

Package: TwoArmSurvSim (via r-universe)

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Title Simulate Survival Data for Randomized Clinical Trials

Version 0.2

Description A system to simulate clinical trials with time to event endpoints. Event simulation is based on Cox models allowing for covariates in addition to the treatment or group factor. Specific drop-out rates (separate from administrative censoring) can be controlled in the simulation. Other features include stratified randomization, non-proportional hazards, different accrual patterns, and event projection (timing to reach the target event) based on interim data.

License GPL (>= 2)

Depends R (>= 4.0.0),blockrand,dplyr,survival,simsurv

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censordata	<i>Censor Events Given a Fixed Dropout Rate</i>
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Description

Censor events given a fixed dropout rate

Usage

```
censordata(simdata,lambda,gamma, dropoutrate,ebx=1,gammac=1,groupfreq=1,
censordist='exponential',timeinterval=NULL,HRPW=FALSE)
```

Arguments

simdata	Simulated event dataset
lambda	lambda for event hazard function
gamma	gamma for event hazard function
dropoutrate	Patient dropout rate with range [0,1). If dropoutrate contains only one number. The program will control the dropout rate at population level(treatment + control). If dropoutrate contains two numbers (ie. c(0.2,0.1)), the program will control the dropout rate of control and treatment arm separately, with the first dropout rate number for control and the second number for treatment. Default value is "0" (no dropout)
ebx	exp(beta*x), if there's no covariates, ebx=1.
groupfreq	frequence of each level of ebx value
timeinterval	time intervals for piecewise baseline hazard function

gammac	gamma for censor hazard function. Default is 1 (exponential)
censordist	censor hazard distribution. Default is exponential
HRPW	Indicator of piecewise hazard ratios. TURE for piecewise. FALSE for non piecewise

censor_surv censor survival event

Description

censor event time

Usage

`censor_surv(eventtime, censortime, x)`

Arguments

eventtime	vector of event times
censortime	vector of censor time
x	covariates matrix

column_freq Calculate the Combination Frequency of Several Columns within a Data Frame

Description

Calculate the combination frequency of several columns in a data frame.

Usage

`column_freq(x, namelist, keepID=FALSE)`

Arguments

x	Input data as a data frame.
namelist	A list of column names that need to be counted.
keepID	If TRUE, the output will keep the unique ID for the column combination.

cov_simu	<i>Simulate Covariates Matrix Based on User Provided Factor Information</i>
----------	---

Description

simulate covariates matrix based on user provided factor information

Usage

```
cov_simu(sample_size = sample_size, factors=factors)
```

Arguments

sample_size	Total number of patients
factors	A list contains basic information about the covariate factors. Each element should have factor's name, number of levels and their frequency, as well as the hazard ratio to the reference group. Factors should be categorical data.

Examples

```
f1<-list(name='Region', N_level=3, prevalence=c(0.1,0.2,0.7), HR=c(1,1,1), strata=TRUE)
f2<-list(name='Gender', N_level=2, prevalence=c(0.5,0.5), HR=c(1,0.9), strata=TRUE)
factors<-list(f1,f2)
cov_simu(sample_size=300, factors=factors)
```

dummy_convert	<i>Convert Categorical Data to Dummy Variables</i>
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Description

Convert Categorical Data to Dummy Variables

Usage

```
dummy_convert(dataset, column_names)
```

Arguments

dataset	Data frame that contains the categorical columns
column_names	A list of column names that need to be converted to dummy variables.

Examples

```
x<-data.frame(trt=as.factor(rbinom(100,1,0.5)), Gender=as.factor(rbinom(100,1,0.5)))
dummy_convert(x,c("trt","Gender"))
```

LambdaCensor	<i>Find the Censor Hazard Function Parameter for Proportional Hazard Model Given a Fixed Dropout Rate</i>
--------------	---

Description

calculate censor hazard function parameter for a given dropout rate.

