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

Imports data.table,
gsDesign,
mvtnorm,
stats

Depends R (>= 3.5.2)

RoxygenNote 7.1.0

R topics documented:

`approx.I` *Approximate information for an arbitrary survival function*

Description

An approximation alternative to the regular prediction of the information/covariance based on the assumed survival functions.

Usage

```
approx.I(
  t.star,
  p,
  S1 = function(x) {     1 },
  S0 = function(x) {     1 },
  func = function(x) {     1 },
  n.length = 1e+06
)
```

Arguments

`t.star`	The ending time of the cumulative informaiton or covariance prediciton.
`p`	Treatment assignment probability.
`S1`	Survival function for the treatment group.
`S0`	Survival function for the control gorup.
`func`	The integrand function.
`n.length`	The number of intervals spitted to obtain the approximate integration.

Author(s)

Lili Wang

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

Examples

```
## Not run:
# Examples for approx.I
eps<-2 # delayed effect
p<-0.5 #treatment assignment
tau<-18 # end of the study
R<-14 # accrual period [0,R]
lambda<-log(2)/6 # control group risk hazard
theta<-0.7 # hazard ratio
lambda.trt<- lambda*theta
rho<- 0 # parameter for the weights
gamma<-1 #parameter for the weights
S1<-function(x){
  ifelse(x>eps,exp(-theta*lambda*x)*getc(theta,lambda,eps),exp(-lambda*x))
  }
  S0<-function(x){
    exp(-lambda*x)
    }
    S_pool<-function(x){
      p*S1(x)+(1-p)*S0(x)
      }
      func<-function(x){
        min((tau-x)/R,1)*(S_pool(x)^rho*(1-S_pool(x))^gamma)^2
        }
 approx.I(t.star=tau,p,S1=S1,S0=S0,fun=func,n.length=1e6)
 I.1(rho,gamma,lambda,theta,eps,R,p,tau)
 # Change the cumulative information up to 10 instead of taus
 func2<-function(x){
   min((10-x)/R,1)*(S_pool(x)^rho*(1-S_pool(x))^gamma)^2
   }
   approx.I(t.star=10,p,S1=S1,S0=S0,fun=func2,n.length=1e6)
   I.1(rho,gamma,lambda,theta,eps,R,p,t.star=10)
   # Covariance approximation for two weights: 1 and G(0,1)
   rho1=rho2=0
   gamma1=0
   gamma2=1
   func3<-function(x){
 min((10-x)/R,1)*(S_pool(x)^rho1*(1-S_pool(x))^gamma1)*(S_pool(x)^rho2*(1-S_pool(x))^gamma2)
  }
  approx.I(t.star=10,p,S1=S1,S0=S0,fun=func3,n.length=1e6)
  I.1.cov(rho1,gamma1,rho2,gamma2,lambda,theta,eps,R,p,t.star=10)

## End(Not run)
```

---

avg.haz *Calcualte the average hazard ratios*

Description

Calculate the average hazard ratios according to Kalbfleisch and Prentice (1981) or in the paper Hasegawa (2014) for piece-wise exponential survival functions (only one change point eps).

Usage

```
avg.haz(theta, eps, lambda, p = 1/2)
```

Arguments

theta	hazard ratio after eps between the treatment and the control group, assuming that the hazard rato is 1 before eps.
eps	The change point, before which, the hazard ratio is 1, and after which, the hazard ratio is theta.
lambda	The constant hazard for the control arm.
p	Treatment assignment probability.

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.

Examples

```
## Not run:
# test
lambda=log(2)/6
theta=0.7
eps=2
avg.haz(theta,eps,lambda)

## End(Not run)
```

---

cor.0 *Predicted cross-test correlation*

Description

These two functions are to predict the correlation between two weighted log-rank tests at certain time `t.star` under either the null hypothesis (using `cor.0`) or the alternative hypothesis (using `cor.1`).

Usage

```
cor.0(rho1, gamma1, rho2, gamma2, lambda, R, p, t.star)

cor.1(rho1, gamma1, rho2, gamma2, lambda, theta, eps, R, p, t.star)
```

Arguments

rho1	First power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
gamma1	Second power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
rho2	First power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
gamma2	Second power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
lambda	Event hazard for the control arm.
R	End of the accrual period.
p	Treatment assignment probability.
t.star	Time point we pause the study to check the cumulative information under the null.
theta	Hazard ratio after the change point (before the change point HR should be 1).
eps	Change point.

Details

These two functions are designed to calculate the predicted correlation between the two weighted log-rank tests at time `t.star` under the two hypotheses. The null hypothesis is an exponential distribution for both the treatment and control arms with hazard `lambda`, while the alternative hypothesis has the control group following an exponential distribution with hazard `lambda`, and the treatment group following a piece-wise exponential distribution with hazard `lambda` before `eps`, but a hazard `theta` times `lambda` after `eps`.

Author(s)

Lili Wang.

