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Description Implements Escalation With Overdose Control trial designs using two drug combinations described by this paper <doi:10.1002/sim.6961>(Tighiouart et al., 2016). It calculates the recommended dose for next cohorts and perform simulations to obtain operating characteristics.

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EWOC.Comb-package *Escalation with Overdose Control using 2 Drug Combinations*

Description

Implements Escalation With Overdose Control trial designs using two drug combinations described by this paper <doi:10.1002/sim.6961>(Tighiouart et al., 2016). It calculates the recommended dose for next cohorts and perform simulations to obtain operating characteristics.

Author(s)

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References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

ewoc2 *Escalation With Overdose Control for two drugs combination*

Description

Finding the doses of next cohort for a phase I clinical trial based on Escalation with Overdose Control (EWOC) design considering the classic parametrization for binary response and two agents.

Usage

```
ewoc2(dose.a, dose.b, resp, theta, alpha, Min.Dose.A, Max.Dose.A, Min.Dose.B, Max.Dose.B,
a01, b01, a10, b10, a00, b00, a, b, delta1x, delta1y, burn, mm, delta1)

## Default S3 method:
ewoc2(dose.a, dose.b, resp, theta, alpha, Min.Dose.A, Max.Dose.A, Min.Dose.B, Max.Dose.B,
a01, b01, a10, b10, a00, b00, a, b, delta1x, delta1y, burn=4000, mm=2000, delta1=0.05)
```

Arguments

dose.a	a numeric vector of allowable doses for drug A
dose.b	a numeric vector of allowable doses for drug B
resp	a numeric vector of allowable responses, 0 or 1
theta	a numeric value defining the proportion of expectd patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.

alpha	a numerical value defining the probability that dose selected by EWOC is higher than the MTD.
Min.Dose.A	a numeric value defining the lower bound of the support of the MTD for drug A
Max.Dose.A	a numeric value defining the upper bound of the support of the MTD for drug A
Min.Dose.B	a numeric value defining the lower bound of the support of the MTD for drug B
Max.Dose.B	a numeric value defining the upper bound of the support of the MTD for drug B
a01	a numeric value for beta prior distribution associated with parameter rho01
b01	a numeric value for beta prior distribution associated with parameter rho01
a10	a numeric value for beta prior distribution associated with parameter rho10
b10	a numeric value for beta prior distribution associated with parameter rho10
a00	a numeric value for beta prior distribution associated with parameter rho00
b00	a numeric value for beta prior distribution associated with parameter rho00
a	a numeric value for gamma prior distribution associated with parameter eta
b	a numeric value for the gamma prior distribution associated with the parameter eta
delta1x	Maximum dose escalation at each step for drug A, the default is 0.2*(Max.Dose.A-Min.Dose.A if not assigned)
delta1y	Maximum dose escalation at each step for drug B, the default is 0.2*(Max.Dose.B-Min.Dose.B if not assigned)
burn	Number of iterations for adaption, see n.adapt in jags.model for detail
mm	Number of iterations to monitor, see n.iter in code.samples for detail
delta1	Threshold for toxicity

Value

data	a data frame containing the current doses and responses set
parameters	list of input parameters
priors	list of prior parameters
nextdose.x	the next recommended doses for drug A
nextdose.y	the next recommended doses for drug B

References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

Examples

```
test = ewoc2(dose.a=c(0,0),dose.b=c(0,0),resp=c(0,0),theta=0.33,alpha=0.25,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1,a01=1,b01=1,a10=1,b10=1,
a00=1,b00=1,a=0.8,b=0.0384)
print(test)
```

ewoc2simu *Generic EWOC2 simulation*

Description

Generic function for simulating EWOC trials for 2 drugs combination

Usage

```
ewoc2simu(ntrials, nsamples, type, trho00, trho01, trho10, teta, nx, ny, tp,
Min.Dose.A, Max.Dose.A, Min.Dose.B, Max.Dose.B, alpha, theta, vai, a01,
b01, a10, b10, a00, b00, a, b, delta1x, delta1y, burn, mm, delta1, seed)

## Default S3 method:
ewoc2simu(ntrials, nsamples, type, trho00, trho01, trho10, teta, nx, ny, tp,
Min.Dose.A, Max.Dose.A, Min.Dose.B, Max.Dose.B, alpha, theta, vai, a01,
b01, a10, b10, a00, b00, a, b, delta1x, delta1y, burn=4000, mm=2000, delta1=0.05, seed)
```

