Package 'CFO'

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Title CFO-Type Designs in Phase I/II Clinical Trials

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Imports survival,dplyr,ggplot2,Iso,pbapply,RColorBrewer,scales

Description In phase I clinical trials, the primary objective is to ascertain the maximum tolerated dose (MTD) corresponding to a specified target toxicity rate. The subsequent phase II trials are designed to examine the potential efficacy of the drug based on the MTD obtained from the phase I trials, with the aim of identifying the optimal biological dose (OBD). The 'CFO' package facilitates the implementation of dose-finding trials by utilizing calibration-free odds type (CFO-type) designs. Specifically, it encompasses the calibration-free odds (CFO) (Jin and Yin (2022) <doi:10.1177/09622802221079353>), randomized CFO (rCFO), precision CFO (pCFO), two-dimensional CFO (2dCFO) (Wang et al. (2023) <doi:10.3389/fonc.2023.1294258>), time-to-event CFO (TITE-CFO) (Jin and Yin (2023) <doi:10.1002/pst.2304>), fractional CFO (fCFO), accumulative CFO (aCFO), TITE-aCFO, and f-aCFO (Fang and Yin (2024) <doi:10.1002/sim.10127>). It supports phase I/II trials for the CFO design and only phase I trials for the other CFO-type designs. The 'CFO' package accommodates diverse CFO-type designs, allowing users to tailor the approach based on factors such as dose information inclusion, handling of late-onset toxicity, and the nature of the target drug (single-drug or drug-combination). The functionalities embedded in 'CFO' package include the determination of the dose level for the next cohort, the selection of the MTD for a real trial, and the execution of single or multiple simulations to obtain operating characteristics. Moreover, these functions are equipped with early stopping and dose elimination rules to address safety considerations. Users have the flexibility to choose different distributions, thresholds, and cohort sizes among others for their specific needs. The output of the 'CFO' package can be summary statistics as well as various plots for better visualization. An interactive web application for CFO is available at the provided URL.

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URL https://clinicaltrialdesign.shinyapps.io/cfoapp

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Contents

`aCFO.next` *Determination of the dose level for next cohort in the accumulative calibration-free odds (aCFO) design for phase I trials*

Description

In the aCFO design for phase I trials, the function is used to determine the dose movement based on the toxicity outcomes of the enrolled cohorts.

Usage

```
aCFO.next(target, ays, ans, currdose,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95)
```

Arguments

target	the target DLT rate.
ays	the cumulative numbers of DLTs observed in patients for all dose levels.
ans	the cumulative numbers of patients for all dose levels.
currdose	the current dose level.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.

Details

The aCFO design is an extension of the CFO design. It integrates dose information from all positions (ranging from the lowest to the highest dose levels) into the decision-making process of the trial. Before assigning the dose level for a new cohort, aCFO compares the evidence from the current dose level with all doses to its left and right. In contrast, the original CFO design makes dose allocation by examining one dose level above and one below the current dose level. Consequently, the aCFO design enhances the utilization of information while maintaining the characteristics of the CFO design (model-free and calibration-free). Additionally, the aCFO design preserves the same early stopping and dose elimination criteria as the CFO design.

Value

The aCFO.next() function returns a list object comprising the following elements:

- target: the target DLT rate.
- ays: the cumulative counts of DLTs observed at all dose levels.
- ans: the cumulative counts of patients treated at all dose levels.
- decision: the decision in the aCFO design, where left, stay, and right represent the movement directions, and stop indicates stopping the experiment.
- currdose: the current dose level.
- nextdose: the recommended dose level for the next cohort. nextdose = 99 indicates that the trial is terminated due to early stopping.
- overtox: the situation regarding which position experiences over-toxicity. The dose level indicated by overtox and all the dose levels above experience over-toxicity. overtox = NA signifies that the occurrence of over-toxicity did not happen.
- toxprob: the expected toxicity probability, $Pr(p_k > \phi | x_k, m_k)$, at all dose levels, where p_k, x_k, and m_k is the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k. NA indicates that there are no patients at the corresponding dose level.

Note

The dose level indicated by `overtox` and all the dose levels above experience over-toxicity, and these dose levels will be eliminated.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*, 43(17), 3210-3226.

Examples

```
## determine the dose level for the next cohort of new patients
ays <- c(0, 0, 1, 0, 0, 0, 0); ans <- c(3, 3, 6, 0, 0, 0, 0)
decision <- aCFO.next(target = 0.2, ays = ays, ans = ans, currdose = 3,
            prior.para = list(alp.prior = 0.2, bet.prior = 0.8))
summary(decision)

ays <- c(3, 0, 0, 0, 0, 0, 0); ans <- c(3, 0, 0, 0, 0, 0, 0)
decision <- aCFO.next(target = 0.2, ays = ays, ans = ans, currdose = 1,
            prior.para = list(alp.prior = 0.2, bet.prior = 0.8))
summary(decision)

ays <- c(0, 0, 0, 0, 0, 0, 3); ans <- c(3, 3, 3, 3, 3, 3, 3)
decision <- aCFO.next(target = 0.2, ays = ays, ans = ans, currdose = 7,
            prior.para = list(alp.prior = 0.2, bet.prior = 0.8))
summary(decision)
```

`CFO.next` *Determination of the dose level for next cohort in the calibration-free odds (CFO) design for phase I trials*

Description

In the CFO design for phase I trials, the function is used to determine the dose movement based on the toxicity outcomes of the enrolled cohorts.

Usage

```
CFO.next(target, cys, cns, currdose,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95)
```

Arguments

`target`	the target DLT rate.
`cys`	the cumulative numbers of DLTs observed at the left, current, and right dose levels.
`cns`	the cumulative numbers of patients treated at the left, current, and right dose levels.
`currdose`	the current dose level.
`prior.para`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of `cutoff.eli = 0.95` for general use.
`early.stop`	the threshold value for early stopping. The default value `early.stop = 0.95` generally works well.

Details

The CFO design determines the dose level for the next cohort by assessing evidence from the current dose level and its adjacent levels. This evaluation is based on odds ratios denoted as O_k, where $k = L, C, R$ represents left, current (central), and right dose levels. Additionally, we define $\overline{O}_k = 1/O_k$. The ratio $O_C/\overline{O}_L$ indicates the inclination for de-escalation, while $\overline{O}_C/O_R$ quantifies the tendency for escalation. Threshold values γ_L and γ_R are chosen to minimize the probability of making incorrect decisions. The decision process is summarized in Table 1 of Jin and Yin (2022). The early stopping and dose elimination rules are implemented to ensure patient safety. If the data suggest excessive toxicity at the current dose level, we exclude that dose level and those higher levels. If the lowest dose level is overly toxic, the trial will be terminated according to the early stopping rule.

Value

The `CFO.next()` function returns a list object comprising the following elements:

- target: the target DLT rate.
- cys: the cumulative counts of DLTs observed at the left, current, and right dose levels.
- cns: the cumulative counts of patients treated at the left, current, and right dose levels.
- decision: the decision in the CFO design, where `left`, `stay`, and `right` represent the movement directions, and `stop` indicates stopping the experiment.
- currdose: the current dose level.
- nextdose: the recommended dose level for the next cohort. `nextdose = 99` indicates that the trial is terminated due to early stopping.
- overtox: the situation regarding which positions experience over-toxicity. The dose level indicated by `overtox` and all the dose levels above experience over-toxicity. `overtox = NA` signifies that the occurrence of over-toxicity did not happen.

- toxprob: the expected toxicity probability, $Pr(p_k > \phi | x_k, m_k)$, at the left, current, and right dose levels, where p_k, x_k, and m_k is the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k. NA indicates that there are no patients at the corresponding dose level.

Note

When the current dose level is the lowest or highest (i.e., at the boundary), the parts in cys and cns where there is no data are filled with NA.
The dose level indicated by overtox and all the dose levels above experience over-toxicity, and these dose levels will be eliminated.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
## determine the dose level for the next cohort of new patients
cys <- c(0, 1, 0); cns <- c(3, 6, 0)
decision <- CFO.next(target=0.2, cys=cys, cns=cns, currdose=3)
summary(decision)

cys <- c(NA, 3, 0); cns <- c(NA, 3, 0)
decision <- CFO.next(target=0.2, cys=cys, cns=cns, currdose=1)
summary(decision)

cys <- c(0, 3, NA); cns <- c(3, 3, NA)
decision <- CFO.next(target=0.2, cys=cys, cns=cns, currdose=7)
summary(decision)
```

CFO.oc *Generate operating characteristics of phase I trials single-drug trials in multiple simulations*

Description

Based on the toxicity outcomes, this function is used to perform multiple simulations for phase I single-drug trials and obtain relevant operating characteristics.

Usage