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

---

data.trim *Trim the data*

Description

Trim the data according to event number or time

Usage

```
data.trim(t, data, trimmed = F)

data.trim.d(d, data, trimmed = F)
```

Arguments

t	Time of interest to pause/stop the study, which could be an interim stage or the final stage.
data	There are two possible structures allowed for this input data. The first type needs to have trimmed=F and include variables: a treatment variable with "experimental" denoting treatment group, cnsr variable with value 1 denoting censoring, ct variable denoting event time from the origin of the study, which equals the sum of entering time enterT and the survival time (time to event or censoring). A dataset simulated from from R package nphsim should fit the first type well enough (see the example1). The second type can be any data.frame or data.table output from a data.trim function, including variables: ct denoting event time from the origin of the study or the sum of entering time and the survival time, survival denoting the survival time or time to event/censoring, delta as an event indicator, enterT as entering time (example 2). For the second type, we set trimmed=T to avoid extra computations, but should be fine if trimmed=F.
trimmed	Whether this data has been trimmed by data.trim or data.trim.d before.
d	Event counts to pause/stop the study.

Details

data.trim is to trim the data upto t, data.trim.d is to trim the data upto the cound d.

Value

Note that data.trim only outputs a data.table odered by ct, the event/censoring time since the start of the study (calendar scale), including variables in the input data.table/frame data, and additional/updated variables of event indicator delta, ct, follow-up time survival since the enrollment. data.trim.d outpus a list of two components. The first component is the data censored with d events have been observed, ordered by ct, the event/censoring time since the start of the study (calendar scale). The second component is the time of the stopping point when d events have been observed.

Author(s)

Lili Wang

See Also

FH.frac.cal

FH.frac.cal *Information fraction for Fleming-Harrington weighted log-rank test*

Description

Monitor the raction for Fleming-Harrington weighted log-rank test for a vector of time points

Usage

```
FH.frac.cal(data, t_vec, I_max, rho, gamma, trimmed)
```

Arguments

`data`	There are two possible structures allowed for this input data. The first type needs to have `trimmed=F` and include variables: a `treatment` variable with "experimental" denoting treatment group, `cnsr` variable with value 1 denoting censoring, `ct` variable denoting event time from the origin of the study, which equals the sum of entering time `enterT` and the survival time (time to event or censoring). A dataset simulated from from R package nphsim should fit the first type well enough (see the example1). The second type can be any data.frame or data.table output from a `data.trim` function, including variables: `ct` denoting event time from the origin of the study or the sum of entering time and the survival time, `survival` denoting the survival time or time to event/censoring, `delta` as an event indicator, `enterT` as entering time (example 2). For the second type, we set `trimmed=T` to avoid extra computations, but should be fine if `trimmed=F`.
`t_vec`	Follow-up time since the origin of the study (not that it's not following the survival time scale, but following the calendar time scale), which could be a vector, to measure the information fraction for these time points.
`I_max`	The evaluated I_{max}, which returned from function `I.1` or `I.0` by setting the `t.start=tau`, where `tau` is the end of the study.
`rho`	First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
`gamma`	Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
`trimmed`	Logical indicator to show whether the `data` input has been "trimmed" by `data.trim` and `data.trim.d` before: adding variables like `delta` indicating events (=1), and `trt` distringuishing the treatment group (=1) from the control group (=0)

Details

Calculation the information fraction for Fleming-Harrington family weighted log-rank tests using the monitored estimated information for numerator, and the predicted information I_{max} as denominator.

Value

This function returns a vector of information fractions corresponding to the input time vector `t_vec`.

Author(s)

Lili Wang

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

See Also

`data.trim`

Examples

```
## Not run:
# install.packages("devtools")
# library(devtools)
# install_github("keaven/nphsim")
# library(nphsim)
eps<-2 # delayed effect
p<-0.5 #treatment assignment
b<-30 # an intrinsic parameter to decide the number of intervals per time unit
tau<- 18 # end of the study
R<-14 # accrual period [0,R]
omega<- tau-R
lambda<-log(2)/6 # control group risk hazard
theta<-0.7 # hazard ratio
lambda.trt<- lambda*theta #hazard after the change point for the treatment arm
rho<- 0 # parameter for the weights
gamma<-1 #parameter for the weights
alpha<-0.025 #type 1 error
beta<-0.1 #type 2 error
# First we decide the sample size:
size_FH <- sample.size_FH(eps,p,b,tau,omega,lambda,lambda.trt,rho, gamma,alpha,beta)
n_FH <-size_FH$n
n_event_FH<-size_FH$n_event
accrual.rt<-n_FH/R # the needed arrual rate
#Generate data accordingly, use eta=1e-5 to inhibit censoring
data_temp <- nphsim(nsim=1,lambdaC=lambda, lambdaE = c(lambda,lambda.trt), ssC=ceiling(n_FH*(1-p)),intervals

# Example 1 for FH.frac.cal: Set trimmed=F and work on the crude dataset from nphsim()
inf_frac_vec1<-FH.frac.cal(data_temp,c(10,15,18),I_denom,rho,gamma,trimmed=F)
inf_frac_vec1

# Example 2 for FH.frac.cal: First trim the data before inputting into FH.frac.cal() setting trimmed=T, and obta
I_denom<-I.1(rho, gamma,lambda,theta,eps,R,p,t.star=tau)*n_FH
tau.star=21 #in case the ratio=1 when t>tau
#Trim the data
data_temp2 <-data.trim(tau.star,data_temp)
t_seq <- seq(0.1,tau.star,0.1) # the time series to check the information fraction
inf_frac_vec2<-FH.frac.cal(data_temp2,t_seq,I_denom,rho,gamma,trimmed=T)
# WLRT at the interim
interim_index<- which.min(abs(inf_frac_vec2-0.6))
interim_time<-t_seq[interim_index]
interim_frac<-inf_frac_vec2[interim_index]
 # WLRT at the final
 final_index<- which.min(abs(inf_frac_vec2-1))
 final_time<-t_seq[final_index]
 final_frac<-inf_frac_vec2[final_index]

## End(Not run)
```

