Package ‘asd’

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Type Package

Title Simulations for adaptive seamless designs

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Description Package runs simulations for adaptive seamless designs with and without early outcomes for treatment selection and subpopulation type designs.

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Description

Functions to run simulations for trial designs that either (i) test a number of experimental treatments against a single control treatment group in a seamless adaptive trial or (ii) test an experimental treatment against a single control treatment group in a seamless adaptive trial with co-primary analyses in a pre-defined subgroup and the full population.

In setting (i) test treatments are compared to the control treatment using Dunnett’s many-to-one testing procedure, with an interim analysis 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 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.

In setting (ii) an interim analysis is undertaken using an early outcome measure and a decision is made on whether to continue with both full and subpopulations, the subpopulation only or the full population, using a pre-defined selection rule. A number of different methods to control the familywise error rate are implemented. Data are simulated for the early and final outcome measures, subpopulation prevalence and correlation between the final and the early outcomes.

Details

Package: asd
Type: Package
Version: 2.0
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License: GPL-3

Simulations are run using the functions (i) treatsel.sim and (ii) subpop.sim. The other functions are not generally to be called by the user.

Author(s)

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

References

Some useful references to adaptive designs and more specifically to the methodology described here:


**See Also**

`treatsel.sim`, `subpop.sim`
Usage

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

Arguments

stage1  Output from function dunnett.test from stage 1 of an ASD
stage2  Output from function dunnett.test 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<weight<1)
method  Select combination test method; available options are "invnorm" or "fisher", with default "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


See Also
treatsel.sim, dunnett.test, hyp.test, select.rule, simeans.binormal
**dunnett.test**

