Package 'Phase12Compare'

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Type Package

Title Simulates SPSO and Efftox Phase 12 Trials with Correlated Outcomes

Version 1.5

Author Andrew G Chapple

Maintainer Andrew G Chapple <achapp@lsuhsc.edu>

Description Simulating and conducting four phase 12 clinical trials with correlated binary bivariate outcomes described. Uses the 'Efftox' (efficacy and toxicity trade-off, <https://biostatistics.mdanderson.org/SoftwareDownload/SingleSoftware/Index/2>) and SPSO (Semi-Parametric Stochastic Ordering) models with Utility and Desirability based objective functions for dose finding.

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`AssignEffTox` *Determines the optimal dose to assign the next patient cohort.*

Description

This function returns the optimal acceptable dose number to assign the next patient cohort or stops the trial if no dose is deemed acceptable.

Usage

```
AssignEffTox(
  YE,
  YT,
  Doses,
  Dose,
  DosesTried,
  Hypermeans,
  Hypervars,
  Contour,
  PiLim,
  ProbLim,
  B
)
```

Arguments

`YE`	Vector containing observed efficacy indicators.
`YT`	Vector containing observed toxicity indicators.
`Doses`	Vector containing numbered Doses of patients in trial.
`Dose`	Vector containing the standardized doses considered.
`DosesTried`	Binary vector corresponding to which doses have been tried.
`Hypermeans`	Vector containing prior hypermeans of length 6 for Eff-Tox parameters.
`Hypervars`	Vector containing prior hypervariances of length 6 for Eff-Tox parameters.

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.
PiLim	Vector of length two with PiLim[1] containing the acceptable lower limit on efficacy probability and PiLim[2] containing the acceptable upper limit on toxicity probability.
ProbLim	Vector of length two with ProbLim[1] containing the probability cutoff for acceptable efficacy probability and ProbLim[2] containing the probability cutoff for acceptable toxicity probability.
B	Number of iterations to perform in the MCMC.

Value

The optimal dose level to administer the next patient cohort.

Examples

```
##Doses, YE,YT
Doses= c(1,1,1,2,2,2,1,1,1,3,3,3,1,1,1,2,2,2)
YE = c(0,0,1,1,1,0,0,0,0,1,1,1,0,0,1,1,1,0)
YT=c(0,0,0,1,1,0,1,0,0,1,1,1,0,0,0,1,0,0)
##Vector of Numerical Doses
Dose = c(1,2,3,3.5,5)
Dose=(Dose-mean(Dose))/sd(Dose)
##Five doses, but only 3 tried so we have
DosesTried=c(1,1,1,0,0)
## Contour Vector
Contour = c(.35, .75,.7,.4)
##Hypermeans
Hypermeans = c(.022,3.45,0,-4.23,3.1,0)
Hypervars = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
Hypervars=Hypervars^2
##Acceptability Criteria
PiLim = c(.3,.4)
ProbLim=c(.1,.1)
##Number of iterations
B=2000
AssignEffTox(YE,YT, Doses, Dose, DosesTried, Hypermeans,  Hypervars, Contour, PiLim,  ProbLim, B )
```

AssignEffToxUT *Determines the optimal dose to assign the next patient cohort.*

Description

This function returns the optimal acceptable dose number to assign the next patient cohort or stops the trial if no dose is deemed acceptable.

Usage

```
AssignEffToxUT(
  YE,
  YT,
  Doses,
  Dose,
  DosesTried,
  Hypermeans,
  Hypervars,
  UT,
  PiLim,
  ProbLim,
  B
)
```

Arguments

YE	Vector containing observed efficacy indicators.
YT	Vector containing observed toxicity indicators.
Doses	Vector containing numbered Doses of patients in trial.
Dose	Vector containing the standardized doses considered.
DosesTried	Binary vector corresponding to which doses have been tried.
Hypermeans	Vector containing prior hypermeans of length 6 for Eff-Tox parameters.
Hypervars	Vector containing prior hypervariances of length 6 for Eff-Tox parameters.
UT	2x2 utility matrix.
PiLim	Vector of length two with PiLim[1] containing the acceptable lower limit on efficacy probability and PiLim[2] containing the acceptable upper limit on toxicity probability.
ProbLim	Vector of length two with ProbLim[1] containing the probability cutoff for acceptable efficacy probability and ProbLim[2] containing the probability cutoff for acceptable toxicity probability.
B	Number of iterations to perform in the MCMC.