FH.table *Basic function for Fleming-Harrington family weighted log-rank tests*

Description

Basic function to build the table for the calculation of the Fleming-Harrington family of weighted log-rank tests.

Usage

```
FH.table(survival, delta, trt, rho, gamma)
```

Arguments

survival	Time to event or censoring.
delta	Event indicator: 1 for observed cases, 0 for censored cases.
trt	Treatment assignment indicator: 1 for treatment group, 0 for control group.
rho, gamma	Parameters for Fleming-Harrington family with $W(t) = S^{\rho}(t^{-})(1 - S(t^{-}))^{\gamma}$.

Value

Build a table for Fleming-Harrington log-rank test which ouputs *ordered* survival as follow-up times, Surv as predictable survival functions $S(t^{-})$, Surv.exact as exact survival functions $S(t)$, delta as event indicators, trt as treatment assignement (treated=1, control=0), weight as weight functon calcualted from the predictable survival functions Surv.

In addition, the output also include O1 as the observed events from the treatment arm, E1 as the expected events from the treatment arm, Cov as the estimated variance without considering the weights.

Author(s)

Lili Wang

FH.test *Fleming-Harrington weighted log-rank tests*

Description

Calculating the Fleming-Harrington weighted log-rank tests

Usage

```
FH.test(survival, delta, trt, rho, gamma)
```

Arguments

survival	Time to event or censoring.
delta	Event indicators.
trt	Treatment assignment indicator with 1 denoting the treated group, and 0 denoting the placebo group.
rho	First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^{-})^{\rho}(1 - S(t^{-}))^{\gamma}$.
gamma	Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^{-})^{\rho}(1 - S(t^{-}))^{\gamma}$.

Value

A list 3 different components

O1	Observed number of weighted events (with a multiplication of corresponding weights) in the treatment arm.
E1	Expected number of weighted events (with a multiplication of corresponding weights) in the treatment arm.
Z	Weighted log-rank test statistic.

Author(s)

Lili Wang

See Also

WLR.test

Examples

```
## Not run:
# Examples for FH.test and WLR.test
set.seed(12345)
data_temp<- nphsim(nsim=1,lambdaC=log(2)/6, lambdaE = c(log(2)/6,log(2)/6*0.7), ssC=250, intervals = c(2),ssE
data_final<-data.trim.d(100,data_temp)[[1]]
rho=1
gamma=0
# compare the 3 different ways below:
#library(survival)
sqrt(survdiff(Surv(survival,delta)~trt, data =data_final,rho=rho)$chisq)
FH.test(survival=data_final$survival,delta=data_final$delta,trt=data_final$trt,rho=rho,gamma=gamma)
WLR.test(survival=data_final$survival,delta=data_final$delta,trt=data_final$trt,w=function(...){survKM_minu

## End(Not run)
```

---

getc *Basic functions*

Description

Some basic functions for information prediction.

Usage

```
getc(theta, lambda, eps)

uv(e, k, lambda, R, t.star)

v(e, k, lambda)

u(e, k, lambda, R, t.star)
```

```
h1(k1, k2, lambda, theta, eps, R, t.star)

h0(k1, k2, lambda, theta, eps, R, t.star)

h.tilde(m, lambda, theta, eps, R, p, t.star)
```

Arguments

theta	Hazard ratio after the change point (before the change point HR should be 1).
lambda	Event hazard for the control arm.
eps	Change point.
e	Some convenience parameter to control the change point, which is usually set to be eps or tau
k, k1, k2, m	Parameters to control the exponential power of the survival functions (the control arm for the null hypothesis or the weighted sum of two arms for the alternative hypothesis).
R	End of the accrual period.
t.star	Time point we pause the study to check the cumulative results.
p	Treatment assignment probability.

