R documentation

of all in 'BOIN2.4'

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R topics documented:

`get.boundary` *Generate the optimal dose escalation and deescalation boundaries for conducting the trial.*

Description

Use this function to generate the optimal dose escalation and deescalation boundaries for conducting the trial.

Usage

```
get.boundary(target, ncohort, cohortsize, n.earlystop = 100, p.saf = 0.6 *
  target, p.tox = 1.4 * target, cutoff.eli = 0.95, extrasafe = FALSE,
  offset = 0.05, print = TRUE)
```

Arguments

`target`	the target toxicity rate
`ncohort`	the total number of cohorts
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. If the number of patients treated at the current dose reaches `n.earlystop`, stop the trial and select the MTD based on the observed data. The default value `n.earlystop=100` essentially turns off the type of early stopping.

p.saf	the highest toxicity probability that is deemed subtherapeutic (i.e., below the MTD) such that dose escalation should be made. The default value is p.saf = 0.6 * target.
p.tox	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4*target.
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (cutoff.eli=0.95) for general use.
extrasafe	set extrasafe=TRUE to impose a more strict stopping rule for extra safety
offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
print	to print out the boundary results.

Details

The dose escalation and deescalation boundaries are all we need to run a phase I trial when using the BOIN design. The decision of which dose to administer to the next cohort of patients does not require complicated computations, but only a simple comparison of the observed toxicity rate at the current dose with the dose escalation and deescalation boundaries. If the observed toxicity rate at the current dose is smaller than or equal to the escalation boundary, we escalate the dose; if the observed toxicity rate at the current dose is greater than or equal to the deescalation boundary, we deescalate the dose; otherwise, we retain the current dose. The dose escalation and deescalation boundaries are chosen to minimize the probability of assigning patients to subtherapeutic or overly toxic doses, thereby optimizing patient ethics. get.boundary() also outputs the elimination boundary, which is used to avoid treating patients at overly toxic doses based on the following Bayesian safety rule: if Pr(pj > phi | mj , nj) > 0.95 and nj >= 3, dose levels j and higher are eliminated from the trial, where pj is the toxicity probability of dose level j, phi is the target toxicity rate, and mj and nj are the number of toxicities and patients treated at dose level j. The trial is terminated if the lowest dose is eliminated. The BOIN design has two built-in stopping rules: (1) stop the trial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial and select the MTD if the number of patients treated at the current dose reaches n.earlystop. The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., n.earlystop) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial early and select the MTD to save the sample size and reduce the trial duration. For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting extrasafe=TRUE, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose >=3, and (ii) Pr(toxicity rate of the lowest dose > target | data) > cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.

Value

get.boundary() returns the optimal dose escalation and deescalation boundaries for running the trial. The dose elimination boundary is also returned for preventing the continuous exposure of patients to overly toxic doses.

Note

We should avoid setting the values of p.saf and p.tox very close to the target. This is because the small sample sizes of typical phase I trials prevent us from differentiating the target toxicity rate

