

Package ‘UnifiedDoseFinding’

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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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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, 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
ntrial	the number of simulated trials
mu_1	the lower bound. The default value is $\mu_1 = 0.6 * \text{target}$
mu_2	the upper bound. The default value is $\mu_2 = 1.4 * \text{target}$
startdose	the starting dose level. The default value is $\text{startdose} = 1$
seed	the seed. The default value is $\text{seed} = 100$

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 <- 15
cohortsize <- 1
ntrial <- 4000
get_oc_gBOIN_Continuous(target = target, c_true = c_true, ncohort = ncohort,
                        cohortsize = cohortsize, ntrial = ntrial)
```

get_oc_gBOIN_TB	<i>Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Toxicity Burden (TB) Score using gBOIN design</i>
-----------------	---

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, 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
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. Nebiyu, 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 <- 9
cohortsize <- 4
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,  
                      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
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 <- 25  
cohortsize <- 1  
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,  
                           ntrial, startdose = 1, seed = 100)
```

Arguments

<code>target</code>	the continuous target score
<code>eps</code>	the decision criterion. The default value is <code>eps = 1</code>
<code>ptox</code>	the true mean value of the continuous measure
<code>ncohort</code>	the number of cohorts
<code>cohortsize</code>	the cohort size
<code>ntrial</code>	the number of simulated trials
<code>startdose</code>	the starting dose level. The default value is <code>startdose = 1</code>
<code>seed</code>	the seed. The default value is <code>seed = 100</code>

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	<i>Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Equivalent Score (ET) using Quasi-CRM design using gBOIN</i>
------------------	--

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 $\text{score} = \text{seq}(0, 1.5, \text{by} = 0.5) / 1.5$
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 $p.saf = 0.6 * \text{target}$
p.tox	upper bound. The default value is $p.tox = 1.4 * \text{target}$
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. The default value is $cutoff.eli = 0.95$
extrasafe	extrasafe set $extrasafe = \text{TRUE}$ to impose a more stringent stopping rule. The default value is $extrasafe = \text{FALSE}$
offset	when $extrasafe = \text{TRUE}$ 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_Quasi_CRM	<i>Generate operating characteristics for finding the maximum tolerated dose (MTD) defined by Equivalent Score (ET) using Quasi-CRM design</i>
------------------	--

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_Quasi_CRM(ptox, skeletons, target, score, cohortsize, ncohort,
                 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 design
target	the target toxicity score
score	the vector weight for ordinal toxicity levels
cohortsize	the cohort size
ncohort	the number of cohort
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_Quasi_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 <- 1
ncohort <- 20

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_Quasi_CRM(ptox = ptox, skeletons = p1, target = target,
                 score = score, cohortsize = cohortsize,
                 ncohort = ncohort)

#####

### 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_Quasi_CRM(ptox = ptox, skeletons = skeletons, target = target,
                 score = score, cohortsize = cohortsize,
                 ncohort = ncohort)

```

next_Ivanova_binary *Determine the dose for the next cohort of new patients of binary end-point 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, 9, 0, 0, 0, 0)
n <- c(3, 22, 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 Ivanova 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 <- 0.3
eps <- 0.1
c_resp <- list(c(0.14934229, 0.33945935, 0.27632487, 0.12546279,
                0.51435981, 0.05242217, 0.23950981, 0.52195215,
                0.33701385, 0.02585574, 0.99308905, 0.16857301,
                0.52921818, 0.37858839, 0.53202138, 0.05568626,
                0.16846483, 0.08393353, 0.36928336, -0.04731884, 0.37412280),
              c(0.7547139, 0.4467885, 0.5274520, 0.2560551, 0.4359545, 0.4385098,
                0.3882733, 0.2444583, 0.6043425),
              0,
              0,
              0,
              0)
n <- c(21, 9, 0, 0, 0, 0)
d <- 2
next_Ivanova_continuous(target = target, eps = eps, c_resp = c_resp,
                       n = n, d = d)
```

next_mtd_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_mtd_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 $0.6 * \text{target}$
mu_2	the upper bound. The default value is $1.4 * \text{target}$

Value

next_mtd_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 <- 0.1
n <- c(14, 1, 0, 0, 0, 0)
y <- c(1.4268322, 0.1631531, 0, 0, 0, 0)
d <- 1
next_mtd_gBOIN_Continuous(target = target, n = n, y = y, d = d)
```

next_mtd_gBOIN_TB	<i>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</i>
-------------------	--

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_mtd_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 $0.6 * \text{target}$
mu_2	the upper bound. The default value is $1.4 * \text{target}$

Value

next_mtd_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. Nebiyu 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(4, 32, 0, 0, 0, 0, 0, 0, 0, 0)
y <- c(6.6, 102.3, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0)
d <- 2
next_mtd_gBOIN_TB(target = target, n = n, y = y, d = d)
```

next_mtd_QuasiBOIN	<i>Determine the dose for the next cohort of new patients based on equivalent score (ET)-defined target using gBOIN design</i>
--------------------	--

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_mtd_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_mtd_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, 9, 9, 0)
y <- c(0.000000, 0.000000, 1.333333, 2.333333, 3.666667, 0.000000)
d <- 4
next_mtd_QuasiBOIN(target = target, n = n, y = y, d = d)
```

next_mtd_Quasi_CRM	<i>Determine the dose for the next cohort of new patients using Quasi-CRM design</i>
--------------------	--

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_mtd_Quasi_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_mtd_Quasi_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(1, 1, 1, 1, 15, 1)
y <- c(0.000000, 0.000000, 0.000000, 0.000000, 4.666667, 1.000000)
next_mtd_Quasi_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_mtd_Quasi_CRM (target = target, n = n, y = y, dose.curr = 5,
                    score = score, skeleton = p1)
```

select_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_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_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, 9, 0, 0, 0, 0)
n <- c(3, 22, 0, 0, 0, 0)
select_Ivanova_binary(target = target, y = y, n = n)
```

select_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_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_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 <- 0.3
c_resp <- list(c(0.14934229, 0.33945935, 0.27632487, 0.12546279,
               0.51435981, 0.05242217, 0.23950981, 0.52195215,
               0.33701385, 0.02585574, 0.99308905, 0.16857301,
               0.52921818, 0.37858839, 0.53202138, 0.05568626,
               0.16846483, 0.08393353, 0.36928336, -0.04731884, 0.37412280),
             c(0.7547139, 0.4467885, 0.5274520, 0.2560551, 0.4359545,
               0.4385098, 0.3882733, 0.2444583, 0.6043425),
             0,
             0,
             0,
             0)
n <- c(21, 9, 0, 0, 0, 0)
select_Ivanova_continuous(target = target, c_resp = c_resp, n = n)
```

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 <- 0.1
n <- c(14, 1, 0, 0, 0, 0)
y <- c(1.4268322, 0.1631531, 0, 0, 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(4, 32, 0, 0, 0, 0, 0, 0, 0)
y <- c(6.6, 102.3, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0, 0.0)
select_mtd_gBOIN_TB(target = target, npts = n, ntox = y)
```

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(0.000000, 0.000000, 1.333333, 2.333333, 3.666667, 0.000000)
select_mtd_QuasiBOIN(target = target, npts = n, ntox = y)
```

select_mtd_Quasi_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_Quasi_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_Quasi_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(1, 1, 1, 1, 15, 1)
y <- c(0.000000, 0.000000, 0.000000, 0.000000, 4.666667, 1.000000)
select_mtd_Quasi_CRM(target = target, n = n, y = y, score = score,
                     skeleton = skeletons)
```


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