```
CFO.oc(nsimu = 5000, design, target, p.true, init.level = 1, ncohort, cohortsize,
       assess.window = NA, tte.para = NA, accrual.rate = NA, accrual.dist = NA,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, seeds = NULL)
```

Arguments

nsimu	the total number of trials to be simulated. The default value is 5000.
design	option for selecting different designs, which can be set as 'CFO', 'aCFO', 'rCFO', 'TITE-CFO', 'TITE-aCFO', 'fCFO', 'f-aCFO', 'bCFO', and 'b-aCFO'. Specifically, 'bCFO' refers to the benchmark CFO design, and 'b-aCFO' denotes the benchmark aCFO design.
target	the target DLT rate.
p.true	the true DLT rates under the different dose levels.
init.level	the dose level assigned to the first cohort. The default value init.level is 1.
ncohort	the total number of cohorts.
cohortsize	the number of patients of each cohort.
assess.window	the maximal assessment window size. NA should be assigned if the design without late-oneset outcomes.
tte.para	the parameter related with the distribution of the time to DLT events. The time to DLT is sampled from a Weibull distribution, with tte.para representing the proportion of DLTs occurring within the first half of the assessment window. NA should be assigned if the design without late-oneset outcomes.
accrual.rate	the accrual rate, i.e., the number of patients accrued per unit time. NA should be assigned if the design without late-onset outcomes.
accrual.dist	the distribution of the arrival times of patients. When accrual.dist = 'fix', it corresponds to all patients in each cohort arriving simultaneously at a given accrual rate. When accrual.dist = 'unif', it corresponds to a uniform distribution, and when accrual.dist = 'exp', it corresponds to an exponential distribution. NA should be assigned if the design without late-oneset outcomes.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seeds	a vector of random seeds for each simulation, for example, seeds = 1:nsimu (default is NULL).

Value

The `CFO.oc()` function returns basic setup of ($simu.setup) and the operating characteristics of the design:

- p.true: the true DLT rates under the different dose levels.
- selpercent: the selection percentage at each dose level.
- npatients: the averaged number of patients treated at each dose level in one simulation.
- ntox: the averaged number of toxicity observed at each dose level in one simulation.
- MTDsel: the percentage of correct selection of the MTD.
- MTDallo: the percentage of patients allocated to the MTD.
- oversel: the percentage of selecting a dose above the MTD.
- overallo: the percentage of allocating patients at dose levels above the MTD.
- averDLT: the percentage of the patients suffering DLT.
- averdur: the average trial duration if trials with late-onset toxicities.
- percentstop: the percentage of early stopping without selecting the MTD.
- simu.setup: the parameters for the simulation set-up.

Note

The operating characteristics are generated by simulating multiple single-drug trials under the pre-specified true toxicity probabilities of the investigational doses. The choice of which design to execute is determined by setting the `design` argument. Some time-related arguments (`assess.window`, `accrual.rate`, `tte.para`, and `accrual.dist`) need to be set as values only when running a design that can handle late-onset toxicities; otherwise, they default to `NA`.
Additionally, in the example, we set `nsimu = 5` for testing time considerations. In reality, `nsimu` is typically set to 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Jin H, Yin G (2023). Time-to-event calibration-free odds design: A robust efficient design for phase I trials with late-onset outcomes. *Pharmaceutical Statistics*. 22(5), 773–783.
Yin G, Zheng S, Xu J (2013). Fractional dose-finding methods with late-onset toxicity in phase I clinical trials. *Journal of Biopharmaceutical Statistics*, 23(4), 856-870.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*, 43(17), 3210-3226.

Examples

```
## setting
nsimu <- 5; target <- 0.2; ncohort <- 10; cohortsize <- 3; init.level <- 1
p.true <- c(0.01, 0.07, 0.20, 0.35, 0.50, 0.65, 0.80)
prior.para = list(alp.prior = target, bet.prior = 1 - target)
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'


## get the operating characteristics for 5 simulations using the f-aCFO design
faCFOoc <- CFO.oc (nsimu, design='f-aCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(faCFOoc)
plot(faCFOoc)


# This test may take longer than 5 seconds to run
# It is provided for illustration purposes only
# Users can run this code directly

## get the operating characteristics for 5 simulations using the CFO design
CFOoc <- CFO.oc (nsimu, design = 'CFO', target, p.true, init.level, ncohort, cohortsize,
      assess.window = NA, tte.para = NA, accrual.rate = NA, accrual.dist = NA, seeds = 1:nsimu)
summary(CFOoc)
plot(CFOoc)

## get the operating characteristics for 5 simulations using the aCFO design
aCFOoc <- CFO.oc (nsimu, design = 'aCFO', target, p.true, init.level, ncohort, cohortsize,
     assess.window = NA, tte.para = NA, accrual.rate = NA, accrual.dist = NA, seeds = 1:nsimu)
summary(aCFOoc)
plot(aCFOoc)

## get the operating characteristics for 5 simulations using the rCFO design
rCFOoc <- CFO.oc (nsimu, design = 'rCFO', target, p.true, init.level, ncohort, cohortsize,
     assess.window = NA, tte.para = NA, accrual.rate = NA, accrual.dist = NA, seeds = 1:nsimu)
summary(rCFOoc)
plot(rCFOoc)

## get the operating characteristics for 5 simulations using the pCFO design
pCFOoc <- CFO.oc (nsimu, design = 'pCFO', target, p.true, init.level, ncohort, cohortsize,
     assess.window = NA, tte.para = NA, accrual.rate = NA, accrual.dist = NA, seeds = 1:nsimu)
summary(pCFOoc)
plot(pCFOoc)

## get the operating characteristics for 5 simulations using the TITE-CFO design
TITECFOoc <- CFO.oc (nsimu, design = 'TITE-CFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(TITECFOoc)
plot(TITECFOoc)
## get the operating characteristics for 5 simulations using the TITE-aCFO design
TITEaCFOoc <- CFO.oc (nsimu, design = 'TITE-aCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(TITEaCFOoc)
```

```
plot(TITEaCFOoc)
## get the operating characteristics for 5 simulations using the fCFO design
fCFOoc <- CFO.oc (nsimu, design = 'fCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(fCFOoc)
plot(fCFOoc)
```

`CFO.selectmtd` *Select the maximum tolerated dose (MTD) for the real single-drug trials*

Description

Select the maximum tolerated dose (MTD) when the real single-drug trials is completed

Usage

```
CFO.selectmtd(target, npts, ntox,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, verbose = TRUE)
```

Arguments

`target`	the target DLT rate.
`npts`	a vector containing the number of patients treated at each dose level.
`ntox`	a vector containing the number of patients who experienced DLT at each dose level.
`prior.para`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of `cutoff.eli = 0.95` for general use.
`early.stop`	the threshold value for early stopping. The default value `early.stop = 0.95` generally works well.
`verbose`	set `verbose=TRUE` to return more details of the results.

Details

`CFO.selectmtd()` selects the MTD based on isotonic estimates of toxicity probabilities. `CFO.selectmtd()` selects as the MTD dose j^*, for which the isotonic estimate of the DLT rate is closest to the target. If there are ties, we select from the ties the highest dose level when the estimate of the DLT rate is smaller than the target, or the lowest dose level when the estimate of the DLT rate is greater than the target. The isotonic estimates are obtained by the pooled-adjacent-violators algorithm (PAVA).

Value

`CFO.selectmtd()` returns

- target: the target DLT rate.
- MTD: the selected MTD. `MTD = 99` indicates that all tested doses are overly toxic.
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval. `p_est = NA` if all tested doses are overly toxic.
- p_overdose: the probability of overdosing defined as $Pr(toxicity > \texttt{target}|data)$. `p_overdose = NA` if all tested doses are overly toxic.

Note

The MTD selection and dose escalation/de-escalation rule are two independent components of the trial design. Isotonic regression is employed to select the MTD after the completion of the trial. When appropriate, another dose selection procedure (e.g., based on a fitted logistic model) can be used to select the MTD after the completion of the trial using the CFO-type design.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Bril G, Dykstra R, Pillers C, Robertson T (1984). Algorithm AS 206: Isotonic regression in two independent variables. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, 33(3), 352–357.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*.

Examples

```
### select the MTD for the CFO-type single-drug trial
n <- c(3,3,27,3,0,0,0)
y <- c(0,0,4,2,0,0,0)
selmtd <- CFO.selectmtd(target=0.2, npts=n, ntox=y)
summary(selmtd)
plot(selmtd)
```

CFO.simu *Conduct one simulation using the calibration-free odds (CFO), accumulative CFO (aCFO) design, or randomized CFO (rCFO) design for phase I trials.*

Description

In the CFO, aCFO, rCFO, and pCFO designs for phase I trials, the function is used to conduct one single simulation and find the maximum tolerated dose (MTD).

Usage

```
CFO.simu(design, target, p.true, init.level = 1, ncohort, cohortsize,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, seed = NULL)
```

Arguments

design	option for selecting different designs, which can be set as 'CFO', 'aCFO', 'rCFO' or 'pCFO'.
target	the target DLT rate.
p.true	the true DLT rates under the different dose levels.
init.level	the dose level assigned to the first cohort. The default value init.level is 1.
ncohort	the total number of cohorts.
cohortsize	the number of patients of each cohort.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seed	an integer to be set as the seed of the random number generator for reproducible results. The default value is set to NULL.

Value

The CFO.simu function returns a list object comprising the following components:

- target: the target DLT rate.
- MTD: the selected MTD. MTD = 99 indicates that the simulation is terminated due to early stopping.

- correct: a binary indicator of whether the recommended dose level matches the correct MTD (1 for yes). The correct MTD is the dose level at which the true DLT rate is closest to the target DLT rate.
- npatients: the total number of patients allocated to all dose levels.
- ntox: the total number of DLTs observed for all dose levels.
- over.doses: a vector indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: a vector including the dose level assigned to each cohort.
- ptoxic: the percentage of subjects assigned to dose levels with a DLT rate greater than the target.
- patientDLT: a vector including the DLT outcome observed for each patient.
- sumDLT: the total number of DLT observed.
- earlystop: a binary indicator of whether the trial is early stopped (1 for yes).
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval. `p_est = NA` if all tested doses are overly toxic.
- p_overdose: p_overdose: the probability of overdosing defined as $Pr(toxicity > \texttt{target}|data)$. `p_overdose = NA` if all tested doses are overly toxic.

Note

The `CFO.simu()` function is designed to conduct a single CFO, aCFO, rCFO or pCFO simulation. If `design = 'CFO'`, it corresponds to the CFO design. If `design = 'aCFO'`, it corresponds to the aCFO design. If `design = 'rCFO'`, it corresponds to the rCFO design. If `design = 'pCFO'`, it corresponds to the pCFO design.
The early stopping and dose elimination rules are incorporated into designs to ensure patient safety and benefit. If there is substantial evidence indicating that the current dose level exhibits excessive toxicity, we exclude the current dose level as well as higher dose levels from the trial. If the lowest dose level is overly toxic, the trial will be terminated according to the early stopping rule. Upon the predefined maximum sample size is reached or the lowest dose level is over-toxicity, the experiment is concluded, and the MTD is determined using isotonic regression.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*, 43(17), 3210-3226.

Examples