Usage

```
LambdaCensor(lambda=lambda,gamma=gamma,theta=theta,ebx=1,gammac=1,
  groupfreq=1,censordist='exponential',timeinterval=NULL)
```

Arguments

lambda	lambda for event hazard function
gamma	gamma for event hazard function
gammac	gamma for censor hazard function. This is required if the censoring hazard function is weibull
theta	Dropout rate
ebx	$\exp(\beta \cdot x)$, if there's no covariates, ebx=1.
groupfreq	frequency of each level of ebx value
censordist	censor hazard function distribution
timeinterval	time intervals for piecewise baseline hazard function

References

Wan F. (2017) *Simulating survival data with predefined censoring rates for proportional hazards models*. *Statist. Med.* 2017; 36(5): 838-854

Martinez EZ, Achcar JA, de Oliveira Peres MV, de Queiroz JAM (2016) *A brief note on the simulation of survival data with a desired percentage of right-censored data*. *Journal of Data Science* . 2016, Vol. 14 Issue 4, p701-712. 12p

Examples

```
lambdac<-LambdaCensor(lambda=0.03,gamma=1,theta=0.2)
```

LambdaCensor_betapw *Find the Censor Hazard Function Parameter for Nonproportional Hazard Model Given a Fixed Dropout Rate*

Description

calculate censor hazard function parameter for a given dropout rate. (for piecewise hazard ratios)

Usage

```
LambdaCensor_betapw(lambda=lambda,gamma=gamma,theta=theta,ebx=1,
  gammac=1,groupfreq=1,censordist='exponential',timeinterval=NULL)
```

Arguments

lambda	lambda for event hazard function
gamma	gamma for event hazard function
gammac	gamma for censor hazard function. This is required if the censoring hazard function is weibull
theta	Dropout rate
ebx	exp(beta*x), if there's no covariates, ebx=1.
groupfreq	frequency of each level of ebx value
censordist	censor hazard function distribution
timeinterval	time intervals for piecewise baseline hazard function

References

Wan F. (2017) *Simulating survival data with predefined censoring rates for proportional hazards models. Statist. Med.* 2017; 36(5): 838-854

Martinez EZ, Achcar JA, de Oliveira Peres MV, de Queiroz JAM (2016) *A brief note on the simulation of survival data with a desired percentage of right-censored data. Journal of Data Science .* 2016, Vol. 14 Issue 4, p701-712. 12p

linear_accrual *Simulate Accrual Time Where the Accrual Rate is Linearly Increased*

Description

simulate accrual time where the accrual rate is linearly increased

Usage

```
linear_accrual(np,rampupt,acceleration)
```

Arguments

np	Total number of patients
rampupt	The length of the ramp up period.
acceleration	The acceleration of the accrual rate (increase of each time unit).

Examples

```
linear_accrual(np=200,rampupt=10,acceleration=5)
```

objfunction	<i>Objective Function for the Finding of Censor Hazard Function Parameter for Proportional Hazard Model</i>
-------------	---

Description

objective function for the finding of censor hazard function parameter.

Usage

```
objfunction(x,lambda,gamma,gammac,theta,ebx,groupfreq,censordist,timeinterval)
```

Arguments

x	Censor hazard function parameter. For exponential or weibull censor hazard, x is lambda, for uniform hazard, x is the maximum time of the censoring window.
lambda	lamda for event hazard function
gamma	gamma for event hazard function
gammac	gamma for censor hazard function. THis is required if the censoring hazard function is weibull
theta	Dropout rate
ebx	$\exp(\beta \cdot x)$, if there's no covariates, $\text{ebx}=1$.
groupfreq	frequence of each level of ebx value
censordist	censor hazard function distribution
timeinterval	time intervals for piecewise baseline hazard function

objfunction_betpw	<i>Objective Function for The Finding of Censor Hazard Function Parameter for Nonproportional Hazard Model</i>
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Description

objective function for the finding of censor hazard function parameter.