from the rates close to it. In addition, in most clinical applications, the target toxicity rate is often a rough guess, and finding a dose level with a toxicity rate reasonably close to the target rate will still be of interest to the investigator. The default values provided by `get.boundary()` are generally reasonable for most clinical applications.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
## Consider a phase I trial aiming to find the MTD with a target toxicity rate of 0.3
## the maximum sample size is 30 patients in cohort size of 3
get.boundary(target=0.3, ncohort=10, cohortsize=3)
```

---

get.oc *Generate operating characteristics for single agent trials*

Description

Obtain the operating characteristics of the BOIN design for single agent trials by simulating trials.

Usage

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

Arguments

`target`	the target toxicity rate
`p.true`	a vector containing the true toxicity probabilities of the investigational dose levels.
`ncohort`	the total number of cohorts
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. If the number of patients treated at the current dose reaches `n.earlystop`, stop the trial and select the MTD based on the observed data. The default value `n.earlystop=100` essentially turns off this type of early stopping.
`startdose`	the starting dose level for the trial

p.saf	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be undertaken. The default value is p.saf=0.6*target.
p.tox	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4*target).
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (cutoff.eli=0.95) for general use.
extrasafe	set extrasafe=TRUE to impose a more stringent stopping rule
offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
ntrial	the total number of trials to be simulated.

Details

The operating characteristics of the BOIN design are generated by simulating trials under the pre-specified true toxicity probabilities of the investigational doses. The BOIN design has two built-in stopping rules: (1) stop the trial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial and select the MTD if the number of patients treated at the current dose reaches n.earlystop. The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., n.earlystop) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial early and select the MTD to save sample size and reduce the trial duration. For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting extrasafe=TRUE, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose >=3, and (ii) Pr(toxicity rate of the lowest dose > target | data) > cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.

Value

get.oc() returns the operating characteristics of the BOIN design as a data frame, including: (1) selection percentage at each dose level (selpercent), (2) the number of patients treated at each dose level (nptsdose), (3) the number of toxicities observed at each dose level (ntoxdose), (4) the average number of toxicities (totaltox), (5) the average number of patients (totaln), and (6) the percentage of early stopping without selecting the MTD (pctearlystop).

Note

We should avoid setting the values of p.saf and p.tox very close to the target. This is because the small sample sizes of typical phase I trials prevent us from differentiating the target toxicity rate from the rates close to it. In addition, in most clinical applications, the target toxicity rate is often a rough guess, and finding a dose level with a toxicity rate reasonably close to the target rate will still be of interest to the investigator. The default values provided by get.oc() are generally reasonable for most clinical applications.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
get.oc(target=0.3, p.true=c(0.05, 0.15, 0.3, 0.45, 0.6), ncohort=1000, cohortsize=3, ntrial=1000)
```

`get.oc.comb` *Generate operating characteristics for drug combination trials*

Description

Obtain the operating characteristics of the BOIN design or waterfall design for drug combination trials. The BOIN design is to find a MTD, and the waterfall design is to find the MTD contour (i.e., multple MTDs in the dose matrix)

Usage

```
get.oc.comb(target, p.true, ncohort, cohortsize, n.earlystop=NULL, startdose=c(1, 1),
               p.saf=0.6*target, p.tox=1.4*target, cutoff.eli=0.95, extrasafe=FALSE,
                   offset=0.05, ntrial=1000, MTD.contour=FALSE)
```

Arguments

`target`	the target toxicity rate
`p.true`	a `J*K` matrix (`J<=K`) containing the true toxicity probabilities of combinations with `J` dose levels of agent A and `K` dose levels of agent B
`ncohort`	a `1*J` vector specifying the number of cohorts for each of `J` subtrials if MTD.contour=TRUE; Otherwise, a scalar specifying the total number of cohorts for the trial.
`cohortsize`	the cohort size
`n.earlystop`	the early stopping parameter. If the number of patients treated at the current dose reaches `n.earlystop`, stop the trial or subtrial and select the MTD based on the observed data. When the waterfall design is used to find the MTD contour, `n.earlystop=12` by default.
`startdose`	the starting dose combination level for drug combination trial
`p.saf`	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be undertaken. The default value is `p.saf=0.6*target`.
`p.tox`	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is `p.tox=1.4*target`.
`cutoff.eli`	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (`cutoff.eli=0.95`) for general use.

extrasafe	set extrasafe=TRUE to impose a more stringent stopping rule
offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
ntrial	the total number of trials to be simulated
MTD.contour	set MTD.contour=TRUE to select the MTD contour (claiming multiple MTDs). Otherwise, BOIN design is used to search for a single MTD.

