Package ‘refineR’

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Description Indirect method for the estimation of reference intervals using Real-
    World Data ('RWD'). It takes routine measurements
    of diagnostic tests, containing pathological and non-
    pathological samples as input and uses sophisticated
    statistical methods to derive a model describing the distribution of the non-
    pathological samples. This distribution can then be
    used to derive reference intervals.
    Furthermore, the package offers functions for printing and plotting the results of the algo-
    rithm. See '?refineR' for a more comprehensive description of the features.
    Version 1.0 of the algorithm is described in detail in Ammer T., Schuetzenmeister A., Prokosch H.-
    U., Rauh M., Rank C.M., Zierk J. "refineR: A Novel Algorithm for Reference Interval Estima-
License GPL (>= 3)
VignetteBuilder knitr, rmarkdown
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Description

This package includes the implementation of the refineR algorithm (Ammer et al., 2021) which is an indirect method for the estimation of reference intervals using Real-World Data (RWD). It takes routine measurements of diagnostic tests, containing pathological and non-pathological samples as input and uses sophisticated statistical methods to derive a model describing the distribution of the non-pathological samples. This distribution can then be used to derive reference intervals. Main function of this package is `findRI` that takes an input data set and tries to find a model that best explains the non-pathological distribution. Furthermore, the package offers functions for printing `print.RWDRI` and plotting `plot.RWDRI` the results of the algorithm operating on S3-objects of class 'RWDRI'.

Details
addGrid

Add a grid to an existing plot.

Description

It is possible to use automatically determined grid lines (x=NULL, y=NULL) or specifying the number of cells x = 3, y = 4 as done by grid. Additionally, x- and y-locations of grid-lines can be specified, e.g. x = 1:10, y = seq(0,10,2).

Usage

```r
addGrid(x = NULL, y = NULL, col = "lightgray", lwd = 1L, lty = 3L)
```

Arguments

- `x` (integer, numeric) single integer specifies number of cells, numeric vector specifies vertical grid-lines
- `y` (integer, numeric) single integer specifies number of cells, numeric vector specifies horizontal grid-lines
- `col` (character) color of grid-lines
- `lwd` (integer) line width of grid-lines
- `lty` (integer) line type of grid-lines

Author(s)

Andre Schuetzenmeister <andre.schuetzenmeister@roche.com>
as.rgb

Convert color-names or RGB-code to possibly semi-transparent RGB-code.

Description

Function takes the name of a color and converts it into the rgb space. Parameter "alpha" allows to specify the transparency within [0,1], 0 meaning completely transparent and 1 meaning completely opaque. If an RGB-code is provided and alpha != 1, the RGB-code of the transparency adapted color will be returned.

Usage

as.rgb(col = "black", alpha = 1)

Arguments

col (character) name of the color to be converted/transformed into RGB-space (code). Only those colors can be used which are part of the set returned by function colors(). Defaults to "black".

alpha (numeric) value specifying the transparency to be used, 0 = completely transparent, 1 = opaque.

Value

RGB-code

Author(s)

Andre Schuetzenmeister <andre.schuetzenmeister@roche.com>

Examples

## Not run:
# convert character string representing a color to RGB-code using alpha-channel of .25 (75)
as.rgb("red", alpha = .25)

# same thing now using the RGB-code of red (alpha=1, i.e. as.rgb("red"))
as.rgb("#FF0000FF", alpha = .25)

## End(Not run)
ashDensity

Estimate density of distribution employing the R package "ash" using R-wrapper function.

Description

Estimate density of distribution employing the R package "ash" using R-wrapper function.

Usage

ashDensity(x, ab, nbin, m, kopt = c(2, 1), normToAB = FALSE)

Arguments

x (numeric) vector of data points
ab (numeric) vector of lower and higher truncation limit of density estimation
nbin (integer) specifying the number of bins used for density estimation
m (integer) specifying the width of the smoothing kernel(s) used for density estimation
kopt (integer) vector specifying the smoothing kernel
normToAB (logical) specifying if the density is normed to the interval ab or to all data points in x

Value

(list) with density estimation (x values, y values, m and ab).

