Package 'dfpk'

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Title Bayesian Dose-Finding Designs using Pharmacokinetics (PK) for Phase I Clinical Trials

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Description Statistical methods involving PK measures are provided, in the dose allocation process during a Phase I clinical trials. These methods, proposed by Ursino et al, (2017) <doi:10.1002/bimj.201600084>, enter pharmacokinetics (PK) in the dose finding designs in different ways, including covariates models, dependent variable or hierarchical models. This package provides functions to generate data from several scenarios and functions to run simulations which their objective is to determine the maximum tolerated dose (MTD).

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Depends R (>= 3.4.0), Rcpp (>= 0.12.11), rstan (>= 2.18.1)

Imports ggplot2 (>= 2.0.0), dfcrm, methods, stats, graphics, grDevices, PK

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RcppModules stan_fit4logit_reg_pkcov_mod, stan_fit4cdf_reg_dtox_mod, stan_fit4logit_reg_pkpop_mod, stan_fit4cdf_reg_pktox_mod, stan_fit4logit_reg_pklogit_mod, stan_fit4reg_auc_mod

LazyData true

NeedsCompilation yes

SystemRequirements GNU make

URL http://github.com/artemis-toumazi/dfpk

BugReports http://github.com/artemis-toumazi/dfpk/issues

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R topics documented:

`dfpk-package` *Bayesian Dose-Finding Designs using Pharmacokinetics (PK) for Phase I Clinical Trials.*

Description

Statistical methods involving PK measures are provided, in the dose allocation process during a Phase I clinical trials. These methods, proposed by Ursino et al, (2017) <doi:10.1002/bimj.201600084>, enter pharmacokinetics (PK) in the dose finding designs in different ways, including covariates models, dependent variable or hierarchical models. This package provides functions to generate data from several scenarios and functions to run simulations which their objective is to determine the maximum tolerated dose (MTD).

Details

The three main functions of the dfpk package are `sim.data`, `nsim` and `nextDose`, for generating PK data based on the input settings, simulating "n" clinical trials and determining the next recommended dose for an ongoing phase I clinical trial based on an enrolled patient's data, respectively. Subsequently, six dose-finding methods/models can be applied: `dtox`, `pktox`, `pkcrm`, `pkcov`, `pkpop`, and `pklogit` which each one creates a Bayesian model and fits it using **Stan**.

Since **dfpk** is based on **Stan** models, a C++ compiler is required. The program Rtools (available on https://cran.r-project.org/bin/windows/Rtools/) comes with a C++ compiler for Windows while on Mac, you should use Xcode. For further instructions on how to get the compilers running, see the prerequisites section on https://github.com/stan-dev/rstan/wiki/RStan-Getting-Started.

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References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

`AUC.estim` *Estimation of the area under the curve, AUC.*

Description

The AUC.estim function uses a compartmentl method or a non-compartmental method to estimate the AUC. In the field of pharmacokinetics, the area under the curve (AUC) is the area under the curve (mathematically known as definite integral) in a plot of concentration of drug in blood plasma against time. AUC is computed as the doses over the second pharmacokinetic's parameter, the clearance (CL).

Usage

```
AUC.estim(t, conc, dose, method = 2)
```

Arguments

`t`	A vector of the sampling time.
`conc`	The concentration of the drug in blood plasma.
`dose`	A vector of dose levels assigned to patients.

`method` A string number specifying the method for calculation of AUC. Possible values are "1" for a compartmental method and "2" for non-compartmental method (default=2).

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References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

pk.estim, nsim

Examples

```
#### A Compartmental method for calculation of AUC ###

dose = c(12.59972, 34.65492, 44.69007, 60.80685, 83.68946, 100.37111)
conc = c(20, 30, 40, 50, 60, 70)
t = seq(0, 24, length.out=48)
auc_estimation <- AUC.estim(t, conc, dose, method = 1)
auc_estimation
```

---

dose-class *An S4 class to perform parameter estimation at each step during a dose-finding trial.*

Description

An S4 class to perform parameter estimation at each step during a dose-finding trial.

Slots

`N` The total number of enrolled patients.

`y` A binary vector of toxicity outcomes from previous patients; 1 indicates a toxicity, 0 otherwise.

`AUCs` A vector with the computed AUC values of each patient.

`doses` A vector with the doses panel.

`x` A vector with the dose level assigned to the patients.

`theta` The toxicity threshold.

`options` a list of Stan model's options.

`newDose` The next recommended dose (RD) level; equals to 0 if the trial has stopped, according to the stopping rules.

`pstim` The estimated mean probabilities of toxicity.

`pstimQ1` The 1st quartile of estimated probability of toxicity.

`pstimQ3` The 3rd quartile of estimated probability of toxicity.

`parameters` The Stan model's estimated parameters.

`model` A character string to specify the selected dose-finding model. See for details `dtox`, `pkcov`, `pkcrm`, `pktox`, `pkpop`, `pklogit`.