Usage

```
objfunction_betapw(x, lambda, gamma, gammac, theta, ebx, groupfreq, censordist, timeinterval)
```

Arguments

x	Censor hazard function parameter. For exponential or weibull censor hazard, x is lambda, for uniform hazard, x is the maximum time of the censoring window.
lambda	lamda for event hazard function
gamma	gamma for event hazard function
gammac	gamma for censor hazard function. THis is required if the censoring hazard function is weibull
theta	Dropout rate
ebx	exp(beta*x), if there's no covariates, ebx=1.
groupfreq	frequence of each level of ebx value
censordist	censor hazard function distribution
timeinterval	time intervals for piecewise baseline hazard function

projection	<i>Event and Trial Projection</i>
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Description

Trial projection given current snapshot dataset.

Usage

```
projection(snapshot_data, enroll_continue=FALSE, samplesize=0, rand_ratio=c(1,1),
blocksize=1, accrual_interval=NULL, accrual_rate=NULL, lambda=NULL,
trtTHR=NULL, dropoutrate=NULL, eventtarget=0, maxlpfollowup=NULL)
```


Arguments

snapshot_data	Snapshot dataset in data frame. Data frame must include column "time", "status" and "accrual". Optional column "onstudy" is indicator of patients are still on study.
rand_ratio	randomization ratio: control vs treatment
enroll_continue	Indicate whether trial is still enrolling new patients. Default is FALSE. if TRUE, user needs provide "samplesize", "rand_ratio", "blocksize", "accrual_interval", "accrual_rate".
samplesize	Total sample size of the trial. only needed if "enroll_continue=TRUE"
blocksize	Randomization blocksize, only needed if "enroll_continue=TRUE"
accrual_interval	accrual time windows. only needed if "enroll_continue=TRUE"
accrual_rate	accrual rate for each time window. only needed if "enroll_continue=TRUE"
lambda	Baseline hazard function parameter for exponential distribution
trtHR	hazard ratio between treatment and control
dropoutrate	Dropout rate
eventtarget	Total target event number
maxlpfollowup	Maximum followup time for last enrolled patient

projection_simulation *Project Final Event Numbers or Trial Stop Time Based on Interim Analysis Data*

Description

Project final event numbers or trial stop time based on interim analysis data

Usage

```
projection_simulation(snapshot_data, rand_ratio=c(1,1), enroll_continue=FALSE,
samplesize=0, blocksize=1,accrual_interval=NULL, accrual_rate=NULL, lambda=NULL,
trtHR=NULL, dropoutrate=NULL,eventtarget=NULL,maxlpfollowup=NULL,N_simulation=1)
```

Arguments

snapshot_data	Snapshot dataset or interim analysis dataset
rand_ratio	Randomization ratio between control and treatment
blocksize	The value of this parameter is used to define the size of the randomization blocks. The actual blocksize is number of treatment levels multiplied by this parameter. Please refer to "blockrand" package for detailed usage.

enroll_continue	True if trial is still in the enrollment period
samplesize	if enroll_continue=TRUE, please provide the total sample size of the trial.
trtHR	Hazard ratio between treatment groups (treatment vs control)
accrual_interval	Time windows for accrual
accrual_rate	accrual rate for each accrual time window
lambda	lambda for event hazard function (exponential)
dropoutrate	Patient dropout rate with range [0,1). If dropoutrate contains only one number. The program will control the dropout rate at population level(treatment + control). If dropoutrate contains two numbers (ie. c(0.2,0.1)), the program will control the dropout rate of control and treatment arm seperately, with the first dropout rate number for control and the second number for treatment. Default value is "0" (no dropout)
eventtarget	Number of target events
maxlpfollowup	maximum follow up time for the last enrolled patient
N_simulation	number of simulations to run

randomize_trt	<i>Generate Block Randomized Treatment Label Based on Covariates Matrix</i>
---------------	---

Description

Generate block randomized treatment label based on covariates matrix

Usage

```
randomize_trt(cov_mat=cov_mat,blocksize=blocksize,trtHR=trtHR,rand_ratio=c(1,1))
```

Arguments

cov_mat	Covariates matrix.
blocksize	Randomization block size
trtHR	Hazard ratio between treatment arms.
rand_ratio	Randomization ratio between control and treatment

randomize_trt2	<i>Generate Block Randomized Treatment Label Based on Covariates Matrix for Two Arm Trial</i>
----------------	---

Description

Generate block randomized treatment label based on covariates matrix for two arm trial.

