Package ‘EDNE.EQ’

Type Package
Title Implements the EDNE-Test for Equivalence
Version 1.0
Date 2020-09-24
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Description Package implements the EDNE-test for equivalence according to Hoffelder et al. (2015) <DOI:10.1080/10543406.2014.920344>. “EDNE” abbreviates “Euclidean Distance between the Non-standardized Expected values”.
  The EDNE-test for equivalence is a multivariate two-sample equivalence test. Distance measure of the test is the Euclidean distance.
  The test is an asymptotically valid test for the family of distributions fulfilling the assumptions of the multivariate central limit theorem (see Hoffelder et al., 2015).
  The function EDNE.EQ() implements the EDNE-test for equivalence according to Hoffelder et al. (2015).
  The function EDNE.EQ.dissolution.profiles() implements a variant of the EDNE-test for equivalence analyses of dissolution profiles (see Suarez-Sharp et al., 2020 <DOI:10.1208/s12248-020-00458-9>).
  EDNE.EQ.dissolution.profiles() checks whether the quadratic mean of the differences of the expected values of both dissolution profile populations is statistically significantly smaller than 10 [% of label claim].
  The current regulatory standard approach for equivalence analyses of dissolution profiles is the similarity factor f2.
  The statistical hypotheses underlying EDNE.EQ.dissolution.profiles() coincide with the hypotheses for f2 (see Hoffelder et al., 2015, Suarez-Sharp et al., 2020).

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EDNE.EQ-package

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Description

Package implements the EDNE-test for equivalence according to Hoffelder et al. (2015) <DOI:10.1080/10543406.2014.920344>. "EDNE" abbreviates "Euclidean Distance between the Non-standardized Expected values". The EDNE-test for equivalence is a multivariate two-sample equivalence test. Distance measure of the test is the Euclidean distance. The test is an asymptotically valid test for the family of distributions fulfilling the assumptions of the multivariate central limit theorem (see Hoffelder et al., 2015).

The function EDNE.EQ() implements the EDNE-test for equivalence according to Hoffelder et al. (2015). The function EDNE.EQ.dissolution.profiles() implements a variant of the EDNE-test for equivalence analyses of dissolution profiles (see Suarez-Sharp et al., 2020 <DOI:10.1208/s12248-020-00458-9>). EDNE.EQ.dissolution.profiles() checks whether the quadratic mean of the differences of the expected values of both dissolution profile populations is statistically significantly smaller than 10 [% of label claim]. The current regulatory standard approach for equivalence analyses of dissolution profiles is the similarity factor f2. The statistical hypotheses underlying EDNE.EQ.dissolution.profiles() coincide with the hypotheses for f2 (see Hoffelder et al., 2015, Suarez-Sharp et al., 2020).

Details

The DESCRIPTION file:

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ex_data_JoBS
Example dataset from Hoffelder et al. (2015)

Author(s)

Thomas Hoffelder
Maintainer: Thomas Hoffelder <thomas.hoffelder@boehringer-ingelheim.com>

References


Examples

# A recalculation of the three-dimensional EDNE example evaluation
# in Hoffelder et al. (2015) can be done with the following code:

data(ex_data_JoBS)

REF_JoBS <- cbind(ex_data_JoBS[ which(ex_data_JoBS$Group==’REF’), ]
[c("Diss_15_min","Diss_20_min","Diss_25_min")])

TEST_JoBS <- cbind(ex_data_JoBS[ which(ex_data_JoBS$Group==’TEST’), ]
[c("Diss_15_min","Diss_20_min","Diss_25_min")])

equivalence_margin_EDNE_JoBS <- 297
test_EDNE_JoBS <- EDNE.EQ(X=REF_JoBS
  , Y=TEST_JoBS
  , eq_margin=equivalence_margin_EDNE_JoBS
  , print.results = TRUE)

