Package 'equivalenceTest'

March 4, 2019

Title Equivalence Test for the Means of Two Normal Distributions

Version 0.0.1.1

Description

Two methods for performing equivalence test for the means of two (test and reference) normal distributions are implemented. The null hypothesis of the equivalence test is that the absolute difference between the two means are greater than or equal to the equivalence margin and the alternative is that the absolute difference is less than the margin. Given that the margin is often difficult to obtain a priori, it is assumed to be a constant multiple of the standard deviation of the reference distribution. The first method assumes a fixed margin which is a constant multiple of the estimated standard deviation of the reference data and whose variability is ignored. The second method takes into account the margin variability. In addition, some tools to summarize and illustrate the data and test results are included to facilitate the evaluation of the data and interpretation of the results.

Depends R (>= 3.0.0)

License GPL-3

Encoding UTF-8

LazyData true

RoxygenNote 6.1.1

Imports polynom, rootSolve, cubature, Rdpack, stats, graphics

RdMacros Rdpack

NeedsCompilation no

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Repository CRAN

Date/Publication 2019-03-04 18:30:03 UTC

R topics documented:

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createEquivTestSmpl   *Create summary information of a dataset*

Description

Create a list of summary statistics of a dataset for equivalence test.

Usage

```
createEquivTestSmpl(smpl)
```

Arguments

smpl   a vector representing the dataset

Value

a list of objects summarizing the dataset

Examples

```
vecT = rnorm(n=20)
s = createEquivTestSmpl(vecT)
```

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dfSatterthwaite   *Compute the Satterthwaite approximation of degree of freedom for t*
                         distribution

Description

Compute the Satterthwaite approximation of degree of freedom for t distribution.

Usage

```
dfSatterthwaite(s1, n1, n1s, s2, n2, n2s)
```

Arguments

s1	sample standard deviation for group 1
n1	sample size for group 1
n1s	adjusted sample size for group 1
s2	sample standard deviation for group 2
n2	sample size for group 2
n2s	adjusted sample size for group 2

Value

degree of freedom

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equivalenceTest	*eqivalenceTest: A package for evaluating equivalence of the means of two normal distributions.*

Description

We implemented two equivalence tests which evaluate equivalence in the means of two normal distributions. The first is discussed by Tsong et al. (2017) and the second by Weng et al. (2018).

Details

Let $X_{I,i} \sim_{IID} N(\mu_I, \sigma_I)$ for $I = T, R$ and $i = 1, ..., n_I$, where T stands for test distribution and R for reference distribution. The equivalence test here considers the following hypotheses,

$$H_0 : |\mu_T - \mu_R| \geq \delta \text{ versus } H_1 : |\mu_T - \mu_R| < \delta,$$

where δ is the equivalence margin.

Let $\hat{\mu}_I$ and $\hat{\sigma}_I^2$ be the sample mean and unbiased sample variance estimates respectively for $I = T, R$. Tsong et al. (2017) define the follows test statistics,

$$\tau_1 = \frac{\hat{\mu}_T - \hat{\mu}_R + \delta}{\sqrt{\hat{\sigma}_T^2/n_T^* + \hat{\sigma}_R^2/n_R^*}},$$

and

$$\tau_2 = \frac{\hat{\mu}_T - \hat{\mu}_R - \delta}{\sqrt{\hat{\sigma}_T^2/n_T^* + \hat{\sigma}_R^2/n_R^*}},$$

where $n_T^* = min\{n_T, 1.5n_R\}$ and $n_R^* = min\{n_R, 1.5n_R\}$ are possibly adjusted sample sizes proposed by Dong et al. (2017).

The null hypothesis H_0 is rejected at nominal size α if both $\tau_1 > t_{1-\alpha,df^*}$ and $\tau_2 < -t_{1-\alpha,df^*}$ where $t_{1-\alpha,df^*}$ is the $(1 - \alpha)$-th quantile of the t-distribution with degree of freedom df^*, which is approximated by the Satterthwaite method with sample size adjusted and given as follows,

$$df^* = \frac{\left(\frac{\hat{\sigma}_T^2}{n_T^*} + \frac{\hat{\sigma}_R^2}{n_T^*}\right)^2}{\frac{1}{n_B-1}\left(\frac{\hat{\sigma}_T^2}{n_T^*}\right)^2 + \frac{1}{n_R-1}\left(\frac{\hat{\sigma}_R^2}{n_R^*}\right)^2}.$$

The above assumes that δ is a predetermined constant. However, in many studies, such constant is not available, and δ must be determined by the study data. A popular choice is $\delta = k\hat{\sigma}_R$. In this case, the above test may not control type I error well.

