Package ‘tsdf’

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Author Wenchuan Guo, Jianan Hui, Bob Zhong
Maintainer Wenchuan Guo <wguo1017@gmail.com>
Description Calculate optimal Zhong’s two-/three-stage Phase II designs (see Zhong (2012) <doi:10.1016/j.cct.2012.07.006>). Generate Target Toxicity decision table for Phase I dose-finding (two-/three-stage). This package also allows users to run dose-finding simulations based on customized decision table.
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Description

adjust Zhong’s 2-/3-stage design for over-/under-running

Usage

adj.two(n1, r1, s1, n2, alpha1, alpha2, beta, pc, pe, ...)

Arguments

n1 sample size at stage 1.

r1 inefficacy boundary at stage 1.

s1 efficacy boundary at stage 1. if no early stopping for efficacy, s1 should equal to n1.

n2 sample size at stage 2.

alpha1 left-side overall type I error.

alpha2 right-side overall type I error.

beta type II error.

pc a numeric vector of response rate. should be a vector with length 1 or 2.

pe alternative hypothesis.

... not used argument.

Details

To be added

Value

An object of class "opt.design" is a list containing:

bdry rejection regions

error true type 1/2 errors

n sample size at each stage

complete complete list of feasible designs

alpha1 input; left-side type I error

alpha2 input; right-side type I error

beta input; type 2 error

pc input; a vector of response rate.

pe input; a vector of alternative response rate

sf input; the alpha-spending function used

stage input; two- or three- stage design is used
dec.sim 

Author(s) 
Wenchuan Guo <wguo1017@gmail.com>, Jianan Hui <jiananhuistat@gmail.com>

Examples 
```
n1 <- 22
r1 <- 6
s1 <- 22
n2 <- 24
pc <- 0.4
pe <- pc + 0.15
alpha1 <- 0.3
alpha2 <- 0.1
beta <- 0.2
out <- adj.two(n1, r1, s1, n2, alpha1, alpha2, beta, pc, pe)
```

Description 
Run dose-finding simulations based on a customized decision table.

Usage 
```
dec.sim(truep, decTable, start.level = 1, nsim = 1000)
```

Arguments 
- **truep**: a vector of length k (the number of doses being considered in the trial), with values equal to the true probabilities of toxicity at the dose levels.
- **decTable**: a customized decision table. (same format as output of `dec.table`)
- **start.level**: starting dose level. Defaults to 1, i.e. the lowest dose level.
- **nsim**: the number of simulation trials. Defaults to 1000.

Details 
Assume there are $d$ dose levels to be studied. Denote the cumulative number of patients treated and cumulative number of DLTs at the current dose level are $n_i$ and $m_i$, respectively. $n_{\text{max}}$ is the maximum number of patients permitted to be treated at each dose level. The procedure is as follows:

- **Step 1**: Update cumulative number of DLTs $m_i$ and total number of patients $n_i$ treated at the current dose and use the decision table to make a decision: if decision is “S” -> step 2; if decision is “D” or “DU” -> step 3; if decision is “E” -> step 4.
- **Step 2**: If $n_i = n_{\text{max}}$, declare dose i as the MTD; otherwise, update $m_i$ and $n_i$ with additional cohort of patients and go to Step 1.
• Step 3: If the current dose level is the highest dose level, then: if $n_i < n_{\text{max}}$, update $m_i$ and $n_i$ with additional cohort of patients and go to Step 1; otherwise, stop the trial and declare that the MTD is higher than the highest dose level (inconclusive); If the current dose is not the lowest dose, then: if $n_{i-1} < n_{\text{max}}$, update $m_{i-1}$ and $n_{i-1}$ with additional cohort of patients and set the current dose level to be the next lower dose level, and go to Step 1; otherwise, stop the trial and declare the next lower dose level is the MTD; Additionally, if the decision is “DU”, record this dose level as DU and never treat additional patients at the current dose level again.

• Step 4: If the current dose level is the highest dose level, then: if $n_i < n_{\text{max}}$, update $m_i$ and $n_i$ with additional cohort of patients and go to Step 1; otherwise, stop the trial and declare that the MTD is higher than the highest dose level (inconclusive); If the next higher dose level is of status DU, then: if $n_i < n_{\text{max}}$, update $m_i$ and $n_i$ with additional cohort of patients and go to step 1; otherwise stop, the current dose level is MTD; Otherwise: if $n_{i+1} < n_{\text{max}}$, update $m_{i+1}$ and $n_{i+1}$ with additional cohort of patients, set the current dose level to be next higher dose level, and go to step 1; else, the current dose level is the MTD.