# Apart from simulation errors, a recalculation of the EDNE results
# of some parts (normal distribution only) of the simulation study in
# Hoffelder et al. (2015) can be done with the following code. Please note that
# the simulation takes approximately 7 minutes for 50.000 simulation
# runs (number_of_simu_runs <- 50000). To shorten calculation time for


library(MASS)

number_of_simu_runs <- 100
set.seed(2020)

mu1 <- c(41,76,97)
mu2 <- mu1 - c(10,10,10)
SIGMA_1 <- matrix(data = c(537.4, 323.8, 91.8,
                          323.8, 207.5, 61.7,
                          91.8, 61.7, 26.1), ncol = 3)
SIGMA_2 <- matrix(data = c(324.1, 233.6, 24.5,
                          233.6, 263.5, 61.4,
                          24.5, 61.4, 32.5), ncol = 3)
SIGMA <- matrix(data = c(430.7, 278.7, 58.1,
                          278.7, 235.5, 61.6,
                          58.1, 61.6, 29.3), ncol = 3)

SIMULATION_SIZE_EDNE <- function(disttype, Hom, Var, mu_1, mu_2
                                   , n_per_group, n_simus) {

  n_success_EDNE <- 0
  if (Hom == "Yes") {
    COVMAT_1 <- SIGMA
    COVMAT_2 <- SIGMA
  } else {
    COVMAT_1 <- SIGMA_1
    COVMAT_2 <- SIGMA_2
  }
  if (Var == "Low") {
    COVMAT_1 <- COVMAT_1 / 4
    COVMAT_2 <- COVMAT_2 / 4
  }

  d <- ncol(COVMAT_1)
  Mean_diff <- mu_1 - mu_2 # Difference of both exp. values
  dist_edne <- crossprod(Mean_diff) # true EDNE distance and equivalence margin

  if (n_per_group == 10) {
    cat("Expected value sample 1: ", mu_1, "\n",
        "Expected value sample 2: ", mu_2, "\n",
        "Covariance matrix sample 1: ", COVMAT_1, "\n",
        "Covariance matrix sample 2: ", COVMAT_2, "\n",
        "EM_EDNE: ", dist_edne, "\n")
  }

  for (i in 1:n_simus) {
    if (disttype == "Normal") {
      REF <- mvrnorm(n = n_per_group, mu = mu_1, Sigma = COVMAT_1)
      TEST <- mvrnorm(n = n_per_group, mu = mu_2, Sigma = COVMAT_2)
    }
n_success_EDNE <- n_success_EDNE + EDNE.EQ.dissolution.profiles(X=REF
Y=TEST
, print.results = FALSE)$testresult.num
}

empirical_succ_prob_EDNE <- n_success_EDNE / n_simus
simuresults <- data.frame(dist = disttype , Hom = Hom , Var = Var
, dimension = d , em_edne = dist_edne
, sample.size = n_per_group
, empirical.size.edne = empirical_succ_prob_EDNE)
)

SIMULATION_LOOP_SAMPLE_SIZE <- function(disttype , Hom , Var , mu_1 , mu_2
, n_simus ) {

run_10 <- SIMULATION_SIZE_EDNE(disttype = disttype , Hom = Hom , Var = Var
, mu_1 = mu_1 , mu_2 = mu_2
, n_per_group = 10 , n_simus = n_simus)
run_30 <- SIMULATION_SIZE_EDNE(disttype = disttype , Hom = Hom , Var = Var
, mu_1 = mu_1 , mu_2 = mu_2
, n_per_group = 30 , n_simus = n_simus)
run_50 <- SIMULATION_SIZE_EDNE(disttype = disttype , Hom = Hom , Var = Var
, mu_1 = mu_1 , mu_2 = mu_2
, n_per_group = 50 , n_simus = n_simus)
run_100 <- SIMULATION_SIZE_EDNE(disttype = disttype , Hom = Hom , Var = Var
, mu_1 = mu_1 , mu_2 = mu_2
, n_per_group = 100 , n_simus = n_simus)
RESULT_MATRIX <- rbind(run_10 , run_30 , run_50 , run_100)
RESULT_MATRIX
}

simu_1 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "Yes"
, Var = "High"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_2 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "Yes"
, Var = "Low"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_3 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "No"
, Var = "High"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_4 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "No"
, Var = "Low"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
FINAL_RESULT <- rbind(simu_1 , simu_2 , simu_3 , simu_4)
EDNE.EQ

