Package 'OneArm2stage'

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Title Optimal One-Arm Two-Stage Phase II Design with Survival Endpoint

Version 1.1.5

Description The proposed two-stage design can be used for single-arm phase II trial designs with time-to-event endpoints, which is desirable for clinical trials on immunotherapies among cancer patients. There're two advantages of the proposed approach: 1) It provides flexible choices of four underlying survival distributions and 2) the power of the design is more accurately calculated using exact variance in one-sample log-rank test. The package can be used for 1) planning the sample size; 2) conducting the interim and final analyses for the Go/No-go decisions. More details about the design method can be found in the paper: Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). <doi:10.1002/pst.1983>.

NeedsCompilation no

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Repository CRAN

RoxygenNote 7.2.1

Imports survival, utils, flexsurv, IPDfromKM

Suggests knitr, rmarkdown, testthat (>= 3.0.0)

VignetteBuilder knitr

Config/testthat/edition 3

License GPL (>= 3)

Depends R (>= 3.5.0)

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R topics documented:

`FitDat` *Fit Historical Survival Data Assuming the Failure Time Follows the Weibull Distribution*

Description

The function fits parametric models with the underlying distributions assumed to be Weibull.

Usage

```
FitDat(data)
```

Arguments

`data`	a historical survival data sample, has to contain two variables 'Time' and 'Cens': *Time*, time under observation during trial for each patient. *Cens*, the status indicator of patients (event = 1, censored = 0).

Value

fit.Weibull Fitted models assuming Weibull distributions.
AIC AIC values from the fitted model.
parameter.estimates the estimated parameters from the fitted model.

References

Wang, M., Rule, S., Zinzani, P. L., Goy, A., Casasnovas, O., Smith, S. D.,..., Robak, T. (2018). Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. The Lancet, 391(10121), 659–667. https://doi.org/10.1016/s0140-6736(17)33108-2

Examples

```
library(IPDfromKM)
# a sample dataset that we already extracted from Wang et al, 2018.
df<- read.csv(system.file("extdata", "df.csv", package = "OneArm2stage"))

# risk time points
trisk <- c(0,2,4,6,8,10,12,14,16,18,20,22,24)

# number of patients at risk at each risk time point
nrisk.radio <- c(124,120,115,110,107,104,103,95,46,18,11,8,0)

# Preprocess the raw coordinates into an proper format for reconstruct IPD
pre_radio <- preprocess(dat=df, trisk=trisk,
```

```
                    nrisk=nrisk.radio,totalpts=NULL,maxy=100)

#Reconstruct IPD
est_radio <- getIPD(prep=pre_radio,armID=0,tot.events=NULL)

# shift the IPD data into the proper format for 'FitDat()'
ipd <- est_radio$IPD
dat3 <- as.data.frame(cbind(rep(0, nrow(ipd)),ipd$time, ipd$status))
colnames(dat3) <- c("Entry", "Time", "Cens")

# use FitDat function to fit the historical dat
modelSelect <- FitDat(dat3)
modelSelect$AIC
# Weibull
# 301.7776

# check the estimated parameters from the modeling results
modelSelect$parameter.estimates
# $Weibull
# shape     scale
# 0.1133671 3.9939753
```

LRT *Conduct Interim or Final Analyses Using One-Sample Log-Rank Test for the Optimal Two-Stage Trials*

Description

Performs the one-sample log-rank test (OSLR) for the time-to-event data from two-stage Phase II clinical trials, assuming the failure time follows one of the four distributions: Weibull, Gamma, log-normal or log-logistic.
This can be used for both unrestricted and restricted follow-up designs.

Usage

```
LRT(dist, shape, S0, x0, data)
```

Arguments

dist	distribution options with 'WB' as Weibull, 'GM' as Gamma, 'LN' as log-normal, 'LG' as log-logistic.
shape	shape parameter for one of the four parametric distributions ('WB', 'GM', 'LN' and 'LG').
S0	the survival probability at a fixed time point x0 under the null hypothesis.
x0	a fixed time point when the survival probability is S0 under null.

data	the time-to-event data for either the interim or final analysis from a two-stage survival trial, contains 2 variables: *time* time period under observation before the time of interim analysis (for interim analysis) or during entire trial (for final analysis) for each patient. *status* status indicator of patients (event = 1, censored = 0).

