

# Package ‘wnl’

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**Version** 0.6.3

**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 ( $\geq$  3.0.0), numDeriv

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wnl-package	<i>Minimization Tool for Pharmacokinetic-Pharmacodynamic Data Analysis</i>
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## 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 [jk@acr.kr](mailto:jk@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	<i>Compare model with Chi-square test</i>
--------	---

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**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 [jsk@acr.kr](mailto:jsk@acr.kr)

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Comp1	<i>One compartment model - analytical</i>
-------	---

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**Description**

It calculates using one compartment model.

**Usage**

```
Comp1(Ke, Ka=0, DH)
```

**Arguments**

Ke	Elimination rate constant
Ka	Absorption rate constant
DH	Expanded dosing history table

**Details**

First compartment is the gut compartment for oral dosing. IV bolus and infusion dosing should be done at the second compartment.

**Value**

This returns a table with the gut and the central compartment columns

**Author(s)**

Kyun-Seop Bae [jsk@acr.kr](mailto:jsk@acr.kr)

**Examples**

```
DAT
DAT2 = ExpandDH(DAT)
X1 = Comp1(Ke=0.1, Ka=1, DAT2)
X1
matplot(DAT2[, "TIME"], X1, type="l")
```

---

 DAT

---

*An Example of Dosing History Table*


---

**Description**

This is a conventional NONMEM input data format.

**Usage**

DAT

**Format**

This data frame has 5 columns with 18 time-points for the simulation.

TIME Time

AMT Amount given for the compartment of CMT column

RATE Infusion rate

CMT Compartment number, 1=gut, 2=central, 3=peripheral, etc.

DV Currently blank and not used.

**Details**

To be used at Comp1 or nComp, expand dosing history with ExpandDH function.

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dx	<i>Simplest diagnostic plot for minimization result</i>
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---

### Description

It performs a simple diagnostic plot from the result of `nlr`.

### Usage

```
dx(r)
```

### Arguments

`r` a result from `nlr` or `wn15`

### Details

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

### Value

This just draws a plot.

### Author(s)

Kyun-Seop Bae `jsk@acr.kr.i`

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ExpandDH	<i>Expand Dosing History Table</i>
----------	------------------------------------

---

### Description

It expands dosing history table.

### Usage

```
ExpandDH(DH, Fo = 1)
```

### Arguments

`DH` Dosing history table of NONMEM type  
`Fo` Bioavailability of the first (gut) compartment

### Details

It expands dosing history table of conventional NONMEM data format. It calculate bioavailable amount, then add time points of non-differentiable, e.g. stopping points of infusion.

**Value**

Returns expanded dosing history table.

**Author(s)**

Kyun-Seop Bae `jsk@acr.kr.i`

**Examples**

```
DAT
ExpandDH(DAT) # One observation point is increased at the time of 27.
```

---

nComp

*Get Amounts of Each Compartments using Lambdas and Coefficients of Multi-compartment Model*

---

**Description**

It calculates using multi-compartment model.

**Usage**

```
nComp(Sol, Ka=0, DH)
```

**Arguments**

Sol	Solution list of lambdas and coefficients
Ka	Absorption rate constant
DH	Expanded dosing history table

**Details**

First compartment is the gut compartment for oral dosing. IV bolus and infusion dosing should be done at the second compartment. If a bolus dose was given at time T, it is reflected at times of larger than T. This is more close to real observation. ADAPT does like this, but NONMEM does not.

**Value**

This returns a table with the gut and the other compartment columns

**Author(s)**

Kyun-Seop Bae `jsk@acr.kr.i`

**Examples**

```
DAT
DAT2 = ExpandDH(DAT)
Sol = SolComp2(K10=0.1, K12=3, K21=1)
X2 = nComp(Sol, Ka=1, DAT2)
X2
matplot(DAT2[, "TIME"], X2, type="l")
```

---

nlr	<i>Nonlinear Regression in R</i>
-----	----------------------------------

---

**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", Sx)
```

**Arguments**

Fx	Function for structural model. It should return a vector of the same length to observations.
Data	Data table which will be used in Fx. Fx should access this with <code>e\$DATA</code> .
pNames	Parameter names in the order of Fx arguments
IE	Initial estimates of parameters
LB	Lower bound for <code>optim</code> function. The default value is 0.
UB	Upper bound for <code>optim</code> function. The default value is <code>1e+06</code> .
Error	Error model. One of "A" for additive error, "POIS" for Poisson error, "P" for proportional error, "C" for combined error model, "S" for general error model. With Error="S", Sx should be provided.
ObjFx	Objective function to be minimized. The 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 <code>optim</code> for more detail.
Sx	Scale function. This is usually the inverse of weight. It should return the same length(nrow) of Y. When Error="S", Scale function should be provided as Sx.

**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 the 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 the 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 <code>optim</code>
Message	Message from <code>optim</code> .
Prediction	Fitted(predicted) values
Residuals	Residuals
Scale	Scales with Error="S". Variances for each points are scale vector multiplied by <code>ScaleErrVar</code> in <code>Est</code> .
Elapsed Time	Consumed time by minimization

**Author(s)**

Kyun-Seop Bae [jsk@acr.kr](mailto:jsk@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)
}
```



pComp

*Plot Compartment Model Diagram***Description**

It plots the diagram of a compartment model.