Details

To prepare the values for the prediction of information values. The control arm is following an exponential with rate lambda, the treatment arm is piece-wise exponential with hazard ratio with respect to the control arm to be 1 before the changing point eps, and theta after the change point. Details can be found in the appendix of the reference paper.

Value

getc returns the $\exp(-\lambda * \epsilon * (1 - \theta))$ which is a multiplier for the survival and hazard of the treatment arm after the change point eps.

Author(s)

Lili Wang

References

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.

GSMC_design *Predicted sample sizes and boundaries for GSMC design*

Description

Compute predicted sample size and boundaries for a group sequential design of max-combo tests.

Usage

```
GSMC_design(
  FHweights,
  interim_ratio,
  error_spend,
  eps,
  p,
  b,
  tau,
  omega,
  lambda,
  lambda.trt,
  rho,
  gamma,
  beta,
  stoch = TRUE,
  range_ext = 200,
  time_ext_multiplier = 1.5,
  time_increment = 0.01,
  n.rep = 5
)
```

Arguments

FHweights	a list of pairs of parameters (rho, gamma) for the Fleming Harrington weighted log-rank tests:$W(t) = S^{\rho}(t^{-})(1 - S(t^{-}))^{\gamma}$. The first one will provide the information fraction we will use to sign the stopping time. Now we only accommodate the surrogate information fraction, i.e., rho = 0 and gamma = 0.
interim_ratio	a vector of ratios between 0 and 1 that sign the stopping time following the first type of information fraction in FHweights, i.e. the event sizes. Note that the last value must be 1, otherwise, the function will automatically append 1 for the final stage.
error_spend	cumulative errors spent at each stage (including the final one). Must be of the same length as interim_ratio or one element shorter if the last value of interim_ratio is less than 1. The last element of error_spend should be type I error alpha.
eps	the change point, before which, the hazard ratio is 1, and after which, the hazard ratio is theta
p	treatment assignment probability.
b	the number of subintervals per time unit.
tau	the end of the follow-up time in the study. Note that this is identical to $T + \tau$ in the paper from Hasegawa (2014).

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, however, we found that this function is quite robust to violations of these assumptions: dropouts, different censoring rates for two arms, and changing accrual rates.
lambda	the hazard for the control group.
lambda.trt	the hazard for the treatment group after time eps.
beta	type II error, 1-power.
stoch	stochastic prediction or not (exact prediction), the former is default.
range_ext	the width to extend the range of sample sizes. If the predicted sample size is not found in the range, try a wider range_ext. It will automatically search for the likely range, but still possibly miss the best one. Its default value is 200.
time_ext_multiplier	compute the time window for the possible stopping time points by multiplying it with the total expected follow-up time tau. The default is 1.5. In other words, when tau = 18, the longest time we consider would be $18 * 1.5 = 27$ months.
time_increment	time increments to compute the predicted stopping time points, the finer the more accurate.
n.rep	same as the one in Maxcombo.sz. The 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.

Details

Predict the sample sizes and boundaries to achieve the targeted type I errors (error spent at each stage) and power. Prediction approaches include the exact prediction or the stochastic prediction approach following 2-piece-wise exponential distributions given in the appendix of the reference paper.

Value

z_alpha_pred	predicted boundary values for all the stages, length is equivalent to the input interim_ratio or error_spend.
z_alpha_vec_pred	predicted boundary values for all the test statistics following index.
d_fixed	the required observed events at each stage.
n_FH	the total required number of subjects according to the defined hazards.
n_event_FH	the total required number of events according to the defined hazards.
index	records the ordered stages for each tests, starting from 1 and ending at the length of interim_ratio or error_spend. It is actually rep(1:length(interim_ratio), each = length
interim_pred0	predicts stopping time points under the null hypothesis following the order of index.
interim_pred1	predicts stopping time points under the alternative hypothesis following the order of index.
Sigma0	predicts correlation matrix under the null hypothesis with each row and column following the test statistics corresponding to index.

Sigma1	predicts correlation matrix under the alternative hypothesis with each row and column following the test statistics corresponding to index.
mu1	the predicts unit mean under the alternative hypothesis, the $\tilde{\mu}$ in formula (5) of the reference paper. The test statistics follow index. It is also the mean of the expectation of each subject scaled weighted log-rank test statistic, which can be approximated using the formula for E^* in Hasegawa 2014 paper. Under null, the predicted mean is otherwise 0, implying no treatment effect.
stoch	input stoch boolean variable, TRUE if stochastic prediction is enabled, FALSE otherwise. The default is TRUE.
FHweights	input FHweights list.
interim_ratio	input interim_ratio vector.
error_spend	input error_spend vector.

Author(s)

Lili Wang

References

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.