```
target <- 0.2; ncohort <- 12; cohortsize <- 3; init.level <- 1
p.true <- c(0.01, 0.07, 0.20, 0.35, 0.50, 0.65, 0.80)
### find the MTD for a single CFO simulation
CFOtrial <- CFO.simu(design = 'CFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
```

```
summary(CFOtrial)
plot(CFOtrial)

# This test may take longer than 5 seconds to run
# It is provided for illustration purposes only
# Users can run this code directly
### find the MTD for a single aCFO simulation
aCFOtrial <- CFO.simu(design = 'aCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
summary(aCFOtrial)
plot(aCFOtrial)
### find the MTD for a single rCFO simulation
rCFOtrial <- CFO.simu(design = 'rCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
summary(rCFOtrial)
plot(rCFOtrial)
#' ### find the MTD for a single pCFO simulation
pCFOtrial <- CFO.simu(design = 'pCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
summary(pCFOtrial)
plot(pCFOtrial)
```

`CFO2d.next` *Determinate the dose level for the next cohort in the two-dimensional calibration-free odds (2dCFO) design for phase I trials.*

Description

In the 2dCFO design for phase I trials, the function is used to determine the dose movement based on the toxicity outcomes of the enrolled cohorts.

Usage

```
CFO2d.next(target, cys, cns, currdose,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, seed = NULL)
```

Arguments

`target`	the target DLT rate.
`cys`	a matrix of the number of DLTs observed for each dose combination.
`cns`	a matrix of the number of patients allocated to each dose combination.
`currdose`	a vector of the current dose indices in the horizontal and vertical direction.
`prior.para`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of `cutoff.eli = 0.95` for general use.

early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seed	an integer to be set as the seed of the random number generator for reproducible results. The default value is set to NULL.

Details

In the 2dCFO design, decision-making within the two-dimensional toxicity probability space is conducted by performing two independent one-dimensional CFO analyses along both the horizontal and vertical axes (Wang et al. 2023).

Value

The CFO2d.next() function returns a list with the following components:

- target: the target DLT rate.
- cys: a 3 by 3 matrix of the number of DLT observed for each dose combination at and around the current dose.
- cns: a 3 by 3 matrix of the number of patients allocated to each dose combination at and around the current dose.
- decision: a vector of length 2 representing the recommended decisions for vertical and horizontal directions, and stop indicates stopping the experiment.
- currdose: the current dose combination.
- nextdose: the recommended dose combination for the next cohort. nextdose = (99, 99) indicates that the trial is terminated due to early stopping.
- overtox: the situation regarding which positions experience over-toxicity. The dose level indicated by overtox and all the dose levels above experience over-toxicity. overtox = NA signifies that the occurrence of over-toxicity did not happen.

Note

When the current dose level is the lowest or highest (i.e., at the boundary), the parts in cys and cns where there is no data are filled with NA.
The dose level indicated by overtox and all the dose levels above experience over-toxicity, and these dose levels will be eliminated.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Wang W, Jin H, Zhang Y, Yin G (2023). Two-dimensional calibration-free odds (2dCFO) design for phase I drug-combination trials. *Frontiers in Oncology*, 13, 1294258.

Examples

```
cns <- matrix(c(3, 3, 0,
                0, 6, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)

cys <- matrix(c(0, 1, 0,
                0, 2, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
currdose <- c(2,3)
decision <- CFO2d.next(target = 0.3, cys, cns, currdose = currdose, seed = 1)
summary(decision)

cns <- matrix(c(NA, NA, NA,
                NA, 6, 0,
                NA, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)

cys <- matrix(c(NA, NA, NA,
                NA, 6, 0,
                NA, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
currdose <- c(1,1)
decision <- CFO2d.next(target = 0.3, cys, cns, currdose = currdose, seed = 1)
summary(decision)
```

CFO2d.oc *Generate operating characteristics of phase I drug-combination trials in multiple simulations*

Description

Based on the toxicity outcomes, this function is used to conduct multiple simulations of phase I drug-combination trials and obtain relevant the operating characteristics.

Usage

```
CFO2d.oc(nsimu = 1000, target, p.true, init.level = c(1,1), ncohort, cohortsize,
               prior.para = list(alp.prior = target, bet.prior = 1 - target),
               cutoff.eli = 0.95, early.stop = 0.95, seeds = NULL)
```

Arguments

nsimu	the total number of trials to be simulated. The default value is 1000.
target	the target DLT rate.
p.true	a matrix representing the true DIL rates under the different dose levels.

init.level	a numeric vector of length 2 representing the initial dose level (default is c(1,1)).
ncohort	the total number of cohorts.
cohortsize	the number of patients of each cohort.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of (cutoff.eli = 0.95) for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seeds	A vector of random seeds for each simulation, for example, seeds = 1:nsimu (default is NULL).

Value

The CFO.oc() function returns basic setup of ($simu.setup) and the operating characteristics of the design:

- p.true: the matrix of the true DLT rates under the different dose levels.
- selpercent: the matrix of the selection percentage of each dose level.
- npatients: a matrix of the averaged number of patients allocated to different doses in one simulation.
- ntox: a matrix of the averaged number of DLT observed for different doses in one simulation.
- MTDsel: the percentage of the correct selection of the MTD.
- MTDallo: the averaged percentage of patients assigned to the target DLT rate.
- oversel: the percentage of selecting a dose above the MTD.
- overallo: the averaged percentage of patients assigned to dose levels with a DLT rate greater than the target.
- averDLT: the averaged total number of DLTs observed.
- percentstop: the percentage of early stopping without selecting the MTD.
- simu.setup: the parameters for the simulation set-up.

Note

In the example, we set nsimu = 10 for testing time considerations. In reality, nsimu is typically set to 1000 or 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Wang W, Jin H, Zhang Y, Yin G (2023). Two-dimensional calibration-free odds (2dCFO) design for phase I drug-combination trials. *Frontiers in Oncology*, 13, 1294258.

Examples

```
## Simulate a two-dimensional dose-finding trial with 20 cohorts of size 3 for 10 replications.
p.true <- matrix(c(0.05, 0.10, 0.15, 0.30, 0.45,
0.10, 0.15, 0.30, 0.45, 0.55,
0.15, 0.30, 0.45, 0.50, 0.60),
nrow = 3, ncol = 5, byrow = TRUE)
target <- 0.3; ncohort <- 12; cohortsize <- 3
CFO2doc <- CFO2d.oc(nsimu = 5, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:5)
summary(CFO2doc)
plot(CFO2doc)
```

`CFO2d.selectmtd` *Select the maximum tolerated dose (MTD) for the real drug combination trials*

Description

Select the maximum tolerated dose (MTD) when the real drug combination trials is completed

Usage

```
CFO2d.selectmtd(target, npts, ntox,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, verbose = TRUE)
```

Arguments

`target`	the target DLT rate.
`npts`	a matrix containing the number of patients treated at each dose level.
`ntox`	a matrix containing the number of patients who experienced DLT at each dose level.
`prior.para`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of `cutoff.eli = 0.95` for general use.
`early.stop`	the threshold value for early stopping. The default value `early.stop = 0.95` generally works well.
`verbose`	set `verbose = TRUE` to return more details of the results.

Details

`CFO2d.selectmtd()` selects the MTD based on isotonic estimates of toxicity probabilities. `CFO2d.selectmtd()` selects as the MTD dose j^*, for which the isotonic estimate of the DLT rate is closest to the target. If there are ties, we select from the ties the highest dose level when the estimate of the DLT rate is smaller than the target, or the lowest dose level when the estimate of the DLT rate is greater than the target. The isotonic estimates are obtained by the pooled-adjacent-violators algorithm (PAVA).

Value

`CFO2d.selectmtd()` returns

- target: the target DLT rate.
- MTD: the selected MTD. `MTD = (99, 99)` indicates that all tested doses are overly toxic.
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval. `p_est = NA` if all tested doses are overly toxic.
- p_est_CI: the credible interval for the isotonic estimate. `p_est_CI = NA` if all tested doses are overly toxic.

Note

The MTD selection and dose escalation/deescalation rule are two independent components of the trial design. Isotonic regression is employed to select the MTD after the completion of the trial. When appropriate, another dose selection procedure (e.g., based on a fitted logistic model) can be used to select the MTD after the completion of the trial using the 2dCFO design.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Wang W, Jin H, Zhang Y, Yin G (2023). Two-dimensional calibration-free odds (2dCFO) design for phase I drug-combination trials. *Frontiers in Oncology*, 13, 1294258.
Bril G, Dykstra R, Pillers C, Robertson T (1984). Algorithm AS 206: Isotonic regression in two independent variables. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, 33(3), 352–357.

Examples

```
ntox <- matrix(c(0, 0, 2, 0, 0,
                 0, 2, 7, 0, 0,
                 0, 2, 0, 0, 0),
               nrow = 3, ncol = 5, byrow = TRUE)

npts <- matrix(c(3,  0, 12, 0, 0,
                 3, 12, 24, 0, 0,
                 3,  3,  0, 0, 0),
```

```
              nrow = 3, ncol = 5, byrow = TRUE)
selmtd <- CFO2d.selectmtd(target=0.3, npts=npts, ntox=ntox)
summary(selmtd)
plot(selmtd)
```

`CFO2d.simu` *Conduct one simulation using the two-dimensional calibration-free odds (2dCFO) design for phase I trials.*

Description

In the 2dCFO design for phase I trials, the function is used to conduct one single simulation and find the maximum tolerated dose (MTD).

Usage