**Usage**

```
pComp(dComp, dRate, Shape="rect", Col=NA, Bx=0.3, By=0.2, Cex=1.0, Lwd=3,
      Radius=0.3, thIn=pi/2, thOut=pi/2, ...)
```

**Arguments**

dComp	data.frame for a compartment model. See the example.
dRate	data.frame for rate information. See the example.
Shape	rectangle or cricle
Col	filling color
Bx	half width of compartment box
By	half height of compartment box
Cex	character expansion
Lwd	line width
Radius	radius of compartment circle
thIn	Input angle in radian
thOut	Output angle in radian
...	arguments to be passed to plot function

**Details**

Flow direction is from the top to bottom.

**Value**

It plots.

**Author(s)**

Kyun-Seop Bae [jk@acr.kr](mailto:jk@acr.kr)

**Examples**

```
dA = data.frame(No = c(1, 2, 3, 4), Name=c("Gut Depot", "Skin Depot", "Central", "Peripheral"),
                Level=c(1, 1, 2, 2), xPos=c(-0.5, 0.5, 0, 1))
dB = data.frame(From = c(1, 2, 3, 4, 3, 0, 0), To=c(3, 3, 4, 3, 5, 1, 2),
                Name=c("KA", "KA2", "K12", "K21", "CL", "F1", "F2"))

pComp(dA, dB)
#par(oma=c(0, 0, 0, 0), mar=c(0, 0, 1, 0)) # If need, adjust margin before calling
pComp(dA, dB, "circ", main="Compartmental Model Diagram")

pComp(dA, dB, "circ", main="Compartmental Model Diagram", Col="#DDEEFF", asp=1)
```

## Secondary

*Get Secondary Parameter Estimates***Description**

Get standard error and relative standard error (cv) of the secondary parameter estimate

**Usage**

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

**Arguments**

Formula	Formula to calculate the secondary parameter estimate
PE	Point estimates of primary parameters 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 [jsk@acr.kr](mailto:jsk@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)
```

---

**SolComp2***Get Lambdas and Coefficients of Two-compartment Model*

---

**Description**

It calculates lambdas and coefficients for two-compartment model from K10, K12, and K21.

**Usage**

```
SolComp2(K10, K12, K21)
```

**Arguments**

K10	Ke, Elimination rate constant from central compartment
K12	Rate constant from the central to the peripheral compartment
K21	Rate constant from the peripheral to the central compartment

**Details**

It calculates lambdas and coefficients of two-compartment model from K10, K12, and K21. Lambdas should have no identical values.

**Value**

This returns a list of lambdas and coefficients.

**Author(s)**

Kyun-Seop Bae [jk@acr.kr.i](mailto:jk@acr.kr.i)

**Examples**

```
DAT
DAT2 = ExpandDH(DAT)
Sol = SolComp2(K10=0.1, K12=3, K21=1)
X2 = nComp(Sol, Ka=1, DAT2)
X2
matplot(DAT2[, "TIME"], X2, type="l")
```

---

**SolComp3***Get Lambdas and Coefficients of Three-compartment Model*

---

**Description**

It calculates lambdas and coefficients for three-compartment model from K10, K12, K21, K13, and K31.

**Usage**

```
SolComp3(K10, K12, K21, K13, K31)
```

**Arguments**

K10	Ke, Elimination rate constant from central compartment
K12	Rate constant from the central to the first peripheral compartment
K21	Rate constant from the first peripheral to the central compartment
K13	Rate constant from the central to the second peripheral compartment
K31	Rate constant from the second peripheral to the central compartment

**Details**

It calculates lambdas and coefficients of two-compartment model from K10, K12, and K21. Lambdas should have no identical values.

**Value**

This returns a list of lambdas and coefficients.

**Author(s)**

Kyun-Seop Bae `jk@acr.kr`

**Examples**

```
DAT
DAT2 = ExpandDH(DAT)
Sol = SolComp3(K10=0.1, K12=3, K21=1, K13=2, K31=0.5)
X3 = nComp(Sol, Ka=1, DAT2)
X3
matplot(DAT2[, "TIME"], X3, type="l")
```

---

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 the same length to observations.
Data	Data table which will be used in Fx. Fx should access this with <code>e\$DATA</code> .
pNames	Parameter names in the order of Fx arguments
IE	Initial estimates of parameters
LB	Lower bound for <code>optim</code> function. The default value is 0.
UB	Upper bound for <code>optim</code> function. The default value is <code>1e+06</code> .
Error	Error model. One of "POIS" for Poisson error, "P" for proportional error, and others for additive error model.
ObjFx	Objective function to be minimized. The 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 the objective function
AIC	Akaike Information Criterion
SBC	Schwarz Bayesian Information Criterion
Condition Number	
	Condition number
Message	Message from <code>optim</code> .
Prediction	Fitted(predicted) values
Residuals	Residuals
Elapsed Time	Consumed time by minimization

## Author(s)

Kyun-Seop Bae [jk@acr.kr](mailto:jk@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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