Replacing δ by $k\sigma_R$, the hypotheses becomes

$$H_0' : |\mu_T - \mu_R| \geq k\sigma_R \text{ versus } H_a'|\mu_T - \mu_R| < k\sigma_R.$$

Weng et al. (2018) proposed an improved Wald test with the following test statistics,

$$\tau_1' = \frac{\hat{\mu}_T - \hat{\mu}_R + k\hat{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_{T,1}^2}{n_T^*} + \left(\frac{1}{n_R^*} + \frac{k^2 V_{n_R}}{n_R - 1}\right)\tilde{\sigma}_{R,1}^2}},$$

$$\tau_2' = \frac{\hat{\mu}_T - \hat{\mu}_R - k\hat{\sigma}_R}{\sqrt{\frac{\tilde{\sigma}_{T,2}^2}{n_T^*} + \left(\frac{1}{n_R^*} + \frac{k^2 V_{n_R}}{n_R - 1}\right)\tilde{\sigma}_{R,2}^2}},$$

where $V_{n_R} = n_R - 1 - 2\frac{\Gamma^2 2(n_R/2)}{\Gamma^2((n_R-1)/2)}$ and $\tilde{\sigma}_{T,i}$ and $\tilde{\sigma}_{R,i}$ are the restricted maximum likelihood estimator of σ_T and σ_R respectively with the constraint $\mu_T - \mu_R = (-1)^i \sigma_R$.

The null hypothesis H_0' is rejected at nominal size α if both $\tau_1' > z_{1-\alpha}$ and $\tau_2' < -z_{1-\alpha}$ where $z_{1-\alpha}$ is the $(1-\alpha)$-th quantile of the standard normal distribution.

For more details, see the cited reference.

References

Dong X, Weng Y, Tsong Y (2017). "Adjustment for unbalanced sample size for analytical biosimilar equivalence assessment." *Journal of biopharmaceutical statistics*, **27**(2), 220–232.

Tsong Y, Dong X, Shen M (2017). "Development of statistical methods for analytical similarity assessment." *Journal of biopharmaceutical statistics*, **27**(2), 197–205.

Weng Y, Tsong Y, Shen M, Wang C (2018). "Improved Wald Test for Equivalence Assessment of Analytical Biosimilarity." *International Journal of Clinical Biostatistics and Biometrics*, **4**(1), 1–10.

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equivTestFixedMargin   *Conduct the equivalence test with fixed margin*

Description

Conduct the equivalence test with fixed margin.

Usage

```
equivTestFixedMargin(vecT, vecR, alpha = 0.05, marginX = 1.5,
  sampleSizeX = 1.5, qa = "", sigmaTOverride = NULL,
  labelT = "Proposed", labelR = "Reference", show.message = FALSE,
  method = "Fixed Margin")
```

Arguments

vecT	the sample data for test product, can be a vector of observed values or a list returned by `createEquivTestSmpl`
vecR	the sample data for reference product, can be a vector of observed values or a list returned by `createEquivTestSmpl`
alpha	the nominal size, default = 0.05
marginX	the margin multiplier, default = 1.5
sampleSizeX	the sample size adjustment coefficient, default = 1.5
qa	a string representing the name of the quality attribute, default = ""
sigmaTOverride	a numeric value to override the estimate for standard deviation of the test product
labelT	the name of the test product, default = "Proposed"
labelR	the name of the reference product, default = "Reference"
show.message	a logic value indicating whether messages are to be shown, default = FALSE
method	a string indicating the method used in the equivalence test.

Value

a list of objects summarizing the data and test results, in particular, `rslt` = 1 if H_0 is rejected, and `rslt` = 0 if H_0 is not rejected.

References

Tsong Y, Dong X, Shen M (2017). "Development of statistical methods for analytical similarity assessment." *Journal of biopharmaceutical statistics*, **27**(2), 197–205.

Examples

```
vecT = rnorm(20,-1.5,1)
vecR = rnorm(20,0,1)
et = equivTestFixedMargin(vecT, vecR)
```

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equivTestFixedMarginCombPlot

Provide a combined plot for equivvalence test

Description

Provide a combined plot for equivalence test, including both scatter plot of the sample data and a bar plot indicating the test result, where the null hypothesis is rejected if the red line representing the mean value of the test product lies within a grey rectangle centered at a blue line representing the mean value of the reference product.

Usage

```
equivTestFixedMarginCombPlot(et)
```

Arguments

et   the list returned by equivTestFixedMargin

Examples

```
vecR = rnorm(20,0,1)
vecT = rnorm(20,-1.5,1)
et = equivTestFixedMargin(vecT,vecR)
equivTestFixedMarginCombPlot(et)
```

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equivTestMWCMLE   *Equivalence test by Modified Wald test with standard error estimated by RMLE (MWCMLE)*

Description

Equivalence test by Modified Wald test with standard error estimated by RMLE (MWCMLE).

Usage

```
equivTestMWCMLE(vecT, vecR, alpha = 0.05, marginX = 1.7,
  method = "MWCMLE")
```

Arguments

vecT   the sample data for test product, can be a vector of observed values or a list
                        returned by createEquivTestSmpl

vecR   the sample data for reference product, can be a vector of observed values or a
                        list returned by createEquivTestSmpl

alpha   the nominal size, default = 0.05

marginX   the margin multiplier, default = 1.5

method   a string indicating the method used in the equivalence test.

