Package 'UnifiedDoseFinding'

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Title Dose-Finding Methods for Non-Binary Outcomes

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Description

In many phase I trials, the design goal is to find the dose associated with a certain target toxicity rate. In some trials, the goal can be to find the dose with a certain weighted sum of rates of various toxicity grades. For others, the goal is to find the dose with a certain mean value of a continuous response. This package provides the setup and calculations needed to run a dose-finding trial with non-binary endpoints and performs simulations to assess design's operating characteristics under various scenarios. Three dose finding designs are included in this package: unified phase I design (Ivanova et al. (2009) <doi:10.1111/j.1541-0420.2008.01045.x>), Quasi-CRM/Robust-Quasi-CRM (Yuan et al. (2007) <doi:10.1111/j.1541-0420.2006.00666.x>, Pan et al. (2014) <doi:10.1371/journal.pone.0098147>) and generalized BOIN design (Mu et al. (2018) <doi:10.1111/rssc.12263>). The toxicity endpoints can be handled with these functions including equivalent toxicity score (ETS), total toxicity burden (TTB), general continuous toxicity endpoints, with incorporating ordinal grade toxicity information into dose-finding procedure. These functions allow customization of design characteristics to vary sample size, cohort sizes, target dose-limiting toxicity (DLT) rates, discrete or continuous toxicity score, and incorporate safety and/or stopping rules.

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Contents

`get_oc_gBOIN_continuous` *Generate operating characteristics for finding the maximum tolerated dose (MTD) using gBOIN design*

Description

Obtain the operating characteristics of the general Bayesian optimal interval (gBOIN) design (Mu et al. 2017) for maximum tolerated dose (MTD)-based dosing-finding trials under the continuous measure

Usage

```
get_oc_gBOIN_continuous(target, c_true, ncohort, cohortsize,
                        n.earlystop = 100, ntrial,
                        mu_1 = 0.6 * target,
                        mu_2 = 1.4 * target,
                        startdose = 1, seed = 100)
```

Arguments

`target`	the continuous target score
`c_true`	the true mean value of the continuous measure
`ncohort`	the number of cohorts
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. The default value is n.earlystop = 100
`ntrial`	the number of simulated trials
`mu_1`	the lower bound. The default value is mu_1 = 0.6 * target

mu_2	the upper bound. The default value is mu_2 = 1.4 * target
startdose	the starting dose level. The default value is startdose = 1
seed	the seed. The default value is seed = 100

Value

get_oc_gBOIN_continuous() returns the operating characteristics of generalized Bayesian optimal interval design (gBOIN) as a list object, including: (1) selection percentage of each dose, (2) the average number of patients treated at each dose

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 1.47
c_true <- c(0.11, 0.25, 0.94, 1.47, 2.38, 2.40)
ncohort <- 10
cohortsize <- 3
ntrial <- 4000
get_oc_gBOIN_continuous(target = target, c_true = c_true,
                        ncohort = ncohort, cohortsize = cohortsize,
                        ntrial = ntrial)
```

---

get_oc_gBOIN_TB *Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Toxicity Burden (TB) Score using gBOIN design*

Description

Obtain the operating characteristics of the generalized Bayesian optimal interval (gBOIN) design (Mu et al. 2017) for maximum tolerated dose (MTD) (defined by the toxicity burden (BT) score proposed by Bekele et al. (2004))-based dosing-finding trials using. The algorithm of this function is exactly same to the get_oc_gBOIN_Continuous() just the input parameter is used by the TB score

Usage

```
get_oc_gBOIN_TB(target, pmat, weight, ncohort, cohortsize,
                n.earlystop = 100, ntrial, mu_1 = 0.6 * target,
                mu_2 = 1.4 * target, startdose = 1, seed = 100)
```

Arguments

target	the target TB score
pmat	pmat is a list. Each element is a matrix, representing the probability of different toxicity type and scale under different dose levels.
weight	the severity weight
ncohort	the number of cohort
cohortsize	the cohort size
n.earlystop	the early stopping parameter. The default value is n.earlystop = 100
ntrial	the number of simulated trial
mu_1	the lower bound. The default value is p.saf = 0.6 * target
mu_2	the upper bound. The default value is mu_2 = 1.4 * target
startdose	the starting dose level. The default value is startdose = 1
seed	the seed. The default value is seed = 100

Value

`get_oc_gBOIN_TB()` returns the operating characteristics of generalized Bayesian optimal interval design as a list object, including: (1) selection percentage of each dose, (2) the average number of patients treated at each dose

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Bekele, B. Nebiyou, and Peter F. Thall. "Dose-finding based on multiple toxicities in a soft tissue sarcoma trial." Journal of the American Statistical Association 99, no. 465 (2004): 26-35.

Rongji Mu, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, Jun Yin: gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points. Royal Statistical Society 2019

Examples