Examples

```
## Not run:
### Parameters
FHweights <- list(
  c(0,0),
  c(0,1),
  c(1,0)
  )
  n_FHweights <- length(FHweights)
  # stop when what proportion of the events have been observed.
  fixed_death_p <-  c(0.6, 0.7, 0.8)
  interim_ratio <- c(fixed_death_p,1)
  n_stage <- length(interim_ratio)
  # treatment assignment.
  p <- 1/2
  # end of the study, chronological assuming it's on the alternative arm.
  tau <- 18
  # end of the accrual period, chronological.
  R <- 14
 # minimum potential follow-up time, not considering dropouts or other subject-specific censoring.
  omega <- (tau-R)
  # waiting time before the change point: can be the delayed effect or the crossing effect
  eps <- 2
  # event hazard of the control arm.
  lambda <- log(2)/6
  # hazard ratio after the change point eps under the alternative hypothesis.
  theta <- 0.6
 # event hazard for the treatment arm under the alternative hypothesis and after the change point eps.
  lambda.trt <- lambda*theta
  # type I error under the control.
  alpha <- 0.025
```

```
  # type II error under the alternative.
  beta <- 0.1
  # Obtain the cumulative errors spent at each stage
  error_spend <- c(0.005, 0.01, 0.015, alpha)
  # number of subintervals for a time unit
  b <- 30
  res <- GSMC_design(
  FHweights,
  interim_ratio,
  error_spend,
  eps,
  p,
  b,
  tau,]
  omega,
  lambda,
  lambda.trt,
  rho,
  gamma,
  beta,
  stoch = F
  )

## End(Not run)
```

`I.0` *Precdict information/covariance under null hypothesis*

Description

Calulcation of the information/covariance based on a presumed survival function under the null.

Usage

```
I.0(rho, gamma, lambda, R, p, t.star)

I.0.cov(rho1, gamma1, rho2, gamma2, lambda, R, p, t.star)
```

Arguments

`rho`	First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
`gamma`	Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
`lambda`	Event hazard for the control arm.
`R`	End of the accrual period.
`p`	Treatment assignment probability.
`t.star`	Time point we pause the study to check the cumulative information under the null.
`rho1, rho2`	First power parameters for the two Fleming-Harrington weights, defined for covariance calculation.

gamma1, gamma2 Second power parameters for the two Fleming-Harrington weights, defined for covariance calculation.

Details

This function is prepared to calculate the predicted information/covariance purely based on the assumed survival function under the null hypothesis: an exponential distribution with hazard lambda.

Author(s)

Lili Wang.

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

See Also

I.1

I.1 *Predicted information/covariance under the alternative hypothesis*

Description

Calulcation of the information/covariance based on a presumed survival function under the alternative hypothesis.

Usage

```
I.1(rho, gamma, lambda, theta, eps, R, p, t.star)

I.1.cov(rho1, gamma1, rho2, gamma2, lambda, theta, eps, R, p, t.star)
```

Arguments

rho	First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
gamma	Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
lambda	Event hazard for the control arm.
theta	Hazard ratio after the change point (before the change point HR should be 1).
eps	Change point.
R	End of the accrual period.
p	Treatment assignment probability.
t.star	Time point we pause the study to check the cumulative information under the null.

rho1	First power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
gamma1	Second power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
rho2	First power parameters for the two Fleming-Harrington weights, defined for covariance calculation.
gamma2	Second power parameters for the two Fleming-Harrington weights, defined for covariance calculation.

Details

This function is prepared to calculate the predicted information/covariance purely based on the assumed survival function under the alternaitve hypothesis: the control group is following an exponential distribution with hazard lambda, while the treatment group is following a piece-wise exponential distribution with same hazard before eps, but a hazard equals theta times the lambda after eps.

Author(s)

Lili Wang.

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

See Also

I.0

I_t *Estimated information based on the data*

Description

Estimate the information based on the data, which is the numerator of the information fraction.

Usage

```
I_t(data_ref, data_check, rho, gamma)

I_t.2(data_ref, data_check, rho, gamma)
```

Arguments

data_ref	Input reference dataset which provides the survival curves for the estimation. It could be some dataset entirely external to data_check. This dataset should include at lease the 3 variables: survival for the time to event or censoring, delta as the event indicator, and trt for the treatment assignment indicator. It will perfectly fit the output dataset from the data.trim functions.
data_check	Input dataset to check the estimated information. It should follow the sample format as data_ref, which includes three variables: survival, delta and trt.
rho	First power parameter for the Fleming-Harrington weight which weighs on the early departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.
gamma	Second power parameter for the Fleming-Harrington weight which weighs on the late departures: $S(t^-)^\rho(1-S(t^-))^\gamma$.

Details

The I_t function estimates the information up to the maximum follow-up time in the data of data_check, which is identical to the numerator of the information fraction proposed by Hasegawa (2016):$\hat{P}_1(t)\hat{P}_0(t)\int_0^t W(t,s)^2N(t,ds)$. Note that the datasets data_check and data_ref input here are output data from data.trim functions, or any datasets including survival as time to event or censoring, delta as event indicators, and trt denotes treatment assignment (1 is treatment, 0 is control). Note that I_t.2 is another option which is slightly different from the one proposed in Hasegawa(2016), but is identical to the estimate of variance of the weighted log-rank test, which considers the total at-risk set $R(t)$ and treatment arm $R_1(t)$: $\int_0^t \frac{R_1(s)R_0(s)}{R(s)^2}W(t,s)^2N(t,ds)$.

