Package 'Immunotherapy.Design'

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Title Study design for immunotherapy clinical trials

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Description Estimate hazard rates and baseline hazards using an EM algorithm.

Depends survival, msm

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NeedsCompilation yes

R topics documented:

`Immunotherapy.Design-package`

Study design for immunotherapy clinical trials

Description

Estimate hazard rates and baseline hazards using an EM algorithm

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> and Bin Zhu <bin.zhu@nih.gov>

data *Data for examples*

Description

Data for examples.

Details

A data frame used in the examples.

Examples

```
data(data, package="Immunotherapy.Design")

# Display some of the data
data[1:5, ]
```

generate_data *Simulated data*

Description

Generate simulated data

Usage

```
generate_data(nmax=500, rand_ratio=0.5, effect_p=0.6, enroll_rate=380*0.25/6,
              lambda1=0.117, HR=0.5, tau=12*5, t1=1)
```

Arguments

nmax	Sample size
rand_ratio	Allocation ratio
effect_p	Proportion of responders in the treatment arm
enroll_rate	Enrollment rate in subjects per month
lambda1	Baseline hazard in terms of months
HR	Hazard ratio
tau	Total study duration
t1	Delayed duration

Value

A data frame with columns:

Name	Description
id	id variable
trt	treatment allocation: 1 = treatment arm
Z	patient's response status
tau	total study duration
enroll_time	patients' enrollment times
time_to_event	patients' event times
event_status	censoring indicator
X	observational time
t1	delayed duration

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> and Bin Zhu <bin.zhu@nih.gov>

Examples

```
data <- generate_data()
data[1:5, ]
```

`getHazard` *Compute initial estimates for the baseline hazard*

Description

Calls the coxph function to compute initial estimates for the baseline hazard

Usage

```
getHazard(time, treatment, event_status)
```

Arguments

`time`	Vector of times.
`treatment`	Binary vector of treatments (1=subject received treatment).
`event_status`	Binary vector of event status (1=subject experienced an event).

Value

Vector of baseline hazards ordered by the event times.

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> and Bin Zhu <bin.zhu@nih.gov>

See Also

`Pembedded.EM.NP`

Examples

```
data(data, package="Immunotherapy.Design")
lambda0 <- getHazard(data[, "X"], data[, "trt"], data[, "event_status"])
lambda0[1:10]
```

`N.Pembedded.P` *Sample Size*

Description

Compute the sample size for a given power for the parametric model

Usage

```
N.Pembedded.P(power=0.8, rand_ratio=0.5, effect_p=0.6, enroll_rate=380*0.25/6,
              lambda1=0.117, HR=0.5, tau=12*5, t1=1, maxiter=1000, stopTol=1e-4,
              alpha=0.05, num_rand=1000, nsim=1000, min.N=100, max.N=700,
              tol.power=0.01, tol.N=1, print=1)
```

Arguments

`power`	The desired power. The default is 0.8.
`rand_ratio`	Allocation ratio
`effect_p`	Proportion of responders in the treatment arm
`enroll_rate`	Enrollment rate in subjects per month
`lambda1`	Baseline hazard in terms of months
`HR`	Hazard ratio
`tau`	Total study duration
`t1`	Delayed duration
`maxiter`	Maximum number of iterations in the EM algorithm. The default is 1000.
`stopTol`	Stopping tolerance in the EM algorithm. The default is 1e-4.
`alpha`	Significance level. The default is 0.05.
`num_rand`	Number of replications in the re-randomization test. The default is 1000.
`nsim`	Number of simulations in computing power. The default is 1000.
`min.N`	Lower bound for the sample size. The default is 100.
`max.N`	Upper bound for the sample size. The default is 700.
`tol.power`	Stopping tolerance for the power. The default is 0.01.
`tol.N`	Stopping tolerance for the sample size. The default is 1.
`print`	0 or 1 to print information. The default is 1.

Details

This uses a bisection method to estimate the sample size. At each iteration, the estimated power `power_est` is computed using `Pow.Pembedded.P` for a given sample size holding all other parameters fixed. The algorithm terminates when `abs(power - power_est) <= tol.power` or when the length of the estimated interval containing the sample size is less than or equal to `tol.N`.

Value

A list containing the sample size and power.