`dosefinding-class` *An S4 class to represent a dosefinding results.*

Description

An S4 class to represent a dosefinding results.

Slots

`pid` The patient's ID provided in the study.

`N` The total sample size per trial.

`time` The sampling time points.

`doses` A vector with the doses panel.

`conc` The estimated concentration values for each patient at each dose.

`p0` The skeleton of CRM for `pkcrm`; defaults to NULL.

`L` The AUC threshold to be set before starting the trial for `pkcrm`; defaults to NULL.

`nchains` The number of chains for the Stan model.

`niter` The number of iterations for the Stan model.

`nadapt` The number of warmup iterations for the Stan model.

`newDose` The next maximum tolerated dose (MTD) if TR=1 otherwise the percentage of MTD selection for each dose level after all trials starting from dose 0; equals to 0 if the trial has stopped before the end, according to the stopping rules.

`MTD` A vector containing the next maximum tolerated doses (MTD) of each trial (TR); equals to 0 if the trial has stopped before the end, according to the stopping rules.

`MtD` The final next maximum tolerated (MTD) dose after all the trials.

`theta` The toxicity target.

`doseLevels` A vector of dose levels assigned to patients in the trial.

`toxicity` The estimated toxicity outcome.

`AUCs` A vector with the computed AUC values of each patient.

`TR` The total number of trials to be simulated.

`preal` The prior toxicity probabilities.

`pstim` The estimated mean probabilities of toxicity.

`pstimQ1` The 1st quartile of estimated probability of toxicity.

`pstimQ3` The 3rd quartile of estimated probability of toxicity.

`model` A character string to specify the selected dose-finding model. See for details `dtox`, `pkcov`, `pkcrm`, `pktox`, `pkpop`, `pklogit`..

`seed` The seed of the random number generator that is used at the beginning of each trial.

`dtox` *Dose finding method DTOX.*

Description

The DTOX model enables us to estimate posterior probability of toxicity p_T versus dose directly. The dose-toxicity model is given by:

$$p_T(d_k, \boldsymbol{\beta}) = \Phi(-\beta_0 + \beta_1 log(d_k))$$

where $\beta_q \sim U(l_q, u_q) \; \forall \; q = 0, 1$ and

$$beta0mean = c(l_0, u_0),$$

$$beta1mean = c(l_1, u_1)$$

where default choices are beta0mean = c(0, 16.71) and beta1mean = c(0, 6.43). So the default choices for model's priors are given by

$$betapriors = c(l_0 = 0, u_0 = 16.71, l_1 = 0, u_1 = 6.43)$$

Finally, the DTOX model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
dtox(y, doses, x, theta, prob = 0.9, options=list(nchains = 4, niter = 4000,
     nadapt = 0.8), betapriors = c(0, 16.71, 0, 6.43), thetaL = NULL,
     auc = NULL, deltaAUC = NULL, p0 = NULL, L = NULL, CI = TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the value for the prior distribution of the regression parameters in the model; defaults to betapriors = c(beta0mean, beta1mean), where beta0mean = c(0, 16.71) and beta1mean = c(0, 6.43).
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by dtox contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

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References

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Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

sim.data, nsim, nextDose

Examples

```
## Not run:
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)

    res <- dtox(y, doses, x, theta, options = options)

## End(Not run)
```

---

invlogit *Inverse logistic functions.*

Description

Inverse-logit function, transforms continuous values to the range (0, 1)

Usage

```
invlogit(x)
```

Arguments

x	A vector of continuous values

Details

The Inverse-logit function defined as: $logit^{-1}(x) = e^x/(1 + e^x)$ transforms continuous values to the range (0, 1), which is necessary, since probabilities must be between 0 and 1 and maps from the linear predictor to the probabilities.

Value

A vector of estimated probabilities

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`nextDose` *Next dose determination of a phase I clinical trial.*

Description

nextDose is used to perform parameter estimation at each step during a dose-finding trial. Determines the next or recommended dose level in a phase I clinical trial.

Usage

```
nextDose(model, y, AUCs, doses, x, theta, options, prob = 0.9,
  betapriors = NULL, thetaL = NULL, p0 = NULL, L = NULL,
  deltaAUC = NULL, CI = TRUE)
```

Arguments

`model`	A character string to specify the selected dose-finding model. See for details dtox, pkcov, pkcrm, pktox, pkpop, pklogit.
`y`	A binary vector of the toxicity outcomes from previous patients; 1 indicates a toxicity, 0 otherwise.
`AUCs`	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
`doses`	A vector with the doses panel.
`x`	A vector with the dose level assigned to the patients.
`theta`	The toxicity threshold.
`options`	A list with the Stan model's options.
`prob`	The threshold of the posterior probability of toxicity for the stopping rule in the selected model; defaults to 0.9. See for details dtox, pkcov, pkcrm, pktox, pkpop, pklogit.
`betapriors`	A vector with the value for the prior distribution of the regression parameters in the model; defaults to NULL.
`thetaL`	A second threshold of AUC in the pkcrm model; defaults to theta in the PKCRM model and NULL for the models dtox, pkcov, pktox, pkpop and pklogit.
`p0`	The skeleton of CRM for pkcrm; defaults to NULL.
`L`	The AUC threshold to be set before starting the trial for pkcrm; defaults to NULL.
`deltaAUC`	A vector of the difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
`CI`	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

