

# Package ‘binMto’

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**Type** Package

**Title** Asymptotic simultaneous confidence intervals for many-to-one comparisons of proportions

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**Depends** mvtnorm

**Description** Asymptotic simultaneous confidence intervals for comparison of many treatments with one control, for the difference of binomial proportions, allows for Dunnett-like-adjustment, Bonferroni or unadjusted intervals. Simulation of power of the above interval methods, approximate calculation of any-pair-power, and sample size iteration based on approximate any-pair power. Exact conditional maximum test for many-to-one comparisons to a control.

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binMto-package	<i>Asymptotic simultaneous confidence intervals for many-to-one comparisons of proportions</i>
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**Description**

Asymptotic simultaneous confidence intervals for comparison of many treatments with one control, for the difference of proportions, allows for Dunnett-like-adjustment, Bonferroni or unadjusted intervals.

**Details**

A formal definition and simulation results of the simultaneous coverage probability under various conditions can be found in Schaarschmidt et al. (2009).

**Author(s)**

Frank Schaarschmidt

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**References**

*Schaarschmidt, F., Biesheuvel, E., Hothorn, L.A. (2009) Asymptotic simultaneous confidence intervals for many-to-one comparisons of binary proportions in randomized clinical trials, Journal of Biopharmaceutical Statistics 19(2):292-310.*

**Examples**

```
# binMto:
# Calculate and plot approximate simultaneous
# confidence intervals for many-to-one comparisons of a
# dichotomous variable in a one-way model.

# Example from Table 5 in Koch, HF and Hothorn, LA,
# JSPI 82, 83-99:
# A toxicity study with 100 mice randomised in 4 groups.
# Response x was number of deaths after 6 months.
# Control (n=40, x=4), 10 mg/kg (n=20, x=1),
# 50 mg/kg (n=20, x=6), 100 mg/kg (n=20, x=8).

# Approximate simultaneous 95% add-4-CI:

many21<-binMto(n=c(40,20,20,20), x=c(4,1,6,8),
  names=c("Control", "10mg", "50mg", "100mg"))

many21
```

```
plot(many21)

# Note that normal approximation becomes problematic for np(1-p)<2.
```

---

apprPower	<i>Approximate power (any rejection!) for many-to-one comparison of binomial proportions</i>
-----------	--

---

### Description

Approximative power to reject the hypothesis that all of the  $k$  differences of proportions of treatment groups vs. control group are zero, i.e.: probability to reject any  $H_0[i]$ :  $p[i]-p[0] = 0$ , For a given setting of  $n[i]$ , and  $p[i]$  assumed under the alternative.

### Usage

```
apprPower(n, pH1, alpha = 0.05, alternative = "greater", method = "Add4")
```

### Arguments

n	vector of integers specifying the number of observations in each group, where the first value is taken as sample size of control group
pH1	numeric vector with values between 0 and 1, specifying the proportions of success under the alternative hypothesis, should have the same length as n
alpha	pre-specified type-I-error
alternative	character string defining the alternative hypothesis, take care, that it fits to the parameters settings specified in pH1
method	character string defining the confidence interval method to be used, one of "Add4", "Add2", "Wald"

### Details

This function uses approximative calculation of any-pair-power of a maximum test as described in Bretz and Hothorn (2002) for a Wald test of multiple contrasts of binary data. Differing from Bretz and Hothorn (2002), unpooled variance estimators are used in the present function. In case of "Add4" and "Add2"-method, the Wald expectation and variance are replaced by that of add-4 and add-2. Since the approximate calculation assumes normality, this function can give misleading results, if sample size is small and/or proportions of success are extreme. The present function only calculates power for the test adjusting via the multivariate-normal-distribution. For Bonferroni-adjusted or unadjusted tests, one can make use of well-known formulas for power and sample size for binary data.

The use of the function `simPower` in this package will result in power estimation closer to the true performance of the methods but is less convenient.

