Package ‘PK’

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all.class

Different generic functions for class PK.

Description

Generic functions for summarizing an object of class PK

Usage

## S3 method for class 'PK'
print(x, digits=max(3,getOption("digits") - 4), ...)

## S3 method for class 'PK'
summary(object, ...)

## S3 method for class 'PK'
plot(x, bygroup=FALSE, col=NULL, pch=NULL, main=NULL, xlab="Time",
     ylab="Concentration", ylim=NULL, xlim=NULL, add=FALSE, ...)

Arguments

x                  An output object of class PK.
digits             Number of significant digits to be printed.
object             An output object of class PK.
bygroup            A logical value indicating whether the plot should highlight the groups.
col                A specification for the default plotting color (default= NULL). See par for more details.
pch                Either an integer specifying a symbol or a single character to be used as the default in plotting points (default= NULL). See par for more details.
main               An overall title for the plot (default= NULL). The default setting produces "Concentration versus time plot".
xlab               A title for the x axis (default= "time").
ylab               A title for the y axis (default= "concentration").
xlim               Numeric vector of length 2, giving the x coordinates range. (default= "NULL").
ylim               Numeric vector of length 2, giving the y coordinates range. (default= "NULL").
add                 A logical value indicating whether to add plot to current plot (default= FALSE).
...                 Further (graphical) arguments to be passed to methods.
Details

print.PK produces a minimal summary of an estimation object from class PK including point estimate, standard error and confidence interval. The confidence interval is the first of "boott", "fieller", "t" or "z" that was originally requested.

summary.PK prints a more detailed summary of an estimation object from class PK. Most notably all confidence intervals originally requested are printed.

plot.PK produces as concentration versus time plot of the data used of an estimation object from class PK.

Value

Screen or graphics output.

Author(s)

Thomas Jaki and Martin J. Wolfsegger

References


See Also

estimator, ci and test
Examples

```r
## serial sampling design: example from Nedelman et al. (1995)
con <- c(2590, 3280, 4900, 7550, 5500, 6650, 2250, 3220, 213, 636)
time <- c(1, 1, 2, 2, 4, 8, 8, 24, 24)

obj <- auc(conc=con, time=time, method=c("z", "t"), design="ssd")
print(obj)
summary(obj)

## serial sampling design: example from Nedelman et al. (1995)
conc.m <- c(391, 396, 649, 1990, 3290, 3820, 844, 1650, 75.7, 288)
conc.f <- c(353, 384, 625, 1410, 1020, 1500, 933, 1030, 0, 80.5)
time <- c(1, 1, 2, 2, 4, 4, 8, 8, 24, 24)

res1 <- auc(conc=conc.m, time=time, method=c("t","z"), design='ssd')
res2 <- auc(conc=conc.f, time=time, method=c("t","z"), design='ssd')

plot(res1, pch=19, ylim=c(0,5000), xlim=c(0,25))
plot(res2, pch=21, col='red', add=TRUE)
legend(x=25, y=5000, xjust=1, pch=c(19,21), col=c('black','red'),
legend=c('Male', 'Female'))

## batch design: example from Jaki and Wolfsegger (2009),
## originally in Holder et al. (1999) using data for call

data(Rats)
data1 <- subset(Rats, Rats$dose==100)
data2 <- subset(Rats, Rats$dose==300)
res1 <- auc(data=data1, method='t', design='batch')
res2 <- auc(data=data2, method='t', design='batch')

plot(res1, col='black', ylim=c(0,8), xlim=c(0,25))
plot(res2, col='red', add=TRUE)
legend(x=0, y=8, xjust=0, lty=1, col=c('black','red'),
legend=c('Dose of 100', 'Dose of 300'))

data3 <- subset(Rats, Rats$dose==100 | Rats$dose==300)
data3$group <- data3$dose
res3 <- auc(data=data3, method='t', design='batch')
plot(res3, bygroup=TRUE)

## complete data design example
## originally in Hand and Crowler (1996)
data(Glucose)
data1 <- subset(Glucose, date==1)
data2 <- subset(Glucose, date==2)
res1 <- auc(conc=data1$conc, time=data1$time, design='complete', method='t')
res2 <- auc(conc=data2$conc, time=data2$time, design='complete', method='t')
plot(res1, pch=19, col='black', ylim=c(0,5))
```
 auc \[ \text{Estimation of confidence intervals for the area under the concentration versus time curve in complete and incomplete data designs} \]

**Description**

Calculation of confidence intervals for an area under the concentration versus time curve (AUC) or for the difference between two AUCs assessed in complete and incomplete data designs.

**Usage**

```r
auc(conc, time, group=NULL, method=c("t", "z", "boott"), alternative=c("two.sided", "less", "greater"), conf.level=0.95, strata=NULL, nsample=1000, design=c("ssd","batch","complete"), data)
```

```r
auc.ssd(conc, time, group=NULL, method=c("t", "z", "boott"), alternative=c("two.sided", "less", "greater"), conf.level=0.95, strata=NULL, nsample=1000, data)
```

```r
auc.batch(conc, time, group=NULL, method=c("t", "z", "boott"), alternative=c("two.sided", "less", "greater"), conf.level=0.95, nsample=1000, data)
```

**Arguments**

- **conc**: Levels of concentrations. For batch designs a list is required, while a vector is expected otherwise.
Time points of concentration assessment. For batch designs a list is required, while a vector is expected otherwise. One time point for each concentration measured needs to be specified.

time

group

A grouping variable (default=NULL). For batch designs a list is required, while a vector is expected otherwise. If specified, a confidence interval for the difference of independent AUCs will be calculated.

group

method

A character string specifying the method for calculation of confidence intervals (default=c("t"", "z", "boott")).

method

alternative

A character string specifying the alternative hypothesis. Possible values are "less", "greater" and "two.sided" (the default).

alternative

conf.level

Confidence level (default=0.95).

conf.level

strata

A vector of one strata variable (default=NULL). Only available for method boott in a serial sampling design.

strata

nsample

Number of bootstrap iterations for method boott (default=1000).

nsample

design

A character string indicating the type of design used. Possible values are "ssd" for a serial sampling design, "batch" for a batch design and "complete" for a complete data design.

design

data

Optional data frame containing variables named as id, conc, time and group.

data

Details

Calculation of confidence intervals for an AUC (from 0 to the last time point) or for the difference between two AUCs for serial sampling, batch and complete data designs. In a serial sampling design only one measurement is available per subject, while in a batch design multiple (but not necessarily all) time points are measured for each subject. In a complete data design measurements are taken for all subjects at all time points. The AUC (from 0 to the last time point) is calculated using the linear trapezoidal rule on the arithmetic means at the different time points.

If group=NULL a confidence interval for an AUC is calculated. If group specifies a factor variable with exactly two levels, a confidence interval for the difference between two independent AUCs is calculated. To obtain confidence intervals for dependent AUCs simply use the difference in concentrations for conc. See the example below.

For serial sampling designs missing data are omitted and unequal sample sizes per time point are allowed. For batch designs missing values are not permitted and at least two subjects are required per batch.

If data is specified the variable names conc, time and group are required and represent the corresponding variables. If design is batch an additional variable id is required to identify the subject.

NOTE: Confidence intervals for AUCs assessed in complete data designs are found using a batch design with one batch based on the asymptotic normal distribution. Conventionally, AUCs are assumed to be log-normal distributed. See the help file auc.complete for some corresponding examples.

Value

An object of the class PK containing the following components:

- est Point estimates.
- CIS Point estimates, standard errors and confidence intervals.
- conc Levels of concentrations.
- conf.level Confidence level.
- design Sampling design used.
- group Grouping variable.
- time Time points measured.

Note

This is a wrapper function for auc.complete, auc.batch and auc.ssd. The function calculates point and interval estimates for AUC (from 0 to the last time point).

Author(s)

Thomas Jaki and Martin J. Wolfsegger

References


See Also

auc.complete, nca, eqv, estimator, ci and test.