An object of class "dose" is returned, consisting of determination of the next recommended dose and estimations. Objects generated by nextDose contain at least the following components:

N	The total number of enrolled patients.
y	A binary vector of toxicity outcomes from previous patients; 1 indicates a toxicity, 0 otherwise.
AUCs	A vector with the computed AUC values of each patient.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The tocixity threshold.
options	List with the Stan model's options.
newDose	The next recommended dose (RD) level; equals to 0 if the trial has stopped, according to the stopping rules.
pstim	The mean values of the estimated probabilities of toxicity.
pstimQ1	The 1st quartile of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
pstimQ3	The 3rd quartile of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.
model	A character string to specify the selected dose-finding model. See for details dtox, pkcov, pkcrm, pktox, pkpop, pklogit.

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References

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Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

nsim

Examples

```
  ## Not run:
doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
theta <- 0.2
options <- list(nchains = 4, niter = 4000, nadapt = 0.9)
AUCs <- c(1.208339,  5.506040,  6.879835,  3.307928,  3.642430,
          10.271291,  3.885522,  3.086622,  2.537158,  5.525917,
          8.522176,  4.642741, 11.048531, 10.246976,  5.226807)
x <- c(1, 2, 3, 4, 5, 6, 4, 4, 4, 5, 5, 4, 4, 5, 5)
y <- c(0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 0, 0)
nextD <- nextDose(model = "pktox", y=y, AUCs=AUCs, doses=doses,
                  x=x, theta=theta, options=options)

## End(Not run)
```

`nsim` *Simulate a single or n prospective clinical trial(s) using the PK measure in the dose finding designs.*

Description

nsim is used to simulate a single or "n" prospective clinical trial(s) using the PK data and then link them to toxicity under a specified dose-toxicity configuration. The objective is to determine the maximum tolerated dose (MTD).

Usage

```
nsim(doses, N, cohort, icon, theta, model, simulatedData, TR, prob = 0.9, AUCmethod = 2,
     options = list(nchains = 4, niter = 4000, nadapt = 0.8), betapriors = NULL,
     thetaL=NULL, p0 = 0, L = 0, CI = FALSE, seed = 190591)
```

Arguments

`doses`	A vector with the doses panel.
`N`	The total sample size per trial.
`cohort`	The cohort size in the trial.
`icon`	A vector containing the index of real blood sampling.
`theta`	The toxicity threshold.
`model`	A character string to specify the selected dose-finding model. See for details `dtox`, `pkcov`, `pkcrm`, `pktox`, `pkpop`, `pklogit`.
`simulatedData`	A list for each trial containing the simulated datasets; a "scen" object. See for details `sim.data`.
`TR`	The total number of trials to be simulated.

prob	The threshold of the posterior probability of toxicity for the stopping rule in the selected model; defaults to 0.9. See for details dtox, pkcov, pkcrm, pktox, pkpop, pklogit.
AUCmethod	A string number specifying the estimation method for AUC. Valid choices are "1" for a "compartmental method" and "2" for non-compartmental method; defaults to 2.
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8)
betapriors	A vector with the value for the prior distribution of the regression parameters in the selected model; defaults to NULL.
thetaL	A second threshold of AUC in the pkcrm model; defaults to theta in the PKCRM model and NULL for the models dtox, pkcov, pktox, pkpop and pklogit.
p0	The skeleton of CRM for pkcrm; defaults to NULL.
L	The AUC threshold to be set before starting the trial for pkcrm; defaults to NULL.
CI	A logical constant indicating the estimated 95% credible interval; defaults to FALSE.
seed	The seed of the random number generator that is used at the beginning of each trial; defaults to 190591.

Value

An object of class "dosefinding" is returned, consisting of determination of the next recommended dose and estimations. Objects generated by nsim contain at least the following components:

pid	The patient's ID during the trial.
N	The total sample size per trial.
time	The sampling time points.
doses	A vector with the doses panel.
conc	The estimated concentration values for each patient at each dose.
nchains	The number of chains in the Stan model.
niter	The number of iterations for each chain in the Stan model.
nadapt	The number of warmup iterations.
newDose	The next maximum tolerated dose (MTD) if TR=1 otherwise the percentage of MTD selection for each dose level after all trials starting from dose 0; equals to 0 if the TR=1 has stopped before the end, according to the stopping rules.
MTD	A vector containing the next maximum tolerated doses (MTD) of each trial (TR); equals to 0 if the trial has stopped before the end, according to the stopping rules.
theta	The tocixity threshold.
doseLevels	A vector of dose levels assigned to patients in the trial.
toxicity	The estimated toxicity outcome.