Value

The returned value is the calculated information estimated from the input dataset data_check using the survival function estimated from data_ref.

Author(s)

Lili Wang

References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

See Also

data.trim

Examples

```
## Not run:
# install.packages("devtools")
# library(devtools)
# install_github("keaven/nphsim")
library(nphsim)
eps<-2 # delayed effect
p<-0.5 #treatment assignment
b<-30 # an intrinsic parameter to decide the number of intervals per time unit
```

```
tau<- 18 # end of the study
R<-14 # accrual period [0,R]
omega<- tau-R
lambda<-log(2)/6 # control group risk hazard
theta<-0.7 # hazard ratio
lambda.trt<- lambda*theta #hazard after the change point for the treatment arm
rho<- 0 # parameter for the weights
gamma<-1 #parameter for the weights
alpha<-0.025 #type 1 error
beta<-0.1 #type 2 error
# First we decide the sample size:
size_FH <- sample.size_FH(eps,p,b,tau,omega,lambda,lambda.trt,rho, gamma,alpha,beta)
n_FH <-size_FH$n
n_event_FH<-size_FH$n_event
accrual.rt<-n_FH/R # the needed arrual rate
#Generate data accordingly, use eta=1e-5 to inhibit censoring
data_temp <- nphsim(nsim=1,lambdaC=lambda, lambdaE = c(lambda,lambda.trt), ssC=ceiling(n_FH*(1-p)),intervals

#Obtain the full information at the final stage based on the generated data
#Trim the data up to the final stage when n_event_FH events have been observed
data_temp1 <-data.trim.d(n_event_FH,data_temp)[[1]]
I_t(data_temp1,data_temp1,rho,gamma) # the estimated information at the final stage
#Trim the data up to certain event numbers at the interim stage when 60% of the events have been observed. Have be
I_t.2(data_temp1,data_temp1,rho,gamma) # If we consider the change of the at-risk set, which is not necessary to
data_temp2 <- data.trim.d(ceiling(0.6*n_event_FH),data_temp1,F)[[1]]
I_t(data_temp1,data_temp2,rho,gamma) # Use the full dataset data_temp to provide the survival function, and che
I_t.2(data_temp1,data_temp2,rho,gamma) # If we consider the change of the at-risk set, which is not necessary to

## End(Not run)
```

`logrank.table` *Basic function for standard log-rank test*

Description

Build the table for log-rank test calculation.

Usage

```
logrank.table(survival, delta, trt)
```

Arguments

`survival`	Time to event or censoring.
`delta`	Event indicator: 1 for observed cases, 0 for censored cases.
`trt`	Treatment assignment indicator: 1 for treatment group, 0 for control group.

Value

Build a table for log-rank test which ouputs *ordered* `survival` as follow-up times, `delta` as event indicators,`trt` as treatment assignement (treated=1, control=0), `Y` as the at-risk numbers, `P1` as the proportion of treated set, `P0` as the proportion of the control set.

In addition, the output also include `O1` as the observed events from the treatment arm, `E1` as the expected events from the treatment arm, `Cov` as the estimated variance.

Author(s)

Lili Wang

See Also

FH.test, I_t.2, WLR.test.cov,WLR.test.cor

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.

Details

Suppose there are 2 stages (1 interim, 1 final), and two tests for a max-combo in each stage, then we have totally 4 test statistics. Let the alpha spending function to be c(alpha1,alpha), and the first two (Z_{11}, Z_{12}) share one cutoff value z1, the latter two share another two (Z_{21}, Z_{22}) share another cutoff value z2. Controlling the type I error is equivalent to ensuring that $P(Z_{11} < z_1, Z_{12} < z_1) = \alpha_1$ and $P(Z_{11} < z_1, Z_{12} < z_1, Z_{21} < z_2, Z_{22} < z_2) = \alpha$ are both satisfied. Note that the vector $[Z_{11}, Z_{12}, Z_{21}, Z_{22}]^T \sim MVN(0, \Sigma_0)$. Sigma0 corresponds to Σ_0, index records the ordered stages of each test statistics, whose order should be identical to the order of rows or columns in Sigma0. Specifically, in this example, index should be c(1,1,2,2). alpha_sp is the alpha spending function, which records how much type I error you would like to spend up to every stage.