Details

The operating characteristics of the BOIN design or waterfall design are generated by simulating trials under the prespecified true toxicity probabilities of the investigational dose combinations. The BOIN and waterfall designs have two built-in stopping rules: (1) stop the trial/subtrial if the lowest dose is eliminated due to toxicity, and no dose should be selected as the MTD; and (2) stop the trial/subtrial and select the MTD if the number of patients treated at the current dose reaches n.earlystop. The first stopping rule is a safety rule to protect patients from the case in which all doses are overly toxic. The rationale for the second stopping rule is that when there is a large number (i.e., n.earlystop) of patients assigned to a dose, it means that the dose-finding algorithm has approximately converged. Thus, we can stop the trial/subtrial early and select the MTD to save sample size and reduce the trial duration.

For some applications, investigators may prefer a more strict safety stopping rule than rule (1) for extra safety when the lowest dose is overly toxic. This can be achieved by setting extrasafe=TRUE, which imposes the following more strict safety stopping rule: stop the trial if (i) the number of patients treated at the lowest dose >=3, and (ii) Pr(toxicity rate of the lowest dose > target | data) > cutoff.eli-offset. As a tradeoff, the strong stopping rule will decrease the MTD selection percentage when the lowest dose actually is the MTD.

Value

get.oc.comb() returns the operating characteristics of the BOIN or waterfall design as a list, including (1) selection percentage at each dose level, (2) the number of patients treated at each dose level, (3) the number of toxicities observed at each dose level, (4) the total correct selection of the MTD, (5) the total percentage of patients treated at the MTD.

Note

We should avoid setting the values of p.saf and p.tox very close to the target. This is because the small sample sizes of typical phase I trials prevent us from differentiating the target toxicity rate from the rates close to it. In addition, in most clinical applications, the target toxicity rate is often a rough guess, and finding a dose level with a toxicity rate reasonably close to the target rate will still be of interest to the investigator. The default values provided by get.oc.comb() are generally reasonable for most clinical applications.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

Lin R. and Yin, G. (2016). Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, Statistical Methods in Medical Research, to appear.

Zhang L. and Yuan, Y. (2016). A Simple Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials, under review.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
p.true<-matrix(c(0.01,0.03,0.15,0.20,0.30,
                 0.03,0.05,0.10,0.30,0.60,
                 0.08,0.10,0.30,0.60,0.75), byrow=TRUE, ncol=5)
## find the MTD contour using waterfall design
get.oc.comb(target=0.3, p.true, ncohort=c(10,5,5), cohortsize=3, n.earlystop=12, startdose=c(1,1),
          ntrial=10, MTD.contour=TRUE)

## find a single MTD using BOIN design
get.oc.comb(target=0.3, p.true, ncohort=20, cohortsize=3, n.earlystop=12, startdose=c(1,1),
       ntrial=10, MTD.contour=FALSE)
```

`get.oc.comb.phase12` *Get the operating characteristics for phase I/II waterfall design*

Description

Obtain the operating characteristics of phase I/II waterfall design, which aims to find the optimal dose combination (ODC), defined as the combination that has the highest efficacy among the doses in the MTD contour.

Usage

