

# Package ‘exact2x2’

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**Type** Package

**Title** Exact Tests and Confidence Intervals for 2x2 Tables

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**Description** Calculates conditional exact tests (Fisher's exact test, Blaker's exact test, or exact McNemar's test) and unconditional exact tests (including score-based tests on differences in proportions, ratios of proportions, and odds ratios, and Boschloo's test) with appropriate matching confidence intervals, and provides power and sample size calculations. Gives melded confidence intervals for the binomial case. Gives boundary-optimized rejection region test (Gabriel, et al, 2018, <DOI:10.1002/sim.7579>), an unconditional exact test for the situation where the controls are all expected to fail.

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exact2x2-package	<i>Exact Tests and Confidence Intervals for 2x2 Tables</i>
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## Description

There are 7 main functions in the package. The `exact2x2` function calculates the exact conditional tests with matching confidence intervals as detailed in Fay (2010a <DOI:10.1093/biostatistics/kxp050>,2010b). The functions `ss2x2` and `power2x2` calculate the sample size and power related to the tests of `exact2x2`. The `uncondExact2x2` and `boschloo` functions calculate unconditional exact tests. The `binomMeld.test` function calculates melded confidence intervals for two sample binomial inferences (see Fay, Proschan, and Brittain, 2015 <DOI:10.1111/biom.12231>). Finally, the `borrTest` function calculates the boundary optimized rejection region test that creates unconditional exact tests that have power optimized when group 1 is expected to have 100 percent failure. For example, in vaccine challenge studies where the control group are all expected to get infected (see Gabriel, et al, 2018 <DOI:10.1002/sim.7579>, the letter about that paper by Martin Andres <DOI:10.1002/sim.7630>, and the response <DOI:10.1002/sim.7684>).

## Details

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## Author(s)

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## References

Fay, M. P. (2010a). Confidence intervals that Match Fisher's exact and Blaker's exact tests. *Biostatistics*, 11: 373-374 (go to doc directory for earlier version or <https://www.niaid.nih.gov/about/brb-staff-fay> for link to official version).

Fay, M.P. (2010b). Two-sided Exact Tests and Matching Confidence Intervals for Discrete Data. *R Journal* 2(1):53-58.

Fay, MP, Proschan, MA, and Brittain, E (2015). Combining One Sample Confidence Procedures for Inference in the Two Sample Case. *Biometrics*. 71: 146-156.

Gabriel, EE, Nason, M, Fay, MP, and Follmann, DA. (2018). A boundary-optimized rejection region test for the two-sample binomial problem. *Statistics in Medicine*. 37(7): 1047-1058 (DOI: 10.1002/sim.7579).

Gabriel, EE, Nason, M, Fay, MP, and Follmann, DA. (2018). Reply to letter from Martin Andres. *Statistics in Medicine* 37(14): 2303-2306.

Martin Andres, Antonio. (2018). Letter to the editor about Gabriel et al. *Statistics in Medicine* 37(14) 2301-2302.

binomMeld.test

*Melded Binomial Confidence Intervals and Tests*

## Description

Creates tests to compare two binomials, giving confidence intervals for either the difference in proportions, the rate ratio, or the odds ratio. The 95 percent confidence intervals have been shown to guarantee nominal coverage by extensive numerical calculations. It has been theoretically proven that the p-values from the one-sided tests on the null hypothesis of equality match Fisher's exact p-values.

## Usage

```
binomMeld.test(x1, n1, x2, n2, nullparm = NULL,
  parmtype = c("difference", "oddsratio", "ratio"),
  conf.level = 0.95, conf.int=TRUE,
  alternative = c("two.sided", "less", "greater"),
  midp=FALSE, nmc=0, eps=10^-8)
```

## Arguments

x1	number of events in group 1
n1	sample size in group 1
x2	number of events in group 2
n2	sample size in group 2
nullparm	value of the parameter of interest at null, default of NULL gives 0 for parmtype='difference' and 1 for parmtype='ratio' or 'oddsratio'
parmtype	type of parameter of interest, one of "difference", "ratio" or "oddsratio" (see details)
conf.level	confidence level
conf.int	logical, calculate confidence intervals?
alternative	alternative hypothesis, one of "two.sided", "less", or "greater" (see details)
midp	logical, do mid-p version of p-value and confidence intervals?
nmc	integer, number of Monte Carlo replications for p-value and CI calculations, 0 (default) means calculate by numeric integration instead
eps	small number used to adjust numeric integration (see note)

## Details

Assume  $X_1 \sim \text{Binomial}(n_1, p_1)$  and  $X_2 \sim \text{Binomial}(n_2, p_2)$ . We want to test hypotheses on a function of  $p_1$  and  $p_2$ . The functions are given by parmtype: difference tests  $p_2 - p_1$ , ratio tests  $p_2/p_1$ , and odds ratio tests  $p_2(1-p_1)/(p_1(1-p_2))$ . Let  $g(p_1, p_2)$  be one of the three functions. So when alternative is "less" we test  $H_0: g(p_1, p_2) \geq \text{nullparm}$  vs.  $H_1: g(p_1, p_2) < \text{nullparm}$ .

For details when midp=FALSE see Fay, Proschan, and Brittain (2015).

When midp=TRUE, the method performs the mid-p version on the p-value and the associated confidence intervals. This means that we replace the confidence distribution random variables in the p-value and CI calculations with a random variable that is a mixture of the lower and upper CD random variables. For example, if W1L and W1U are the lower and upper confidence distribution random variables for group 1, then we replace those values in all calculations with  $W1_{\text{midp}} = U1 * W1L + (1 - U1) * W1U$ , where U1 is a Bernoulli with parameter 0.5. For a discussion of mid-p values and the associated confidence intervals in a closely related context, see the vignette on mid-p-values or Fay and Brittain (2016, especially the Appendix).

## Value

An object of class 'htest'. A list with elements

statistic	proportion of events in group 1
parameter	proportion of events in group 2
p.value	p-value
conf.int	confidence interval
estimate	estimate of $g(p_1, p_2)$ by plugging in sample proportions, i.e., unconditional MLE
null.value	value of $g(p_1, p_2)$ under null
alternative	type of alternative hypothesis
method	description of test
data.name	character explicit description of data

## Note

For numeric integration, the integrate function may have problems if nearly all of the integrand values are about 0 within the range of integration. Because of this, we use the eps value to make sure we integrate over ranges in which the integrand is nontrivially greater than 0. We restrict the range then add eps back to the p-value so that if the integrate function works perfectly, then the p-values would be very slightly conservative (for very small eps). There is no need to adjust the eps value. See code for detailed description of how eps is used in the calculation before changing it from the default.

