Package 'sp23design'

October 14, 2022

Type Package

Title Design and Simulation of Seamless Phase II-III Clinical Trials

Version 0.9-1

Date 2022-04-18

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Description
Provides methods for generating, exploring and executing seamless Phase II-III designs of Lai, Lavori and Shih using generalized likelihood ratio statistics. Includes pdf and source files that describe the entire R implementation with the relevant mathematical details.

Depends R (>= 3.0)

Imports mvtnorm, survival

Suggests RUnit

License LGPL-3

NeedsCompilation no

Repository CRAN

Date/Publication 2022-04-19 10:00:02 UTC

R topics documented:

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sp23design-package	*sp23design: A package for the design, exploration and execution of seamless Phase II-II clinical trials*

Description

This package implements the methodology described in the paper below

Details

Package:	sp23design
Type:	Package
Version:	1.0
Date:	2011-05-05
License:	LGPL?
LazyLoad:	yes

The most important functions in this package are generateSP23Design, exploreSP23Design, executeSP23Design, and analyzeSP23Design

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

Maintainer: Balasubramanian Narasimhan <naras@stat.stanford.edu>

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
## Not run:
```

```
    catn <- function(...) cat(..., "\n")

    trialParameters <- list(minimumNumberOfEvents = 20,
                            minimumIncreaseInV = 0.2,
                            numberRecruitedEachYear = c(80, 120, 160, 160),
                            followupTime = 3,
                            adminCensoringTime = 7,
                            interimLookTime = c(1, 2, 3, 5, 7),
                            type1ErrorForResponse = 0.05,
                            type2ErrorForResponse = 0.01,
                            glrBoundarySidedness = "one", # one sided or two-sided
                            type1Error = 0.05,
                            type2Error = 0.10,
                            epsType1 = 1/3,
                            epsType2 = 1/3)

    trueParameters <- list(p0 = 0.3,
                           p1 = 0.3,
                           pdiffHyp=0.3,
                           theta = list(
                               alpha = 0,
                               beta = 0,
                               gamma = 0),
                           baselineLambda = 0.35,
                           etaHyp = 0.25)
  rngSeed <- 9872831
  sp23Design <- generateSP23Design(trueParameters, trialParameters)
  print(sp23Design)
  trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=rngSeed)
  result <- analyzeSP23Design(sp23Design, trialHistory)$designSummary
 catn("numberOfTimesH0RIsRejectedAtFirstLook", result[["numberOfTimesH0RIsRejectedAtFirstLook"]])
 catn("numberOfTimesH0RIsRejected", result[["numberOfTimesH0RIsRejected"]])
 catn("numberOfTimesStoppedForFutility", result[["numberOfTimesStoppedForFutility"]])
 catn("numberOfTimesH0SIsAccepted", result[["numberOfTimesH0SIsAccepted"]])
 catn("numberOfTimesH0SIsRejected", result[["numberOfTimesH0SIsRejected"]])
 catn("numberOfTimesFutilityDecidedAtLastLook",result[["numberOfTimesFutilityDecidedAtLastLook"]])
 catn("numberOfTimesTrialEndedAtLook", result[["numberOfTimesTrialEndedAtLook"]])
 catn("avgExitTime", result[["avgExitTime"]])

 ## End(Not run)
```

| analyzeSP23Design | *Analyses the results of running a design. If a trial history, such as the result of the function* executeSP23Design *or a history of the actual conduct of a single trial is provided, it returns the analysis results.* |

Description

Produces analysis results from the run of a single trial or a number of simulations.

Usage

