Package 'GSMC'

December 6, 2020

Type Package

Title Group Sequential Design for Maxcombo tests

Version 0.1.1

Date 2020-12-06

Author Lili Wang, Xiaodong Luo, Cheng Zheng

Maintainer Lili Wang <lilywang@umich.edu>

Description This R package is to prepare group sequential eesign for maxcombo tests without conducting simulations

License GPL-2

Encoding UTF-8

Suggests nphsim, IAfrac

Imports mvtnorm, gsDesign

Depends R (>= 3.5.2)

RoxygenNote 7.1.0

R topics documented:

`Maxcombo.bd` *Boundary calculation for GSMC*

Description

Boundary calculation for interim analysis with max-combo tests based on correlation matrix and the alpha spending function.

Usage

```
Maxcombo.bd(Sigma0, index, alpha_sp, n.rep = 5)
```

Arguments

Sigma0	Correlation matrix for all the test statistics.
index	Vector of non-decreasing integer starting from 1 to indicate which stage each column or row of the correlation matrix Sigma0 corresponds to.
alpha_sp	Vector of errors to spend up to each stage.
n.rep	number of repeats to take the median for output

Value

z_alpha	Boundary values for all the stages.
z_alpha_vec	Boundary values for all the test statistics correponding to index.

Author(s)

Lili Wang

Examples

```
 #install.packages("gsDesign")
 library(gsDesign)
 alpha=0.025
 beta=0.1
 # If there are two stages (K=2), with on interim stage and a final stage
# First we obtain the errors spent at each stage to be identical to the ones from regular interim analysis assum
x <- gsDesign::gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log(0.7))
 (z <- x$upper$bound)
 x
 Sigma0_v<-rep(0.5,6)
 Sigma0<-matrix(1, ncol=4,nrow=4)
 Sigma0[upper.tri(Sigma0)]<- Sigma0_v
 Sigma0[lower.tri(Sigma0)]<- t(Sigma0)[lower.tri(t(Sigma0))]
 Sigma0
alpha_interim<-pnorm(z[1],lower.tail = F) # The error you would like to spend at the interim stage
 zz<-Maxcombo.bd(Sigma0 = Sigma0,index=c(1,1,2,2),alpha_sp=c(alpha_interim,alpha))

 zz$z_alpha # boundary value for each stage
 zz$z_alpha_vec # boundary value for each test statistic correponding to index
 mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1],2),corr=Sigma0[1:2,1:2])[[1]]
 1-alpha_interim
 1-mvtnorm::pmvnorm(upper =zz$z_alpha_vec,corr=Sigma0)[[1]]
 alpha
 # What if we do not consider interim stage but with only a final stage? (K=1)
 zz1<-Maxcombo.bd(Sigma0 = Sigma0[3:4,3:4],index=c(1,1),alpha_sp=c(alpha))
 mvtnorm::pmvnorm(upper=rep(zz1$z_alpha,2),corr=Sigma0[1:2,1:2])[[1]]
 1-alpha
 # This function will also fit 2 or any number of interims (K>=3)
 # Let there are 3 stages, Let us try controlling the error spent at each stage.
 stage_p<-c(0.5,0.7,0.8,0.9)
x <- gsDesign::gsDesign(k=5, test.type=1, timing=stage_p, sfu="OF", alpha=alpha, beta=beta,delta=-log(0.7))
 (z <- x$upper$bound)
alpha_sp<- cumsum(x$upper$prob[,1]) # the theoretical cumulative errors spent at each stage
# 2 tests per stage
Sigma0_v<-rep(0.5,choose(10,2))
Sigma0<-matrix(1, ncol=10,nrow=10)
```

```
Sigma0[upper.tri(Sigma0)]<- Sigma0_v
Sigma0[lower.tri(Sigma0)]<- t(Sigma0)[lower.tri(t(Sigma0))]
Sigma0

zz<-Maxcombo.bd(Sigma0 = Sigma0,index=c(1,1,2,2,3,3,4,4,5,5),alpha_sp=alpha_sp)

zz$z_alpha # boundary value for each stage
zz$z_alpha_vec # boundary value for each test statistic correponding to index
# interim 1
mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1],2),corr=Sigma0[1:2,1:2])[[1]] # expected error spent at this stage
1-alpha_sp[1] #compare with the expected error spent at this stage
# above two rows are very close to each other, same for the following pairs.
# interim 2
mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1:2],each=2),corr=Sigma0[1:4,1:4])[[1]]
1-alpha_sp[2]
# interim 3
mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1:3],each=2),corr=Sigma0[1:6,1:6])[[1]]
1-alpha_sp[3]
# interim 4
mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1:4],each=2),corr=Sigma0[1:8,1:8])[[1]]
1-alpha_sp[4]
# final stage
mvtnorm::pmvnorm(upper=rep(zz$z_alpha[1:5],each=2),corr=Sigma0[1:10,1:10])[[1]]
1-alpha_sp[5]
```