Author(s)

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See Also

Pow.Pembedded.P

Pembedded.EM.NP *EM algorithm*

Description

Non-parametric EM algorithm

Usage

```
Pembedded.EM.NP(data, time.var="X", trt.var="trt", status.var="event_status",
          effect_p=0.6, t1=1, lambda0=NULL, probResponder=NULL,
          stopTol=1e-4, maxiter=10000, print=0)
```

Arguments

data	Data frame or matrix containing a time-to-event variable (time.var), a treatment variable (trt.var), and a censoring variable (status.var).
time.var	Time-to-event variable name in data. The default is "X".
trt.var	Binary treatment variable name in data coded as 0 for controls and 1 for subjects that received treatment.
status.var	Name of the binary censoring variable in data coded as 0 for censored subjects and 1 for subjects that experienced an event.
effect_p	Proportion of responders. The default is 0.6.
t1	Delayed duration. The default is 1.
lambda0	NULL or vector of initial estimates for the baseline hazards corrsponding to the ordered event times. The default is NULL and will be computed from getHazard.
probResponder	NULL or vector of initial probabilities of a subject being a responder. The default is NULL so that the initial probability is 0.5 for treated subjects and 0 for controls.
stopTol	Stopping tolerance. The default is 1e-4.
maxiter	Maximum number of iterations. The default is 10000.
print	0-2 to print information. Larger values will print more information. The default is 0.

Value

A list containing the objects:

Name	Description
converged	TRUE if EM algorithm converged
logHR	estimated log(hazard ratio)
baseline	matrix of event times and baseline hazards
probResponder	estimated probability of a subject being a responder

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> and Bin Zhu <bin.zhu@nih.gov>

See Also

getHazard, Pembedded.EM.P

Examples

```
data(data, package="Immunotherapy.Design")
ret <- Pembedded.EM.NP(data)
ret$logHR
```

Pembedded.EM.P *EM algorithm*

Description

Parametric EM algorithm

Usage

```
Pembedded.EM.P(data, time.var="X", trt.var="trt", status.var="event_status",
          effect_p=0.6, t1=1, probResponder=NULL,
          stopTol=1e-5, maxiter=10000, print=0)
```

Arguments

data	Data frame or matrix containing a time-to-event variable (time.var), a treatment variable (trt.var), and a censoring variable (status.var).
time.var	Observational time variable name in data (months). The default is "X".
trt.var	Binary treatment assignment indicator name in data coded as 0 for controls and 1 for treated subjects.
status.var	Name of the binary censoring variable in data coded as 0 for censored subjects and 1 for subjects that experienced an event.
effect_p	Proportion of responders among the treated subjects. The default is 0.6.
t1	Delayed duration. The default is 1 (month).
probResponder	NULL or vector of initial probabilities of a treated subject being a responder. The default is NULL so that the initial probability is 0.5 for treated subjects.
stopTol	Stopping tolerance. The default is 1e-5.
maxiter	Maximum number of iterations. The default is 10000.
print	0-2 to print information. Larger values will print more information. The default is 0.

Value

A list containing the objects:

Name	Description
converged	TRUE if EM algorithm converged
lambda	estimated hazard rate
baseline	estimated baseline hazard
probResponder	estimated probability of a treated subject being a responder

Author(s)

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See Also

Pembedded.EM.NP

Examples

```
data(data, package="Immunotherapy.Design")
ret <- Pembedded.EM.P(data)
ret$lambda
```

Pembedded.ReRandomizationTest.NP

Randomization test

Description

Compute a randomization test p-value where test statistic is calculated based on a non-parametric model.

Usage

```
Pembedded.ReRandomizationTest.NP(data, time.var="X", trt.var="trt", status.var="event_status",
        effect_p=0.6, t1=1, stopTol=1e-4, maxiter=10000, print=0, num_rand=100)
```

Arguments

data	Data frame or matrix containing a time-to-event variable (time.var), a treatment variable (trt.var), and a censoring variable (status.var).
time.var	Observational time variable name in data.
trt.var	Name of treatment assignment indicator in data coded as 0 for control subjects and 1 for treated subjects.
status.var	Name of the binary censoring variable in data coded as 0 for censored subjects and 1 for subjects that experienced an event.
effect_p	Proportion of responders among the treated subjects. The default is 0.6.
t1	Delayed duration. The default is 1 (month).
stopTol	Stopping tolerance in the EM algorithm. The default is 1e-4.

maxiter	Maximum number of iterations in the EM algorithm. The default is 10000.
print	0-2 to print information. Larger values will print more information. The default is 0.
num_rand	The number of replications in the re-randomization test. The default is 100.

Details

In each randomization, the treatment label is resampled and then the EM algorithm is called. The final p-value is based on all re-randomizations in which the EM algorithm converged.

Value

A list containing the objects:

Name	Description
p.val.rerand	re-randomization test p-value
baseline	matrix of event times and baseline hazards from observed data
logHR	log(hazard ratio) from observed data

Author(s)

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See Also

Pembedded.ReRandomizationTest.P

Examples

```
data(data, package="Immunotherapy.Design")
set.seed(1)
# Will take a few minutes to complete
#ret <- Pembedded.ReRandomizationTest.NP(data)
```

Pembedded.ReRandomizationTest.P

Randomization test

Description

Compute a randomization test p-value where test statisitic is calculated based on a parametric model.