Examples

#### serial sampling design:

```r
# example from Bailer (1988)
time <- c(rep(0.4), rep(1.5, 4), rep(3, 4), rep(5, 4), rep(8, 4))
grp1 <- c(0.0658, 0.0320, 0.0338, 0.0438, 0.0059, 0.0038, 0.0084, 0.0088, 0.0000, 0.0017, 0.0028, 0.0055, 0.0000, 0.0037, 0.0000, 0.0000, 0.0000, 0.0000, 0.0000)
grp2 <- c(0.2287, 0.3824, 0.2402, 0.2373, 0.1252, 0.0446, 0.0638, 0.0511, 0.0132, 0.0000, 0.0117, 0.0126, 0.0000, 0.0440, 0.0039, 0.0040, 0.0000, 0.0000, 0.0000)
grp3 <- c(0.4285, 0.5180, 0.3690, 0.5428, 0.0983, 0.0928, 0.1128, 0.1157, 0.0234, 0.0311, 0.0344, 0.0349, 0.0032, 0.0052, 0.0049, 0.0000, 0.0000, 0.0000, 0.0000)
```
```
auc(conc=grp1, time=time, method='z', design='ssd')
auc(conc=grp2, time=time, method='z', design='ssd')
auc(conc=grp3, time=time, method='z', design='ssd')

## function call with data frame using simultaneous confidence intervals based
## on bonferroni adjustment
data <- data.frame(conc=c(grp1, grp2, grp3), time=rep(time, 3),
                  group=c(rep(1, length(grp1)), rep(2, length(grp2)),
                         rep(3, length(grp3))))

auc(subset(data, group==1 | group==2)$conc, subset(data, group==1 | group==2)$time,
     group=subset(data, group==1 | group==2)$group, method=c('z', 't'),
     conf.level=1-0.05/3, design='ssd')

auc(subset(data, group==1 | group==2)$conc, subset(data, group==1 | group==2)$time,
     group=subset(data, group==1 | group==2)$group, method=c('z', 't'),
     conf.level=1-0.05/3, design='ssd')

auc(subset(data, group==2 | group==3)$conc, subset(data, group==2 | group==3)$time,
     group=subset(data, group==2 | group==3)$group, method=c('z', 't'),
     conf.level=1-0.05/3, design='ssd')

## example from Nedelmann et al. (1995)
data(CPI975)
data <- CPI975[dose>=30 ,]

auc(data=subset(data, sex=='m' & dose==30), method=c('z', 't'), design='ssd')
auc(data=subset(data, sex=='f' & dose==30), method=c('z', 't'), design='ssd')

auc(data=subset(data, sex=='m' & dose==100), method=c('z', 't'), design='ssd')
auc(data=subset(data, sex=='f' & dose==100), method=c('z', 't'), design='ssd')

## comparing dose levels
data$concadj <- data$conc / data$dose
data.100 <- subset(data, dose==100)
data.30  <- subset(data, dose==30)
res.100 <- auc(conc=data.30$concadj, time=data.30$time, method='t',
               design='ssd')
res.30  <- auc(conc=data.100$concadj, time=data.100$time, method='t',
               design='ssd')
plot(res.30, ylim=c(0, 140), xlim=c(0,25), pch=19, ylab='Dose-normalized concentration',
     main='Comparison of doses')
plot(res.100, col='red', pch=21, add=TRUE)
legend(x=25, y=140, xjust=1, lty=1, col=c('black','red'),
       legend=c('Dose of 30', 'Dose of 100'))

res <- auc(conc=data$concadj, time=data$time, group=data$dose, method=c('t','z'),
            design='ssd')
print(res)
summary(res)

## comparing two dose level using stratified resampling per gender
## caution this might take a few minutes
set.seed(260151)
```
auc(conc=data$conca, time=data$time, group=data$dose, method='boott',
    strata=data$sex, design='ssd', nsample=500)

### batch design:
# a batch design example from Holder et al. (1999).
data(Rats)
data <- subset(Rats,Rats$dose==100)

# two-sided CI: data call
auc(data=data,method=c('z', 't'), design='batch')
# one-sided CI: data call
auc(data=data,method=c('z', 't'), alternative="less", design='batch')

## difference of two AUCs in batch design from Jaki and Wolfsegger (2009),
## originally in Holder et al. (1999).
data <- subset(Rats,Rats$dose==100 | Rats$dose==300 )
data$group <- data$dose
data$conc <- data$conc / data$dose

data call
res1 <- auc(data=subset(data, dose==100), method='z', design='batch')
res2 <- auc(data=subset(data, dose==300), method='z', design='batch')
plot(res1, col='black', ylim=c(0,0.06), xlim=c(0,25), ylab='Dose-normalized concentration',
     main='Comparison of doses')
plot(res2, col='red', add=TRUE)
legend(x=0, y=0.06, lty=1, col=c('black','red'),
      legend=c('Dose of 100', 'Dose of 300'))

auc(data=data, method='z', design='batch')

## difference of two dependent AUCs in a batch design from Wolfsegger and Jaki (2009)
conc <- list(batch1=c(0.46, 0.2, 0.1, 0.1, 1.49, 1.22, 1.27, 0.53, 0.51, 0.36, 0.44),
             batch2=c(1.51, 1.80, 2.52, 1.91, 0.88, 0.66, 0.96, 0.48),
             batch3=c(1.52, 1.46, 2.55, 1.04, 0.54, 0.61, 0.55, 0.27))
time <- list(batch1=c(0,0,0,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1),
             batch2=c(5/60, 5/60, 5/60, 5/60, 4,4,4),
             batch3=c(0.5, 0.5, 0.5, 0.5, 0.5, 0.5, 0.5))
group <- list(batch1=c(1,1,2,2,1,1,2,2,1,1,2,2), batch2=c(1,1,2,2,1,1,2,2),
              batch3=c(1,1,2,2,1,1,2,2))

# find difference in concentration and the corresponding times
dconc <- NULL
dtime <- NULL
gbps <- unique(unlist(group))
B <- length(conc)
for(i in 1:B){
    dconc[i] <- conc[[i]][group[i]]-gps[i] - conc[[i]][group[[i]]==gps[[2]]]
dtime[i] <- time[[i]][group[[i]]==gps[[1]]]
}

names(dconc) <- names(conc)

auc(conc=dconc, time=dtime, group=FALSE, method="t", conf.level=0.90, design="batch")
## Additional Code Snippet

```r
## example with overlapping batches (Treatment A in Example of Jaki & Wolfsegger 2012)
conc <- list(batch1=c(0,0,0,0, 69.7,37.2,213,64.1, 167,306,799,406, 602,758,987,627, 1023,1124,1381,880, 1388,1374,1756,1120, 1481,1129,1665,1998, 1346,1043,1529,1481, 658,576,772,851, 336,325,461,492, 84,75.9,82.6,116),
batch2=c(0,0,0, 29.2,55.9,112.2, 145,153,169, 282,420,532, 727,1033,759, 1360,1388,1425, 1939,1279,1318, 1614,1205,1542, 1238,1113,1386, 648,770,786, 392,438,511, 77.3,50.1,97.9)),

time <- list(batch1=rep(c(0,0.5,0.75,1,1.5,2,3,4,8,12,24), each=4),
batch2=rep(c(0,0.25,0.5,0.75,1,1.5,2,3,4,8,12,24), each=3)),

auc.batch(conc, time, method=c("t","z"), conf.level=0.9)

## example from Gibaldi and Perrier (1982, page 430) for an individual AUC
time <- c(0, 0.165, 0.5, 1, 1.5, 3, 5, 7.5, 10)
conc <- c(0, 65.03, 28.69, 10.04, 4.93, 2.29, 1.36, 0.71, 0.38)
auc(conc=conc, time=time, design="complete")

## data Indometh
require(datasets)
Indometh$id <- as.character(Indometh$Subject)
Indometh <- Indometh[order(Indometh$id, Indometh$time),]
Indometh <- Indometh[order(Indometh$time),]
res <- auc.complete(conc=Indometh$conc, time=Indometh$time, method='t')
plot(res)

## more informative plot
split.screen(c(1,2))
screen(1)
plot(x=c(0,8), y=c(0,3), type='n', main='Observed concentration time-profiles',
xlab='Time', ylab='Concentration', las=1)
for(i in unique(Indometh$Subject)) {
  temp <- subset(Indometh, Subject==i)
  points(x=temp$time, y=temp$conc, type='b')
}

screen(2)
plot(x=c(0,8), y=c(0.01, 9), type='n', main='Log-linear concentration time-profiles',
xlab='Time', ylab='Log of concentration', xaxt='n', log='y')
axis(side=2, at=c(0.01, 0.1, 1, 10), tcl=-0.2, labels=FALSE)
axis(side=2, at=c(0.1, 1, 10), tcl=-0.2, labels=FALSE)
axis(side=2, at=c(1, 10, 1), tcl=-0.2, labels=FALSE)
for(i in unique(Indometh$Subject)) {
  temp <- subset(Indometh, Subject==i)
  points(x=temp$time, y=temp$conc, type='b')
}
close.screen(all = TRUE)
```
auc.complete