```
target <- 3.344
ncohort <- 10
cohortsize <- 3
ntrial <- 1000
rate <- 1.1
weight <- rate * rbind(c(0,1,1.5,5,6), c(0,2.5,6,rep(0,2)), c(0,2,3,6,0),
                       c(0,1.5,2,0,0), c(0,0.5,1,0,0))
pmat <- list()
pmat[[1]] <- rbind(c(0.5,0.5,rep(0,3)),
                   c(1,rep(0,4)),
                   c(1,rep(0,4)),
                   c(1,rep(0,4)),
```

```
                    c(0.5,0,0.5,0,0))
  pmat[[2]] <- rbind(c(0.5,0,0.5,0,0),
                    c(1,rep(0,4)),
                    c(0.5,0.5,0,0,0),
                    c(0.5,0.5,rep(0,3)),
                    c(0.46,0,0.54,rep(0,2)))
  pmat[[3]] <- rbind(c(0.5,0,0.5,0,0),
                    c(0.4,0.6,0,0,0),
                    c(0.25,0.75,0,0,0),
                    c(0.5,0.5,0,0,0),
                    c(1,0,0,0,0))
  pmat[[4]] <- rbind(c(0.5,0,0.5,0,0),
                    c(0.4,0.6,0,0,0),
                    c(0.25,0.75,0,0,0),
                    c(0.5,0.5,0,0,0),
                    c(0.5,0,0.5,0,0))
  pmat[[5]] <- rbind(c(0.5,0,0.5,0,0),
                    c(0,1,0,0,0),
                    c(0.25,0.75,0,0,0),
                    c(0.5,0.5,0,0,0),
                    c(0.5,0,0.5,0,0))
  pmat[[6]] <- rbind(c(0,0.5,0.5,0,0),
                    c(0,1,0,0,0),
                    c(0,1,0,0,0),
                    c(0.5,0.5,0,0,0),
                    c(0.5,0,0.5,0,0))
  pmat[[7]] <- rbind(c(0,0.5,0.5,0,0),
                    c(0,1,0,0,0),
                    c(0,1,0,0,0),
                    c(0,0.5,0.5,0,0),
                    c(0.5,0,0.5,0,0))
  pmat[[8]] <- rbind(c(0,0.5,0.5,0,0),
                    c(0,1,0,0,0),
                    c(0,0,1,0,0),
                    c(0,0.5,0.5,0,0),
                    c(0.5,0,0.5,0,0))
  pmat[[9]] <- rbind(c(0,0,1,0,0),
                    c(0,1,0,0,0),
                    c(0,0,1,0,0),
                    c(0,0,1,0,0),
                    c(0,0,1,0,0))
  pmat[[10]] <- rbind(c(0,0,1,0,0),
                     c(0,1,0,0,0),
                     c(1/3,0,0,2/3,0),
                     c(0,0,1,0,0),
                     c(0,0,1,0,0))
  get_oc_gBOIN_TB(target = target, pmat = pmat, weight = weight,
                  ncohort = ncohort, cohortsize = cohortsize,
                  ntrial = ntrial)
```

`get_oc_Ivanova_binary` *Generate operating characteristics for finding the maximum tolerated dose (MTD) of binary endpoint using design by Ivanova et al (2009)*

Description

Obtain the operating characteristics of the dose-finding design of binary endpoint by Ivanova et al (2009)

Usage

