

Package ‘bifactorial’

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Title Inferences for bi- and trifactorial trial designs

Depends mvtnorm,multcomp,lattice,graphics,methods,Rcpp (>= 0.8.8)

LinkingTo Rcpp

Description This package makes global and multiple inferences for given bi- and trifactorial clinical trial designs using bootstrap methods and a classical approach.

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R topics documented:

avemax	2
bifactorial	4
carpetcube	5
multinf	7
sidbp	10
Index	11

 avemax

AVE- and MAX-test

Description

Compute global tests for factorial dose-response designs following Hung (2000) or by a bootstrap algorithm.

Usage

```
avetest(C, test=NULL, method="bootstrap", nboot=NULL, simerror=NULL, ...)
maxtest(C, test=NULL, method="bootstrap", nboot=NULL, simerror=NULL, ...)
```

Arguments

C	An object of class <code>carpet</code> or <code>cube</code> .
test	Either <code>"ttest"</code> or <code>"ztest"</code> - the test statistic for the inferences to be based on. Use <code>"ztest"</code> for binary data applications.
method	The calculation method - use <code>"bootstrap"</code> for a resampling-based approach and <code>"hung"</code> for calculations using the multivariate normal distribution.
nboot	The number of bootstrap iterations to use.
simerror	Prespecified simulation standard error.
...	Any further arguments.

Details

When handling with data from factorial clinical trial designs, one is often interested in the question whether dose combinations in the trial have got a better effect than all of their component drugs, because regulatoric requirements demand a contribution to the efficacy by all components. The decision if any of the tested combination drugs has got this property can be based on the AVE- or MAX-statistics proposed by Hung, Chi and Lipicky (1993). The hypothesis that this is true for none of the combinations is rejected if the largest or the average of the min-statistics is sufficiently high. The functions `avetest` and `maxtest` calculate the corresponding p-values on `carpet` or `cube` objects with a new bootstrap algorithm, which is default, or by the multivariate method for unbalanced designs from Hung (2000). A resampling-based method is available also for binary data applications. The desired simulation accuracy always needs to be specified by the number `nboot` of simulations to perform or an upper bound `simerror` for the simulation standard error. If both are given, the two constraints will be held simultaneously. Depending on the type of data, the calculations can be based on Student's t-test for metric data or the Z-statistic for binary applications.

Value

An object of class `avetest` or `maxtext`, respectively, with the following slots. The slot name is available for the MAX-test only.

p	p-value for the AVE- or MAX-test.
---	-----------------------------------

stat	Observed AVE- or MAX-statistic.
test	Type of test statistic which the AVE- or MAX-test was based on.
method	Algorithm used for the calculation.
nboot	Total number of resampling iterations.
simerror	Simulation standard error.
name	Combination group where the maximum of the min-statistics was observed.
duration	Total computing duration in seconds.
call	The function call.

Note

The performance of the bootstrap-based approach and the method from Hung (2000) has been compared and discussed. All algorithms perform very conservative if the means in the marginal treatment groups are close for the combinations.

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References

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- Hung HMJ (2000): Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. *Statist Med* 19, pp. 2079-2087

See Also

[bifactorial](#), [carpet](#), [cube](#), [mintest](#), [margint](#)

Examples

```
#Hypertension example from Hung (2000)
n<-c(75,75,74,48,74,75,74,49,48,50,48,48)
m<-c(0,1.4,2.7,4.6,1.8,2.8,5.7,8.2,2.8,4.5,7.2,10.9)
s<-rep(7.07,12)
x<-list(12)
for(i in 1:12){
  x[[i]]<-rnorm(n[i],mean=0,sd=1)
  x[[i]]<-((x[[i]]-mean(x[[i]]))*(s[i]/sd(x[[i]])))+m[i]
```

```
}  
hung<-carpet(x,D=c(2,3))  
avetest(hung,test="ttest",nboot=20000)  
maxtest(hung,test="ttest",nboot=20000)
```

bifactorial

General information on the package

Description

Factorial clinical trial designs can be used to test for the efficacy of combination drugs with two or more components, where inference on the question if a combination therapy is more efficacious than both of its components is based on the min-test proposed by Laska and Meisner (1989). This is due to regulatoric demands requiring a contribution of all compounds in a combination drug. The AVE- and MAX-approaches proposed by Hung, Chi and Lipicky (1993) test for the existence of any desirable combination.