Value

the functions summary.dec.sim is used to obtain and print a summary table of the results (recommended). An object of class "dec.sim" is a list containing:

- mtd a vector of dose levels giving the recommended maximum tolerated dose (MTD) at the end of the trial.
- mtd.prob a vector of length $k$ giving the average proportions of selected as MTD at each dose level.
- over.prob a vector of length $k$ giving the average proportions of selected as over the MTD at each dose level.
- n.patients the average number of patients dosed at each level.
- dlt the average number of DLTs experienced at each dose level.
- truep input; true probabilities of toxicity.
- start.level input; starting dose level.
- nsim input; number of simulated trails.

Author(s)

Wenchuan Guo <wguo1017@gmail.com>

Examples

```r
tuep <- c(0.3, 0.45, 0.5, 0.6)
res <- dec.table(0.6, 0.4, 0.2, 0.3, c(3, 3, 3))
out <- dec.sim(truep, res$table, start.level = 2, nsim = 1000)
summary(out, pt = 0.3)
```
generate three-stage dose-finding decision table

Description
Generate three stage dose finding decision table

Usage
dec.table(alpha.l, alpha.r, alpha.u, pt, n, sf.param = 4, pe.par = 0.25, ...)

Arguments
alpha.l
left-side overall type 1 error. Control the upper bound of dose escalation.
alpha.r
right-side overall type 1 error. Control the lower bound of dose de-escalation.
alpha.u
right-side overall type 1 error. This also controls the lower bound of dose de-escalation, but it is used to find lower bound for "DU".
pt
a numeric vector of target toxicity. Should be a vector with 1 or 2 (when the target is an interval).
n
a vector of sample size at each stage. sum(n) is the total sample size. For A+B designs, n is a vector with length 2; for A+B+C designs, n has length 3.
sf.param
a single real value specifying the gamma parameter for which Hwang-Shih-DeCani spending is to be computed; allowable range is [-40, 40]. Increasing this parameter implies that more error is spent early stage and less is available in late stage. Default to 4.
pe.par
alternative hypothesis that used to calculate power/type 2 error. The alternative is set to be pe = pt + pe.par. Default to 0.25.
...
not used argument.

Details
Alpha-spending method is added to two-/three-stage designs. dec.table supports Hwang-Shih-DeCani spending function.

Value
An object of class "dec.table" is a list containing:
table
the generated decision table.
alpha.two
a vector of true type 1 error for two-tailed test.
alpha.one
a vector of true type 1 error for right-tailed test.
beta
a single value of true type 2 error (depends on alternative).
E
a vector of "E" bound.
D
a vector of "D" bound.
DU a vector of "DU" bound.
pt input; a vector of target toxicity
n input; a vector with sample size at each stage.
sf.param input; the alpha-spending function parameter used.

Author(s)
Wenchuan Guo <wguo007@ucr.edu>

Examples
alpha.l <- 0.6
alpha.r <- 0.4
alpha.u <- 0.1
pt <- 0.3
# print out decision table for a 3+3+3 design
n <- rep(3, 3)
dec.table(alpha.l, alpha.r, alpha.u, pt, n)$table
# 3+3 design
n <- rep(3, 2)
dec.table(alpha.l, alpha.r, alpha.u, pt, n)$table

Description
calculate optimal 2-/3-stage design given by Bob Zhong

Usage
opt.design(
  alpha1,
  alpha2,
  beta,
  pc,
  pe,
  stage = 2,
  stop.eff = FALSE,
  frac_n1 = NULL,
  frac_n2 = NULL,
  sf.param = NULL,
  show = FALSE,
  nmax = 100,
  n.choice = 1,
  ...
)
**Arguments**

- **alpha1**: left-side overall type I error.
- **alpha2**: right-side overall type I error.
- **beta**: type II error
- **pc**: a numeric vector of response rate. Should be a vector with length 1 or 2.
- **pe**: alternative hypothesis.
- **stage**: 2 or 3. Default to 2 (2-stage design).
- **stop_eff**: logical flag. Default to FALSE. If `stop_eff = TRUE`, the trial may stop for efficacy at interim.
- **frac_n1**: proportion of n1. For 2-stage design, default to `c(0.3, 0.6)`, i.e. the range of n1 is 0.2*n to 0.5*n. For 3-stage design, default to `c(0.2, 0.3)`, i.e. the range of n1 is 0.2*n to 0.3*n.
- **frac_n2**: proportion of n2. Used for 3-stage design. Default to `c(0.2, 0.4)`.
- **sf.param**: a single real value specifying the gamma parameter for which Hwang-Shih-DeCani spending is to be computed; allowable range is [-40, 40]. Increasing this parameter implies that more error is spent early stage and less is available in late stage. For two-stage designs, default to `NULL` (alpha-spending is not used); for three-stage designs, default to 4.
- **show**: logical. If TRUE, current sample size is shown as total sample size increase.
- **nmax**: maximum sample size. Default to 100.
- **n.choice**: stop criterion for the search of feasible designs. Stop if number of designs is more than `n.choice`.
- **...**: not used argument.