Value

The optimal dose level to administer the next patient cohort.

GETBIN *Generate binary bivariate data.*

Description

Generates binary bivariate data from a 2x2 matrix of probabilities.

Usage

```
GETBIN(PVEC)
```

Arguments

PVEC	Contains TRUE pi00,pi10, pi01, pi11 for each dose

Value

Binary bivariate random variate (YE,YT).

GetDesire *Returns the desireability value of a dose.*

Description

Takes estimated posterior mean efficacy and toxicity values and returns the posterior mean desireability 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.

Value

Computes the real-valued desireability for an estimated (PE, PT) pair and elicited co

Examples

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

GetEfftoxContour *Assigns next patient cohort based on the Efftox model with a Desirability based objective function.*

Description

Provides the optimal dose level as determined by the Efftox model, posterior mean toxicity probability, efficacy probability, and desirability of each dose level. Doses that are unacceptably toxic or inefficous have a desirability of 0.

Usage

```
GetEfftoxContour(
  YE,
  YT,
  Doses,
  Dose,
  Dosetried,
  cohort,
  Contour,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansEFF,
  HypervarsEFF,
  B
)
```

Arguments

YE	Length n binary indicator vector of efficacy status.
YT	Length n binary indicator vector of toxicity status.
Doses	Length n vector of integer Doses given to patients.
Dose	Vector of standardized log-dose levels considered in the trial.
Dosetried	Binary vector corresponding to which doses have been tried.
cohort	Cohort size for the trial.
Contour	Contour vector for desirability function. Contains in order: (pi_1,E,pi_2,T,pi_3,E,pi_4,T).
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.

HypermeansEFF	Hypermeans for the Efftox model. In order, entries are hypermeans for (beta_0,E,beta_1,E,beta_2,E,beta_
HypervarsEFF	Hypervariances for the Efftox model. In order, entries are hypervariances for (beta_0,E,beta_1,E,beta_2,E,beta_0,T,beta_1,T,psi).
B	Number of iterations to run for the MCMC.

Value

A list containing the optimal dose level to assign the next patient cohort in the first entry and a matrix in the second entry, with rows corresponding to (1) the dose #, (2) mean posterior toxicity probability at each dose, mean posterior efficacy probability at each dose, and acceptable posterior desirability score of each dose level (0s indicate the dose is not acceptably efficous or toxic).

Examples

```
##Get the Data
##True Tox Prob
PT = c(.1,.2,.25,.5,.7)
##True EFF Prob
PE = c(.3,.4,.7,.5,.5)
Doses=c(1,1,1,2,2,2,3,3,3,2,2,2,1,1,1,2,2,2,3,3,3)
YE=Doses
YT=Doses
Dosetried=rep(0,length(PE))
##Generate data
for(k in 1:length(PE)){
if(sum(Doses==k)){
##Dose level has been tried
Dosetried[k]=1
YE[Doses==k]=rbinom(sum(Doses==k),1,PE[k])
YT[Doses==k]=rbinom(sum(Doses==k),1,PT[k])
}
}
##Hypermeans and hypervariances
HypermeansEFF = c(.022,3.45,0,-4.23,3.1,0)
HypervarsEFF = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
HypervarsEFF=HypervarsEFF^2
##Vector of Numerical Doses
Dose = c(1,2,3,3.5,5)
##Dose for Eff-Tox
Dose=log(Dose)-mean(log(Dose))
##Trial parameters
cohort=3
##Contour vector
Contour = c(.35, .75,.7,.4)
CutE=.3 ##Efficacy threshold
CutT=.4 ##Toxicity threshold
AcceptE=.3 ##Eff acceptability threshold
AcceptT= .3 ##Tox acceptability threshold
B=100##Number of iterations
GetEfftoxContour(YE, YT,Doses,Dose, Dosetried,
cohort, Contour,CutE, CutT, AcceptE, AcceptT,
HypermeansEFF, HypervarsEFF,B )
```

`GetEfftoxUt` *Assigns next patient cohort based on the Efftox model with a Utility based objective function.*

Description

Provides the optimal dose level as determined by the Efftox model, posterior mean toxicity probability, efficacy probability, and mean utility of each dose level. Doses that are unacceptably toxic or inefficous have a utility of 0.