Usage

```
randomize_trt2(cov_mat=cov_mat,blocksize=blocksize,rand_ratio=c(1,1))
```

Arguments

cov_mat	Covariates matrix.
blocksize	Randomization block size
rand_ratio	Randomization ratio between control and treatment

run_simulation	<i>Run Clinical Trial Simulations Based on User Defined Trial Settings</i>
----------------	--

Description

Runs single or mutple clinical trial (Time to event endpoint) simulations based on the clinical trial settings. Trial data summary will be provied for each simulation. Cox model will be fitted afther trial simulation. If stratification factors were provided, stratified cox model results will also be provided. If "N_simulation" is set to 1, one simulation dataset will be generated.

Usage

```
run_simulation(samplesize, rand_ratio=c(1,1), blocksize, factors=NULL, trtHR=trtHR,
trt_timeinterval=NULL, accrual_interval=NULL, accrual_rate=NULL, rampuptime=NULL,
acceleration=NULL, lambda, gamma, timeinterval=NULL, dropoutrate=0, gammac=1,
censordist='exponential', eventtarget=NULL,maxlpfollowup=NULL, N_simulation=1,
alpha=0.05)
```

Arguments

samplesize	Total number of patients in the simulated clinical trial
rand_ratio	Randomization ratio between control and treatment
blocksize	The value of this parameter is used to define the size of the randomization blocks. The actual blocksize is number of treatment levels multiplied by this parameter. Please refer to "blockrand" package for detailed usage.
factors	stratification factors. Default is NULL
trtHR	Hazard ratio between treatment groups (treatment vs control)
trt_timeinterval	Time windows for trtHR when trtHR is piecewise. Always start with time 0. Example: c(0,10,30)
accrual_interval	Time windows for accrual
accrual_rate	accrual rate for each accrual time window
rampuptime	rampup time for linear increased accrual
acceleration	acceleration rate for linear increased accrual
lambda	lambda for event hazard function
gamma	gamma for event hazard function
timeinterval	time intervals for piecewise baseline hazard function
dropoutrate	Patient dropout rate with range [0,1). If dropoutrate contains only one number. The program will control the dropout rate at population level(treatment + control). If dropoutrate contains two numbers (ie. c(0.2,0.1)), the program will control the dropout rate of control and treatment arm separately, with the first dropout rate number for control and the second number for treatment. Default value is "0" (no dropout)
gammac	gamma for censor hazard function. Default is 1 (exponential)
censordist	censor hazard distribution. Can be "weibull", "exponential" or "uniform". Default is exponential
eventtarget	Number of target events
maxlpfollowup	maximum follow up time for the last enrolled patient
N_simulation	number of simulations to run
alpha	Two sided alpha for testing power calculation

Value

TrilInfo	Summary of the simulated trial data
ModelResult	Cox model results comparing treatment vs control
StraModelResult	Stratified Cox model results comparing treatment vs control
Data	simulated dataset only if "N_simulateion" is set to 1

Examples

```
f1<-list(name='Region', N_level=3, prevalence=c(0.1,0.2,0.7), HR=c(1,0.7,0.9), strata=TRUE)
f2<-list(name='Gender', N_level=2, prevalence=c(0.5,0.5), HR=c(1,0.9), strata=TRUE)
f3<-list(name='Stage', N_level=4, prevalence=c(0.2,0.25,0.3,0.25), HR=c(1,1.05,1.3,1.5),
strata=TRUE)

factors<-list(f1,f2,f3)

samplesize<-400
blocksize<-2
accrual_interval<-c(0,5,10)
accrual_rate<-c(5,10,20)
trtHR<-0.7
lambda<-0.03
gamma<-1.2
dropoutrate<-0.2
eventtarget<-240
N_simulation<-10

out<-run_simulation(samplesize=samplesize,blocksize=blocksize,factors=factors,
accrual_interval=accrual_interval,accrual_rate=accrual_rate, trtHR=trtHR, lambda=lambda,
gamma=gamma,dropoutrate=dropoutrate,eventtarget=eventtarget,N_simulation=N_simulation)
```

run_simulation_simsurv

*Run Clinical Trial Simulations Based on survival data generated by
simsurv package*

