Package 'IAfrac'

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Type Package

Title Tools for weighted log-rank tests

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Author Lili Wang, Xiaodong Luo, Cheng Zheng

Maintainer Lili Wang <lilywang@umich.edu>

Description Sample size calculation and information fraction estimation for weighted log-rank tests.

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Encoding UTF-8

RoxygenNote 6.1.1

Depends data.table, survival

Suggests gsDesign, nphsim

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

```
# 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)
```

---

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.

Details

This is to estimate the average hazard ratios when there exist non-proportional hazard ratios.

$$AHR(x) = \frac{\frac{1}{2p}(1-e^{-2p\lambda\epsilon}) + \frac{\theta}{p(1+theta)}e^{-\lambda\epsilon(1+p-\theta(1-p))}}{\frac{1}{2p}(1-e^{-2p\lambda\epsilon}) + \frac{1}{p(1+theta)}e^{-\lambda\epsilon(1+p-\theta(1-p))}}$$

Author(s)

Lili Wang

References

Kalbfleisch, J. D., & Prentice, R. L. (2011). The statistical analysis of failure time data (Vol. 360). John Wiley & Sons.

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

```
# test
lambda=log(2)/6
theta=0.7
eps=2
avg.haz(theta,eps,lambda)
```

`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

```
# 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 = c(eps),ssE=ceiling(n_FH*p),
                              gamma=accrual.rt, R=R, eta=1e-5, fixEnrollTime = TRUE)$simd

# 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]
```

`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

```
# 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
```

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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 hypotheiss).

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.

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

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

IAfrac *IAfrac: A package for interim analysis using weighted log-rank tests*

Description

The IAfrac package implements Hasegawa (2014) and (2016) proposals for weighted log-rank tests in piece-wise expornential distributed survival functions. The current version only considers two pieces with only one change point (epsilon). This R package provides four categories of important functions: sample size, information fraction, weighted log-rank test, data manipulation.

Sample size functions

The sample size calculation functions implement methods proposed in Hasegawa (2014). They are recorded in R/Hasegama2014.R.

Information fraction functions

The iformaiton fraction functions implement methods proposed in Hasegawa (2016). They are recorded in R/Hasegama2016.R.

Weightd log-rank test

The weighted log-rank test functions are newly written functions for weighted log-rank tests. They are recorded in R/WLRT.R.

Data manipulation functions

The data manipulation functions are prepared to trim the data either according to the follow-up time or the event counts. They are recorded in R/data_manipulation.R.

`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):$\hat{P}_1(t)\hat{P}_0(t)\int_0^t W(t,s)^2 N(t,ds)$. 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 $R_1(t)$: $\int_0^t \frac{R_1(s)R_0(s)}{R(s)^2} W(t,s)^2 N(t,ds)$.

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

```
# 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 = c(eps),ssE=ceiling(n_FH*p),
                              gamma=accrual.rt, R=R, eta=1e-5, fixEnrollTime = TRUE)$simd

#Obtain the full information at the final stage based on the generated data
#Trim the data upto 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 upto 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
```

---

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

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sample.size_FH *Sample size calculation for Fleming-Harrington weighted log-rank tests*

Description

This sample size calculation method was proposed by 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

Details

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).

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

```
# 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
```

`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

```
# 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
```

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)

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

cor.0,cor.1, I_t.

Examples

```
# 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)
```

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