Arguments

ntrials	a number indicating the number of trials to be simulated
nsamples	a number indicating the number of patients enrolled for each clinical trial
type	a character indicating the type of design, could be 'continous' or 'discrete' or their initials
trho00	a numeric value indicating the true value of the parameter rho00, the probability of DLT when the levels of drugs A and B are both 0
trho01	a numeric value indicating the true value of the parameter rho01, the probability of DLT when the levels of drugs A and B are 0 and 1, respectively
trho10	a numeric value indicating the true value of the parameter rho10, the probability of DLT when the levels of drugs A and B are 1 and 0, respectively
teta	a numeric value indicating the true value of the eta, the interaction parameter
nx	a numeric value indicating the number of dose levels for drug A. It's only necessary if type = 'discrete'
ny	a numeric value indicating the number of dose levels for drug B. It's only necessary if type = 'discrete'
tp	a numerical vector indicating the true probabilities of DLT at each dose combinations, the order is by Drug B first, only necessary if type = 'discrete'
Min.Dose.A	a numeric value defining the lower bound of the support of the MTD for drug A
Max.Dose.A	a numeric value defining the upper bound of the support of the MTD for drug A
Min.Dose.B	a numeric value defining the lower bound of the support of the MTD for drug B
Max.Dose.B	a numeric value defining the upper bound of the support of the MTD for drug B
alpha	a numerical value defining the probability that dose selected by EWOC is higher than the MTD.

theta	a numeric value defining the proportion of expectd patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD.
vai	a numeric value indicating variable alpha increment for each new cohort
a01	a numeric value for beta prior distribution associated with parameter rho01
b01	a numeric value for beta prior distribution associated with parameter rho01
a10	a numeric value for beta prior distribution associated with parameter rho10
b10	a numeric value for beta prior distribution associated with parameter rho10
a00	a numeric value for beta prior distribution associated with parameter rho00
b00	a numeric value for beta prior distribution associated with parameter rho00
a	a numeric value for gamma prior distribution associated with parameter eta
b	a numeric value for gamma prior distribution associated with parameter eta
delta1x	Maximum dose escalation at each step for drug A, the default is 0.2*(Max.Dose.A-Min.Dose.A if not assigned)
delta1y	Maximum dose escalation at each step for drug B, the default is 0.2*(Max.Dose.B-Min.Dose.B if not assigned)
burn	Number of iterations for adaption, see n.adapt in jags.model for detail
mm	Number of iterations to monitor, see n.iter in code.samples for detail
delta1	Threshold for toxicity
seed	a numeric value used in random number generation

Value

type	same as input parameter type
parameters	list of input parameters
priors	list of prior parameters
Dose.A	a matrix ntrials x nsamples containing the doses of drug A assigned for each patient in a trial and each trial in the simulation
Dose.B	a matrix ntrials x nsamples containing the doses of drug B assigned for each patient in a trial and each trial in the simulation
Resp	a matrix ntrials x nsamples containing ones and zeros indicating the occurance of DLT (1) and the absence of DLT (0) for each patient in the trial and each trial in the simulation
rho00	a numeric vector ntrials x 1 containing the estimated rho00 parameter for each trial in the simulation
rho01	a numeric vector ntrials x 1 containing the estimated rho01 parameter for each trial in the simulation
rho10	a numeric vector ntrials x 1 containing the estimated rho10 parameter for each trial in the simulation
eta	a numeric vector ntrials x 1 containing the estimated eta parameter for each trial in the simulation

postlow	a matrix ntrials x nsamples/2 containing posterior probability of DLT at lower doses (both 0 for durg A and B) at each step in a trial and each trial in the simulation
postdlts	a matrix (nx x ny x ntrials) x 4 containing posterior probability of DLT at each dose combination sets in each trial in the simulation. This is used to test whether or not a discrete set of MTDs was selected from a continous MTD curve is kept or dropped. It's avaiable only when type = 'discrete'