`Maxcombo.beta.n` *The type II errors/Powers for a range of sample sizes*

Description

To obtain a spectrum of powers or type II errors for a range of sample sizes n or d

Usage

```
Maxcombo.beta.n(Sigma1, mu1, z_alpha_vec, interim_vec, R, n_seq, n.rep = 5)

Maxcombo.beta.d(
  Sigma1,
  mu1,
  z_alpha_vec,
  interim_vec,
  R,
  d_seq,
  sum_D,
  n.rep = 5
)
```

Arguments

`Sigma1`	The correlation matrix under the alternative hypothesis.
`mu1`	The unit mu under the alternative hypothesis (the mean of the expectation of each subject scaled weighted log-rank test statistic, which can be approximated using the fomula for \equnE^* in Hasegawa 2014 paper.).

z_alpha_vec	Same as the one exported from Maxcombo.bd, which is the boundaries for ordered test statistics, its order should be consistent to the rows and columns in Sigma1.
interim_vec	The vector of the interims in each stages, not that it should be a repeat vector with same iterim values for all the test statitics at same stages.
R	End of the enrollment time, which is identical to R defined in other functions like I.1.
n_seq	The sequence of number of patients.
n.rep	number of repeats to take the median for output
d_seq	The sequence of number of expected events.
sum_D	Same as the exported value from sample.size_FH, the summed D^* in Hasegawa (2014).

Author(s)

Lili Wang

See Also

Maxcombo.sz

Examples

```
#install.packages("mvtnorm")
#library(mvtnorm)
#install.packages("gsDesign")
#library(gsDesign)
alpha=0.025
beta=0.1
# If there are two stages (K=2), with on interim stage and a final stage
# First we obtain the errors spent at each stage to be identical to the ones from regular interim analysis assumi
x <- gsDesign::gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log(0.7))
(z <- x$upper$bound)
x
Sigma0_v<-rep(0.5,6)
Sigma0<-matrix(1, ncol=4,nrow=4)
Sigma0[upper.tri(Sigma0)]<- Sigma0_v
Sigma0[lower.tri(Sigma0)]<- t(Sigma0)[lower.tri(t(Sigma0))]
Sigma0
alpha_interim<-pnorm(z[1],lower.tail = F) # The error you would like to spend at the interim stage
zz<-Maxcombo.bd(Sigma0 = Sigma0,index=c(1,1,2,2),alpha_sp=c(alpha_interim,alpha))
zz$z_alpha # boundary value for each stage
zz$z_alpha_vec # boundary value for each test statistic correponding to index
# Correlation matrix under the alternative hypothesis
Sigma1_v<-rep(0.5,6)
Sigma1<-matrix(1, ncol=4,nrow=4)
Sigma1[upper.tri(Sigma1)]<- Sigma1_v
Sigma1[lower.tri(Sigma1)]<- t(Sigma1)[lower.tri(t(Sigma1))]
Sigma1
# Define mu1
mu1=c(0.1,0.1,0.2,0.2)
# Obtain the sample size
Maxcombo.sz(Sigma1=Sigma1,mu1=mu1,z_alpha_vec=zz$z_alpha_vec,beta=0.1,interim_vec=c(10,10,18,18),R=14,n_ra
# need 232 patients, 140 deaths
```

```
#Obatain the spectrum of powers or type II errors in the input range
power_n<-1-Maxcombo.beta.n(Sigma1=Sigma1,mu1=mu1,z_alpha_vec=zz$z_alpha_vec,interim_vec=c(10,10,18,18),R=14
plot(x=seq(100,1000,50),y=power_n,type="l",col=1,lwd=2,main=expression(paste(1-beta," vs n")),ylab = express
power_d<-1-Maxcombo.beta.n(Sigma1=Sigma1,mu1=mu1,z_alpha_vec=zz$z_alpha_vec,interim_vec=c(10,10,18,18),R=14
plot(x=seq(60,600,30),y=power_d,type="l",col=1,lwd=2,main=expression(paste(1-beta," vs d")),ylab = expressio
```

`Maxcombo.sz` *Sample size calculation*

Description

Sample size calculation to control the type II error or the power of an interim analysis with Maxcombo tests.

Usage

```
Maxcombo.sz(
  Sigma1,
  mu1,
  z_alpha_vec,
  beta,
  interim_vec,
  R,
  n_range,
  sum_D,
  n.rep = 5
)
```

Arguments

`Sigma1`	The correlation matrix under the alternative hypothesis.
`mu1`	The unit mu under the alternative hypothesis (the mean of the expectation of each subject scaled weighted log-rank test statistic, which can be approximated using the fomula for \equnE^* in Hasegawa 2014 paper.).
`z_alpha_vec`	Same as the one exported from Maxcombo.bd, which is the boundaries for ordered test statistics, its order should be consistent to the rows and columns in `Sigma1`.
`beta`	Type II error.
`interim_vec`	The vector of the interims in each stages, not that it should be a repeat vector with same iterim values for all the test statitics at same stages.
`R`	End of the enrollment time, which is identical to `R` defined in other functions like `I.1`.
`n_range`	The range ot the expected patient numbers.
`sum_D`	Same as the exported value from `sample.size_FH`, the summed D^* in Hasegawa (2014).
`n.rep`	number of repeats to take the median for output

