Package ‘linpk’

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Title Generate Concentration-Time Profiles from Linear PK Systems
Description Generate concentration-time profiles from linear pharmacokinetic (PK) systems, possibly with first-order absorption or zero-order infusion, possibly with one or more peripheral compartments, and possibly under steady-state conditions. Single or multiple doses may be specified. Secondary (derived) PK parameters (e.g. Cmax, Ctrough, AUC, Tmax, half-life, etc.) are computed.
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as.data.frame.pkprofile

Coerce a pkprofile to a data.frame

Description

Coerce a pkprofile to a data.frame

Usage

## S3 method for class 'pkprofile'
as.data.frame(x, ..., col.names = c("time", "conc"),
   .state = FALSE)

Arguments

x          An object of class pkprofile.
...        Further arguments passed along.
col.names  Character vector of length 2 giving the names for the time and concentration columns.
.state     Include the complete state along with time and conc?

Value

A data.frame with columns time and conc (or the names specified in col.names). If .state == TRUE, then the complete state is appended (as a matrix column).

blockdiag

Construct a block-diagonal matrix.

Description

Construct a block-diagonal matrix.

Usage

blockdiag(...)
cor2cov

Arguments

Any number of square matrices making up the diagonal blocks of the matrix.

Value

A block-diagonal matrix.

Examples

blockdiag(matrix(1L, 2, 2), 2, matrix(3, 4, 4))

cor2cov

Convert from standard deviation and correlation matrix to covariance matrix.

Description

Convert from standard deviation and correlation matrix to covariance matrix.

Usage

cor2cov(cor, sd)

Arguments

cor A correlation matrix. If sd is missing, the diagonal entries are taken to be the standard deviations, otherwise they are ignored.

sd A vector of standard deviations (optional).

Value

A covariance matrix.

Examples

cor2cov(matrix(c(1, 0.5, 0.5, 1), 2, 2), 0.1)
dose.frame  

*Get the doses from a PK profile.*

**Description**

Get the doses from a PK profile.

**Usage**

`dose.frame(x)`

**Arguments**

- `x`  
  A object of class `pkprofile`.

**Value**

A data.frame containing the realized doses, one per row. The data.frame has all the columns described in `pkprofile`, except `addl`, since all additional doses have been expanded to individual rows. It also has a `conc` column with the simulated concentration at the time of the dose.

**See Also**

`pkprofile`

**Examples**

```r
t.obs <- seq(0, 6*24, 0.5)
y <- pkprofile(t.obs, cl=0.5, vc=11, ka=1.3,
              dose=list(t.dose=c(0, 24*2 + 14), amt=c(100, 50), addl=c(4, 0), ii=24))
dose.frame(y)
```

---

finalstate  

*Get the final state or time of a PK profile.*

**Description**

Get the final state or time of a PK profile.

**Usage**

`finalstate(x)`  

`finaltime(x)`

---

**Examples**

```r
t.obs <- seq(0, 6*24, 0.5)
y <- pkprofile(t.obs, cl=0.5, vc=11, ka=1.3,
              dose=list(t.dose=c(0, 24*2 + 14), amt=c(100, 50), addl=c(4, 0), ii=24))
dose.frame(y)
```
Arguments

x A object of class pkprofile.

Value

A numeric vector containing the state of each compartment at the final observation time (finalstate), or the final observation time itself (finaltime).

See Also

- pkprofile for generating a PK profile.
- pkprofileNpkprofile for appending to an existing PK profile.

Examples

# Administer a dose at time 0 and a second dose using the final state from the first dose (at 12h) as the initial state for the second dose.
t.obs <- seq(0, 12, 0.1)
y <- pkprofile(t.obs, cl=0.25, vc=5, ka=1, dose=list(t.dose=0, amt=1))
finalstate(y)
y2 <- pkprofile(t.obs, cl=0.25, vc=5, ka=1, dose=list(t.dose=0, amt=1), initstate=finalstate(y))
plot(y, xlim=c(0, 24), ylim=c(0, max(y2)), col="blue") # First dose
lines(t.obs+12, y2, col="red") # Second dose

# Add a vertical line to show where the first profile ends.
abline(v=finaltime(y), col="gray75", lty=2)

---

generateETA Generate individual random effects from a multivariate normal distribution.

