R documentation

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R topics documented:

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

Description

In the aCFO design, 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.

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, 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
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*

Description

In the CFO design, 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:

- taget: 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.

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, 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 sigle-drug trials in multiple simulations*

Description

This function is used to perform multiple simulations for 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'`, `'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 prespecified 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 = 100 for testing time considerations. In reality, nsimu is typically set to 5000 to ensure the accuracy of the results.

Author(s)

Jialu Fang, 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.

Examples

```
## setting
nsimu <- 100; 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)
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 100 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 100 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 100 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 100 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 100 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)
## get the operating characteristics for 100 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)
## get the operating characteristics for 100 simulations using the bCFO design
bCFOoc <- CFO.oc (nsimu, design = 'bCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(bCFOoc)
plot(bCFOoc)
## get the operating characteristics for 100 simulations using the b-aCFO design
baCFOoc <- CFO.oc (nsimu, design = 'b-aCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
summary(baCFOoc)
plot(baCFOoc)
```

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

Description

Select the maximum tolerated dose (MTD) when the real single-drug trial 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.
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval.
- p_overdose: the probability of overdosing defined as $Pr(toxicity > \texttt{target}|data)$

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, 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). lgorithm AS 206: Isotonic regression in two independent variables. *Journal of the Royal Statistical Society. Series C (Applied Statistics)*, 33(3), 352–357.

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) or accumulative CFO (aCFO) design.*

Description

In the CFO and aCFO designs, 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'` and `'aCFO'`.
`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 target DLT rate (1 for yes).
- npatients: the total number of patients allocated for all dose levels.
- ntox: the total number of DLTs observed for all dose levels.
- npercent: the percentage of subjects assigned to the target DLT rate.
- over.doses: a vector indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: a vector including the dose level assigned for 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).

Note

The CFO.simu() function is designed to conduct a single CFO or aCFO simulation. If design = 'CFO', it corresponds to the CFO design. If design = 'aCFO', it corresponds to the aCFO design. The early stopping and dose elimination rules are incorporated into the CFO or aCFO design 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, 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 <- 0.2; 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)
### 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)
```

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

Description

This function is used to determine the next dose level for the next cohort in the 2dCFO design.

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 for 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 for 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, 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)
```

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

Description

This function is used to conduct multiple simulations of 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 for 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 = 100` 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, 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 100 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 <- 20; cohortsize <- 3
CFO2doc <- CFO2d.oc(nsimu = 100, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:100)
summary(CFO2doc)
plot(CFO2doc)
```

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

Description

Select the maximum tolerated dose (MTD) when the real drug combination trial 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.
- p_est: the isotonic estimate of the DLT probablity at each dose and associated 95% credible interval.
- p_est_CI: the credible interval for the isotonic estimate.

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, 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). lgorithm 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.*

Description

In the 2dCFO design, 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 target DLT rate (1 for yes).
- npatients: a matrix of the number of patients allocated for different doses.
- ntox: a matrix of the number of DLT observed for different doses.
- npercent: the percentage of patients assigned to the target DLT rate.
- over.doses: a matrix indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: the dose combination assigned for 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).

Author(s)

Jialu Fang, 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)
```

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

Description

The function is used to determine the next dose level in the CFO-type design with late-onset toxicity, 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 accumulative CFO (f-aCFO) design and benchmark aCFO design.

Usage

```
lateonset.next(design, target, p.true, 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.
`p.true`	the true DLT rates under the different 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 pre-specified, 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 benchmark aCFO design. These two 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).

Author(s)

Jialu Fang, 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.

Examples

```
target <- 0.2; p.true <- c(0.01, 0.07, 0.20, 0.35, 0.50, 0.65, 0.80)
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, p.true, 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, p.true, 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, p.true, 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, p.true, 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, p.true, 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, p.true, 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.*

Description

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, 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 accumulative CFO (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 target DLT rate (1 for yes).
- npatients: the total number of patients allocated for all dose levels
- ntox: the total number of DLTs observed for all dose levels.
- npercent: the percentage of subjects assigned to the target DLT rate.
- over.doses: a vector indicating whether each dose is overdosed or not (1 for yes).
- cohortdose: a vector including the dose level assigned for 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).
- 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, 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.

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)
## find the MTD for a single benchmark CFO simulation
bCFOtrial <- lateonset.simu (design = 'bCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(bCFOtrial)
plot(bCFOtrial)
## find the MTD for a single benchmark aCFO simulation
baCFOtrial <- lateonset.simu (design = 'b-aCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
summary(baCFOtrial)
plot(baCFOtrial)
```

---

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 selesction percentage, the averaged number of patients allocated for 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 doesn't need to input this parameter.

Value

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

Author(s)

Jialu Fang, Wenliang Wang, and Guosheng Yin

Examples

```
###### single-drug trial ######

############design without late-onset outcomes################
nsimu <- 100; 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
## CFO design
CFOtrial <- CFO.simu(design = 'CFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
plot(CFOtrial)

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)
plot(CFOoc)
## aCFO design
aCFOtrial <- CFO.simu(design = 'aCFO', target, p.true, init.level, ncohort, cohortsize, seed = 1)
plot(aCFOtrial)
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)
plot(aCFOoc)


###############design with late-onset outcomes################
assess.window <- 3; accrual.rate <- 2; tte.para <- 0.5; accrual.dist <- 'unif'
## TITE-CFO design
 TITECFOtrial <- lateonset.simu (design = 'TITE-CFO', target, p.true, init.level,
           ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
plot(TITECFOtrial)
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)
plot(TITECFOoc)
## TITE-aCFO design
TITEaCFOtrial <- lateonset.simu (design = 'TITE-aCFO', target, p.true, init.level,
           ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
plot(TITEaCFOtrial)
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)
```

```
plot(TITEaCFOoc)
## fCFO design
fCFOtrial <- lateonset.simu (design = 'fCFO', target, p.true, init.level,
          ncohort, cohortsize, assess.window, tte.para, accrual.rate, accrual.dist, seed = 1)
plot(fCFOtrial)
fCFOoc <- CFO.oc (nsimu, design = 'fCFO', target, p.true, init.level, ncohort, cohortsize,
        assess.window, tte.para, accrual.rate, accrual.dist, seeds = 1:nsimu)
plot(fCFOoc)
## 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)
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)

## select the MTD based on the trial data
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)



###### drug-combination trial ######
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

## 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 = 100, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:100)
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)
```

`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.

Author(s)

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Examples

```
## settings for 1dCFO
nsimu <- 100; 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
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, p.true, 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)

## 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 <- 20; 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 = 100, target, p.true, init.level = c(1,1), ncohort, cohortsize,
                    seeds = 1:100)
summary(CFO2doc)
```

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