```
get.oc.comb.phase12(p.truetox, p.trueeff, target, eff.lb = 0.2, ncohort1,
  cohortsize1, n.earlystop = 10, ncohort2, cohortsize2, cutoff.eli = 0.95,
  cutoff.eff, p.saf = 0.6 * target, p.tox = 1.4 * target,
  extrasafe = FALSE, offset = 0.05, ntrial = 1000)
```

Arguments

`p.truetox`	a `J*K` matrix (`J<=K`) containing the true toxicity probabilities of combinations with `J` dose levels of agent A and `K` dose levels of agent B
`p.trueeff`	a `J*K` matrix (`J<=K`) containing the true efficacy probability of combinations with `J` dose levels of agent A and `K` dose levels of agent B
`target`	the target toxicity rate
`eff.lb`	the lower bound for efficacy
`ncohort1`	a `1*J` vector specifying the number of cohorts for each of `J` subtrials in phase I
`cohortsize1`	the cohort size for phase I

n.earlystop	the early stopping parameter for phase I. If the number of patients treated at the current dose reaches n.earlystop, stop the trial and select the MTD based on the observed data. The default value n.earlystop=100 essentially turns off this type of early stopping.
ncohort2	the total number of cohorts for phase II
cohortsize2	the cohort size for phase II
cutoff.eli	the cutoff for dose elimination rule
cutoff.eff	the cutoff for futility stopping
p.saf	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be undertaken. The default value is p.saf=0.6*target.
p.tox	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4*target.
extrasafe	set extrasafe=TRUE to impose a more stringent stopping rule
offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
ntrial	the total number of trials to be simulated

Details

get.oc.comb.phase12() is consisted of two parts. In the phase I part, the waterfall design is used to find the MTD contour on the basis of only toxicity. Once the MTD contour is identified, these MTDs are seamlessly moved to phase II to evaluate efficacy. Each of the MTDs forms a treatment arm. Patients are eqally randomized into these arms to evaluate efficacy. Toxicity and efficacy monitoring will be conducted after every cohortsize2 patients enrolled into each of treatment arms.

Value

This function returns the operating characteristics of the waterfall design as a list, including (1) selection percentage at each dose level (selpercent), (2) the number of patients treated at each dose (npts), (3) the number of toxicities observed at each dose (ntox), (4) the number of efficacy/response observed at each dose (neff) (5) the total sample size (totaln).

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

Lin R. and Yin, G. (2016). Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, Statistical Methods in Medical Research, to appear.

Zhang L. and Yuan, Y. (2016). A Simple Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials, under review.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
p.truetox<-matrix(c(0.03,0.10,0.28, 0.10,0.30,0.50), nrow=2, byrow=TRUE)
p.trueeff<-matrix(c(0.20,0.30,0.50, 0.25,0.35,0.55), nrow=2, byrow=TRUE)
get.oc.comb.phase12(p.truetox, p.trueeff, target=0.30, eff.lb=0.2,
         ncohort1=c(12,8), cohortsize1=3, n.earlystop=12,
         ncohort2=12, cohortsize2=3, cutoff.eff =0.9, ntrial=10)
```

`next.comb` *Determine the dose combination for the next cohort of new patients for drug-combination trials that aim to find a MTD*

Description

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

Usage

```
next.comb(target, npts, ntox, dose.curr, n.earlystop=100,
                 p.saf=0.6*target, p.tox=1.4*target, cutoff.eli=0.95,
                 extrasafe=FALSE, offset=0.05)
```

Arguments

`target`	the target toxicity rate
`npts`	a `J*K` matrix (`J<=K`) containing the number of patients treated at each dose combination
`ntox`	a `J*K` matrix (`J<=K`) containing the number of patients experienced dose-limiting toxicity at each dose combination
`dose.curr`	the current dose combination
`n.earlystop`	the early stopping parameter. If the number of patients treated at the current dose reaches `n.earlystop`, stop the trial and select the MTD based on the observed data. The default value `n.earlystop=100` essentially turns off this type of early stopping.
`p.saf`	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be undertaken. The default value is `p.saf=0.6*target`.
`p.tox`	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is `p.tox=1.4*target`.
`cutoff.eli`	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (`cutoff.eli=0.95`) for general use.
`extrasafe`	set `extrasafe=TRUE` to impose a more stringent stopping rule
`offset`	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when `extrasafe=TRUE`. A larger value leads to a more strict stopping rule. The default value `offset=0.05` generally works well.

Details

This function is used to determine dose combination for conducting combination trials. Given the currently observed data, `next.comb()` determines dose combination for treating the next cohort of new patients. The currently observed data include: the number of patients treated at each dose combination (i.e., `npts`), the number of patients who experienced dose-limiting toxicities at each dose combination (i.e.,`ntox`), and the level of current dose (i.e., `dose`).

