Package 'dfcrm'

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Title Dose-Finding by the Continual Reassessment Method

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Description Provides functions to run the CRM and TITE-CRM in phase I trials and calibration tools for trial planning purposes.

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Contents

cohere *Coherence of two-stage CRM*

Description

Returns a message on the coherence status of a two-stage CRM design.

Usage

```
cohere(prior, target, x0, method = "bayes", model = "empiric",
    intcpt = 3, scale = sqrt(1.34), detail = TRUE)
```

Arguments

prior	A vector of initial guesses of toxicity probabilities associated the doses.
target	The target DLT rate.
x0	The initial design containing a non-decreasing sequence of dose levels. The length of the initial design is the sample size.
method	A character string to specify the method for parameter estimation. The default method "bayes" estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by "mle".
model	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.
scale	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
detail	If TRUE, details about incoherent escalations will be displayed.

Value

message	A string character giving a message regarding the coherence status of a two-stage CRM design.

References

Cheung, Y. K. (2005). Coherence principles in dose-finding studies. Biometrika 92:863-873.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

crm

Examples

```
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
x0 <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3), rep(5,3), rep(6,9))

# The above design is coherent when target rate = 0.20
foo <- cohere(prior, target=0.2, x0)
foo

# The design is incoherent if a larger target DLT rate is used.
foo2 <- cohere(prior, target=0.3, x0)
```

---

crm *Executing the CRM*

Description

`crm` is used to compute a dose for the next patient in a phase I trial according to the CRM.

Usage

```
crm(prior, target, tox, level, n = length(level), dosename = NULL,
    include = 1:n, pid = 1:n, conf.level = 0.9, method = "bayes",
    model = "empiric", intcpt = 3, scale = sqrt(1.34), model.detail = TRUE,
    patient.detail = TRUE, var.est = TRUE)
```

Arguments

`prior`	A vector of initial guesses of toxicity probabilities associated the doses.
`target`	The target DLT rate.
`tox`	A vector of patient outcomes; 1 indicates a toxicity, 0 otherwise.
`level`	A vector of dose levels assigned to patients. The length of `level` must be equal to that of `tox`.
`n`	The number of patients enrolled.
`dosename`	A vector containing the names of the regimens/doses used. The length of `dosename` must be equal to that of `prior`.
`include`	A subset of patients included in the dose calculation.
`pid`	Patient ID provided in the study. Its length must be equal to that of `level`.
`conf.level`	Confidence level for the probability/confidence interval of the returned dose-toxicity curve.
`method`	A character string to specify the method for parameter estimation. The default method `"bayes"` estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by `"mle"`.
`model`	A character string to specify the working model used in the method. The default model is `"empiric"`. A one-parameter logistic model is specified by `"logistic"`.

intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.
scale	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
model.detail	If FALSE, the model content of an "mtd" object will not be displayed. Default is TRUE.
patient.detail	If FALSE, patient summary of an "mtd" object will not be displayed. Default is TRUE.
var.est	If TRUE, variance of the estimate of the model parameter and probability/confidence interval for the dose-toxicity curve will be computed

Details

For maximum likelihood estimation, the variance of the estimate of β (post.var) is approximated by the posterior variance of β with a dispersed normal prior.

The empiric model is specified as $F(d, \beta) = d^{\exp(\beta)}$. The logistic model is specified as logit $(F(d, \beta))$ = intcpt $+ \exp(\beta) \times d$. For method="bayes", the prior on β is normal with mean 0. Exponentiation of β ensures an increasing dose-toxicity function.

Value

An object of class "mtd" is returned, consisting of the summary of dose assignments thus far and the recommendation of dose for the next patient.

prior	Initial guesses of toxicity rates.
target	The target probability of toxicity at the MTD.
ptox	Updated estimates of toxicity rates.
ptoxL	Lower confidence/probability limits of toxicity rates.
ptoxU	Upper confidence/probability limits of toxicity rates.
mtd	The updated estimate of the MTD.
prior.var	The variance of the normal prior.
post.var	The posterior variance of the model parameter.
estimate	Estimate of the model parameter.
method	The method of estimation.
model	The working model.
dosescaled	The scaled doses obtained via backward substitution.
tox	Patients' toxicity indications.
level	Dose levels assigned to patients.