Bootstrap-based methods are implemented as well as classical approaches available from literature to obtain p-values and confidence intervals in such designs. For the min-test, analytical methods use a normality and homoscedasticity assumption on the data (Hung, Chi and Lipicky, 1993 and Hung, 2000). Critical values needed for determination of confidence intervals are calculated using quantiles of the multivariate t-distribution (Bretz, Genz and Hothorn 2001). These methods fail when handling with data that are skewed or heteroscedastic over the treatment groups. Furthermore, no analytical approach is available for the trifactorial case and the AVE- and MAX-tests on binary data. In the bootstrap approach, only the empirical distribution of the data is used and thus the results are valid for any distributional shape, provided that sufficiently large samples are available. Less analytical framework is needed to handle with the distributional properties of the tests. Further information on resampling-based methods and theoretical backgrounds are given in Westfall and Young (1993).

Anyway, the problem of the extremely decreasing power for small values of the so-called nuisance parameters indicating the response differences between the marginal treatment groups cannot be resolved by the bootstrap approach. Any algorithm based on estimates for the nuisance parameters other than the assumption that they are infinite will exceed the given significance level (Snapinn, 1987).

The package contains the generic functions `mintest` and `marginint` to test for mean differences of given numeric data vectors and differences in event rates for binary data applications. Method `dispatch` is available for objects of class `carpet` or `cube`, which will lead to min-test results on a bi- or trifactorial design and corresponding confidence intervals comparing combination treatments with their respective component therapies. Implementations for global tests are also available by the generic functions `avetest` and `maxtest`.

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- Laska EM, Meisner MJ (1989): Testing whether an identified treatment is best. *Biometrics* 45, pp. 1139-1151
- Snapinn SM (1987): Evaluating the efficacy of a combination therapy. *Statist Med* 6, pp. 657-665
- Westfall PH, Young SS (1993): Resampling-based multiple testing. John Wiley & Sons, Inc., New York

carpetcube

Objects for handling with bi- and trifactorial trial data

Description

Create objects representing bi- or trifactorial clinical trial designs.

Usage

```
carpet(data,D,...)
cube(data,D,...)
```

Arguments

- | | |
|------|---|
| data | A list of numeric or binary data vectors from the trial. See the details below for the order in which the list is to be given. |
| D | An integer vector of length 2 for carpet objects and of length 3 for cube objects, specifying the number of doses of the components drugs in the trial. |
| ... | Any further arguments. |

Details

The function `carpet` creates objects of class `carpet` from the specified data in the list that are used row-wise to fill up the 2-factorial treatment groups, i.e. in the order (0,0), (0,1),..., (0,D[2]), (1,0), ..., (1,D[2]), ..., (D[1],D[2]); resulting in a $(D[1]+1) \times (D[2]+1)$ data array.

To represent trifactorial designs for the evaluation of a three-compound combination, an object of class `cube` can be created using the function `cube`. The data in the treatment groups are then filled up in the order (0,0,0), ..., (0,0,D[3]) first, then (0,1,0), ..., (0,1,D[3]) and up to (0,D[2],0), ..., (0,D[2],D[3]). This is the order also for the values 0, ..., D[1] for the first component group, always taking the data successively from the list elements of data. The result is a $(D[1]+1) \times (D[2]+1) \times (D[3]+1)$ data array. Methods for multiple inference and global tests can be applied to `carpet` and `cube` objects.

Value

An object of class `carpet` or `cube`, respectively, with the following slots.

<code>data</code>	The data list specified in the construction.
<code>D</code>	Vector of maximum doses specified in the construction.
<code>n</code>	Numeric vector of sample sizes in the respective groups.

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- Hung HMJ (2000): Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. *Statistics in Medicine* 19, pp. 2079-2087

See Also

[bifactorial](#), [mintest](#), [margint](#), [avetest](#), [maxtest](#)

Examples

```
#Hypertension example from Hung (2000)
data(sidbp)
x<-split(sidbp$ynrmhom,sidbp$cb)
bifactorial<-carpet(data=x,D=c(2,3))
```

multinf

Multiple inference

Description

Compute adjusted p-values and simultaneous confidence intervals for given bi- and trifactorial design data.