Description

Generate individual random effects from a multivariate normal distribution.

Usage

generateETA(n, omegaLT, omega = LTmat(omegaLT),
eta.names = sprintf("ETA%d", 1:nrow(omega)))

Arguments

n The number of individuals.
omegaLT A numeric vector giving the elements of the lower triangle of the covariance matrix by row.
omega The covariance matrix.
eta.names A character vector of names for each random effect.
Value

An $n \times p$ matrix, where each row contains the vector of random effects for one individual ($p$ is the size of the covariance matrix).

See Also

LTmat blockdiag

Examples

```r
omegALT <- c(0.123, 0.045, 0.678)
genre ETA(10, omegALT)
```

```r
halflife <- c(0.123, 0.045, 0.678)
genre ETA(10, omegALT)
```

halflife  

*Halflives of a linear PK system.*

Description

Half-lives of a linear PK system.

Usage

```r
halflife(x)
```

Arguments

- **x**: A object of class `pkprofile`.

Value

A numeric vector containing the half-lives for the different phases of the system. The number of phases generally equal the number of compartments, plus one for the absorption phase if the system has first order absorption (i.e. if `ka` is specified). The values are returned sorted in ascending order, so the first corresponds to the alpha phase, the second beta, the third gamma, and so on. The absorption half-life, if present, comes last (it can also be identified by comparing it to the value of $\log(2)/ka$).

Examples

```r
y <- pkprofile(0, cl=0.25, vc=5, ka=1.1)
halflife(y)
log(2)/1.1
```

```r
y <- pkprofile(0, cl=0.25, vc=5, ka=0.01) # Flip-flop kinetics
halflife(y)
log(2)/0.01
```

# Three-compartment model
### linpkApp

*Runs the interactive shiny app.*

#### Description

Runs the interactive shiny app.

#### Usage

```r
linpkApp(...)```

#### Arguments

... Arguments passed to `shiny::runApp()`.

#### Value

Called for its side effects.

#### Note

The app requires the following packages:

- 'shiny'
- 'shinyjs'
- 'shinyAce'
- 'dygraphs'

Make they are installed or the app won’t work.

#### Examples

```r
## Not run:
linpkApp()

## End(Not run)```
**LTmat**  
*Construct a symmetric matrix from its lower triangle.*

**Description**  
Construct a symmetric matrix from its lower triangle.

**Usage**  
`LTmat(LT)`

**Arguments**  
- `LT`  
  A numeric vector giving the elements of the lower triangle of the matrix by row (see examples).

**Value**  
A symmetric matrix.

**Examples**  
```r  
LTmat(1:6)  
```

---

**pkprofile**  
*Generate a concentration-time profile.*

**Description**  
This function generates concentration-time profiles from a linear pharmacokinetic (PK) system, possibly with first-order absorption or zero-order infusion, possibly with one or more peripheral compartments, and possibly under steady-state conditions. Single or multiple doses may be specified.

**Usage**  
pkprofile(...)  

```r  
## Default S3 method:  
pkprofile(t.obs = seq(0, 24, 0.1), cl = 1, vc = 5,  
  q = numeric(0), vp = numeric(0), ka = 0, dose = list(t.dose = 0, amt =  
  1, rate = 0, dur = 0, ii = 24, addl = 0, ss = 0, cmt = 0, lag = 0, f = 1),  
  sc = vc, initstate = NULL, ...)  

## S3 method for class 'matrix'  
pkprofile(A, t.obs = seq(0, 24, 0.1), dose = list(t.dose =  
  0, amt = 1, rate = 0, dur = 0, ii = 24, addl = 0, ss = 0, cmt = 0, lag = 0, f  
  = 1), defdose = 1, sc = 1, initstate = NULL, ...)  
```
Arguments

... Further arguments passed along to other methods.

\texttt{t.obs} A numeric vector of times at which to observe concentrations.

\texttt{c1} Central clearance parameter.

\texttt{vc} Central volume parameter.

\texttt{q} Inter-compartmental clearance. Can be a vector for more than one peripheral compartment, or empty for none. Must match \texttt{vp} in length.

\texttt{vp} Peripheral volume. Can be a vector for more than one peripheral compartment, or empty for none. Must match \texttt{q} in length.

