

Package ‘asd’

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asd-package

Simulation Tools for Adaptive Seamless Design (ASD)

Description

Functions to run simulations for a trial design that tests a number of experimental treatments against a single control treatment group in a seamless adaptive trial. Test treatments are compared to the control treatment using Dunnett's many-to-one testing procedure. An interim analysis is undertaken using an early outcome measure. A decision is made on which of the treatments to take forward, using a pre-defined selection rule. Data are simulated for the final outcome measure that is allowed to be correlated with the early outcome measure. Data from the interim and final analyses for the final outcome measure are combined together using either the inverse normal or Fisher combination test and hypotheses are either rejected or accepted after controlling the familywise error rate at the selected level.

Details

Package: asd
Type: Package
Version: 1.0
Date: 2009-12-04
License: GPL-2
LazyLoad: yes

Simulations are run using the functions [asd.sim](#) and [gasd.sim](#).

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Adaptive designs are described in more detail:

Thall PF, Simon R, Ans Ellenberg SS. A two-stage design for choosing amongst several experimental treatments and a control in clinical trials. *Biometrics* 1988;45:537-547.

Thall PF, Simon, R, Ans Ellenberg SS. Two-stage selection and testing designs for comparative clinical trials. *Biometrika* 1989;75,303-310.

Bauer P, Kieser M. Combining different phases in the development of medical treatments within a single trial. *Statistics in Medicine* 1999;18:1833-1848.

Stallard N, Todd S. Sequential designs for phase II and phase III clinical trials incorporating treatment selection. *Statistics in Medicine* 2003;22:689-703.

Posch M, Koenig F, Branson M, Brannath W, Dunger-Baldauf C, Bauer P. Testing and estimation in flexible group sequential designs with adaptive treatment selection. *Statistics in Medicine* 2005;24:3697-3714.

Bretz F, Schmidli H, Koenig F, Racine A, Maurer W. Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: General concepts. *Biometrical Journal* 2006;48:623-634.

Koenig F, Brannath W, Bretz F, Posch M. Adaptive Dunnett tests for treatment selection. *Statistics in Medicine* 2008;27:1612-1625.

Stallard N, Friede T. A group-sequential design for clinical trials with treatment selection. *Statistics in Medicine* 2008;27:6209-6227.

See Also

[asd.sim](#), [gasd.sim](#)

asd.sim

ASD Simulation for Normal Data

Description

Function `asd.sim` runs simulations for a trial design that tests a number of experimental treatments against a single control treatment group in a seamless adaptive trial. Test treatments are compared to the control treatment using Dunnett's many-to-one testing procedure. An interim analysis is undertaken using an early outcome measure, assumed to be normally distributed, and characterized by standardized treatment effects with variances assumed to be equal to one, for each treatment (and control). A decision is made on which of the treatments to take forward, using a pre-defined selection rule. Data are simulated for the final outcome measure, also characterized by standardized treatment effects, with variance assumed equal to one and a fixed correlation between the final and the early outcomes. Data from the interim and final analyses for the final outcome measure are combined together using either the inverse normal or Fisher combination test and hypotheses are tested at the selected level.

Usage

```
asd.sim(nsamp = c(32, 32), early = c(0, 0, 0), final = c(0, 0, 0),
       nsim = 1000, corr = 0, seed = 12345678, select = 0, epsilon = 1,
       thresh = 1, level = 0.025, ptest = seq(1:length(early)),
       reall = FALSE, fu = FALSE, estim = FALSE, method = "invnorm")
```

Arguments

nsamp	Vector of sample sizes for each treatment group, at interim and final analysis or a vector of the total sample sizes at each stage if reallocate is TRUE for the epsilon and futility rule.
early	Vector of standardized treatment effects for the early outcome measure (maximum 8 treatments).
final	Vector of standardized treatment effects for the final outcome measure.
nsim	Number of simulations (maximum=10,000,000).
corr	Correlation between early and final outcomes.
seed	Seed number.
select	Selection rule type; 0 = select all treatments, 1 = select maximum, 2 = select maximum two, 3 = select maximum three, 4 = epsilon rule (select means within epsilon of maximum), 5 = randomly select a single treatment and 6 = threshold rule (select means greater than or equal to threshold). See select.rule .
epsilon	For select = 4, set epsilon criterion.
thresh	For select = 6, set threshold criterion.
level	Test level (default=0.025).
ptest	Vector of treatment numbers for determining power. For example, c(1,2) will count rejections of one or both hypotheses for testing treatments 1 and 2 against the control.
reall	Logical indicating if reallocation should be used for the second stage. This is implemented only for the epsilon and threshold rules. Default is FALSE.
fu	Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up. Default is FALSE.
estim	Logical indicating if mean and variance of final outcome should be estimated. Default is FALSE.
method	Select combination method. Available options are “invnorm” or “fisher”. Default is “invnorm”.