Usage

```
GetEfftoxUt(
  YE,
  YT,
  Doses,
  Dose,
  Dosetried,
  cohort,
  UT,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansEFF,
  HypervarsEFF,
  B
)
```

Arguments

`YE`	Length n binary indicator vector of efficacy status.
`YT`	Length n binary indicator vector of toxicity status.
`Doses`	Length n vector of integer Doses given to patients.
`Dose`	Vector of standardized log-dose levels considered in the trial.
`Dosetried`	Binary vector corresponding to which doses have been tried.
`cohort`	Cohort size for the trial.
`UT`	Utility matrix for the four bivariate (efficacy, toxicity) events.
`CutE`	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
`CutT`	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
`AcceptE`	Posterior probability threshold for efficacy acceptability.
`AcceptT`	Posterior probability threshold for toxicity acceptability.

HypermeansEFF	Hypermeans for the Efftox model. In order, entries are hypermeans for (beta_0,E,beta_1,E,beta_2,E,beta_
HypervarsEFF	Hypervariances for the Efftox model. In order, entries are hypervariances for (beta_0,E,beta_1,E,beta_2,E,beta_0,T,beta_1,T,psi).
B	Number of iterations to run for the MCMC.

Value

A list containing the optimal dose level to assign the next patient cohort in the first entry and a matrix in the second entry, with rows corresponding to (1) the dose #, (2) mean posterior toxicity probability at each dose, mean posterior efficacy probability at each dose, and acceptable posterior utility score of each dose level (0s indicate the dose is not acceptably efficous or toxic).

Examples

```
##Get the Data
##True Tox Prob
PT = c(.1,.2,.25,.5,.7)
##True EFF Prob
PE = c(.3,.4,.7,.5,.5)
Doses=c(1,1,1,2,2,2,3,3,3,2,2,2,1,1,1,2,2,2,3,3,3)
YE=Doses
YT=Doses
Dosetried=rep(0,length(PE))
##Generate data
for(k in 1:length(PE)){
if(sum(Doses==k)){
##Dose level has been tried
Dosetried[k]=1
YE[Doses==k]=rbinom(sum(Doses==k),1,PE[k])
YT[Doses==k]=rbinom(sum(Doses==k),1,PT[k])
}
}
##Hypermeans and hypervariances
HypermeansEFF = c(.022,3.45,0,-4.23,3.1,0)
HypervarsEFF = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
HypervarsEFF=HypervarsEFF^2
##Vector of Numerical Doses
Dose = c(1,2,3,3.5,5)
##Dose for Eff-Tox
Dose=log(Dose)-mean(log(Dose))
##Trial parameters
cohort=3
##Utility Matrix
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
CutE=.3 ##Efficacy threshold
CutT=.4 ##Toxicity threshold
AcceptE=.3 ##Eff acceptability threshold
AcceptT= .3 ##Tox acceptability threshold
B=100##Number of iterations
GetEfftoxUt(YE, YT,Doses,Dose, Dosetried,
cohort, UT,CutE, CutT, AcceptE, AcceptT,
HypermeansEFF, HypervarsEFF,B )
```

GetPriorsSPSO *Returns prior dose-specific means and prior ESS for the SPSO model.*

Description

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

Usage

```
GetPriorsSPSO(PROBST, PROBSE, tau, Var, HypVar, PGLOBAL)
```

Arguments

PROBST	Elicited prior toxicity probability at each dose.
PROBSE	Elicted prior efficacy probability at each dose.
tau	Frailty variance parameter.
Var	Latent parameter variance for normal probability of efficacy and toxicity.
HypVar	Hypervariance on dose specific mean efficacy and toxicity parameters.
PGLOBAL	Global monotonicity probability of dose-efficacy curve.

Value

A list contianing (1) the prior effective sample size, (2) the vector of dose-specific efficacy probability prior mean parameters and, (3) the vector of dose-specific toxicity probability prior mean parameters.