Author(s)

Christopher Rank <christopher.rank@roche.com>, Tatjana Ammer <tatjana.ammer@roche.com>

BoxCox

One-parameter Box-Cox transformation.

Description

One-parameter Box-Cox transformation.

Usage

BoxCox(x, lambda)
calculateCostHist

Arguments

- x: (numeric) data to be transformed
- lambda: (numeric) Box-Cox transformation parameter

Value

(numeric) vector with Box-Cox transformation of x

Author(s)

Andre Schuetzenmeister <andre.schuetzenmeister@roche.com>

calculateCostHist  Calculate costs for a specific combinations of lambda, muVec and sigmaVec.

Description

Calculate costs for a specific combinations of lambda, muVec and sigmaVec.

Usage

```r
calculateCostHist(
    lambda,
    muVec,
    sigmaVec,
    HistData,
    alpha = 0.01,
    alphaMcb = 0.1,
    pNormLookup
)
```

Arguments

- lambda: (numeric) transformation parameter for inverse Box-Cox transformation
- muVec: (numeric) vector of mean values of non-pathological Gaussian distribution in transformed space
- sigmaVec: (numeric) vector of sd values of non-pathological Gaussian distribution in transformed space
- HistData: (list) with histogram data generated by function `generateHistData`
- alpha: (numeric) specifying the confidence region used for selection of histogram bins in cost calculation
- alphaMcb: (numeric) specifying the confidence level defining the maximal allowed counts below asymmetric confidence region
- pNormLookup: (list) with lookup table for pnormApprox function `pnormApprox`
**defineSearchRegions**

**Value**

(numeric) vector with (lambda, mu, sigma, P, cost).

**Author(s)**

Tatjana Ammer <tatjana.ammer@roche.com>

---

**defineSearchRegions**  
*Helper function to define search regions for mu and sigma and to get the region around the main peak 'ab'*

**Description**

The function estimates the start search regions for mu and sigma for each lambda. Further it determines an appropriate region around the main peak 'ab' that is used for all lambdas.

**Usage**

defineSearchRegions(x, lambdaVec, roundingBase, abEst = NULL)

**Arguments**

- **x**  
  (numeric) values specifying data points comprising pathological and non-pathological values
- **lambdaVec**  
  (numeric) transformation parameter for inverse Box-Cox transformation
- **roundingBase**  
  (numeric) describing the rounding base of the dataset
- **abEst**  
  (numeric) vector with already estimated abSearchReg and abHist for second definition of search regions

**Value**

(list) with (abEst, search region for mu and sigma)

**Author(s)**

Tatjana Ammer <tatjana.ammer@roche.com>
estimateAB

*Helper function to find region around the main peak of a distribution*

**Description**

Helper function to find region around the main peak of a distribution

**Usage**

```r
estimateAB(x)
```

**Arguments**

- `x` (numeric) vector of data points

**Value**

(list) with two numeric vectors with lower and upper bound of region around the main peak used for 1) defining the search regions and 2) estimating the histogram with overlapping bins

**Author(s)**

Tatjana Ammer <tatjana.ammer@roche.com>

findMainPeak

*Helper function to find the main peak of a distribution*

**Description**

The function uses a combination of the area under the curve between valleys and the peak height to detect the main peak.

**Usage**

```r
findMainPeak(x, ab, mStart, withHeight = FALSE, prevPeak = NULL)
```

**Arguments**

- `x` (numeric) vector of data points
- `ab` (numeric) vector specifying the lower and higher truncation limit of density estimation
- `mStart` (integer) specifying the width of the smoothing kernel(s) used for density estimation
- `withHeight` (logical) specifying if only the area under the curve (FALSE) or a combination of AUC and peak height (TRUE) should be used to detect the main peak
- `prevPeak` (numeric) specifying the modEst of the previously estimated peak
findPeaksAndValleys

Value

(list) with the two numeric values peakInd, modEst, and a density list

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

findPeaksAndValleys  Find the index of the peaks and valleys of the density estimation.

Description

Find the index of the peaks and valleys of the density estimation.

Usage

findPeaksAndValleys(Dens)

Arguments

Dens  (list) with density estimation (x values, y values)

Value

(list) specifying the index of the peaks and valleys of the density estimation.

