Package 'UtilityFrailtyPH12'

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Type Package

Title Implementing EFF-TOX and Monotone Utility Based Phase 12 Trials

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Description Contains functions for simulating phase 12 trial designs described by Chapple and Thall (2019) including simulation and the EFF-TOX trial and simulation and implementation of the U12 trial. Functions for implementing the EFF-TOX trial are found in the package 'Phase123'.

License GPL-2

Imports Rcpp (>= 0.12.18), bindata, mvtnorm, Phase123

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R topics documented:

GetDesire   *Returns the desireability value of a dose.*

Description

Takes estimated posterior mean efficacy and toxicity values and returns the posterior mean desire-ability score for a given tradeoff contour.

Usage

```
GetDesire(PE, PT, Contour)
```

Arguments

PE   True or estimated probability of efficacy.

PT   True of estimated probability of toxicity.

Contour   Vector containing 4 entries used to make the desireability function. Contour(1) contains a desired toxicity probability given efficacy, Countour(2) contains a desired efficacy probability given toxicity, and (Contour(3),Contour(4)) is an equally desireable pair of efficacy and toxicity probabilities that are non zero or one.

Examples

```
PE=.6
PT=.2
##Contour values
Contour=c(.35,.7,.8,.6)
GetDesire(PE,PT,Contour)
```

GetOptimalUT   *Gives the dose to assign the next patient cohort using monotone utility based phase 12 trial.*

Description

Gives the dose to assign the next patient cohort using the monotone utility based phase 12 trial using either adaptive randomization or fixed dose assignment. If the trial has been completed, AR equals FALSE will give the optimal dose level for the trial.

Usage

```
GetOptimalUT(YE, YT, Doses, DoseTried, AR, UT, CutE, CutT, AcceptE,
  AcceptT, HypermeansE, HypermeansT, Hypervars)
```

Arguments

YE	Vector of patient efficacy status.
YT	Vector of patient toxicity status.
Doses	Vector of patient dose assignment.
DoseTried	Vector containing 1s for doses tried and 0 otherwise.
AR	Logical stating whether or not to adaptively randomize the next cohort of patients. If the trial has been completed, AR equals FALSE will give the optimal dose level for the trial.
UT	Utility Matrix with entries U11, U22 elicited and U12 equals 100, U21 equals 0.
CutE	Cutoff for efficacy acceptability.
CutT	Cutoff for toxicity acceptability.
AcceptE	Probability threshold for efficacy acceptability.
AcceptT	Probability threshold for toxicity acceptability.
HypermeansE	Dose-specific hypermeans for efficacy.
HypermeansT	Dose-specific hypermeans for toxcity.
Hypervars	Length 3 vector of hypervariances. Hypervars[1] contains the Latent parameter variance for normal probability of efficacy and toxicity. Hypervars[2] contains the hypervariance on dose specific mean efficacy and toxicity parameters and Hypervars[3] contains the frailty variance parameter.

Value

A numerical value of the dose to assign the next patient cohort to. If the trial has been completed, this is the optimal dose. If a value of 0 is returned, no doses are acceptable and the trial should be stopped.

Examples

```
library(mvtnorm)
##Data Here
YE=rbinom(30,1,.8)
YT=rbinom(30,1,.3)
Doses=sample(1:3,30,replace=TRUE)
DoseTried=c(1,1,1,0,0)
##UTILITIES
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
##Safety Parameters
CutE=.3
CutT=.4
AcceptE=.1
AcceptT=.1
##Hyperparameters for Utility
HypermeansE=c(-1.189, -0.357,  0.360,  0.546,  0.743)
HypermeansT=c(-2.325, -1.811, -1.464, -1.189, -0.740)
Hypervars=c(1,36,1)
```

```
##Adaptively randomize or not?
AR=FALSE
GetOptimalUT( YE,YT, Doses,DoseTried,AR, UT, CutE, CutT,
AcceptE, AcceptT, HypermeansE, HypermeansT,Hypervars)
```

GetPriors   *Returns prior dose-specific means.*

Description

Uses elicited efficacy and toxicity dose-specific parameters along with latent prior variance, dose-specific mean hypervariance and frailty variance to determine dose-specific prior means for efficacy and toxicity and prints the prior effective sample size associated with the specified prior parameters.