```
analyzeSP23Design(sp23Design, trialHistory = NULL, data = NULL,
  col=c("red", "red", "brown", "brown"), lty=c(1,2,1,2))
```

Arguments

sp23Design	The design object typically produced by calling [generateSP23Design](#).
trialHistory	Typically the result of calling [executeSP23Design](#) which is a single data frame, or, the result produced by calling [exploreSP23Design](#) which is a list of data frames, one for each simulation.
data	This is only used when the argument trialHistory is a single data frame, in which case, it should be the data generated in the clinical trial.
col	Colors used for the survival plots
lty	Line types for the survival plots

Details

If trialHistory is a single data frame, the naive response estimates and a survival plot are produced. Otherwise, the counts of the number of times the various hypothesis are rejected and other details are returned.

Value

A list of two items named responseSummary and designSummary If trialHistory is a single data frame, the naive response estimates are returned in responseSummary and a survival plot is produced. Otherwise, the counts of the number of times the various hypothesis are rejected and other details are returned in designSummary.

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
## Not run:
  catn <- function(...) cat(..., "\n")

  trialParameters <- list(minimumNumberOfEvents = 20,
                          minimumIncreaseInV = 0.2,
                          numberRecruitedEachYear = c(80, 120, 160, 160),
                          followupTime = 3,
                          adminCensoringTime = 7,
                          interimLookTime = c(1, 2, 3, 5, 7),
                          type1ErrorForResponse = 0.05,
```

```
                              type2ErrorForResponse = 0.01,
                              glrBoundarySidedness = "one", # one sided or two-sided
                              type1Error = 0.05,
                              type2Error = 0.10,
                              epsType1 = 1/3,
                              epsType2 = 1/3)

   trueParameters <- list(p0 = 0.3,
                              p1 = 0.3,
                              pdiffHyp=0.3,
                              theta = list(
                                   alpha = 0,
                                   beta = 0,
                                   gamma = 0),
                              baselineLambda = 0.35,
                              etaHyp = 0.25)
   rngSeed <- 9872831
   sp23Design <- generateSP23Design(trueParameters, trialParameters)
   print(sp23Design)
   trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=rngSeed)
   result <- analyzeSP23Design(sp23Design, trialHistory)$designSummary
 catn("numberOfTimesH0RIsRejectedAtFirstLook",result[["numberOfTimesH0RIsRejectedAtFirstLook"]])
 catn("numberOfTimesH0RIsRejected", result[["numberOfTimesH0RIsRejected"]])
 catn("numberOfTimesStoppedForFutility", result[["numberOfTimesStoppedForFutility"]])
 catn("numberOfTimesH0SIsAccepted", result[["numberOfTimesH0SIsAccepted"]])
 catn("numberOfTimesH0SIsRejected", result[["numberOfTimesH0SIsRejected"]])
 catn("numberOfTimesFutilityDecidedAtLastLook",result[["numberOfTimesFutilityDecidedAtLastLook"]])
 catn("numberOfTimesTrialEndedAtLook", result[["numberOfTimesTrialEndedAtLook"]])
 catn("avgExitTime", result[["avgExitTime"]])

## End(Not run)
```

---

computeDGivenXi	*Given the estimates of the π and θ, compute d.*

Description

This function computes d via

$$d(\pi, \xi) = \{\pi_0 a + (1 - \pi_0)\} - \{\pi_1 abc + (1 - \pi_1)b\}$$

Usage

```
computeDGivenXi(piVec, xiVec)
```

Arguments

piVec	The two-element vector of (π_0, π_1)
xiVec	The three-element vector of $(a = e^\alpha, b = e^\beta, c = e^\gamma)$

Details

This is an approximation to the hazard ratio

Value

The computed value of d, a scalar

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

computeGammaSubT	*Compute the estimate of the variance of the generalized likelihood ratio statistic at time t*

Description

This function computes the variance of the generalized likelihood ratio statistic at interim stopping times

Usage

```
computeGammaSubT(thetaHat, pi, interimData)
```

Arguments

thetaHat	The three-element vector of (α, β, γ)
pi	The two-element vector of (π_0, π_1)
interimData	The interim data at time t as a data frame

Details

The function builds a hessian matrix and uses a reparametrization to compute Γ_t, the variance of the generalized likelihood ration stochastic process at time t.

Value

A scalar value of the variance Γ_t

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

computeResponseSummary

Given interim data, compute the response end-point summary

Description

Compute the response end-point summary for interim data. This will include the proportion of responses, the proportion of people on treatment and control etc.