An alternative method of calculation is to use Monte Carlo simulation (option with nmc>0). This provides a check of the numeric integration. There is no need to do Monte Carlo simulations for routine use. Please inform the package maintainer if the p-values or confidence intervals are substantially different when nmc=0 and nmc=10<sup>7</sup>.

## Author(s)

Michael P. Fay

## References

Fay, MP, Proschan, MA, and Brittain, E (2015) Combining One Sample Confidence Procedures for Inferences in the Two Sample Case. *Biometrics* 71: 146-156.

Fay, Michael P., and Erica H. Brittain. (2016). Finite sample pointwise confidence intervals for a survival distribution with right-censored data. *Statistics in medicine*. 35: 2726-2740.

## Examples

```
# Note the p-value for all tests of equality
# (Null Hypthesis: true prop 1=true prop 2)
# are the same, and equal to the
# Fisher's exact (central) p-value
binomMeld.test(3,5,1,8,parmtpe="difference")
binomMeld.test(3,5,1,8,parmtpe="ratio")
# note that binomMeld.test gives the unconditional MLE
# for the odds ratio, while fisher.test and exact2x2
# gives the conditional MLE for the odds ratio
# (also fisher.test gives the odds ratio defined as
# the inverse of how it is defined in binomMeld.test)
binomMeld.test(3,5,1,8,parmtpe="oddsratio")
exact2x2(matrix(c(1,8-1,3,5-3),2,2),tsmethod="central")
```

---

 borrTest

---

*Boundary-Optimized Rejection Region Test*


---

## Description

An unconditional exact test for the two-sample binomial problem when it is expected that  $\theta_1$  (probability of an event in group 1) will be close to 1. Used for test versus control when all controls are expected to fail.

## Usage

```
borrTest(x1, n1, x2, n2, tuningParm = 0.025,
  parmtpe = c("ratio", "difference", "oddsratio"),
  nullparm = NULL, alternative = c("less", "greater", "two.sided"),
  conf.int = TRUE, conf.level = 0.975,
  controlUC = ucControl(), controlborr = borrrControl(), ...)
```

```
borrPvals(n1,n2, tuningParm=0.025,
  parmtpe = c("ratio", "difference","oddsratio"),
  nullparm = NULL, alternative = c("less", "greater","two.sided"),
  conf.int = TRUE, conf.level = 0.975,
  controlUC=ucControl(), controlborr=borrrControl(),...)
```

```
borrOrdering(n1,n2,tuningParm = .025,
  controlborr=borrrControl())
```

**Arguments**

x1	number of events in group 1
n1	sample size in group 1
x2	number of events in group 2
n2	sample size in group 2
tuningParm	tuning parameter, default is 0.025 and designs BORR tests with maximum power for one-sided 0.025 tests
parmtype	parameter type, either 'ratio' for $\theta_2/\theta_1$ , 'difference' for $\theta_2-\theta_1$ , or 'oddsratio' for $\theta_2*(1-\theta_1)/(\theta_1*(1-\theta_2))$ .
nullparm	null parameter value, default=NULL gives parameter value for $\theta_1=\theta_2$ (e.g., 1 for 'ratio' or 0 for 'difference' ).
alternative	alternative hypothesis, BORR tests are designed for alternative='less' (see Note for other alternatives)
conf.int	logical, should confidence interval be calculated?
conf.level	confidence level, default is 0.975 (see note)
controlUC	a list of control parameters to define algorithms in the call to <a href="#">uncondExact2x2</a> , see <a href="#">ucControl</a>
controlborr	a list of control parameters to define algorithms, see <a href="#">borrControl</a>
...	extra arguments passed (for future development)

**Details**

The boundary-optimized rejection region test is designed to test the one-sided alternative that  $\theta_2 < \theta_1$ , where  $X_1$  is binomial( $n_1, \theta_1$ ), and  $X_2$  is binomial( $n_2, \theta_2$ ). The test is designed to be optimal when  $\theta_1$  is very close to 1. For example, in a vaccine malaria challenge study where we expect all  $n_1$  individuals that got the control vaccine to have the event (get malaria when challenged with malaria). For details see Gabriel et al (2018).

The function `borrTest` tests the results of one study, and returns an `hstest` object. The function `borrPvals` calculates the p-values for every possible result of a study. The function `borrOrdering` orders every possible result of the study. See [borrOrderingInternal](#) for calculation details.

**Value**

The function `borrPvals` returns a  $(n_1+1)$  by  $(n_2+1)$  matrix of p-values for all possible  $x_1$  and  $x_2$  values. The function `borrOrdering` returns a matrix with the rank of all possible  $x_1$  and  $x_2$  values. The function `borrTest` returns a list of class `hstest` with elements:

statistic	proportion in sample 1
parameter	proportion in sample 2
p.value	p-value from test
conf.int	confidence interval on parameter given by <code>parmtype</code>
estimate	MLE estimate of parameter given by <code>parmtype</code>
null.value	null hypothesis value of parameter given by <code>parmtype</code>

alternative	alternative hypothesis
method	description of test
data.name	description of data

### Note

The tests are designed to have good power for the one-sided test that  $H_0: \theta_2 \geq \theta_1$ , with alternative  $H_1: \theta_2 < \theta_1$  at significance level equal to `tuningParm`. Since the default `tuningParm` is 0.025, the default confidence level is 0.975 so that the confidence intervals will be compatible with the test where the one-sided p-values reject at level 0.025.

Sometimes you may want two-sided confidence intervals on the parameter of interest. If you ask for a two-sided alternative, then the confidence interval and the resulting p-value will be two-sided as well. The default is a 'central' interval, so the two-sided p-value should be twice the minimum of the one-sided p-values. Further, with a `conf.level` of 0.95 for the two-sided alternative, the error on each side will be bounded by 0.025.