```
get_oc_Ivanova_binary(target, eps = 1, truetox, ncohort, cohortsize,
                      n.earlystop = 100, ntrial, startdose = 1,
                      seed = 100)
```

Arguments

`target`	the target toxicity rate
`eps`	the decision criterion. The default value is eps = 1
`truetox`	a vector containing the true toxicity probabilities of the investigational dose levels
`ncohort`	the number of cohorts
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. The default value is n.earlystop = 100
`ntrial`	the number of trials
`startdose`	the starting dose level. The default value is startdose = 1
`seed`	the seed. The default value is seed = 100

Value

`get_oc_Ivanova_binary()` returns the operating characteristics of Ivanova design as a list object, including: (1) selection percentage at each dose level (2) patients treated at each dose level

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 0.3
truetox <- c(0.30, 0.45, 0.50, 0.55, 0.60, 0.65)
ncohort <- 10
cohortsize <- 3
ntrial <- 4000
get_oc_Ivanova_binary(target = target, truetox = truetox, ncohort = ncohort,
                      cohortsize = cohortsize, ntrial = ntrial)
```

`get_oc_Ivanova_continuous` *Generate operating characteristics for finding the maximum tolerated dose (MTD) of continuous endpoint using design by Ivanova et al (2009)*

Description

Obtain the operating characteristics of the dose-finding design of continuous endpoint by Ivanova et al (2009)

Usage

```
get_oc_Ivanova_continuous(target, eps = 1, ptox, ncohort,
                          cohortsize, n.earlystop = 100,
                          ntrial, startdose = 1, seed = 100)
```

Arguments

`target`	the continuous target score
`eps`	the decision criterion. The default value is eps = 1
`ptox`	the true mean value of the continuous measure
`ncohort`	the number of cohorts
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. The default value is n.earlystop = 100
`ntrial`	the number of simulated trials
`startdose`	the starting dose level. The default value is startdose = 1
`seed`	the seed. The default value is seed = 100

Value

`get_oc_Ivanova_continuous()` returns the operating characteristics of Ivanova design as a list object, including: (1) selection percentage at each dose level (2) patients treated at each dose level

Author(s)

Chia-Wei Hsu, Fang Wang, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 1.47
ptox <- c(0.11, 0.25, 0.94, 1.47, 2.38, 2.40)
ncohort <- 10
cohortsize <- 3
ntrial <- 4000
get_oc_Ivanova_continuous(target = target, ptox = ptox, ncohort = ncohort,
                          cohortsize = cohortsize, ntrial = ntrial)
```

---

get_oc_QuasiBOIN *Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Equivalent Score (ET) using Quasi-CRM design using gBOIN*

Description

Obtain the operating characteristics of Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014) for finding the maximum tolerated dose (MTD) using Equivalent Score (ET) derived from toxicity grade information using the gBOIN design (Mu et al. 2017)

Usage

```
get_oc_QuasiBOIN(target, p.true, score, ncohort, cohortsize, n.earlystop = 100,
                 startdose = 1, p.saf = 0.6 * target, p.tox = 1.4 * target,
                 cutoff.eli = 0.95, extrasafe = FALSE, offset = 0.05,
                 ntrial = 1000, seed = 100)
```

Arguments

target	the target DLT rate
p.true	the true toxicity probability at each dose level
score	the default value is score = seq(0, 1.5, by = 0.5) / 1.5
ncohort	the number of cohorts
cohortsize	the cohort size
n.earlystop	the early stopping parameter. The default value is n.earlystop = 100
startdose	the starting dose level. The default value is startdose = 1

p.saf	lower bound. The default value is p.saf = 0.6 * target
p.tox	upper bound. The default value is p.tox = 1.4 * target
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. The default value is cutoff.eli = 0.95
extrasafe	extrasafe set extrasafe = TRUE to impose a more stringent stopping rule. The default value is extrasafe = FALSE
offset	when extrasafe = TRUE will have effect. The default value is offset = 0.05
ntrial	the number of simulated trials
seed	the seed. The default value is seed = 100

Value

`get_oc_QuasiBOIN()` returns the operating characteristics of Bayesian optimal interval design as a list object, including: (1) the target DLT rate, (2) the true DLT rate at different scale for each dose level, (3) number of cohort, (4) cohortsize, (5) starting dose level, (6) lower bound, (7) upper bound, (8) selection percentage of each dose level, (9) the average number of patients treated at each dose, (10) the average number of patients responded to toxicity at each dose level

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 0.47 / 1.5
p.true <- matrix(c(0.83, 0.12, 0.04, 0.01,
                   0.75, 0.15, 0.07, 0.03,
                   0.62, 0.18, 0.11, 0.09,
                   0.51, 0.19, 0.14, 0.16,
                   0.34, 0.16, 0.15, 0.35,
                   0.19, 0.11, 0.11, 0.59), ncol = 4, byrow = TRUE)
score <- seq(0, 1.5,by = 0.5) / 1.5
ncohort <- 10
cohortsize <- 3
ntrial <- 4000
get_oc_QuasiBOIN(target = target, p.true = p.true, score = score, ncohort = ncohort,
                 cohortsize = cohortsize, ntrial = ntrial)
```

get_oc_RQ_CRM *Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Equivalent Score (ET) using Quasi-CRM design*