Usage

```
computeResponseSummary(interimData)
```

Arguments

interimData	The interim data for the clinical trial

Details

The result is a vector of counts and proportions

Value

m0	number on control arm
m1	number on treatment arm
y0	number of responses in control
y1	number of responses in treatment
numberOfTotalResponses	
	number of total responses in both arms
controlRespProp	
	the proportion of responders in control arm
treatmentRespProp	
	the proportion of responders in the treatment arm
pooledProp	the pooled response proportion

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
## Not run:
  trialParameters <- list(minimumNumberOfEvents = 20,
                          minimumIncreaseInV = 0.2,
                          numberRecruitedEachYear = c(80, 120, 160, 160),
                          followupTime = 3,
                          adminCensoringTime = 7,
                          interimLookTime = c(1, 2, 3, 5, 7),
                          type1ErrorForResponse = 0.05,
                          type2ErrorForResponse = 0.01,
                          glrBoundarySidedness = "one", # one sided or two-sided
                          type1Error = 0.05,
                          type2Error = 0.10,
                          epsType1 = 1/3,
                          epsType2 = 1/3)

  trueParameters <- list(p0 = 0.3,
                         p1 = 0.3,
                         pdiffHyp=0.3,
                         theta = list(
                                 alpha = 0,
                                 beta = 0,
                                 gamma = 0),
                         baselineLambda = 0.35,
                         etaHyp = 0.25)
  rngSeed <- 9872831

  d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                                 nFUp = trialParameters$followupTime,
                                 pi0 = trueParameters$p0,
                                 pi1 = trueParameters$p1,
                                 theta = trueParameters$theta,
                                 lambda0 = trueParameters$baselineLambda)
  dInterim <- generateInterimData(d, trialParameters$interimLookTime[2],
                                   trialParameters$adminCensoringTime)
  computeResponseSummary(dInterim)

## End(Not run)
```

---

executeSP23Design *Given a design object, interim data and the current calendar time, conduct the interim analysis for the time*

Description

This function is designed to be used in the field. Assuming a particular design is chosen, it conducts the interim analysis for a specific calendar time and provides the means for deciding whether to stop for futility or efficacy.

Usage

```
executeSP23Design(sp23DesignObject, data, currentCalendarTime)
```

Arguments

sp23DesignObject

    A seamless phase II-III design object, typically one produced by the generateSP23Design function

data   The interim data, something akin to that produced by the function generateInterimData

currentCalendarTime

    The current calendar time of the interim data. This better be one of the specified interim looks, or the function stops.

Details

This function is designed to be used in the field, although there are parts of it that are currently problematic. For example, in the field, there is typically no inkling of a responder or non-responder and yet the function as it currently stands is too wedded to the simulation scenario. Not hard to fix though.

Value

A vector of quantities is returned.

m0	number on control arm
m1	number on treatment arm
y0	number of responses in control
y1	number of responses in treatment
pi0Hat	estimate of the proportion of responders among control
pi1Hat	estimate of the proportion of responders among treatment
pi0HatH0	estimate of the proportion of responders among control under H_0
pi1HatH0	estimate of the proportion of responders among control under H_0
pi0HatH1	estimate of the proportion of responders among control under H_1
pi1HatH1	estimate of the proportion of responders among control under H_1
glrRespH0	estimate of the generalized likelihood ratio statistic for response under H_0
glrRespH1	estimate of the generalized likelihood ratio statistic for response under H_1
glrSurvH0	estimate of the generalized likelihood ratio statistic for survival under H_0
glrSurvH1	estimate of the generalized likelihood ratio statistic for survival under H_1
alphaHat	the estimate of α
alphaHatH0	the estimate of α under H_0
alphaHatH1	the estimate of α under H_1
betaHat	the estimate of β
betaHatH0	the estimate of β under H_0

betaHatH1	the estimate of β under H_1
gammaHat	the estimate of γ
gammaHatH0	the estimate of γ under H_0
gammaHatH1	the estimate of γ under H_1
hazard	the estimate of d
v	the estimate of Γ_t
rejectH0R	a flag indicating if H_0^R was rejected at the interim look
acceptH0R	a flag indicating if H_0^R was accepted (futility) at the interim look
rejectH0S	a flag indicating if H_0^S was rejected at the interim look
acceptH0S	a flag indicating if H_0^S was accepted (futility) at the interim look
b.metas.Last	the last Haybittle-Peto boundary for the survival end-point, if computed

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
## Not run:
  trialParameters <- list(minimumNumberOfEvents = 20,
                          minimumIncreaseInV = 0.2,
                          numberRecruitedEachYear = c(80, 120, 160, 160),
                          followupTime = 3,
                          adminCensoringTime = 7,
                          interimLookTime = c(1, 2, 3, 5, 7),
                          type1ErrorForResponse = 0.05,
                          type2ErrorForResponse = 0.01,
                          glrBoundarySidedness = "one", # one sided or two-sided
                          type1Error = 0.05,
                          type2Error = 0.10,
                          epsType1 = 1/3,
                          epsType2 = 1/3)

  trueParameters <- list(p0 = 0.3,
                         p1 = 0.3,
                         pdiffHyp=0.3,
                         theta = list(
                                 alpha = 0,
                                 beta = 0,
                                 gamma = 0),
                         baselineLambda = 0.35,
                         etaHyp = 0.25)
  rngSeed <- 9872831
```

```
    sp23Design <- generateSP23Design(trueParameters, trialParameters)
    d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                                   nFUp = trialParameters$followupTime,
                                   pi0 = trueParameters$p0,
                                   pi1 = trueParameters$p1,
                                   theta = trueParameters$theta,
                                   lambda0 = trueParameters$baselineLambda)
    result <- executeSP23Design(sp23Design, d, trialParameters$interimLookTime[2])

## End(Not run)
```