```
CFO2d.simu(target, p.true, init.level = c(1,1), ncohort, cohortsize,
                 prior.para = list(alp.prior = target, bet.prior = 1 - target),
                 cutoff.eli = 0.95, early.stop = 0.95, seed = NULL)
```

Arguments

`target`	the target DLT rate.
`p.true`	a matrix representing the true DIL rates under the different dose levels.
`init.level`	the dose level assigned to the first cohort. The default value `init.level` is `c(1,1)`.
`ncohort`	the total number of cohorts.
`cohortsize`	the number of patients of each cohort.
`prior.para`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of (`cutoff.eli = 0.95`) for general use.
`early.stop`	the threshold value for early stopping. The default value `early.stop = 0.95` generally works well.
`seed`	an integer to be set as the seed of the random number generator for reproducible results. The default is set to `NULL`.

Details

The `CFO2d.simu()` function simulates the operating characteristics of the 2dCFO design in a dose-combination trial. The early stopping and dose elimination rules are incorporated into the 2dCFO design to ensure patient safety and benefit.

Value

The `CFO2d.simu()` function returns a list with the following components:

- target: the target DLT rate.
- MTD: a vector of length 2 representing the recommended dose level. `MTD = (99, 99)` indicates that this trial is terminated due to early stopping.
- correct: a binary indicator of whether the recommended dose level matches the correct MTD (1 for yes). The correct MTD is the dose level at which the true DLT rate is closest to the target DLT rate.
- npatients: a matrix of the number of patients allocated to different doses.
- ntox: a matrix of the number of DLT observed for different doses.
- npercent: the percentage of patients assigned to the correct MTD.
- over.doses: a matrix indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: the dose combination assigned to each cohort.
- ptoxic: the percentage of subjects assigned to dose levels with a DLT rate greater than the target.
- patientDLT: the DLT observed at each cohort.
- sumDLT: the total number of DLT observed.
- earlystop: a binary indicator of whether the trial is early stopped (1 for yes).
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval. `p_est = NA` if all tested doses are overly toxic.
- p_est_CI: the credible interval for the isotonic estimate. `p_est_CI = NA` if all tested doses are overly toxic.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Wang W, Jin H, Zhang Y, Yin G (2023). Two-dimensional calibration-free odds (2dCFO) design for phase I drug-combination trials. *Frontiers in Oncology*, 13, 1294258.

Examples

```
## Simulate a two-dimensional dose-finding trial with 20 cohorts of size 3.
p.true <- matrix(c(0.05, 0.10, 0.15, 0.30, 0.45,
                   0.10, 0.15, 0.30, 0.45, 0.55,
                   0.15, 0.30, 0.45, 0.50, 0.60),
                 nrow = 3, ncol = 5, byrow = TRUE)
target <- 0.3; ncohort <- 20; cohortsize <- 3
CFO2dtrial <- CFO2d.simu(target, p.true, init.level = c(1,1), ncohort, cohortsize, seed = 1)
summary(CFO2dtrial)
plot(CFO2dtrial)
```

CFOeff.next *Determination of the dose level for next cohort in the calibration-free odds (CFO) design for phase I/II trials*

Description

In the CFO design for phase I/II trials, the function is used to determine the dose movement based on the toxicity outcomes and efficacy outcomes of the enrolled cohorts.

Usage

```
CFOeff.next(target, axs, ays, ans, currdose,
                  prior.para=list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5),
                cutoff.eli=0.95, early.stop=0.95, effearly.stop = 0.9, mineff)
```

Arguments

target	the target DLT rate.
axs	the cumulative counts of efficacy outcomes at all dose levels.
ays	the cumulative counts of DLTs observed at all dose levels.
ans	the cumulative counts of patients treated at all dose levels.
currdose	the current dose level.
prior.para	the prior parameters for two beta distributions, where set as list(alp.prior = target, bet.prior = 1 - target, alp.prior.eff = 0.5, bet.prior.eff = 0.5) by default. alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior). alp.eff.prior and bet.eff.prior represent the parameters of the Jeffreys' prior distribution for the efficacy probability at any dose level. This prior distribution is specified as Beta(alpha.eff.prior, beta.eff.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping due to overly toxic. The default value early.stop = 0.95 generally works well.
effearly.stop	the threshold value for early stopping due to low efficacy. The trial would be terminated early if $Pr(q_k < \psi \mid y_k, m_k \geq 3)$ is smaller than the value of effearly.stop where q_k, y_k and m_k are the efficacy probability, the number of efficacy outcomes and the number of patients at dose level k. ψ is the the lowest acceptable efficacy rate which is set by mineff here. By default, effearly.stop is set as 0.9.
mineff	the lowest acceptable efficacy rate.

Details

The CFO design for phase I/II trials will determine admissible set A_n through the dose escalation rules for the MTD. The current dose is set as d_n. If the decision is to de-escalate the dose, the set A_n will be $\{1, \ldots, d_n - 1\}$. If the decision is to stay at the current dose, then the admissible set A_n will be $\{1, \ldots, d_n\}$. If the decision is to escalate the dose, then A_n will be $\{1, \ldots, d_n + 1\}$. The dose level d_{n+1} for the next cohort will be selected from A_n by using the rule: $d_{n+1} = argmax_{k \in A_n} Pr(q_k = max_{j \in A_n}\{q_j\}|D_n)$ where D_n and q_k are the current data and the efficacy probability for dose level k.

Value

The `CFOeff.next()` function returns a list object comprising the following elements:

- target: the target DLT rate.
- axs: the cumulative counts of efficacy outcomes at all dose levels.
- ays: the cumulative counts of DLTs observed at all dose levels.
- ans: the cumulative counts of patients treated at all dose levels.
- decision: the decision in the CFO design, where `de-escalation`, `stay`, and `escalation` represent the movement directions of the dose level, `stop_for_tox` indicates stopping the experiment because the lowest dose level is overly toxic and `stop_for_low_eff` indicates that all dose level in the admissible set shows low efficacy.
- currdose: the current dose level.
- nextdose: the recommended dose level for the next cohort. `nextdose = 99` indicates that the trial is terminated due to early stopping.
- overtox: the situation regarding which positions experience over-toxicity. The dose level indicated by `overtox` and all the dose levels above experience over-toxicity. `overtox = NA` signifies that the occurrence of over-toxicity did not happen.
- toxprob: the expected toxicity probability, $Pr(p_k > \phi|x_k, m_k)$, for doses in admissible set, where p_k, x_k, and m_k are the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k.
- effprob: the empirical probability of $Pr(q_k = max_{j \in A_n}\{q_j\}|D_n)$ for doses in admissible set, where q_k is efficacy probability at dose level k. A_n is the admissible set determined through the dose escalation rules for the MTD and D_n is the current cumulative dataset.
- admset: the admissible set A_n. The dose level for the next cohort will be selected from A_n.
- class: the phase of the trial.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
axs = c(3, 1, 7, 11, 26); ays = c(0, 0, 0, 0, 6); ans = c(6, 3, 12, 17, 36)
target <- 0.4
decision <- CFOeff.next(target,axs,ays,ans,currdose = 3, mineff = 0.3)
summary(decision)
#early stop for overly toxic
axs = c(13, 11, 7, 11, 26); ays = c(25, 18, 12, 17, 26); ans = c(36, 23, 22, 27, 36)
target <- 0.4
decision <- CFOeff.next(target,axs,ays,ans,currdose = 1, mineff = 0.3)
summary(decision)

#early stop for low efficacy
axs = c(0, 0, 0, 0, 0); ays = c(2, 1, 1, 1, 6); ans = c(36, 23, 22, 27, 36)
target <- 0.4
decision <- CFOeff.next(target,axs,ays,ans,currdose = 1, mineff = 0.3)
summary(decision)
```

`CFOeff.oc` *Generate operating characteristics of phase I/II trials single-drug trials in multiple simulations.*

Description

Based on the toxicity outcomes and efficacy outcomes, this function is used to perform multiple simulations for phase I/II single-drug trials and obtain relevant operating characteristics.

Usage

```
CFOeff.oc(target, p.true=p.true, pE.true=pE.true, prior.para =
                 list(alp.prior = target, bet.prior = 1 - target,
                 alp.prior.eff = 0.5, bet.prior.eff = 0.5),
                 init.level = 1, cohortsize=cohortsize, ncohort=ncohort,
                 nsimu, cutoff.eli=0.95,
                 early.stop=0.95, effearly.stop = 0.9, mineff,
                 seeds = NULL)
```

Arguments

`target`	the target DLT rate.
`p.true`	the true DLT rates under the different dose levels.
`pE.true`	the true efficacy rates under the different dose levels.
`prior.para`	the prior parameters for two beta distributions, where set as `list(alp.prior = target, bet.prior = 1 - target, alp.prior.eff = 0.5, bet.prior.eff = 0.5)` by default. `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`). `alp.eff.prior` and `bet.eff.prior`

represent the parameters of the Jeffreys' prior distribution for the efficacy probability at any dose level. This prior distribution is specified as Beta(`alpha.eff.prior`, `beta.eff.prior`).

`init.level` the dose level assigned to the first cohort. The default value `init.level` is 1.

`cohortsize` the number of patients in each cohort.

`ncohort` the total number of cohorts.

`nsimu` the total number of trials to be simulated.

`cutoff.eli` the cutoff to eliminate overly toxic doses for safety. We recommend the default value of `cutoff.eli` = `0.95` for general use.

`early.stop` the threshold value for early stopping due to overly toxic. The default value `early.stop` = `0.95` generally works well.

`effearly.stop` the threshold value for early stopping due to low efficacy. The trial would be terminated early if $Pr(q_k < \psi | y_k, m_k \geq 3)$ is smaller than the value of `effearly.stop` where q_k, y_k and m_k are the efficacy probability, the number of efficacy outcomes and the number of patients at dose level k. ψ is the the lowest acceptable efficacy rate which is set by `mineff` here. By default, `effearly.stop` is set as `0.9`.

`mineff` the lowest acceptable efficacy rate.

`seeds` a vector of random seeds for each simulation, for example, `seeds` = `1:nsimu` (default is `NULL`).

Value

The `CFOeff.oc()` function returns a list object, which includes the basic setup (`simu.setup`), comprising the following components:

- p.true: the true DLT rates under the different dose levels.
- pE.true: the true efficacy rates under the different dose levels.
- selpercent: the selection percentage at each dose level.
- npatients: the averaged number of patients treated at each dose level in one simulation.
- ntox: the averaged number of toxicity observed at each dose level in one simulation.
- neff: the averaged number of efficacy outcome at each dose level in one simulation.
- OBDsel: the percentage of correct selection of the OBD.
- OBDallo: the percentage of patients allocated to the OBD.
- averDLT: the percentage of the patients suffering DLT.
- avereff: the percentage of the patients with efficacy outcomes.
- percentstop: the percentage of early stopping without selecting the OBD.
- simu.setup: the parameters for the simulation set-up.
- class: the phase of the trial.