Description

Obtain the operating characteristics of Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014) for finding the maximum tolerated dose (MTD) using Equivalent Score (ET) derived from toxicity grade information

Usage

```
get_oc_RQ_CRM(ptox, skeletons, target, score, cohortsize,
              ncohort, n.earlystop = 100, start.dose = 1,
              mselection = 1, cutoff.eli = 0.90, ntrial = 10,
              seed = 100)
```

Arguments

ptox	true toxicity probability at each dose level
skeletons	a matrix to provide multiple skeletons with each row presenting a skeleton. If just one row, the function implements the Quasi-CRM design; if >=2 rows, the function implements the Robust-Quasi-CRM designn
target	the target toxicity score
score	the vector weight for ordinal toxicity levels
cohortsize	the cohort size
ncohort	the number of cohort
n.earlystop	the early stopping parameter. The default value is n.earlystop = 100
start.dose	the starting dose level. The default value is start.dose = 1
mselection	mselection = 1 (or 0) indicate to use Bayesian model selection (or mode averaging) to make inference across multiple skeletons. The default value is mselection = 1. It only applies to the Robust-Quasi-CRM design
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. The default value is cutoff.eli = 0.90
ntrial	the number of simulated trials. The default value is ntrial = 10
seed	the seed. The default value is seed = 100

Value

get_oc_RQ_CRM() returns the operating characteristics of (Robust)-Quasi-CRM design as a list object, including: (1) selection percentage at each dose level (2) patients treated at each dose level

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Examples

```
### Scenario 1 in Yuan et al. (2007) and Pan et al. (2014)
target <- 0.47
score <- c(0, 0.5, 1, 1.5)
cohortsize <- 3
ncohort <- 10
ntrial <- 10

ptox <- matrix(nrow = 4, ncol = 6)
ptox[1,] <- c(0.83, 0.75, 0.62, 0.51, 0.34, 0.19)
ptox[2,] <- c(0.12, 0.15, 0.18, 0.19, 0.16, 0.11)
ptox[3,] <- c(0.04, 0.07, 0.11, 0.14, 0.15, 0.11)
ptox[4,] <- c(0.01, 0.03, 0.09, 0.16, 0.35, 0.59)


### specify one skeleton (Quasi-CRM design)
p1 <- c(0.11, 0.25, 0.40, 0.55, 0.75, 0.85)

get_oc_RQ_CRM(ptox = ptox, skeletons = p1, target = target,
              score = score, cohortsize = cohortsize,
              ncohort = ncohort, ntrial = ntrial)




##########################################

### specify three skeletons (Quasi-CRM design)
p1 <- c(0.11, 0.25, 0.40, 0.55, 0.75, 0.85)
p2 <- c(0.05, 0.10, 0.15, 0.25, 0.40, 0.65)
p3 <- c(0.20, 0.40, 0.60, 0.75, 0.85, 0.95)
skeletons <- rbind(p1, p2, p3)


get_oc_RQ_CRM(ptox = ptox, skeletons = skeletons, target = target,
              score = score, cohortsize = cohortsize,
              ncohort = ncohort, ntrial = ntrial)
```

`next_gBOIN_continuous` *Determine the dose for the next cohort of new patients for single-agent trials that aim to find a maximum tolerated dose (MTD) using gBOIN design*

Description

Determine the dose for the next cohort of new patients for single-agent trials that aim to find a MTD under continuous measure using gBOIN design (Mu et al., 2017)

Usage

```
next_gBOIN_continuous(target, n, y, d, mu_1 = 0.6 * target, mu_2 = 1.4 * target)
```

Arguments

`target`	the continuous target score
`n`	the number of patients enrolled at each dose level
`y`	the toxicity score at each dose level
`d`	the current dose level
`mu_1`	the lower bound. The default value is 0.6 * target
`mu_2`	the upper bound. The default value is 1.4 * target