References

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

Examples

```
# Create a simple data set
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2
level <- c(3, 4, 4, 3, 3, 4, 3, 2, 2, 2)
y <- c(0, 0, 1, 0, 0, 1, 1, 0, 0, 0)
foo <- crm(prior, target, y, level)
ptox <- foo$ptox  # updated estimates of toxicity rates
```

`crmsens` *Model Sensitivity in the CRM*

Description

Evaluate the model sensitivity in the CRM by indifference intervals.

Usage

```
crmsens(prior, target, model = "empiric", intcpt = 3, eps = 1e-06,
    maxit = 100, detail = FALSE)
```

Arguments

`prior`	A vector of initial guesses of toxicity probabilities associated the doses.
`target`	The target DLT rate.
`model`	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
`intcpt`	The intercept of the working logistic model. The default is 3. If `model`="empiric", this argument will be ignored.
`eps`	Error tolerance in the computation of indifference intervals.
`maxit`	Maximum number of iterations in the computation of indifference intervals.
`detail`	If TRUE, the details of the "H sets" will be displayed. Default is FALSE.

Value

The function `crmsens` returns the model sensitivity for the model specifications given by the user.

`Hset`	The "H sets" of the model parameter.
`iint`	The indifference intervals of the dose-toxicity model associated with the test doses.

References

Cheung, Y. K. and Chappell, R. (2002). A simple technique to evaluate model sensitivity in the continual reassessment method. Biometrics 58:671-674.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

crm, getprior

Examples

```
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2
foo <- crmsens(prior, target, model="logistic", intcpt=2, detail=TRUE)
```

---

crmsim *CRM Simulator*

Description

crmsim is used to generate simulation replicates of phase I trial using the (group) CRM under a specified dose-toxicity configuration.

Usage

```
crmsim(PI, prior, target, n, x0, nsim = 1, mcohort = 1, restrict = TRUE,
    count = TRUE, method = "bayes", model = "empiric", intcpt = 3,
    scale = sqrt(1.34), seed = 1009)
```

Arguments

PI	A vector of the true toxicity probabilites associated with the doses.
prior	A vector of initial guesses of toxicity probabilities associated with the doses. Must be of same length as PI.
target	The target DLT rate.
n	Sample size of the trial.
x0	The initial design. For one-stage TITE-CRM, it is a single numeric value indicating the starting dose. For two-stage TITE-CRM, it is a non-decreasing sequence of dose levels of length n.
nsim	The number of simulations. Default is set at 1.
mcohort	The number of patients enrolled before the next model-based update. Default is set at 1, i.e., a fully sequential update.
restrict	If TRUE, restrictions apply during the trials to avoid (1) skipping doses in escalation and (2) escalation immediately after a toxic outcome (i.e., incoherent escalation). If FALSE, dose assignments are purely model-based.

count	If TRUE, the number of the current simulation replicate will be displayed.
method	A character string to specify the method for parameter estimation. The default method "bayes" estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by "mle".
model	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.
scale	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
seed	Seed of the random number generator.

Value

An object of class "sim" is returned, consisting of the operating characteristics of the design specified. The time component of the design is suppressed for the CRM simulator. All "sim" objects generated by crmsim contain at least the following components:

PI	True toxicity rates.
prior	Initial guesses of toxicity rates.
target	The target probability of toxicity at the MTD.
n	Sample size.
x0	The initial design.
MTD	Distribution of the MTD estimates. If nsim=1, this is a single numeric value of the recommended MTD of in simulated trial.
level	Average number of patients treated at the test doses. If nsim=1, this is a vector of length n indicating the doses assigned to the patients in the simulated trial.
tox	Average number of toxicities seen at the test doses. If nsim=1, this is a vector of length n indicating the toxicity outcomes of the patients in the simulated trial.
beta.hat	The estimates of the model parameter throughout the simulated trial(s). The dose assignment of the jth patient in each trial corresponds to the jth element in each row.
final.est	The final estimates of the model parameter of the simulated trials.