Confidence intervals for the area under the concentration versus time curve in complete data designs

Description

Examples to find confidence intervals for the area under the concentration versus time curve (AUC) in complete data designs.

Usage

```
auc.complete(conc, time, group=NULL, method=c("t", "z", "boott"),
             alternative=c("two.sided", "less", "greater"),
             conf.level=0.95, nsample=1000, data)
```

Arguments

- **conc**: Levels of concentrations as a vector.
- **time**: Time points of concentration assessment as a vector. One time point for each concentration measured needs to be specified.
- **group**: A grouping variable as a vector (default=NULL). If specified, a confidence interval for the difference of independent AUCs will be calculated.
- **method**: A character string specifying the method for calculation of confidence intervals (default=c("t", "z", "boott")).
- **alternative**: A character string specifying the alternative hypothesis. Possible values are "less", "greater" and "two.sided" (the default).
- **conf.level**: Confidence level (default=0.95).
- **nsample**: Number of bootstrap iterations for method boott (default=1000).
- **data**: Optional data frame containing variables named as conc, time and group.

Details

This function computes confidence intervals for an AUC (from 0 to the last time point) or for the difference between two AUCs in complete data designs.

To compute confidence intervals in complete data designs the design is treated as a batch design with a single batch. More information can therefore be found under auc. A corresponding reminder message is produced if confidence intervals can be computed, ie when at least 2 measurements at each time point are available.

The above approach, though correct, is often inefficient and so we will illustrate alternative methods in this help file. A general implementation is not provided as the most efficient analysis strongly depends on the context. The interested reader is refered to chapter 8 of Cawello (2003).
If data is specified the variable names `conc`, `time` and `group` are required and represent the corresponding variables.

**Value**

An object of the class PK containing the following components:

- 
  - `est` Point estimates.
  - `cis` Point estimates, standard errors and confidence intervals.
  - `conc` Levels of concentrations.
  - `conf.level` Confidence level.
  - `design` Sampling design used.
  - `group` Grouping variable.
  - `time` Time points measured.

**Author(s)**

Thomas Jaki and Martin Wolfsegger

**References**


**See Also**

`auc`, `estimator`, `ci` and `test`

**Examples**

```r
## example from Gibaldi and Perrier (1982, page 436) for an individual AUC
time <- c(0, 0.165, 0.5, 1, 1.5, 3, 5, 7.5, 10)
conc <- c(0, 65.03, 28.69, 10.04, 4.93, 2.29, 1.36, 0.71, 0.38)
auc.complete(conc=conc, time=time)

## dataset Indometh of package datasets
## calculate individual AUCs
require(datasets)
row <- 1
res <- data.frame(matrix(nrow=length(unique(Indometh$Subject)), ncol=2))
colnames(res) <- c("id", "auc")
```
for(i in unique(Indometh$Subject)){
  temp <- subset(Indometh, i==Subject)
  res[row, 1] <- i
  res[row, 2] <- auc.complete(data=temp[,c("conc","time")])$est[1,1]
  row <- row + 1
}
print(res)

# function to get geometric mean and corresponding CI
gm.ci <- function(x, conf.level=0.95){
  res <- t.test(x=log(x), conf.level=conf.level)
  out <- data.frame(gm=as.double(exp(res$estimate)),
                   lower=exp(res$conf.int[1]),
                   upper=exp(res$conf.int[2]))
  return(out)
}

# geometric mean and corresponding CI: assuming log-normal distributed AUCs
gm.ci(res[,2], conf.level=0.95)

# arithmetic mean and corresponding CI: assuming normal distributed AUCs
# or at least asymptotic normal distributed arithmetic mean
t.test(x=res[,2], conf.level=0.95)

# alternatively: function auc.complete
set.seed(300874)
Indometh$id <- as.character(Indometh$Subject)
Indometh <- Indometh[order(Indometh$id, Indometh$time),]
Indometh <- Indometh[order(Indometh$time),]
auc.complete(conc=Indometh$conc, time=Indometh$time, method=c("t"))

## example for comparing AUCs assessed in a repeated complete data design
## (dataset: Glucose)
## calculate individual AUCs
data(Glucose)
res <- data.frame(matrix(nrow=length(unique(Glucose$id)) x 2, ncol=3))
colnames(res) <- c('id', 'date', 'auc')
row <- 1
for(i in unique(Glucose$id)){
  for(j in unique(Glucose$date)){
    temp <- subset(Glucose, id==i & date==j)
    res[row, c(1,2)] <- c(i,j)
    res[row, 3] <- auc.complete(data=temp[,c("conc","time")])$est[1,1]
    row <- row + 1
  }
}
res <- res[order(res$id, res$date),]
print(res)

# assuming log-normally distributed AUCs
# geometric means and corresponding two-sided CIs per date
tapply(res$auc, res$date, gm.ci)
biexp

Two-phase half-life estimation by biexponential model

Description

Estimation of initial and terminal half-life by fitting a biexponential model.

Usage

```
biexp(conc, time, log.scale=FALSE, tol=1E-9, maxit=500)
```

Arguments

- **conc**: Levels of concentrations as a vector.
- **time**: Time points of concentration assessment as a vector. One time point for each concentration measured needs to be specified.
- **log.scale**: Logical value indicating whether fitting is performed on the observed or log-scale (default=FALSE).
- **tol**: Relative error tolerance (default=1E-9).
- **maxit**: Maximum number of iterations (default=500).

Details

Estimation of initial and terminal half-life using the biexponential \( y = a_1 \exp(-b_1 x) + a_2 \exp(-b_2 x) \) model with a parameterization to ensure \( b_1 > b_2 > 0 \) fitted by the least squares criteria with function `optim` of package `base` with method "Nelder-Mead". Curve peeling (Foss, 1969) is used get start values for nonlinear model fitting. When no adequate starting values are determined by curve peeling, a single exponential model is fitted with starting values obtained from an OLS regression on log transformed values with a parameterization to ensure a slope > 0.

Fitting on the log-scale is based on the transform-both-sides approach described for example in chapter 4 of Bonate (2006) which is useful for some error distributions. An additional discussion regarding weighting schemes can be found in Gabrielsson and Weiner (2000, pages 368-374).
**Value**

A list of S3 class "halflife" containing the following components:

- **parms**: half-life and model estimates.
- **time**: time points of concentration assessments.
- **conc**: levels of concentrations.
- **method**: "biexp".

**Note**

Records including missing values and values below or equal to zero are omitted.