The EDNE-test for equivalence

Description
The function EDNE.EQ() implements the EDNE-test for equivalence according to Hoffelder et al. (2015). It is a multivariate two-sample equivalence procedure. Distance measure of the test is the Euclidean distance.

Usage
EDNE.EQ(X, Y, eq_margin, alpha = 0.05, print.results = TRUE)

Arguments
X numeric data matrix of the first sample (REF). The rows of X contain the individual observations of the REF sample, the columns contain the variables/components of the multivariate sample.

Y numeric data matrix of the second sample (TEST). The rows of Y contain the individual observations of the TEST sample, the columns contain the variables/components of the multivariate sample.

eq_margin numeric (>0). The equivalence margin of the test.

alpha numeric (0<alpha<1). The significance level of the EDNE-test for equivalence. Usually set to 0.05 which is the default.

print.results logical; if TRUE (default) summary statistics and test results are printed in the output. If NO no output is created

Details
This function implements the EDNE-test for equivalence. Distance measure of the test is the Euclidean distance. The test is an asymptotically valid test for the family of distributions fulfilling the assumptions of the multivariate central limit theorem (for further details see Hoffelder et al.,2015).

Value
a data frame; three columns containing the results of the test

data frame; three columns containing the results of the test

p.value numeric; the p-value of the equivalence test according to Hoffelder et al. (2015)

testresult.num numeric; 0 (null hypothesis of nonequivalence not rejected) or 1 (null hypothesis of nonequivalence rejected, decision in favor of equivalence)

testresult.text character; test result of the test in text mode
Author(s)
Thomas Hoffelder <thomas.hoffelder at boehringer-ingelheim.com>

References

Examples
# A recalculation of the three-dimensional EDNE example evaluation
# in Hoffelder et al. (2015) can be done with the following code:

data(ex_data_JoBS)
REF_JoBS <- cbind(ex_data_JoBS[ which(ex_data_JoBS$Group=="REF"), ]
[c("Diss_15_min","Diss_20_min","Diss_25_min")])
TEST_JoBS <- cbind(ex_data_JoBS[ which(ex_data_JoBS$Group=="TEST"), ]
[c("Diss_15_min","Diss_20_min","Diss_25_min")])
equivalence_margin_JoBS <- 297
test_EDNE_JoBS <- EDNE.EQ(X=REF_JoBS
 , Y=TEST_JoBS
 , eq_margin=equivalence_margin_JoBS
 , print.results = TRUE)

EDNE.EQ.dissolution.profiles

The EDNE-test for equivalence for dissolution profile data

Description
The function EDNE.EQ.dissolution.profiles() implements a variant of the EDNE-test for equivalence with a concrete equivalence margin for analyses of dissolution profiles. It is a multivariate two-sample equivalence procedure. Distance measure of the test is the Euclidean distance. The equivalence margin is compliant with current regulatory requirements. (see Hoffelder et al., 2015).