Value

`next_gBOIN_continuous()` returns recommended dose level for the next cohort as a numeric value under continuous measure

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 1.47
n <- c(3, 3, 3, 9, 0, 0)
y <- c(0.1951265, 1.5434317, 2.1967343, 13.9266838, 0, 0)
d <- 4
next_gBOIN_continuous(target = target, n = n, y = y, d = d)
```

`next_gBOIN_TB` *Determine the dose for the next cohort of new patients for single-agent trials that aim to find a maximum tolerated dose (MTD) defined by Toxicity Burden (TB) Score using gBOIN design*

Description

Determine the dose for the next cohort of new patients for single-agent trials that aim to find the MTD defined by the toxicity burden (BT) score proposed by Bekele et al. (2004) using the generalized Bayesian optimal interval (gBOIN) design (Mu et al. 2017) . The algorithm of this function is exactly same to the next_mtd_gBOIN_Continuous() just the input parameter is used by the TB score

Usage

```
next_gBOIN_TB(target, n, y, d, mu_1 = 0.6 * target, mu_2 = 1.4 * target)
```

Arguments

`target`	the target TB score
`n`	the number of patients enrolled at each dose level
`y`	the toxicity score at each dose level
`d`	the current dose level
`mu_1`	the lower bound. The default value is 0.6 * target
`mu_2`	the upper bound. The default value is 1.4 * target

Value

`next_gBOIN_TB()` returns recommended dose level for the next cohort as a numeric value under ordinal measure

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

B. Nebiyou Bekele & Peter F Thall (2004) Dose-Finding Based on Multiple Toxicities in a Soft Tissue Sarcoma Trial, Journal of the American Statistical Association

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 3.344
n <- c(3, 9, 6, 0, 0, 0, 0, 0, 0, 0)
y <- c(5.5, 26.95, 25.3, 0, 0, 0, 0, 0, 0, 0)
d <- 2
next_gBOIN_TB(target = target, n = n, y = y, d = d)
```

`next_Ivanova_binary` *Determine the dose for the next cohort of new patients of binary endpoint using design by Ivanova et al (2009)*

Description

Determine the dose for the next cohort of new patients for single-agent trials of binary endpoint that aim to find a MTD using design by Ivanova et al (2009)

Usage

```
next_Ivanova_binary(target, eps, y, n, d)
```

Arguments

`target`	the target toxicity rate
`eps`	the decision criterion
`y`	the number of toxicity patients at each dose level
`n`	the number of patients enrolled at each dose level
`d`	the current dose level

Value

`next_Ivanova_binary()` returns recommended dose level for the next cohort as a numeric value

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 0.3
eps <- 1
y <- c(0, 4, 0, 0, 0, 0)
n <- c(3, 15, 0, 0, 0, 0)
d <- 2
next_Ivanova_binary(target = target, eps = eps, y = y, n = n, d = d)
```

`next_Ivanova_continuous` *Determine the dose for the next cohort of new patients using Inanova design*

Description

Determine the dose for the next cohort of new patients for single-agent trials that aim to find a MTD

Usage

```
next_Ivanova_continuous(target, eps, c_resp, n, d)
```

Arguments

`target`	the target toxicity score
`eps`	the decision criterion
`c_resp`	the list object. Each element contains continuous value for each measurement at the certain dose level
`n`	the number of patients enrolled at each dose level
`d`	the current dose level

Value

`next_Ivanova_continuous()` returns recommended dose level for the next cohort as a numeric value

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 1.47
eps <- 1
c_resp <- list(c(0, 0.05475884, 0.12446843, 0.10131912),
               c(0, 0.4716962, 0.2792428, 0.3296575),
               c(0, 0.3931168, 1.6116607, 0.1642561),
               c(0, 0.9410027, 1.6021326, 1.6115235,
                 1.1735981, 2.5575655, 1.6513679, 1.4269044,
                 0.8983843, 2.2209587),
               0,
               0)
n <- c(3, 3, 3, 9, 0, 0)
d <- 4
next_Ivanova_continuous(target = target, eps = eps, c_resp = c_resp,
                        n = n, d = d)
```

`next_QuasiBOIN` *Determine the dose for the next cohort of new patients based on equivalent score (ET)-defined target using gBOIN design*