Examples

```
library(mvtnorm)
##Elicited probabilities of toxicity
PROBST=c(.05,.10,.15,.20,.30)
##Elicited probabilities of efficacy
PROBSE=c(.2,.4,.6,.65,.7)
##Sigma_0
Var=1
##Sigma_mu
HypVar=16
##Frailty Variance
tau=1
##Global Monotonicity Probability
PGLOBAL=.1
Z=GetPriorsSPSO(PROBST,PROBSE,tau,Var,HypVar,PGLOBAL)
Z
```

GetSpsoContour *Assigns next patient cohort based on the SPSOP model with a Utility based objective function.*

Description

Provides the optimal dose level as determined by the SPSO model, posterior mean toxicity probability, efficacy probability, and desirability of each dose level. Doses that are unacceptably toxic or inefficous have a desirability of 0.

Usage

```
GetSpsoContour(
  YE,
  YT,
  Doses,
  Dosetried,
  cohort,
  Contour,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansE,
  HypermeansT,
  Hypervars,
  B
)
```

Arguments

YE	Length n binary indicator vector of efficacy status.
YT	Length n binary indicator vector of toxicity status.
Doses	Length n vector of integer Doses given to patients.
Dosetried	Binary vector corresponding to which doses have been tried.
cohort	Cohort size for the trial.
Contour	Contour vector for desirability function. Contains in order: (pi_1,E,pi_2,T,pi_3,E,pi_4,T).
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansE	Hypermeans for dose-specific efficacy parameters.

HypermeansT	Hypermeans for dose-specific toxcity parameters.
Hypervars	Hypervariances needed for the SPSO model. Contains, in order (sigma_0^2, sigma_mu^2,tau).
B	Number of iterations to run for the MCMC.

Value

A list containing the optimal dose level to assign the next patient cohort in the first entry and a matrix in the second entry, with rows corresponding to (1) the dose #, (2) mean posterior toxicity probability at each dose, mean posterior efficacy probability at each dose, and acceptable posterior desirability score of each dose level (0s indicate the dose is not acceptably efficous or toxic).

Examples

```
##Get the Data
##True Tox Prob
PT = c(.1,.2,.25,.5,.7)
##True EFF Prob
PE = c(.3,.4,.7,.5,.5)
Doses=c(1,1,1,2,2,2,3,3,3,2,2,2,1,1,1,2,2,2,3,3,3)
YE=Doses
YT=Doses
Dosetried=rep(0,length(PE))
##Generate data
for(k in 1:length(PE)){
if(sum(Doses==k)){
##Dose level has been tried
Dosetried[k]=1
YE[Doses==k]=rbinom(sum(Doses==k),1,PE[k])
YT[Doses==k]=rbinom(sum(Doses==k),1,PT[k])
}
}
##Hyperparameters
HypermeansE=c(-1,-.5,0,.5,1,2)
HypermeansT=HypermeansE
Hypervars=c(1,16,1)
##Trial parameters
cohort=3
##Contour vector
Contour = c(.35, .75,.7,.4)
CutE=.3 ##Efficacy threshold
CutT=.4 ##Toxicity threshold
AcceptE=.3 ##Eff acceptability threshold
AcceptT= .3 ##Tox acceptability threshold
B=100##Number of iterations
GetSpsoContour(YE,YT,Doses,Dosetried,cohort,Contour,CutE, CutT, AcceptE, AcceptT,
HypermeansE,  HypermeansT,Hypervars,B )
```

GetSpsoUt *Assigns next patient cohort based on the SPSOP model with a Utility based objective function.*

Description

Provides the optimal dose level as determined by the SPSO model, posterior mean toxicity probability, efficacy probability, and mean utility of each dose level. Doses that are unacceptably toxic or inefficous have a utility of 0.

Usage

```
GetSpsoUt(
  YE,
  YT,
  Doses,
  Dosetried,
  cohort,
  UT,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansE,
  HypermeansT,
  Hypervars,
  B
)
```

Arguments

YE	Length n binary indicator vector of efficacy status.
YT	Length n binary indicator vector of toxicity status.
Doses	Length n vector of integer Doses given to patients.
Dosetried	Binary vector corresponding to which doses have been tried.
cohort	Cohort size for the trial.
UT	Utility matrix for the four bivariate (efficacy, toxicity) events.
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansE	Hypermeans for dose-specific efficacy parameters.