**Author(s)**

Martin J. Wolfsegger and Thomas Jaki

**References**


**See Also**

lee
Examples

### example from Pinheiro J.C. and Bates D.M. (2000, page 279)
### dataset Indometh of package datasets

```r
require(datasets)
data <- subset(Indometh, Subject==2)
time <- data$time
conc <- data$conc

# fitting on observed and log-scale
res.obs <- biexp(conc=conc, time=time, log.scale=FALSE)
res.log <- biexp(conc=conc, time=time, log.scale=TRUE)

print(res.obs$parms)
print(res.log$parms)

plot(res.obs, ylim=c(0,5), xlim=c(0, max(time)), las=1)
plot(res.log, ylim=c(0,5), xlim=c(0, max(time)), las=1, add=TRUE, lty=2)
legend(x=0, y=5, lty=c(1,2), legend=c("fitted on observed scale", "fitted on log-scale"))

# get residuals using function nls with tol=Inf
parms.obs <- list(a1=res.obs$parms[3,1], b1=res.obs$parms[2,1],
b2=res.obs$parms[2,2])
parms.log <- list(a1=res.log$parms[3,1], b1=res.log$parms[2,1],
b2=res.log$parms[2,2])

mod.obs <- nls(conc ~ a1*exp(-b1*time) + a2*exp(-b2*time), start=parms.obs,
control=nls.control(tol=Inf))
mod.log <- nls(conc ~ a1*exp(-b1*time) + a2*exp(-b2*time), start=parms.log,
control=nls.control(tol=Inf))

# identical estimates to mod.log but different SEs
summary(nls(log(conc)-log(a1*exp(-b1*time) + a2*exp(-b2*time)), start=parms.log,
control=nls.control(tol=Inf)))

# different approach using weighted least squares (WLS) in nls
mod.ols <- nls(conc ~ a1*exp(-b1*time) + a2*exp(-b2*time), start=parms.obs)
mod.wls1 <- nls(conc ~ a1*exp(-b1*time) + a2*exp(-b2*time), start=parms.obs,
weight=1/predict(mod.ols)^2)
mod.wls2 <- nls(conc ~ a1*exp(-b1*time) + a2*exp(-b2*time), start=parms.obs,
weight=1/predict(mod.ols)^2)

split.screen(c(2,2))
screen(1)
plot(ylim=c(-0.35,0.35), y=resid(mod.obs), x=predict(mod.obs), las=1,
main='Fitted using biexp on observed scale', xlab='Predicted', ylab='Residual')
abline(h=0)
screen(2)
plot(ylim=c(-0.35,0.35), y=resid(mod.log), x=predict(mod.log), las=1,
main='Fitted using biexp on log-scale', xlab='Predicted', ylab='Residual')
abline(h=0)
screen(3)
plot(ylim=c(-0.35,0.35), y=resid(mod.wls1), x=predict(mod.wls1), las=1,
main='Fitted using biexp on observed scale', xlab='Predicted', ylab='Residual')
abline(h=0)
screen(4)
plot(ylim=c(-0.35,0.35), y=resid(mod.wls2), x=predict(mod.wls2), las=1,
main='Fitted using biexp on log-scale', xlab='Predicted', ylab='Residual')
abline(h=0)
```
main='Fitted using nls with weights 1/predict(mod.ols)^1', xlab='Predicted', ylab='Residual')
abline(h=0)
screen(4)
plot(ylim=c(-0.35,0.35), y=resid(mod.wls2), x=predict(mod.wls2), las=1,
main='Fitted using nls with weights 1/predict(mod.ols)^2', xlab='Predicted', ylab='Residual')
abline(h=0)
close.screen(all.screens=TRUE)

### example for a serial sampling data design from Wolfsegger and Jaki (2009)
conc <- c(2.01, 2.85, 2.43, 0.85, 1.00, 0.91, 0.46, 0.35, 0.63, 0.39, 0.32,
0.45, 0.11, 0.18, 0.19, 0.08, 0.09, 0.06)
time <- c(rep(5/60,3), rep(3,3), rep(6,3), rep(9,3), rep(16,3), rep(24,3))
res.biexp1 <- biexp(conc=conc, time=time, log=TRUE)
res.biexp2 <- biexp(conc=conc, time=time, log=FALSE)
print(res.biexp1$parms)
print(res.biexp2$parms)
split.screen(c(1,2))
screen(1)
plot(x=c(0,25), y=c(0,3), type='n', las=1,
ylab='Plasma concentration (IU/mL)', xlab='Time (hours)'
points(x=time, y=conc, pch=21)
plot(res.biexp1, pch=NA, add=TRUE, lty=1)
plot(res.biexp2, pch=NA, add=TRUE, lty=2)
legend(x=25, y=3, xjust=1, col=c('black', 'black'), lty=c(1,2),
title='Nonlinear fitting with function biexp:',
legend=c('option: log=TRUE', 'option: log=FALSE'))
close.screen(1)
screen(2)
plot(x=c(0,25), y=c(0.01, 10), type='n', log='y', yaxt='n',
ylab='Plasma concentration (IU/mL)', xlab='Time (hours)'
axis(side=2, at=c(0.01, 0.1, 1, 10), labels=c('0.01', '0.1', '1', '10'), las=1)
axis(side=2, at=seq(2.9,1), tcl=-0.25, labels=FALSE)
axis(side=2, at=seq(0.2,0.9,0.1), tcl=-0.25, labels=FALSE)
axis(side=2, at=seq(0.02,0.09,0.01), tcl=-0.25, labels=FALSE)
points(x=time, y=conc, pch=21)
plot(res.biexp1, pch=NA, add=TRUE, lty=1)
plot(res.biexp2, pch=NA, add=TRUE, lty=2)
legend(x=25, y=10, xjust=1, col=c('black', 'black'), lty=c(1,2),
title='Nonlinear fitting with function biexp:',
legend=c('option: log=TRUE', 'option: log=FALSE'))
close.screen(all.screens=TRUE)

### example from Gabrielsson and Weiner (2000, page 743)
### endogenous concentration is assumed to be constant over time
dose <- 36630
time <- c(-1, 0.167E-01, 0.1167, 0.1670, 0.25, 0.583, 0.8330, 1.083, 1.583, 2.083, 4.083, 8.083,
12, 23.5, 24.25, 26.75, 32)
conc <- c(20.34, 3683, 884.7, 481.1, 215.6, 114, 95.8, 87.89, 60.19, 60.17, 34.89, 20.99, 20.54,
```r
19.28, 18.18, 19.39, 22.72)
data <- data.frame(conc, time)

### get starting values using function biexp using naive adjustment for endogenous concentration
### by subtraction of pre-value
data$concadj <- data$conc - data$conc[1]
data$concadj[min(which(data$concadj<0)); nrow(data)] <- NA
res.biexp <- biexp(conc=data$concadj[-1], time=data$time[-1],$parms
start <- list(a1=res.biexp[3,1], k1=res.biexp[2,1], a2=res.biexp[3,2], k2=res.biexp[2,2])

### specify indicator variable enabling inclusion of pre-dose concentration for fitting
data$i1 <- ifelse(data$time < 0, 1, 0)
data$i2 <- ifelse(data$time < 0, 0, 1)

### assuming constant absolute error: ordinary least squares
mod.ols <- nls(conc ~ i1*base + i2*(base + a1*exp(-k1*time) + a2*exp(-k2*time)),
               start=c(base=20.34, start), data=data, trace=TRUE)

### assuming constant relative error (i.e. proportional error - weight of 2): weighted least
### squares
mod.wls <- nls(conc ~ i1*base + i2*(base + a1*exp(-k1*time) + a2*exp(-k2*time)),
               start=c(base=20.34, start), data=data, weight=1/predict(mod.ols)^2, trace=TRUE)

### assuming constant relative error (i.e. proportional error - weight of 2): iteratively
### re-weighted least squares
mod.irwls <- mod.wls
for(i in 1:10){
  print(as.vector(coef(mod.irwls)))
  mod.irwls <- nls(conc ~ i1*base + i2*(base + a1*exp(-k1*time) + a2*exp(-k2*time)),
                   start=c(base=20.34, start), data=data, weight=1/predict(mod.irwls)^2)
}
summary(mod.ols)
summary(mod.wls)
summary(mod.irwls)

newdata <- data.frame(time=seq(0, 32, 0.01))
newdata$i1 <- ifelse(newdata$time < 0, 1, 0)
newdata$i2 <- ifelse(newdata$time < 0, 0, 1)
plot(conc ~ time, data=data, ylim=c(10, 1E4), log='y', xlab='Time (hours)', ylab='Log of concentration (pmol/L)'
     axis(side=2, at=c(10, 100, 1000, 10000), las=1)
axis(side=2, at=seq(1E1, 1E2, 1E1), tcl=0.25, labels=FALSE)
axis(side=2, at=seq(1E2, 1E3, 1E2), tcl=0.25, labels=FALSE)
axis(side=2, at=seq(1E3, 1E4, 1E3), tcl=0.25, labels=FALSE)
points(x=newdata$time, y=predict(mod.irwls, newdata), type='l')

### get total clearance (cls), inter-compartmental distribution (cld), and volume of distributions
### from macro constant parametrization according to Gabrielsson and Weiner (2000)
parm <- coef(mod.wls)[-1]

### get micro constants
```
# turnover model to account for endogenous baseline according to Gabrielsson and Weiner
# using a biexponential (i.e. two-compartment) model parametrized in terms of clearance