Description

Determine the dose for the next cohort of new patients for single-agent trials that aim to find a MTD defined by the Equivalent Score (ET) in Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014) using the gBOIN design (Mu et al. 2017)

Usage

```
next_QuasiBOIN(target, n, y, d, p.saf = 0.6 * target, p.tox = 1.4 * target,
               cutoff.eli = 0.95, extrasafe = FALSE, n.earlystop = 100)
```

Arguments

`target`	the target DLT rate
`n`	the number of patients enrolled at each dose level
`y`	the toxicity score at each dose level
`d`	the current dose level
`p.saf`	the lower bound. The default value is p.saf = 0.6 * target
`p.tox`	the upper bound. The default value is p.tox = 1.4 * target
`cutoff.eli`	the cutoff to eliminate an overly toxic dose for safety. The default value is cutoff.eli = 0.95
`extrasafe`	extrasafe set extrasafe = TRUE to impose a more stringent stopping . The default value is extrasafe = FALSE
`n.earlystop`	the early stopping parameter. The default value is n.earlystop = 100

Value

next_QuasiBOIN() returns recommended dose level for the next cohort as a numeric value under quasi-binary measure

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 0.47 / 1.5
n <- c(3, 3, 6, 3, 3, 0)
y <- c(0, 0, 1.333333, 0, 1, 0)
d <- 5
next_QuasiBOIN(target = target, n = n, y = y, d = d)
```

---

next_RQ_CRM *Determine the dose for the next cohort of new patients using Quasi-CRM design*

Description

Determine the dose for the next cohort of new patients for single-agent trials that aim to find a MTD defined by the Equivalent Score (ET) using Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014)

Usage

```
next_RQ_CRM(target, n, y, dose.curr, score, skeleton,
            cutoff.eli = 0.90, mselection = 1)
```

Arguments

target	the target toxicity score
n	the number of patients treated at each dose level
y	the toxicity score at each dose level
dose.curr	the current dose level
score	the vector weight for ordinal toxicity levels
skeleton	a matrix to provide multiple skeletons with each row presenting a skeleton
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. The default value is cutoff.eli = 0.90
mselection	mselection = 1 (or 0) indicate to use Bayesian model selection (or mode averaging) to make inference across multiple skeletons. The default value is mselection = 1

Value

`next_RQ_CRM()` returns recommended dose level for the next cohort as a numeric value

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Examples

```
### Implement Robust-Quasi-CRM design (Pan et al. 2014) with pre-specifying 3 skeletons
target <- 0.47
score <- c(0, 0.5, 1, 1.5)
p1 <- c(0.11, 0.25, 0.40, 0.55, 0.75, 0.85)
p2 <- c(0.05, 0.10, 0.15, 0.25, 0.40, 0.65)
p3 <- c(0.20, 0.40, 0.60, 0.75, 0.85, 0.95)
skeletons <- rbind(p1, p2, p3)
n <- c(3, 3, 3, 9, 3, 0)
y <- c(0, 0, 1, 1.333333, 3, 0)

## Example to get the ET score 1 on dose 3
## Assume three patients their corresponding score on the dose 3 is
## 0.5, 0.5 and 0.5. Then we calculate ET score as this:
## (0.5 + 0.5 + 0.5) / 1.5 = 1

## Example to get the ET score 1.333333 on dose 4
## Assume nine patients their corresponding score on the dose 4 is
```

```
## 0, 0, 0, 0, 0, 0, 0.5, 0.5 and 1. Then we calculate ET score as this:
## (0 + 0 + 0 + 0 + 0 + 0 + 0.5 + 0.5 + 1) / 1.5 = 1.333333

next_RQ_CRM(target = target, n = n, y = y, dose.curr = 5,
            score = score, skeleton = skeletons)

### Implement Quasi-CRM design (Yuan et al. 2007) with pre-specifying/using 1 skeletons
next_RQ_CRM(target = target, n = n, y = y, dose.curr = 5,
            score = score, skeleton = p1)
```

`select_mtd_gBOIN_continuous` *Select the maximum tolerated dose (MTD) for single agent trials using gBOIN design*

Description

Select the maximum tolerated dose (MTD) when the trial is completed using gBOIN design (Mu et al. 2017)

Usage