**Examples**

```r
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**

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

**Arguments**

- **Z**: A vector of test statistics
- **select**: A 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 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**


**See Also**

- `treatsel.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, 0))

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

---

gsubpop.sim  

ASD simulation for subpopulation selection

Description

Function subpop.sim runs simulations for a trial design that tests an experimental treatment against
a single control treatment group in a seamless adaptive trial with co-primary analyses in a pre-
defined subgroup and the full population. An interim analysis is undertaken using an early outcome
measure and a decision is made on whether to continue with both full and subpopulations, the sub-
population only or the full population, using a pre-defined selection rule. A number of different
methods to control the family wise error rate are implemented; (i) the treatment is compared to the
control in the subpopulation and full populations using Simes test and the inverse normal combina-
tion function used to combine p-values before and after design adaptation, (ii) as (i) but the bivariate
normal method of Spiessens and Debois (2010) is used to control the type I error rate, (iii) as (i)
but a Bonferroni test is used and (iv) a conditional error function approach using the Spiessens and
Debois test. Data are simulated for the early and final outcome measures, subpopulation prevalence
and correlation between the final and the early outcomes. This function should not generally be
called by the user. The more user-friendly function subpop.sim covers most common applications.

Usage

gsubpop.sim(z.early=NULL, z1=z1, z2=z2, sprev=sprev, 
corr=NULL, selim=NULL, nsim=nsim, seed=12345678,
level=level, select="thresh", wt=NULL, method="CT-SD")

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>z.early</td>
<td>Vector of test statistics for early outcome subpopulation and full population i.e. c(sub, full)</td>
</tr>
<tr>
<td>z1</td>
<td>Vector of test statistics for final outcome subpopulation and full population i.e. c(sub, full)</td>
</tr>
<tr>
<td>z2</td>
<td>Vector of test statistics for final outcome subpopulation and full population, and subpopulation and full population when both are selected i.e. c(sub only, full only, sub, full)</td>
</tr>
<tr>
<td>sprev</td>
<td>Subpopulation prevalence</td>
</tr>
</tbody>
</table>
Correlation between early and final outcomes

Upper and lower limits for the difference between test statistics for the threshold rule

Number of simulations (maximum=10,000,000)

Seed number

Test level (default=0.025)

Selection rule type; available options are “thresh” and “futility”

User set weight for combination test

Test type; available options are “CT-Simes”, “CT-SD”, “CT-Bonferroni” or “CEF”

A structured description of the methodology and the simulation model is given by Friede et al. (2012).

Table of counts; (i) the number of times the subpopulation, full population or both population are selected (n), (ii) the number of times the subpopulation is rejected when either it alone or both populations are selected (Hs), (iii) the number of times the full population is rejected when either it alone or both populations are selected (Hf), (iv) the number of times both populations are rejected (Hs+Hf) and (v) the number of times the intersection hypothesis is rejected (Hs+f)

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


See Also

subpop.sim
Examples

gsubpop.sim(z.early=c(-1,-1),z1=c(-1,-1),z2=c(-1,0,-1,0),sprev=c(0.5,0.5),
corr=0.5,selim=c(-0.5,0.5),nsim=1000,seed=12345678,level=0.025,
select="thresh",wt=0.5,method="CT-SD")

gtreatsel.sim  ASD simulation for treatment selection

Description

Function treatsel.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 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, and 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 tested at the selected level. This function should not generally be called by the user. The more user-friendly function treatsim covers most common applications.

Usage

gtreatsel.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=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="invmnorm")

Arguments

z1    Vector of test statistics for the final outcome measure based on stage 1 data
z2    Vector of test statistics for the final outcome measure based on stage 2 data
zearly    Vector of test statistics for the early outcome measure
v1    Vector of variances for the final outcome measure based on stage 1 data; in format control treatment variance followed by the test treatment variances
v2    Vector of variances for the final outcome measure based on stage 2 data; format as v1
vearly    Vector of variances for the early outcome measure; format as v1
corr    Vector of correlations between the early and final outcome measures for the control and test treatments; format as v1
weight    Weighting between stages 1 and 2; default is for equal weighting (0.5)
nsim    Number of simulations (maximum=10,000,000)
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 control

fu Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up; default TRUE

method Select combination method; available options are “invnorm” or “fisher”, with default “invnorm”

Details

A structured description of the the methodology and the simulation model is given by Friede et al. (2011) and implementation by Parsons et al. (2012).

Value

count.total Number of times one or more treatments are selected

select.total Number of times each test treatment is selected

reject.total Number of times each hypothesis is rejected

sim.reject Number of times one or more of the treatments selected using ptest is rejected

Author(s)

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

References


See Also

treatsel.sim
Examples

greatsel.sim(z1=c(1,0,2),z2=c(1,0,2),early=c(1,0,1),
   v1=c(1,1,1),v2=c(1,1,1),nearly=c(1,1,1),
   corr=0,weight=0.25,nsim=500,seed=12345678,
   select=1,level=0.025,ptest = c(1:3),method="fisher")

hyp.test

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

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>comb.test</td>
<td>Output from function combn.test</td>
</tr>
<tr>
<td>level</td>
<td>Test level (default=0.025)</td>
</tr>
<tr>
<td>full.hyp</td>
<td>Logical indicating whether the full set of intersection hypotheses should be reported; default FALSE</td>
</tr>
</tbody>
</table>

Details

In order to control the familywise type I error rate in the strong sense at the pre-specified level $\alpha$ 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 $\alpha$.

Value

<table>
<thead>
<tr>
<th>Value</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>reject</td>
<td>Matrix indicating whether elementary hypotheses have been rejected</td>
</tr>
<tr>
<td>all.rejects</td>
<td>Matrix indicating rejections for each intersection hypothesis, if full.hyp=TRUE</td>
</tr>
<tr>
<td>all.hyp</td>
<td>Matrix labelling each intersection hypothesis, if full.hyp=TRUE</td>
</tr>
</tbody>
</table>

Author(s)

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

References

select.rule

See Also
treatsel.sim, dunnett.test, combn.test, select.rule, simeans.binormal

Examples

```r
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

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

Arguments

- `x` Vector of test statistics.
- `type` Decision rule type; 0, 1, 2, 3, 4, 5 or 6 (see below for details); default is 0.
- `epsilon` For type = 4, set epsilon criterion
- `thresh` 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
simeans.binormal

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 dunnett.test

Author(s)