---

exploreSP23Design	*Explore a specified design by simulation*

Description

Explore a chosen design by generating simulated datasets and storing data from simulations for further analysis

Usage

```
exploreSP23Design(sp23Design, numberOfSimulations = 25, rngSeed = 12345,
showProgress = TRUE)
```

Arguments

sp23Design	A design object typically created by the function [generateSP23Design](#)
numberOfSimulations	
	The number of simulations to use, default 25
rngSeed	A seed for the random number generator for reproducibility
showProgress	A flag (default TRUE) to show progress or not

Details

This function is used while exploring the characteristics of a design. Results are accumulated and can be fed into analysis functions to inform choices.

Value

A list of length numberOfSimulations where each entry is a data frame with number of interim looks rows and the following variables in the column.

m0	number on control arm
m1	number on treatment arm
y0	number of responses in control
y1	number of responses in treatment

pi0Hat	estimate of the proportion of responders among control
pi1Hat	estimate of the proportion of responders among treatment
pi0HatH0	estimate of the proportion of responders among control under H_0
pi1HatH0	estimate of the proportion of responders among control under H_0
pi0HatH1	estimate of the proportion of responders among control under H_1
pi1HatH1	estimate of the proportion of responders among control under H_1
glrRespH0	estimate of the generalized likelihood ratio statistic for response under H_0
glrRespH1	estimate of the generalized likelihood ratio statistic for response under H_1
glrSurvH0	estimate of the generalized likelihood ratio statistic for survival under H_0
glrSurvH1	estimate of the generalized likelihood ratio statistic for survival under H_1
alphaHat	the estimate of α
alphaHatH0	the estimate of α under H_0
alphaHatH1	the estimate of α under H_1
betaHat	the estimate of β
betaHatH0	the estimate of β under H_0
betaHatH1	the estimate of β under H_1
gammaHat	the estimate of γ
gammaHatH0	the estimate of γ under H_0
gammaHatH1	the estimate of γ under H_1
hazard	the estimate of d
v	the estimate of Γ_t
rejectH0R	a flag indicating if H_0^R was rejected at the interim look
acceptH0R	a flag indicating if H_0^R was accepted (futility) at the interim look
rejectH0S	a flag indicating if H_0^S was rejected at the interim look
acceptH0S	a flag indicating if H_0^S was accepted (futility) at the interim look
b.metas.Last	the last Haybittle-Peto boundary for the survival end-point, if computed

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, 2011, (submitted).

