Package ‘wnl’

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Version 0.4.0

Title Minimization Tool for Pharmacokinetic-Pharmacodynamic Data Analysis

Description This is a set of minimization tools (maximum likelihood estimation and least square fitting) to solve examples in the Johan Gabrielsson and Dan Weiner's book ``Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications" 5th ed. (ISBN:9198299107). Examples include linear and nonlinear compartmental model, turn-over model, single or multiple dosing bolus/infusion/oral models, allometry, toxicokinetics, reversible metabolism, in-vitro/in-vivo extrapolation, enterohepatic circulation, metabolite modeling, Emax model, inhibitory model, tolerance model, oscillating response model, enantiomer interaction model, effect compartment model, drug-drug interaction model, receptor occupancy model, and rebound phenomena model.

Depends R (>= 3.0.0), numDeriv

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NeedsCompilation no

LazyLoad yes

Repository CRAN

URL https://cran.r-project.org/package=wnl

R topics documented:

wnl-package *Minimization Tool for Pharmacokinetic-Pharmacodynamic Data Analysis*

Description

This is a minimization tool to solve the examples in the book Gabrielsson J, Weiner D. 'Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications' 5th ed. 2016. (ISBN:9198299107).

Details

This is a set of minimization tools to solve all the examples in the book 'Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications' 5th ed. 2016..

Author(s)

Kyun-Seop Bae <k@acr.kr>

References

Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications. 5th ed. 2016.

Examples

```
tData = Theoph
colnames(tData) = c("ID", "BWT", "DOSE", "TIME", "DV")

fPK = function(THETA)     # Prediction function
{
  DOSE = 320000           # in microgram
  TIME = e$DATA[,"TIME"]  # use data in e$DATA

  K    = THETA[1]
  Ka   = THETA[2]
  V    = THETA[3]

  Cp   = DOSE/V*Ka/(Ka - K)*(exp(-K*TIME) - exp(-Ka*TIME))
  return(Cp)
}

IDs = unique(tData[,"ID"])
nID = length(IDs)
for (i in 1:nID) {
  Data = tData[tData$ID == IDs[i],]
  Res = nlr(fPK, Data, pNames=c("k", "ka", "V"), IE=c(0.1, 3, 500),
            SecNames=c("CL", "Thalf", "MRT"), SecForms=c(~V*k, ~log(2)/k, ~1/k))
  print(paste("## ID =", i, "##"))
  print(Res)
}
```

`cmpChi` *Compare model with Chi-square test*

Description

It performs chi-square test for two models comparison.

Usage

```
cmpChi(r1, r2)
```

Arguments

`r1`	A result from `nlr`
`r2`	Another result from `nlr`

Details

One model should include the other model.

Value

Returns a p-value from `pchisq`

Author(s)

Kyun-Seop Bae <k@acr.kr>

`dx` *Simplest diagnostic plot for minimization result*

Description

It performs simplest diagnostic plot from the result of `nlr`.

Usage

```
dx(r)
```

Arguments

`r`	a result from `nlr` or `wnl5`

Details

This plots 'Observation vs. Prediction' and 'Normalized Redisual vs. Prediction' only. Normalized residual are meant to be distributed as standard normal distribution, N(0, 1).

Value

This just draws plot.

Author(s)

Kyun-Seop Bae <k@acr.kr>

nlr *Nonlinear Regression in R*

Description

It performs nonlinear regression usually for pharmacokinetic and pharmacodynamic models.

Usage

```
nlr(Fx, Data, pNames, IE, LB, UB, Error="A", ObjFx=ObjDef, SecNames, SecForms,
    Method="L-BFGS-B")
```

Arguments

`Fx`	Function for structural model. It should return a vector of same length to observations.
`Data`	Data table which will be used in Fx. Fx should access this with `e$DATA`.
`pNames`	Parameter names in the order of Fx arguments
`IE`	Initial estimates of parameters
`LB`	Lower bound for `optim` function. Default value is 0.
`UB`	Upper bound for `optim` function. Default value is 1e+06.
`Error`	Error model. One of `"A"` for additive error, `"POIS"` for poisson error, `"P"` for proportional error, and `"C"` for combined error model.
`ObjFx`	Objective function to be minimized. Default is maximum likelihood estimation function(-2 log likelihood).
`SecNames`	Names of secondary parameter estimates
`SecForms`	Formula to calculate the secondary parameter estimates
`Method`	`"L-BFGS-B"` is default. See `optim` for more detail.

Details

This uses scaled transformed parameters and environment `e` internally.

