Package 'iAdapt'

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Type Package

Title Two-Stage Adaptive Dose-Finding Clinical Trial Design

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Description Simulate and implement early phase two-stage adaptive dose-finding design developed by Chiuzan et al. (2018) <DOI:10.1080/19466315.2018.1462727>.

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R topics documented:

`eff.stg1` *Generates efficacy outcomes for stage 1*

Description

Function `eff.stg1()` uses a beta-binomial distribution to generate outcomes (Ys) corresponding to acceptable dose assignments from stage 1.

Usage

```
eff.stg1(dose, dose.tox, p1, p2, K, coh.size, m, v, nbb = 100)
```

Arguments

`dose`	number of doses to be tested (scalar)
`dose.tox`	vector of true toxicities for each dose. Values range from 0 - 1.
`p1`	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
`p2`	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2
`K`	threshold for LR. Takes integer values: 1,2,...(recommended K=2)
`coh.size`	cohort size (number of patients) per dose (Stage 1)
`m`	vector of mean efficacies per dose. Values range from 0 - 100. (e.g, T cell persistence - values b/w 5 and 80 per cent)
`v`	vector of efficacy variances per dose. Values range from 0 - 1. (e.g., 0.01)
`nbb`	binomial parameter (default = 100 cells per patient)

Value

List of efficacy outcomes for subject enrolled during stage 1 (dose-escalation)

- Y.safe - vector of efficacy outcomes for each subject enrolled on an acceptably toxic dose
- d.safe - vector of dose allocation for each subject enrolled on an acceptably toxic dose
- tox.safe - number of dose-limiting toxicities for each safe dose level
- Y.alloc - vector of efficacy outcomes for all subjects enrolled on all doses (safe and unsafe)
- d.alloc - vector of dose allocation for all subjects enrolled on all doses (safe and unsafe)

Examples

```
# Number of pre-specified dose levels
dose <- 5
# Vector of true toxicities associated with each dose
dose.tox <- c(0.05, 0.10, 0.20, 0.35, 0.45)
# Acceptable (p_yes) and unacceptable (p_no) DLT rates used for establishing safety
p_no <- 0.40
p_yes <- 0.15

# Likelihood-ratio (LR) threshold
K <- 2

# Cohort size used in stage 1
coh.size <- 3

# Vector of true mean efficacies per dose (here mean percent persistence per dose)
m <- c(5, 15, 40, 65, 80)   # MUST BE THE SAME LENGTH AS dose.tox

# Efficacy(equal) variance per dose
v <- rep(0.01, 5)

# Total sample size (stages 1&2)
N <- 25

# Stopping rule: if dose 1 is the only safe dose, allocate up to 9 pts.
stop.rule <- 9

eff.stg1(dose = dose, dose.tox = dose.tox, p1 = p_no, p2 = p_yes, K = K,
coh.size = coh.size, m, v, nbb = 100)
```

LRtox *Calculates likelihood of safety for single dose*

Description

Function `LRtox()` calculates the likelihood of safety for a single dose and designates whether to escalate to the next dose (safe) or stop dose escalation and move onto stage 2 (unsafe).

Usage

```
LRtox(coh.size, x, p1, p2, K = 2)
```

Arguments

`coh.size`	cohort size (number of patients) per dose (Stage 1)
`x`	number of observed DLTs
`p1`	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
`p2`	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2
`K`	threshold for LR. Takes integer values: 1,2,...(recommended K=2)

Value

List object that gives the likelihood ratio of safety and indicates whether to escalate to the next highest dose level, or stop dose escalation and move onto stage 2.

Examples

```
LRtox(coh.size=3,x=2,p1=0.40,p2=0.15,K=2)
LRtox(coh.size=3,x=1,p1=0.40,p2=0.15,K=2)
```

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rand.prob *Calculates randomization probabilities and dose allocation for next patient*

Description

Function `rand.prob()` calculates the updated randomization probabilities based on observed efficacies up to that point. It also gives the dose allocation for the next enrolled patient based on these probabilities.

Usage

```
rand.prob(y.eff, d.safe)
```

Arguments

`y.eff`	vector of all efficacy outcomes for each dose allocation
`d.safe`	vector of dose assignment

Value

List object giving

- Rand.Prob - randomization probability for each safe dose (from stage 1)
- Next.Dose - the dose to enroll the next patient on

Examples

```
y.eff <- c(9, 1, 0, 34, 10, 27, 38, 42, 60, 75, 48, 62)
d.safe <- c(1, 1, 1, 2, 2, 2, 3, 3, 3, 4, 4, 4)
rand.prob(y.eff, d.safe)
```

rand.stg2 *Stage 2 Adaptive Randomization*

Description

Function rand.stg2() fits a linear regression for the continuous efficacy outcomes, computes the randomization probabilities/dose and allocates the next patient to a dose that is considered acceptably safe and has the highest efficacy. Dose safety is still monitored using LR and doses that become unacceptable are discarded.