AUCs	A vector with the computed AUC values of each patient.
TR	The total number of trials to be simulated.
preal	The prior toxicity probabilities.
pstim	The mean values of the estimated probabilities of toxicity.
pstimQ1	The 1st quartile of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
pstimQ3	The 3rd quartile of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
model	A character string to specify the selected dose-finding model. See for details dtox, pkcov, pkcrm, pktox, pkpop, pklogit.
seed	The seed of the random number generator that is used at the beginning of each trial.

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References

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Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

sim.data

Examples

```
## Not run:
    TR = 10                                  # Total number of simulations
    N = 30
    limitTox <- 10.96
    PKparameters <- c(2, 10, 100)              # PK parameters ka,CL,V
    omegaIIV <- 0.7
    omegaAlpha <- 0
    doses <- c(12.59972, 34.65492, 44.69007, 60.80685, 83.68946, 100.37111)
    timeSampling <- seq(0, 24, length.out=48)
    sigma <- rep(0.2, length(timeSampling))

    gen.scen <- sim.data(PKparameters,omegaIIV,omegaAlpha,sigma,doses,
                         limitTox,timeSampling, N, TR)

    cohort = 1
    simulatedData <- gen.scen
```

```
icon <- c(2:6, round(seq(9, 48, ((48-9)/4))))
theta <- 0.2

##############################################
############### Select a model ###############
##############################################

model = "pktox"

##########################################
############ Run the simulation(s) #########
##########################################

results_sim <- nsim(doses, N, cohort, icon, theta, model, simulatedData, TR,
                    AUCmethod = 1)
results_sim

## End(Not run)
```

---

pk.estim *The pharmacokinetic's (PK) measure of exposure.*

Description

Estimation of the pharmacokinetic's (PK) measure of exposure.

Usage

```
pk.estim(par, t, dose, conc)
```

Arguments

par	The pharmacokinetic's parameters.
t	The time sampling.
dose	The doses levels of the drug.
conc	The concentration of the drug in blood plasma.

Author(s)

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References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

AUC.estim, nsim

Examples

```
par <- c(2,10,100)
conc <- c(20,30,40,50,60,70)
t <- seq(0,24,length.out=48)
dose <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
pk.estim(par,t,dose,conc)
```

---

pkcov *Dose finding method PKCOV.*

Description

The PKCOV model is a modification of the method proposed by Piantadosi and Liu (1996) who suggested to use the AUC as covariate for p_T, probability of toxicity, through the logit link. Therefore, the dose-toxicity model is:

$$logit(p_T(d_k, \Delta z_{dk}, \boldsymbol{\beta})) = -\beta_0 + \beta_1 log(d_k) + \beta_2 \Delta z_{dk}$$

where $\boldsymbol{\beta} = (\beta_1, \beta_2)$, β_0 is a constant with $\beta_0 = -beta0mean$,

$$\beta_1 \sim U(l_1, u_1),$$

$$\beta_2 \sim U(0, 5),$$

$$beta1mean = c(l_1, u_1)$$

where default choices are beta0mean = -14.76, beta1mean = c(0, 8.23) and Δz_{dk} is the difference between the logarithm of population AUC at dose d_k and z, the logarithm of AUC of the subject at the same dose. Therefore, the default choices for model's priors are given by

$$betapriors = c(beta0mean = -14.76, l_1 = 0, u_1 = 8.23)$$

Finally, the PKCOV model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
pkcov(y,auc,doses,x,theta, deltaAUC, prob = 0.9, options=list(nchains = 4,
      niter = 4000, nadapt = 0.8), betapriors = c(-14.76, 0, 3.23+5),
      thetaL = NULL, p0 = NULL, L = NULL, CI =TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the value for the prior distribution of the regression parameters in the model; defaults to betapriors = c(beta0mean, beta1mean), where beta0mean = -14.76 and beta1mean = c(0, 8.23).
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by pkcov contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Piantadosi, S. and Liu, G. (1996) Improved designs for dose escalation studies using pharmacokinetic measurements. Statistics in Medicine, 15 (15), 1605-1618.

See Also

sim.data, nsim, nextDose

Examples

```
## Not run:
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2
    AUCs <-  c(0.43, 1.4, 5.98, 7.98, 11.90, 3.45)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)
    deltaAUC <- c(0, 1.3, -0.34, -2.7, 0.39, -2.45)
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    res <- pkcov(y, AUCs, doses, x, theta, deltaAUC, options=options)

## End(Not run)
```