HypermeansT	Hypermeans for dose-specific toxcity parameters.
Hypervars	Hypervariances needed for the SPSO model. Contains, in order (sigma_0^2, sigma_mu^2,tau).
B	Number of iterations to run for the MCMC.

Value

A list containing the optimal dose level to assign the next patient cohort in the first entry and a matrix in the second entry, with rows corresponding to (1) the dose #, (2) mean posterior toxicity probability at each dose, mean posterior efficacy probability at each dose, and acceptable posterior utility score of each dose level (0s indicate the dose is not acceptably efficous or toxic).

Examples

```
##Get the Data
##True Tox Prob
PT = c(.1,.2,.25,.5,.7)
##True EFF Prob
PE = c(.3,.4,.7,.5,.5)
Doses=c(1,1,1,2,2,2,3,3,3,2,2,2,1,1,1,2,2,2,3,3,3)
YE=Doses
YT=Doses
Dosetried=rep(0,length(PE))
##Generate data
for(k in 1:length(PE)){
if(sum(Doses==k)){
##Dose level has been tried
Dosetried[k]=1
YE[Doses==k]=rbinom(sum(Doses==k),1,PE[k])
YT[Doses==k]=rbinom(sum(Doses==k),1,PT[k])
}
}
##Hyperparameters
HypermeansE=c(-1,-.5,0,.5,1,2)
HypermeansT=HypermeansE
Hypervars=c(1,16,1)
##Trial parameters
cohort=3
#'##UTILITY Matrix
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
CutE=.3 ##Efficacy threshold
CutT=.4 ##Toxicity threshold
AcceptE=.3 ##Eff acceptability threshold
AcceptT= .3 ##Tox acceptability threshold
B=100##Number of iterations
GetSpsoUt(YE,YT,Doses,Dosetried,cohort,UT,CutE, CutT, AcceptE, AcceptT,
HypermeansE,  HypermeansT,Hypervars,B )
```

ReturnOpt *Obtains optimal dose level.*

Description

Gives the optimal dose level to assign the next patient cohort to based on the vector of optimality function values for each dose level (desirability or utility based) and the doses tried throughout the trial.

Usage

```
ReturnOpt(Desire, DoseTried)
```

Arguments

Desire	Vector of optimality function values for each dose level.
DoseTried	Binary vector containing 1 for doses that have been tried during the trial and 0 otherwise.

Value

Optimal dose level to assign the next patient cohort.

RunAdaptiveEffToxTrialCORR *Simulates utility based Efftox trials*

Description

Simulates utility based Efftox trials

Usage

```
RunAdaptiveEffToxTrialCORR(
  DoseStart,
  Dose,
  Hypermeans,
  Hypervars,
  UT,
  PiLim,
  ProbLim,
  cohort,
  NET,
  NF,
  B,
```

```
  nSims,
  PMAT
)
```

Arguments

DoseStart	Dose level to START the EFF-Tox Trial
Dose	Vector of Doses considered in the trial
Hypermeans	6 vector of prior means
Hypervars	6 vector of prior standard deviations
UT	2x2 matrix of utilities corresponding to the four binary bivariate (toxicity, efficacy) events.
PiLim	2 vector of acceptable limits
ProbLim	2 vector of cutoff for acceptabilities
cohort	Cohort size
NET	Maximum Sample size to run the EFFtox Trial, must be divisible by cohort
NF	Minimum sample size to begin adaptive randomization, must be divisible by count
B	Number of reps to perform in MCMC
nSims	Number of Simulated trials to run.
PMAT	Contains TRUE pi00,pi10, pi01, pi11 for each dose

Value

Trial simulation results to be processed for operating characteristics summaries.

RunAdaptiveEffToxTrialCORRCONTOUR

Simulates desirability based Efftox trials

Description

Simulates Efftox trials based on the desirability tradeoff contour.