### Author(s)

Martha Nason, Erin Gabriel, Michael P. Fay

### References

- Gabriel, EE, Nason, M, Fay, MP, and Follmann, DA. (2018). A boundary-optimized rejection region test for the two-sample binomial problem. *Statistics in Medicine*. 37(7): 1047-1058 (DOI: 10.1002/sim.7579).
- Gabriel, EE, Nason, M, Fay, MP, and Follmann, DA. (2018). Reply to letter from Martin Andres. *Statistics in Medicine* 37(14): 2303-2306.
- Martin Andres, Antonio. (2018). Letter to the editor about Gabriel et al. *Statistics in Medicine* 37(14) 2301-2302.

### Examples

```
## Not run: borrTest(4,4,1,4)
# Note Figure 2 in Gabriel et al is incorrect. The correct value
# is in the response letter, and given by
borrOrdering(4,4,tuningParm=0.025)$rankMat
```

---

boschloo

*Boschloo's test for 2x2 Tables*

---

### Description

Boschloo's test is an exact unconditional test for 2x2 tables based on ordering the sample space by Fisher's exact p-values. This function generalizes that test in several ways (see details).

**Usage**

```
boschloo(x1, n1, x2, n2, alternative = c("two.sided", "less", "greater"),
         or = NULL, conf.int = FALSE, conf.level = 0.95, midp = FALSE,
         tsmethod = c("central", "minlike"), control=ucControl())
```

**Arguments**

x1	number of events in group 1
n1	sample size in group 1
x2	number of events in group 2
n2	sample size in group 2
alternative	alternative hypothesis, one of "two.sided", "less", or "greater", default is "two.sided" (see details)
or	odds ratio under the null hypothesis
conf.int	logical, calculate confidence interval?
conf.level	confidence level
midp	logical. Use mid-p-value method?
tsmethod	two-sided method, either "central" or "minlike" (see details)
control	list of algorithm parameters, see <a href="#">ucControl</a>

**Details**

The traditional Boschloo (1970) test is to use Fisher's exact p-values (under the null that  $p_1=p_2$ ) to order the sample space and to use that ordering to perform an unconditional exact test. Here we generalize this to test for different null hypothesis values (other than odds ratios of 1).

For the two-sided alternatives, the traditional method uses `tsmethod='minlike'` (for example, in the `Exact R` package) but our default is `tsmethod='central'`. The one-sided tests use ordering by the appropriate p-value (or 1 minus the p-value for `alternative='greater'` so that the ordering function follows our convention for user supplied ordering functions, see `method='user'` option in [uncondExact2x2](#)).

The option `midp` orders the sample space by the mid-p value associated with Fisher's exact test, and additionally gives mid-p values. This means that unlike the `midp=FALSE` case, when `midp=TRUE` the test is not exact (i.e., guaranteed to bound the type I error rate at the nominal level), but has type I error rates that are on average (over the possible null parameter values) closer to the nominal level.

If you want to order by the mid-p values from Fisher's exact test but get an exact test, use the `method="FisherAdj"` with `midp=FALSE` in [uncondExact2x2](#).

The `boschloo` function only gives confidence intervals for the odds ratio, for getting confidence intervals closely related to Boschloo p-values (but not exactly matching Boschloo p-values) for the difference or ratio, use [uncondExact2x2](#) with `method="FisherAdj"`.



**Value**

a list of class 'htest' with elements:

statistic	proportion in sample 1
parameter	proportion in sample 2
p.value	p-value from test
conf.int	confidence interval on odds ratio
estimate	odds ratio estimate
null.value	null hypothesis value of odds ratio
alternative	alternative hypothesis
method	description of test
data.name	description of data

**References**

Boschloo, R. D. "Raised conditional level of significance for the 2x2-table when testing the equality of two probabilities." *Statistica Neerlandica* 24.1 (1970): 1-9.

**See Also**

`exact.test` in package **Exact** for Boschloo test p-value computation. Also see method "FisherAdj" in `uncondExact2x2` for a closely related test.

**Examples**

```
# defaults to the central two-sided version
boschloo(1,5,6,7)
boschloo(1,5,6,7,alternative="greater")
## traditional two-sided Boschloo test (not central!)
boschloo(1,5,6,7, tsmethod="minlike")
```

---

exact2x2

*Exact Conditional Tests for 2 by 2 Tables of Count Data*

---

**Description**

Performs exact conditional tests for two by two tables. For independent binary responses, performs either Fisher's exact test or Blaker's exact test for testing hypotheses about the odds ratio. The commands follow the style of `fisher.test`, the difference is that for two-sided tests there are three methods for calculating the exact test, and for each of the three methods its matching confidence interval is returned (see details). For paired binary data resulting in a two by two table, performs an exact McNemar's test.

**Usage**

```

exact2x2(x, y = NULL, or = 1, alternative = "two.sided",
         tsmethod = NULL, conf.int = TRUE, conf.level = 0.95,
         tol = 0.00001, conditional = TRUE, paired=FALSE,
         plot=FALSE, midp=FALSE)
fisher.exact(x, y = NULL, or = 1, alternative = "two.sided",
            tsmethod = "minlike", conf.int = TRUE, conf.level = 0.95,
            tol = 0.00001, midp=FALSE)
blaker.exact(x, y = NULL, or = 1, alternative = "two.sided",
            conf.int = TRUE, conf.level = 0.95, tol = 0.00001)
mcnemar.exact(x,y=NULL, conf.level=.95)

```

**Arguments**

x	either a two-dimensional contingency table in matrix form, or a factor object.
y	a factor object; ignored if x is a matrix.
or	the hypothesized odds ratio. Must be a single numeric.
alternative	indicates the alternative hypothesis and must be one of "two.sided", "greater" or "less". if "two.sided" uses method defined by tsmethod.
tsmethod	one of "minlike", "central", or "blaker". NULL defaults to "minlike" when paired=FALSE and "central" when paired=TRUE or midp=TRUE. Defines type of two-sided method (see details). Ignored if alternative="less" or "greater".
conf.int	logical indicating if a confidence interval should be computed.
conf.level	confidence level for the returned confidence interval. Only used if conf.int = TRUE.
tol	tolerance for confidence interval estimation.
conditional	TRUE. Unconditional exact tests should use <a href="#">uncondExact2x2</a> .
paired	logical. TRUE gives exact McNemar's test, FALSE are all other tests
midp	logical. TRUE gives mid p-values and mid-p CIs. Not supported for tsmethod='minlike' or 'blaker'
plot	logical. TRUE gives basic plot of point null odds ratios by p-values, for greater plot control use <a href="#">exact2x2Plot</a> . Not supported for midp=TRUE.