---

pkcrm *Dose finding method PKCRM.*

Description

The PKCRM model is a combination of PKLIM as given below:

$$z_i|\boldsymbol{\beta}, \nu \sim N\left(\beta_0 + \beta_1 \log d_i, \nu^2\right)$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)$ are the regression parameters and ν is the standard deviation, and the Continual Reassessment Method's (CRM) model:

$$p_T(d_k, \beta) = d_k^{\beta}(CRM)$$

The default choices of the priors are:

$$\boldsymbol{\beta}|\nu \sim N(m, \nu * beta0),$$

$$\nu \sim Beta(1, 1),$$

$$m = (-log(CL_{pop}), 1)$$

where Cl_{pop} is the population clearance. where default choices are $Cl_{pop} = 10$ and beta0 = 10000. Therefore, the default choices for model's priors are given by

$$betapriors = c(Cl_{pop} = 10, beta0 = 10000)$$

For the CRM model:

Skeleton CRM = (0.01, 0.05, 0.1, 0.2, 0.35, 0.45) and

$$\beta \sim N(0, 1.34)$$

Finally, the PKCRM model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
pkcrm(y, auc, doses, x, theta, p0, L, prob = 0.9, options = list(nchains = 4,
      niter = 4000, nadapt = 0.8), betapriors = c(10, 10000), thetaL=NULL,
      deltaAUC = NULL, CI = TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the value for the prior distribution of the regression parameters in the model; defaults to betapriors = c(Cl_{pop}, beta0), where Cl_{pop} = 10 and beta0 = 10000.
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by pkcrm contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Patterson, S., Francis, S., Ireson, M., Webber, D., and Whitehead, J. (1999) A novel bayesian decision procesure for early-phase dose-finding studies. Journal of Biopharmaceutical Statistics, 9 (4), 583-597.

Whitehead, J., Patterson, S., Webber, D., Francis, S., and Zhou, Y. (2001) Easy-to-implement bayesian methods for dose-escalation studies in healthy volunteers. Biostatistics, 2 (1), 47-61.

See Also

sim.data, nsim, nextDose

Examples

```
## Not run:
    p0 <- c(.01,.05,.1,.2,.35,0.45)         # Skeleton of CRM
    L <- log(15.09)                         # Threshold set
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    AUCs <-  c(0.43, 1.4, 5.98, 7.98, 11.90, 3.45)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)

    res <- pkcrm(y, AUCs, doses, x, theta, p0, L, options = options)

## End(Not run)
```

pklogit *Dose finding method PKLOGIT.*

Description

The PKLOGIT model, inspired by Whitehead et al. (2007), uses z_i instead of dose d_i as a covariate in a logistic regression model for p_T. Therefore, we have that:

$$\text{logit}(p_T(z, \boldsymbol{\beta})) = -\beta_2 + \beta_3 z$$

with a bivariate Uniform distribution as prior distribution for $\boldsymbol{\beta} = (\beta_2, \beta_3)$ and the hierarchical model of PK-toxicity for z_i given as:

$$z_i|\boldsymbol{\beta}, \nu \sim N\left(\beta_0 + \beta_1 \log d_i, \nu^2\right)$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)$ are the regression parameters and ν is the standard deviation.

The default choices of the priors are:

$$\boldsymbol{\beta}|\nu \sim N(m, \nu * beta0),$$

$$\nu \sim Beta(1, 1),$$

$$m = (-log(CL_{pop}), 1),$$

where Cl_{pop} is the population clearance.

$$\beta_2 \sim U(0, beta2mean),$$

$$\beta_3 \sim U(0, beta3mean)$$

where default choices are $Cl_{pop} = 10$, beta0 = 10000, beta2mean = 20 and beta3mean = 10. Therefore, the default choices for model's priors are given by

$$betapriors = c(Cl_{pop} = 10, beta0 = 10000, beta2mean = 20, beta3mean = 10)$$

Finally, the PKLOGIT model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
pklogit(y, auc, doses, x, theta, prob = 0.9, options = list(nchains = 4, niter = 4000,
        nadapt = 0.8), betapriors = c(10, 10000, 20, 10), thetaL = NULL,
        p0=NULL, L=NULL, deltaAUC=NULL, CI = TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the values for the prior distribution of the regression parameters in the model; defaults to betapriors = c(Cl_{pop}, beta0, beta2mean, beta3mean), where $Cl_{pop} = 10$, beta0 = 10000, beta2mean = 20 and beta3mean = 10.
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by pklogit contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Whitehead, J., Zhou, Y., Hampson, L., Ledent, E., and Pereira, A. (2007) A bayesian approach for dose-escalation in a phase i clinical trial incorporating pharmacodynamic endpoints. Journal of Biopharmaceutical Statistics, 17 (6), 1117-1129.