Details

A structured description of the algorithm used to perform the simulations is given below:

- (1) Generate a random sample of bivariate normal effects, using the function [simeans.binormal](#), based on a treatment group sample size of nsamp for the interim and final analyses for the control and n test treatments with expected standardized effects given by the early and final outcomes.
- (2) Calculate n test statistics for the early outcome (based on data from (1)) comparing each test treatment to the control and use the function [select.rule](#) at the interim analysis (using options type, epsilon, thresh, and reall as appropriate) to select treatments for the final analysis.
- (3) Implement the Dunnett test ([dunnett.test](#)) for the test statistics from (2) (*dunnett1*), with appropriate modification depending on whether patients are followed-up.
- (4) Generate a random sample of normal effects based on a treatment group sample size of nsamp[2] for the final analysis for the control and n test treatments with expected standardized effects given by final. Calculate n test statistics comparing each treatment to the control, for the selected treatments from(2). Implement the Dunnett test ([dunnett.test](#)) for these test statistics (*dunnett2*), with

appropriate modification depending on which treatments are selected.

(5) Outputs *dunnett1* and *dunnett2* are combined using either the “fisher” or the “inverse normal” combination function (*combn.test*).

(6) Hypotheses are tested using the output of the combination function and function *hyp.test* at the selected level.

(7) For each iteration an indicator records whether each elementary hypothesis (comparing each test treatment to the control) is rejected or accepted. If one or more of the treatments selected using option *ptest* is rejected then this is recorded.

(8) Steps (1) to (7) are repeated *nsim* times.

(9) The results are summarised by *count.total* which reports the number of times one or more treatments are selected at interim, *select.total* which reports the number of times each test treatment is selected, *reject.total* which gives the number of times each hypothesis is rejected and *sim.reject* which gives the number of times one or more of the treatments selected using *ptest* is rejected.

If *real1* is TRUE, then *nsamp[1]* and *nsamp[2]* represent the total number of patients at each stage, and patients are divided equally between treatment groups depending on the number of test treatments and the number of test treatments selected at the interim analysis. If *estim* is TRUE then means and variances are estimated and reported for each of the two stages.

Value

<i>count.total</i>	Number of times one or more treatments are selected.
<i>select.total</i>	Number of times each test treatment is selected.
<i>reject.total</i>	Number of times each hypothesis is rejected.
<i>sim.reject</i>	Number of times one or more of the treatments selected using <i>ptest</i> is rejected.
<i>est.mean</i>	Estimates of the mean standardized treatment effects at stages 1 and 2 for each treatment. When <i>estim</i> is TRUE.
<i>est.N</i>	Estimates of the denominator population for estimating the variance at stages 1 and 2 for each treatment. When <i>estim</i> is TRUE.
<i>est.var</i>	Estimates of the variances of the standardized treatment effects at stages 1 and 2 for each treatment. When <i>estim</i> is TRUE.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Friede T, Parsons N, Stallard S, Todd S, Valdes Marquez E, Chataway J, Nicholas R. Designing a Seamless Phase II/III Clinical Trial using Early Outcomes for Treatment Selection: an Application in Multiple Sclerosis. Submitted to *Statistics in Medicine*.

Bretz F, Schmidli H, Koenig F, Racine A, Maurer W. Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: General concepts. *Biometrical Journal* 2006;48:623-634.