**Details**

The two-stage design setup is: n1 patients are treated in the first stage. At the end of the first stage, either the trial continues to the second stage or inefficacy is concluded and the trial is stopped (early termination), depending on the number of responses observed at the first stage. If the trial does continue to the second stage, additional n2 patients are treated. Three-stage design is an extension of two-stage design where one stage is added between Stage 1 and 2. The left-side rejection region is response \( \leq r_i \) for \( i = 1, 2, \) or 3 and right-side rejection region is response \( > s \). Alpha-spending method is added to two-/three-stage designs. `opt.design` supports Hwang-Shih-DeCani spending function. You can change the definition of HSD function to use a different spending function.

**Value**

An object of class "opt.design" is a list containing:

- **bdry**: rejection regions
- **error**: true type 1/2 errors
- **n**: sample size at each stage
- **complete**: complete list of feasible designs
alpha1  input; left-side type 1 error
alpha2  input; right-side type 1 error
beta    input; type 2 error
pc      input; a vector of response rate.
pe      input; a vector of alternative response rate
sf      input; the alpha-spending function used
stage   input; two- or three- stage design is used

Author(s)
Wenchuan Guo <wguo1017@gmail.com>, Jianan Hui <jiananhuistat@gmail.com>

References

Examples
alpha1 <- 0.15
alpha2 <- 0.10
beta <- 0.15
pc <- 0.25
pe <- pc + 0.20
# calculate optimal two-stage design without using alpha-spending
opt.design(alpha1, alpha2, beta, pc, pe, stage=2)
## Not run:
# calculate optimal two-stage design with Pocock-like spending function
opt.design(alpha1, alpha2, beta, pc, pt, stage = 2, sf.param = 1)
# calculate optimal three-stage design with =Oâ€™Brien-Fleming like spending function
opt.design(alpha1, alpha2, beta, pc, pt, stage = 3, sf.param = -4)
## End(Not run)

plot.dec.sim  plot simulation results from a dec.sim object

Description
Three plots are currently available: a plot of true toxicity at each dose level (type = "s"); a bar plot of the probability of selecting as the MTD for each dose level (type = "prob"); a bar plot of the average number of patients treated at each dose level (type = "np"); a bar plot of the average number of patients experienced DLT at each dose level (type = "dlt") and type = "all" generates all above plots.
## plot.dec.table

plot decision table from a "dec.table" object.

### Description

plot method for class "dec.table"

### Usage

```r
## S3 method for class 'dec.sim'
plot(
  x,
  pt,
  s = 1,
  type = c("all", "s", "prob", "np", "dlt"),
  label = TRUE,
  col = "cornflowerblue",
  text.col = "darkblue",
  cex = 1,
  ...
)
```

### Arguments

- **x**: an object of class "dec.sim" or "sl.sim", a result of a call to `dec.sim` or `sl.sim`.
- **pt**: a vector with target toxicity for each scenario.
- **s**: scenario to be plotted. Defaults to 1.
- **type**: plot type. See descriptions above.
- **label**: a logical value indicating if values are shown on plot.
- **col**: graphical parameter `col`; see details `par`.
- **text.col**: plotting color of text shown.
- **cex**: graphical parameter `cex`; see details `par`.
- **...**: arguments to be passed to `plot` methods.

### Examples

```r
# generate decision table
dt <- dec.table(0.6,0.4,0.2,0.3,c(3,3,3))
# simulate trials from test data
test.file <- system.file("extdata", "testS.csv", package = "tsdf")
out <- sl.sim(dt$table, test.file)
plot(out, pt=rep(0.3,2), s=1, type="all")
plot(out, pt=rep(0.3,2), s=2, type="prob")
plot(out, pt=rep(0.3,2), s=1, type="np")
plot(out, pt=rep(0.3,2), s=2, type="dlt")
```
Usage

```r
## S3 method for class 'dec.table'
plot(x, ...)
```

Arguments

- `x`: an object of class "dec.table", a result of a call to `dec.table`.
- `...`: Not used argument.