See Also

sim.data, nsim, nextDose

Examples

```
## Not run:
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    AUCs <-  c(0.43, 1.4, 5.98, 7.98, 11.90, 3.45)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)

    res <- pklogit(y, AUCs, doses, x, theta, options = options)

## End(Not run)
```

---

pkpop *Dose finding method PKPOP.*

Description

The PKPOP model is a variation of the PKLOGIT model which replaced AUCs (z_j) with AUC of the population ($z_{k,pop}$), where $z_{k,pop}$ is the mean value of the logarithm of AUC at dose k, predicted by the hierarchical model:

$$z_i|\boldsymbol{\beta}, \nu \sim N\left(\beta_0 + \beta_1 \log d_i, \nu^2\right)$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)$ are the regression parameters and ν is the standard deviation. and the logistic regression model:

$$\text{logit}(p_T(z_{k,pop}, \boldsymbol{\beta})) = -\beta_3 + \beta_4 z_{k,pop}$$

with a bivariate Uniform distribution as prior distribution for the parameters $\boldsymbol{\beta} = (\beta_3, \beta_4)$.

The default choices of the priors are:

$$\boldsymbol{\beta}|\nu \sim N(m, \nu * beta0),$$

$$\nu \sim Beta(1, 1),$$

$$m = (-log(CL_{pop}), 1),$$

where Cl_{pop} is the population clearance.

$$\beta_3 \sim U(0, beta3mean),$$

$$\beta_4 \sim U(0, beta4mean)$$

where default choices are $Cl_{pop} = 10$, beta0 = 10000, beta3mean = 10 and beta4mean = 5. Therefore, the default choices for model's priors are given by

$$betapriors = c(Cl_{pop} = 10, beta0 = 10000, beta3mean = 10, beta4mean = 5)$$

Finally, the PKPOP model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
pkpop(y, auc, doses, x, theta, prob = 0.9, options = list(nchains = 4, niter = 4000,
      nadapt = 0.8), betapriors = c(10, 10000, 10, 5), thetaL = NULL, p0=NULL,
      L=NULL, deltaAUC=NULL, CI = TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the value for the prior distribution of the regression parameters in the model; defaults to betapriors = c(Cl_{pop}, beta0, beta3mean, beta4mean), where $Cl_{pop} = 10$, beta0 = 10000, beta3mean = 10 and beta4mean = 5.
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by pkpop contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Patterson, S., Francis, S., Ireson, M., Webber, D., and Whitehead, J. (1999) A novel bayesian decision procedure for early-phase dose-finding studies. Journal of Biopharmaceutical Statistics, 9 (4), 583-597.

Whitehead, J., Patterson, S., Webber, D., Francis, S., and Zhou, Y. (2001) Easy-to-implement bayesian methods for dose-escalation studies in healthy volunteers. Biostatistics, 2 (1), 47-61.

Whitehead, J., Zhou, Y., Hampson, L., Ledent, E., and Pereira, A. (2007) A bayesian approach for dose-escalation in a phase i clinical trial incorporating pharmacodynamic endpoints. Journal of Biopharmaceutical Statistics, 17 (6), 1117-1129.

See Also

pklogit, sim.data, nsim, nextDose

Examples

```
## Not run:
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2      # choice
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    AUCs <-  c(0.43, 1.4, 5.98, 7.98, 11.90, 3.45)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)

    res <- pkpop(y, AUCs, doses, x, theta, options = options)

## End(Not run)
```

pktox *Dose finding method PKTOX.*

Description

The PKTOX model is essentially the PKLOGIT model with a probit regression model replacing the logistic regression, that is given by:

$$p_T(z, \boldsymbol{\beta}) = \Phi(-\beta_2 + \beta_3 z)$$

with a bivariate Uniform distribution as prior distribution for the parameters $\boldsymbol{\beta} = (\beta_2, \beta_3)$ and the hierarchical model of PK-toxicity for z_i given as:

$$z_i|\boldsymbol{\beta}, \nu \sim N\left(\beta_0 + \beta_1 \log d_i, \nu^2\right)$$

where $\boldsymbol{\beta} = (\beta_0, \beta_1)$ are the regression parameters and ν is the standard deviation.

The default choices of the priors are:

$$\boldsymbol{\beta}|\nu \sim N(m, \nu * beta0),$$

$$\nu \sim Beta(1, 1),$$

$$m = (-log(CL_{pop}), 1),$$

where Cl_{pop} is the population clearance.

$$\beta_2 \sim U(0, beta2mean),$$

$$\beta_3 \sim U(0, beta3mean)$$

where default choices are $Cl_{pop} = 10$, beta0 = 10000, beta2mean = 20 and beta3mean = 10. Therefore, the default choices for model's priors are given by

$$betapriors = c(Cl_{pop} = 10, beta0 = 10000, beta2mean = 20, beta3mean = 10)$$

Finally, the PKTOX model has the following stopping rule in toxicity: if

$$P(p_T(dose) > theta) > prob$$

then, no dose is suggested and the trial is stopped.