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

findRI  Function to estimate reference intervals for a single population

Description

The function estimates the optimal parameters lambda, mu and sigma for a raw data set containing pathological and non-pathological values. The optimization is carried out via a multi-level grid search to minimize the cost function (negative log-likelihood with regularization) and to find a model that fits the distribution of the physiological values and thus separates pathological from non-pathological values.
findRI

Usage

findRI(
  Data = NULL,
  model = c("BoxCox", "modBoxCoxFast", "modBoxCox"),
  NBootstrap = 0,
  seed = 123,
  ...
)

Arguments

Data (numeric) values specifying data points comprising pathological and non-pathological values
model (character) specifying the applied model (can be either "BoxCox" (default), "modBoxCoxFast" or "modBoxCox"), option "modBoxCoxFast" and "modBoxCox" first runs the original optimization using the Box-Cox transformation, afterwards the modified Box-Cox transformation is utilized and an optimal shift is identified ('fast': only 1 iteration is carried out to find a shift)
NBootstrap (integer) specifying the number of bootstrap repetitions
seed (integer) specifying the seed used for bootstrapping
... additional arguments to be passed to the method

Value

(object) of class "RWDRI" with parameters optimized

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

Examples

# first example
data(testcase1)
resRI <- findRI(Data = testcase1)
print(resRI)
plot(resRI, showPathol = FALSE)

# second example
data(testcase2)
resRI <- findRI(Data = testcase2)
print(resRI, RIperc = c(0.025, 0.5, 0.975))
plot(resRI, showPathol = FALSE)

# third example, with bootstrapping
data(testcase3)
resRI <- findRI(Data = testcase3, NBootstrap = 30, seed = 123)
### findRoundingBase

Estimate rounding base of the input data.

**Description**

Estimate rounding base of the input data.

**Usage**

```r
findRoundingBase(x)
```

**Arguments**

- `x` (numeric) vector of data points

**Value**

(numeric) with estimated rounding base (e.g. 0.001 when rounded to 3 digits)

**Author(s)**

Christopher Rank <christopher.rank@roche.com>, Tatjana Ammer <tatjana.ammer@roche.com>
generateHistData  Generate list with histogram data.

Description

Generate list with histogram data.

Usage

generateHistData(x, ab, roundingBase)

Arguments

x  (numeric) vector of data points
ab  (numeric) vector of lower and higher limit embedding appropriate region with the main peak
roundingBase  (numeric) describing the rounding base of the dataset

Value

(list) with histogram data used in the calculation of cost.

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

getRI  Method to calculate reference intervals (percentiles) for objects of class 'RWDRI'

Description

Method to calculate reference intervals (percentiles) for objects of class 'RWDRI'

Usage

getRI(
  x,
  RIperc = c(0.025, 0.975),
  CIprop = 0.95,
  pointEst = c("fullDataEst", "medianBS", "meanBS"),
  Scale = c("original", "transformed")
)
getSumForPArea

Arguments

x (object) of class ‘RWDRI’
RIperc (numeric) value specifying the percentiles, which define the reference interval
CIprop (numeric) value specifying the central region for estimation of confidence intervals
pointEst (character) specifying the point estimate determination: (1) using the full dataset ("fullDataEst"), (2) calculating the median from all bootstrap samples ("medianBS"), (2) works only if NBootstrap > 0 (3) calculating the mean from all bootstrap samples ("meanBS"), (3) works only if NBootstrap > 0
Scale (character) specifying if percentiles are calculated on the original scale ("Or") or the transformed scale ("Tr")

Value

(data.frame) with columns for percentile, point estimate and confidence intervals.

Author(s)

Christopher Rank <christopher.rank@roche.com>, Tatjana Ammer <tatjana.ammer@roche.com>

getSumForPArea  Helper function to calculate the amount of observed and estimated data points within specified regions around the peak.

Description

The function helps to define the search region for P (fraction of non-pathological samples).