**Value**

a single numeric value: the approximate any-pair power

**Note**

The results of this functions are roughly checked by comparison with results of power simulation, which indicate that the approximations are reasonable for at least moderate  $n$  and not too extreme proportions. The performance of a corresponding test using the add-4 or add-2 adjustment is not described.

**Author(s)**

Frank Schaarschmidt

**References**

Bretz,F and Hothorn, LA (2002): Detecting dose-response using contrasts: asymptotic power and sample size determination for binomial data. *Statistics in Medicine* 21, 3325-3335.

**See Also**

simPower

**Examples**

```
# Recalculate the power of the Dunnett-contrast
# for the first setting in Bretz and Hothorn (2002, Table III),
# using a balanced design and the allocation rule  $n_0/n_i = \sqrt{k}$ 
# of Dunnett(1955), desiring a power of 80 percent.
# Note that differing from Bretz and Hothorn (2002)
# in the present function unpooled variance estimators
# are used, what might lead to different results.

apprPower(n=c(196, 196, 196, 196, 196),
  pH1=c(0.45, 0.45, 0.5, 0.5, 0.6),
  alpha=0.05, alternative="greater", method="Wald")

apprPower(n=c(294, 147, 147, 147, 147 ),
  pH1=c(0.45, 0.45, 0.5, 0.5, 0.6),
  alpha=0.05, alternative="greater", method="Wald")
```

**Description**

Approximate simultaneous confidence intervals for many-to-one comparisons of proportions. The add-4, add-2, Newcombes Hybrid Score interval for the difference of proportions can be calculated using either quantiles of the multivariate normal distribution (Dunnett) standard normal quantiles (Bonferroni or unadjusted.)

**Usage**

```
binMto(x, ...)

## Default S3 method:
binMto(x, n, names = NULL,
       base = 1, conf.level = 0.95, alternative = "two.sided",
       method = "Add4", adj = "Dunnett", ...)

## S3 method for class 'formula'
binMto(formula, data, base=1, conf.level=0.95,
       alternative="two.sided", method="Add4", adj="Dunnett", ...)
```

**Arguments**

x	vector giving the number of success in the groups
n	vector giving the number of trials, i.e. the sample size of each group
names	(character-)vector specifying the names of groups given in x and n, ignored if formula and data.frame are used
formula	a formula specifying a response and treatment variable like: response~treatment; the response must consist of 0,1 (failure and success)
data	data.frame containing the response and treatment variable specified in formula
base	a numeric value specifying which group to be treated as control group
conf.level	confidence level
alternative	character string, one of "two.sided", "less", "greater"
method	character string specifying the method of CI construction to used, one of: "Add4": adding-4-method (Agresti and Caffo, 2000), conservative, recommended for small sample sizes, "Add2": adding-2-method (Brown and Li, 2005), less conservative, recommended for one-sided limits, "NHS": Newcombes Hybrid Score method (Newcombe, 1998), "Wald": Wald method, not recommended, only for large sample sizes and not too extreme proportions.

adj character string, specifying the adjustment for multiplicity, one of: "Dunnett": Recommended, using quantiles of the multivariate normal distribution adjusting for multiplicity and correlation between comparisons depending on sample size and estimated proportion (Piegorisch, 1991), "Bonf": Simple Bonferroni-adjustment, conservative for large number of comparisons, "Unadj": Unadjusted interval, i.e. each with local confidence level = conf.level

... arguments to be passed to the methods binMto.formula and binMto.default

### Details

All methods only asymptotically hold the nominal confidence level. Thus they can not be recommended if sample size is combined with extreme proportions of success (close to 0 or 1). Among the available methods Add-4 is most appropriate for small sample sizes, if conservative performance is acceptable.