Description

Runs single or mutiple clinical trial (Time to event endpoint) simulations based survival time generated by simsurv package. Trial data summary will be provided for each simulation. Cox model will be fitted afther trial simulation. If stratification factors were provided, stratified cox model results will also be provided. If "N_simulation" is set to 1, one simulation dataset will be generated.

Usage

```
run_simulation_simsurv(samplesize, rand_ratio=c(1,1), blocksize, factors=NULL,
accrual_interval=NULL,accrual_rate=NULL, eventtarget=NULL,maxlpfollowup=NULL,
N_simulation=1,alpha=0.05,simsurv1=NULL, simsurv2=NULL)
```

Arguments

samplesize	Total number of patients in the simulated clinical trial
rand_ratio	Randomization ratio between control and treatment
blocksize	The value of this parameter is used to define the size of the randomization blocks. The actual blocksize is number of treatment levels multiplied by this parameter. Please refer to "blockrand" package for detailed usage.
factors	stratification factors. Default is NULL
accrual_interval	Time windows for accrual
accrual_rate	accrual rate for each accrual time window
eventtarget	Number of target events
maxlpfollowup	maximum follow up time for the last enrolled patient
N_simulation	number of simulations to run
alpha	Two sided alpha for testing power calculation
simsurv1	simsurv command to generate survival time. Design matrix should set to "x". Please refer to examples.
simsurv2	simsurv command to generate dropout time.

Value

TrilInfo	Summary of the simulated trial data
ModelResult	Cox model results comparing treatment vs control
StraModelResult	Stratified Cox model results comparing treatment vs control
Data	simulated dataset only if "N_simulation" is set to 1

Examples

```
# Example 1, compare simsurv and TwoArmSurvSim, trtHR=0.7 eventtarget=247, power should be 0.8

f1<-list(name='Gender', N_level=2, prevalence=c(0.5,0.5), HR=c(1,0.9), strata=TRUE)
factors=list(f1)

samplesize = 400
blocksize = 2
accrual_interval = c(0,5,10)
accrual_rate = c(5,10,20)
eventtarget = 247
N_simulation = 1

# Simsurv

simsurv1 <- "simsurv(lambdas = 0.03, gammas = 1,
```

```

betas = c(trt = log(0.7),Gender.1=log(0.9)),x = x)"
simsurv2 <-NULL

out<-run_simulation_simsurv(samplesize=samplesize,blocksize=blocksize,factors=factors,
accrual_interval=accrual_interval,accrual_rate=accrual_rate, eventtarget=eventtarget,
N_simulation=N_simulation,simsurv1=simsurv1,simsurv2=simsurv2)

# example 2, Time dependent treatment effect.
# h(t)=h0(t)*exp(beta0*x+beta1*x*log(t)). beta0=log(0.7), beta1=0.15

simsurv1 <- "simsurv( lambdas = 0.1, gammas = 1.5,betas = c(trt = log(0.7)),
x = x, tde = c(trt = 0.15),tdefunction = \"log\")"
simsurv2 <-NULL

```

self_blockrand	<i>Block Randomization</i>
----------------	----------------------------

Description

Block randomization

Usage

```
self_blockrand(N=N, trt_levels=trt_levels,blocksize=blocksize,rand_ratio=rand_ratio)
```

Arguments

N	Total number of patients
trt_levels	treatment levels in vector. for example, c(0,1) for control vs treatment trial.
blocksize	Randomization block size
rand_ratio	Randomization ratio between control and treatment

Examples

```
self_blockrand(N=100, trt_levels=c(0,1),blocksize=2,rand_ratio=c(1,1))
```

step_accrual *Simulate Accrual Time*

Description

Simulate accrual time

Usage

```
step_accrual(np, tt, arate)
```

Arguments

np	Total number of patients
tt	Time windows
arate	accrual rate for each time windows

Examples

```
timeinterval<-c(0,5,10)
accrualrate<-c(10,15,20)
N<-200
accrual<-step_accrual(N,timeinterval,accrualrate)
```

surv_data_simulation *Simulate Survival Data*

Description

Simulate survival data given design matrix and covariates (betas).