## Not run: require(rgenoud)
require(deSolve)

k <- 2  # assuming proportional error - weighting in function objfun

## increase values of popNsize and maxNgeneration to get better starting values
## values of 1P are used for illustration purpose only
options(warn = -1) # omit warning when hard maximum limit is hit
options(warn = 0) # set back to default

## get cls, cld, vc, and vt
vc <- as.double(dose / (parm[1] + parm[2]))
cld <- k12*vc
vt <- cld / k21
print(c(cls, cld, vc, vt))

# grid search to get starting values for Nelder-Mead
# increase values of pop.size and max.generation to get better starting values
# values of 10 are used for illustration purpose only
options(warn = -1) # omit warning when hard maximum limit is hit

gen <- genoud(objfun, nvars=5, max=FALSE, pop.size=10, max.generation=10,
  starting.value=c(1500, cls, cld, vc, vt), BFGS=FALSE,
  print.level=1, boundary.enforcement=2,
  Domains=matrix(c(0,0,0,0,0,1E4,1E3,1E3,1E3,1E3,1E3,1E3),5,2),
  MemoryMatrix=TRUE)

options(warn = 0) # set back to default

opt <- optim(gen$par, objfun, method="Nelder-Mead")

trn.wls <- nls(conc ~ modfun(time, synt, cls, cld, vc, vt), data=data,
  start=list(synt=opt$par[1], cls=opt$par[2], cld=opt$par[3], vc=opt$par[4],
  vt=opt$par[5]),

trn.wls <- nls(conc ~ modfun(time, synt, cls, cld, vc, vt), data=data,
  start=list(synt=opt$par[1], cls=opt$par[2], cld=opt$par[3], vc=opt$par[4],
  vt=opt$par[5]),
Function to extract confidence interval(s)

Description

Generic function that extracts the confidence interval(s) of an object of class PK.

Usage

```r
ci(obj, method=NULL)
```

Arguments

- `obj`: An output object of class PK.
- `method`: A character string specifying the method of the confidence interval. If NULL (default) all intervals are returned.

Details

Generic function to allow easy extraction of confidence intervals.

Value

A matrix containing confidence interval bounds.

Author(s)

Thomas Jaki

References


See Also

`estimator` and `test`
Examples

```r
# Example from Nedelman et al. (1995)
conc <- c(2790, 3280, 4980, 7550, 5500, 6650, 2250, 3220, 213, 636)
time <- c(1, 1, 2, 2, 4, 4, 8, 8, 24, 24)

obj <- auc(conc=conc, time=time, method=c("z", "t"), design="ssd")

## all requested ci's
ci(obj)

## a specific ci
ci(obj, method="t")
```

**CPI975**

*Plasma levels of CPI975 in rats following a single oral dose*

---

**Description**

The CPI975 data frame has 60 rows and 4 columns.

**Format**

This data frame contains the following columns:

- **conc** a numeric vector giving the measured plasma level (microgram/mL).
- **time** a numeric vector giving the time since administration (hours).
- **sex** a factor indicating the gender of the rat.
- **dose** a numeric vector indicating the dose administrated (mg/kg).

**Details**

Nedelman *et al.* (1995). Table 2 describes serial sampling design were the plasma levels are measured at 5 time points over 24 hours for 10 rats. The same experiment was repeated with different oral dosages and gender.

**Source**

Bioequivalence between AUCs

Description

Confidence intervals for the ratio of independent or dependent area under the concentration versus time curves (AUCs) to the last time point.

Usage

```r
eqv(conc, time, group, dependent=FALSE, method=c("fieller", "z", "boott"),
    conf.level=0.90, strata=NULL, nsample=1000,
    design=c("ssd","batch","complete"), data)

eqv.ssd(conc, time, group, dependent=FALSE, method=c("fieller", "z", "boott"),
    conf.level=0.90, strata=NULL, nsample=1000, data)

eqv.batch(conc, time, group, dependent=FALSE,
    method=c("fieller", "z", "boott"),
    conf.level=0.90, nsample=1000, data)

eqv.complete(conc, time, group, dependent=FALSE,
    method=c("fieller", "z", "boott"),
    conf.level=0.90, nsample=1000, data)
```

Arguments

- **conc**: Levels of concentrations. For batch designs a list is required, while a vector is expected otherwise.
- **time**: Time points of concentration assessment. For batch designs a list is required, while a vector is expected otherwise. One time point for each concentration measured needs to be specified.
- **group**: A grouping variable. For batch designs a list is required, while a vector is expected otherwise.
- **dependent**: Logical variable indicating if concentrations are measured on the same subjects for both AUCs (default=FALSE).
- **method**: A character string specifying the method for calculation of confidence intervals (default=c("fieller", "z", "boott").
- **conf.level**: Confidence level (default=0.90).
- **strata**: A vector of one strata variable (default=NULL). Only available for method boott in a serial sampling design.
- **nsample**: Number of bootstrap iterations for method boott (default=1000).
- **design**: A character string indicating the type of design used. Possible values are ssd (the default) for a serial sampling design, batch for a batch design and complete for a complete data design.
- **data**: Optional data frame containing variables named as id, conc, time and group.
Details

Calculation of confidence intervals for the ratio of (independent or dependent) AUCs (from 0 to the last time point) for serial sampling, batch and complete data designs. In a serial sampling design only one measurement is available per subject, while in a batch design multiple time points are measured for each subject. In a complete data design measurements are taken for all subjects at all time points. The AUC (from 0 to the last time point) is calculated using the linear trapezoidal rule on the arithmetic means at the different time points.

The estimation for the complete data design is done by treating the complete data design as a batch design with a single batch. This approach, though correct, is often inefficient. A general implementation is not provided as the most efficient analysis strongly depends on the context. The interested reader is referred to chapter 8 of Cawello (2003) while some examples can be found under auc.complete.

dependent specifies if the AUCs are dependent, that is measured on the same subjects. If FALSE, the intervals are based on the method of Jaki et al. (2009) for the serial sampling design and on Jaki et al. (in press) for the batch design. For dependent AUCs the method of Wolfsegger and Jaki (in press), which assumes that animals, batches and time points are equal for both AUCs, is used. Note that the option dependent is not used in serial sampling designs as by definition only one sample is obtained per subject then.

The fieller method is based on Fieller’s theorem (1954) which uses the asymptotic standard errors of the individual AUCs and a critical value from a t-distribution with Satterthwaite’s approximation (1946) to the degrees of freedom for calculation of confidence intervals. The z method is based on the limit distribution for the ratio using the critical value from a normal distribution for calculation of confidence intervals.