### Value

A list containing:

conf.int a matrix containing estimates, lower and upper confidence limits

and further values specified in the function call, apply str() to the output for details

### Author(s)

Frank Schaarschmidt

### References

*Schaarschmidt, F., Biesheuvel, E., Hothorn, L.A. (2009) Asymptotic simultaneous confidence intervals for many-to-one comparisons of binary proportions in randomized clinical trials, Journal of Biopharmaceutical Statistics 19(2):292-310.*

### Examples

```
# 1) Simultaneous CI for Dunnett contrasts for
# the example in Table 1 of Bretz F and Hothorn LA (2002):
# Detecting dose-response using contrasts: asymptotic
# power and sample size determination for binomial data.
# Statistics in Medicine 21, 3325-3335.
```

```
binMto(x=c(9,19,21,21,24),
       n=c(20,43,42,42,41),
       names = c("Placebo", 0.125, 0.5, 0.75, 1) )
```

```
plot(binMto(x=c(9,19,21,21,24),
            n=c(20,43,42,42,41),
            names = c("Placebo",0.125,0.5,0.75,1) ))
```

```
#####
```

```
# 2) Berth-Jones, J., Todd, G., Hutchinson, P.E.,
# Thestrup-Pedersen, K., Vanhoutte, F.P. (2000):
# Treatment of Psoriasis with oral liarozole:
# a dose-ranging study.
# British Journal of Dermatology 143 (6), 1170-1176.

# Three doses of a compound (liarozole) were compared
# to a group treated with placebo. The primary variable
# was defined as the proportion of patients with an at
# least marked improvement of psoriasis symptoms.
# A total of 139 patients were assigned to the 4 treatment
# groups, sample sizes were 34,35,36,34, for the Placebo,
# 50mg, 75mg, and 150mg treatments, respectively.
# The number of patients with marked improvement of
# symptoms was 2,6,4,13 in the 4 treatment groups.

# two-sided Add-4 95-percent confidence intervals:

binMto(x=c(2,6,4,13),
       n=c(34,35,36,34),
       names = c("Placebo", "50mg", "75mg", "150mg") )

plot(binMto(x=c(2,6,4,13),
            n=c(34,35,36,34),
            names = c("Placebo", "50mg", "75mg", "150mg") ))

# One-sided Add-4 95-percent confidence intervals
# (for higher values in treatments than in control):

binMto(x=c(2,6,4,13),
       n=c(34,35,36,34),
       names = c("Placebo", "50mg", "75mg", "150mg"),
       alternative="greater" )

# Comparison with a 2x4 table Chisquare-Test:

x<-c(2,6,4,13)
n<-c(34,35,36,34)
tab<-rbind(x, n-x)

chisq.test(tab, correct=TRUE)
```

**Description**

For internal use.

**Usage**

```
Add4(nx, ny, X, Y, quantile, alternative)
Add2(nx, ny, X, Y, quantile, alternative)
NHS(nx, ny, X, Y, quantile, alternative)
Wald(nx, ny, X, Y, quantile, alternative)
```

**Arguments**

<code>nx</code>	a single numeric value, number of trials in sample x
<code>ny</code>	a single numeric value, number of trials in sample y
<code>X</code>	a single numeric value, number of successes in sample x
<code>Y</code>	a single numeric value, number of successes in sample y
<code>quantile</code>	e.g. <code>qnorm(p=0.975)</code> for a two-sided 95 percent confidence interval
<code>alternative</code>	a character string, one of "two.sided", "less", "greater"

**Value**

	A list containing
<code>conf.int</code>	vector giving lower and upper bound
<code>estimate</code>	estimated difference px-py

**Author(s)**

Frank Schaarschmidt

**References**

*Schaarschmidt, F., Biesheuvel, E., Hothorn, L.A. (2009):* Asymptotic simultaneous confidence intervals for many-to-one comparisons of binary proportions in randomized clinical trials, *Journal of Biopharmaceutical Statistics* 19(2):292-310.

*Agresti, A. and Caffo, B. (2000):* Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. *American Statistician* 54 (4), 280-288.