Usage

```
surv_data_simulation(lambda,gamma,x,betas=NULL, dropoutrate=0,
  gammac=1,censordist='exponential',timeinterval=NULL,trt_timeinterval=NULL)
```


Arguments

lambda	lambda for event hazard function
gamma	gamma for event hazard function
x	design matrix
betas	coefficients for the covariates. The length of betas should be the same of number of columns of x
dropoutrate	Patient dropout rate with range [0,1). If dropoutrate contains only one number. The program will control the dropout rate at population level(treatment + control). If dropoutrate contains two numbers (ie. c(0.2,0.1)), the program will control the dropout rate of control and treatment arm separately, with the first dropout rate number for control and the second number for treatment. Default value is "0" (no dropout)
gammac	gamma for censor hazard function. Default is 1 (exponential)
censordist	censor hazard distribution. Default is exponential
timeinterval	time intervals if the baseline hazard function is piecewise.
trt_timeinterval	Time windows for piecewise hazard ratios

Examples

```

N<-400
x<-data.frame(arm=rbinom(N,1,0.5), factor1=rbinom(N,1,0.7), factor2=rbinom(N,1,0.8))
betas<-c(arm=-0.35667,factor1=0.3,factor2=-0.1)

data<-surv_data_simulation(lambda=0.2,gamma=2,x=x,betas=betas,dropoutrate=0.2)

```

trial_data_simulation *Simulate Clinical Trial with Accrual Time and Trial Stop Rules*

Description

Simulate clinical trial by adding accrual time to the simulated survival data. And cut the trial at the target event time or at the maximum follow up time

Usage

```
trial_data_simulation(simdata,accrual,eventtarget=NULL,maxlpfollowup=NULL)
```

Arguments

simdata	A data frame contains simulated survival time and censor status.
accrual	Simulated accrual time.
eventtarget	Target number of events of the trial
maxlpfollowup	The maximum follow up time for the last enrolled patient.

 weibullsim

Simulate Event Time with weibull Hazard Function

Description

Simulate event time with weibull hazard function

Usage

```
weibullsim(N=NULL,lambda,gamma,x=NULL,betas=NULL)
```

Arguments

N	Total number of patients
lambda	lambda for event hazard function
gamma	gamma for event hazard function
x	design matrix
betas	covariates for design matrix

Examples

```
data<-weibullsim(N=300,lambda=0.03,gamma=0.9)
```

weibullsim_betapw	<i>Simulate Event Time with weibull Hazard Function and Piecewise Hazard Ratios</i>
-------------------	---

Description

Simulate event time with weibull hazard function for piecewise hazard ratios

Usage

```
weibullsim_betapw(lambda, gamma, t, x, betas)
```

Arguments

lambda	lambda for event hazard function
gamma	gamma for event hazard function
x	design matrix
betas	covariates for design matrix
t	Time windows for piecewise hazard ratios

weibullsim_pw	<i>Simulate event time with weibull hazard function. The parameters can be piecewise.</i>
---------------	---

Description

Simulate event time with weibull hazard function given the piecewise parameters.

Usage

```
weibullsim_pw(lambda, gamma, t, x, betas=NULL)
```

Arguments

lambda	lambda for event hazard function. It will be a vector for piecewise hazard function.
gamma	gamma for event hazard function. It will be a vector for piecewise hazard function.
x	design matrix
betas	covariates for desing matrix
t	time intervals for piecewise weibull parameters.

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