Package ‘rld’

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Description Analyzes data from repeated low-dose challenge experiments and provide vaccine efficacy estimates. In addition, this package can provide guidance to design repeated low-dose challenge studies.
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Description

This package can analyze the data from repeated low-dose (RLD) challenge experiments for evaluating effect of treatment (vaccine). Based on the fit of a discrete-time survival model with gamma distributed random effect and a complementary log-log link function, this package can provide estimates of regression parameters for effects of treatment and challenge dose, as well as estimates of treatment (vaccine) efficacy. In addition, this package can test regression parameters and frailty variance parameter using likelihood ratio test. Also it can help users design the RLD study by performing power analysis.

Details

Package: rld
Type: Package
Version: 1.0
Date: 2017-01-11
License: GPL (>= 2)

This package is created based on a paper written by Kang et al. (2015). In this paper, the authors proposd to use a discrete-time survival model with random effects to model the data from repeated low-dose challenge experiments.

Author(s)

Bin Yao <byao@fredhutch.org>, Ying Huang <yhuang@fhcrc.org> and Chaeryon Kang <crkang@pitt.edu>

References


Description

This function estimates the per-challenge probability of infection.
Usage

calcpk(object, predlevel, CIllevel = 0.95)

Arguments

object  a fitted object of class inheriting from "rld".
predlevel  a value or a vector indicating covariate for prediction of per-challenge probability of infection.
CIlevel  confidence level. The default is 0.95.

Details

Calculate the per-challenge risk of infection for the contrast group and reference group.

Value

pk  risk of infection for the contrast group.
pk_se  standard error of the estimated pk.
lwr  lower bound value of the confidence interval of the estimated pk.
upr  upper bound value of the confidence interval of the estimated pk.

Note

The variable names in the predlevel should match the names in the data frame.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang

References


See Also

calcVEk, calcVEt

Examples

data(SampleData)
newdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
fitout <- rld(formula = survival::Surv(time, delta)~factor(dose)+trt+I(I(dose==3)*trt),
  data = newdata, frailty = TRUE)

predictdata <- 1
names(predictdata) <- c("trt")

pkout <- calcpk(object = fitout, predlevel = predictdata, CIllevel = 0.95)
summary(pkout)
### calcVEk

**Calculate Per-Challenge Vaccine Efficacy**

**Description**

This function calculates the estimated per-challenge vaccine efficacy.

**Usage**

```r
calcVEk(object, newdata, CIlevel=0.95)
```

**Arguments**

- `object`: a fitted object of class inheriting from "rld".
- `newdata`: a data list for predicting vaccine efficacy where "contrgroup" and "refgroup" list names must be included.
- `CIlevel`: a confidence level. The default is 0.95.

**Details**

Per-challenge vaccine efficacy is defined as the relative reduction in the risk of infection caused by vaccination at a particular challenge, conditional on non-infection before the challenge. Please refer to Kang et al. (2015) for more details about the formula.

**Value**

- `VE`: the vaccine efficacy estimates for contrast group and reference group.
- `se`: standard deviations of per-challenge vaccine efficacy estimates.
- `lwr`: a vector containing the lower bound values of confidence interval for VE.
- `upr`: a vector containing the upper bound values of confidence interval for VE.

**Note**

In the newdata list for vaccine efficacy prediction, users must assign variable names in the contrast group and reference group.

**Author(s)**

Bin Yao, Ying Huang and Chaeryon Kang

**References**

See Also
calcvet, calcpk

Examples

data(SampleData)
augdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
fitout <- rld(formula = survival::Surv(time, delta)~factor(dose)+trt+I(I(dose==3)*trt),
data = augdata, frailty = TRUE)

contrgroup <- 1
refgroup <- 0
predata <- list(contrgroup, refgroup)
names(predata) <- c("contrgroup", "refgroup")
names(predata$contrgroup) <- c("trt")
names(predata$refgroup) <- c("trt")

vekout <- calcvek(object = fitout, newdata = predata, Clevel = 0.95)
summary(vekout)
**Value**

- **VE**  
  A vector containing vaccine efficacy estimates for contrast group and reference group.