References

O'Quigley, J. O., Pepe, M., and Fisher, L. (1990). Continual reassessment method: A practical design for phase I clinical trials in cancer. Biometrics 46:33-48.

Cheung, Y. K. (2005). Coherence principles in dose-finding studies. Biometrika 92:863-873.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

crm, titesim.

Examples

```
PI <- c(0.10, 0.20, 0.40, 0.50, 0.60, 0.65)
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2
x0 <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3), rep(5,3), rep(6,9))

# Generate a single replicate of two-stage group CRM trial of group size 3
foo <- crmsim(PI, prior, target, 24, x0, mcohort=3)
## Not run: plot(foo,ask=T)  # summarize trial graphically

# Generate 10 replicates of CRM trial with 24 subjects
foo10 <- crmsim(PI, prior, target, 24, 3, nsim=10, mcohort=2)
foo10
```

`getinit` *Calibrating an initial design*

Description

Returns an initial design that is compatible with the specified CRM setup when used in a two-stage design.

Usage

```
getinit(prior, target, n, nK = round(n/3), method = "bayes",
    model = "empiric", intcpt = 3, scale = sqrt(1.34), detail = FALSE)
```

Arguments

`prior`	A vector of initial guesses of toxicity probabilities associated the doses.
`target`	The target DLT rate.
`n`	The sample size of the trial.
`nK`	The minimum number of subjects required at the highest test dose in case of no toxicity throughout the trial.
`method`	A character string to specify the method for parameter estimation. The default method "bayes" estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by "mle".
`model`	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
`intcpt`	The intercept of the working logistic model. The default is 3. If `model`="empiric", this argument will be ignored.
`scale`	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
`detail`	If TRUE, intermediate designs will be displayed.

Details

An initial design will be incompatible to the CRM setup if the escalation pace is too conservative, i.e. slow. The algorithm in `getinit` starts the search of a compatible design with an aggressive initial design that starts a trial at the second highest dose. A more conservative design will be subsequently tested for compatibility if the current design is compatible. The sequence returned may be viewed as a conservative compatible initial design.

Value

A non-decreasing sequence of dose levels is returned.

References

Cheung, Y. K. (2005). Coherence principles in dose-finding studies. Biometrika 92:863-873.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

`cohere`

Examples

```
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2

# Seach stops because it requires at least 8 subjects at the highest dose
getinit(prior, target, 25, nK=8, method="mle", detail=TRUE)

# Search stops because an incompatible design is reached
getinit(prior, 0.3, 25, nK=8, method="mle", detail=TRUE)
```

---

getn *Sample size calculator for CRM trials*

Description

Sample size calculator for a one-stage Bayesian CRM (see Details for design specification).

Usage

```
getn(apcs, target, nlevel, psi, correction = TRUE, detail = FALSE)
```

Arguments

apcs	The desired average probability of correction selection (PCS) under the logistic calibration set.
target	The target DLT rate.
nlevel	The number of test doses.
psi	Effect size, i.e., odds ratio of the logistic dose-toxicity curves.
correction	Continuity correction is applied in the sample size calculation if TRUE (default). Otherwise if FALSE.
detail	Print only essential results for trial planning if FALSE (default). Otherwise if TRUE.

Details

The sample size calculation is based on empirical approximation for the CRM using the power (or empiric) dose-toxicity function, $F(d, \beta) = d^{\exp(\beta)}$, where β has a normal prior with mean 0 and variance 1.34, and the starting dose is the median level. The "skeleton" is obtained by setting halfwidth at $0.25\times$ target, and nu at the median level in the function getprior.

The calculation is intended to serve as an initial sample size for the CRM calibration process depicted in Figure 7.1 in Cheung (2011).