Details

Assume that there are 2 stages (1 interm, 1 final), and two tests for a max-combo in each stage, then we have 4 test statistics, and the two cutoff values for the two stages have been determined by `Maxcombo.bd` in advance using their correlation matrix and the error spending function α_1, α. The goal of this function is to control the sample size n (number of patients for both arms) or d (observed events) to achieve the ideal type II error β or the power $(1-\beta)$, i.e. ¶$(Z_{11} < z_1, Z_{12} < z_1, Z_{21} < z_2, Z_{22} < z_2) = \beta$.

Value

`n`	The number of patients needed for the trial to achieve the predefined power.
`d`	The number of events needed for the trial to achieve the predefined power.
`sum_D`	The input `sum_D` value.

Author(s)

Lili Wang

References

Hasegawa, T. (2014). Sample size determination for the weighted log-rank test with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 13(2), 128-135.

See Also

`Maxcombo.beta.n`

Examples

```
#install.packages("mvtnorm")
library(mvtnorm)
#install.packages("gsDesign")
library(gsDesign)
alpha=0.025
beta=0.1
# If there are two stages (K=2), with on interim stage and a final stage
# First we obtain the errors spent at each stage to be identical to the ones from regular interim analysis assumi
x <- gsDesign::gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log(0.7))
(z <- x$upper$bound)
x
Sigma0_v<-rep(0.5,6)
Sigma0<-matrix(1, ncol=4,nrow=4)
Sigma0[upper.tri(Sigma0)]<- Sigma0_v
Sigma0[lower.tri(Sigma0)]<- t(Sigma0)[lower.tri(t(Sigma0))]
Sigma0
alpha_interim<-pnorm(z[1],lower.tail = F) # The error you would like to spend at the interim stage
zz<-Maxcombo.bd(Sigma0 = Sigma0,index=c(1,1,2,2),alpha_sp=c(alpha_interim,alpha))
zz$z_alpha # boundary value for each stage
zz$z_alpha_vec # boundary value for each test statistic correponding to index
# Correlation matrix under the alternative hypothesis
Sigma1_v<-rep(0.5,6)
Sigma1<-matrix(1, ncol=4,nrow=4)
Sigma1[upper.tri(Sigma1)]<- Sigma1_v
```

```
Sigma1[lower.tri(Sigma1)]<- t(Sigma1)[lower.tri(t(Sigma1))]
Sigma1
# Define mu1
mu1=c(0.1,0.1,0.2,0.2)
# Obtain the sample size
Maxcombo.sz(Sigma1=Sigma1,mu1=mu1,z_alpha_vec=zz$z_alpha_vec,beta=0.1,interim_vec=c(10,10,18,18),R=14,n_ran
# need 232 patients, 140 deaths
```

---

stoch_pred *A stochastic-process way of prediction*

Description

A stochastic-process way of prediction of the expected event counts, mean difference, and the information(variance) or the covariance

Usage

```
stoch_pred(eps, p, b, tau, omega, lambda, theta, rho, gamma, R)

stoch_pred.cov(
  eps,
  p,
  b,
  tau,
  omega,
  lambda,
  theta,
  rho1,
  gamma1,
  rho2,
  gamma2,
  R
)
```

Arguments

eps	Delayed treatment effect time.
p	Probability of treatment assignment.
b	The number of subintervals at each time point.
omega	The minimum follow-up time for all the patients. Note that Hasegawa(2014) assumes that the accrual is uniform between time 0 and R, and there does not exist any censoring except for the administrative censoring at the ending time τ. Thus this value omega is equivalent to tau-R. Through our simulation tests, we found that this function is quite robust to violations of these assumptions: dropouts, different cenosring rates for two arms, and changing accrual rates.
lambda	The hazard for the control group.

`theta` The hazard ratio after the delayed time `eps` for the treatment arm.

`rho, rho1, rho2`
The first parameter for Fleming Harrington weighted log-rank test:$W(t) = S^{\rho}(t^{-})(1 - S(t^{-}))^{\gamma}$.

`R` The accrual period.

Value

`sum_D` The mean expected event ratio, multiplied by `n`, the sample size, it is equal to the stochastically predicted number of events.

`inf or covariance`
The information/variance or covariance (averaged for each subject) , should multiplied by `n`, which is the sample size to obtain the stochastically predicted information.

`E.star` The unit mean, correspoinding to E^* in Hasegawa(2014)

`trt_vs_ctrl_N` The ratio of the samples sizes between the two arms, treatment vs control, corresonding to the time vector `t_vec`.

`t_vec` The time sequence corresponding to `trt_vs_ctrl_N`.

Author(s)

Lili Wang

References

Hasegawa, T. (2014). Sample size determination for the weighted log-rank test with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 13(2), 128-135.

Index