- **se**  
  A vector containing standard deviations of per-challenge vaccine efficacy estimates.

- **lwr**  
  A vector containing lower bound of confidence interval for VE(t).

- **upr**  
  A vector containing upper bound value of confidence interval for VE(t).

- **time**  
  A vector containing challenge times.

**Author(s)**

Bin Yao, Ying Huang and Chaeryon Kang

**References**


**See Also**

- `calcVEk`
- `calcpk`

**Examples**

```r
data(SampleData)
augdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
fitout <- rld(formula = survival::surv(time, delta)~factor(dose)+trt*I(I(dose==3)*trt),
              data = augdata, frailty = TRUE)
contrgroup <- 1
refgroup <- 0
predata <- list(contrgroup, refgroup)
names(predata) <- c("contrgroup", "refgroup")
names(predata$contrgroup) <- c("trt")
names(predata$refgroup) <- c("trt")

VEout <- calcVEt(object = fitout, nexposure = c(10, 10, 2), newdata = predata, CIlevel = 0.95)
summary(VEout)
```

### lrtest

**Likelihood Ratio Test**

**Description**

This function performs likelihood ratio test (LRT) to test regression parameters in the mean model and frailty variance parameter `nu`. 

---

**Value**

- **VE**  
  A vector containing vaccine efficacy estimates for contrast group and reference group.

- **se**  
  A vector containing standard deviations of per-challenge vaccine efficacy estimates.

- **lwr**  
  A vector containing lower bound of confidence interval for VE(t).

- **upr**  
  A vector containing upper bound value of confidence interval for VE(t).

- **time**  
  A vector containing challenge times.

**Author(s)**

Bin Yao, Ying Huang and Chaeryon Kang

**References**


**See Also**

- `calcVEk`
- `calcpk`

**Examples**

```r
data(SampleData)
augdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
fitout <- rld(formula = survival::surv(time, delta)~factor(dose)+trt*I(I(dose==3)*trt),
              data = augdata, frailty = TRUE)
contrgroup <- 1
refgroup <- 0
predata <- list(contrgroup, refgroup)
names(predata) <- c("contrgroup", "refgroup")
names(predata$contrgroup) <- c("trt")
names(predata$refgroup) <- c("trt")

VEout <- calcVEt(object = fitout, nexposure = c(10, 10, 2), newdata = predata, CIlevel = 0.95)
summary(VEout)
```
Usage

```
lrtest(model1, model2, TestNu=TRUE, Siglevel=0.05)
```

Arguments

- `model1`: a result of the nested model which is returned by `rld`.
- `model2`: a result of the full model which is returned by `rld`.
- `TestNu`: logic value: If TRUE, the frailty variance parameter will be tested. Otherwise, the regression parameters will be tested. The default is TRUE.
- `Siglevel`: a value: significance level. The default is 0.05.

Details

Under the null hypothesis of frailty variance parameter \( \nu=0 \), the test statistic converges to a mixture of chi-squared distribution. For regression parameters, under the null hypothesis \( \beta=0 \), the test statistic converges to chi-squared distribution. Please refer to Kang et al.(2015) for more details.

Value

- `statistic`: a value: test statistic.
- `df`: a value: degree of freedom.
- `pvalue`: the p-value.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang

References


See Also

`rld`

Examples

```r
#test frailty variance parameter
data(SampleData)
newdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
fitout1 <- rld(formula = survival::Surv(time, delta)-factor(trt)+factor(dose), data = newdata, frailty = FALSE)
fitout2 <- rld(formula = survival::Surv(time, delta)-factor(trt)+factor(dose), data = newdata, frailty = TRUE)
testnu <- lrtest(model1 = fitout1, model2 = fitout2, TestNu=TRUE)
```

## Not run:

```r
#test regression parameters
```
rld

Fit a Discrete-Time Survival Model

Description

This function fits a discrete-time survival model with and without random effects.