Value

An object of class "crmsize" is returned, consisting of the following components:

n	The calculated sample size.
astar	The desired average PCS.
target	The target DLT rate.
nlevel	The number of test doses.
psi	Odds ratio.
bstar	An intermediate value used to calculate the sample size. Shown only if detail=TRUE.
efficiency	Ratio of required sample sizes of the optimal benchmark and the CRM. Shown only if detail=TRUE.
correction	Whether continuity correction is applied. Shown only if detail=TRUE.
na	The CRM sample size before rounding up.
nb	The sample size lower bound before rounding up.
messages	String characters prompt warning messages and caveats regarding the sample size calculation.

References

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

getprior

Examples

```
apcs <- 0.6
target <- 0.25
nlevel <- 5
psi <- 1.8

# Sample size calculation with continuity correction
obj = getn(apcs, target, nlevel, psi, correction=TRUE)
obj

N = obj$n
```

---

getprior *Calibrating prior DLT rates*

Description

Returns a vector of initial guesses of toxicity probabilities associated the doses for a given model sensitivity (set of indifference intervals).

Usage

```
getprior(halfwidth, target, nu, nlevel, model = "empiric", intcpt = 3)
```

Arguments

halfwidth	The desired halfwidth of the indifference intervals.
target	The target DLT rate.
nu	The prior guess of MTD.
nlevel	The number of test doses.
model	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.

Details

getprior is an "inverse" function of crmsens which gives the indifference intervals for a given set of initial guesses.

Value

A vector of length nlevel is returned.

References

Cheung, Y. K. and Chappell, R. (2002). A simple technique to evaluate model sensitivity in the continual reassessment method. Biometrics 58:671-674.

Lee, S. M. and Cheung Y. K. (2009). Model calibration in the continual reassessment method. Clinical Trials 6, 227-238.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

crmsens

Examples

```
target <- 0.25
delta <- 0.10
mtd0 <- 3

# initial DLT rates with indifference intervals [0.15, 0.35].
prior <- getprior(delta, target, mtd0, nlevel=6, model="logistic")
```

---

titecrm *Executing the TITE-CRM*

Description

titecrm is used to compute a dose for the next patient in a phase I trial according to the TITE-CRM.

Usage

```
titecrm(prior, target, tox, level, n = length(level), weights = NULL,
followup = NULL, entry = NULL, exit = NULL, obswin = NULL,
scheme = "linear", conf.level = 0.9, dosename = NULL, include = 1:n,
pid = 1:n, method = "bayes", model = "empiric", var.est = TRUE,
scale = sqrt(1.34), intcpt = 3, model.detail = TRUE, patient.detail = TRUE,
tite = TRUE)
```

Arguments

prior	A vector of initial guesses of toxicity probabilities associated the doses.
target	The target DLT rate.
tox	A vector of patient outcomes; 1 indicates a toxicity, 0 otherwise.
level	A vector of dose levels assigned to patients. The length of level must be equal to that of tox.
n	The number of patients enrolled.

weights	A vector of weights assigned to observations. A weight must be between 0 and 1. If given, the arguments followup, entry, exit, obswin, and scheme will be ignored. If not supplied, users must provide follow-up information via the argument followup or entry and exit, as well as the observation window obswin. The length of weights must be equal to that of tox.
followup	A vector of follow-up times of patients. If given, the arguments entry and exit will be ignored.
entry	A vector of entry times of the patients.
exit	A vector of exit times of the patients due to either end of follow-up or toxicity.
obswin	The observation window with respect to which the MTD is defined. If not supplied, users must provide weights.
scheme	A character string to specify the method for assigning weights. Default is "linear". An adaptive weight function is specified by "adaptive".
conf.level	Confidence level for the probability/confidence interval of the returned dose-toxicity curve.
dosename	A vector containing the names of the regimens/doses used. The length of dosename must be equal to that of prior.
include	A subset of patients included in the dose calculation.
pid	Patient ID provided in the study. Its length must be equal to that of level.
method	A character string to specify the method for parameter estimation. The default method "bayes" estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by "mle".
model	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
var.est	If TRUE, variance of the estimate of the model parameter and probability/confidence interval for the dose-toxicity curve will be computed.
scale	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.
model.detail	If FALSE, the model content of an "mtd" object will not be displayed. Default is TRUE.
patient.detail	If FALSE, patient summary of an "mtd" object will not be displayed. Default is TRUE.
tite	If FALSE, the time components in patient summary of an "mtd" object will be omitted. Default in TRUE.