See Also[gasd.sim](#)**Examples**

```
## 3 treatments, one effective with size 0.3, and one effective with size 0.2
## Correlation between early and final outcomes is 0.3
## Select one treatment at the interim analysis
## 32 patients in each group at stage 1 and stage 2
## Count rejections in treatment groups 1 and/or 2
asd.sim(nsamp=c(32,32),early=c(0.3,0.2,0),final=c(0.3,0.2,0),
        nsim=100,corr=0.3,seed=145514,select=1,epsilon=1,reall=FALSE,
        level=0.025,ptest=c(1,2),fu=FALSE,method="invnorm")

## Allow more than one treatment to be selected at the interim analysis
asd.sim(nsamp=c(32,32),early=c(0.3,0.2,0),final=c(0.3,0.2,0),
        nsim=100,corr=0.3,seed=145514,select=4,epsilon=0.5,reall=FALSE,
        level=0.025,ptest=c(1,2),fu=FALSE,method="invnorm")
```

combn.test

*Combination Tests for ASD***Description**

Implements weighted inverse normal and Fisher combination tests for combining p -values for adaptive seamless designs.

Usage

```
combn.test(stage1, stage2, weight = 0.5, method = "invnorm")
```

Arguments

stage1	Output from function <code>dunnett.test</code> from stage 1 of an ASD.
stage2	Output from function <code>dunnett.test</code> from stage 2 of an ASD.
weight	Weight indicating how p -values from stages 1 and 2 are combined. Default weight is 0.5 indicating equal weighting between stages ($0 < \text{weight} < 1$).
method	Select combination test method. Available options are “invnorm” or “fisher”. Default is “invnorm”.

Details

The basic ideas of the combination test approach were proposed by Bauer and Kieser (1999) and make use of a combination function (Bauer and Kohne, 1994) to combine stagewise p -values to allow for interim adaptations and the application of the closed test principle (Marcus *et al.*, 1976) to control the overall test size across multiple hypotheses.

Value

method	Selected method of combining p -values.
zscores	Z-scores for each hypothesis.
hyp.comb	A list of matrices indicating the structure of the intersection hypotheses.
weights	Weights used for each stage.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Bauer P, Kieser M. Combining different phases in the development of medical treatments within a single trial. *Statistics in Medicine* 1999;18:1833-1848.

Bauer P, Kohne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994;50:1029-1041.

Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;63:655-660.

Lehmacher W, Wassmer G. Adaptive sample size calculations in group sequential trials. *Biometrics* 1999;55:1286-1290.

See Also

[asd.sim](#), [gasd.sim](#), [dunnett.test](#), [hyp.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
stage1 <- dunnett.test(c(0.75,1.5,2.25))
stage2 <- dunnett.test(c(0.15,1.75,2.15))
combn.test(stage1,stage2,weight=0.5,method="invnorm")
```

dunnett.test

Dunnett Test

Description

Implements Dunnett's test (Dunnett, 1955) for many-to-one comparisons.

Usage

```
dunnett.test(Z = Z, select = rep(1, length(Z)))
```

Arguments

Z	A vector of test statistics.
select	Selected treatments to include in the test. Default is to include all treatments. Vector of length Z; to include treatments set values to one and to exclude treatments set values to zero.

Details

A many-to-one comparison test for the the null hypothesis that all the treatment effects are equal to zero against the alternative that at least one is larger than zero.

Value

pvalues	A list of matrices of p -values for all intersection hypotheses.
zscores	A list of matrices of z-scores for all intersection hypotheses.
hyp.comb	A list of matrices indicating the structure of the intersection hypotheses.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association* 1955;50:1096-1121.

See Also

[asd.sim](#), [gasd.sim](#), [combn.test](#), [hyp.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
dunnett.test(c(0.75, 1.5, 2.25))

# select two treatments only
dunnett.test(c(0.75, 1.5, 2.25), select=c(1, 1, 0))

# set test statistic to -Inf
dunnett.test(c(0.75, 1.5, -Inf))
```

gasd.sim

*General ASD Simulation***Description**

Function `gasd.sim` is a generalization of function `asd.sim` for non-normal data through the use of expected test statistics, that are assumed to be normally distributed, and a more general statement of the variances and correlations. The structure of the outputs of this function are equivalent to `asd.sim`, but the inputs differ somewhat.