Value

z the OSLR test statistic for the interim or final analysis, depending on data used.
O the observed number of events.
E the expected number of events.

References

Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). Two-stage phase II survival trial design. Pharmaceutical Statistics. 2020;19:214-229. https://doi.org/10.1002/pst.1983

Examples

```
dat<- read.csv(system.file("extdata", "kj1_final.csv", package = "OneArm2stage"))
LRT(dist="WB", shape=1, S0=0.62, x0=2, data=dat)
# O       E       Z
# 18.0000 16.3598 -0.4055
```

`Optimal.KJ` *Optimal Two-Stage Design Using One-Sample Log-Rank Test with Unrestricted Follow-Up*

Description

Optima.KJ() calculates the design parameters (e.g., t1, n1, n, c1, c) in the optimal two-stage design with unrestricted follow-up based on the one-sample log-rank (OSLR) test.

Usage

```
Optimal.KJ(dist, shape, S0, x0, hr, tf, rate, alpha, beta, prStop = NULL)
```

Arguments

dist	distribution options with 'WB' as Weibull, 'GM' as Gamma, 'LN' as log-normal, 'LG' as log-logistic.
shape	shape parameter for the baseline hazard function assuming one of the four parametric distributions ('WB', 'GM', 'LN' and 'LG').
S0	survival probability at the fixed time point x0 under the null hypothesis.
x0	a fixed time point where the survival probability is S0 under null.
hr	hazard ratio, s1=s0^hr where s1 is the survival probability under HA and s0 is that under H0.

tf	unrestricted follow-up time, the time period from the entry of the last patient to the end of the trial. If tf is too long, the function might throw an error.
rate	a constant accrual rate. Please consider use a reasonable rate value. If the rate is too small, the function might throw an error.
alpha	type I error.
beta	type II error.
prStop	the user-defined early stopping probability under H0, default to be NULL.

Value

nsignle the required sample size for the single-stage design.
tasingle the estimated accrual time for the single-stage design.
csingle the critical value for the single-stage design.
n1 and *n* required sample sizes in the two-stage design for the interim and final stage, respectively.
c1 and *c* critical values in two-stage designs for interim and final analysis, respectively.
t1 the interim analysis time in the two-stage design.
MTSL the maximum total study length (the sum of accrual time and unrestricted follow-up time).
ES the expected sample size under null in the two-stage design.
PS the probability of early stopping under null in the two-stage design.

References

Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). Two-stage phase II survival trial design. Pharmaceutical Statistics. 2020;19:214-229. https://doi.org/10.1002/pst.1983

Examples

```
# 1. An example when solution can be found.
# Optimal.KJ(dist="WB", shape=1, S0=0.62, x0=2, hr=0.467, tf=2, rate=5,
#                     alpha=0.05, beta=0.2)
# $param
#   dist shape   S0    hr alpha beta rate x0 tf
# 1   WB     1 0.62 0.467  0.05  0.2    5  2  2

# $Single_stage
#   nsingle tasingle  csingle
# 1      25        5 1.644854

# $Two_stage
#   n1     c1  n      c     t1 MTSL      ES     PS
# 1 16 -0.302 26 1.6135 3.0593  7.2 21.9185 0.3813

# 2. An example when rate is too small and solution can not be found.
# Optimal.KJ(dist="GM", shape=1, S0=0.62, x0=2, hr=0.467, tf=2, rate=0.1,
#                alpha=0.05, beta=0.2)

# Error: solution for ta in single stage cannot be found,
#        please try to use a faster rate or a shorter tf.
#
# The above message occurs because the accrual rate is too slow, try to use
```

```
# a more reasonable value for rate.

# 3. An example when tf is too long and solution can not be found.
# Optimal.KJ(dist="GM", shape=1, S0=0.62, x0=2, hr=0.467, tf=100, rate=5,
#      alpha=0.05, beta=0.2)
#
# Error: solution for ta in single stage cannot be found,
#        please try to use a faster rate or a shorter tf.
#
# The above error message occurs because tf is too long, try to use
# a more reasonable value for follow-up time.

# 4. An example when early stopping probability is pre-defined as 0.65
# Optimal.KJ(dist="WB", shape=1, S0=0.62, x0=2, hr=0.467, tf=2, rate=5, alpha=0.05,
# beta=0.2, prStop=0.65)
# $Single_stage
#   nsingle tasingle  csingle
# 1      25        5 1.644854

# $Two_stage
#   n1     c1  n      c     t1 MTSL      ES     PS
# 1 21 0.3867 27 1.5842 4.1786  7.4 23.0273 0.6505
```

`Optimal.rKJ` *Optimal Two-Stage Design Using One-Sample Log-Rank Test with Restricted Follow-Up*

Description

Optimal.rKJ() calculates the design parameters (e.g., t1, n1, n, c1, c) in the optimal two-stage design with restricted follow-up based on the one-sample log-rank (OSLR) test.