Usage

```
rand.stg2(dose, dose.tox, p1, p2, K, coh.size, m, v, N, stop.rule = 9,
  cohort = 1, samedose = TRUE, nbb = 100)
```

Arguments

dose	number of doses to be tested (scalar)
dose.tox	vector of true toxicities for each dose. Values range from 0 - 1.
p1	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
p2	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2
K	threshold for LR. Takes integer values: 1,2,...(recommended K=2)
coh.size	cohort size (number of patients) per dose (Stage 1)
m	vector of mean efficacies per dose. Values range from 0 - 100. (e.g, T cell persistence - values b/w 5 and 80 per cent)
v	vector of efficacy variances per dose. Values range from 0 - 1. (e.g., 0.01)
N	total sample size for stages 1&2
stop.rule	if only dose 1 safe, allocate up to 9 (default) patients at dose 1 to collect more info
cohort	cohort size (number of patients) per dose (Stage 2). Default is 1.
samedose	designates whether the next patient is allocated to the same dose as the previous patient. Default is TRUE. Function adjusts accordingly.
nbb	binomial parameter (default = 100 cells per patient)

Value

List of the following objects:

- Y.final - vector of all efficacy outcomes (Ys) corresponding to dose assignments (Stages 1&2)
- d.final - vector of all dose assignments(Stage 1&2)

If no dose allocation, put NAs in d.final and y.final.

Examples

```
# Number of pre-specified dose levels
dose <- 5
# Vector of true toxicities associated with each dose
dose.tox <- c(0.05, 0.10, 0.20, 0.35, 0.45)
# Acceptable (p_yes) and unacceptable (p_no) DLT rates used for establishing safety
p_no <- 0.40
p_yes <- 0.15

# Likelihood-ratio (LR) threshold
K <- 2

# Cohort size used in stage 1
coh.size <- 3

# Vector of true mean efficacies per dose (here mean percent persistence per dose)
m <- c(5, 15, 40, 65, 80)   # MUST BE THE SAME LENGTH AS dose.tox

# Efficacy(equal) variance per dose
v <- rep(0.01, 5)

# Total sample size (stages 1&2)
N <- 25

# Stopping rule: if dose 1 is the only safe dose, allocate up to 9 pts.
stop.rule <- 9

rand.stg2(dose, dose.tox, p_no, p_yes, K, coh.size, m, v, N, stop.rule = stop.rule,
cohort = 1, samedose = TRUE, nbb = 100)
```

`safe.dose` *Identify safe/acceptable doses*

Description

Function `safe.dose()` distinguishes acceptable from unacceptable doses

Usage

```
safe.dose(dose, dose.tox, p1, p2, K, coh.size)
```

Arguments

`dose`	number of doses to be tested (scalar)
`dose.tox`	vector of true toxicities for each dose. Values range from 0 - 1.
`p1`	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
`p2`	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2

K	threshold for LR. Takes integer values: 1,2,...(recommended K=2)
coh.size	cohort size (number of patients) per dose (Stage 1)

Value

List of the following objects:

- alloc.safe - matrix of assignments only for acceptable doses (to be used in stage 2) and their corresponding toxicities
- alloc.total - vector of all dose assignments from stage 1
- n1 - total number of subjects allocated in stage 1

Examples

```
dose = 5                                        # Dose levels
dose.tox <- c(0.05, 0.10, 0.15, 0.20, 0.30)   # True toxicity per dose
p1 = 0.40                                       # Unacceptable DLT rate
p2 = 0.15                                       # Acceptable DLT rate
K = 2                                           # Likelihood-ratio (LR) threshold
coh.size = 3                                    # Assign 3 pts per dose in stage 1

safe.dose(dose = dose, dose.tox = dose.tox, p1 = p1, p2 = p2, K = K, coh.size = coh.size)
```

---

sim.summary *Visualize simulation results*

Description

Results from simulated trials (using `sim.trials()` function) displayed in tabular and/or graphical format

Usage

```
sim.summary(sims)
```

Arguments

sims	output from sim.trials

Value

Printed tables and a list of the following objects:

- pct.treated - IQR (25th percentile, median, 75th percentile) of percent of subjects treated at each dose level
- efficacy - IQR of efficacy observed at each dose level

Examples

```
# Number of pre-specified dose levels
dose <- 5
# Vector of true toxicities associated with each dose
dose.tox <- c(0.05, 0.10, 0.20, 0.35, 0.45)
# Acceptable (p_yes) and unacceptable (p_no) DLT rates used for establishing safety
p_no <- 0.40
p_yes <- 0.15

# Likelihood-ratio (LR) threshold
K <- 2

# Cohort size used in stage 1
coh.size <- 3

# Vector of true mean efficacies per dose (here mean percent persistence per dose)
m <- c(5, 15, 40, 65, 80)   # MUST BE THE SAME LENGTH AS dose.tox

# Efficacy(equal) variance per dose
v <- rep(0.01, 5)

# Total sample size (stages 1&2)
N <- 25

# Stopping rule: if dose 1 is the only safe dose, allocate up to 9 pts.
stop.rule <- 9

simulations = sim.trials(numsims = 100, dose, dose.tox, p1 = p_no, p2 = p_yes, K,
coh.size, m, v, N, stop.rule = stop.rule, cohort = 1, samedose = TRUE, nbb = 100)

summary = sim.summary(simulations)
```