**Details**

The motivation for this package is to match the different two-sided conditional exact tests for 2x2 tables with the appropriate confidence intervals.

There are three ways to calculate the two-sided conditional exact tests, motivated by three different ways to define the p-value. The usual two-sided Fisher's exact test defines the p-value as the sum of probability of tables with smaller likelihood than the observed table (tsmethod="minlike"). The central Fisher's exact test defines the p-value as twice the one-sided p-values (but with a maximum p-value of 1). Blaker's (2000) exact test defines the p-value as the sum of the tail probability in the observed tail plus the largest tail probability in the opposite tail that is not greater than the observed tail probability.

In [fisher.test](#) the p-value uses the two-sample method associated with tsmethod="minlike", but the confidence interval method associated with tsmethod="central". The probability that the lower

central confidence limit is less than the true odds ratio is bounded by  $1-(1-\text{conf.level})/2$  for the central intervals, but not for the other two two-sided methods. The confidence intervals in for `exact2x2` match the test associated with `alternative`. In other words, the confidence interval is the smallest interval that contains the confidence set that is the inversion of the associated test (see Fay, 2010). The functions `fisher.exact` and `blaker.exact` are just wrappers for certain options in `exact2x2`.

If `x` is a matrix, it is taken as a two-dimensional contingency table, and hence its entries should be nonnegative integers. Otherwise, both `x` and `y` must be vectors of the same length. Incomplete cases are removed, the vectors are coerced into factor objects, and the contingency table is computed from these.

P-values are obtained directly using the (central or non-central) hypergeometric distribution.

The null of conditional independence is equivalent to the hypothesis that the odds ratio equals one. ‘Exact’ inference can be based on observing that in general, given all marginal totals fixed, the first element of the contingency table has a non-central hypergeometric distribution with non-centrality parameter given by the odds ratio (Fisher, 1935). The alternative for a one-sided test is based on the odds ratio, so `alternative = "greater"` is a test of the odds ratio being bigger than or.

When `paired=TRUE`, this denotes there is some pairing of the data. For example, instead of Group A and Group B, we may have pretest and posttest binary responses. The proper two-sided test for such a setup is McNemar’s Test, which only uses the off-diagonal elements of the 2x2 table, and tests that both are equal or not. The exact version is based on the binomial distribution on one of the off-diagonal values conditioned on the total of both off-diagonal values. We use `binom.exact` from the `exactci` package, and convert the p estimates and confidence intervals (see note) to odds ratios (see Breslow and Day, 1980, p. 165). The function `mcnemar.exact` is just a wrapper to call `exact2x2` with `paired=TRUE`, `alternative="two.sided"`, `tsmethod="central"`. One-sided exact McNemar-type tests may be calculated using the `exact2x2` function with `paired=TRUE`. For details of McNemar-type tests see Fay (2010, R Journal).

The mid p-value is an adjusted p-value to account for discreteness. The mid-p adjustment is not guaranteed to give type I error rates that are less than or equal to nominal levels, but gives p-values that lead to the probability of rejection that is sometimes less than the nominal level and sometimes greater than the nominal level. This adjustment is sometimes used because exact p-values for discrete data cannot give actual type I error rates equal to the nominal value unless randomization is done (and that is not typically done because two researchers doing the same method could get different answers). Essentially, exact p-values lead to the probability of rejecting being less than the nominal level for most parameter values in the null hypothesis in order to make sure that it is not greater than the nominal level for ANY parameter values in the null hypothesis. The mid p-value was studied by Lancaster (1961), and for the 2x2 case by Hirji et al (1991).

## Value

A list with class `"hctest"` containing the following components:

<code>p.value</code>	the p-value of the test
<code>conf.int</code>	a confidence interval for the odds ratio
<code>estimate</code>	an estimate of the odds ratio. Note that the <i>conditional</i> Maximum Likelihood Estimate (MLE) rather than the unconditional MLE (the sample odds ratio) is used.
<code>null.value</code>	the odds ratio under the null, or.

alternative	a character string describing the alternative hypothesis
method	a character string, changes depending on alternative and tsmethod
data.name	a character string giving the names of the data

**Note**

The default exact confidence intervals for the odds ratio when paired=TRUE (those matching the exact McNemar's test) are transformations of the Clopper-Pearson exact confidence intervals for a single binomial parameter which are central intervals. See note for [binom.exact](#) for discussion of exact binomial confidence intervals.

**Author(s)**

Michael Fay

**References**

- Blaker, H. (2000) Confidence curves and improved exact confidence intervals for discrete distributions. *Canadian Journal of Statistics* 28: 783-798.
- Breslow, NE and Day NE (1980). *Statistical Methods in Cancer Research: Vol 1-The analysis of Case-Control Studies*. IARC Scientific Publications. IARC, Lyon.
- Fay, M. P. (2010). Confidence intervals that Match Fisher's exact and Blaker's exact tests. *Biostatistics*, 11: 373-374 (go to doc directory for earlier version or <https://www.niaid.nih.gov/about/brb-staff-fay> for link to official version).
- Fay M.P. (2010). Two-sided Exact Tests and Matching Confidence Intervals for Discrete Data. *R Journal* 2(1):53-58.
- Fisher, R.A. (1935) The logic of inductive inference. *Journal of the Royal Statistical Society Series A* 98:39-54.
- Hirji, K.F., Tan, S-J, and Elashoff, R.M. (1991). A quasi-exact test for comparing two binomial proportions. *Statistics in Medicine* 10: 1137-1153.
- Lancaster, H.O. (1961). Significance tests in discrete distributions. *JASA* 56: 223-234.