Usage

```
mintest(C, test=NULL, method="bootstrap", nboot=NULL, simerror=NULL, ...)
margin(C, test=NULL, method="bootstrap", nboot=NULL, simerror=NULL,
       alpha=0.05, ...)
```

Arguments

C	An object of class carpet or cube.
method	The calculation method - use "bootstrap" for a resampling-based approach, "hung" for the min-test approach of Hung (2000) and "tdistr" for interval calculations based on the multivariate t-distribution.
test	Either "ttest" or "ztest" - the test statistic for the inferences to be based on. Use "ztest" for binary data applications.
alpha	Simultaneous level of the confidence intervals.
nboot	Number of resampling iterations to use.
simerror	Prespecified simulation standard error.
...	Any further arguments.

Details

The generic functions `mintest` and `margin` calculate adjusted p-values and simultaneous confidence intervals for the test of parametric differences between prespecified treatment groups on bi- or trifactorial design clinical trials. If an object of class `carpet` is committed, `mintest` will return adjusted p-values for the min-test on combination superiority in bifactorial clinical trial designs (Laska and Meisner, 1989). The alternative hypothesis of this test is that the detected effect size for the combination treatment is better than for both single component groups; i.e. the test results in only one p-value for each combination. The generic function `margin` will, when applied to `carpet` objects, return simultaneous confidence intervals for the parametric differences between each combination treatment group and its respective components. Depending on the type of data, the calculations can be based on Student's t-test for metric data or the Z-statistic for binary applications.

By default, the calculations are performed by a resampling-based approach. The desired simulation accuracy always needs to be specified by the number `nboot` of bootstrap iterations to perform or an upper bound `simerror` for the simulation standard error. If both are given, the two constraints will be held simultaneously. On the other hand, the multivariate normal approach for unbalanced designs from Hung (2000) is available when the argument `method` is set to the value "hung". For the

trifactorial case, no such approach is available and thus the calculations are based on the bootstrap approach, performing a generalized min-test on the data, if an object of class `cube` is committed. The interval calculations are based on the multivariate t-distribution if `"tdistr"` is specified.

In the classical approach to the min-test, a normality assumption for the data is used and the desired critical values are calculated using quantiles of the multivariate t-distribution. However, this method fails when handling with data that are skewed or heteroscedastic over the treatment groups. When using the bootstrap, only the empirical distribution of the data is used and thus the results are always valid, provided that a sufficiently large samples are available. When handling with data from bifactorial clinical trial designs, bootstrap methods need much less analytical framework on the distributional properties of the tests than if the approach given by Hung (2000) is used. In particular, the restriction to only two compounds is not needed and binary data applications can be handled analogously. The theory of resampling-based multiple testing has been extensively discussed by Westfall and Young (1993).

The calculation of simultaneous confidence intervals is much easier because the c.d.f. of the min-statistic is not needed. Hence this is leading to an ordinary multiple contrast problem.

Value

An object of class `mintest` or `margint` with the following slots.

<code>p</code>	Adjusted p-values for the respective combination groups.
<code>stat</code>	The observed values of the min-statistics.
<code>kiu</code>	The lower limits of the confidence intervals.
<code>kio</code>	The upper limits of the confidence intervals.
<code>alpha</code>	One minus the nominal coverage probability of the confidence intervals.
<code>gnames</code>	Names of the combination groups.
<code>cnames</code>	The names of the contrasts for comparisons of the combinations with their respective components.
<code>test</code>	Type of test statistics that the min-tests were based on.
<code>method</code>	The method used for calculation.
<code>nboot</code>	Number of bootstrap replications used.
<code>simerror</code>	Maximum of the simulation standard errors in the combination groups.
<code>duration</code>	Total computing duration in seconds.
<code>call</code>	Function call.

Note

Performance of the implemented methods has been evaluated and compared. The min-test performs very conservative if the means in the marginal treatment groups are close for a combination.

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- Frommolt P, Hellmich M (2009): Resampling in multiple-dose factorial designs. *Biometrical J* 51(6), pp. 915-31
- Hung HMJ, Chi GYH, Lipicky RJ (1993): Testing for the existence of a desirable dose combination. *Biometrics* 49, pp. 85-94
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- Westfall PH, Young SS (1993): Resampling-based multiple testing. John Wiley & Sons, Inc., New York

See Also

[bifactorial](#), [carpet](#), [cube](#), [avetest](#), [maxtest](#),

Examples

```
#AML example from Huang et al. (2007) with data from
#Issa et al. (2004) and Petersdorf et al. (2007)
n<-c(10,31,17,100,50,50,101,50,50)
p<-c(0.00,0.45,0.65,0.30,0.71,0.70,0.59,0.64,0.75)
y<-list()
for(i in 1:9){
  y[[i]]<-0
  while((sum(y[[i]])!=round(n[i]*p[i]))||(length(y[[i]])==1)){
    y[[i]]<-rbinom(n[i],1,p[i])
  }
}

aml<-carpet(data=y,D=c(2,2))
mintest(aml,test="ztest",nboot=25000)
margint(aml,test="ztest",nboot=25000)
```