Usage

```
Optimal.rKJ(
  dist = "WB",
  shape,
  S0,
  x0,
  hr,
  x,
  rate,
  alpha,
  beta,
  prStop = NULL
)
```

Arguments

dist	distribution options with 'WB' as Weibull, 'GM' as Gamma, 'LN' as log-normal, 'LG' as log-logistic for the baseline hazard function. Default="WB".
shape	shape parameter for the baseline hazard function assuming one of the four parametric distributions ('WB', 'GM', 'LN' and 'LG').
S0	survival probability at a fixed time point x0 under the null hypothesis.
x0	a fixed time point where the survival probability is S0 under null.
hr	the hazard ratio, s1=s0^hr where s1 is the survival probability under HA and s0 is that under H0.
x	the restricted follow-up time period.
rate	a constant accrual rate.
alpha	type I error.
beta	type II error.
prStop	the user-defined early stopping probability under H0, default to be NULL.

Value

nsignle the required sample size for the single-stage design.
tasingle the estimated accrual time for the single-stage design.
csingle the critical value for the single-stage design.
n1 and *n* required sample sizes in the two-stage design for interim and final stage, respectively.
c1 and *c* critical values in two-stage designs for the interim and final analysis, respectively.
t1 the interim analysis time in the two-stage design.
MTSL the maximum total study length (the sum of accrual time and restricted follow-up time).
ES the expected sample size in the two-stage design.
PS the probability of early stopping under null in the two-stage design.

References

Wu, J, Chen L, Wei J, Weiss H, Chauhan A. (2020). Two-stage phase II survival trial design. Pharmaceutical Statistics. 2020;19:214-229. https://doi.org/10.1002/pst.1983

Examples

```
# when early stopping probability is NOT pre-defined
# Optimal.rKJ(dist="WB", shape=1,S0=0.20,x0=2,hr=0.569,x=2,rate=5,alpha=0.05,
# beta=0.2)
# $param
#   dist shape  S0    hr alpha beta rate x0 x
# 1   WB     1 0.2 0.569  0.05  0.2    5  2 2
#
# $Single_stage
#   nsingle tasingle  csingle
# 1      32      6.4 1.644854
#
# $Two_stage
#   n1     c1  n     c     t1 MTSL      ES     PS
```

```
# 1 21 0.0355 33 1.633 4.1882  8.6 26.7993 0.5142

# when early stopping probability is pre-defined as 0.65
# Optimal.rKJ(dist="WB", shape=1,S0=0.20,x0=2,hr=0.569,x=2,rate=5,alpha=0.05,
# beta=0.2, prStop=0.65)
# $Single_stage
#  nsingle tasingle  csingle
# 1     32      6.4 1.644854
#
# $Two_stage
#   n1    c1  n     c     t1 MTSL      ES     PS
# 1 24 0.387 34 1.622 4.6959  8.8 27.1552 0.6506
```

`Sim_KJ` *Calculate Empirical Power by Simulation for the Optimal Two-Stage Design Using One-Sample Log-Rank Test with Unrestricted Follow-Up*

Description

Sim_KJ() can be used to calculate empirical power and type-I error by simulation given the design parameters (e.g., n1, n, c1, c) obtained from the optimal two-stage design with unrestricted follow-up.