`sim.trials` *Simulate full trial (both stages) x times*

Description

Results are displayed in a matrix format, where each row represents one trial simulation

Usage

```
sim.trials(numsims, dose, dose.tox, p1, p2, K, coh.size, m, v, N,
  stop.rule = 9, cohort = 1, samedose = TRUE, nbb = 100)
```

Arguments

`numsims`	number of simulated trials
`dose`	number of doses to be tested (scalar)

dose.tox	vector of true toxicities for each dose. Values range from 0 - 1.
p1	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
p2	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2
K	threshold for LR. Takes integer values: 1,2,...(recommended K=2)
coh.size	cohort size (number of patients) per dose (Stage 1)
m	vector of mean efficacies per dose. Values range from 0 - 100. (e.g, T cell persistence - values b/w 5 and 80 per cent)
v	vector of efficacy variances per dose. Values range from 0 - 1. (e.g., 0.01)
N	total sample size for stages 1&2
stop.rule	if only dose 1 safe, allocate up to 9 (default) patients at dose 1 to collect more info
cohort	cohort size (number of patients) per dose (Stage 2). Default is 1.
samedose	designates whether the next patient is allocated to the same dose as the previous patient. Default is TRUE. Function adjusts accordingly.
nbb	binomial parameter (default = 100 cells per patient)

Value

List of the following objects:

- sim.Y - estimated efficacy per each dose assignment
- sim.d - dose assignment for each patient in the trial

Examples

```
# Number of pre-specified dose levels
dose <- 5
# Vector of true toxicities associated with each dose
dose.tox <- c(0.05, 0.10, 0.20, 0.35, 0.45)
# Acceptable (p_yes) and unacceptable (p_no) DLT rates used for establishing safety
p_no <- 0.40
p_yes <- 0.15

# Likelihood-ratio (LR) threshold
K <- 2

# Cohort size used in stage 1
coh.size <- 3

# Vector of true mean efficacies per dose (here mean percent persistence per dose)
m <- c(5, 15, 40, 65, 80)   # MUST BE THE SAME LENGTH AS dose.tox

# Efficacy(equal) variance per dose
v <- rep(0.01, 5)

# Total sample size (stages 1&2)
N <- 25
```

```
# Stopping rule: if dose 1 is the only safe dose, allocate up to 9 pts.
stop.rule <- 9

sim.trials(numsims = 10, dose, dose.tox, p1 = p_no, p2 = p_yes, K,
coh.size, m, v, N, stop.rule = stop.rule, cohort = 1, samedose = TRUE, nbb = 100)
```

`tox.profile` *Generates DLTs and calculate the likelihood-ratio (LR) for each dose*

Description

Gives toxicity profile (number of dose-limiting toxicities) and likelihood ratio of safety for each dose.

Usage

```
tox.profile(dose, dose.tox, p1, p2, K, coh.size)
```

Arguments

`dose`	number of doses to be tested (scalar)
`dose.tox`	vector of true toxicities for each dose. Values range from 0 - 1.
`p1`	toxicity under null (unsafe DLT rate). Values range from 0 - 1.
`p2`	toxicity under alternative (safe DLT rate). Values range from 0 - 1; p1 > p2
`K`	threshold for LR. Takes integer values: 1,2,...(recommended K=2)
`coh.size`	cohort size (number of patients) per dose (Stage 1)

Value

4-column matrix containing dose assignment, dose-limiting toxicities at each dose, cohort number, and likelihood ratio.

Examples

```
# Number of pre-specified dose levels
dose <- 5
# Vector of true toxicities associated with each dose
dose.tox <- c(0.05, 0.10, 0.20, 0.35, 0.45)
# Acceptable (p2) and unacceptable (p1) DLT rates used for establishing safety
p1 <- 0.40
p2 <- 0.15

# Likelihood-ratio (LR) threshold
K <- 2

# Cohort size used in stage 1
```

```
coh.size <- 3

# Vector of true mean efficacies per dose (here mean percent persistence per dose)
m <- c(5, 15, 40, 65, 80)   # MUST BE THE SAME LENGTH AS dose.tox

# Efficacy(equal) variance per dose
v <- rep(0.01, 5)

# Total sample size (stages 1&2)
N <- 25

# Stopping rule: if dose 1 is the only safe dose, allocate up to 9 pts.
stop.rule <- 9

tox.profile(dose = dose, dose.tox = dose.tox, p1 = p1, p2 = p2, K = K, coh.size = coh.size)
```

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