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

See Also

  treatsel.sim, dunnett.test, hyp.test, combn.test, simeans.binormal

Examples

```r
# 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

- **samp1**
  Mean of sample 1
- **samp2**
  Mean of sample 2
Author(s)

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

See Also

treatsel.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)
Arguments

n List giving sample sizes for each treatment group at stage 1 (interim) and stage 2 (final) analyses; `enrich` allows for sample size modifications if the subgroup only is selected at stage 1

effect List giving effect sizes for early and final outcomes

outcome List giving outcome type for early and final outcomes; available options are “N”, “T” and “B”, for normal, time-to-event and binary data

tcontrol Optional list giving effect sizes for early and final outcomes

sprev Subpopulation prevalence

nsim Number of simulations (maximum=10,000,000)

corr Correlation between early and final outcomes

seed Seed number

select Selection rule type; available options are “thresh” and “futility”

weight Optional user set weight for combination test; default is to use those suggested by Jenkins *et al.* (2011)

selim Upper and lower limits for the difference between test statistics for the threshold rule

level Test level (default=0.025)

method Test type; available options are “CT-Simes”, “CT-SD”, “CT-Bonferroni” or “CEF”

sprev.fixed Logical indicating whether subpopulation prevalence is fixed at each simulation; default TRUE

file File name to dump output; if unset will default to R console

Details

A structured description of the methodology and the simulation model is given by Friede *et al.* (2012).

Value

results Table of counts; (i) the number of times the subpopulation, full population or both population are selected (n), (ii) the number of times the subpopulation is rejected when either it alone or both populations are selected (Hs), (iii) the number of times the full population is rejected when either it alone or both populations are selected (Hf), (iv) the number of times both populations are rejected (Hs+Hf) and (v) the number of times the intersection hypothesis is rejected (Hs+f)

Author(s)

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

References


See Also
gsubpop.sim

Examples

```r
# hazard ratio in subgroup = 0.6 and full population = 0.9
# for both early and final time-to-event outcomes
# subgroup prevalence = 0.3 and correlation = 0.5
# futility stopping rule, with limits 0 and 0
subpop.sim(n=list(stage1=100,enrich=200,stage2=300),
  effect=list(early=c(0.6,0.9),final=c(0.6,0.9)),
  sprev=0.3,outcome=list(early="T",final="T"),nsim=100,
  corr=0.5,seed=1234,select="futility",weight=NULL,
  selim=c(0,0),level=0.025,method="CT-SD",file=""
)
```

treatsel.sim

ASD simulation for treatment selection

Description

Function `treatsel.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 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, and 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 tested at the selected level.
Usage

treatsel.sim(n=list(stage1=32,stage2=32),
  effect=list(early=c(0,0,0),final=c(0,0,0)),
  outcome=list(early="N",final="N"),nsim=1000,
  corr=0,seed=12345678,select=0,epsilon=1,
  weight=NULL,thresh=1,level=0.025,ptest=c(1),
  method="invnorm",fu=FALSE,file = "")

Arguments

n List giving sample sizes for each treatment group at stage 1 (interim) and stage 2 (final) analyses

effect List giving effect sizes for early and final outcomes

outcome List giving outcome type for early and final outcomes; available options are "N", "T" and "B", for normal, time-to-event and binary data

nsim Number of simulations (maximum=10,000,000)
corr Correlation between early and final outcomes

seed Seed number

select Selection rule type (select.rule): 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)

epsilon For select = 4, set epsilon criterion

weight Optional user set weight for combination test; default is to use those suggested by Jenkins et al. (2011)

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

method Select combination method; available options are "invnorm" or "fisher", with default "invnorm".

fu Logical indicating whether patients from dropped treatments (after interim selection) should be followed-up; default FALSE

file File name to dump output; if unset will default to R console

Details

A structured description of the methodology and the simulation model is given by Friede et al. (2011) and implementation by Parsons et al. (2012).
Value

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

Author(s)

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

References


See Also

gtreatsel.sim

Examples

```r
# two test treatment groups
# effect size = 0.3 for group 1
# for both early and final normal outcomes
# correlation = 0.3
# select one treatment only at interim
treatsel.sim(n=list(stage1=100,stage2=300),
  effect=list(early=c(0,0.3,0),final=c(0,0.3,0)),
  outcome=list(early="N",final="N"),
  nsim=100,corr=0.3,seed=145514,select=1,
  level=0.025,ptest=c(1,2),fu=FALSE,
  method="invnorm",file="")

# five test treatment groups
# correlation = 0.3
# flexible selection rule, with epsilon = 1
treatsel.sim(n=list(stage1=100,stage2=300),
  effect=list(early=c(0,0.3,0.2,0.1,0.3,0.05),
              final=c(0,0.2,0.3,0.2,0.1,0.5)),
  ...)
```
outcome=list(early="N",final="N"),
nsim=200,corr=0.3,seed=145514,select=4,epsilon=1,
level=0.025,pvalue=c(1:5),method="invnorm")
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