*Brown, L. and Li, X. (2005):* Confidence intervals for two sample binomial distribution. *Journal of Statistical Planning and Inference* 130, 359-375.

*Newcombe, R.G. (1998):* Interval estimation for the difference between independent proportions: comparison of eleven methods. *Statistics in Medicine* 17, 873-890.

**See Also**

`pairwise.prop.test`

---

`ec.mto`*Exact conditional test for many-to-one comparisons of proportions*

---

**Description**

This function calculates the exact distribution of the maximum of test statistics with unpooled variance estimators for the difference of many-to-one comparisons of proportion. Using this, p-values for the max-test are computed.

**Usage**

```
ec.mto(n, x, alternative = "less")
```

**Arguments**

<code>n</code>	vector of integers specifying the number of trials in each group, where the first value is taken as control
<code>x</code>	vector of integers specifying the number of successes in each group, where the first value is taken as control
<code>alternative</code>	a character string, one of "two.sided", "greater", "less"

**Value**

a single numeric value, the p.value of the maximum test

**Author(s)**

Frank Schaarschmidt

**References**

*Koch, H.F. and Hothorn, L.A. (1999):* Exact unconditional distributions for dichotomous data in many-to-one comparisons. *Journal of Statistical Planning and Inference* 82, 83-99 (section 2.1)

**Examples**

```
# Example from Koch and Hothorn (1999), Table 5:  
# Chronic toxicity study in mice over six months.
```

```
ec.mto(n=c(40,20,20,20), x=c(4,1,6,8),  
       alternative= "two.sided")
```

```
ec.mto(n=c(40,20,20,20), x=c(4,1,6,8),  
       alternative= "less")
```

```
ec.mto(n=c(40,20,20,20), x=c(4,1,6,8),
```

```
alternative= "greater")
```

---

Mtoquant

*Calculating quantiles for the many-to-one comparisons of proportions*


---

### Description

For internal use only. Returns appropriate quantiles of multivariate normal distribution taking correlation into account, or from standard normal distribution, depending on specified arguments.

### Usage

```
Mtoquant(nc, nx, pc, px, conf.level = 0.95, adj = "Dunnett", alternative = "two.sided")
```

### Arguments

nc	number of trials in the control group
nx	numeric vector giving the number of trials in the treatment groups
pc	proportion of success in the control group
px	numeric vector giving proportions of success in the treatment groups
conf.level	confidence level
adj	specifying the way of adjustment "Dunnett", "Bonferroni", "Unadj"
alternative	one of "two.sided", "less" or "greater"

### Value

The appropriate quantile for CI construction in binMto.

### Author(s)

Frank Schaarschmidt

### References

*Schaarschmidt, F., Biesheuvel, E., Hothorn, L.A. (2009)* Asymptotic simultaneous confidence intervals for many-to-one comparisons of binary proportions in randomized clinical trials, *Journal of Biopharmaceutical Statistics* 19(2):292-310.

*Piegorsch, W.W. (1991):* Multiple comparisons for analyzing dichotomous response. *Biometrics* 47, 45-57.

nbinMto

*Sample size iteration for many-to-one comparisons of binomials***Description**

This function iteratively increases sample size until a pre-specified any-pair power of a test is achieved. Here, only power to reject the null hypothesis of no difference between treatment and control ( $H_0[i]: p[i] - p[0]=0$ ) is covered. Approximative calculation of power is used, the ratio of sample size to the control group to the treatment groups can be specified.