References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

Examples

```
# continous
test1 = ewoc2simu(ntrials=10, nsamples=40, type="c", trho00=0.01,trho01=0.2, trho10=0.9,teta=20,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20, a01=1,b01=1,
a10=1,b10=1, a00=1,b00=1,a=0.8,b=0.0384)

print(test1)
plot(test1, type="MTD")
plot(test1, type="bias")
plot(test1, type="percent")

# discrete
tp = c(0.03,0.05,0.08,0.05,0.08,0.13,0.08,0.13,0.2,0.13,0.2,0.29,0.2,0.29,0.4,0.29,0.4,0.53)
test2 = ewoc2simu(ntrials=10, nsamples=40, type="d", nx=6, ny=3, tp=tp,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20,
a01=1,b01=1,a10=1,b10=1,a00=1,b00=1,a=0.8,b=0.0384)

print(test2)
plot(test2, type="MTD")
plot(test2, type="percent")
```

---

mtdcurve *Generating MTD curve based on logistic model for two drugs*

Description

Generating MTD curve based on logistic model for two drugs

Usage

```
mtdcurve(rho00, rho01, rho10, eta, theta)
```

Arguments

rho00	a numeric value indicating the true value of the parameter rho00, the probability of DLT when the levels of drugs A and B are both 0
rho01	a numeric value indicating the true value of the parameter rho01, the probability of DLT when the levels of drugs A and B are 0 and 1, respectively
rho10	a numeric value indicating the true value of the parameter rho10, the probability of DLT when the levels of drugs A and B are 1 and 0, respectively
eta	a numeric value indicating the true value of the eta, the interaction parameter
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD

Value

a plot showing the MTD curve based on the logistic model

Examples

```
mtdcurve(rho00=0.01, rho01=0.2, rho10=0.9, eta=20, theta=0.2)
```

---

pdlt *Generating probability of DLT based on the EWOC2 model*

Description

Generating probabiity of DLT based on the EWOC 2 drugs combination model

Usage

```
pdlt(rho00, rho01, rho10, eta, theta, x, y)
```

Arguments

rho00	a numeric value indicating the true value of the parameter rho00, the probability of DLT when the levels of drugs A and B are both 0
rho01	a numeric value indicating the true value of the parameter rho01, the probability of DLT when the levels of drugs A and B are 0 and 1, respectively
rho10	a numeric value indicating the true value of the parameter rho10, the probability of DLT when the levels of drugs A and B are 1 and 0, respectively
eta	a numeric value indicating the true value of the eta, the interaction parameter
theta	a numerical value defining the proportion of expected patients to experience a medically unacceptable, dose-limiting toxicity (DLT) if administered the MTD
x	a numeric value of dose level for drug A
y	a numeric value of dose level for drug B

Value

a numeric value indicating the probability of DLT with doses from input based on the logistic model

Examples

```
pdlt(rho00=0.01, rho01=0.2, rho10=0.9, eta=20, theta=0.2, x=0.2, y=0.3)
```

`plot.ewoc2simu` *EWOC for 2 drugs combination trial design characteristics*

Description

Function to plot the trial design characteristics from EWOC 2 drugs combination simulation results

Usage

```
## S3 method for class 'ewoc2simu'
plot(x, type = "MTD", conf.reg=0.9, plot.figure="Y",...)
```

Arguments

`x`	an object of class "ewoc2simu", usually a result of a call to ewoc2simu
`type`	a character indicating the type of plots a user requests, could be "MTD", "bias", or "percent". For discrete simulations, "bias" is not available
`conf.reg`	confidence level that controls the region of the doses from the last trial in the MTD plot
`plot.figure`	a character indicating whether user wants the plot, 'Y' would be yes, otherwise would be no. It's mainly for internal uses
`...`	arguments passed to or from methods

Value

No return value, called for side effects.