Usage

```
GetPriors(PROBST, PROBSE, Var, HypVar, tau, B)
```

Arguments

PROBST	Elicited prior toxicity probability at each dose.
PROBSE	Elicted prior efficacy probability at each dose.
Var	Latent parameter variance for normal probability of efficacy and toxicity.
HypVar	Hypervariance on dose specific mean efficacy and toxicity parameters.
tau	Frailty variance parameter.
B	Number of prior samples to draw for calculating ESS. Suggested values of ten thousand.

Value

A list contianing the vector of dose-specific efficacy probability prior mean parameters and the vector of dose-specific toxicity probability prior mean parameters.

Examples

```
library(mvtnorm)
PROBST=c(.05,.10,.15,.20,.30)
PROBSE=c(.2,.4,.6,.65,.7)
Var=1
HypVar=36
tau=1
B=100
Z=GetPriors(PROBST,PROBSE,Var,HypVar,tau,B)
```

RunAdaptiveEFFTOX   *Simulates replications from EFF-TOX phase 12 trial.*

Description

Simulates trial replications from the EFF-TOX phase 12 trial trial using either adaptive random-
ization or fixed dose assignment. Prints the true utility scores, dose selection probability, average
number of patients treated at each dose, average number of responses, average number of toxicities,
and Delta value. Returns trial outcomes.

Usage

```
RunAdaptiveEFFTOX(NSims, Dose, PE, PT, corET, Nmax, cohort, NF, Contour,
  CutE, CutT, AcceptE, AcceptT, HypermeansEFF, HypervarsEFF)
```

Arguments

NSims	Number of simulations.
Dose	Log-standardized doses (log(Raw Dose)-mean(log(Raw Dose))).
PE	True Efficacy Probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between Efficacy and Toxicity status.
Nmax	Maximum Sample size.
cohort	Cohort Size.
NF	Number of fixed assignment patients until adaptive randomization. If NF equals Nmax, the trial is conducted without adaptive randomization.
Contour	Vector containing 4 entries used to make the desireability function. Contour(1) contains a desired toxicity probability given efficacy, Countour(2) contains a desired efficacy probability given toxicity, and (Contour(3),Contour(4)) is an equally desireable pair of efficacy and toxicity probabilities that are non zero or one.
CutE	Cutoff for efficacy acceptability.
CutT	Cutoff for toxicity acceptability.
AcceptE	Probability threshold for efficacy acceptability.
AcceptT	Probability threshold for toxicity acceptability.
HypermeansEFF	Vector containing prior hypermeans of length 6 for EFF-TOX parameters
HypervarsEFF	Vector containing prior hypervariances of length 6 for EFF-TOX parameters

Value

A list of size NSims with results from each simulated trial. Each entry contains a list with (1) the
optimal dose selected, (2) the posterior mean utility for each dose level, (3) a matrix containing the
dose given, the efficacy outcome and the toxicity outcome for each patient.

References

Thall, P.F. and Cook, J.D. (2004). Dose-finding based on efficacy-toxicity trade-offs. Biometrics 60, 684-693.

Chapple AG, Thall PF. A Hybrid Phase 123 Clinical Trial Design Allowing Dose Re-optimization in Phase III. Biometrics. Epub ahead of print 26 October 2018.

Examples

```
##Trial PArameters here
Nmax=30 ##Number of patients to enroll
NF=30 ##Number until AR if NF=Nmax, there's no AR.
cohort=3
#' Raw Dose Values
Dose = c(1,2,3,3.5,5)
Dose=log(Dose)-mean(log(Dose))
## Contour Vector
Contour = c(.35, .75,.7,.4)
#Starting Dose
DoseStart=1
##Safety Parameters
CutE=.3
CutT=.4
AcceptE=.1
AcceptT=.1
##Hypermeans
HypermeansEFF = c(.022,3.45,0,-4.23,3.1,0)
##Hypervariances
HypervarsEFF = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
HypervarsEFF=HypervarsEFF^2
#True Efficacy and Toxicity probabilities
PE=c(.2,.4,.6,.7,.7)
PT=c(.2,.2,.2,.3,.5)
corET=0
##Number of simulations
NSims=2
RESULTS=RunAdaptiveEFFTOX(NSims,Dose,PE, PT, corET, Nmax, cohort,
NF, Contour, CutE, CutT, AcceptE, AcceptT, HypermeansEFF, HypervarsEFF )
```

RunAdaptiveUT	*Simulates replications from the monotone utility based phase 12 trial.*

Description

Simulates trial replications from the monotone utility based phase 12 trial using either adaptive randomization or fixed dose assignment. Prints the true utility scores, dose selection probability, average number of patients treated at each dose, average number of responses, average number of toxicities, and Delta value. Returns trial outcomes.