Details

See Weng et al. (2018).

Value

a list containing the test result

References

Weng Y, Tsong Y, Shen M, Wang C (2018). "Improved Wald Test for Equivalence Assessment of Analytical Biosimilarity." *International Journal of Clinical Biostatistics and Biometrics*, **4**(1), 1–10.

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equivTestPlot	*Plot the equivalence test result*

Description

Plot the equivalence test result including the margin, confidence intervals of the mean difference, and estimated mean difference.

Usage

```
equivTestPlot(meanDif, ci, alpha, margin, qaNameLong, testDrugName = "",
  refDrugName = "", showDrugName = FALSE, showQA = FALSE,
  showCINumbers = FALSE)
```

Arguments

meanDif	difference between mean of test and reference product
ci	confidence interval for mean difference, a vector of two values
alpha	nominal level of the hypothesis test
margin	a vector consisting of lower margin and upper margin
qaNameLong	the quality attribute name
testDrugName	test drug name
refDrugName	reference drug name
showDrugName	logic value indicating if the drug names are to be shown.
showQA	logic value indicating if the quality attribute (QA) is to be shown.
showCINumbers	whether CI values are shown in the figure.

Examples

```
equivTestPlot(0.623,c(-2,2),0.05,c(-9.79,9.79),
  "q a","test","reference")
equivTestPlot(0.623,c(-2,2),0.05,c(-9.79,9.79),
  "Relative Potency","test","reference",showDrugName = TRUE,showQA=TRUE,showCINumbers = TRUE)
equivTestPlot(0.5,c(-1.05,2.05),0.05,c(-9.79,9.79),
  "Relative Potency","test","reference",showQA=TRUE,showCINumbers = TRUE)
```

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histWNormDensity   *Histogram with a fitted normal density function*

Description

Provide a histogram with a fitted normal density.

Usage

```
histWNormDensity(x, main = "")
```

Arguments

x	the data
main	the title of the plot

Examples

```
x = rnorm(20)
histWNormDensity(x)
```

RMLE_equivTest   *Perform restricted MLE (RMLE) to estimate parameters under the constraint defined by the boundary of null hypothesis*

Description

Perform restricted MLE (RMLE) to estimate parameters under the constraint defined by the boundary of null hypothesis, $\mu_T - \mu_R = \eta\sigma_R$ where η is the margin multiplier.

Usage

```
RMLE_equivTest(nT, nR, smplMuT, smplMuR, smplSigmaT, smplSigmaR, vecT,
  vecR, eta)
```

Arguments

nT	sample size for test data
nR	sample size for reference data
smplMuT	sample mean for test data
smplMuR	sample mean for reference data
smplSigmaT	sample standard deviation for test data
smplSigmaR	sample standard devivation for reference data
vecT	a vector of observations for test product
vecR	a vector of observations for reference product
eta	the margin multipler

Value

a list containing the RMLE for the means and standard deviations for both test and reference data

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scatterPlotEquivTestData

Provide a side-by-side scatter plot of two or three datasets for equivalence test.

Description

Provide a side-by-side scatter plot of two samples for equivalence test.

Usage

```
scatterPlotEquivTestData(vecT, vecR, vecR1 = NULL, qa = ",
  labelT = "Test", labelR = "Reference", labelR1 = "Reference1")
```

Arguments

vecT	a vector of the sample for test product
vecR	a vector of the sample for reference product
vecR1	a vector of the sample for reference product R1
qa	a string representing the name of the quality attribute, default = ""
labelT	the name of the test product, default = "Proposed"
labelR	the name of the reference product, default = "Reference"
labelR1	label for reference product R1

Examples

```
vecT = rnorm(20,-1.5,1)
vecR = rnorm(20,0,1)
vecR1 = rnorm(20,0,1)
scatterPlotEquivTestData(vecT,vecR,labelT="T",labelR="R",qa="potency")
scatterPlotEquivTestData(vecT,vecR,vecR1,labelT="T",labelR="R",labelR1="R1",qa="potency")
```

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summarizeSample   *Summarize data for equivalence test*

Description

Summarize data for equivalence test, can be two datasets or three datasets.

Usage

```
summarizeSample(vecT, labelT, vecR, labelR, vecR1 = NULL, labelR1 = "")
```

Arguments

vecT	vector of sample for T
labelT	label for T
vecR	vector of sample for R
labelR	label for R
vecR1	vector of sample for R1
labelR1	label for R1

Value

a data.frame consisting the sample size, min, max, mean, SD, and percentage coefficient of variation for the samples

Examples

```
vecT = rnorm(10,-1.5,1)
vecR = rnorm(10)
vecR1 = rnorm(15,1,2)
ss = summarizeSample(vecT,"T",vecR,"R",vecR1,"R1")
```

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