References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

Examples

```
# continous
test1 = ewoc2simu(ntrials=10, nsamples=40, type="c", trho00=0.01,trho01=0.2, trho10=0.9,teta=20,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20, a01=1,b01=1,
a10=1,b10=1, a00=1,b00=1,a=0.8,b=0.0384)

print(test1)
plot(test1, type="MTD")
plot(test1, type="bias")
plot(test1, type="percent")

# discrete
tp = c(0.03,0.05,0.08,0.05,0.08,0.13,0.08,0.13,0.2,0.13,0.2,0.29,0.2,0.29,0.4,0.29,0.4,0.53)
test2 = ewoc2simu(ntrials=10, nsamples=40, type="d", nx=6, ny=3, tp=tp,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20,
a01=1,b01=1,a10=1,b10=1,a00=1,b00=1,a=0.8,b=0.0384)

print(test2)
plot(test2, type="MTD")
plot(test2, type="percent")
```

---

print.ewoc2 *Summarizing EWOC2 next doses results*

Description

Summarizing EWOC2 next doses result

Usage

```
## S3 method for class 'ewoc2'
print(x, ...)
```

Arguments

x	an object of class "ewoc2", usually, a result of a call to ewoc2
...	arguments passed to or from methods

Value

a data.frame of 2 x 4 with columns for cohort, patients, recommended dose of drug A and recommended dose of drug B for next cohort or 2 patients

References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

Examples

```
test = ewoc2(dose.a=c(0,0),dose.b=c(0,0),resp=c(0,0),theta=0.33,alpha=0.25, Min.Dose.A=0,
Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1,a01=1,b01=1,a10=1,b10=1,a00=1,b00=1,a=0.8,b=0.0384)
print(test)
```

`print.ewoc2simu` *Summarizing EWOC2 simulation results*

Description

Summarizing EWOC2 simulation results

Usage

```
## S3 method for class 'ewoc2simu'
print(x, ...)
```

Arguments

x	an object of class "ewoc2simu", usually, a result of a call to ewoc2simu
...	arguments passed to or from methods

Value

a data.frame of 7 x 1 with row represent Accuracy square discrepancy (sq), Accuracy absolute discrepancy (abs), Accuracy overdose (od), percent Selection, Average percent DLT, percent Trials with DLT rate > theta+0.05, percent Trials with LDT rate > theta+0.1

References

Tighiouart M, Li Q and Rogatko A. A Bayesian adaptive design for estimating the maximuym tolerated dose curve using drug combinations in cancer phase I clinical trials. Statistics in Medicine. 2017, 36: 280-290.

Examples

```
# continous
test1 = ewoc2simu(ntrials=10, nsamples=40, type="c", trho00=0.01,trho01=0.2, trho10=0.9,teta=20,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20, a01=1,b01=1,
a10=1,b10=1, a00=1,b00=1,a=0.8,b=0.0384)

print(test1)
plot(test1, type="MTD")
plot(test1, type="bias")
plot(test1, type="percent")
```

```
# discrete
tp = c(0.03,0.05,0.08,0.05,0.08,0.13,0.08,0.13,0.2,0.13,0.2,0.29,0.2,0.29,0.4,0.29,0.4,0.53)
test2 = ewoc2simu(ntrials=10, nsamples=40, type="d", nx=6, ny=3, tp=tp,
Min.Dose.A=0, Max.Dose.A=1, Min.Dose.B=0, Max.Dose.B=1, alpha=0.25, theta=0.20,
a01=1,b01=1,a10=1,b10=1,a00=1,b00=1,a=0.8,b=0.0384)

print(test2)
plot(test2, type="MTD")
plot(test2, type="percent")
```

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