Details

The adaptive weighting scheme is given in Cheung and Chappell (2000) given in the reference list.

Value

An object of class "mtd" is returned, consisting of the summary of dose assignments thus far and the recommendation of dose for the next patient.

`prior`	Initial guesses of toxicity rates.
`target`	The target probability of toxicity at the MTD.
`ptox`	Updated estimates of toxicity rates.
`ptoxL`	Lower confidence/probability limits of toxicity rates.
`ptoxU`	Upper confidence/probability limits of toxicity rates.
`mtd`	The updated estimate of the MTD.
`prior.var`	The variance of the normal prior.
`post.var`	The posterior variance of the model parameter.
`estimate`	Estimate of the model parameter.
`method`	The method of estimation.
`model`	The working model.
`dosescaled`	The scaled doses obtained via backward substitution.
`tox`	Patients' toxicity indications.
`level`	Dose levels assigned to patients.
`followup`	Follow-up times of patients.
`obswin`	Observation window with respect to which the MTD is defined.
`weights`	Weights assigned to patients.
`entry`	Entry times of patients.
`exit`	Exit times of patients.
`scheme`	Weighting scheme.

References

Cheung, Y. K. and Chappell, R. (2000). Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics 56:1177-1182.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

`crm`

Examples

```
# Create a simple data set
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2
level <- c(3, 3, 3, 4, 4, 3, 2, 2, 2, 3)
y <- c(0, 0, 1, 0, 1, 0, 0, 0, 0, 0)
u <- c(178, 181, 168, 181, 24, 181, 179, 102, 42, 3)
tau <- 180
foo <- titecrm(prior, target, y, level, followup=u, obswin=tau)
rec <- foo$mtd  # recommend a dose level for next patient

# An example with adaptive weight
foo2 <- titecrm(prior, target, y, level, followup=u, obswin=tau, scheme="adaptive")
wts <- foo2$weights

# The `weights' argument makes `followup' and `obswin' obsolete
foo3 <- titecrm(prior, target, y, level, weights=wts, followup=u, obswin=tau)
## Not run: plot(foo3, ask=T)

## Patient time information via `entry' and `exit' arguments
# entry time (days since study begins)
entry <- c(7, 29, 49, 76, 92, 133, 241, 303, 363, 402)
# exit time (days since study begins)
exit <- c(185, 210, 217, 257, 116, 314, 420, 405, 405, 405)
foo4 <- titecrm(prior, target, y, level, exit=exit, entry=entry, obswin=tau)
## Not run: plot(foo4, ask=T)
```

`titesim` *TITE-CRM Simulator*

Description

`titesim` is used to generate simulation replicates of phase I trial using the TITE-CRM under a specified dose-toxicity configuration.

Usage

```
titesim(PI, prior, target, n, x0, nsim = 1, restrict = TRUE, obswin = 1,
tgrp = obswin, rate = 1, accrual = "fixed", surv = "uniform", scheme =
"linear", count = TRUE, method = "bayes", model = "empiric", intcpt = 3,
scale = sqrt(1.34), seed = 1009)
```

Arguments

`PI`	A vector of the true toxicity probabilites associated with the doses.
`prior`	A vector of initial guesses of toxicity probabilities associated with the doses. Must be of same length as `PI`.