**See Also**

[fisher.test](#) or [mcnemar.test](#)

**Examples**

```
## In example 1, notice how fisher.test rejects the null at the 5 percent level,
## but the 95 percent confidence interval on the odds ratio contains 1
## The intervals do not match the p-value.
## In fisher.exact you get p-values and the matching confidence intervals
example1<-matrix(c(6,12,12,5),2,2,dimnames=list(c("Group A", "Group B"),c("Event", "No Event")))
example1
fisher.test(example1)
fisher.exact(example1, tsmethod="minlike")
fisher.exact(example1, tsmethod="central")
blaker.exact(example1)
```

```
## In example 2, this same thing happens, for
## tsmethod="minlike"... this cannot be avoided because
## of the holes in the confidence set.
##
example2<-matrix(c(7,255,30,464),2,2,dimnames=list(c("Group A", "Group B"),c("Event", "No Event")))
example2
fisher.test(example2)
exact2x2(example2,tsmethod="minlike")
## you can never get a test-CI inconsistency when tsmethod="central"
exact2x2(example2,tsmethod="central")
```

---

exact2x2Plot

*Plot p-value function for one 2 by 2 table.*


---

### Description

Plots two-sided p-values as a function of odds ratios. Can plot three types of p-values: the two-sided Fisher's exact, the central Fisher's exact (i.e., twice the one-sided Fisher's exact), and Blaker's exact.

### Usage

```
exact2x2Plot(x, y=NULL, OR = NULL, ndiv = 1000, tsmethod=NULL,
  method = NULL, paired=FALSE, orRange = NULL, dolog = TRUE,
  dolines = FALSE, dopoints = TRUE, doci=TRUE,
  alternative=c("two.sided", "less", "greater"),
  conf.level=.95, alphaline=TRUE, newplot = TRUE, ...)
```

### Arguments

x	matrix representing the 2 by 2 table
y	a factor object; ignored if x is a matrix.
OR	odds ratio values for plot, if NULL divides orRange into ndiv pieces
ndiv	number of pieces to divide up odds ratio range
tsmethod	either "minlike", "blaker" or "central"
method	same as tsmethod, kept for backward compatability
paired	logical, do paired analysis giving McNemar's test p-values
orRange	range for calculating odds ratios
dolog	logical, plot odds ratios on log scale?
dolines	logical, add lines to a plot?
dopoints	logical, add points to a plot?
doci	logical, add vertical lines at confidence interval?
alternative	one of "two.sided", "less", "greater", type of alternative for p-values
conf.level	when doci=TRUE, level for confidence interval to be plotted
alphaline	logical, if doci=TRUE should a line be drawn at the significance level?
newplot	logical, start a new plot?
...	values passed to plot, points, or lines statement

**See Also**[exact2x2](#)**Examples**

```
example1<-matrix(c(6,12,12,5),2,2,dimnames=list(c("Group A","Group B"),c("Event","No Event")))
example1
exact2x2Plot(example1)
## add lines from central Fisher's exact
exact2x2Plot(example1,method="central",dolines=TRUE,newplot=FALSE,col="red")
```

---

**plotT***Plot or Print ordering function for unconditional exact test*

---

**Description**

The function `orderMat` prints the values for the ordering function for all possible values of X1 and X2 in matrix form.

The function `plotT` plots the ranking of the ordering function on an  $n1+1$  by  $n2+1$  grid, where each square represents a possible values for  $(x1,x2)$ . The default colors are from dark blue (highest) to light blue to white (middle) to light red to dark red (lowest), with black=NA.

**Usage**

```
plotT(x, ...)

## S3 method for class 'function'
plotT(x, n1, n2, delta0 = 1, main = "",...)

## S3 method for class 'numeric'
plotT(x, n1, n2, delta0 = 1, main = "",...)

orderMat(x, ...)

## S3 method for class 'function'
orderMat(x,n1,n2,delta0,graphStyle=FALSE,...)

## S3 method for class 'numeric'
orderMat(x,n1,n2,delta0,graphStyle=FALSE,...)
```

**Arguments**

x	object, either a Tstat function, or a vector of all $(n1+1)*(n2+1)$ possible values of the function (see details).
n1	sample size in group 1
n2	sample size in group 2
delta0	null value of parameter (if needed for Tstat function)
main	plot title
graphStyle	logical, order rows with lowest x1 value on the bottom?
...	arguments to be passed to the Tstat function

**Details**

If x is all the values of the Tstat function, then the values should be ordered by cycling through the x1 values (0 to n1) for each x2 value. Specifically, it should be the result of `Tstat(X1, n1, X2, n2, delta0)` where `X1=rep(0:n1, n2+1)` and `X2=rep(0:n2, each=n1+1)`.

**Examples**

```
parorig<- par(no.readonly=TRUE)
par(mfrow=c(2,2),mar=c(1,3,3,1))
TT1<-pickTstat(method="score", parmtype="ratio", tsmethod="central", alternative="two.sided")
round(orderMat(TT1,8,8,1,graphStyle=TRUE),2)
TT2<-pickTstat(method="simple", parmtype="ratio", tsmethod="central", alternative="two.sided")
TT3<-pickTstat(method="simple", parmtype="difference", tsmethod="central", alternative="two.sided")
plotT(TT2, 8,8, 1, main="Ratio, Simple")
plotT(TT3, 8,8, 0, main="Difference, Simple")
plotT(TT1, 8,8, 1, main="Ratio, Score (delta0=1)")
TF<-pickTstat(method="FisherAdj", parmtype="ratio", tsmethod="central", alternative="two.sided")
plotT(TF,8,8,1, main="FisherAdj")
par(parorig)
```

power2x2

---

*Calculate exact power or sample size for conditional tests for two independent binomials.*

---

**Description**

Power is calculated by power2x2 which calls [exact2x2](#) function repeatedly. Default (`strict=FALSE`) does not count rejections in the wrong direction.

Sample size is calculated by ss2x2 which calls power2x2 repeatedly finding the lowest sample size that has at least the nominal power, using the [uniroot.integer](#) function from the `ssanv` package.

