2.1	first parameter of the second distribution.

par2.2	second parameter of the second distribution.
par3.1	first parameter of the third distribution.
par3.2	second parameter of the third distribution.
rho	3-dimensional vector of prevalences.
costs	cost matrix. Costs should be entered as a 3x3 matrix, where the first row corresponds to the costs associated with the classification of subjects in state 1 (C11, C12 and C13), second row corresponds to the costs associated with the classification of subjects in state 2 (C21, C22 and C23) and the third row corresponds to the costs associated with classification of subjects in state 3 (C31, C32, C33), where Cij is the cost of classifying an individual of class i as class j. Default cost values are a combination of costs that leads to the same thresholds as the Youden index method (see **References** for details).
q1	probability of the distribution taking lower values in order to determine a low quantile. Default, 0.05. See **Details**.
q2	probability of the middle distribution in order to determine a medium quantile. Default, 0.5. See **Details**.
q3	probability of the the distribution taking higher values in order to determine a high quantile. Default, 0.95. See **Details**.
tol	tolerance to be used in function `uniroot`. Default, 10^(-8).

Details

Parameters `dist1`, `dist2` and `dist3` can be chosen between the following 2-parameter distributions: `"beta"`, `"cauchy"`, `"chisq"` (chi-squared), `"gamma"`, `"lnorm"` (lognormal), `"logis"` (logistic), `"norm"` (normal) and `"weibull"`.

Parameters q1, q2 and q3 are used to determine two intervals where the `uniroot` function should look for the two threshold estimates. Thus, the first threshold is expected to be found between quantile-1(q1) and quantile-2(q2) and the second one, between quantile-2(q2) and quantile-3(q3), being quantile-i() the quantile function for the i-th distribution, i=1,2,3.

Value

An object of class `thresTH3`, which is a list with five components:

thres1	first threshold estimate.
thres2	second threshold estimate.
prev	prevalences provided by the user.
costs	cost matrix provided by the user.
method	method used in the estimation. For an object of class `thresTH3` it is always equal to `"theoretical"` (meaning that the population-based method has been used).

Note

It is assumed that `dist1` is the distribution with lower values and `dist3` is the one taking higher values. If that is not the case, `dist1`, `dist2` and `dist3` (and the corresponding parameters) are re-ordered as needed.

References

Skaltsa K, Jover L, Fuster D, Carrasco JL. (2012). Optimum threshold estimation based on cost function in a multistate diagnostic setting. Statistics in Medicine, 31:1098-1109.

Examples

```
# example 1
dist <- "norm"
par1.1 <- 0
par1.2 <- 1
par2.1 <- 2
par2.2 <- 1
par3.1 <- 4
par3.2 <- 1
rho <- c(1/3, 1/3, 1/3)

thresTH3(dist, dist, dist,
  par2.1, par2.2, par1.1, par1.2,
  par3.1, par3.2, rho)


# example 2
dist1 <- "norm"
dist2 <- "lnorm"
dist3 <- "lnorm"
par1.1 <- 0
par1.2 <- 1
par2.1 <- 1
par2.2 <- 0.5
par3.1 <- 2
par3.2 <- 0.5
rho <- rep(1/3, 3)

thresTH3(dist1, dist2, dist3, par1.1, par1.2, par2.1, par2.2, par3.1, par3.2, rho)
```

Index