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

```
## Not run:
 #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]

## End(Not run)
```

`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 formula 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 formula 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

Examples

```
## Not run:
# 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 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
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_range = c(100,1000),
sum_D = 0.6)
# need 232 patients, 140 deaths

## End(Not run)
```

`sample.size_FH` *Sample size calculation for Fleming-Harrington weighted log-rank tests This sample size calculation method was proposed by Hasegawa (2014). This function is to calculate the sample size for Fleming-Harrington weighted log-rank tests with piece-wise exponential distributed survival curves in described in Hasegawa(2014).*

Description

Sample size calculation for Fleming-Harrington weighted log-rank tests This sample size calculation method was proposed by Hasegawa (2014). This function is to calculate the sample size for Fleming-Harrington weighted log-rank tests with piece-wise exponential distributed survival curves in described in Hasegawa(2014).

Usage

```
sample.size_FH(
  eps,
  p,
  b,
  tau,
  omega,
  lambda,
  lambda.trt,
  rho,
  gamma,
  alpha,
  beta
)
```

Arguments

eps	The change point, before which, the hazard ratio is 1, and after which, the hazard ratio is theta
p	Treatment assignment probability.
b	The number of subintervals per time unit.
tau	The end of the follow-up time in the study. Note that this is identical to $T + \tau$ in the paper from Hasegawa (2014).
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.
lambda.trt	The hazard for the treatment group after time eps.
rho	The first parameter for Fleming Harrington weighted log-rank test:$W(t) = S^{\rho}(t^{-})(1 - S(t^{-}))^{\gamma}$.
gamma	The second parameter for Fleming Harrington weighted log-rank test:$W(t) = S^{\rho}(t^{-})(1 - S(t^{-}))^{\gamma}$.
alpha	Type I error.
beta	Type II error.

Value

n	The needed sample size.
n_event	The needed event numbers for both arms together.
E.star	The unit mean, correspoinding to E^* in Hasegawa(2014)
sum_D	The cumulative D, and ceiling(n*D) is quivalent to n_vent.

Note

This function is based on a R function from Dr. Ting Ye's paper : Ye, T., & Yu, M. (2018). A robust approach to sample size calculation in cancer immunotherapy trials with delayed treatment effect. Biometrics, 74(4), 1292-1300.

Author(s)

Lili Wang, Ting Ye

References

Ye, T., & Yu, M. (2018). A robust approach to sample size calculation in cancer immunotherapy trials with delayed treatment effect. Biometrics, 74(4), 1292-1300. 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.

Examples

```
## Not run:
# Example 1 from Hasegawa (2014)
p<-2/3
tau<-66
omega<-18
eps<-6
m1=21.7  #median survival time for placebo group
m2=25.8  # median survival time for treatment group
lambda<-log(2)/m1
lambda.trt<-log(2)*(m1-eps)/(m2-eps)/m1
theta=lambda.trt/lambda
alpha<-0.025
beta<-0.1
rho=0
gamma=1
b=30
sample.size_FH(eps,p,b,tau,omega,lambda,lambda.trt,rho, gamma,alpha,beta)$n
#1974, identical to the paper's report

## End(Not run)
```

---

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:$W(t) = S^{\rho}(t^{-})(1-S(t^{-}))^{\gamma}$.
gamma, gamma1, gamma2	the second 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 formula (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.

`survKM_minus` *Calculate the survival functions*

Description

Calculate the survival function, either the predictable one $S(t^-)$ using `survKM_minus` or $S(t)$ using `survKM_exact`.

Usage

```
survKM_minus(v, survival, delta)

survKM_exact(v, survival, delta)
```

Arguments

`v`	Time vector to give the corresponding survival functions.
`survival`	Input follow-up times.
`delta`	Input event indicators.

Value

`survKM_minus` returns the predictable one $S(t^-)$, and `survKM_exact` returns $S(t)$.

Author(s)

Lili Wang

`WLR.test` *Weighted log-rank tests with any input weight*

Description

Weighted log-rank test for any input weight function.

Usage

```
WLR.test(survival, delta, trt, w = function(v, ...) {
    1
})
```

Arguments

`survival`	Time to event or censoring.
`delta`	Event indicator: 1 for observed cases, 0 for censored cases.
`trt`	Treatment assignment indicator: 1 for treatment group, 0 for control
`w`	Weight function, with default to be 1, which is similar to the use of input arbitray weight in `WLR.test.cov`. Please also refer to the examples as well.

Author(s)

Lili Wang

See Also

FH.test

Examples

```
## Not run:
# Examples for FH.test and WLR.test
set.seed(12345)
data_temp<- nphsim(nsim=1,lambdaC=log(2)/6, lambdaE = c(log(2)/6,log(2)/6*0.7), ssC=250, intervals = c(2),ssE
data_final<-data.trim.d(100,data_temp)[[1]]
rho=1
gamma=0
# compare the 3 different ways below:
#library(survival)
sqrt(survdiff(Surv(survival,delta)~trt, data =data_final,rho=rho)$chisq)
FH.test(survival=data_final$survival,delta=data_final$delta,trt=data_final$trt,rho=rho,gamma=gamma)
WLR.test(survival=data_final$survival,delta=data_final$delta,trt=data_final$trt,w=function(...){survKM_minu

## End(Not run)
```

WLR.test.cov *Estimate the covariance and correlation between two arbitrary weights*

Description

These two functions estimate the covariance and correlations between the two arbitrary weight functions, which are not necessary to be Fleming-Harrington family.