**Usage**

```
power2x2(p0,p1,n0,n1=NULL,sig.level=0.05,
         alternative=c("two.sided","one.sided"),paired=FALSE,
         strict=FALSE,tsmethod=NULL,nullOddsRatio=1,
         errbound=10^-6,approx=FALSE)
```

```
ss2x2(p0,p1,power=.80,n1.over.n0=1,sig.level=0.05,
       alternative=c("two.sided","one.sided"),paired=FALSE,
       strict=FALSE,tsmethod=NULL,nullOddsRatio=1,
       errbound=10^-6,print.steps=FALSE, approx=FALSE)
```

**Arguments**

p0	true event rate in control group
p1	true event rate in treatment group
n0	number of observations in control group
n1	number of observations in treatment group (if NULL n1=n0)
sig.level	significance level (Type I error probability)
power	minimum power for sample size calculation
n1.over.n0	ratio of n1 over n0, allows for non-equal sample size allocation
alternative	character, either "two.sided" or "one.sided", one sided tests the proper direction according to p0 and p1
strict	use strict interpretation of two-sided test, if TRUE counts rejections in wrong direction
tsmethod	two.sided method, ignored if strict=FALSE, or alternative equals 'less' or 'greater'. see <a href="#">exact2x2</a> for details.
nullOddsRatio	null odds ratio value for tests
paired	logical. TRUE gives power for McNemar's test, FALSE are all other tests (see warning)
print.steps	logical, print steps for calculation of sample size?
errbound	bound on error of calculation
approx	give sample size or power using normal approximation only

**Details**

Assuming  $X_0 \sim \text{Binomial}(n_0, p_0)$  and  $X_1 \sim \text{Binomial}(n_1, p_1)$ , calculates the power by repeatedly calling `exact2x2` and summing probability of rejection. For speed, the function does not calculate the very unlikely values of  $X_0$  and  $X_1$  unless `errbound=0`. Power is exact, but may underestimate by at most `errbound`.

When `strict=FALSE` we do not count rejections in the wrong direction. This means that we must know the direction of the rejection, so two.sided tests are calculated as one.sided tests (in the correct direction) with level equal to `sig.level/2`. This is like using the `tsmethod='central'`.

When `approx=TRUE` for `power2x2` use a continuity corrected normal approximation (Fleiss, 1981, p. 44). For `ss2x2`



**Value**

Both `power2x2` and `ss2x2` return an object of class 'power.htest'. A list with elements

<code>power</code>	power to reject
<code>n0</code>	sample size in control group
<code>n1</code>	sample size in treatment group
<code>p0</code>	true event rate in control group
<code>p1</code>	true event rate in treatment group
<code>sig.level</code>	Significance level (Type I error probability)
<code>alternative</code>	alternative hypothesis
<code>note</code>	note about error bound
<code>method</code>	description

**Warning**

There may be convergence issues using `strict=FALSE` with `tsmethod="minlike"` or `"blaker"` since the power is not guaranteed to be increasing in the sample size.

When `paired=TRUE` the model for the power calculation is fairly restrictive. It assumes that there is no correlation between the two groups. A better power function is probably needed for this case.

**Note**

The calculations in `ss2x2` can be slow when `p0` is close to `p1` and/or the power is large. If `p0` and `p1` are close with large power, it may be safer to first calculate `ss2x2` with `approx=TRUE` to see what the starting value will be close to. If the starting sample sizes are large (>100), it may take a while.

Note when `strict=FALSE` (default), the `two.sided` results at the 0.05 level for Fisher's exact test are like the `one.sided` Fisher's exact test at the 0.025 level.

**Author(s)**

Michael P. Fay

**See Also**

See `ss.nonadh` function (`refinement="Fisher.exact"`) from the `ssanv` package for calculation that accounts for nonadherence in proportion of subjects. That function calls `fisher.test`

**Examples**

```
power2x2(.2, .8, 12, 15)
# calculate sample size with 2:1 allocation to groups
ss2x2(.2, .8, n1.over.n0=2, power=.8, approx=TRUE)
ss2x2(.2, .8, n1.over.n0=2, power=.8, print.steps=TRUE)
```

uncondExact2x2

*Unconditional exact tests for 2x2 tables***Description**

The uncondExact2x2 function tests 2x2 tables assuming two independent binomial responses. Unlike the conditional exact tests which condition on both margins of the 2x2 table (see [exact2x2](#)), these unconditional tests only condition on one margin of the 2x2 table (i.e., condition on the sample sizes of the binomial responses). This makes the calculations difficult because now there is a nuisance parameter and calculations must be done over nearly the entire nuisance parameter space.

**Usage**

```
uncondExact2x2(x1, n1, x2, n2,
  parmtype = c("difference", "ratio", "oddsratio"), nullparm = NULL,
  alternative = c("two.sided", "less", "greater"),
  conf.int = FALSE, conf.level = 0.95,
  method = c("FisherAdj", "simple", "score", "wald-pooled", "wald-unpooled", "user",
    "user-fixed"),
  tsmethod = c("central", "square"), midp = FALSE,
  gamma = 0, EplusM=FALSE, tiebreak=FALSE,
  plotprobs = FALSE, control=ucControl(), Tfunc=NULL,...)

uncondExact2x2Pvals(n1, n2, ...)
```

**Arguments**

x1	number of events in group 1
n1	sample size in group 1
x2	number of events in group 2
n2	sample size in group 2
parmtype	type of parameter of interest, one of "difference", "ratio" or "oddsratio" (see details)
nullparm	value of the parameter of interest at null hypothesis, NULL defaults to 0 for parmtype='difference' and 1 for parmtype='ratio' or 'oddsratio'
alternative	alternative hypothesis, one of "two.sided", "less", or "greater", default is "two.sided" (see details)
conf.int	logical, calculate confidence interval?
conf.level	confidence level
method	method type, one of "FisherAdj" (default), "simple", "simpleTB", "wald-pooled", "wald-unpooled", "score", "user", or "user-fixed" (see details)
tsmethod	two-sided method, either "central" or "square" (see details)
midp	logical. Use mid-p-value method?

gamma	Beger-Boos adjustment parameter. 0 means no adjustment. (see details).
EplusM	logical, do the E+M adjustment? (see details)
tiebreak	logical, do tiebreak adjustment? (see details)
plotprobs	logical, plot probabilities?
control	list of algorithm parameters, see <a href="#">ucControl</a>
Tfunc	test statistic function for ordering the sample space when method='user', ignored otherwise (see details)
...	extra arguments passed to Tfunc (for uncondExact2x2), or passed to uncondExact2x2 (for uncondExact2x2Pvals)

## Details

The `uncondExact2x2` function gives unconditional exact tests and confidence intervals for two independent binomial observations. The `uncondExact2x2Pvals` function repeatedly calls `uncondExact2x2` to get the p-values for the entire sample space.