Usage

rld(formula, data, na.action, initial=NULL, lower=NULL, upper=NULL, frailty=TRUE)

Arguments

formula a formula object, with the response on the left of a ~ operator, and the terms on the right. The response must be a survival object as returned by Surv function. The terms is a series of terms which specify linear predictors for response.

data a data.frame in which to interpret the variables named in the formula. This augmented data frame can be returned by function transdata.

na.action a function which indicates what should happen when the data contain NAs.

initial a vector of initial values for the paramters to be optimized over. If NULL, the default initial values will be used.

lower a vector of lower bound values for the paramters. If NULL, the default lower bound will be used.

upper a vector of upper bound values for the parameters. If NULL, the default upper bound will be used.

frailty logic value: if TRUE, the discrete-time survival model with random effects will be run. Otherwise it is assumed that there is no random effect. The default is TRUE.

Details

Kang et al. (2015) proposed to use a discrete-time survival model with gamma-distributed random effects and a complementarty log-log link function to model data from repeated low-dose challenge studies, assuming an animal’s risks of infection across challenges are independent of each other conditional on random effects. Please refer to Kang et al.(2015) for more details.
Value

`rld` returns an object of class “rld”. The functions `summary` is used to obtain and print a summary of the results.

- `coefficients`: a vector of parameter estimates.
- `hessian`: the hessian matrix returned from the function `optim`.
- `X`: the design matrix created based on the input formula.
- `VEexpr`: the formula expression on the right of `~` operator.
- `loglikvalue`: the log-likelihood value.
- `call`: the matched call.
- `frailty`: the chosen model.
- `augdata`: the augmented data set.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang

References


See Also

`rld.fit`

Examples

data(SampleData)
newdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))

#interaction between the highest dose level and treatment assignment
#under the discrete-time survival model with random effects

fitout1 <- rld(formula = survival::Surv(time, delta)~factor(dose)+trt+I(1(dose==3)*trt),
   data = newdata, frailty = TRUE)
#summary(fitout1)

## Not run:
#main effects model without random effectsss
ini <- rep(0.5, 4)
lwr <- rep(-Inf, 4)
upr <- rep(Inf, 4)

fitout2 <- rld(formula = survival::Surv(time, delta)~factor(dose)+trt,
   initial = ini, lower = lwr, upper = upr, data = newdata,
   frailty = FALSE)
#summary(fitout2)

## End(Not run)
Description

This function performs power analysis to design a repeated low-dose challenge experiment with a vaccine and a placebo arm.

Usage

```r
rld.design(nsim, nv, np, ndlevel, nexposure, rho, p0, RR,
           method=c("LRT", "log-rank"), Siglevel)
```

Arguments

- `nsim`: a value indicating the number of simulations to run.
- `nv`: a value indicating the number of subjects in vaccine group.
- `np`: a value indicating the number of subjects in placebo group.
- `ndlevel`: a value indicating the number of dose levels.
- `nexposure`: a vector of challenges or exposures for all dose levels.
- `rho`: a value: intracluster correlation between underlying continuous responses.
- `p0`: probability of infection in placebo group at each challenge dose level.
- `RR`: a value: relative risk of vaccine relative to placebo at each challenge dose level.
- `method`: "LRT": likelihood ratio test; "log-rank": log-rank test.
- `Siglevel`: a value indicating significance level.

Details

Users need to specify the parameters of the experiment. The function will generate the data from the discrete-time survival model with random effects. The power is defined as the proportion of rejecting the null hypothesis that treatment has no effect. There are only two groups in the study, i.e. vaccine group and placebo group. There are two types of test available for use, likelihood ratio test and log-rank test. Note that likelihood ratio test takes more simulation time than log-rank test because of model fitting.