The boott method uses the asymptotic standard errors of the ratio of two AUCs while the critical value is obtained by the bootstrap-t approach and follows the idea discussed in the context of serial sampling designs in Jaki T. et al. (2009). An equivalent approach is used in batch designs as well. Using boott an additional strata variable for bootstrapping can be specified in serial sampling designs.

If data is specified the variable names conc, time and group are required and represent the corresponding variables. If design is batch an additional variable id is required to identify the subject.

Value

An object of the class PK containing the following components:

est Point estimates.
CIs
conc
cnf.level
design
group
time

Point estimates, standard errors and confidence intervals.
Levels of concentrations.
Confidence level.
Sampling design used.
Grouping variable.
Time points measured.

Note
This is a wrapper function for eqv.complete, eqv.batch and eqv.ssd. The function calculates point and interval estimates for the ratio of AUCs (from 0 to the last time point).

Author(s)
Thomas Jaki

References


**See Also**

`auc`, `estimator`, `ci` and `test`.

**Examples**

```r
## example of a serial sampling design from Nedelman et al. (1995)
data(CPI975)
data <- subset(CPI975, dose>=30)
data$concadj <- data$conc / data$dose

# fieller and z-interval for ratio of dose-normalized AUCs
eqv(conc=data$concadj, time=data$time, group=data$dose, method=c("z","fieller"), design="ssd")

# bootstrap-t interval for ratio of dose-normalized AUCs stratified for sex
set.seed(310578)
eqv(conc=data$concadj, time=data$time, group=data$dose, method="boott", strata=data$sex, nsample=500, design="ssd")

## Example of an independent batch design from Yeh (1990)
conc <- list(batch1=c(0,0,0,0,0,0, 4.690,2.070,6.450,0.1,0.852,0.136, 4.690,4.060,6.450,0.531,1.2,0.607),
  batch2=c(4,1.3,3.2,0.074,0.164,0.267, 6.68,3.83,6.08,0.669,1.21,0.878, 8.13,9.54,6.29,0.923,1.65,1.04),
  batch3=c(9.360,13.5,48,1.090,1.370,1.430, 5.180,5.180,2.79,0.804,1.47,1.26, 1.060,2.15,0.827,0.217,0.42,0.35))
time <- list(batch1=c(rep(0,6),rep(1,6),rep(4,6)),
  batch2=c(rep(0.5,6),rep(2,6),rep(6,6)),
  batch3=c(rep(8,6),rep(12,6),rep(24,6)))
group <- list(batch1=rep(c(1,2),each=3),3),
  batch2=rep(c(1,2),each=3),3),
  batch3=rep(c(1,2),each=3),3))
eqv(conc=conc, time=time, group=group, dependent=FALSE, method=c("fieller"), conf.level=0.90, design="batch")

## example of independent batch data with overlapping batches
 estimator

## Description

Generic function that extracts the point estimate(s) of an object of class PK.

---

eqv(conc=conc, time=time, group=group, dependent=FALSE, method=c("fieller"), conf.level=0.90, design="batch")

eqv(conc=conc, time=time, group=group, dependent=TRUE, method=c("fieller", "z"), conf.level=0.90, design="complete")
Usage

```r
estimator(obj, se=FALSE)
```  
Arguments

- `obj` An output object of class PK.
- `se` Logical variable indicating if the standard error should be provided as well (default=FALSE).

Details

Generic function to allow easy extraction of point estimates.

Value

A matrix containing the point estimate(s) and optionally the standard error(s).

Author(s)

Thomas Jaki

References


See Also

`ci` and `test`

Examples

```r
# Example from Nedelman et al. (1995)
conc <- c(2790, 3280, 4980, 7550, 5500, 6650, 2250, 3220, 213, 636)
time <- c(1, 1, 2, 2, 4, 4, 8, 8, 24, 24)

obj <- auc(conc=conc, time=time, method=c('z', 't'), design='ssd')
estimator(obj, TRUE)
```
**Glucose**

*Baseline adjusted glucose levels following alcohol ingestion*

---

**Description**

The Glucose data frame has 196 rows and 4 columns. The dataset is originally in package nlme as Glucose2.

**Format**

This data frame contains the following columns:

- **id**: a factor with levels 1 to 7 identifying the subject whose glucose level is measured.
- **date**: a factor with levels 1 2 indicating the occasion in which the experiment was conducted.
- **time**: a numeric vector giving the time since alcohol ingestion (in min/10).
- **conc**: a numeric vector giving the blood glucose level (in mg/dl) adjusted for baseline.

**Details**

Hand and Crowder (Table A.14, pp. 180-181, 1996) describe data on the blood glucose levels measured at 14 time points over 5 hours for 7 volunteers who took alcohol at time 0. The same experiment was repeated on a second date with the same subjects but with a dietary additive used for all subjects.

Dataset was corrected for baseline using the following code:

```r
## dataset Glucose2 of package nlme
require(nlme)
Glucose2 <- Glucose2[order(Glucose2$Subject, Glucose2$Date, Glucose2$Time),]
## adjust for pre-infusion levels measured at time points -1 and 0
data <- NULL
for(i in unique(Glucose2$Subject)){
  for(j in unique(Glucose2$Date)){
    temp <- subset(Glucose2, Subject==i & Date==j)
    temp$Conc <- temp$glucose - mean(c(temp$glucose[1], temp$glucose[2]))
    temp$Conc <- ifelse(temp$Conc < 0 | temp$Time <= 0, 0, temp$Conc)
    ## handle intermediate values > 0
    index1 <- which.max(temp$Conc)
    index2 <- which.min(temp$Conc[-c(1:index1)]) + index1
    if(temp$Conc[index2]==0){temp$Conc[c(index2:nrow(temp))] <- 0}
    data <- rbind(data,temp)
  }
}
Glucose <- subset(data, Time >= 0,
  select=c('Subject', 'Date', 'Time', 'Conc'))
names(Glucose) <- c("id","date","time","conc")
```
Two-phase half-life estimation by linear fitting

Description

Estimation of initial and terminal half-life by two-phase linear regression fitting.

Usage

```r
lee(conc, time, points=3, method=c("ols", "lad", "hub", "npr"), lt=TRUE)
```

Arguments

- `conc` Levels of concentrations.
- `time` Time points of concentration assessment.
- `points` Minimum number of data points in the terminal phase (default=3).
- `method` Method of model fitting (default=ols).
- `lt` Logical value indicating whether requesting a longer terminal than initial half-life (default=TRUE).

Details

Estimation of initial and terminal half-life based on the method of Lee et al. (1990). This method uses a two-phase linear regression approach separate the model into two straight lines based on the selection of the log10 transformed concentration values. For two-phase models the initial and terminal half-lives were determined from the slopes of the regression lines. If a single-phase model is selected by this method, the corresponding half-life is utilized as both initial and terminal phase half-life. Half-life is determined only for decreasing initial and terminal phases.

The method ols uses the ordinary least squares regression (OLS) to fit regression lines.

The method lad uses the absolute deviation regression (LAD) to fit regression lines by using the algorithm as described in Birkes and Dodge (chapter 4, 1993) for calculation of regression estimates.

The method hub uses the Huber M regression to fit regression lines. Huber M-estimates are calculated by non-linear estimation using the function optim, where OLS regression parameters are
used as starting values. The function that is minimized involved $k = 1.5 \times 1.483 \times \text{MAD}$, where MAD is defined as the median of absolute deviation of residuals obtained by a least absolute deviation (LAD) regression based on the observed data. The initial value of MAD is used and not updated during iterations (Holland and Welsch, 1977).

The method $npr$ uses the nonparametric regression to fit regression lines by using the algorithm as described in Birkes and Dodge (chapter 6, 1993) for calculation of regression estimates.

The selection criteria for the best tuple of regression lines is the sum of squared residuals for the $ols$ method, the sum of Huber $M$ residuals for the $hub$ method, the sum of absolute residuals for the $lad$ method and the sum of a function on ranked residuals for the $npr$ method (see Birkes and Dodge (page 115, 1993)). Calculation details can be found in Wolfsegger (2006).

When $lt\text{=}\text{TRUE}$, the best two-phase model where terminal half-life $\geq$ initial half-life $\geq 0$ is selected. When $lt\text{=}\text{FALSE}$, the best two-phase model among all possible tuples of regression is selected which can result in longer initial half-life than terminal half-life and/or in half-lifes $< 0$.

**Value**

A list of S3 class "halflife" containing the following components:

- **parms** half-life and model estimates.
- **chgpt** change point between initial and terminal phase.
- **time** time points of concentration assessments.
- **conc** levels of concentrations.
- **method** "lee".

**Note**

Records including missing values and concentration values below or equal to zero are omitted.

**Author(s)**

Martin J. Wolfsegger

**References**


Examples

#### example for preparation 1 from Lee et al. (1990)