Usage

```
gasd.sim(z1 = c(0, 0, 0), z2 = c(0, 0, 0), zearly = c(0, 0, 0), v1 = c(1, 1, 1, 1),
        v2 = c(1, 1, 1, 1), vearly = c(1, 1, 1, 1), corr = c(0, 0, 0, 0), weight = 0.5,
        nsim = 1000, seed = 12345678, select = 0, epsilon = 1, thresh = 1, level = 0.025,
        ptest = seq(1:length(z1)), fu = FALSE, method = "invnorm")
```

Arguments

<code>z1</code>	Vector of test statistics for the final outcome measure based on stage 1 data (maximum 8 treatments).
<code>z2</code>	Vector of test statistics for the final outcome measure based on stage 2 data.
<code>zearly</code>	Vector of test statistics for the early outcome measure.
<code>v1</code>	Vector of variances for the final outcome measure based on stage 1 data; in format control treatment variance followed by the test treatment variances.
<code>v2</code>	Vector of variances for the final outcome measure based on stage 2 data; format as <code>v1</code> .
<code>vearly</code>	Vector of variances for the early outcome measure; format as <code>v1</code> .
<code>corr</code>	Vector of correlations between the early and final outcome measures for the control and test treatments; format as <code>v1</code> .
<code>weight</code>	Weighting between stages 1 and 2; default is for equal weighting (0.5).
<code>nsim</code>	Number of simulations (maximum=10,000,000).
<code>seed</code>	Seed number.
<code>select</code>	Selection rule type; 0 = select all treatments, 1 = select maximum, 2 = select maximum two, 3 = select maximum three, 4 = epsilon rule (select means within epsilon of maximum), 5 = randomly select a single treatment and 6 = threshold rule (select means greater than or equal to threshold). See select.rule .
<code>epsilon</code>	For <code>select = 4</code> , set epsilon criterion.
<code>thresh</code>	For <code>select = 6</code> , set threshold criterion.
<code>level</code>	Test level (default=0.025).
<code>ptest</code>	Vector of treatment numbers for determining power. For example, <code>c(1,2)</code> will count rejections of one or both hypotheses for testing treatments 1 and 2 against control.

fu	Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up. Default is TRUE.
method	Select combination method. Available options are “invnorm” or “fisher”. Default is “invnorm”.

Details

This function is a generalization of `asd.sim`; see [asd.sim](#) for full details. The algorithm implemented in `gasd.sim` is the same as that implemented in `asd.sim` except that the full trivariate normal distribution of the test statistics (see Friede *et al.* (2010)) is used to generate samples for treatment selection and hypotheses testing. For full definitions of the inputs necessary for this function see (see Friede *et al.* (2010)).

Value

<code>count.total</code>	Number of times one or more treatments are selected.
<code>select.total</code>	Number of times each test treatment is selected.
<code>reject.total</code>	Number of times each hypothesis is rejected.
<code>sim.reject</code>	Number of times one or more of the treatments selected using <code>ptest</code> is rejected.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Friede T, Parsons N, Stallard S, Todd S, Valdes Marquez E, Chataway J, Nicholas R. Designing a Seamless Phase II/III Clinical Trial using Early Outcomes for Treatment Selection: an Application in Multiple Sclerosis. Submitted to *Statistics in Medicine*.

Bretz F, Schmidli H, Koenig F, Racine A, Maurer W. Confirmatory seamless phase II/III clinical trials with hypotheses selection at interim: General concepts. *Biometrical Journal* 2006;48:623-634.

See Also

[asd.sim](#)

Examples

```
## General use of function
gasd.sim(z1=c(1.6,0,0),z2=c(1.6,0,0),zearly=c(0.8,0.8,0),
        v1=c(2,5,1,1),v2=c(2,5,1,1),vearly=c(2,10,1,1),
        corr=c(0.5,0.5,0,0),weight=0.5,nsim=100,
        seed=145514,select=1,epsilon=1,thresh=1,
        level=0.025,ptest=c(1),fu=FALSE,method="invnorm")

## asd.sim
```

```
## increase nsim to 10000 for more precise estimate
asd.sim(nsamp=c(32,128),early=c(0.3,0,0),final=c(0.3,0,0),
        nsim=100,corr=0,seed=145514,select=1,epsilon=1,real=FALSE,
        level=0.025,ptest=c(1,2,3),fu=FALSE,method="invnorm")

## gasd.sim should approximtely replicate asd.sim
## increase nsim to 10000 for more precise estimate
gasd.sim(z1=c(1.2,0,0),z2=c(2.4,0,0),zearly=c(1.2,0,0),
        v1=c(1,1,1,1),v2=c(1,1,1,1),vearly=c(1,1,1,1),
        corr=c(0,0,0,0),weight=0.2,nsim=100,
        seed=145514,select=1,epsilon=1,thresh=1,
        level=0.025,ptest=c(1,2,3),fu=FALSE,method="invnorm")
```

hyp.test

Closed Testing for ASD

Description

Implements the closure principle (Marcus *et al.*, 1976) for controlling the familywise type I error rate in ASD.