Let  $X_1$  be binomial( $n_1, \theta_1$ ) and  $X_2$  be binomial( $n_2, \theta_2$ ). The `parmtype` determines the parameter of interest: 'difference' is  $\theta_2 - \theta_1$ , 'ratio' is  $\theta_2/\theta_1$ , and 'oddsratio' is  $(\theta_2*(1-\theta_1))/(\theta_1*(1-\theta_2))$ .

The options `method`, `parmtype`, `tmethod`, `alternative`, `EplusM`, and `tiebreak` define some built-in test statistic function, `Tstat`, that is used to order the sample space, using [pickTstat](#) and [calcTail](#). The first 5 arguments of `Tstat` must be `Tstat(X1, N1, X2, N2, delta0)`, where  $X_1$  and  $X_2$  must allow vectors, and `delta0` is the null parameter value (but `delta0` does not need to be used in the ordering). Ordering when `parmtype="ratio"` or `parmtype="oddsratio"` is only used when there is information about the parameter. So the ordering function value is not used for ordering when  $x_1=0$  and  $x_2=0$  for `parmtype="ratio"`, and it is not used when  $(x_1=0$  and  $x_2=0)$  or  $(x_1=n_1$  and  $x_2=n_2)$  for `parmtype="oddsratio"`.

We describe the ordering functions first for the basic case, the case when `tmethod="central"` or `alternative!="two.sided"`, `EplusM=FALSE`, and `tiebreak=FALSE`. In this basic case the ordering function, `Tstat`, is determined by `method` and `parmtype`:

- `method='simple'` - `Tstat` essentially replaces  $\theta_1$  with  $x_1/n_1$  and  $\theta_2$  with  $x_2/n_2$  in the parameter definition. If `parmtype='difference'` then `Tstat(X1, N1, X2, N2, delta0)` returns  $X_2/N_2 - X_1/N_1 - \text{delta0}$ . If `parmtype='ratio'` then the `Tstat` function returns  $\log(X_2/N_2) - \log(X_1/N_1) - \log(\text{delta0})$ . If `parmtype='oddsratio'` we get  $\log(X_2*(N_1 - X_1) / (\text{delta0} * X_1 * (N_2 - X_2)))$ .
- `method='wald-pooled'` - `Tstat` is a Z statistic on the difference using the pooled variance (not allowed if `parmtype!="difference"`)
- `method='wald-unpooled'` - `Tstat` is a Z statistics on the difference using unpooled variance (not allowed if `parmtype!="difference"`)
- `method='score'` - `Tstat` is a Z statistic formed using score statistics, where the parameter is defined by `parmtype`, and the constrained maximum likelihood estimates of the parameter are calculated by [constrMLE.difference](#), [constrMLE.ratio](#), or [constrMLE.oddsratio](#).
- `method='FisherAdj'` - `Tstat` is a one-sided Fisher's 'exact' mid p-value. The mid p-value is an adjustment for ties that technically removes the 'exactness' of the Fisher's p-value...BUT, here we are only using it to order the sample space, so the results of the resulting unconditional test will still be exact.

- `method='user'` - Tstat is a user supplied statistic given by Tfunc, it must be a function with the first 5 elements of its call being (X1, N1, X2, N2, delta0). The function must return a vector of length the same as X1 and X2, where higher values suggest larger theta2 compared to theta1 (when `tsmethod!="square"`) or higher values suggest more extreme (when `tsmethod=="square"` and `alternative=="two.sided"`). A slower algorithm that does not require monotonicity of one-sided p-values with respect to delta0 is used.
- `method='user-fixed'` - For advanced users. Tstat is a user supplied statistic given by Tfunc. It should have first 5 elements as described above but its result should not change with delta0 and it must meet Barnard's convexity conditions. If these conditions are met (the conditions are not checked, since checking them will slow the algorithm), then the p-values will be monotonic in delta0 (the null parameter for a two-sided test) and we can use a faster algorithm.

In the basic case, if `alternative="two.sided"`, the argument `tsmethod="central"` gives the two-sided central method. The p-value is just twice the minimum of the one-sided p-values (or 1 if the doubling is greater than 1).

Now consider cases other than the basic case. The `tsmethod="square"` option gives the square of the test statistic (when `method="simple"`, `"score"`, `"wald-pooled"`, or `"wald-unpooled"`) and larger values suggest rejection in either direction (unless `method='user'`, then the user supplies any test statistic for which larger values suggest rejection).

The `tiebreak=TRUE` option breaks ties in a reasonable way when `method="simple"` (see 'details' section of `calcTall`). The `EplusM=TRUE` option performs Lloyd's (2008) E+M ordering on Tstat (see 'details' section of `calcTall`).

If `tiebreak=TRUE` and `EplusM=TRUE`, the tiebreak calculations are always done first.

Berger and Boos (1994) developed a very general method for calculating p-values when a nuisance parameter is present. First, calculate a  $(1-\gamma)$  confidence interval for the nuisance parameter, check for the supremum over the union of the null hypothesis parameter space and that confidence interval, then add back  $\gamma$  to the p-value. This adjustment is valid (in other words, applied to exact tests it still gives an adjustment that is exact). The Berger-Boos adjustment is applied when  $\gamma > 0$ .

When `method='simple'` or `method='user-fixed'` does a simple grid search algorithm using `unirootGrid`. No checks are done on the Tstat function when `method='user-fixed'` to make sure the simple grid search will converge to the proper answer. So `method='user-fixed'` should be used by advanced users only.

When `midp=TRUE` the mid p-value is calculated (and the associated confidence interval if `conf.int=TRUE`) instead of the standard p-value. Loosely speaking, the standard p-value calculates the probability of observing equal or more extreme responses, while the mid p-value calculates the probability of more extreme responses plus 1/2 the probability of equally extreme responses. The tests and confidence intervals when `midp=TRUE` are not exact, but give type I error rates and coverage of confidence intervals closer to the nominal values. The mid p-value was studied by Lancaster (1961), see vignette on mid p-values for details.

## Value

The function `uncondExact2x2Pvals` returns a  $(n1+1)$  by  $(n2+1)$  matrix of p-values for all possible  $x1$  and  $x2$  values, while `uncondExact2x2` returns a list of class 'htest' with elements:

statistic          proportion in sample 1

parameter	proportion in sample 2
p.value	p-value from test
conf.int	confidence interval on parameter given by parmtime
estimate	MLE estimate of parameter given by parmtime
null.value	null hypothesis value of parameter given by parmtime
alternative	alternative hypothesis
method	description of test
data.name	description of data

**Warning**

The algorithm for calculating the p-values and confidence intervals is based on a series of grid searches. Because the grid searches are often trying to optimize non-monotonic functions, the algorithm is not guaranteed to give the correct answer. At the cost of increasing computation time, better accuracy can be obtained by increasing `control$nPgrid`, and less often by increasing `control$NCIgrid`.