Examples

```
## Not run:
  trialParameters <- list(minimumNumberOfEvents = 20,
                          minimumIncreaseInV = 0.2,
                          numberRecruitedEachYear = c(80, 120, 160, 160),
                          followupTime = 3,
                          adminCensoringTime = 7,
                          interimLookTime = c(1, 2, 3, 5, 7),
                          type1ErrorForResponse = 0.05,
                          type2ErrorForResponse = 0.01,
                          glrBoundarySidedness = "one", # one sided or two-sided
                          type1Error = 0.05,
                          type2Error = 0.10,
                          epsType1 = 1/3,
                          epsType2 = 1/3)

  ## Case C of table 1 in paper
  caseC.TrueParameters <- list(p0 = 0.3,
                               p1 = 0.6,
                               pdiffHyp=0.3,
                               theta = list(
                                   alpha = 0,
                                   beta = 0,
                                   gamma = 0),
                               baselineLambda = 0.35,
                               etaHyp = 0.25)
  ## Do case C as example
  sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
  trialHistory <- exploreSP23Design(sp23Design, numberOfSimulations=25, rngSeed=2387487)

## End(Not run)
```

---

generateClinicalTrialData

> *A function to generate some clinical trial data according the joint model of response and survival for simulations*

Description

The data is generated according to the model specified in the reference below, specifically,

$$\lambda(t \mid Y, Z) = \lambda_0(t) \exp(\alpha Y + \beta Z + \gamma Y Z)$$

Usage

```
generateClinicalTrialData(nRec, nFUp, pi0, pi1, theta, lambda0, blockSize = 10)
```

Arguments

nRec	the number of patients recruited every year. Length(nRec) is the number of years of recruitment
nFUp	the number of additional years of followup
pi0	the probability of response under control arm
pi1	the probability of response under treatment arm
theta	the three dimensional parameter (α, β, γ) of the joint response/survival model
lambda0	the baseline hazard rate
blockSize	the size of the blocks for randomization of the treatment/control; we use block randomization

Details

Generates data from an exponentail distribution according to the model and adhering to the recruitment goals for each calendar year

Value

A data frame consisting of the following variables.

entryTime	entry time of the patient into the trial
responseIndicator	
	an indicator of patient being a responder or not
treatmentIndicator	
	an indicator of patient being in treatment arm or control
timeToEvent	the time to event or death in the language of the paper

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
```

```
                                type2Error = 0.10,
                                epsType1 = 1/3,
                                epsType2 = 1/3)

    trueParameters <- list(p0 = 0.3,
                              p1 = 0.3,
                              pdiffHyp=0.3,
                              theta = list(
                                      alpha = 0,
                                      beta = 0,
                                      gamma = 0),
                              baselineLambda = 0.35,
                              etaHyp = 0.25)
    rngSeed <- 9872831

    d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                                    nFUp = trialParameters$followupTime,
                                    pi0 = trueParameters$p0,
                                    pi1 = trueParameters$p1,
                                    theta = trueParameters$theta,
                                    lambda0 = trueParameters$baselineLambda)
```

---

generateInterimData   *Generate interim data for a clinical trial from a data set.*

Description

Generate interim data at a given time from a dataset

Usage