Note

In the example, we set `nsimu` = `3` for testing time considerations. In reality, `nsimu` is typically set as 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 12; nsimu = 3; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.oc (target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
summary(result)
plot(result)
#earlystop for overly tox
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 12; nsimu = 3; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.75, 0.77, 0.81, 0.82, 0.86)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.oc (target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
summary(result)
plot(result)

#earlystop for lower efficacy
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 20; nsimu = 3; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.001, 0.001, 0.001, 0.002, 0.003)
result <- CFOeff.oc (target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
summary(result)
plot(result)
```

`CFOeff.selectobd` *Select the optimal biological dose (OBD) for the real single-drug trials*

Description

Select the optimal biological dose (OBD) when the real single-drug trials is completed

Usage

```
CFOeff.selectobd(target, txs, tys, tns, prior.para, mineff, effearly.stop)
```

Arguments

target	the target DLT rate.
txs	the cumulative counts of efficacy outcomes at all dose levels.
tys	the cumulative counts of DLTs observed at all dose levels.
tns	the cumulative counts of patients treated at all dose levels.
prior.para	the prior parameters for two beta distributions, where set as list(alp.prior.eff = 0.5, bet.prior.eff = 0.5) by default. alp.eff.prior and bet.eff.priorrepresent the parameters of the Jeffreys' prior distribution for the efficacy probability at any dose level.This prior distribution is specified as Beta(alpha.eff.prior, beta.eff.prior).
mineff	the lowest acceptable efficacy rate.
effearly.stop	the threshold value for early stopping due to low efficacy. The trial would be terminated early if $Pr(q_k < \psi \mid y_k, m_k \geq 3)$ is smaller than the value of effearly.stop where q_k, y_k and m_k are the efficacy probability, the number of efficacy outcomes and the number of patients at dose level k. ψ is the the lowest acceptable efficacy rate which is set by mineff here. By default, effearly.stop is set as 0.9.

Value

The CFOeff.selectobd() function returns a list object comprising the following elements:

- OBD: the selected OBD. OBD = 99 indicates that all tested doses are overly toxic or having low efficacy.
- MTD: MTD here is get by using function CFO.selectmtd. MTD is used as the upper bound of the admissible set.
- OBD.probs: the probability that each dose level would be selected as OBD. The probability indicates that q_k corresponds to dose level k being the highest in the admissible set. q_k is efficacy probability correspond to dose level k here.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
target <- 0.3; mineff<- 0.3
txs <- c(3, 1, 7, 11, 26); tys <- c(0, 0, 0, 0, 6); tns <- c(6, 3, 12, 17, 36)
prior.para = list(alp.prior.eff = 0.5, bet.prior.eff = 0.5)
effearly.stop <- 0.95
result <- CFOeff.selectobd(target, txs, tys, tns, prior.para, mineff, effearly.stop)
summary(result)

##Low efficacy
target <- 0.3; mineff<- 0.3
txs = c(0, 0, 0, 0, 0); tys = c(2, 1, 1, 1, 6); tns = c(36, 23, 22, 27, 36)
prior.para = list(alp.prior.eff = 0.5, bet.prior.eff = 0.5)
effearly.stop <- 0.95
result <- CFOeff.selectobd(target, txs, tys, tns, prior.para, mineff, effearly.stop)
summary(result)


##High toxicity
target <- 0.3; mineff<- 0.3
txs = c(3, 1, 7, 11, 26); tys = c(36, 23, 22, 27, 36); tns = c(36, 23, 22, 27, 36)
prior.para = list(alp.prior.eff = 0.5, bet.prior.eff = 0.5)
effearly.stop <- 0.95
result <- CFOeff.selectobd(target, txs, tys, tns, prior.para, mineff, effearly.stop)
summary(result)
```

`CFOeff.simu` *Conduct one simulation using the calibration-free odds (CFO) design for phase I/II trials*

Description

In the CFO design for phase I/II trials, the function is used to conduct one single simulation and find the optimal biological dose (OBD).

Usage

```
CFOeff.simu(target, p.true, pE.true, ncohort=10, init.level=1,  cohortsize=3,
                  prior.para = list(alp.prior = target, bet.prior = 1 - target,
                   alp.prior.eff = 0.5, bet.prior.eff = 0.5),
                   cutoff.eli = 0.95, early.stop = 0.95,
                   effearly.stop = 0.9, mineff, seed = NULL)
```

Arguments

`target`	the target DLT rate.
`p.true`	the true DLT rates under the different dose levels.

pE.true	the true efficacy rates under the different dose levels.
ncohort	the total number of cohorts.
init.level	the dose level assigned to the first cohort. The default value of init.level is 1.
cohortsize	the number of patients of each cohort.
prior.para	the prior parameters for two beta distributions, where set as list(alp.prior = target, bet.prior = 1 - target, alp.prior.eff = 0.5, bet.prior.eff = 0.5) by default. alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior). alp.eff.prior and bet.eff.prior represent the parameters of the Jeffreys' prior distribution for the efficacy probability at any dose level. This prior distribution is specified as Beta(alpha.eff.prior, beta.eff.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping due to overly toxic. The default value early.stop = 0.95 generally works well.
effearly.stop	the threshold value for early stopping due to low efficacy. The trial would be terminated early if $Pr(q_k < \psi \mid y_k, m_k \geq 3)$ is smaller than the value of effearly.stop where q_k, y_k and m_k are the efficacy probability, the number of efficacy outcomes and the number of patients at dose level k. ψ is the the lowest acceptable efficacy rate which is set by mineff here. By default, effearly.stop is set as 0.9.
mineff	the lowest acceptable efficacy rate.
seed	an integer to be set as the seed of the random number generator for reproducible results. The default value is set to NULL.

Value

The CFOeff.simu function returns a list object comprising the following components:

- OBD: the selected OBD. OBD = 99 indicates that the simulation is terminated due to early stopping.
- target: the target DLT rate.
- npatients: the total number of patients allocated to all dose levels.
- neff: the total number of efficacy outcomes for all dose levels.
- ntox: the total number of DLTs observed for all dose levels.
- pE.true: the true efficacy rates under the different dose levels.
- p.true: the true DLT rates under the different dose levels.
- cohortdose: a vector including the dose level assigned to each cohort.
- ptoxic: the percentage of subjects assigned to dose levels with a DLT rate greater than the target.
- patientDLT: a vector including the DLT outcome observed for each patient.
- patienteff: a vector including the efficacy outcome observed for each patient.

- over.doses: a vector indicating whether each dose is overdosed or not (1 for yes).
- under.eff: a vector indicating whether the efficacy of each dose is lower than acceptable efficacy rate (1 for yes).
- correct: a binary indicator of whether the recommended dose level matches the correct OBD (1 for yes). The correct OBD is the dose level in the admissible set with the upper bound being the correct MTD, which has the highest true efficacy probability.
- OBDprob: the probability that each dose level would be selected as OBD. The probability indicates that q_k corresponds to dose level k being the highest in the admissible set. q_k is efficacy probability correspond to dose level k here.
- sumDLT: the total number of DLT observed.
- sumeff: the total number of efficacy outcome observed.
- earlystop: a binary indicator of whether the trial is early stopped (1 for yes).
- stopreason: the reason for earlystop. `overly_toxic` represents the trial was terminated beacuse all tested doses were overly toxic. `low_efficacy` represents the trial was terminated because all tested doses show low efficacy.
- class: the phase of the trial.

Note

The `CFOeff.simu` function is designed to conduct a single CFO simulation for phase I/II trials. The dose elimination rule is the same as the case in phase I (refer to the function `CFO.simu`). As for early stopping rule, compared to the case of phase I, the rule in this case further considers the efficacy data to terminate the trial early if none of the admissible dose levels show adequate efficacious effect.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 20; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
                      prior.para, mineff = mineff, seed = 1)
summary(result)
plot(result)
### overly toxic
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 20; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
```

```
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.55, 0.57, 0.61, 0.62, 0.66)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
                      prior.para, mineff = mineff, seed = 1)
summary(result)
plot(result)

### low efficacy
target <- 0.30; mineff <- 0.30; cohortsize = 3; ncohort = 20; init.level = 1
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.001, 0.003, 0.004, 0.005, 0.006)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
                      prior.para, mineff = mineff, seed = 1)
summary(result)
plot(result)
```

`gammatable` *Generating table of threshold γ_L and γ_R in the calibration-free odds (CFO) design*

Description

Generate all the possible thresholds under different m_C, m_L and m_R

Usage

```
gammatable(npatient, target,
           para.prior = list(alp.prior = target, bet.prior = 1 - target))
```

Arguments

`npatient`	the numbers of patients involved in the trial.
`target`	the target DLT rate.
`para.prior`	the prior parameters for a beta distribution, where set as `list(alp.prior = target, bet.prior = 1 - target)` by default, `alp.prior` and `bet.prior` represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(`alpha.prior`, `beta.prior`).

Value

The `gammatable()` function returns a list object comprising the following elements:

- gammatb.left: the table of threshold γ_L under different m_L and m_C where m_C and m_L represent the number of patients at current dose level and left dose level.
- gammatb.right: the table of threshold γ_R under different m_R and m_C where m_C and m_R represent the number of patients at current dose level and right dose level.

Note

This function generate two matrices. `gammatb.left` contains the threshold γ_L, and `gammatb.right` contains the threhold γ_R. For matrix `gammatb.left`, the row index represent the number of patients at left dose level, and the column index represent the number of patients at current dose level. For matrix `gammatb.right`, the row index represent the number of patients at right dose level, and the column index represent the number of patients at current dose level. For example, if you want to get the threshold γ_L in the case of $m_C = 12, m_L = 13$, you can reach it by `result$gammatb.left[13,12]`

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
npatient <- 3; target <- 0.3
para.prior = list(alp.prior = target, bet.prior = 1 - target)
result <- gammatable(npatient, target, para.prior)
plot(result)
#This example may cost you a long time to run
npatient <- 30; target <- 0.3
para.prior = list(alp.prior = target, bet.prior = 1 - target)
result <- gammatable(npatient, target, para.prior)
plot(result)
```

---

lateonset.next *Determination of the dose level for next cohort in the calibration-free odds type (CFO-type) design with late-onset toxicity for phase I trials*

Description

Based on the toxicity outcomes of the enrolled cohorts, the function is used to determine the next dose level in the CFO-type designs with late-onset toxicity for phase I trials, specifically, including time-to-event CFO (TITE-CFO) design, fractional CFO (fCFO) design, benchmark CFO design, time-to-event accumulative CFO (TITE-aCFO) design, fractional aCFO (f-aCFO) design, and benchmark aCFO design.

