Package 'SimDissolution'

January 20, 2025

Type Package

Title Modeling and Assessing Similarity of Drug Dissolutions Profiles

Version 0.1.0

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Description Implementation of a model-based bootstrap approach for testing whether two formulations are similar. The package provides a function for fitting a pharmacokinetic model to time-concentration data and comparing the results for all five candidate models regarding the Residual Sum of Squares (RSS). The candidate set contains a First order, Hixson-Crowell, Higuchi, Weibull and a logistic model. The assessment of similarity implemented in this package is performed regarding the maximum deviation of the profiles. See Moellenhoff et al. (2018) <doi:10.1002/sim.7689> for details.

License GPL (>= 2)

Encoding UTF-8

LazyData true

Depends dplyr, alabama, mvtnorm, graphics

RoxygenNote 6.1.1

NeedsCompilation no

Repository CRAN

Date/Publication 2019-09-27 10:20:11 UTC

Contents

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example_data   *Time-Concentration data for two formulas*

Description

(Artificial) Concentration data for 2 formulas, each including 12 tablets. Concentrations are measured at six points in time.

Usage

```
data(example_data)
```

Format

A data frame with 24 rows and 8 variables including tablet, group and measurements at six points in time.

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f2   *Function for computing the f2*

Description

Function for computing the f2, time points have to be identical. Validity criteria of the f2 have to be be checked in advance. See Moellenhoff et al. (2018) <doi:10.1002/sim.7689>

Usage

```
f2(conc1, conc2)
```

Arguments

conc1, conc2   data frames containing the concentrations obtained for each of the two formulations

Value

a single value for the f2

References

Moellenhoff et al. (2018) <doi:10.1002/sim.7689>

Examples

```
data(example_data)
conc1<-select(filter(example_data,Group=="1"),-Tablet,-Group)
conc2<-select(filter(example_data,Group=="2"),-Tablet,-Group)
f2(conc1=conc1,conc2=conc2)
```

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fit_pharm_mod	*Fitting a pharmacokinetic model to concentration data*

Description

This function fits a pharmacokinetic model (dissolution profile) to time-concentration data using non-linear least squares regression. The model can be chosen from a candidate set containing a First order, Hixson-Crowell,Higuchi, Weibull and a logistic model. See Moellenhoff et al. (2018) <doi:10.1002/sim.7689> for details.

Usage

```
fit_pharm_mod(time, conc, m, plot = TRUE)
```

Arguments

time	a vector containing the time points of measurements
conc	data frame or matrix containing the concentrations (see the example)
m	model type. Built-in models are "firstorder", "hixson", "higuchi", "weibull" and "logistic"
plot	plot of the model, default is TRUE.

Value

A list containing the model type and the obtained parameters, further the RSS for all possible models. Furthermore a plot is given.

References

Moellenhoff et al. (2018) <doi:10.1002/sim.7689>

Examples

```
data(example_data)
conc1 <- select(filter(example_data,Group=="1"),-Tablet,-Group)
time <- c(10,15,20,30,45,60)
fit_pharm_mod(time,conc1,m="logistic")
```

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sim_test	*Bootstrap test for the assessment of similarity of drug dissolutions profiles via maximum deviation*

Description

Function for testing whether two dissolution profiles are similar concerning the hypotheses $H_0 : \max_{t \in \mathcal{T}} |m_1(t, \beta_1) - m_2(t, \beta_2)| \geq \epsilon$ *vs.* $H_1 : \max_{t \in \mathcal{T}} |m_1(t, \beta_1) - m_2(t, \beta_2)| < \epsilon$.

m_1 and m_2 are pharmacokinetic models chosen from a candidate set containing a First order, Hixson-Crowell,Higuchi, Weibull and a logistic model.

See Moellenhoff et al. (2018) <doi:10.1002/sim.7689> for details.

Usage

```
sim_test(time1, time2 = time1, conc1, conc2, m1, m2, epsilon = 10,
  B = 1000, plot = FALSE)
```

Arguments

time1, time2	vectors containing the time points of measurements for each of the two formulations; if not further specified the time points are identical in both groups
conc1, conc2	data frames or matrices containing the concentrations obtained for each of the two formulations (see the example)
m1, m2	model types. Built-in models are "firstorder", "hixson", "higuchi", "weibull" and "logistic"
epsilon	positive argument specifying the equivalence threshold (in %), default is 10% corresponding to an f2 of 50 according to current guidelines
B	number of bootstrap replications. If missing, default value of B is 1000
plot	if TRUE, a plot of the absolute difference curve of the two estimated models will be given. The default is FALSE.

Value

A list containing the p.value, the types of models, the f2, the maximum absolute difference of the models, the estimated model parameters, the number of bootstrap replications and a summary of the bootstrap test statistic. Furthermore plots of the two models are given.

References

Moellenhoff et al. (2018) <doi:10.1002/sim.7689>

EMA (2010) <https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf>

Examples

```
data(example_data)
conc1 <- select(filter(example_data,Group=="1"),-Tablet,-Group)
conc2 <- select(filter(example_data,Group=="2"),-Tablet,-Group)
time <- c(10,15,20,30,45,60)
sim_test(time1=time,time2=time,conc1=conc1,conc2=conc2,m1="logistic",m2="logistic",B=500,plot=TRUE)
```

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