```
generateInterimData(clinicalTrialDF, interimTime, administrativeCensoringTime)
```

Arguments

clinicalTrialDF

> The data frame from which to generate the interim data. It is assumed that the variables entryTime, responseIndicator, treatmentIndicator and timeToEvent are present

interimTime   the interim time for which the data is to generated

administrativeCensoringTime

> The administrative censoring time when the study concludes

Details

As it stands this function also is geared towards the simulation scenario. Needs to be cleaned up a bit.

Value

Returns a subset of the input data frame with the following additional variables.

delta   the event indicator

eventTime   calendar event time

Furthermore, the timeToEvent variable is appropriately calculated

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III
Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
trialParameters <- list(minimumNumberOfEvents = 20,
                         minimumIncreaseInV = 0.2,
                         numberRecruitedEachYear = c(80, 120, 160, 160),
                         followupTime = 3,
                         adminCensoringTime = 7,
                         interimLookTime = c(1, 2, 3, 5, 7),
                         type1ErrorForResponse = 0.05,
                         type2ErrorForResponse = 0.01,
                         glrBoundarySidedness = "one", # one sided or two-sided
                         type1Error = 0.05,
                         type2Error = 0.10,
                         epsType1 = 1/3,
                         epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                        p1 = 0.3,
                        pdiffHyp=0.3,
                        theta = list(
                                alpha = 0,
                                beta = 0,
                                gamma = 0),
                        baselineLambda = 0.35,
                        etaHyp = 0.25)
rngSeed <- 9872831

d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                               nFUp = trialParameters$followupTime,
                               pi0 = trueParameters$p0,
                               pi1 = trueParameters$p1,
                               theta = trueParameters$theta,
                               lambda0 = trueParameters$baselineLambda)
dInterim <- generateInterimData(d, trialParameters$interimLookTime[2],
                                trialParameters$adminCensoringTime)
```

---

generateSP23Design	*Generate a seamless Phase II-III design object given some the true parameters and clinical trial parameters*

Description

Generate a seamless Phase II-III design object given some the true parameters and clinical trial parameters

Usage

```
generateSP23Design(trueParameters, trialParameters)
```

Arguments

trueParameters   A list consisting of several components including p0, the true probability of response under control, p1, the true probability of response under treatment, theta, a list of three items (α, β, γ), baselineLambda, the base line hazard rate (constant for now), etaHyp, the hypothesized non-null hazard d.

trialParameters

A list constisting of several components including numberRecruitedEachYear, a vector of recruitment numbers for each year, interimLookTime, the calendar interim look times, followupTime, the follow-up time, adminCensoringTime, the administrative censoring time, glrBoundarySidedness, either one or two-sided generalized likelihood ratio boundaries, default one-sided, typeIError, the type I error desired, type2Error, the type II error desired, used only for computing futility boundaries (only nominally used; need to clarify), epsTypeI, the fraction to spend in interim looks for the modified Haybittle-Peto boundaries, epsTypeII, the fraction to spend in interim looks for the modified Haybittle-Peto boundaries.

Details

Generates a design object that is used throughout the simulation or an actual analysis.

Value

An informal sp23Design object, a list of four items

trueParameters   exactly the input above

trialParameters

       exactly the input above

glrBoundary   a matrix of dimension number of interim looks by 4, containing the boundaries for futility and efficacy for both response and survival

interimLookHistoryDF

       A data frame as described in exploreSP23Design.

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III
Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

See Also

exploreSP23Design and examples in the examples subdirectory of this package

Examples

```
## trial parameters in paper
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
                        epsType2 = 1/3)

## Case C of table 1 in paper
caseC.TrueParameters <- list(p0 = 0.3,
                             p1 = 0.6,
                             pdiffHyp=0.3,
                             theta = list(
                               alpha = 0,
                               beta = 0,
                               gamma = 0),
                             baselineLambda = 0.35,
                             etaHyp = 0.25)


## Do case C as example
sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
```

---

hessian   *A utility function to compute the hessian of the generalized (condi-*
                                 tional) partial likelihood ratio statistic

---

Description

A utility function to compute the hessian of the generalized (conditional) partial likelihood ratio statistic

Usage

```
hessian(theta, pi, interimData)
```

Arguments

theta	The three-element vector (α, β, γ)
pi	The two-element vector (π_0, π_1)
interimData	The interim data frame

Details

Computes the hessian

Value

A 3×3 matrix of the hessian

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik1	*Compute the response log-likelihood*

Description

Compute the response log-likelihood

Usage

```
loglik1(piVec, respSummary)
```

Arguments

piVec	The two-element vector of (π_0, π_1)
respSummary	A vector consisting of the summary of data described in computeResponseSummary