Usage

```
pktox(y, auc, doses, x, theta, prob = 0.9, options = list(nchains = 4, niter = 4000,
      nadapt = 0.8), betapriors = c(10, 10000, 20, 10), thetaL = NULL,
      p0=NULL, L=NULL, deltaAUC=NULL, CI = TRUE)
```

Arguments

y	A binary vector of patient's toxicity outcomes; TRUE indicates a toxicity, FALSE otherwise.
doses	A vector with the doses panel.
x	A vector with the dose level assigned to the patients.
theta	The toxicity target.
prob	The threshold of the posterior probability of toxicity for the stopping rule; defaults to 0.9.
betapriors	A vector with the value for the prior distribution of the regression parameters in the model; defaults to betapriors = c(Cl_{pop}, beta0, beta2mean, beta3mean), where $Cl_{pop} = 10$, beta0 = 10000, beta2mean = 20 and beta3mean = 10.
options	A list with the Stan model's options; the number of chains, how many iterations for each chain and the number of warmup iterations; defaults to options = list(nchains = 4, niter = 4000, nadapt = 0.8).
auc	A vector with the computed AUC values of each patient for pktox, pkcrm, pklogit and pkpop; defaults to NULL.
deltaAUC	The difference between computed individual AUC and the AUC of the population at the same dose level (defined as an average); argument for pkcov; defaults to NULL.
p0	The skeleton of CRM for pkcrm; defaults to NULL (must be defined only in the PKCRM model).
L	The AUC threshold to be set before starting the trial for pklogit, pkcrm and pktox; defaults to NULL (must be defined only in the PKCRM model).
thetaL	A second threshold of AUC; must be defined only in the PKCRM model.
CI	A logical constant indicating the estimated 95% credible interval; defaults to TRUE.

Value

A list is returned, consisting of determination of the next recommended dose and estimations of the model. Objects generated by pktox contain at least the following components:

newDose	The next maximum tolerated dose (MTD); equals to "NA" if the trial has stopped before the end, according to the stopping rules.
pstim	The mean values of estimated probabilities of toxicity.
p_sum	The summary of the estimated probabilities of toxicity if CI = TRUE, otherwise is NULL.
parameters	The estimated model's parameters.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Whitehead, J., Zhou, Y., Hampson, L., Ledent, E., and Pereira, A. (2007) A bayesian approach for dose-escalation in a phase i clincial trial incorporating pharmacodynamic endpoints. Journal of Biopharmaceutical Statistics, 17 (6), 1117-1129.

See Also

pklogit, sim.data, nsim, nextDose

Examples

```
## Not run:
    doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
    theta <- 0.2
    options <- list(nchains = 2, niter = 4000, nadapt = 0.8)
    AUCs <-  c(0.43, 1.4, 5.98, 7.98, 11.90, 3.45)
    x <- c(1,2,3,4,5,6)
    y <- c(FALSE,FALSE,FALSE,FALSE,TRUE,FALSE)

    res <- pktox(y, AUCs, doses, x, theta, options = options)

## End(Not run)
```

`plot,dose,missing-method`

The graphical representation of dose escalation for each patient in the trial.

Description

The graphical representation of dose escalation for each patient in the trial.

Usage

```
## S4 method for signature 'dose,missing'
plot(x, y = NA, ask = TRUE, CI = TRUE, ...)
```

Arguments

x	a "dose" object.
y	the "y" argument is not used in the plot-method for "dose" object.
ask	Choose plot or not; defaults to TRUE.
CI	Indicate if the "dose" object includes the 95% credible interval for the posterior dose response plot; defaults to TRUE.
...	other arguments to the plot.default function can be passed here.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

---

plot,dosefinding,missing-method

The graphical representation of dose-finding results.

Description

A plot selection showing either the dose escalation allocation of the selected trial or the plot of the final posterior distributions of the probability of toxicity at each dose or the boxplot of the sampling distribution of the probability of toxicity at each dose in the end of the trial over the total number of trials.

Usage

```
## S4 method for signature 'dosefinding,missing'
plot(x, y = NA, TR = 1, ask = TRUE,
  CI = TRUE, ...)
```

Arguments

x	a "dosefinding" object.
y	the "y" argument is not used in the plot-method for "dosefinding" object.
TR	The number of the selected trial that user wants to plot; defaults to 1.
ask	Choose plot or not; defaults to TRUE.

CI	Indicate if the "dosefinding" object includes the 95% credible interval for the posterior dose response plot; defaults to TRUE.
...	other arguments to the plot.default function can be passed here.

Author(s)

Artemis Toumazi <artemis.toumazi@artemis.com>, Moreno Ursino <moreno.ursino@inserm.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

---

plot,scen,missing-method

The graphical representation of the drug's concentration in the plasma at time t after the drug administration.

Description

The graphical representation of the drug's concentration in the plasma at time t after the drug administration.

Usage

```
## S4 method for signature 'scen,missing'
plot(x, y = NA, col = rainbow(length(x@doses)),
  xlab = "Time (hours)", ylab = "Concentration (mg/L)",
  main = "Pharmacokinetics: Concentration vs Time", ...)
```

Arguments

x	a "scen" object or a list of the selected trial from a "scen" object.
y	the "y" argument is not used in the plot-method for "scen" object.
col	the color argument to the plot.default function.
xlab	the label of x-axis.
ylab	the label of y-axis.
main	the title of the graph.
...	other arguments to the plot.default function can be passed here.