target	The target DLT rate.
n	Sample size of the trial.
x0	The initial design. For one-stage TITE-CRM, it is a single numeric value indicating the starting dose. For two-stage TITE-CRM, it is a non-decreasing sequence of dose levels of length n.
nsim	The number of simulations. Default is set at 1.
restrict	If TRUE, restrictions apply during the trials to avoid (1) skipping doses in escalation and (2) escalation immediately after a toxic outcome (i.e., incoherent escalation). If FALSE, dose assignments are purely model-based.
obswin	The observation window with respect to which the MTD is defined.
tgrp	The minimum waiting time between two dose cohorts at the initial stage. Default is set as obswin, i.e., complete follow-up in all current patients is required before escalation to the next dose group. This argument is used only in two-stage TITE-CRM.
rate	Patient arrival rate: Expected number of arrivals per observation window. Example: obswin=6 and rate=3 means expecting 3 patients arrive in 6 time units.
accrual	Patient accrual scheme. Default is "fixed" whereby inter-patient arrival is fixed. Alternatively, use "poisson" to simulate patient arrivals by the Poisson process.
surv	Distribution for time-to-toxicity. Default is "uniform" where toxicity, if occurs, occurs uniformly on the interval [0,obswin]. Other survival distributions including exponential and Weibull are to be made available.
scheme	A character string to specify the method for assigning weights. Default is "linear". An adaptive weight is specified by "adaptive".
count	If TRUE, the number of the current simulation replicate will be displayed.
method	A character string to specify the method for parameter estimation. The default method "bayes" estimates the model parameter by the posterior mean. Maximum likelihood estimation is specified by "mle".
model	A character string to specify the working model used in the method. The default model is "empiric". A one-parameter logistic model is specified by "logistic".
intcpt	The intercept of the working logistic model. The default is 3. If model="empiric", this argument will be ignored.
scale	Standard deviation of the normal prior of the model parameter. Default is sqrt(1.34).
seed	Seed of the random number generator.

Value

An object of class "sim" is returned, consisting of the operating characteristics of the design specified.

For a "sim" object with nsim=1, the time component of individual subjects in the simulated trial is available via the values arrival, toxicity.time, and toxicity.study.time which respectively contain patients' arrival times, times-to-toxicity, and the times-to-toxicity per study time.

For a "sim" object with nsim>1, the time component of the design is summarized via the value Duration, which is the duration of the simulated trials, computed by adding the arrival time of the last patient and obswin.

All "sim" objects contain at least the following components:

PI	True toxicity rates.
prior	Initial guesses of toxicity rates.
target	The target probability of toxicity at the MTD.
n	Sample size.
x0	The initial design.
MTD	Distribution of the MTD estimates. If nsim=1, this is a single numeric value of the recommended MTD of in simulated trial.
level	Average number of patients treated at the test doses. If nsim=1, this is a vector of length n indicating the doses assigned to the patients in the simulated trial.
tox	Average number of toxicities seen at the test doses. If nsim=1, this is a vector of length n indicating the toxicity outcomes of the patients in the simulated trial.
beta.hat	The estimates of the model parameter throughout the simulated trial(s). The dose assignment of the jth patient in each trial corresponds to the jth element in each row.
final.est	The final estimates of the model parameter of the simulated trials.

References

Cheung, Y. K. and Chappell, R. (2000). Sequential designs for phase I clinical trials with late-onset toxicities. Biometrics 56:1177-1182.

Cheung, Y. K. (2005). Coherence principles in dose-finding studies. Biometrika 92:863-873.

Cheung, Y. K. (2011). Dose Finding by the Continual Reassessment Method. New York: Chapman & Hall/CRC Press.

See Also

crmsim, titecrm.

Examples

```
PI <- c(0.10, 0.20, 0.40, 0.50, 0.60, 0.65)
prior <- c(0.05, 0.10, 0.20, 0.35, 0.50, 0.70)
target <- 0.2
x0 <- c(rep(1,3), rep(2,3), rep(3,3), rep(4,3), rep(5,3), rep(6,9))

# Generate a single replicate of two-stage TITE-CRM trial of size 24
foo <- titesim(PI, prior, target, 24, x0, obswin=6, rate=4, accrual="poisson")
## Not run: plot(foo, ask=T)  # summarize trial graphically

# Generate 10 replicates of TITE-CRM trial of size 24
foo10 <- titesim(PI, prior, target, 24, 3, nsim=10, obswin=6, rate=4, accrual="poisson")

foo10
```

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