\texttt{ka} First-order absorption rate parameter. Set to 0 to indicate that there is no first-order absorption (i.e. bolus or infusion).

\texttt{dose} A \texttt{list} or \texttt{data.frame} containing dose information. May contain the following elements:

\begin{itemize}
  \item \texttt{t.dose} Dose time (default 0).
  \item \texttt{amt} Dose amount (default 1).
  \item \texttt{rate} Rate of zero-order infusion, or 0 to ignore (default 0). Only one of \texttt{rate} and \texttt{dur} should be specified unless \texttt{amt} is missing.
  \item \texttt{dur} Duration of zero-order infusion, or 0 to ignore (default 0). Only one of \texttt{rate} and \texttt{dur} should be specified unless \texttt{amt} is missing.
  \item \texttt{ii} Interdose interval (default 24). Only used if \texttt{addl} or \texttt{ss} are used.
  \item \texttt{addl} Number of additional doses (default 0). The total number of doses given is \texttt{addl} + 1.
  \item \texttt{ss} Indicates that a dose is given under steady-state conditions (default 0 or FALSE; converted to \texttt{logical} internally).
  \item \texttt{cmt} The number of the compartment into which the dose is administered. The default value is 0, which indicates the depot compartment for first-order absorption (i.e. \texttt{ka} > 0), and central compartment otherwise.
  \item \texttt{lag} Time lag (default 0).
  \item \texttt{f} Bioavailable fraction (default 1).
  \item \texttt{sc} A scaling constant for the central compartment. Concentrations are obtained by dividing amounts by this constant.
  \item \texttt{initstate} A numeric vector containing values to initialize the compartments.
  \item \texttt{A} A matrix of first-order rate constants between the compartments.
  \item \texttt{defdose} The default dose compartment when the compartment is missing or 0.
\end{itemize}

Value

An object of class "\texttt{pkprofile}" , which simply a numeric vector of concentration values with some attributes attached to it. This object has its own methods for \texttt{print}, \texttt{plot}, \texttt{lines} and \texttt{points}.

Methods (by class)

\begin{itemize}
  \item \texttt{default}: Default method.
  \item \texttt{matrix}: Matrix method.
\end{itemize}
Warning

Pay attention to the default arguments. They are there for convenience, but may lead to undesired results if one is not careful.

See Also

- halflife
- secondary
- print.pkprofile
- plot.pkprofile
- lines.pkprofile
- points.pkprofile

Examples

# Default values, a bolus injection
y <- pkprofile()
plot(y)

t.obs <- seq(0, 24, 0.1)
dur <- 1
amt <- 1
ka <- 1
cl <- 0.25
vc <- 5
q <- 2.5
vp <- 10

# One-compartment model with first-order absorption, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, ka=ka, dose=list(amt=amt))
plot(y)

# Two-compartment model with first-order absorption, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, vp=vp, q=q, ka=ka, dose=list(amt=amt))
plot(y)

# One-compartment model with zero-order infusion, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, dose=list(dur=dur, amt=amt))
plot(y)

# Two-compartment model with zero-order infusion, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, vp=vp, q=q, dose=list(dur=dur, amt=amt))
plot(y)

# Two-compartment model with bolus injection, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, vp=vp, q=q, dose=list(amt=amt))
plot(y)

# Two-compartment model with bolus injection into the peripheral compartment, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, vp=vp, q=q, dose=list(amt=amt, cmt=2))
plot(y)

# Two-compartment model with zero-order infusion into the peripheral compartment, single dose
y <- pkprofile(t.obs, cl=cl, vc=vc, vp=vp, q=q, dose=list(amt=amt, cmt=2, dur=dur))
plot(y)

t.obs <- seq(0, 24*6, 1)

# One-compartment model with first-order absorption, multiple doses
y <- pkprofile(t.obs, cl=cl, ka=ka, dose=list(t.dose=seq(0, 24*5, 12), amt=amt))
plot(y)

# One-compartment model with first-order absorption, multiple doses specified by addl and ii
y <- pkprofile(t.obs, cl=cl, ka=ka, dose=list(t.dose=0, amt=amt, addl=9, ii=12))
plot(y, type="b")
points(y, col="blue")