```r
time <- c(0.5, 1.0, 4.0, 8.0, 12.0, 24.0)
conc <- c(75, 72, 61, 54, 36, 6)
res1 <- lee(conc=conc, time=time, method='ols', points=2, lt=TRUE)
res2 <- lee(conc=conc, time=time, method='ols', points=2, lt=FALSE)
plot(res1, log='y', ylim=c(1,100))
plot(res2, add=TRUE, lty=2)
```

#### example for preparation 2 from Lee et al. (1990)

```r
time <- c(0.5, 1.0, 2.0, 6.5, 8.0, 12.5, 24.0)
conc <- c(75, 55, 48, 51, 39, 9, 5)
res3 <- lee(conc=conc, time=time, method='ols', points=2, lt=FALSE)
print(res3$parms)
plot(res2, log='y', ylim=c(1,100), lty=1, pch=20)
plot(res3, add=TRUE, lty=2, pch=21)
legend(x=0, y=10, pch=c(20,21), lty=c(1,2), legend=c('Preperation 1', 'Preperation 2'))
```

#### artificial example

```r
time <- seq(1:10)
conc <- c(1,2,3,4,5,5,4,3,2,1)
res4 <- lee(conc=conc, time=time, method='lad', points=2, lt=FALSE)
plot(res4, log='y', ylim=c(1,7), main='', xlab='', ylab='', pch=19)
```

#### dataset Indometh of package datasets

```r
require(datasets)
res5 <- data.frame(matrix(ncol=3, nrow=length(unique(Indometh$Subject))))
colnames(res5) <- c('ID', 'initial', 'terminal')
row <- 1
for(i in unique(Indometh$Subject)){
  temp <- subset(Indometh, Subject==i)
  res5[row, 1] <- unique(temp$Subject)
  res5[row, c(2:3)] <- lee(conc=temp$conc, time=temp$time, method='lad')$parms[1,]
  row <- row + 1
}
non-compartmental estimation of the area under the concentration versus time curve (AUC) to the last time point, AUC to infinity, area under the first moment curve (AUMC) to infinity, mean residence time (MRT), non-compartmental half-life, total clearance and volume of distribution at steady state.

Usage

nca(conc, time, n.tail=3, dose=0, method=c("z", "boott"), conf.level=0.95, nsample=1000, design=c("ssd","batch","complete"), data)
nca.ssd(conc, time, n.tail=3, dose=0, method=c("z", "boott"),

---

nca

Estimation of various PK parameters

Description

Non-compartmental estimation of the area under the concentration versus time curve (AUC) to the last time point, AUC to infinity, area under the first moment curve (AUMC) to infinity, mean residence time (MRT), non-compartmental half-life, total clearance and volume of distribution at steady state.

Usage

nca(conc, time, n.tail=3, dose=0, method=c("z", "boott"), conf.level=0.95, nsample=1000, design=c("ssd","batch","complete"), data)
nca.ssd(conc, time, n.tail=3, dose=0, method=c("z", "boott"),
Arguments

conc  Levels of concentrations. For batch designs a list is required, while a vector is expected otherwise.
time  Time points of concentration assessment. For batch designs a list is required, while a vector is expected otherwise. One time point for each concentration measured needs to be specified.
n.tail Number of last data points used for tail area correction (default=3).
dose  Dose administered as an IV bolus (default=0).
method A character string specifying the method for calculation of confidence intervals (default=c("z", "boott").
conf.level Confidence level (default=0.95).
nsample Number of bootstrap iterations for bootstrap-t interval (default=1000).

Details

Estimation of the area under the concentration versus time curve from zero to the last time point (AUC 0-tlast), total area under the concentration versus time curve from zero to infinity (AUC 0-Inf), area under the first moment curve for zero to infinity (AUMC 0-Inf), mean residence time (MRT), non-compartmental half-life (HL), total clearance (CL) and volume of distribution at steady state (Vss). In a serial sampling design only one measurement is available per subject at a specific time point, while in a batch design multiple time points are measured for each subject. In a complete data design measurements are taken for all subjects at all time points.

A constant coefficient of variation at the last n.tail time points is assumed.

The use of the standard errors and confidence intervals for the MRT and Vss from batch designs is depreciated due to very slow asymptotic that usually lead to severe undercoverage. For complete data designs only point estimates are provided. The parameters method, conf.level and nsample=1000 are therefore not used. If data for only one subject is provided, the parameters are estimated for this subject while the geometric mean of the estimated parameters is found for multiple subjects (see Cawello, 2003, p. 114).
The AUC 0-t\textsubscript{last} is calculated using the linear trapezoidal rule on the arithmetic means at the different time points while the extrapolation necessary for the AUC 0-Inf and AUMC 0-Inf is achieved assuming an exponential decay on the last n\_tail time points. The other parameters are functions of these PK parameters and of the dosage and are defined as in Wolfsegger and Jaki (2009).

Two different confidence intervals are computed: an asymptotic confidence interval and a bootstrap-\textit{t} interval. The \textit{z} method is based on the limit distribution of the parameter using the critical value from a normal distribution for calculation of confidence intervals together with asymptotic variances. The bootstrap-\textit{t} interval uses the same asymptotic variances, but while the critical value is obtained by the bootstrap-\textit{t} approach. If \textit{nsample}=0 only the asymptotic interval will be computed.

If data is specified the variable names \textit{conc} and \textit{time} are required and represent the corresponding variables.

Note that some estimators as provided assume IV bolus administration. If an oral administration is used
- The clearance needs to be adjusted by the bioavailability, \textit{f}. This can be achieved by either multiplying the obtained estimator by \textit{f} or adjusting the dose parameter accordingly.
- The MRT estimate produced corresponds to the mean transit time (MTT) which is the sum of MRT and mean absorption time (MAT).
- HL and Vss are functions of the MRT and hence they will not be valid under oral administration.

**Value**

An object of the class PK containing the following components:

- \textit{est} Point estimates.
- \textit{CIs} Point estimates, standard errors and confidence intervals.
- \textit{conc} Levels of concentrations.
- \textit{conf\_level} Confidence level.
- \textit{design} Sampling design used.
- \textit{time} Time points measured.

**Note**

At present only the option serial sampling design is available.

**Author(s)**

Thomas Jaki and Martin J. Wolfsegger
References


See Also

auc, estimator, ci and test.