Details

Computes the log-likelihood

Value

the log-likelihood

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik1GivenDelta   *Computes the constrained response log-likelihood (on the alternative)*

Description

Computes the constrained response log-likelihood (on the alternative)

Usage

```
loglik1GivenDelta(p, respSummary, delta = 0)
```

Arguments

p	The probability π_0
respSummary	A vector consisting of the summary of data described in computeResponseSummary
delta	The scalar value of the difference $\pi_1 - \pi_0$

Details

Computes the constrained response log-likelihood (on the alternative)

Value

the (constrained) response log likelihood

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik2 *Computes the survival log-likelihood*

Description

Computes the survival log-likelihood

Usage

```
loglik2(theta, interimData)
```

Arguments

theta   the three-element vector of (α, β, γ)

interimData   The interim data

Details

Computes the survival log-likelihood

Value

the survival log-likelihood

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

loglik2.repar0 *Computes the constrained survival log-likelihood*

Description

Computes the constrained survival log-likelihood

Usage

```
loglik2.repar0(xi, interimData, pi0, pi1, eta.hyp = 0)
```

Arguments

xi	the three-element vector of $(a = e^\alpha, b = e^\beta, c = e^\gamma)$
interimData	the interim data
pi0	the value π_0
pi1	the value π_1
eta.hyp	The hypothesised difference d in the alternative hypothesis

Details

This uses the reparametrization above in terms of (a, b, c) rather than (α, β, γ)

Value

The constrained survival log-likelihood

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

mHP.b	*Compute the modified Haybittle-Peto boundary*

Description

Compute the modified Haybittle-Peto boundary

Usage

```
mHP.b(mu = c(0, 0), v = c(1, 2), alpha = 0.05, eps = 1/2, side = c("one", "two"))
```

Arguments

mu	The mean vector
v	The variance vector, usually proportional to information in calendar time
alpha	The significance desired
eps	The fraction of alpha to use
side	one-sided or two-sided (one or two)

Details

Compute the modified Haybittle-Peto boundary

Value

the modified Haybittle-Peto boundary

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

mHP.c   *Compute the modified Haybittle-Peto boundary for the final look*

Description

Compute the modified Haybittle-Peto boundary for the final look

Usage

```
mHP.c(mu = c(0, 0, 0), v = c(1, 2, 3), b = 3, alpha = 0.05,
      eps = 1/2, side = c("one", "two"))
```

Arguments

mu	the mean vector
v	The variance vector, usually proportional to information in calendar time
b	The (constant) modified Haybittle-Peto boundary, typically computed by mHP.b
alpha	The significance level desired
eps	The fraction of alpha to use
side	one-sided or two-sided (one or two)

Details

Compute the modified Haybittle-Peto boundary for the final look

Value

the modified Haybittle-Peto boundary for the final look

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

---

performInterimLook   *Perform an interim look in a seamless Phase II-III clinical trial*

Description

Perform an interim look in a seamless Phase II-III clinical trial

Usage

```
performInterimLook(k, trueParameters, trialParameters, glrBoundary,
                   interimData, interimLookHistoryDF, argRejectH0R)
```

Arguments

k	the index of the look
trueParameters	the true parameters, usually available in an object generated by generateSP23Design
trialParameters	
	the trial parameters, usually available in an object generated by generateSP23Design
glrBoundary	the generalized likelihood ratio boundaries, usually available in an object produced by generateSP23Design
interimData	the interim data
interimLookHistoryDF	
	the interim look history data frame matrix described in exploreSP23Design
argRejectH0R	A flag that indicates whether H_0^R has been rejected in the previous look; A value of FALSE is used for first look.