# One-compartment model with first-order absorption, multiple doses under steady-state conditions
yss <- pkprofile(t.obs, cl=cl, ka=ka, dose=list(t.dose=0, amt=amt, addl=9, ii=12, ss=1))
lines(yss, col="red")
points(yss, col="green")

# One-compartment model with zero-order infusion, multiple doses specified by addl and ii
y <- pkprofile(t.obs, cl=cl, dose=list(dur=dur, amt=amt, addl=9, ii=12))
plot(y, log="y")

# One-compartment model with zero-order infusion, multiple doses under steady-state conditions
yss <- pkprofile(t.obs, cl=cl, dose=list(dur=dur, amt=amt, addl=9, ii=12, ss=1))
lines(yss, col="red")

---

**pkprofile**

*Continue an existing concentration-time profile.*

**Description**

This method can be used to append to an existing PK profile, for instance to simulate a PK profile with parameters that change over time. Each time the parameters change, a new call to this method is used to advance the system with the new parameter values.

**Usage**

```r
## S3 method for class 'pkprofile'
pkprofile(obj, t.obs = finaltime(obj) + seq(0, 24, 0.1),
          ..., append = TRUE)
```

**Arguments**

- `obj` An object returned from a previous call to `pkprofile`. 
t.obs         A numeric vector of times at which to observe concentrations.
...           Further arguments passed along.
append        Should the new profile be appended to the current samples? Otherwise, only the
              new samples are returned.

Value

An object of class "pkprofile".

Warning

The new parameters take effect at the time when the previous profile ends. If the previous profile
ends before the new sampling starts, the new parameters will be used to advance the system to the
start of the new sampling.

Any ongoing zero-order infusion at the end of the previous profile is dropped. The remaining
infusion amount will NOT be carried forward.

See Also

pkprofile

Examples

t.obs <- seq(0, 24, 0.1)
amt <- 1
ka <- 1
c1 <- 0.25
vc <- 5

# One-compartment model with first-order absorption
# First dose at time 0
y <- pkprofile(t.obs, cl=c1, vc=vc, ka=ka, dose=list(t=0, amt=amt))

# Second dose at 24h with a lower clearance
y <- pkprofile(y, t.obs+24, cl=0.5*c1, vc=vc, ka=ka, dose=list(t=24, amt=amt))

# Third dose at 48h with a higher clearance
y <- pkprofile(y, t.obs+48, cl=2*c1, vc=vc, ka=ka, dose=list(t=48, amt=amt))
plot(y)
Usage

secondary(x, From = NULL, To = NULL, include.dose.times = T)

Arguments

x
A object of class `pkprofile`.

From
A vector of interval start times. The defaults is the times of the doses.

To
A vector of interval end times. The defaults is the time of the next dose, or last observation time.

include.dose.times
Should dose times (and end of infusion times) be considered in addition to the simulation times?

Value

A `data.frame` with one row for each time interval and with the following columns:

From  The time of the start of the interval. Can differ from the specified start time because it always corresponds to an actual data point.

To   The time of the end of the interval. Can differ from the specified end time because it always corresponds to an actual data point.

n  The number of distinct data points in the interval used to derive AUC, Cmax, etc.

Ctough  Concentration at the time of dose (i.e. just prior to the dose). Only present if the start of the interval corresponds to a dose time.

Cmin  Minimum concentration over the interval.

Tmin  Time of the minimum concentration over the interval.

Cmax  Maximum concentration over the interval.

Tmax  Time of the maximum concentration over the interval.

Cave  Average concentration over the interval (calculated by the trapezoid rule).

AUC  Area under the concentration-time curve over the interval (calculated by the trapezoid rule).

Examples

t.obs <- seq(0, 24*4, 0.1)
y <- pkprofile(t.obs, cl=0.25, vC=5, ka=1, dose=list(t.dose=0, amt=1, addl=6, ii=12))
secondary(y)
secondary(y, 0, 48)
secondary(y, 0, Inf)
sum(secondary(y)$AUC)  # Same as above
plot(y)
with(secondary(y), points(Tmax, Cmax, pch=19, col="blue"))
with(secondary(y), points(Tmin, Cmin, pch=19, col="red"))
with(secondary(y), points(From, Ctough, pch=19, col="green"))
with(secondary(y), points(From + 6, Cave, pch=19, col="purple", cex=2))
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