**Author(s)**

Michael P. Fay, Sally A. Hunsberger

**References**

- Berger, R. L. and Boos, D. D. (1994). P values maximized over a confidence set for the nuisance parameter. *Journal of the American Statistical Association* 89 1012-1016.
- Lancaster, H.O. (1961). Significance tests in discrete distributions. *JASA* 56: 223-234.
- Lloyd, C. J. (2008). Exact p-values for discrete models obtained by estimation and maximization. *Australian & New Zealand Journal of Statistics* 50 329-345.

**See Also**

See [boschloo](#) for unconditional exact tests with ordering function based on Fisher's exact p-values.

**Examples**

```
# default uses method="FisherAdj"
uncondExact2x2(1,10,9,10,
               parmtime="ratio")
uncondExact2x2(1,10,9,10,
               method="score", parmtime="ratio")
```

---

uncondPower2x2                      *Calculate power or sample size for any 2x2 test.*

---

### Description

The function [Power2x2](#) and [SS2x2](#) calculates the power or sample size for any 2x2 test, while the function [uncondPower2x2](#) calculates power for only tests supported by [uncondExact2x2Pvals](#).

### Usage

```
Power2x2(n1, n2, theta1, theta2, alpha, pvalFunc, ...)
```

```
uncondPower2x2(n1,n2, theta1, theta2, alpha, ...)
```

```
SS2x2(theta1, theta2, alpha, pvalFunc, power=0.90,
       n1start=10, increaseby=1, n2.over.n1=1,
       maxiter=50, printSteps=TRUE, ...)
```

### Arguments

n1	sample size in group 1
n2	sample size in group 2
theta1	probability of success in group 1
theta2	probability of success in group 2
alpha	significance level
pvalFunc	function that inputs x1,n1,x2,n2 and outputs a p-value.
power	target power
n1start	value of n1 for first iteration
increaseby	positive integer, how much to increase n1 by for each iteration
n2.over.n1	ratio of n2/n1
maxiter	maximum number of iterations
printSteps	logical, should the power and sample size be printed after each iteration?
...	arguments passed to <a href="#">uncondExact2x2Pvals</a> (for <a href="#">uncondPower2x2</a> ), or to <a href="#">Power2x2</a> (for <a href="#">SS2x2</a> ). Not used and saved for future use for <a href="#">Power2x2</a> .

### Details

The function [Power2x2](#) is a very simple function to calculate power. It calculates power where rejection is when the p-value from [pvalFunc](#) is less than or equal to [alpha](#). The function [SS2x2](#) repeatedly calls [Power2x2](#) as it increases the sample size, stopping when the power is greater than 'power'.

The function [uncondPower2x2](#) is similar except the p-values are calculated by [uncondExact2x2Pvals](#).

**Value**

the power functions return only the power. The sample size function returns a list of class 'ht-est.power'.

**See Also**

For power and sample size for conditional exact tests (e.g., Fisher's exact tests) see [power2x2](#) and [ss2x2](#).

**Examples**

```
library(exact2x2)
Power2x2(3,4,.1,.9,0.025, pvalFunc=
  function(x1,n1,x2,n2){
    boschloo(x1,n1,x2,n2, alternative="greater",
             or=1,tsmethod="central", midp=TRUE)$p.value
  }
)
##
## Not run:
SS2x2(.1,.9,0.025, n1start=5, pvalFunc=
  function(x1,n1,x2,n2){
    boschloo(x1,n1,x2,n2, alternative="greater",
             or=1,tsmethod="central", midp=TRUE)$p.value
  }
)
## End(Not run)
```

---

unirootGrid

*Function to find a root by grid search.*


---

**Description**

Find the root (value where the function equals 0) of a monotonic function, `func`, using a halving algorithm grid search.

**Usage**

```
unirootGrid(func, power2 = 12, step.up = TRUE, pos.side = FALSE,
  print.steps = FALSE, power2grid = power2gridRatio, ...)
```

**Arguments**

<code>func</code>	monotonic function
<code>power2</code>	positive integer, number of grid points is $1+2^{\text{power2}}$
<code>step.up</code>	logical, start the search at the lower end of the grid and step up?
<code>pos.side</code>	logical, should the root be on the positive side? In other words, should $\text{func}(\text{root}) \geq 0$

<code>print.steps</code>	logical, should each step that is evaluated be printed?
<code>power2grid</code>	function that returns the grid. Take one argument, <code>power2</code>
<code>...</code>	arguments passed to <code>func</code>

### Details

The grid is defined with the `power2grid` argument that defines a function with an argument `power2`, and returns a grid with  $1+2^{\text{power2}}$  elements. The root is found by a halving algorithm on the grid, so `func` is calculated only  $\text{power2}+1$  times. The ‘root’ is the element that is closest to the root, either on the positive side (`pos.side=TRUE`) or not.

The `unirootGrid` function calls `uniroot.integer` and finds roots based on grid search. The functions `power2gridRatio` and `power2gridDifference` create grids for searching (0,Inf) and (-1,1) respectively. The `power2gridRatio` grid is equally spaced on the log scale with about half of the grid between 0.5 and 2. The function `power2grid` allows more flexibility in defining grids.

### Value

A list with elements:

<code>iter</code>	number of iterations
<code>f.root</code>	value of <code>func</code> at root
<code>root</code>	root, element on the grid that is closest to the root on the negative side (if <code>pos.side=FALSE</code> )
<code>bound</code>	interval for the accuracy

### Author(s)

Michael P. Fay

### See Also

[uniroot](#) and [uniroot.integer](#)

### Examples

```
# print.steps prints all iterations,
# with x=rank of grid value (e.g., x=1 is lowest value in grid)
# f(x) really is f(grid[x]) where grid is from the power2grid function
unirootGrid(function(x){ x - .37}, power2=10, power2grid=power2gridRatio,
  print.steps=TRUE, pos.side=TRUE)
```



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