**Usage**

```
nbinMto(Ntotal = 500, pH1, ratio = 1, alpha = 0.05, power = 0.8, alternative = "two.sided", method = "Add
```

**Arguments**

Ntotal	a single number or vector with two integers specifying the maximum or the range of total sample size allowed in iteration
pH1	numeric vector with values between 0 and 1, specifying the proportions of success under the alternative hypothesis; the first value will be taken as the proportion of the control group, and will be assumed for the null hypothesis
ratio	a single positive number, specifying the ratio between sample size of control group to treatment groups: ratio= $n_0/n_i$
alpha	pre-specified type-I-error of the test
power	desired power
alternative	character string defining the alternative hypothesis, take care, that it fits to the parameters settings specified in pH1
method	character string defining the confidence interval method to be used, one of "Add4", "Add2", "Wald"
trace	logical, indicating whether only the step achieving pre-sepcified power (FALSE) shall be shown or all iteration steps are to be displayed (TRUE)

**Details**

This function uses approximative calculation of any-pair-power of a maximum test as described in Bretz and Hothorn (2002) for a Wald test of multiple contrasts of binary data. Differing from Bretz and Hothorn (2002), unpooled variance estimators are used in the present function. In case of "Add4" and "Add2"-method, the Wald expectation and variance are replaced by that of add-4 and add-2. Since the approximate calculation assumes normality, this function can give misleading results, if sample size is small and/or proportions of success are extreme. The present function only calculates power for the test adjusting via the multivariate-normal-distribution. For Bonferroni-adjusted or unadjusted tests, one can make use of well-known formulas for power and sample size for binary data.

The use of the function simPower in this package will result in power estimation closer to the true performance of the methods but is less convenient.

**Value**

A matrix containing in columns: n of the single groups, the total n, the approximative any-pair-power.

**Note**

The results of this functions are roughly checked by comparison with results of power simulation, which indicate that the approximations are reasonable for at least moderate n and not too extreme proportions. The performance of a corresponding test using the add-4 or add-2 adjustment is not described.

**Author(s)**

Frank Schaarschmidt

**References**

**Bretz,F and Hothorn, LA (2002):** Detecting dose-response using contrasts: asymptotic power and sample size determination for binomial data. *Statistics in Medicine* 21, 3325-3335.

**See Also**

[simPower](#) to estimate the power of all methods in binMto by simulation

**Examples**

```
# Iterate the sample size necessary to achieve
# a power of 80% to reject the null of no treatment
# effects in a dose-response trial for comparing
# four doses with placebo. The assumed proportions
# of success are 0.45 for the placebo,
# and 0.45, 0.5, 0.5, 0.6 for the increasing doses.
# Assume that only an increase of response is of interest:
# alternative="greater"

# a) use a balanced design: ratio=1

nbinMto(Ntotal = 2000, pH1=c(0.45, 0.45, 0.5, 0.5, 0.6),
  ratio = 1, alpha = 0.05, power = 0.8,
  alternative = "greater", method = "Wald", trace = FALSE)

nbinMto(Ntotal = 2000, pH1=c(0.45, 0.45, 0.5, 0.5, 0.6),
  ratio = 2, alpha = 0.05, power = 0.8,
  alternative = "greater", method = "Wald", trace = FALSE)

# Compare with the results in Bretz and Hothorn (2002),
# Table III. Note, that in the present function unpooled
# variance estimators are used, while Bretz and Hothorn use
# a pooled variance estimator.
```

---

plot.binMto                      *Plot confidence intervals calculated using binMto.*

---

### Description

A plot function for confidence intervals calculated using binMto.

### Usage

```
## S3 method for class 'binMto'
plot(x, ltyH0 = 3, H0line = 0,
     ltyCI = 2, main = NULL, xlab = NULL, ...)
```

### Arguments

x	an object of class 'binMto' obtained from function binMto
ltyH0	numerical value specifying the line type of the vertical line in the plot, see ?par for options
H0line	a numerical value, specifying where to draw a vertical line in the plot
ltyCI	numerical value specifying the line type of the confidence intervals in the plot, see ?par for options
main	a main title as in ?plot
xlab	a x-axis label as in ?plot
...	further arguments as given in ?plot or ?par

### Author(s)

Frank Schaarschmidt

### References

The example below, see: *Bretz, F. and Hothorn, L.A. (2002): Detecting dose-response using contrasts: Asymptotic power and sample size determination for binomial data. Statistics in Medicine 21, 3325-3335.*