Usage

getSumForPArea(pLimitMin, pLimitMax, countsPred, HistData, lambda, mu, sigma)

Arguments

pLimitMin (numeric) vector specifying the lower limits for the regions next to the peak
pLimitMax (numeric) vector specifying the upper limits for the regions next to the peak
countsPred (numeric) vector with the predicted counts
HistData (list) with histogram data generated by function generateHistData
lambda (numeric) transformation parameter for inverse Box-Cox transformation
mu (numeric) parameter of the mean of non-pathological distribution
sigma (numeric) parameter of the standard deviation of non-pathological distribution
Value

(list) with two numeric vectors specifying the amount of observed and estimated data points surrounding the peak

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

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`invBoxCox`  
*Inverse of the one-parameter Box-Cox transformation.*

**Description**

Inverse of the one-parameter Box-Cox transformation.

**Usage**

`invBoxCox(x, lambda)`

**Arguments**

- `x`: (numeric) data to be transformed
- `lambda`: (numeric) Box-Cox transformation parameter

**Value**

(numeric) vector with inverse Box-Cox transformation of `x`

**Author(s)**

Andre Schuetzenmeister <andre.schuetzenmeister@roche.com>

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`optimizeGrid`  
*Helper function for grid search for mu and sigma.*

**Description**

Helper function for grid search for mu and sigma.

**Usage**

`optimizeGrid(currentBestParam, paramUnique, iter, sigmLimit = TRUE)`
Arguments

- `currentBestParam` (numeric) value specifying the current best value for this parameter
- `paramUnique` (numeric) vector of possible values for this parameter
- `iter` (integer) indicating the number of iteration, as in the first iteration the search region is larger than in the following iterations
- `sigmLimit` (logical) specifying if parameter is sigma and thus minimum is 0

Value

(vector) specifying the new search region for the parameter to be optimized

Author(s)

Tatjana Ammer <tatjana.ammer@roche.com>

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**plot.RWDRI**

*Standard plot method for objects of class 'RWDRI'*

---

Description

Standard plot method for objects of class 'RWDRI'

Usage

```r
## S3 method for class 'RWDRI'
plot(
  x,
  Scale = c("original", "transformed"),
  RIperc = c(0.025, 0.975),
  Nhist = 60,
  showCI = TRUE,
  showPathol = FALSE,
  scalePathol = TRUE,
  showBSModels = FALSE,
  showValue = TRUE,
  CIprop = 0.95,
  pointEst = c("fullDataEst", "medianBS", "meanBS"),
  xlim = NULL,
  ylim = NULL,
  xlab = NULL,
  ylab = NULL,
  title = NULL,
  ...
)
```
Arguments

- **x**: (object) of class 'RWDRI'
- **Scale**: (character) specifying if the plot is generated on the original scale ("original") or the transformed scale ("transformed")
- **RIperc**: (numeric) value specifying the percentiles, which define the reference interval (default c(0.025, 0.975))
- **Nhist**: (integer) number of bins in the histogram (derived automatically if not set)
- **showCI**: (logical) specifying if the confidence intervals are shown
- **showPathol**: (logical) specifying if the estimated pathological distribution shall be shown
- **scalePathol**: (logical) specifying if the estimated pathological distribution shall be weighted with the ratio of pathol/non-pathol
- **showBSModels**: (logical) specifying if the estimated bootstrapping models shall be shown
- **showValue**: (logical) specifying if the exact value of the estimated reference intervals shall be shown above the plot
- **CIprop**: (numeric) value specifying the central region for estimation of confidence intervals
- **pointEst**: (character) specifying the point estimate determination: (1) using the full dataset ("fullDataEst"), (2) calculating the median from all bootstrap samples ("medianBS"), (2) works only if NBootstrap > 0, (3) calculating the mean from all bootstrap samples ("meanBS"), (3) works only if NBootstrap > 0
- **xlim**: (numeric) vector specifying the limits in x-direction
- **ylim**: (numeric) vector specifying the limits in y-direction
- **xlab**: (character) specifying the x-axis label
- **ylab**: (character) specifying the y-axis label
- **title**: (character) specifying plot title
- **...**: additional arguments passed forward to other functions

Value

No return value. Instead, a plot is generated.

Author(s)

Christopher Rank <christopher.rank@roche.com>, Tatjana Ammer <tatjana.ammer@roche.com>
Description

Approximate calculation of CDF of normal distribution.