Usage

```
lateonset.next(design, target, ndose, currdose, assess.window, enter.times, dlt.times,
    current.t, doses, prior.para = list(alp.prior = target, bet.prior = 1 - target),
      cutoff.eli = 0.95, early.stop = 0.95)
```

Arguments

design	option for selecting different designs, which can be set as 'TITE-CFO', 'TITE-aCFO', 'fCFO', 'f-aCFO', 'bCFO', and 'b-aCFO'. Specifically, 'bCFO' refers to the benchmark CFO design, and 'b-aCFO' denotes the benchmark aCFO design.
target	the target DLT rate.
ndose	the number of dose levels.
currdose	the current dose level.
assess.window	the maximal assessment window size.
enter.times	the time that each participant enters the trial.
dlt.times	the time to DLT for each subject in the trial. If no DLT occurs for a subject, dlt.times is set to 0.
current.t	the current time.
doses	the dose level for each subject in the trial.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.

Details

Late-onset outcomes commonly occur in phase I trials involving targeted agents or immunotherapies. The TITE framework and fractional framework serve as two imputation methods to handle pending data related to late-onset outcomes. This approach extends the CFO, and aCFO designs to integrate time information for delayed outcomes, leading to the development of TITE-CFO, fCFO, TITE-aCFO, and f-aCFO designs.
In the TITE framework context, an assumption about the distribution of time to DLT must be prespecified, whereas the fractional framework does not require justification for a specific distribution of the time to DLT. Consequently, fCFO, and f-aCFO adapt to a more diverse range of scenarios.
The function lateonset.next() also provides the option to execute the benchmark CFO and aCFO designs. These three methods await complete observation of toxicity outcomes for the previous cohorts before determining the next dose assignment. This enhances precision but comes at the expense of a prolonged trial duration.

Value

The lateonset.next() function returns

- target: the target DLT rate.
- decision: the decision in the CFO design, where left, stay, and right represent the movement directions, and stop indicates stopping the experiment.
- currdose: the current dose level.

- nextdose: the recommended dose level for the next cohort.
- overtox: the situation regarding which position experiences over-toxicity. The dose level indicated by `overtox` and all the dose levels above experience over-toxicity. `overtox = NA` signifies that the occurrence of over-toxicity did not happen.
- over.doses: a vector indicating whether the dose level (from the first to last dose level) is over-toxic or not (1 for yes).
- toxprob: the expected toxicity probability, $Pr(p_k > \phi | x_k, m_k)$, at all dose levels, where p_k, x_k, and m_k is the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k. `NA` indicates that there are no patients at the corresponding dose level.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Jin H, Yin G (2023). Time-to-event calibration-free odds design: A robust efficient design for phase I trials with late-onset outcomes. *Pharmaceutical Statistics*, 22(5), 773–783.
Yin G, Zheng S, Xu J (2013). Fractional dose-finding methods with late-onset toxicity in phase I clinical trials. *Journal of Biopharmaceutical Statistics*, 23(4), 856-870.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*.

Examples

```
target <- 0.2; ndose <- 7
enter.times<- c(0, 0.266, 0.638, 1.54, 2.48, 3.14, 3.32, 4.01, 4.39, 5.38, 5.76,
                6.54, 6.66, 6.93, 7.32, 7.66, 8.14, 8.74)
dlt.times<- c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0.610, 0, 2.98, 0, 0, 1.95, 0, 0, 1.48)
current.t<- 9.41
doses<-c(1, 1, 1, 2, 2, 2, 3, 3, 3, 4, 4, 4, 3, 3, 3, 4, 4, 4)
## determine the dose level for the next cohort using the TITE-CFO design
decision <- lateonset.next(design = 'TITE-CFO', target, ndose, currdose = 4, assess.window = 3,
                enter.times, dlt.times, current.t, doses)
summary(decision)
## determine the dose level for the next cohort using the TITE-aCFO design
decision <- lateonset.next(design = 'TITE-aCFO', target, ndose, currdose = 4, assess.window = 3,
                enter.times, dlt.times, current.t, doses)
summary(decision)
## determine the dose level for the next cohort using the f-CFO design
decision <- lateonset.next(design = 'fCFO', target, ndose, currdose = 4, assess.window = 3,
                enter.times, dlt.times, current.t, doses)
summary(decision)
## determine the dose level for the next cohort using the f-aCFO design
decision <- lateonset.next(design = 'f-aCFO', target, ndose, currdose = 4, assess.window = 3,
                enter.times, dlt.times, current.t, doses)
summary(decision)
```

```
## determine the dose level for the next cohort using the benchmark CFO design
decision <- lateonset.next(design = 'bCFO', target, ndose, currdose = 4, assess.window = 3,
               enter.times, dlt.times, current.t, doses)
summary(decision)
## determine the dose level for the next cohort using the benchmark aCFO design
decision <- lateonset.next(design='b-aCFO', target, ndose, currdose = 4, assess.window = 3,
               enter.times, dlt.times, current.t, doses)
summary(decision)
```

`lateonset.simu` *Conduct one simulation using the calibration-free odds type (CFO-type) design with late-onset toxicity for phase I trials.*

Description

Based on the toxicity outcomes of the enrolled cohorts, the function is used to conduct one single simulation and find the maximum tolerated dose (MTD) for the CFO-type designs with late-onset toxicities for phase I trials, specifically, including time-to-event CFO (TITE-CFO) design, fractional CFO (fCFO) design, benchmark CFO design, time-to-event accumulative CFO (TITE-aCFO) design, fractional aCFO (f-aCFO) design, and benchmark aCFO design.

Usage

```
lateonset.simu(design, target, p.true, init.level = 1, ncohort, cohortsize,
       assess.window, tte.para, accrual.rate, accrual.dist,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, seed = NULL)
```

Arguments

`design`	option for selecting different designs, which can be set as `'TITE-CFO'`, `'TITE-aCFO'`, `'fCFO'`, `'f-aCFO'`, `'bCFO'`, and `'b-aCFO'`. Specifically, `'bCFO'` refers to the benchmark CFO design and `'b-aCFO'` denotes the benchmark aCFO design.
`target`	the target DLT rate.
`p.true`	the true DLT rates under the different dose levels.
`init.level`	the dose level assigned to the first cohort. The default value `init.level` is 1.
`ncohort`	the total number of cohorts.
`cohortsize`	the number of patients of each cohort.
`assess.window`	the maximal assessment window size.
`tte.para`	the parameter related with the distribution of the time to DLT events. The time to DLT is sampled from a Weibull distribution, with `tte.para` representing the proportion of DLTs occurring within the first half of the assessment window.
`accrual.rate`	the accrual.rate rate, i.e., the number of patients accrued per unit time.

accrual.dist	the distribution of the arrival times of patients. When accrual.dist = 'fix', it corresponds to all patients in each cohort arriving simultaneously at a given accrual rate. When accrual.dist = 'unif', it corresponds to a uniform distribution, and when accrual.dist = 'exp', it corresponds to an exponential distribution.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seed	an integer to set as the seed of the random number generator for reproducible results. The default value is set to NULL.

Value

The lateonset.simu() function returns a list object comprising the following components:

- target: the target DLT rate.
- MTD: the selected MTD. MTD = 99 indicates that this trial is terminated due to early stopping.
- correct: a binary indicator of whether the recommended dose level matches the correct MTD (1 for yes). The correct MTD is the dose level at which the true DLT rate is closest to the target DLT rate.
- npatients: the total number of patients allocated to all dose levels
- ntox: the total number of DLTs observed for all dose levels.
- over.doses: a vector indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: a vector including the dose level assigned to each cohort.
- ptoxic: the percentage of subjects assigned to dose levels with a DLT rate greater than the target.
- patientDLT: a vector including the DLT outcome observed for each patient.
- sumDLT: the total number of DLT observed.
- earlystop: a binary indicator of whether the trial is early stopped (1 for yes).
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval. p_est = NA if all tested doses are overly toxic.
- p_overdose: p_overdose: the probability of overdosing defined as $Pr(toxicity >$ target$|data)$. p_overdose = NA if all tested doses are overly toxic.
- totaltime: the duration of the trial.
- entertimes: the time that each participant enters the trial.
- DLT.times: the time to DLT for each subject in the trial. If no DLT occurs for a certain subject, DLT.times is 0.

Note

The early stopping and dose elimination rules are incorporated into the design to ensure patient safety and benefit.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.
Jin H, Yin G (2023). Time-to-event calibration-free odds design: A robust efficient design for phase I trials with late-onset outcomes. *Pharmaceutical Statistics*. 22(5), 773–783.
Yin G, Zheng S, Xu J (2013). Fractional dose-finding methods with late-onset toxicity in phase I clinical trials. *Journal of Biopharmaceutical Statistics*, 23(4), 856-870.
Fang J, Yin G (2024). Fractional accumulative calibration-free odds (f-aCFO) design for delayed toxicity in phase I clinical trials. *Statistics in Medicine*.