Usage

```
hyp.test(comb.test, level = level, full.hyp = FALSE)
```

Arguments

comb.test	Output from function combn.test.
level	Test level (default=0.025).
full.hyp	Logical indicating whether the full set of intersection hypotheses should be reported. Default is FALSE.

Details

In order to control the familywise type I error rate in the strong sense at the pre-specified level α the closure principle (Marcus *et al.*, 1976) is applied. This means that an individual null hypothesis is rejected if and only if all intersection hypotheses are also rejected at level α .

Value

reject	Matrix indicating whether elementary hypotheses have been rejected.
all.rejects	Matrix indicating rejections for each intersection hypothesis, if full.hyp=TRUE.
all.hyp	Matrix labelling each intersection hypothesis, if full.hyp=TRUE.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

References

Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;63:655-660.

See Also

[asd.sim](#), [gasd.sim](#), [dunnett.test](#), [combn.test](#), [select.rule](#), [simeans.binormal](#)

Examples

```
stage1 <- dunnett.test(c(0.75,1.5,2.25))
stage2 <- dunnett.test(c(0.15,1.75,2.15))
comb.test <- combn.test(stage1,stage2,weight=0.5)
hyp.test(comb.test,level=0.025,full.hyp=FALSE)

# more output
hyp.test(comb.test,level=0.025,full.hyp=TRUE)
```

select.rule

Selection Rules for Interim Analysis in ASD

Description

Function `select.rule` provides a number of options for selecting treatments at an interim analysis in ASD.

Usage

```
select.rule(x, type = 0, epsilon = 1, thresh = 1)
```

Arguments

<code>x</code>	Vector of test statistics.
<code>type</code>	Decision rule type; 0, 1, 2, 3, 4, 5 or 6. See below for details. Default is 0.
<code>epsilon</code>	For type = 4, set epsilon criterion.
<code>thresh</code>	For type = 6, set threshold criterion.

Details

There are seven types of selection rule available:

- (0) Select all treatments.
- (1) Select one treatment; largest value of x .
- (2) Select two treatments; two largest values of x .
- (3) Select three treatments; three largest values of x .
- (4) Epsilon rule; select all x within epsilon of maximum.
- (5) Randomly select one treatment.
- (6) Threshold rule; select all x larger than thresh.

Value

select	Indicator vector that shows treatments selected (1) or not selected (0).
z	Vector of same length as select set to -Inf if not selected and 0 otherwise. For use with function <code>dunnett.test</code> .

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

See Also

[asd.sim](#), [gasd.sim](#), [dunnett.test](#), [hyp.test](#), [combn.test](#), [simeans.binormal](#)

Examples

```
# select maximum treatment
select.rule(x=c(5.3,5.2,1.3,4.5,-1.3),type=4,epsilon=1)
```

simeans.binormal *Simulate Bivariate Normal Means*

Description

Simulates bivariate normal means; for use with `asd.sim` and `gasd.sim` in ASD.

Usage

```
simeans.binormal(n = n, means = means, vars = vars, corr = corr)
```

Arguments

n	Number of records used to calculate means.
means	Vector of expected means for two samples.
vars	Vector of expected variances for two samples.
corr	Correlation between two samples

Details

Uses function `rmvnorm` from package `mvtnorm` to generate means from correlated normal variates.

Value

<code>samp1</code>	Mean of sample 1.
<code>samp2</code>	Mean of sample 2.

Author(s)

Nick Parsons (<nick.parsons@warwick.ac.uk>)

See Also

[asd.sim](#), [gasd.sim](#), [dunnett.test](#), [hyp.test](#), [select.rule](#), [combn.test](#)

Examples

```
# need to load mvtnorm
library(mvtnorm)

# generate data
set.seed(1234)
simeans.binormal(n=10, means=c(2, 3), vars=c(1, 5), corr=0.5)
```

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