Author(s)

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References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

---

scen-class *An S4 class to represent a simulated scenarios.*

Description

An S4 class to represent a simulated scenarios.

Slots

`PKparameters` Subject's pharmacokinetic's (PK) parameters from the population distributions defined by the population mean.

`nPK` The length of the time points.

`time` The sampling time points.

`idtr` The id number of the corresponding simulated dataset.

`N` The total sample size per trial.

`doses` A vector with the doses panel.

`preal` The prior toxicity probabilities.

`limitTox` The toxicity threshold.

`omegaIIV` The inter-individual variability for the clearance and the volume of distribution.

`omegaAlpha` The patient's sensitivity parameter.

`conc` The concentration computed at the PK population values.

`concPred` The concentration values with proportional errors for each patient at each dose.

`tox` The toxicity outcome.

`tab` A summary matrix containing the sampling time points at the first row followed by concPred, parameters and alphaAUC. It used by the simulation function nsim.

`parameters` The simulated PK parameters of each patient.

`alphaAUC` A vector with the computed AUC values of each patient.

show-methods *S4 Methods for Function* show

Description

S4 Methods for function show.

Methods

`signature(object = "dosefinding")` S4 method to store and present the dose-finding results.

`signature(object = "scen")` S4 method to store and present the simulated datasets.

`signature(object = "dose")` S4 method to store and present the next recommended dose level in an ongoing trial.

sim.data *Generate and store PK and toxicity data.*

Description

This function can be used to generate and store PK and toxicity data in order to be used for simulation according to the dose-finding model.

Usage

```
sim.data(PKparameters, omegaIIV, omegaAlpha, sigma, doses, limitTox,
         timeSampling, N, TR, seed=190591)
```

Arguments

PKparameters	Subject's pharmacokinetic's (PK) parameters from the population distributions defined by the population mean.
omegaIIV	The inter-individual variability for the clearance and the volume of distribution; possible values may be 70% or 30% in different simulated data.
omegaAlpha	The patient's sensitivity parameter.
sigma	The additive or proportional error.
doses	A vector with the doses panel.
limitTox	The toxicity threshold.
timeSampling	The sampling time points.
N	The total sample size per trial.
TR	The total number of simulated datasets.
seed	The seed of the random number generator that is used at the beginning of each trial; defaults to 190591.

Value

An object of class "scen" is returned, consisting of simulated PK and toxicity data. Objects generated by sim.data contain at least the following components:

PKparameters	Subject's pharmacokinetic's (PK) parameters from the population distributions defined by the population mean.
nPK	The length of the time points.
time	The sampling time points.
idtr	The id number of the corresponding simulated dataset.
N	The total sample size per trial.
doses	A vector with the doses panel.
preal	The prior toxicity probabilities.
limitTox	The tocixity threshold.
omegaIIV	The inter-individual variability for the clearance and the volume of distribution.
omegaAlpha	The patient's sensitivity parameter.
conc	The concentration computed at the PK population values.
concPred	The concentration values with proportional errors for each patient at each dose.
tox	The toxicity outcome.
parameters	The simulated PK parameters of each patient.
alphaAUC	A vector with the computed AUC values of each patient.
tab	A summary matrix containing the sampling time points at the first row followed by concPred, parameters and alphaAUC. It used by the simulation function nsim.

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References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

See Also

nsim

Examples

```
TR = 10
N = 30
limitTox <- 10.96
PKparameters <- c(2,10,100)       # PK parameters ka,CL,V
omegaIIV <- 0.7                   # Inter-individual
omegaAlpha <- 0
doses <- c(12.59972,34.65492,44.69007,60.80685,83.68946,100.37111)
timeSampling <- seq(0,24,length.out=48)
sigma <- rep(0.2,length(timeSampling))  # sigma: Additive or proportional error

gen.scen <- sim.data(PKparameters,omegaIIV,omegaAlpha,sigma,doses,
                     limitTox,timeSampling, N, TR, seed=190591)
gen.scen[[1]]     # returns the first simulated dataset.


#### Graphical representation of the first simulated data
# plot(gen.scen[[1]])
```

---

stan_f *The data stan_f includes all the Stan models that dfpk package uses.*

Description

A character vector with paths to .stan files to include in the package.

Usage

```
data("stan_f")
```

References

Ursino, M., et al, (2017) Dose-finding methods for Phase I clinical trials using pharmacokinetics in small populations, Biometrical Journal, <doi:10.1002/bimj.201600084>.

Toumazi, A., et al, (2018) dfpk: An R-package for Bayesian dose-finding designs using pharmacokinetics (PK) for phase I clinical trials, Computer Methods and Programs in Biomedicine, <doi:10.1016/j.cmpb.2018.01.023>.

Examples

```
data(stan_f)
## maybe str(stan_f) ; plot(stan_f) ...
```

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