Usage

```
RunAdaptiveEffToxTrialCORRCONTOUR(
  DoseStart,
  Dose,
  Hypermeans,
  Hypervars,
  Contour,
  PiLim,
  ProbLim,
```

```
  cohort,
  NET,
  NF,
  B,
  nSims,
  PMAT
)
```

Arguments

DoseStart	Dose level to START the EFF-Tox Trial
Dose	Vector of Doses considered in the trial
Hypermeans	6 vector of prior means
Hypervars	6 vector of prior standard deviations
Contour	4 vector used to specify the tradeoff contour.
PiLim	2 vector of acceptable limits
ProbLim	2 vector of cutoff for acceptabilities
cohort	Cohort size
NET	Maximum Sample size to run the EFFtox Trial, must be divisible by cohort
NF	Minimum sample size to begin adaptive randomization, must be divisible by count
B	Number of reps to perform in MCMC
nSims	Number of Simulated trials to run.
PMAT	Contains TRUE pi00,pi10, pi01, pi11 for each dose

Value

Trial simulation results to be processed for operating characteristics summaries.

SimEfftoxContour *Simulates trial replications from the Efftox model with desirability optimality function.*

Description

Simulates replications from a Bayesian adaptive phase 12 clinical trial design using the Efftox model and a optimality function based on the desirability tradeoff contour.

Usage

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

Arguments

NSims	Number of trial simulations to run.
Dose	Logarithm of raw dose levels - the average logarithm of the raw dose levels.
PE	True efficacy probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between efficacy and toxicity probability.
Nmax	Maximum trial sample size.
cohort	Patient cohort size.
Contour	Contour vector for desirability function. Contains in order: (pi_1,E,pi_2,T,pi_3,E,pi_4,T).
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansEFF	Hypermeans for the Efftox model. In order, entries are hypermeans for (beta_0,E,beta_1,E,beta_2,E,beta_
HypervarsEFF	Hypervariances for the Efftox model. In order, entries are hypervariances for (beta_0,E,beta_1,E,beta_2,E,beta_0,T,beta_1,T,psi).

Value

A list with the first entry corresponding to a matrix with: (1) True toxicity probabilities at each dose, (2) True efficacy probabilities at each dose, (3) True Desirability of each dose, (4) Optimal dose selection probability, (5) Average sample size of patients treated at each dose. The second entry of the list contains a vector with rows corresponding to (1) the true binary bivariate correlation between efficacy and toxicity, (2) Stopping probability of the trial, (3) Average number of efficacy events, (4) Average number of toxicity events, and (5) Delta.

Examples

```
library(mvtnorm)
##True toxicity probability
PT=c(.05,.10,.15,.20,.30)
##True Efficacy Probability
PE=c(.2,.4,.6,.65,.7)
#True Correlation
corET=.5
##Number of simulations
NSims=1 ##Increase this when using
##Hypermeans and hypervariances
HypermeansEFF = c(.022,3.45,0,-4.23,3.1,0)
HypervarsEFF = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
HypervarsEFF=HypervarsEFF^2
##Trial Parameters
##Cohort Size, N^F and N_ET
cohort=3
##Starting Dose
DoseStart=1
##Vector of Numerical Doses
Dose = c(1,2,3,3.5,5)
##Dose for Eff-Tox
Dose=log(Dose)-mean(log(Dose))
Nmax=30 ##Max Sample Size
#Acceptability Criterion
CutE=.3
CutT=.4
##Limits on acceptability
AcceptE=.1
AcceptT=.1
##Contour vector
Contour = c(.35, .75,.7,.4)
RESULTS=SimEfftoxContour(NSims, Dose,PE,  PT, corET,
Nmax, cohort, Contour, CutE, CutT, AcceptE,AcceptT,  HypermeansEFF, HypervarsEFF)
RESULTS
```

`SimEfftoxUt` *Simulates trial replications from the Efftox model with utility optimality function.*

Description

Simulates replications from a Bayesian adaptive phase 12 clinical trial design using the Efftox model and a optimality function based on mean utility. Does not assign patient cohorts to unacceptably toxic or inefficous dose levels.

