Package 'EDNE.EQ'

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Type Package

Title Implements the EDNE-Test for Equivalence

Version 1.0

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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).

Imports MASS

License GPL-3

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Contents

EDNE.EQ-package *Implements the EDNE-Test for Equivalence*

Description

Package implements the EDNE-test for equivalence according to Hoffelder et al. (2015) <DOI:10.1080/10543406.2014.9203
"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:

Package:	EDNE.EQ
Type:	Package
Title:	Implements the EDNE-Test for Equivalence
Version:	1.0
Date:	2020-09-24
Author:	Thomas Hoffelder
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Description:	Package implements the EDNE-test for equivalence according to Hoffelder et al. (2015) <DOI:10.1080/10543
Imports:	MASS
License:	GPL-3

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                        profile data
ex_data_JoBS            Example dataset from Hoffelder et al. (2015)
```

Author(s)

Thomas Hoffelder

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References

EMA (2010). Guidance on the Investigation of Bioequivalence. European Medicines Agency, CHMP, London. Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

FDA (1997). Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Food and Drug Administration FDA, CDER, Rockville. URL: https://www.fda.gov/media/70936/download

Hoffelder, T., Goessl, R., Wellek, S. (2015). Multivariate Equivalence Tests for Use in Pharmaceutical Development. *Journal of Biopharmaceutical Statistics*, 25:3, 417-437. URL: http://dx.doi.org/10.1080/10543406.2014.920344

Suarez-Sharp, S., Abend, A., Hoffelder, T., Leblond, D., Delvadia, P., Kovacs, E., Diaz, D.A. (2020). In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, When - Workshop Summary Report. *The AAPS Journal*, 22:74. URL: http://dx.doi.org/10.1208/s12248-020-00458-9

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
# 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
```

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

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

Hoffelder, T., Goessl, R., Wellek, S. (2015). Multivariate Equivalence Tests for Use in Pharmaceutical Development. *Journal of Biopharmaceutical Statistics*, 25:3, 417-437. URL: http://dx.doi.org/10.1080/10543406.2014.920344

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.

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	numeric (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

- EDNE.EQ.dissolution.profiles
- T2EQ.dissolution.profiles.hoffelder

and f2 have in common that they all check wether 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

- EDNE.EQ.dissolution.profiles
- 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)

Thomas Hoffelder <thomas.hoffelder at boehringer-ingelheim.com>

References

EMA (2010). Guidance on the Investigation of Bioequivalence. European Medicines Agency, CHMP, London. Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. URL: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf

FDA (1997). Guidance for Industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. Food and Drug Administration FDA, CDER, Rockville. URL: https://www.fda.gov/media/70936/download

Hoffelder, T., Goessl, R., Wellek, S. (2015). Multivariate Equivalence Tests for Use in Pharmaceutical Development. *Journal of Biopharmaceutical Statistics*, 25:3, 417-437. URL: http://dx.doi.org/10.1080/10543406.2014.920344

Suarez-Sharp, S., Abend, A., Hoffelder, T., Leblond, D., Delvadia, P., Kovacs, E., Diaz, D.A. (2020). In Vitro Dissolution Profiles Similarity Assessment in Support of Drug Product Quality: What, How, When - Workshop Summary Report. *The AAPS Journal*, 22:74. URL: http://dx.doi.org/10.1208/s12248-020-00458-9

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

Hoffelder, T., Goessl, R., Wellek, S. (2015), "Multivariate Equivalence Tests for Use in Pharmaceutical Development", *Journal of Biopharmaceutical Statistics*, 25:3, 417-437.

References

URL: http://dx.doi.org/10.1080/10543406.2014.920344

Examples

```
data(ex_data_JoBS)
```

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