Usage

```
Sim_KJ(dist, shape, S0, S1, x0, tf, rate, t1, c1, c, n1, n, N, seed = 123)
```

Arguments

`dist`	distribution options with 'WB' as Weibull, 'GM' as Gamma, 'LN' as log-normal, 'LG' as log-logistic for the baseline hazard function.
`shape`	shape parameter of the baseline hazard function assuming one of the four possible parametric distributions ('WB', 'GM', 'LN' and 'LG').
`S0`	survival probability at a fixed time point x0 under the null hypothesis.
`S1`	survival probability at a fixed time point x0 under the alternative hypothesis.
`x0`	a fixed time point where the survival probabilities are known for both null and alternative hypotheses.
`tf`	unrestricted follow-up time, the time period from the entry of the last patient to the end of the trial.
`rate`	a constant accrual rate.
`t1`	the interim analysis time as given by the two-stage design.
`c1`	the critical value given by the two-stage design for the interim analysis.
`c`	the critical value given by the two-stage design for the final analysis.

n1	the required sample size given by the two-stage design for the interim analysis.
n	the required sample size given by the two-stage design for the final stage.
N	number of trials in the simulation.
seed	seed for random number generation.

Value

a numeric value that is either the empirical power (when S1=S0^hr) or the type I-error (when S1=S0).

Examples

```
Design2 <- Optimal.KJ(dist="WB", shape=1, S0=0.62, x0=2, hr=0.467, tf=2, rate=5,
alpha=0.05, beta=0.2)
# ##' # $Two_stage
#   n1     c1  n      c     t1 MTSL      ES     PS
# 1 16 -0.302 26 1.6135 3.0593  7.2 21.9187 0.3813

# calculate empirical power and type I error given the above design parameters
Sim_KJ(dist="WB", shape=1, S0=0.62, S1=0.62^(0.467), x0=2, tf=2, rate=5, t1=3.0593,
    c1=-0.302, c=1.6135, n1=16, n=26, N=10000, seed=5868)
# empirical power
# 0.813

Sim_KJ(dist="WB", shape=1, S0=0.62, S1=0.62, x0=2, tf=2, rate=5, t1=3.0593,
    c1=-0.302, c=1.6135, n1=16, n=26, N=10000, seed=5868)
# empirical type-I error
# 0.037
```

Sim_rKJ *Calculate Empirical Power by Simulation for the Optimal Two-Stage Design Using One-Sample Log-Rank Test with Restricted Follow-Up*

Description

Sim_rKJ() can be used to calculate empirical power and type-I error by simulation given the design parameters (e.g., n1, n, c1, c) obtained from the optimal two-stage design with restricted follow-up.

Usage

```
Sim_rKJ(dist, shape, S0, S1, x0, x, rate, t1, c1, c, n1, n, N, seed = 123)
```

Arguments

dist	distribution options with 'WB' as Weibull, 'GM' as Gamma, 'LN' as log-normal, 'LG' as log-logistic for the baseline hazard function.
shape	shape parameter of the baseline hazard function assuming one of the four possible parametric distributions ('WB', 'GM', 'LN' and 'LG').

S0	survival probability at a fixed time point x0 under the null hypothesis.
S1	survival probability at a fixed time point x0 under the alternative hypothesis.
x0	a fixed time point where the survival probabilities are known for both null and alternative hypotheses.
x	the restricted follow-up time period.
rate	a constant accrual rate.
t1	the interim analysis time in the two-stage design.
c1	the critical value in two-stage designs for the interim analysis.
c	the critical value in two-stage designs for the final analysis.
n1	the required sample size in the two-stage design for the interim analysis.
n	the required sample size in the two-stage design for the final stage.
N	number of trials in the simulation.
seed	seed for random number generation.

Value

a numeric value that is either the empirical power (when S1=S0^hr) or the type I-error (when S1=S0).

Examples

```
Design3 <- Optimal.rKJ(dist="WB", shape=0.5, S0=0.3, x0=1, hr=0.65, x=1, rate=10,
alpha=0.05, beta=0.2)
# Design3$Two_stage
# n1     c1      n    c      t1      MTSL   ES      PS
# 38     0.1688  63   1.6306 3.7084  7.3    48.3058 0.567

# calculate empirical power and type I error given the above design parameters
Sim_rKJ(dist="WB", shape=0.5, S0=0.3, S1=0.3^(0.65), x0=1, x=1, rate=10, t1=3.7084,
    c1=0.1688, c=1.6306, n1=38, n=63, N=10000, seed=5868)
# empirical power
# 0.796

Sim_rKJ(dist="WB", shape=0.5, S0=0.3, S1=0.3, x0=1, x=1, rate=10, t1=3.7084,
    c1=0.1688, c=1.6306, n1=38, n=63, N=10000, seed=5868)
# empirical type-I error
# 0.041
```

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