Examples

```r
### serial sampling designs
### example for a serial sampling data design from Wolfsegger and Jaki (2009)
conc <- c(0, 0, 0, 2.01, 2.85, 2.43, 0.85, 1.00, 0.91, 0.46, 0.35, 0.63, 0.39, 0.32,
          0.45, 0.11, 0.18, 0.19, 0.08, 0.09, 0.06)
time <- c(rep(0,3), rep(5/60,3), rep(3,3), rep(6,3), rep(9,3), rep(16,3), rep(24,3))

# Direct call of the function
# CAUTION: this might take a few minutes
# Note: 1E4 bootstrap replications were used in the example given
# in Wolfsegger and Jaki (2009)
set.seed(34534)
nca.ssd(conc=conc, time=time, n.tail=4, dose=200, method=c("z","boott"),
        conf.level=0.95, nsample=500)

# Call through the wrapper function using data
data <- data.frame(conc=conc, time=time)
nca(data=data, n.tail=4, dose=200, method="z",
    conf.level=0.95, design="ssd")

### batch design:
### a batch design example from Holder et al. (1999).
data(Rats)
data <- subset(Rats,Rats$dose==100)

# using the wrapper function
```
nca(data=data, n.tail=4, dose=100, method="z", conf.level=0.95, design="batch")

# direct call
nca.batch(data=data, n.tail=4, dose=100, method="z", conf.level=0.95)

## example with overlapping batches (Treatment A in Example of Jaki & Wolfsegger 2012)
conc <- list(batch1=c(0,0,0,0, 69.7,37.2,213,64.1, 167,386,799,406, 602,758,987,627, 1023,1124,1301,880, 1388,1374,1756,1120, 1481,1129,1665,1598, 1346,1043,1529,1481, 658,576,772,851, 336,325,461,492, 84,75.9,82.6,116),
batch2=c(0,0,0, 29.2,55.9,112.2, 145,153,169, 282,420,532, 727,1033,759, 1360,1388,1425, 1939,1279,1318, 1614,1205,1542, 1238,1113,1386, 648,770,786, 392,438,511, 77.3,98.1,97.9)),
time <- list(batch1=rep(c(0,0.5,0.75,1,1.5,2,3,4,8,12,24),each=4),
batch2=rep(c(0,0.25,0.5,0.75,1,1.5,2,3,4,8,12,24),each=3))
nca.batch(conc,time,method="z",n.tail=4,dose=80)

##### complete data design
## example from Gibaldi and Perrier (1982, page 436) for individual PK parameters
time <- c(0,0.165, 0.5, 1, 1.5, 3, 5, 7.5, 10)
conc <- c(0, 65.03, 28.69, 10.04, 4.93, 2.29, 1.36, 0.71, 0.38)
# using the wrapper function
nca(conc=conc, time=time, n.tail=3, dose=1E6, design="complete")
# direct call
nca.complete(conc=conc, time=time, n.tail=3, dose=1E6)

PKNews

| Shows changes and news |

Description

Functions showing changes since previous versions.

Usage

PKNews()

Details

Displays the changes and news given in the NEWS file of the package.

Value

Screen output.

Author(s)

Thomas Jaki
Examples

PKNews()

plot.halflife

Plot regression lines used for half-life estimation

Description

This method plots objects of S3 class "halflife" (biexp and lee).

Usage

## S3 method for class 'halflife'
plot(x, xlab='Time', ylab='Concentration',
     main='Half-life Estimation', xlim=NULL, ylim=NULL, add=FALSE, ...)

Arguments

x An object of S3 class "halflife" (biexp and lee).
xlab A label for the x axis.
ylab A label for the y axis.
main A main title for the plot.
xlim The x limits (min, max) of the plot.
ylim The y limits (min, max) of the plot.
add A logical value indicating whether to add plot to current plot (default=FALSE).
... Other parameters to be passed through to plotting functions.

Value

none

Author(s)

Martin J. Wolfsegger
Rats

Plasma levels in female rats following a single oral dose

Description

The Rats data frame has 126 rows and 4 columns.

Format

This data frame contains the following columns:

- id: a numeric vector identifying the animal whose plasma level is measured.
- conc: a numeric vector giving the measured plasma level (microgram/mL).
- time: a numeric vector giving the time since administration (hours).
- dose: a numeric vector indicating the dose administered (mg/kg).

Details

Holder et al. (1999), Table 4 describes data on the plasma levels measured at 6 time points over 24 hours for 9 female rats. The same experiment was repeated with different oral dosages.

Source


Rep.tox

Plasma levels in rats following daily intravenous administration in a repeated dose toxicity study

Description

The Rep.tox data frame has 28 rows and 4 columns and gives the plasma levels of 6 rats in a repeated dose toxicity study.

Format

This data frame contains the following columns:

- id: a numeric vector identifying the animal whose plasma level is measured.
- conc: a numeric vector giving the measured plasma level (IU/mL).
- time: a numeric vector giving the time since administration (hours).
- day: a numeric vector indicating the day the data were collected.
Details

In this study the compound is administered daily to 6 Rats over 14 days. Plasma levels are measured at 7 time points over 12 hours after the first administration and after the 14th administration.

Source


test

*Function for hypothesis testing for objects of class PK*

Description

Generic function for hypothesis testing based on an object of class PK.

Usage

test(obj, theta=0, method = c("t", "fieller", "z", "resample"), nsample = 1000)

## S3 method for class 'PKtest'
print(x,hyp=FALSE,...)

## S3 method for class 'PKtest'
summary(object,...)

Arguments

<table>
<thead>
<tr>
<th>Argument</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>obj</td>
<td>An output object of class PK.</td>
</tr>
<tr>
<td>x</td>
<td>An output object of class PKtest.</td>
</tr>
<tr>
<td>object</td>
<td>An output object of class PK test.</td>
</tr>
<tr>
<td>theta</td>
<td>The reference value to be tested against. If multiple parameters are to be tested a vector can be supplied.</td>
</tr>
<tr>
<td>method</td>
<td>A character string specifying the method for calculation of the test statistic. Possible values are t (the default) and fieller for a t-test based method, z for a z-test and resample for either a bootstrap or a permutation test.</td>
</tr>
<tr>
<td>nsample</td>
<td>Number of resamples for the permutation/bootstrap test (default=1000).</td>
</tr>
<tr>
<td>hyp</td>
<td>Logical variable indicating if hypothesis tests should be printed explicitly (default=FALSE).</td>
</tr>
<tr>
<td>...</td>
<td>Arguments to be passed to methods, such as graphical.</td>
</tr>
</tbody>
</table>
Details

Generic function to perform hypothesis test(s).

The reference value for the test is to be specified in theta. If multiple tests are performed theta can be a vector.

For method "resample" a permutation test is used for the difference of AUCs while a one-sample bootstrap test based on inverting a bootstrap-t statistic is implemented.

Value

An object of the class PKtest containing the following components:

- **stat**: Test statistics.
- **p.value**: p-values.
- **theta**: Reference value(s) tested against.
- **conf.level**: Confidence level.
- **alternative**: Type of alternative used.
- **df**: Degrees of freedom of method "t".
- **design**: Sampling design used.
- **method**: Type of test used.

Author(s)

Thomas Jaki

References


See Also

auc, eqv and nca.

Examples

```r
## example for a serial sampling data design from Wolfsegger and Jaki (2009)
conc <- c(0, 0, 0, 2.01, 2.85, 2.43, 0.85, 1.00, 0.91, 0.46, 0.35, 0.63, 0.39, 0.32, 
          0.45, 0.11, 0.18, 0.19, 0.08, 0.09, 0.06)
time <- c(rep(0.3), rep(5/60.3), rep(3,3), rep(6,3), rep(9,3), rep(16,3), rep(24,3))

obj <- nca(conc=conc, time=time, n.tail=4, dose=200, method="z", 
           conf.level=0.95, design="ssd")

## testing all parameters against different values using a z-test
res <- test(obj, theta=c(11, 12, 90, 7, 5, 16, 120), method="z")
print(res)

## a batch design example from Holder et al. (1999).
data(Rats)
data <- subset(Rats,Rats$dose==100)

obj <- auc(data=data,method=c('z','t'), design='batch')

## t-test
res <- test(obj, theta=100, method="t")

## making the hypothesis explicit
summary(res)

## bootstrap test for bioequivalence
# Note: This can take a few seconds
data(Glucose)
## one-sided permutation test
obj <- auc(conc=Glucose$conc, time=Glucose$time, group=Glucose$date, 
           method=c("t"), conf.level=0.90, alternative='less', 
           nsample=100, design="complete")

test(obj, theta=1, method="resample", nsample=100)
```
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