```
select_mtd_gBOIN_continuous(target, npts, ntox)
```

Arguments

`target`	the continuous target score
`npts`	the number of patients enrolled at each dose level
`ntox`	the toxicity score at each dose level

Value

`select_mtd_gBOIN_continuous()` returns the selected dose

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Rongji Mu, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, Jun Yin: gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points. Royal Statistical Society 2019

Examples

```
target <- 1.47
n <- c(3, 3, 3, 9, 0, 0)
y <- c(0.1951265, 1.5434317, 2.1967343, 13.9266838, 0, 0)
select_mtd_gBOIN_continuous(target = target, npts = n, ntox = y)
```

`select_mtd_gBOIN_TB` *Select the maximum tolerated dose (MTD) defined by Toxicity Burden (TB) Score for single agent trials using gBOIN design*

Description

Select the maximum tolerated dose (MTD) defined by the toxicity burden (BT) score proposed by Bekele et al. (2004) when the trial is completed using the generalized Bayesian optimal interval (gBOIN) design (Mu et al. 2017). The algorithm of this function is exactly same to the Select_mtd_gBOIN.Continuous() just the input parameter is used by the TB score

Usage

```
select_mtd_gBOIN_TB(target, npts, ntox)
```

Arguments

`target`	the continuous target score
`npts`	the number of patients enrolled at each dose level
`ntox`	the toxicity score at each dose level

Value

`select_mtd_gBOIN_TB()` returns the selected dose

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

B. Nebiyou Bekele & Peter F Thall (2004) Dose-Finding Based on Multiple Toxicities in a Soft Tissue Sarcoma Trial, Journal of the American Statistical Association

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 3.344
n <- c(3, 9, 6, 0, 0, 0, 0, 0, 0, 0)
y <- c(5.5, 26.95, 25.3, 0, 0, 0, 0, 0, 0, 0)
select_mtd_gBOIN_TB(target = target, npts = n, ntox = y)
```

`select_mtd_Ivanova_binary` *Select the maximum tolerated dose (MTD) of binary endpoint for single agent trials using design by Ivanova et al (2009)*

Description

Select the maximum tolerated dose (MTD) when the trial is completed for binary endpoint using design by Ivanova et al (2009)

Usage

```
select_mtd_Ivanova_binary(target, y, n)
```

Arguments

`target`	the target toxicity rate
`y`	the number of toxicity patients at each dose level
`n`	the number of patients enrolled at each dose level

Value

`select_mtd_Ivanova_binary()` returns a list object including: (1) dose selected (2) patients treated at each dose level

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 0.3
y <- c(0, 4, 0, 0, 0, 0)
n <- c(3, 15, 0, 0, 0, 0)
select_mtd_Ivanova_binary(target = target, y = y, n = n)
```

`select_mtd_Ivanova_continuous` *Select the maximum tolerated dose (MTD) for single agent trials of continuous endpoint using design by Ivanova et al (2009)*

Description

Select the maximum tolerated dose (MTD) when the trial is completed for continuous endpoint using design by Ivanova et al (2009)

Usage

```
select_mtd_Ivanova_continuous(target, c_resp, n)
```

Arguments

`target`	the target toxicity score
`c_resp`	list object. Each element contains continuous value for each measurement
`n`	the number of patients enrolled at each dose level

Value

`select_mtd_Ivanova_continuous()` returns a list object including: (1) dose selected (2) patients treated at each dose level

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Ivanova, Anastasia, and Se Hee Kim. "Dose finding for continuous and ordinal outcomes with a monotone objective function: a unified approach." Biometrics 65, no. 1 (2009): 307-315.

Examples

```
target <- 1.47
c_resp <- list(c(0, 0.05475884, 0.12446843, 0.10131912),
               c(0, 0.4716962, 0.2792428, 0.3296575),
               c(0, 0.3931168, 1.6116607, 0.1642561),
               c(0, 0.9410027, 1.6021326, 1.6115235,
                 1.1735981, 2.5575655, 1.6513679, 1.4269044,
                 0.8983843, 2.2209587),
               0,
               0)
n <- c(3, 3, 3, 9, 0, 0)
select_mtd_Ivanova_continuous(target = target, c_resp = c_resp, n = n)
```

`select_mtd_QuasiBOIN` *Select the maximum tolerated dose (MTD)-defined by equivalent score (ET) using gBOIN design*

Description

Select the maximum tolerated dose (MTD) defined by the Equivalent Score (ET) in Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014) when the trial is completed using the gBOIN design (Mu et al. 2017)

Usage