Details

`plot.dec.table` prints the decision boundarys.

Examples

```r
truep <- c(0.3, 0.45, 0.5, 0.6)
out <- dec.table(0.6, 0.4, 0.2, 0.3, c(3,3,3))
plot(out)
```

---

print.dec.table

`print.dec.table` prints decision table from a "dec.table" object.

Description

`print` method for class "dec.table"

Usage

```r
## S3 method for class 'dec.table'
print(x, ...)
```

Arguments

- `x`: an object of class "dec.table", a result of a call to `dec.table`.
- `...`: Not used argument.

Details

`print.dec.table` prints the decision table with legend keys.

Examples

```r
print(dec.table(0.6, 0.4, 0.2, 0.3, c(3,3,3)))
```
**print.opt.design**

Print Zhong's design from a "opt.design" object.

**Description**

Print method for class "opt.design"

**Usage**

```r
## S3 method for class 'opt.design'
print(x, ...)
```

**Arguments**

- `x` | An object of class "opt.design", a result of a call to `opt.design`.
- `...` | Not used argument.

**Examples**

```r
alpha1 <- 0.20
alpha2 <- 0.1
beta <- 0.20
pc <- 0.5
pt <- pc + 0.2
out <- opt.design(alpha1, alpha2, beta, pc, pt, stage = 2, sf.param = 1)
print(out)
```

---

**sl.sim**

Dose-finding simulations for a list of scenarios

**Description**

Run dose-finding simulations based on a customized decision table for a list of scenarios.

**Usage**

```r
sl.sim(decTable, file, header = TRUE, sep = ",", ...)```

**Arguments**

- `decTable` | A customized decision table. (same format as output of `dec.table`)
- `file` | The name of the file which the data are to be read from. See details in `read.table`.
- `header` | A logical value indicating whether the file contains the names of the variables as its first line. Default is FALSE. See details in `read.table`.
- `sep` | The field separator character. Default is ",". See details in `read.table`.
- `...` | Arguments to be passed to `read.table` methods.
Details

In each line of the input file, the parameters must be ordered in accordance as follows: pt, start.level, nsim, truep. See details in read.table. The algorithm for dose-finding is described in dec.sim.

Value

The function summary is used to obtain and print a summary table of the results. An object of class "dec.sim" (1 scenario) or "sl.sim" (more than 1 scenarios) is a list containing:

- **MTD**: A vector of dose levels giving the recommended maximum tolerated dose (MTD) at the end of the trial.
- **n.patients**: The average number of patients dosed at each level.
- **truep**: input; true probabilities of toxicity.
- **start.level**: input; starting dose level.
- **nsim**: input; number of simulated trails.

Author(s)

Wenchuan Guo <wguo007@ucr.edu>

Examples

dt <- dec.table(0.6,0.4,0.2,0.3,c(3,3,3))
test.file <- system.file("extdata", "testS.csv", package = "tsdf")
# use a customized decision table
table.file <- system.file("extdata", "decTable.csv", package = "tsdf")
dec <- read.table(table.file, sep=".", col.names=c(3,4,8,10), row.names = 1, check.names = FALSE)
out1 <- sl.sim(dt$table, test.file)
out2 <- sl.sim(dec, test.file)

summary.dec.sim

Summarizing simulation results from a dec.sim object

Description

summary method for class "dec.sim".

Usage

## S3 method for class 'dec.sim'
summary(object, pt, ...)

Arguments

- **object**: an object of class "dec.sim", a result of a call to dec.sim or sl.sim.
- **pt**: target toxicity for each scenario.
- **...**: Not used argument.
Details

summary is used for formatting important statistics for dose-finding simulation. Giving the target toxicity, it returns the probability of selecting current dose level as the MTD and over the MTD, probability of selecting the true MTD, probability of subjects treated at or below the true MTD, etc. The MTD is defined as the highest dose level such that the toxicity probability is less than target toxicity probability, if target is less than the smallest probability, then the lowest dose level is set as MTD. For example, if target is 0.3 and true toxicity for five doses are 0.1, 0.25, 0.35, 0.40, then MTD is dose 2.

Examples

test.file <- system.file("extdata", "testS.csv", package = "tsdf")
dt <- dec.table(0.6, 0.4, 0.2, 0.3, c(3,3,3))
out <- sl.sim(dt$table, test.file)
pt <- c(0.3, 0.4)
summary(out, pt)
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