### Examples

```
# 1) Simultaneous CI for Dunnett contrasts
# for the example in Table 1 of

binMto(x=c(9,19,21,21,24), n=c(20,43,42,42,41), names = c("Placebo",0.125,0.5,0.75,1) )
plot(binMto(x=c(9,19,21,21,24), n=c(20,43,42,42,41), names = c("Placebo",0.125,0.5,0.75,1) ))
```

---

```
print.binMto          Print function for objects of class "binMto"
```

---

### Description

A print functions for objects produced by calling binMto.

### Usage

```
## S3 method for class 'binMto'
print(x, digits=4, ...)
```

### Arguments

x	an object of class "binMto", as can be calculated using <a href="#">binMto</a>
digits	digits for rounding the output
...	further arguments to be passed to print

### Author(s)

Frank Schaarschmidt

---

```
simPower          Simulation of power for the methods in binmto
```

---

### Description

Simulation of the any-pair-power and coverage probability if interval methods given in binmto are used for a decision on hypothesis, for a given setting of sample sizes (n), assumed parameters (pH1), and parameters to test against (H0diff), and confidence interval method.

### Usage

```
simPower(H0diff, pH1, n, n.sim = 1000, conf.level = 0.95, alternative = "two.sided", method = "Add4", ad
```

### Arguments

H0diff	numeric vector or matrix, specifying the differences to test against, i.e. parameters in the null hypothesis
pH1	numeric vector or matrix, specifying the proportions assumed under the alternative the first value of the vector or the first row of the column are taken for the control group
n	a vector or matrix of sample sizes, should have the same length or number of columns as pH1 the first value of the vector or the first row of the column are taken for the control group

n.sim	number of simulations to be run
conf.level	nominal confidence level of the interval
alternative	character string defining the alternative hypothesis to be tested, take care, that it fits to the parameters settings specified in pH1
method	confidence interval method to be used, see ?binmto for details
adj	adjustment method to be used, see ?binmto for details

### Details

The function nbinmto uses approximative power calculation to iterate sample size. Since it assumes normal distribution, it can have misleading results for small sample sizes and extreme proportions. Then, the simulation of power, which takes the true distribution into account, will lead to better choice of sample size. Either one setting can be simulated, if vectors are given as input values, or several designs or settings can be simulated, if input values are given as matrices, where the columns represent the values of single groups or hypotheses to be tested and each row represents one setting. Take care that n and pH1 should have the same length (k+1 groups), but H0diff should be one shorter in length or ncol of the matrix (k hypothesis).

### Value

A matrix containing the hypotheses to be tested, the parameters assumed under the alternative, the any-pair-power and the coverage probability for the setting under the alternative in the columns

### Author(s)

Frank Schaarschmidt

### Examples

```
# three groups are to be tested vs. a control
# test the null-hypothesis that all treatments have the same proportion of success: H0diff=c(0,0,0)
# assume that the proportion of success is 0.2 in the control group, and 0.3,0.4,0.5 in the three treatment groups
# simulate power for balanced designs with 20, 30,...,100 observations per group

# create a matrix for the sample sizes to be used for simulation and have a look at it:

ni<-matrix(rep(seq(20,100,10), times=4), ncol=4)
ni

#
# two-sided testing:

simPower(H0diff=c(0.1,0.1,0.1), pH1=c(0.2,0.3,0.4,0.5), n=ni, n.sim=1000, alternative="two.sided")

# one-sided:

simPower(H0diff=c(0.1,0.1,0.1), pH1=c(0.2,0.3,0.4,0.5), n=ni, n.sim=1000, alternative="greater")

# this will not make sense:
```

```
# simPower(H0diff=c(0.1,0.1,0.1), pH1=c(0.2,0.3,0.4,0.5), n=ni, n.sim=1000, alternative="less")
```

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