`sidbp`*Data of sitting distolic blood pressure (SiDBP)*

Description

These data have been simulated with respect to the descriptive statistics given in the bifactorial hypertension clinical trial reported by Hung (2000). Various distributional properties have been realized for normal and skewed cases with equal variances as well as with linearly increasing variances. The latter means that the coefficient of variation is held constant over the treatment groups. The group defining variable is named `cb` in the data set. It has got the levels $(0, 0)$, $(1, 0)$, \dots , $(2, 3)$ according to the respective dose combinations. The data vectors with the different distributional properties are `ynrmhom`, `ynrmhet`, `yloghom` and `yloghet`.

Format

A data frame with 738 observations on the following 5 variables.

`cb` a factor with levels $(0, 0)$, $(0, 1)$, \dots , $(2, 3)$

`ynrmhom` A vector of normal and homoscedastic data.

`ynrmhet` A vector of normal and heteroscedastic data.

`yloghom` A vector of lognormal and homoscedastic data.

`yloghet` A vector of lognormal and heteroscedastic data.

References

Hung HMJ (2000): Evaluation of a combination drug with multiple doses in unbalanced factorial design clinical trials. *Statistics in Medicine* 19, pp. 2079-2087

Examples

```
data(sidbp)
```

Index

- *Topic **classes**
 - carpetcube, 5
- *Topic **datasets**
 - sidbp, 10
- *Topic **design**
 - avemax, 2
 - bifactorial, 4
 - carpetcube, 5
 - multinf, 7
- *Topic **htest**
 - avemax, 2
 - bifactorial, 4
 - multinf, 7
- *Topic **iteration**
 - avemax, 2
 - bifactorial, 4
 - multinf, 7
- *Topic **multivariate**
 - avemax, 2
 - bifactorial, 4
 - multinf, 7
- *Topic **package**
 - bifactorial, 4

- avemax, 2
- avetest, 6, 9
- avetest (avemax), 2
- avetest, ANY-method (avemax), 2
- avetest, carpet-method (avemax), 2
- avetest, cube-method (avemax), 2
- avetest-class (avemax), 2

- bifactorial, 3, 4, 6, 9
- bifactorial-package (bifactorial), 4

- carpet, 3, 9
- carpet (carpetcube), 5
- carpet, ANY, ANY-method (carpetcube), 5
- carpet, list, numeric-method (carpetcube), 5

- carpet-class (carpetcube), 5
- carpetcube, 5
- cube, 3, 9
- cube (carpetcube), 5
- cube, ANY, ANY-method (carpetcube), 5
- cube, list, numeric-method (carpetcube), 5
- cube-class (carpetcube), 5

- margint, 3, 6
- margint (multinf), 7
- margint, ANY-method (multinf), 7
- margint, carpet-method (multinf), 7
- margint, cube-method (multinf), 7
- margint-class (multinf), 7
- maxtest, 6, 9
- maxtest (avemax), 2
- maxtest, ANY-method (avemax), 2
- maxtest, carpet-method (avemax), 2
- maxtest, cube-method (avemax), 2
- maxtest-class (avemax), 2
- mintest, 3, 6
- mintest (multinf), 7
- mintest, ANY-method (multinf), 7
- mintest, carpet-method (multinf), 7
- mintest, cube-method (multinf), 7
- mintest-class (multinf), 7
- multinf, 7

- plot, carpet, missing-method (carpetcube), 5
- plot, cube, missing-method (carpetcube), 5
- plot, margint, missing-method (multinf), 7
- plot, mintest, missing-method (multinf), 7

- show, avetest-method (avemax), 2
- show, carpet-method (carpetcube), 5
- show, cube-method (carpetcube), 5
- show, margint-method (multinf), 7
- show, maxtest-method (avemax), 2
- show, mintest-method (multinf), 7

sidbp, [10](#)
summary, avetest-method (avemax), [2](#)
summary, carpet-method (carpetcube), [5](#)
summary, cube-method (carpetcube), [5](#)
summary, margint-method (multinf), [7](#)
summary, maxtest-method (avemax), [2](#)
summary, mintest-method (multinf), [7](#)