Value

- `method`: a character which is either a "LRT" or "log-rank".
- `power`: a value: statistical power.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang
References


Examples

designout <- rldNdesign(nsim = 50, nv = 25, np = 25, ndlevel = 3, nexposure = c(10, 10, 2),
rho = 0.2, p0 = c(0.16, 0.22, 0.27), RR = c(0.3, 0.45, 0.55),
method = "log-rank", Siglevel = 0.05)

---

**rld.fit**

*Discrete-Time Survival Model Fitting Function*

Description

This is the function called by rld that do the actual computation.

Usage

rld.fit(X, C, delta, initial, lower, upper, frailty)

Arguments

- **X**: a design matrix created based on the input formula.
- **C**: a vector containing censoring times.
- **delta**: a vector containing censoring status in which "1" denotes failure, "0" denotes right-censoring.
- **initial**: a vector containing initial values for the parameters to be optimized over.
- **lower**: a vector containing lower bound values for the parameters to be optimized over.
- **upper**: a vector containing upper bound values for the parameters to be optimized over.
- **frailty**: logical value: If TRUE, a discrete-time survival model with random effects will be used.

Details

optim is used to maximize the log-likelihood function. Method "L-BFGS-B" is that of Byrd et. al (1995) which allows box constraints, that is each variable can be given a lower and/or upper bound.

Value

- **coefficients**: parameter estimates.
- **hessian**: hessian matrix.
- **LikFunValue**: log-likelihood value.
Note

Don’t use this function when you are not familiar with the whole computational procedure.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang

References


See Also

rld, optim

Examples

data(SampleData)
newdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
formulaexp <- survival::Surv(time, delta)-factor(dose)+trt+I(I(dose==3)*trt)
designmat <- model.matrix(formulaexp, data = newdata)
time <- SampleData$time
status <- SampleData$delta
inival <- rep(0.5, 6)
lwrval <- c(rep(-Inf, 5), 0.01)
uprval <- rep(Inf, 6)
frailty <- TRUE

rld.fit(X = designmat, C = time, delta = status, initial = inival,
lower = lwrval, upper = uprval, frailty = frailty)

SampleData
Simulated Sample Data for Illustration

Description

This is a simulated data set containing 3 variables:

Usage

data(SampleData)
transdata

Format
A data frame with 50 observations on the following 3 variables.
- time: numeric vector: failure or censoring times, whichever comes first
- delta: numeric vector: censoring status
- trt: numeric vector: vaccination status

Details
The dataset is artificial and used to test out some of the features of rld.

Examples
```r
data(SampleData)
```

---

transdata

Transfer Input Data Frame to Model Fitting Data Frame

Description
This function transfers the original input data frame to required data frame for model fitting.

Usage
```r
transdata(data, ndlevel, nexposure)
```

Arguments
- data: a data frame which must include variables named "time" and "delta".
- ndlevel: a value: number of dose levels.
- nexposure: a vector: number of challenges or exposures for each dose level.

Details
The original data frame from users include the time points when the subjects are right-censored or failed, the censoring status, vaccination status and baseline information. In addition, users must provide dose information including dose level and number of challenges or exposures for each dose level. However, the original data frame cannot be used directly to create design matrix because dose levels are time-dependent. Therefore, this function lists all time points before or at the right-censoring time or failure time for each subject. Then for each subject the function replicates each dose level multiple times according to the number of challenges the subject receives at each dose level. Finally, the function replicates the vaccination status and baseline information and returns a whole data frame.

Value
a data frame containing variables "id", "time", "delta", "dose", vaccination status and baseline information.
Note

The original data frame must have "time" and "delta" variables.

Author(s)

Bin Yao, Ying Huang and Chaeryon Kang

Examples

data(SampleData)
newdata <- transdata(data = SampleData, ndlevel = 3, nexposure = c(10, 10, 2))
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