Usage

```
Pembedded.ReRandomizationTest.P(data, time.var="X", trt.var="trt", status.var="event_status",
       effect_p=0.6, t1=1, stopTol=1e-5, maxiter=10000, print=0, num_rand=10000)
```

Arguments

data	Data frame or matrix containing a time-to-event variable (time.var), a treatment variable (trt.var), and a censoring variable (status.var).
time.var	Observational variable name in data.
trt.var	Name of treatment assignment indicator in data coded as 0 for control subjects and 1 for treated subjects.
status.var	Name of the binary censoring variable in data coded as 0 for censored subjects and 1 for subjects that experienced an event.
effect_p	Proportion of responders among the treated subjects. The default is 0.6.
t1	Delayed duration. The default is 1 (month).
stopTol	Stopping tolerance in the EM algorithm. The default is 1e-5.
maxiter	Maximum number of iterations in the EM algorithm. The default is 10000.
print	0-2 to print information. Larger values will print more information. The default is 0.
num_rand	The number of replications in the re-randomization test. The default is 10000.

Details

In each randomization, the treatment label is resampled and then the EM algorithm is called. The final p-value is based on all randomizations in which the EM algorithm converged.

Value

A list containing the objects:

Name	Description
p.val.rerand	re-randomization test p-value
baseline	estimated baseline hazard from observed data
lambda	estimated hazard rate from observed data

Author(s)

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See Also

Pembedded.ReRandomizationTest.NP

Examples

```
data(data, package="Immunotherapy.Design")
set.seed(1)
ret <- Pembedded.ReRandomizationTest.P(data)
ret$p.val.rerand
```

Pow.Pembedded.NP *Power*

Description

Compute the power for the non-parametric model

Usage

```
Pow.Pembedded.NP(nmax=500, rand_ratio=0.5, effect_p=0.6, enroll_rate=380*0.25/6,
                lambda1=0.117, HR=0.5, tau=12*5, t1=1, maxiter=1000, stopTol=1e-4,
                        alpha=0.05, num_rand=1000, nsim=1000, print=0)
```

Arguments

nmax	Sample size
rand_ratio	Probability of assignment to treatment arm
effect_p	Proportion of responders in the treatment arm
enroll_rate	Enrollment rate in subjects per month
lambda1	Baseline hazard in terms of months
HR	Hazard ratio
tau	Total study duration
t1	Delayed duration in months
maxiter	Maximum number of iterations in the EM algorithm. The default is 10000.
stopTol	Stopping tolerance in the EM algorithm. The default is 1e-4.
alpha	Significance level. The default is 0.05.
num_rand	The number of replications in the re-randomization test. The default is 1000.
nsim	The number of simulations. The default is 1000.
print	0 or 1 to print information. The default is 0.

Details

For each simulation, a simulated data set is created from the generate_data function and then an estimated p-value is computed by calling Pembedded.ReRandomizationTest.NP. The power is calculated as the proportion of iterations whose estimated p-value was less than or equal to alpha.

Value

A list containing the power and the number of simulated datasets used in the calculation.

Author(s)

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See Also

Pow.Pembedded.P

Pow.Pembedded.P *Power*

Description

Compute the power for the parametric model

Usage

```
Pow.Pembedded.P(nmax=500, rand_ratio=0.5, effect_p=0.6, enroll_rate=380*0.25/6,
                lambda1=0.117, HR=0.5, tau=12*5, t1=1, maxiter=1000, stopTol=1e-4,
                        alpha=0.05, num_rand=1000, nsim=1000, print=0)
```

Arguments

nmax	Sample size
rand_ratio	Probability of assignment to treatment arm
effect_p	Proportion of responders in the treatment arm
enroll_rate	Enrollment rate in subjects per month
lambda1	Baseline hazard in terms of months
HR	Hazard ratio
tau	Total study duration
t1	Delayed duration in months
maxiter	Maximum number of iterations in the EM algorithm. The default is 10000.
stopTol	Stopping tolerance in the EM algorithm. The default is 1e-4.
alpha	Significance level. The default is 0.05.
num_rand	The number of replications in the re-randomization test. The default is 1000.
nsim	The number of simulations. The default is 1000.
print	0 or 1 to print information. The default is 0.

Details

For each simulation, a simulated data set is created from the generate_data function and then an estimated p-value is computed by calling Pembedded.ReRandomizationTest.P. The power is calculated as the proportion of iterations whose estimated p-value was less than or equal to alpha.

Value

A list containing the power and the number of simulated datasets used in the calculation.

Author(s)

Zhenzhen Xu <Zhenzhen.Xu@fda.hhs.gov> and Bin Zhu <bin.zhu@nih.gov>

See Also

N.Pembedded.P

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