

# Package ‘wnl’

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**Version** 0.8.2

**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 (>= 3.5.0), numDeriv

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|             |  |
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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 <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>

---

Comp1

*One compartment model - analytical*

---

### 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 <k@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.

---

dx

*Simplest diagnostic plot for minimization result*

---

**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 <k@acr.kr>

---

EnvObj

*Environment's Objects*

---

**Description**

Get an environment's visible objects as a list.

**Usage**

```
EnvObj(envir = e)
```

**Arguments**

envir            environment to get its content

**Details**

All the visible objects in the environment including functions and data will be returned.

**Value**

All visible objects as a list

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

---

|          |                                    |
|----------|------------------------------------|
| 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 <k@acr.kr>

**Examples**

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

---

|       |                                     |
|-------|-------------------------------------|
| hSkew | <i>Hougaard Measure of Skewness</i> |
|-------|-------------------------------------|

---

**Description**

Hougaard measure of skewness with nonlinear regression

**Usage**

hSkew(rx)

**Arguments**

rx                    a result of nls function

**Details**

Hougaard measure of skewness can be used to check if the parameters of nonlinear regression behavior in linear fashion, i.e. symmetric confidence interval. Be cautious on the variable name conflict. All the variables in the nonlinear function should be able to be accessed by the function.

**Value**

Hougaard estimate of skewness for each parameter

(0, 0.1]            The estimate is very close-to-linear in behavior.  
 (0.1, 0.25]        The estimate is reasonably close-to-linear in behavior.  
 (0.25, 1]          The skewness is apparent.  
 >1                  The estimate is considerably nonlinear in behavior.

**Author(s)**

Kyun-Seop Bae k@acr.kr

**References**

EL-Shehawy SA. On Calculating the Hougaard Measure of Skewness in a Nonlinear Regression Model with Two Parameters. J Math & Stat. 2009;5(4):360-364.

**Examples**

```
r1 = nls(density ~ b1*conc/(b2 + conc), DNase[DNase$Run == 1, ], start=list(b1=3, b2=5))
hSkew(r1)
```

---

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**

|     |   |
|-----|---|
| So1 | 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 <k@acr.kr>

**Examples**

```
DAT
DAT2 = ExpandDH(DAT)
So1 = SolComp2(K10=0.1, K12=3, K21=1)
X2 = nComp(So1, Ka=1, DAT2)
X2
matplot(DAT2[, "TIME"], X2, type="l")
```

---

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", Sx, conf.level=0.95, k, fix=0)
```

**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 e\$DATA.                     |
| pNames | Parameter names in the order of Fx arguments   |

|            |   |
|------------|---|
| IE         | Initial estimates of parameters   |
| LB         | Lower bound for opt im function. The default value is 0.  |
| UB         | Upper bound for opt im function. The default value is 1e+06.  |
| 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 opt im 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.  |
| conf.level | Confidence level for confidence interval  |
| k          | 1/k likelihood interval(LI) will be provided. Currently recommended value is $\exp(\text{qf}(1 - \alpha, 1, \text{nRec}-\text{nPara})/2) + 1$ .   |
| fix        | indices of parameters to fix  |

### Details

This uses scaled transformed parameters and environment e internally.

### Value

|                          |   |
|--------------------------|---|
| Est                      | Point estimate(PE) with standard error(SE) and relative standard error(RSE)   |
| LI                       | 1/k likelihood interval, at which likelihood drops to 1/k of maximum likelihood. This reflects asymmetry better than confidence interval. This is estimated likelihood interval, not profile likelihood interval. |
| Skewness                 | Hougaard's skewness measure. This is printed only with additive error model. See also hSkew   |
| 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 optim   |
| Message      | Message from optim.   |
| Prediction   | Fitted(predicted) values  |
| Residuals    | Residuals   |
| Scale        | Scales with Error="S". Variances for each points are scale vector multiplied by ScaleErrVar in Est. |
| 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)
}

# Another example from radioimmunoassay(RIA)
d1 = data.frame(conc = c(200, 100, 50, 25, 12.5, 6.25, 3.125, 0),
                DV = c(1.78, 1.5, 1.17, 0.74, 0.51, 0.31, 0.19, 0.04))

PRED = function(TH) TH[1] + TH[2]*d1$conc^TH[4]/(TH[3]^TH[4] + d1$conc^TH[4])
Scale = function(TH) 1/(PRED(TH) - (TH[1] + TH[2])/2)^2

nlr(PRED, d1, pNames=c("R0", "Rmax", "RC50", "Hill"), IE=c(0.1, 3, 50, 1),
    Error="S", Sx=Scale)
```

---

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 <k@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)
```

pProf

*Plot Likelihood or Objective Fnnction Value Profile***Description**

It plots estimated likelihood profile. This is not profile likelihood profile.

**Usage**

```
pProf(Bag = e, Title = "", ...)
```

**Arguments**

|       |   |
|-------|---|
| Bag   | an environment or an object containing the objects of resultant environment e after nlr() |
| Title | title for the plot  |
| ...   | arguments to pass to the plot function  |

**Details**

This plots likelihood profile from the result of nlr() function. Bag should contain the results of nlr().

**Value**

No values but a plot.

**Author(s)**

Kyun-Seop Bae <k@acr.kr>

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 <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)
```

---

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 <k@acr.kr>

### Examples

```
DAT
DAT2 = ExpandDH(DAT)
So1 = SolComp2(K10=0.1, K12=3, K21=1)
X2 = nComp(So1, 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 <k@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 e\$DATA.                                       |
| pNames | Parameter names in the order of Fx arguments   |
| IE     | Initial estimates of parameters  |
| LB     | Lower bound for opt im function. The default value is 0.   |
| UB     | Upper bound for opt im function. The default value is 1e+06.   |
| 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 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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