Usage

```
RunAdaptiveUT(NSims, PE, PT, corET, Nmax, cohort, NF, UT, CutE, CutT,
    AcceptE, AcceptT, HypermeansE, HypermeansT, Hypervars)
```

Arguments

NSims	Number of simulations.
PE	True Efficacy Probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between Efficacy and Toxicity status.
Nmax	Maximum Sample size.
cohort	Cohort Size.
NF	Number of fixed assignment patients until adaptive randomization. If NF equals Nmax, the trial is conducted without adaptive randomization.
UT	Utility Matrix with entries U11, U22 elicited and U12 equals 100, U21 equals 0.
CutE	Cutoff for efficacy acceptability.
CutT	Cutoff for toxicity acceptability.
AcceptE	Probability threshold for efficacy acceptability.
AcceptT	Probability threshold for toxicity acceptability.
HypermeansE	Dose-specific hypermeans for efficacy.
HypermeansT	Dose-specific hypermeans for toxcity.
Hypervars	Length 3 vector of hypervariances. Hypervars[1] contains the Latent parameter variance for normal probability of efficacy and toxicity. Hypervars[2] contains the hypervariance on dose specific mean efficacy and toxicity parameters and Hypervars[3] contains the frailty variance parameter.

Value

A list of size NSims with results from each simulated trial. Each entry contains a list with (1) the optimal dose selected, (2) the posterior mean utility for each dose level, (3) a matrix containing the dose given, the efficacy outcome and the toxicity outcome for each patient.

Examples

```
library(bindata)
library(mvtnorm)
##Trial PArameters here
Nmax=30 ##Number of patients to enroll
NF=30 ##Number until AR if NF=Nmax, there's no AR.
cohort=3
##UTILITIES
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
##Safety Parameters
CutE=.3
```

```
CutT=.4
AcceptE=.1
AcceptT=.1
##Hyperparameters for Utility
HypermeansE=c(-1.189, -0.357,  0.360,  0.546,  0.743)
HypermeansT=c(-2.325, -1.811, -1.464, -1.189, -0.740)
Hypervars=c(1,36,1)
#True Efficacy and Toxicity probabilities
PE=c(.2,.4,.6,.7,.7)
PT=c(.2,.2,.2,.3,.5)
corET=0
##Number of simulations
NSims=2
RESULTS=RunAdaptiveUT(NSims, PE, PT, corET,  Nmax,
cohort,NF, UT, CutE, CutT, AcceptE,
AcceptT, HypermeansE, HypermeansT, Hypervars)
```

UTEFFTOX   *Samples from the posterior of the utility based phase12 model.*

Description

Takes arguments of data, hypermens and hypervariance vectors and returns a list of posterior samples from the Utility based phase12 model decribed by Chapple and Thall (2019).

Usage

```
UTEFFTOX(YE, YT, Doses, HypermeansEFF, HypermeansTOX, Hypervars, B)
```

Arguments

YE	Binary indicator vector of efficacy status.
YT	Binary indicator vector of toxicity status.
Doses	Vector of integer Doses given to patients.
HypermeansEFF	Vector of length nDose for dose prior means for efficacy.
HypermeansTOX	Vector of length nDose for dose prior means for toxicity
Hypervars	Length 5 vector of hypervariances. Hypervars(1) and Hypervars(2) contains the Latent parameter variance for normal probability of efficacy and toxicity. Hypervars(3) and Hypervars(4) contains the hypervariance on dose specific mean efficacy and toxicity parameters and Hypervars(5) contains the frailty variance parameter.
B	Number of iterations to run for the MCMC.

Value

A list of posterior samples after burnin in order: Posterior efficacy dose-vector, Posterior toxicity dose-vector, Posterior correlation.

Examples

```
n=100  #Generate Data
YE=rbinom(n,1,.6)
YT=rbinom(n,1,.2)
nDose=5
Doses=sample(1:nDose,n,replace=TRUE)
##Hyperparameters
HypermeansEFF=c(-1,-.5,0,.5,1,2)
HypermeansTOX=HypermeansEFF
Hypervars=c(1,1,36,36,1)
B=100
UTEFFTOX(YE, YT,Doses,HypermeansEFF,HypermeansTOX, Hypervars, B)
```

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