Package 'GSMC'

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Type Package

Title Group Sequential Design for Maxcombo tests

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

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Encoding UTF-8

RoxygenNote 6.1.1

Depends mvtnorm, gsDesign

Suggests nphsim, IAfrac

R topics documented:

`Maxcombo.bd` *Boundary calculation for GS-MC*

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)
```

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.

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 regul
  x <- gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log
  (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 in
  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
  pmvnorm(upper=rep(zz$z_alpha[1],2),corr=Sigma0[1:2,1:2])[[1]]
  1-alpha_interim
  1-pmvnorm(upper =zz$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))
  pmvnorm(upper=rep(zz1$z_alpha,2),corr=Sigma0[1:2,1:2])[[1]]
  1-alpha
  # This function will also fit 2 or any number of interims (K>=3)
  # Let there are 3 stages, Let us try controlling the error spent at each stage.
  stage_p<-c(0.5,0.7,0.8,0.9)
  x <- gsDesign(k=5, test.type=1, timing=stage_p, sfu="OF", alpha=alpha, beta=beta,delta=
  (z <- x$upper$bound)
  alpha_sp<- cumsum(x$upper$prob[,1]) # the theoretical cumulative errors spent at each s
# 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
pmvnorm(upper=rep(zz$z_alpha[1],2),corr=Sigma0[1:2,1:2])[[1]] # expected error spent at t
1-alpha_sp[1] #compare with the expected error spent at this stage
# above two rows are very close to each other, same for the following pairs.
# interim 2
pmvnorm(upper=rep(zz$z_alpha[1:2],each=2),corr=Sigma0[1:4,1:4])[[1]]
1-alpha_sp[2]
# interim 3
pmvnorm(upper=rep(zz$z_alpha[1:3],each=2),corr=Sigma0[1:6,1:6])[[1]]
1-alpha_sp[3]
# interim 4
pmvnorm(upper=rep(zz$z_alpha[1:4],each=2),corr=Sigma0[1:8,1:8])[[1]]
1-alpha_sp[4]
# final stage
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)

Maxcombo.beta.d(Sigma1, mu1, z_alpha_vec, interim_vec, R, d_seq, sum_D)
```

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.
`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
x <- gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log(0
(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 inte
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
# 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$z_alpha_vec,interim_vec=c
plot(x=seq(100,1000,50),y=power_n,type="l",col=1,lwd=2,main=expression(paste(1-beta," vs
power_d<-1-Maxcombo.beta.n(Sigma1=Sigma1,mu1=mu1,z_alpha_vec=zz$z_alpha_vec,interim_vec=c
plot(x=seq(60,600,30),y=power_d,type="l",col=1,lwd=2,main=expression(paste(1-beta," vs d"
```

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)
```

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).

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
x <- gsDesign(k=2, test.type=1, timing=0.6, sfu="OF", alpha=alpha, beta=beta,delta=-log(0
(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 inte
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
# need 232 patients, 140 deaths
```

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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.

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