Examples

```
target <- 0.2; ncohort <- 12; cohortsize <- 3; init.level <- 1
p.true <- c(0.01, 0.07, 0.20, 0.35, 0.50, 0.65, 0.80)
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'
## find the MTD for a single TITE-CFO simulation
TITECFOtrial <- lateonset.simu (design = 'TITE-CFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(TITECFOtrial)
plot(TITECFOtrial)
## find the MTD for a single TITE-aCFO simulation
TITEaCFOtrial <- lateonset.simu (design = 'TITE-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(TITEaCFOtrial)
plot(TITEaCFOtrial)
## find the MTD for a single fCFO simulation
fCFOtrial <- lateonset.simu (design = 'fCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(fCFOtrial)
plot(fCFOtrial)
## find the MTD for a single f-aCFO simulation
faCFOtrial <- lateonset.simu (design = 'f-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(faCFOtrial)
plot(faCFOtrial)
```

pCFO.next *Determination of the dose level for next cohort in the precision calibration-free odds (pCFO) design for phase I trials*

Description

In the pCFO design for phase I trials, the function is used to determine the dose movement based on the toxicity outcomes of the enrolled cohorts.

Usage

```
pCFO.next(target, cys, cns, currdose,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95)
```

Arguments

target	the target DLT rate.
cys	the cumulative numbers of DLTs observed at the left, current, and right dose levels.
cns	the cumulative numbers of patients treated at the left, current, and right dose levels.
currdose	the current dose level.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.

Value

The pCFO.next() function returns a list object comprising the following elements:

- target: the target DLT rate.
- cys: the cumulative counts of DLTs observed at the left, current, and right dose levels.
- cns: the cumulative counts of patients treated at the left, current, and right dose levels.
- decision: the decision in the pCFO design, where left, stay, and right represent the movement directions, and stop indicates stopping the experiment.
- currdose: the current dose level.
- nextdose: the recommended dose level for the next cohort. nextdose = 99 indicates that the trial is terminated due to early stopping.

- overtox: the situation regarding which positions experience over-toxicity. The dose level indicated by `overtox` and all the dose levels above experience over-toxicity. `overtox = NA` signifies that the occurrence of over-toxicity did not happen.
- toxprob: the expected toxicity probability, $Pr(p_k > \phi | x_k, m_k)$, at the left, current, and right dose levels, where p_k, x_k, and m_k is the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k. `NA` indicates that there are no patients at the corresponding dose level.

Note

When the current dose level is the lowest or highest (i.e., at the boundary), the parts in `cys` and `cns` where there is no data are filled with `NA`.
The dose level indicated by `overtox` and all the dose levels above experience over-toxicity, and these dose levels will be eliminated.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
## determine the dose level for the next cohort of new patients
cys <- c(0, 1, 0); cns <- c(3, 6, 0)
decision <- pCFO.next(target=0.2, cys=cys, cns=cns, currdose=3)
summary(decision)

cys <- c(NA, 3, 0); cns <- c(NA, 3, 0)
decision <- pCFO.next(target=0.2, cys=cys, cns=cns, currdose=1)
summary(decision)

cys <- c(0, 3, NA); cns <- c(3, 3, NA)
decision <- pCFO.next(target=0.2, cys=cys, cns=cns, currdose=7)
summary(decision)
```

---

plot.cfo *Plot the results by other functions*

Description

Plot the objects returned by other functions, including (1) dose allocation of a single trial; (2) the estimate of toxicity probability for each dose and corresponding 95% credible interval; (3) operating characteristics of multiple simulations, including MTD selection percentage, the averaged number of patients allocated to different doses in one simulation and the averaged number of DLT observed for different doses in one simulation.

Usage

```
## S3 method for class 'cfo'
plot(x, ..., name = deparse(substitute(x)))
```

Arguments

x	the object returned by other functions
...	ignored arguments
name	the name of the object to be plotted. User does not need to input this parameter.

Value

plot() returns a figure or a series of figures depending on the object entered.

Note

In the example, we set nsimu = 5 for testing time considerations. In reality, nsimu is typically set to 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

Examples

```
## settings for 1dCFO
nsimu <- 5; ncohort <- 12; cohortsize <- 3; init.level <- 1
p.true <- c(0.02, 0.05, 0.20, 0.28, 0.34, 0.40, 0.44); target <- 0.2
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'

## plot the object returned by CFO.simu()
CFOtrial <- CFO.simu(design = 'CFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
plot(CFOtrial)

## plot the object returned by CFO.selectmtd()
selmtd <- CFO.selectmtd(target=0.2, npts=c(3,3,27,3,0,0,0), ntox=c(0,0,4,2,0,0,0))
plot(selmtd)


# This test may take longer than 5 seconds to run
# It is provided for illustration purposes only
# Users can run this code directly

## plot the object returned by lateonset.simu()
## f-aCFO design
faCFOtrial <- lateonset.simu (design = 'f-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
plot(faCFOtrial)

## summarize the object returned by CFO.oc()
```

```
faCFOoc <- CFO.oc (nsimu, design = 'f-aCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
plot(faCFOoc)

## settings for 2dCFO
p.true <- matrix(c(0.05, 0.10, 0.15, 0.30, 0.45,
                   0.10, 0.15, 0.30, 0.45, 0.55,
                   0.15, 0.30, 0.45, 0.50, 0.60),
                 nrow = 3, ncol = 5, byrow = TRUE)
target <- 0.3; ncohort <- 12; cohortsize <- 3

## plot the single simulation returned by CFO2d.simu()
CFO2dtrial <- CFO2d.simu(target, p.true, init.level = c(1,1), ncohort, cohortsize, seed = 1)
plot(CFO2dtrial)

## plot the multiple simulation returned by CFO2d.oc()
CFO2doc <- CFO2d.oc(nsimu = 5, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:5)
plot(CFO2doc)

## select a MTD based on the trial data
ntox <- matrix(c(0, 0, 2, 0, 0, 0, 2, 7, 0, 0, 0, 2, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
npts <- matrix(c(3, 0, 12, 0, 0, 3, 12, 24, 0, 0, 3, 3, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
selmtd <- CFO2d.selectmtd(target=0.3, npts=npts, ntox=ntox)
plot(selmtd)

## summarize the object returned by CFOeff.next()
decision <- CFOeff.next(target=0.4,axs=c(3,1,7,11,26),ays=c(0,0,0,0,6),
              ans= c(6, 3, 12, 17, 36), currdose = 3, mineff = 0.3)
plot(decision)

## summarize the object returned by CFOeff.simu()
target <- 0.30; mineff <- 0.30
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
                      prior.para, mineff = mineff, seed = 1)
plot(result)

## summarize the object returned by CFOeff.oc()
nsimu = 10
result <- CFOeff.oc(target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
plot(result)
```

print.cfo *Generate descriptive summary for objects returned by other functions*

Description

Generate descriptive summary for objects returned by other functions.

Usage

```
## S3 method for class 'cfo'
print(x, ...)
```

Arguments

x	the object returned by other functions
...	ignored arguments

Details

print() prints the objects returned by other functions.

Value

print() prints the objects returned by other functions.

Note

In the example, we set nsimu = 5 for testing time considerations. In reality, nsimu is typically set to 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

Examples

```
## settings for 1dCFO
nsimu <- 5; ncohort <- 12; cohortsize <- 3; init.level <- 1
p.true <- c(0.02, 0.05, 0.20, 0.28, 0.34, 0.40, 0.44); target <- 0.2
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'

## summarize the object returned by CFO.next()
decision <- CFO.next(target = 0.2, cys = c(0, 1, 0), cns = c(3, 6, 0), currdose = 3)
print(decision)

## summarize the object returned by lateonset.next()
enter.times<- c(0, 0.266, 0.638, 1.54, 2.48, 3.14, 3.32, 4.01, 4.39, 5.38, 5.76,
                6.54, 6.66, 6.93, 7.32, 7.65, 8.14, 8.74)
dlt.times<- c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0.995, 0, 0, 0, 0, 0, 0, 0, 2.58)
current.t<- 9.41; ndose = 7
```

```
doses<-c(1, 1, 1, 2, 2, 2, 3, 3, 3, 4, 4, 4, 3, 3, 3, 4, 4, 4)
decision <- lateonset.next(design = 'f-aCFO', target, ndose, currdose = 4, assess.window,
               enter.times, dlt.times, current.t, doses)
print(decision)

## summarize the object returned by CFO.selectmtd()
selmtd <- CFO.selectmtd(target=0.2, npts=c(3,3,27,3,0,0,0), ntox=c(0,0,4,2,0,0,0))
print(selmtd)

## summarize the object returned by CFO.simu()
aCFOtrial <- CFO.simu(design = 'aCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
print(aCFOtrial)



# This test may take longer than 5 seconds to run
# It is provided for illustration purposes only
# Users can run this code directly

## summarize the object returned by lateonset.simu()
faCFOtrial <- lateonset.simu (design = 'f-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
print(faCFOtrial)

## summarize the object returned by CFO.oc()
faCFOoc <- CFO.oc (nsimu, design = 'f-aCFO', target, p.true, init.level, ncohort, cohortsize,
                   assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
print(faCFOoc)

## settings for 2dCFO
p.true <- matrix(c(0.05, 0.10, 0.15, 0.30, 0.45,
0.10, 0.15, 0.30, 0.45, 0.55,
0.15, 0.30, 0.45, 0.50, 0.60),
nrow = 3, ncol = 5, byrow = TRUE)

cns <- matrix(c(3, 3, 0,
                0, 6, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
cys <- matrix(c(0, 1, 0,
                0, 2, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
currdose <- c(2,3); target <- 0.3; ncohort <- 12; cohortsize <- 3

## summarize the object returned by CFO2d.next()
decision <- CFO2d.next(target, cys, cns, currdose = currdose, seed = 1)
print(decision)

## summarize the object returned by CFO2d.selectmtd()
ntox <- matrix(c(0, 0, 2, 0, 0, 0, 2, 7, 0, 0, 0, 2, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
npts <- matrix(c(3, 0, 12, 0, 0, 3, 12, 24, 0, 0, 3, 3, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
selmtd <- CFO2d.selectmtd(target=0.3, npts=npts, ntox=ntox)
```