Usage
EDNE.EQ.dissolution.profiles(X, Y, alpha = 0.05, print.results = TRUE)

Arguments
X numeric data matrix of the first sample (REF). The rows of X contain the individual observations of the REF sample, the columns contain the variables/components of the multivariate sample. More precisely, the variables are the measured dissolution time points and the rows contain the individual dissolution profiles.
**EDNE.EQ.dissolution.profiles**

Y  
numeric data matrix of the second sample (TEST). The rows of Y contain the individual observations of the TEST sample, the columns contain the variables/components of the multivariate sample. More precisely, the variables are the measured dissolution time points and the rows contain the individual dissolution profiles.

alpha  
umeric (0<alpha<1). The significance level of the test. Usually set to 0.05 which is the default.

print.results  
logical; if TRUE (default) summary statistics and test results are printed in the output. If NO no output is created

**Details**

This function implements a variant of the EDNE-test for equivalence with a concrete equivalence margin for analyses of dissolution profiles. The current regulatory standard approach for comparing dissolution profiles is the similarity factor f2 (see FDA, 1997, EMA, 2010, among others). Analogous to f2 the equivalence margin implemented in this function is defined by a shift of 10 [% of label claim] at all dissolution time points. Thus, the statistical hypotheses of f2 and EDNE.EQ.dissolution.profiles() coincide (see Hoffelder et al., 2015, Suarez-Sharp et al., 2020). The test checks whether the quadratic mean of the differences between REF and TEST mean profiles is statistically significantly smaller than 10%.

With f2, the current regulatory standard approach for comparing dissolution profiles, the type I error cannot be controlled. According to EMA (2010) "similarity acceptance limits should be pre-defined and justified and not be greater than a 10% difference". The functions

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- T2EQ.dissolution.profiles.hoffelder

and f2 have in common that they all check whether a kind of average difference between the expected values is smaller than 10 [% of label claim] (see Suarez-Sharp et al., 2020). Thus, the methods

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- T2EQ.dissolution.profiles.hoffelder

are compliant with current regulatory requirements. In contrast to the standard approach f2 they allow (at least approximate) type I error control.

**Value**

- a data frame; three columns containing the results of the test
- p.value  
numeric; the p-value of the equivalence test according to Hoffelder et al. (2015)
- testresult.num  
numeric; 0 (null hypothesis of nonequivalence not rejected) or 1 (null hypothesis of nonequivalence rejected, decision in favor of equivalence)
- testresult.text  
character; test result of the test in text mode

**Author(s)**

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References


Examples

# Apart from simulation errors, a recalculation of the EDNE results
# of some parts (normal distribution only) of the simulation study in
# Hoffelder et al. (2015) can be done with the following code. Please note that
# the simulation takes approximately 7 minutes for 50,000 simulation
# runs (number_of_simu_runs <- 50000). To shorten calculation time for
# test users, number_of_simu_runs is set to 100 here and can/should be adapted.

library(MASS)
number_of_simu_runs <- 100
set.seed(2020)

mu1 <- c(41, 76, 97)
mu2 <- mu1 - c(10, 10, 10)
SIGMA_1 <- matrix(data = c(537.4 , 323.8 , 91.8 ,
                          323.8 , 207.5 , 61.7 ,
                          91.8 , 61.7 , 26.1) ,ncol = 3)
SIGMA_2 <- matrix(data = c(324.1 , 233.6 , 24.5 ,
                          233.6 , 263.5 , 61.4 ,
                          24.5 , 61.4 , 32.5) ,ncol = 3)
SIGMA <- matrix(data = c(430.7 , 278.7 , 58.1 ,
                          278.7 , 235.5 , 61.6 ,
                          58.1 , 61.6 , 29.3) ,ncol = 3)

SIMULATION_SIZE_EDNE <- function(disttype , Hom , Var , mu_1 , mu_2 , n_per_group , n_simus ) {
  n_success_EDNE <- 0
  if ( Hom == "Yes" ) {
    COVMAT_1 <- SIGMA
    COVMAT_2 <- SIGMA
  }
else {
  COVMAT_1 <- SIGMA_1
  COVMAT_2 <- SIGMA_2
}
if ( Var == "Low" ) {
  COVMAT_1 <- COVMAT_1 / 4
  COVMAT_2 <- COVMAT_2 / 4
}

d <- ncol(COVMAT_1)
Mean_diff <- mu_1 - mu_2  # Difference of both exp. values
dist_edne <- crossprod(Mean_diff)  # true EDNE distance and equivalence margin