Usage

```
WLR.test.cov(
  survival,
  delta,
  trt,
  w1 = function(v, ...) {     1 },
  w2 = function(v, ...) {     1 }
)

WLR.test.cor(
  survival,
  delta,
  trt,
  w1 = function(v, ...) {     1 },
  w2 = function(v, ...) {     1 }
)
```

Arguments

survival	The time to event or censoring, not that, it's the follow-up time after entoring, you may also consider as the total at-risk time.
delta	The event indicator, with 1 indicating observed events, and 0 indicating censoring.
trt	The treatment assignment indicator, with 1 indicating treatment group, and 0 as control group.
w1	It has the default function which will return standard log-rank test with weight 1 and thus the function will be reduced to a variance for log-rank tests, and correlation always equals 1. If the two weights are identical, WLR.test.cov is equivalent to the estimated variance, and WLR.test.cor is always equal to 1. The function can be any non-negative functions with a basic argument v as the input time vector, which are corresponding to the follow-up times. Optionally, there are two additional variables,follow-up time survival and event indicator delta to make the weights dependent on the survival functions (like the Fleming-Harrington family). It would be better if the function itself has ... as the last argument, so that it can be robust to any misspecification of the variable names, and thus, it will just ignore the misspecified ones. Please refer to the examples to figure out how to define the Fleming-Harrington and any other weight functions.
w2	Same requirements as the other argument w1. Just not that if they are identical, WLR.test.cov returns the variance like I.t, and WLR.test.cor always returns 1.

Details

Any two weight functions can be assigned to arguments w1 and w2. Two examples, one is Fleming-Harrington family and the other is not, are demonstrated in the examples section.

Value

The two functions, WLR.test.cov returns the covariance, WLR.test.cor returns the correlation coefficient estimate solely based on the input data.

Author(s)

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References

Hasegawa, T. (2016). Group sequential monitoring based on the weighted log-rank test statistic with the Fleming–Harrington class of weights in cancer vaccine studies. Pharmaceutical statistics, 15(5), 412-419.

See Also

cor.0,cor.1, I_t.

Examples

```
## Not run:
# install.packages("devtools")
# library(devtools)
# install_github("keaven/nphsim")
# library(nphsim)

eps<-2 # delayed effect
p<-0.5 #treatment assignment
b<-30 # an intrinsic parameter to decide the number of intervals per time unit
tau<- 18 # end of the study
R<-14 # accrual period [0,R]
omega<- tau-R
lambda<-log(2)/6 # control group risk hazard
theta<-0.7 # hazard ratio
lambda.trt<- lambda*theta #hazard after the change point for the treatment arm
rho<- 0 # parameter for the weights
gamma<-1 #parameter for the weights
alpha<-0.025 #type 1 error
beta<-0.1 #type 2 error
# First we decide the sample size:
size_FH <- sample.size_FH(eps,p,b,tau,omega,lambda,lambda.trt,rho, gamma,alpha,beta)
n_FH <-size_FH$n
n_event_FH<-size_FH$n_event
d_fixed<-ceiling(-0.6*n_event_FH)
accrual.rt<-n_FH/R # the needed arrual rate
#Generate data accordingly, use eta=1e-5 to inhibit censoring
data_temp <- nphsim(nsim=1,lambdaC=lambda, lambdaE = c(lambda,lambda.trt),
                  ssC=ceiling(n_FH*(1-p)),intervals = c(eps),ssE=ceiling(n_FH*p),
                            gamma=accrual.rt, R=R, eta=1e-5, fixEnrollTime = TRUE)$simd
# Example 1 for WLR.test.cov and WLR.test.cor: Fleming-Harrington family Weights
# I will let w1 be the default 1
# define a WLRT for w2 accodring to the rho and gamma defined above.
w2<-function(...){survKM_minus(...)^rho*(1-survKM_minus(...))^gamma}
data_interim<-data.trim.d(d_fixed,data_temp)[[1]] #data trimmed at the interim stage, the second enry on the li
data_final<-data.trim.d(n_event_FH,data_temp)[[1]] #data trimmed at the final stage
WLR.test.cov(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w2=w2)
WLR.test.cor(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w2=w2)

# The variance should be identical to the output from I_t and correlation is 1 if two weights are identical.
WLR.test.cov(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w1=w2,w2=w2)
I_t.2(data_interim,data_interim,rho,gamma)
WLR.test.cor(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w1=w2,w2=w2)

#Example 2 for WLR.test.cov and WLR.test.cor: any Weights
w2_2<-function(v,...){1-exp(-v*0.25)}
WLR.test.cov(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w2=w2_2)
WLR.test.cor(survival=data_interim$survival,delta=data_interim$delta,trt=data_interim$trt,w2=w2_2)

## End(Not run)
```

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