Value

`Est`	Point estimate(PE) with standard error(SE) and relative standard error(RSE)
`Cov`	Variance-covariance matrix of objective function at the value of point estimates
`run$m`	Count of positive residuals
`run$n`	Count of negative residuals
`run$run`	Count of runs of residuals
`run$p.value`	P value of run test with excluding zero points
`Objective Function Value`	Minimum value of objective function

`-2LL`	-2 times log likelihood
`AIC`	Akaike Information Criterion
`AICc`	Corrected Akaike Information Criterion
`BIC`	Schwarz Bayesian Information Criterion
`Convergence`	Convergence code from `optim`
`Message`	Message from `optim`.
`Prediction`	Fitted(predicted) values
`Residuals`	Residuals
`Elapsed Time`	Consumed time by minimization

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
tData = Theoph
colnames(tData) = c("ID", "BWT", "DOSE", "TIME", "DV")

fPK = function(THETA) # Prediction function
{
  DOSE = 320000 # in microgram
  TIME = e$DATA[,"TIME"] # use data in e$DATA

  K    = THETA[1]
  Ka   = THETA[2]
  V    = THETA[3]

  P  = DOSE/V*Ka/(Ka - K) * (exp(-K*TIME) - exp(-Ka*TIME))
  return(P)
}

IDs = unique(tData[,"ID"])
nID = length(IDs)
for (i in 1:nID) {
  Data = tData[tData$ID == IDs[i],]
  Res = nlr(fPK, Data, pNames=c("k", "ka", "V"), IE=c(0.1, 3, 500),
            SecNames=c("CL", "Thalf", "MRT"), SecForms=c(~V*k, ~log(2)/k, ~1/k))
  print(paste("## ID =", i, "##"))
  print(Res)
}
```

`Secondary` *Get Secondary Parameter Estimates*

Description

Get standard error and relative standard error (cv) of secondary paramter estimate

Usage

```
Secondary(Formula, PE, COV)
```

Arguments

`Formula`	Formula to calculate the secondary parameter estimate
`PE`	Point estimates of primary estimates with names
`COV`	Variance-covariance matrix of primary estimates

Details

Variables within `Formula` should exist in the names of `PE` vector.

Value

This returns point estimate, standard error, relative standard error of the secondary parameter estimate.

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
tData = Theoph
colnames(tData) = c("ID", "BWT", "DOSE", "TIME", "DV") # Table requires DV column

fPK = function(THETA) # Prediction function
{
  AMT  = 320000 # in microgram
  TIME = e$DATA[,"TIME"]
  V  = THETA[1]
  K  = THETA[2]
  Ka = THETA[3]
  Cp = AMT/V*Ka/(Ka - K)*(exp(-K*TIME) - exp(-Ka*TIME))
  return(Cp)
}
Data = tData[tData$ID == 1,]
Res = nlr(fPK, Data, pNames=c("V", "K", "Ka"), IE=c(30000, 0.1, 2))
Secondary(~V*K, Res$Est["PE",1:e$nPara], Res$Cov)
```

`wnl5` *Old type WinNonlin - Least Square not MLE*

Description

It performs old type Winnonlin regression.

Usage

```
wnl5(Fx, Data, pNames, IE, LB, UB, Error="A", ObjFx=ObjLS)
```

Arguments

`Fx` Function for structural model. It should return a vector of same length to observations.

`Data` Data table which will be used in Fx. Fx should access this with `e$DATA`.

`pNames` Parameter names in the order of Fx arguments

`IE` Initial estimates of parameters

`LB` Lower bound for `optim` function. Default value is 0.

`UB` Upper bound for `optim` function. Default value is 1e+06.

`Error` Error model. One of `"POIS"` for poisson error, `"PROP"` for proportional error, and others for additive error model.

`ObjFx` Objective function to be minimized. Default is least square function.

Details

This uses scaled transformed parameters and environment `e` internally. Here we do not provide standard error. If you want standard error, use `nlr`.

Value

`PE` Point estimates

`WRSS` Weighted Residual Sum of Square

`run$m` Count of positive residuals

`run$n` Count of negative residuals

`run$run` Count of runs of residuals

`run$p.value` P value of run test with excluding zero points

`Objective Function Value`
Minimum value of objective function

`AIC` Akaike Information Criterion

`SBC` Schwarz Bayesian Information Criterion

`Condition Number`
Condition number

`Message` Message from `optim`.

`Prediction` Fitted(predicted) values

`Residuals` Residuals

`Elapsed Time` Consumed time by minimization

Author(s)

Kyun-Seop Bae <k@acr.kr>

Examples

```
tData = Theoph
colnames(tData) = c("ID", "BWT", "DOSE", "TIME", "DV")

fPK = function(THETA) # Prediction function
{
  DOSE = 320000 # in microgram
  TIME = e$DATA[,"TIME"] # use data in e$DATA

  K  = THETA[1]
  Ka = THETA[2]
  V  = THETA[3]
  Cp  = DOSE/V*Ka/(Ka - K)*(exp(-K*TIME) - exp(-Ka*TIME))
  return(Cp)
}

IDs = unique(tData[,"ID"])
nID = length(IDs)
for (i in 1:nID) {
  Data = tData[tData$ID == IDs[i],]
  Res = wnl5(fPK, Data, pNames=c("k", "ka", "V"), IE=c(0.1, 3, 500))
  print(paste("## ID =", i, "##"))
  print(Res)
}
```

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