if ( n_per_group == 10 ) {
  cat("Expected value sample 1: ", mu_1, ",\n",
  "Expected value sample 2: ", mu_2, ",\n",
  "Covariance matrix sample 1: ", COVMAT_1, ",\n",
  "Covariance matrix sample 2: ", COVMAT_2, ",\n",
  "EM_EDNE: ", dist_edne, ",\n")
}

for ( i in 1:n_simus ) {
  if ( disttype == "Normal" ) {
    REF <- mvrnorm(n = n_per_group, mu=mu_1, Sigma=COVMAT_1)
    TEST<- mvrnorm(n = n_per_group, mu=mu_2, Sigma=COVMAT_2)
  }

  n_success_EDNE <- n_success_EDNE + EDNE.EQ.dissolution.profiles(X=REF, Y=TEST, print.results = FALSE)$testresult.num

  empirical_succ_prob_EDNE <- n_success_EDNE / n_simus
  simuresults <- data.frame(dist = disttype, Hom = Hom, Var = Var, dimension = d, em_edne = dist_edne,
                           sample.size = n_per_group, empirical.size.edne = empirical_succ_prob_EDNE)
}

SIMULATION_LOOP_SAMPLE_SIZE <- function(disttype, Hom, Var, mu_1, mu_2, n_simus)
{
  run_10 <- SIMULATION_SIZE_EDNE(disttype = disttype, Hom = Hom, Var = Var, mu_1 = mu_1, mu_2 = mu_2,
                                     n_per_group = 10, n_simus = n_simus)
  run_30 <- SIMULATION_SIZE_EDNE(disttype = disttype, Hom = Hom, Var = Var, mu_1 = mu_1, mu_2 = mu_2,
                                     n_per_group = 30, n_simus = n_simus)
  run_50 <- SIMULATION_SIZE_EDNE(disttype = disttype, Hom = Hom, Var = Var, mu_1 = mu_1, mu_2 = mu_2,
                                     n_per_group = 50, n_simus = n_simus)
  run_100 <- SIMULATION_SIZE_EDNE(disttype = disttype, Hom = Hom, Var = Var, mu_1 = mu_1, mu_2 = mu_2,
                                    n_per_group = 100, n_simus = n_simus)
  RESULT_MATRIX <- rbind(run_10, run_30, run_50, run_100)
RESULT_MATRIX
}
simu_1 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "Yes"
, Var = "High"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_2 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "Yes"
, Var = "Low"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_3 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "No"
, Var = "High"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
simu_4 <- SIMULATION_LOOP_SAMPLE_SIZE(disttype = "Normal", Hom = "No"
, Var = "Low"
, mu_1 = mu1
, mu_2 = mu2
, n_simus = number_of_simu_runs)
FINAL_RESULT <- rbind(simu_1, simu_2, simu_3, simu_4)
cat("**** Simu results n_simu_runs: ",number_of_simu_runs," **** \n")
FINAL_RESULT

---

ex_data_JoBS  

**Example dataset from Hoffelder et al. (2015)**

**Description**

Multivariate example dataset of dissolution profiles. Dataset consists of two three-dimensional samples. The names of the three variables are "Diss_15_min", "Diss_20_min" and "Diss_25_min". Variable "Group" discriminates between first sample (Group == "REF") and second sample (Group == "Test"). Sample size is 12 per group.

**Usage**

`data("ex_data_JoBS")`

**Format**

A data frame with 24 observations on the following 4 variables.

Group  a factor with levels REF TEST
Diss_15_min  a numeric vector
Diss_20_min  a numeric vector
Diss_25_min  a numeric vector
Details

Example dataset from Hoffelder et al. (2015).

Source


References

URL: [http://dx.doi.org/10.1080/10543406.2014.920344](http://dx.doi.org/10.1080/10543406.2014.920344)

Examples

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