Usage

```
SimEfftoxUt(
```

```
  NSims,
  Dose,
  PE,
  PT,
  corET,
  Nmax,
  cohort,
  UT,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansEFF,
  HypervarsEFF
)
```

Arguments

NSims	Number of trial simulations to run.
Dose	Logarithm of raw dose levels - the average logarithm of the raw dose levels.
PE	True efficacy probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between efficacy and toxicity probability.
Nmax	Maximum trial sample size.
cohort	Patient cohort size.
UT	Utility matrix for the four bivariate (efficacy, toxicity) events.
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansEFF	Hypermeans for the Efftox model. In order, entries are hypermeans for (beta_0,E,beta_1,E,beta_2,E,beta_
HypervarsEFF	Hypervariances for the Efftox model. In order, entries are hypervariances for (beta_0,E,beta_1,E,beta_2,E,beta_0,T,beta_1,T,psi).

Value

A list with the first entry corresponding to a matrix with: (1) True toxicity probabilities at each dose, (2) True efficacy probabilities at each dose, (3) True mean utility of each dose, (4) Optimal dose selection probability, (5) Average sample size of patients treated at each dose. The second entry of the list contains a vector with rows corresponding to (1) the true binary bivariate correlation between efficacy and toxicity, (2) Stopping probability of the trial, (3) Average number of efficacy events, (4) Average number of toxicity events, and (5) Delta.

Examples

```
library(mvtnorm)
##True toxicity probability
PT=c(.05,.10,.15,.20,.30)
##True Efficacy Probability
PE=c(.2,.4,.6,.65,.7)
#True Correlation
corET=.5
##Number of simulations
NSims=1 ##Increase this when using
##Hypermeans and hypervariances
HypermeansEFF = c(.022,3.45,0,-4.23,3.1,0)
HypervarsEFF = c(2.6761, 2.6852, .2, 3.1304, 3.1165, 1)
HypervarsEFF=HypervarsEFF^2
##Trial Parameters
##Cohort Size, N^F and N_ET
cohort=3
##Starting Dose
DoseStart=1
##Vector of Numerical Doses
Dose = c(1,2,3,3.5,5)
##Dose for Eff-Tox
Dose=log(Dose)-mean(log(Dose))
Nmax=30 ##Max Sample Size
#Acceptability Criterion
CutE=.3
CutT=.4
##Limits on acceptability
AcceptE=.1
AcceptT=.1
##UTILITY Matrix
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
RESULTS=SimEfftoxUt(NSims, Dose,PE,  PT, corET,
Nmax, cohort, UT, CutE, CutT, AcceptE,AcceptT,  HypermeansEFF, HypervarsEFF)
RESULTS
```

`SimSpsoContour` *Simulates trial replications from the SPSO model with desirability optimality function.*

Description

Simulates replications from a Bayesian adaptive phase 12 clinical trial design using the SPSO model and a optimality function based on the desirability tradeoff contour.

Usage

```
SimSpsoContour(
  NSims,
```

```
  PE,
  PT,
  corET,
  Nmax,
  cohort,
  Contour,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansE,
  HypermeansT,
  Hypervars
)
```

Arguments

NSims	Number of trial simulations to run.
PE	True efficacy probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between efficacy and toxicity probability.
Nmax	Maximum trial sample size.
cohort	Patient cohort size.
Contour	Contour vector for desirability function. Contains in order: (pi_1,E,pi_2,T,pi_3,E,pi_4,T).
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansE	Hypermeans for dose-specific efficacy parameters.
HypermeansT	Hypermeans for dose-specific toxcity parameters.
Hypervars	Hypervariances needed for the SPSO model. Contains, in order (sigma_0^2, sigma_mu^2,tau).

Value

A list with the first entry corresponding to a matrix with: (1) True toxicity probabilities at each dose, (2) True efficacy probabilities at each dose, (3) True Desirability of each dose, (4) Optimal dose selection probability, (5) Average sample size of patients treated at each dose. The second entry of the list contains a vector with rows corresponding to (1) the true binary bivariate correlation between efficacy and toxicity, (2) Stopping probability of the trial, (3) Average number of efficacy events, (4) Average number of toxicity events, and (5) Delta.