Details

Perform an interim look in a seamless Phase II-III clinical trial

Value

a vector of named values described in exploreSP23Design, essentially providing a new row to the interim look history data frame

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
trialParameters <- list(minimumNumberOfEvents = 20,
                        minimumIncreaseInV = 0.2,
                        numberRecruitedEachYear = c(80, 120, 160, 160),
                        followupTime = 3,
                        adminCensoringTime = 7,
                        interimLookTime = c(1, 2, 3, 5, 7),
                        type1ErrorForResponse = 0.05,
                        type2ErrorForResponse = 0.01,
                        glrBoundarySidedness = "one", # one sided or two-sided
                        type1Error = 0.05,
                        type2Error = 0.10,
                        epsType1 = 1/3,
                        epsType2 = 1/3)

trueParameters <- list(p0 = 0.3,
                       p1 = 0.3,
                       pdiffHyp=0.3,
                       theta = list(
                               alpha = 0,
                               beta = 0,
                               gamma = 0),
                       baselineLambda = 0.35,
                       etaHyp = 0.25)
rngSeed <- 9872831

sp23Design <- generateSP23Design(trueParameters, trialParameters)
d <- generateClinicalTrialData(nRec = trialParameters$numberRecruitedEachYear,
                               nFUp = trialParameters$followupTime,
                               pi0 = trueParameters$p0,
                               pi1 = trueParameters$p1,
                               theta = trueParameters$theta,
                               lambda0 = trueParameters$baselineLambda)
dInterim <- generateInterimData(d, trialParameters$interimLookTime[1],
                                 trialParameters$adminCensoringTime)
dInterim <- dInterim[order(dInterim$timeToEvent), ]
## This is a tricky function to use for all but the first interim look;
## see executeSP23Design code for details! Reason: interim look k depends
## on results of interim look k-1
##
performInterimLook(1, sp23Design$trueParameters, trialParameters, sp23Design$glrBoundary,
                   dInterim, sp23Design$interimLookHistoryDF,
                   argRejectH0R = FALSE)
```

---

resetSP23Design	*Reset the design object so that counts and results are zeroed out*

Description

Reset the design object so that counts and results are zeroed out

Usage

```
resetSP23Design(sp23Design)
```

Arguments

sp23Design   An object usually the result of generateSP23Design

Details

Reset the design object so that counts and results are zeroed out

Value

A new `sp23Design` object with counts and results zeroed out

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III
Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

Examples

```
## Not run:
  trialParameters <- list(minimumNumberOfEvents = 20,
                    minimumIncreaseInV = 0.2,
                    numberRecruitedEachYear = c(80, 120, 160, 160),
                    followupTime = 3,
                    adminCensoringTime = 7,
                    interimLookTime = c(1, 2, 3, 5, 7),
                    type1ErrorForResponse = 0.05,
                    type2ErrorForResponse = 0.01,
                    glrBoundarySidedness = "one", # one sided or two-sided
                    type1Error = 0.05,
                    type2Error = 0.10,
                    epsType1 = 1/3,
                    epsType2 = 1/3)

  ## Case C of table 1 in paper
  caseC.TrueParameters <- list(p0 = 0.3,
                          p1 = 0.6,
                          pdiffHyp=0.3,
                          theta = list(
                              alpha = 0,
                              beta = 0,
                              gamma = 0),
                          baselineLambda = 0.35,
                          etaHyp = 0.25)
```

```
   ## Do case C as example
   sp23Design <- generateSP23Design(caseC.TrueParameters, trialParameters)
   ## do something ...
   sp23Design <- resetSP23Design(sp23Design)

 ## End(Not run)
```

---

solveForCGivenABD	*A convenience function to reduce dimension by solving for one variable c in terms of others a, b, d*

Description

A convenience function to reduce dimension by solving for one variable c in terms of others a, b, d

Usage

```
solveForCGivenABD(piVec, a, b, d)
```

Arguments

piVec	The two-element vector of (π_0, π_1)
a	The value for a
b	The value for b
d	The value for d

Details

Just solves the equation in closed form

Value

the value for c

Author(s)

Mei-Chiung Shih, Balasubramanian Narasimhan, Pei He

References

Lai, Tze Leung and Lavori, Philip W. and Shih, Mei-Chiung. Sequential Design of Phase II-III Cancer Trials, Statistics in Medicine, Volume 31, issue 18, p.1944-1960, 2012.

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