```
select_mtd_QuasiBOIN(target, npts, ntox, cutoff.eli = 0.95, extrasafe = FALSE,
                     offset = 0.05, print = FALSE)
```

Arguments

`target`	the target DLT rate
`npts`	the number of patients enrolled at each dose level
`ntox`	the toxicity score at each dose level
`cutoff.eli`	the cutoff to eliminate an overly toxic dose for safety. The default value is cutoff.eli = 0.95
`extrasafe`	extrasafe set extrasafe = TRUE to impose a more stringent stopping rule. The default value is extrasafe = FALSE
`offset`	when extrasafe = TRUE will have effect. The default value is offset = 0.05
`print`	print the additional result or not. The default value is print = FALSE

Value

`select_mtd_QuasiBOIN()` returns the selected dose

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Mu, Rongji, Ying Yuan, Jin Xu, Sumithra J. Mandrekar, and Jun Yin. "gBOIN: a unified model-assisted phase I trial design accounting for toxicity grades, and binary or continuous end points." Journal of the Royal Statistical Society. Series C: Applied Statistics 68, no. 2 (2019): 289-308.

Examples

```
target <- 0.47 / 1.5
n <- c(3, 3, 6, 9, 9, 0)
y <- c(0, 0, 1.333333, 2.333333, 3.666667, 0)
select_mtd_QuasiBOIN(target = target, npts = n, ntox = y)
```

`select_mtd_RQ_CRM` *Select the maximum tolerated dose (MTD) using Quasi-CRM design*

Description

Select the maximum tolerated dose (MTD) defined by the Equivalent Score (ET) when the trial is completed using Quasi-CRM design (Yuan et al. 2007) and Robust-Quasi-CRM design (Pan et al. 2014)

Usage

```
select_mtd_RQ_CRM(target, n, y, score, skeleton, mselection = 1)
```

Arguments

`target`	the target toxicity score
`n`	the number of patients treated at each dose level
`y`	the toxicity score at each dose level
`score`	the vector weight for ordinal toxicity levels
`skeleton`	a matrix to provide multiple skeletons with each row presenting a skeleton
`mselection`	mselection = 1 (or 0) indicate to use Bayesian model selection (or mode averaging) to make inference across multiple skeletons. The default value is mselection = 1

Value

`select_mtd_RQ_CRM()` returns a vector to indicate which dose is selected

Author(s)

Chia-Wei Hsu, Haitao Pan, Rongji Mu

References

Yuan, Z., R. Chappell, and H. Bailey. "The continual reassessment method for multiple toxicity grades: a Bayesian quasi-likelihood approach." Biometrics 63, no. 1 (2007): 173-179.

Pan, Haitao, Cailin Zhu, Feng Zhang, Ying Yuan, Shemin Zhang, Wenhong Zhang, Chanjuan Li, Ling Wang, and Jielai Xia. "The continual reassessment method for multiple toxicity grades: a Bayesian model selection approach." PloS one 9, no. 5 (2014): e98147.

Examples

```
target <- 0.47
score <- c(0, 0.5, 1, 1.5)
p1 <- c(0.11, 0.25, 0.40, 0.55, 0.75, 0.85)
p2 <- c(0.05, 0.10, 0.15, 0.25, 0.40, 0.65)
p3 <- c(0.20, 0.40, 0.60, 0.75, 0.85, 0.95)
skeletons <- rbind(p1, p2, p3)
n <- c(3, 3, 3, 9, 3, 0)
y <- c(0, 0, 1, 1.333333, 3, 0)

## Example to get the ET score 1 on dose 3
## Assume three patients their corresponding score on the dose 3 is
## 0.5, 0.5 and 0.5. Then we calculate ET score as this:
## (0.5 + 0.5 + 0.5) / 1.5 = 1

## Example to get the ET score 1.333333 on dose 4
## Assume nine patients their corresponding score on the dose 4 is
## 0, 0, 0, 0, 0, 0, 0.5, 0.5 and 1. Then we calculate ET score as this:
## (0 + 0 + 0 + 0 + 0 + 0 + 0.5 + 0.5 + 1) / 1.5 = 1.333333

select_mtd_RQ_CRM(target = target, n = n, y = y, score = score,
                  skeleton = skeletons)
```

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