Usage

```r
pnormApprox(q, pNormVal, mean = 0, oneOverSd = 1, oneOverH = 10)
```

Arguments

- **q**: (numeric) vector of quantiles of data points
- **pNormVal**: (numeric) vector of lookup table for pNorm
- **mean**: (numeric) vector of mean values
- **oneOverSd**: (numeric) reciprocal vector of sd values
- **oneOverH**: (numeric) defining the precision of the approximation

Value

(numeric) vector of approximate CDFs of normal distribution.

Author(s)

Christopher Rank <christopher.rank@roche.com>

---

Description

Standard print method for objects of class 'RWDRI'

Usage

```r
# S3 method for class 'RWDRI'
print(
  x,
  Rlperc = c(0.025, 0.975),
  C1prop = 0.95,
  pointEst = c("fullDataEst", "medianBS", "meanBS"),
  ...
)
```
Arguments

- **x** (object) of class 'RWDRI'
- **RIperc** (numeric) value specifying the percentiles, which define the reference interval
- **CIprop** (numeric) value specifying the central region for estimation of confidence intervals
- **pointEst** (character) specifying the point estimate determination: (1) using the full dataset ("fullDataEst"), (2) calculating the median from all bootstrap samples ("medianBS"), (2) works only if NBootstrap > 0 (3) calculating the mean from all bootstrap samples ("meanBS"), (3) works only if NBootstrap > 0
- ... additional arguments passed forward to other functions.

Value

No return value. Instead, a summary is printed.

Author(s)

Christopher Rank <christopher.rank@roche.com>

testcase1

Simulated Testcase 1.

Description

This dataset consists of N = 10,000 simulated measurements with 80% non-pathological and 20% pathological samples. Ground Truth for reference intervals (2.5% perc., 97.5% perc): [10.2, 29.8]

Usage

```r
data(testcase1)
```

Format

Numeric vector with data points.
Simulated Testcase 2.

Description
This dataset consists of $N = 50,000$ simulated measurements with 60% non-pathological and 40% pathological samples. Ground Truth for reference intervals (2.5% perc., 97.5% perc): [59.8, 160]

Usage
data(testcase2)

Format
Numeric vector with data points.

Simulated Testcase 3.

Description
This dataset consists of $N = 75,000$ simulated measurements with 96% non-pathological and 4% pathological samples. Ground Truth for reference intervals (2.5% perc., 97.5% perc): [9.04, 13]

Usage
data(testcase3)

Format
Numeric vector with data points.

Simulated Testcase 4.

Description
This dataset consists of $N = 100,000$ simulated measurements with 90% non-pathological and 10% pathological samples. Ground Truth for reference intervals (2.5% perc., 97.5% perc): [10, 50]

Usage
data(testcase4)

Format
Numeric vector with data points.
Simulated Testcase 5.

Description

This dataset consists of $N = 250,000$ simulated measurements with 80% non-pathological and 20% pathological samples. Ground Truth for reference intervals (2.5% perc., 97.5% perc): [0.25, 4]

Usage

data(testcase5)

Format

Numeric vector with data points.

testParam

Helper function to find optimal parameters lambda, mu and sigma.

Description

Helper function to find optimal parameters lambda, mu and sigma.

Usage

testParam(
    lambdaVec,  
    bestParam,  
    Data,       
    HistData,   
    startValues, 
    NIter,      
    alpha = 0.01, 
    alphaMcb = 0.1
)

Arguments

lambdaVec (numeric) transformation parameter for inverse Box-Cox transformation
bestParam (numeric) vector containing best guess for lambda, mu, sigma, P, cost
Data (numeric) values specifying percentiles or data points comprising pathological and non-pathological values
HistData (list) with histogram data
startValues (list) with start search regions for mu and sigma
**testParam**

- **NIter** (integer) specifying the number of iterations for optimized grid-search
- **alpha** (numeric) specifying the confidence region used for selection of histogram bins in cost calculation
- **alphaMcb** (numeric) specifying the confidence level defining the maximal allowed counts below the asymmetric confidence region

**Value**

(numeric) vector with best parameters for lambda, mu, sigma, P, cost.

**Author(s)**

Tatjana Ammer <tatjana.ammer@roche.com>
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