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 design for maxcombo tests without doing simulations

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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 cumulative errors to spend up to each stage.
n.rep	number of repeats to take the median for output since the called likelihood generator of a multivariate normal distribution pmvnorm is not determinant. The default n.rep value is 5.

Value

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

Author(s)

Lili Wang

References

Wang, L., Luo, X., & Zheng, C. (2021). A Simulation-free Group Sequential Design with Maxcombo Tests in the Presence of Non-proportional Hazards. Journal of Pharmaceutical Statistics.

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 assuming that the interim stage
  happened at 60% of events have been observed. The error spending
   function used below is O\'Brien-Fleming.
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
# The error you would like to spend at the interim stage:
alpha_interim <- pnorm(z[1],lower.tail = F)

zz <- Maxcombo.bd(
Sigma0 = Sigma0,
```

```
  index = c(1, 1, 2, 2),
  alpha_sp = c(alpha_interim, alpha))


  # boundary value for each stage
  zz$z_alpha
  # boundary value for each test statistic correponding to index
  zz$z_alpha_vec
  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?
  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 power for a vector of sample sizes*

Description

To obtain a spectrum of power for a vector of numbers of subjects (n) using `Maxcombo.beta.n` or events (d) using `Maxcombo.beta.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 E^* 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

```
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(Sigma0)]
Sigma0
alpha_stage <- c(0.01,0.025) # The error you would like to spend at the interim stage
zz <- Maxcombo.bd(Sigma0 = Sigma0,index=c(1,1,2,2),alpha_sp=alpha_stage)
zz$z_alpha # boundary value for each stage
zz$z_alpha_vec # boundary value for each test statistic corresponding
to the index
```

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 E^* 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

stoch_pred *A stochastic prediction results*

Description

A stochastic-process way of prediction of the expected event ratio (D), mean difference (μ), and the information(variance) using `stoch_pred` or the covariance using `stoch_pred.cov`.

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 sub-intervals at each time point, the larger the finer splitting for more accurate computation. Usually $b = 30$ is sufficient.
`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`.
`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. Once being multiplied by `n`, it will become the stochastically predicted event size.

`inf or covariance`
: The information/variance or covariance (averaged for each subject), should be multiplied by `n`, which gives the stochastically predicted information.

`E.star`
: The unit mean, corresponding to E^* in Hasegawa(2014), or the $\tilde{\mu}$ of fomula (8) in Wang et al(2021).

`trt_vs_ctrl_N`
: The ratio of the samples sizes between the two arms, treatment vs control, corresponding 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. Wang, L., Luo, X., & Zheng, C. (2021). A Simulation-free Group Sequential Design with Max-combo Tests in the Presence of Non-proportional Hazards. Journal of Pharmaceutical Statistics.

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