Value

the dose for treating the next cohort of new patients.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

Lin R. and Yin, G. (2016). Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, Statistical Methods in Medical Research, to appear.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
# make the decision of dose escalation/deescalation during the course of trial conduct
# matrix n contains the number of patients treated at each dose combination
# matrix y contains the number of patients experienced toxicity at each dose combination
n<-matrix(c(3, 0, 0, 0, 0, 7, 6, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
y<-matrix(c(0, 0, 0, 0, 0, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0), ncol=5, byrow=TRUE)
next.comb(target=0.3, npts=n, ntox=y, dose.curr=c(2, 2))
```

---

next.subtrial — *Determine the starting dose and the dose-searching space for next subtrial in waterfall design*

Description

Determine the starting dose and the dose-searching space for next subtrial after the current subtrial is completed when using the waterfall design

Usage

```
next.subtrial(target, npts, ntox, p.saf = 0.6 * target, p.tox = 1.4 *
  target, cutoff.eli = 0.95, extrasafe = FALSE, offset = 0.05)
```

Arguments

target	the target toxicity rate
npts	a J*K matrix (J<=K) containing the number of patients treated at each dose combination
ntox	a J*K matrix (J<=K) containing the number of patients who experienced dose-limiting toxicities at each dose combination
p.saf	the highest toxicity probability that is deemed subtherapeutic (i.e. below the MTD) such that dose escalation should be undertaken. The default value is p.saf=0.6*target.
p.tox	the lowest toxicity probability that is deemed overly toxic such that deescalation is required. The default value is p.tox=1.4*target.
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (cutoff.eli=0.95) for general use.
extrasafe	set extrasafe=TRUE to impose a more stringent stopping rule
offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.

Details

For the waterfall design, this function is used to obtain the starting dose and dose-searching space for the next subtrial when the current subtrial is completed. The input data include: the number of patients treated at each dose combination (i.e., npts), the number of patients who experienced dose-limiting toxicities at each dose combination (i.e., ntox).

Value

next.subtrial() returns the starting dose and the dose-searching space for the next subtrial.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

Lin R. and Yin, G. (2016). Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, Statistical Methods in Medical Research, to appear.

Zhang L. and Yuan, Y. (2016). A Simple Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials, under review.

See Also

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Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
n<-matrix(c(6, 0, 0, 0,
           6, 10, 12, 0,
           9, 12, 0, 0), ncol=4, byrow=TRUE)
y<-matrix(c(0, 0, 0, 0,
            1, 1, 4, 0,
            2, 3, 0, 0), ncol=4, byrow=TRUE)

next.subtrial(target=0.3, npts=n, ntox=y)
```

`select.mtd` *Select the maximum tolerated dose (MTD) for single agent trials*

Description

Select the maximum tolerated dose (MTD) when the single-agent trial is completed

Usage

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

Arguments

`target`	the target toxicity rate
`npts`	a vector containing the number of patients treated at each dose level
`ntox`	a vector containing the number of patients who experienced dose-limiting toxicity at each dose level
`cutoff.eli`	the cutoff to eliminate overly toxic doses for safety. We recommend the default value of (`cutoff.eli=0.95`) for general use.
`extrasafe`	set `extrasafe=TRUE` to impose a more strict stopping rule for extra safety
`offset`	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when `extrasafe=TRUE`. A larger value leads to a more strict stopping rule. The default value `offset=0.05` generally works well.
`print`	to print out the dose selection result

Details

`select.mtd()` selects the MTD based on isotonic estimates of toxicity probabilities. `select.mtd` selects as the MTD dose j*, for which the isotonic estimate of the toxicity rate is closest to the target. If there are ties, we select from the ties the highest dose level when the estimate of the toxicity rate is smaller than the target, or the lowest dose level when the estimate of the toxicity rate is greater than the target. The isotonic estimates are obtained by the pooled-adjacent-violators algorithm (PAVA) (Barlow, 1972).

Value

`select.mtd()` returns the MTD based on the trial data.

Note

The MTD selection and dose escalation/deescalation rule are two independent components of the trial design. 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 BOIN design.