Examples

```
library(mvtnorm)
##True toxicity probability
PT=c(.05,.10,.15,.20,.30)
##True Efficacy Probability
PE=c(.2,.4,.6,.65,.7)
#True Correlation
corET=.5
##Number of simulations
NSims=1 ##Increase this when using
##Hypermeans and hypervariances
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(1,16,1)
##Trial Parameters
##Cohort Size, N^F and N_ET
cohort=3
##Starting Dose
DoseStart=1
Nmax=30 ##Max Sample Size
#Acceptability Criterion
CutE=.3
CutT=.4
##Limits on acceptability
AcceptE=.1
AcceptT=.1
##Contour vector
Contour = c(.35, .75,.7,.4)
RESULTS=SimSpsoContour(NSims, PE, PT, corET, Nmax, cohort, Contour,
CutE, CutT, AcceptE, AcceptT,HypermeansE, HypermeansT, Hypervars)
RESULTS
```

`SimSpsoUt` *Simulates trial replications from the SPSO model with desirability optimality function.*

Description

Simulates replications from a Bayesian adaptive phase 12 clinical trial design using the SPSO model and a optimality function based on the desirability tradeoff contour.

Usage

```
SimSpsoUt(
  NSims,
  PE,
  PT,
  corET,
  Nmax,
```

```
  cohort,
  UT,
  CutE,
  CutT,
  AcceptE,
  AcceptT,
  HypermeansE,
  HypermeansT,
  Hypervars
)
```

Arguments

NSims	Number of trial simulations to run.
PE	True efficacy probability for each dose.
PT	True toxicity probaiblity for each dose.
corET	Correlation parameter between efficacy and toxicity probability.
Nmax	Maximum trial sample size.
cohort	Patient cohort size.
UT	Utility matrix for the four bivariate (efficacy, toxicity) events.
CutE	Cutoff for efficacy probability acceptability. Dose-efficacy probabilities must be larger than this for patient assignment.
CutT	Cutoff for toxicity probability acceptability. Dose-toxicity probabilities must be smaller than this for patient assignment.
AcceptE	Posterior probability threshold for efficacy acceptability.
AcceptT	Posterior probability threshold for toxicity acceptability.
HypermeansE	Hypermeans for dose-specific efficacy parameters.
HypermeansT	Hypermeans for dose-specific toxcity parameters.
Hypervars	Hypervariances needed for the SPSO model. Contains, in order (sigma_0^2, sigma_mu^2,tau).

Value

A list with the first entry corresponding to a matrix with: (1) True toxicity probabilities at each dose, (2) True efficacy probabilities at each dose, (3) True mean utility of each dose, (4) Optimal dose selection probability, (5) Average sample size of patients treated at each dose. The second entry of the list contains a vector with rows corresponding to (1) the true binary bivariate correlation between efficacy and toxicity, (2) Stopping probability of the trial, (3) Average number of efficacy events, (4) Average number of toxicity events, and (5) Delta.

Examples

```
library(mvtnorm)
##True toxicity probability
PT=c(.05,.10,.15,.20,.30)
```

```
##True Efficacy Probability
PE=c(.2,.4,.6,.65,.7)
#True Correlation
corET=.5
##Number of simulations
NSims=1 ##Increase this when using
##Hypermeans and hypervariances
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(1,16,1)
##Trial Parameters
##Cohort Size, N^F and N_ET
cohort=3
##Starting Dose
DoseStart=1
Nmax=30 ##Max Sample Size
#Acceptability Criterion
CutE=.3
CutT=.4
##Limits on acceptability
AcceptE=.1
AcceptT=.1
##UTILITY Matrix
UT = matrix(c(38.23529,100,0,61.76471),nrow=2,byrow=TRUE)
RESULTS=SimSpsoUt(NSims, PE, PT, corET, Nmax, cohort, UT,
CutE, CutT, AcceptE, AcceptT,HypermeansE, HypermeansT, Hypervars)
RESULTS
```

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 3 vector of hypervariances.Hypervars(1) contains sigma_0^2, Hypervars(2) contains sigma_mu, Hypervars(3) contains tau - the frailty variance.
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(1,16,1)
B=100
UTEFFTOX(YE, YT,Doses,HypermeansEFF,HypermeansTOX, Hypervars, B)
```

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