```
print(selmtd)

## summarize the object returned by CFO2d.simu()
CFO2dtrial <- CFO2d.simu(target, p.true, init.level = c(1,1), ncohort, cohortsize, seed = 1)
print(CFO2dtrial)

## summarize the object returned by CFO2d.oc()
CFO2doc <- CFO2d.oc(nsimu = 5, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:5)
print(CFO2doc)

## summarize the object returned by CFOeff.next()
decision <- CFOeff.next(target=0.4,axs=c(3,1,7,11,26),ays=c(0,0,0,0,6),
              ans= c(6, 3, 12, 17, 36), currdose = 3, mineff = 0.3)
print(decision)

## summarize the object returned by CFOeff.simu()
target <- 0.30; mineff <- 0.30
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
                      prior.para, mineff = mineff, seed = 1)
print(result)

## summarize the object returned by CFOeff.oc()
nsimu = 10
result <- CFOeff.oc(target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
print(result)
```

`rCFO.next` *Determination of the dose level for next cohort in the randomized calibration-free odds (rCFO) design for phase I trials*

Description

In the rCFO design for phase I trials, the function is used to determine the dose movement based on the toxicity outcomes of the enrolled cohorts.

Usage

```
rCFO.next(target, cys, cns, currdose,
       prior.para = list(alp.prior = target, bet.prior = 1 - target),
       cutoff.eli = 0.95, early.stop = 0.95, seed)
```

Arguments

target	the target DLT rate.
cys	the cumulative numbers of DLTs observed at the left, current, and right dose levels.
cns	the cumulative numbers of patients treated at the left, current, and right dose levels.
currdose	the current dose level.
prior.para	the prior parameters for a beta distribution, where set as list(alp.prior = target, bet.prior = 1 - target) by default, alp.prior and bet.prior represent the parameters of the prior distribution for the true DLT rate at any dose level. This prior distribution is specified as Beta(alpha.prior, beta.prior).
cutoff.eli	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of cutoff.eli = 0.95 for general use.
early.stop	the threshold value for early stopping. The default value early.stop = 0.95 generally works well.
seed	an integer to be set as the seed of the random number generator for reproducible results. The default value is set to NULL.

Details

The original CFO design makes deterministic dose movement by constructing two odds ratios, $\pi_L = O_C/\overline{O}_L$ and $\pi_R = \overline{O}_C/O_R$, and comparing them against thresholds γ_L and γ_R, respectively. The rCFO design introduces a randomization scheme, normalizes odds ratios, π_L, and π_R into probabilities, and constructs probabilities for dose escalation, de-escalation, and staying at the same dose.

Value

The rCFO.next() function returns a list object comprising the following elements:

- target: the target DLT rate.
- cys: the cumulative counts of DLTs observed at the left, current, and right dose levels.
- cns: the cumulative counts of patients treated at the left, current, and right dose levels.
- decision: the decision in the CFO design, where left, stay, and right represent the movement directions, and stop indicates stopping the experiment.
- currdose: the current dose level.
- nextdose: the recommended dose level for the next cohort. nextdose = 99 indicates that the trial is terminated due to early stopping.
- overtox: the situation regarding which positions experience over-toxicity. The dose level indicated by overtox and all the dose levels above experience over-toxicity. overtox = NA signifies that the occurrence of over-toxicity did not happen.
- toxprob: the expected toxicity probability, $Pr(p_k > \phi | x_k, m_k)$, at the left, current, and right dose levels, where p_k, x_k, and m_k is the dose-limiting toxicity (DLT) rate, the numbers of observed DLTs, and the numbers of patients at dose level k. NA indicates that there are no patients at the corresponding dose level.

Note

When the current dose level is the lowest or highest (i.e., at the boundary), the parts in `cys` and `cns` where there is no data are filled with `NA`.
The dose level indicated by `overtox` and all the dose levels above experience over-toxicity, and these dose levels will be eliminated.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

References

Jin H, Yin G (2022). CFO: Calibration-free odds design for phase I/II clinical trials. *Statistical Methods in Medical Research*, 31(6), 1051-1066.

Examples

```
## determine the dose level for the next cohort of new patients
cys <- c(0, 1, 0); cns <- c(3, 6, 0)
decision <- rCFO.next(target=0.2, cys=cys, cns=cns, currdose=3)
summary(decision)

cys <- c(NA, 3, 0); cns <- c(NA, 3, 0)
decision <- rCFO.next(target=0.2, cys=cys, cns=cns, currdose=1)
summary(decision)

cys <- c(0, 3, NA); cns <- c(3, 3, NA)
decision <- rCFO.next(target=0.2, cys=cys, cns=cns, currdose=7)
summary(decision)
```

---

summary.cfo *Generate descriptive summary for objects returned by other functions*

Description

Generate descriptive summary for objects returned by other functions.

Usage

```
## S3 method for class 'cfo'
summary(object, ...)
```

Arguments

`object`	the object returned by other functions.
`...`	ignored arguments

Value

`summary()` prints the objects returned by other functions.

Note

In the example, we set `nsimu = 5` for testing time considerations. In reality, `nsimu` is typically set to 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, Ninghao Zhang, Wenliang Wang, and Guosheng Yin

Examples

```
## settings for 1dCFO
nsimu <- 5; ncohort <- 12; cohortsize <- 3; init.level <- 1
p.true <- c(0.02, 0.05, 0.20, 0.28, 0.34, 0.40, 0.44); target <- 0.2
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'

## summarize the object returned by CFO.next()
decision <- CFO.next(target = 0.2, cys = c(0, 1, 0), cns = c(3, 6, 0), currdose = 3)
summary(decision)

## summarize the object returned by lateonset.next()
enter.times<- c(0, 0.266, 0.638, 1.54, 2.48, 3.14, 3.32, 4.01, 4.39, 5.38, 5.76,
               6.54, 6.66, 6.93, 7.32, 7.65, 8.14, 8.74)
dlt.times<- c(0, 0, 0, 0, 0, 0, 0, 0, 0, 0.995, 0, 0, 0, 0, 0, 0, 0, 2.58)
current.t<- 9.41; ndose<-7
doses<-c(1, 1, 1, 2, 2, 2, 3, 3, 3, 4, 4, 4, 3, 3, 3, 4, 4, 4)
decision <- lateonset.next(design = 'f-aCFO', target, ndose, currdose = 4, assess.window,
               enter.times, dlt.times, current.t, doses)
summary(decision)

## summarize the object returned by CFO.selectmtd()
selmtd <- CFO.selectmtd(target=0.2, npts=c(3,3,27,3,0,0,0), ntox=c(0,0,4,2,0,0,0))
summary(selmtd)

## summarize the object returned by CFO.simu()
aCFOtrial <- CFO.simu(design = 'aCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
summary(aCFOtrial)



# This test may take longer than 5 seconds to run
# It is provided for illustration purposes only
# Users can run this code directly

## summarize the object returned by lateonset.simu()
faCFOtrial <- lateonset.simu (design = 'f-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(faCFOtrial)
```

```
## summarize the object returned by CFO.oc()
faCFOoc <- CFO.oc (nsimu, design = 'f-aCFO', target, p.true, init.level, ncohort, cohortsize,
                   assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(faCFOoc)

## settings for 2dCFO
p.true <- matrix(c(0.05, 0.10, 0.15, 0.30, 0.45,
0.10, 0.15, 0.30, 0.45, 0.55,
0.15, 0.30, 0.45, 0.50, 0.60),
nrow = 3, ncol = 5, byrow = TRUE)

cns <- matrix(c(3, 3, 0,
                0, 6, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
cys <- matrix(c(0, 1, 0,
                0, 2, 0,
                0, 0, 0),
              nrow = 3, ncol = 3, byrow = TRUE)
currdose <- c(2,3); target <- 0.3; ncohort <- 12; cohortsize <- 3

## summarize the object returned by CFO2d.next()
decision <- CFO2d.next(target, cys, cns, currdose = currdose, seed = 1)
summary(decision)

## summarize the object returned by CFO2d.selectmtd()
ntox <- matrix(c(0, 0, 2, 0, 0, 0, 2, 7, 0, 0, 0, 2, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
npts <- matrix(c(3, 0, 12, 0, 0, 3, 12, 24, 0, 0, 3, 3, 0, 0, 0), nrow = 3, ncol = 5, byrow = TRUE)
selmtd <- CFO2d.selectmtd(target=0.3, npts=npts, ntox=ntox)
summary(selmtd)

## summarize the object returned by CFO2d.simu()
CFO2dtrial <- CFO2d.simu(target, p.true, init.level = c(1,1), ncohort, cohortsize, seed = 1)
summary(CFO2dtrial)

## summarize the object returned by CFO2d.oc()
CFO2doc <- CFO2d.oc(nsimu = 5, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:5)
summary(CFO2doc)

## summarize the object returned by CFOeff.next()
decision <- CFOeff.next(target=0.4,axs=c(3,1,7,11,26),ays=c(0,0,0,0,6),
              ans= c(6, 3, 12, 17, 36), currdose = 3, mineff = 0.3)
summary(decision)

## summarize the object returned by CFOeff.simu()
target <- 0.30; mineff <- 0.30
prior.para = list(alp.prior = target, bet.prior = 1 - target,
                  alp.prior.eff = 0.5, bet.prior.eff = 0.5)
p.true=c(0.05, 0.07, 0.1, 0.12, 0.16)
pE.true=c(0.35, 0.45, 0.5, 0.55, 0.75)
result <- CFOeff.simu(target, p.true, pE.true, ncohort, init.level, cohortsize,
```

```
                        prior.para, mineff = mineff, seed = 1)
summary(result)

## summarize the object returned by CFOeff.oc()
nsimu = 10
result <- CFOeff.oc(target, p.true, pE.true, prior.para,
          init.level,cohortsize, ncohort, nsimu, mineff = mineff, seeds = 1:nsimu)
summary(result)
```

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