Author(s)

Suyu Liu and Ying Yuan

References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
n<-c(3, 3, 15, 9, 0)
y<-c(0, 0, 4, 4, 0)
select.mtd(target=0.3, npts=n, ntox=y)
```

---

select.mtd.comb — *Select the maximum tolerated dose (MTD) or MTD contour for drug combination trials*

Description

Select the maximum tolerated dose (MTD) or MTD contour after the drug combination trial is completed using the BOIN design or waterfall design

Usage

```
select.mtd.comb(target, npts, ntox, cutoff.eli = 0.95, extrasafe = FALSE,
  offset = 0.05, print = TRUE, MTD.contour = FALSE)
```

Arguments

target	the target toxicity rate
npts	a J*K matrix (J<=K) containing the number of patients treated at each dose combination
ntox	a J*K matrix (J<=K) containing the number of patients experienced dose-limiting toxicity at each dose combination
cutoff.eli	the cutoff to eliminate an overly toxic dose for safety. We recommend the default value of (cutoff.eli=0.95) for general use.
extrasafe	set extrasafe=TRUE to impose a more strict stopping rule for extra safety

offset	a small positive number (between 0 and 0.5) to control how strict the stopping rule is when extrasafe=TRUE. A larger value leads to a more strict stopping rule. The default value offset=0.05 generally works well.
print	to print out the dose selection results.
MTD.contour	set MTD.contour=TRUE to select the MTD contour, otherwise select a single MTD. The value of MTD.contour should be consistent with that in get.oc.comb().

Details

select.mtd.comb() selects a MTD or the MTD contour based on matrix isotonic estimates of toxicity probabilities, depending on MTD.contour is set as TRUE or FALSE. The (matrix) isotonic estimates are obtained by the R package (Iso::biviso).

Value

the MTD(s) based on the trial data.

Note

The MTD selection and dose escalation/deescalation rule are two independent components of the trial design. 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 BOIN or waterfall design.

Author(s)

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References

Liu S. and Yuan, Y. (2015). Bayesian Optimal Interval Designs for Phase I Clinical Trials, Journal of the Royal Statistical Society: Series C, 64, 507-523.

Lin R. and Yin, G. (2016). Bayesian Optimal Interval Designs for Dose Finding in Drug-combination Trials, Statistical Methods in Medical Research, to appear.

Zhang L. and Yuan, Y. (2016). A Simple Bayesian Design to Identify the Maximum Tolerated Dose Contour for Drug Combination Trials, under review.

See Also

Tutorial: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/BOIN2.4_tutorial.pdf

Paper: http://odin.mdacc.tmc.edu/~yyuan/Software/BOIN/paper.pdf

Examples

```
## Select the MTD based on the data from a 3x5 combination trial
## matrix n contains the number of patients treated at each dose combination
## matrix y contains the number of patients experienced toxicity at each dose combination

n<-matrix(c(3, 5, 0, 0, 0, 7, 6, 15, 0, 0, 0, 0, 4, 0, 0), ncol=5, byrow=TRUE)
y<-matrix(c(0, 1, 0, 0, 0, 1, 1, 4, 0, 0, 0, 0, 2, 0, 0), ncol=5, byrow=TRUE)
select.mtd.comb(target=0.3, npts=n, ntox=y, MTD.contour=FALSE)

## Select the MTD contour based on the data from a 3x4 combination trial
```

```
## matrix n contains the number of patients treated at each dose combination
## matrix y contains the number of patients experienced toxicity at each dose combination

n<-matrix(c(6, 9, 24, 0,  6, 24, 9, 0,  12, 18, 0, 0), ncol=4, byrow=TRUE)
y<-matrix(c(0, 1,  5, 0,  1,  5, 4, 0,  1, 5, 0, 0), ncol=4, byrow=TRUE)
select.mtd.comb(target=0.3, npts=n, ntox=y, MTD.contour=TRUE)
```

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