

# Development of R packages: 'NonCompart' and 'ncar' for noncompartmental analysis (NCA)

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Noncompartmental analysis (NCA) is a primary analytical approach for pharmacokinetic studies, and its parameters act as decision criteria in bioequivalent studies. Currently, NCA is usually carried out by commercial softwares such as WinNonlin®. In this article, we introduce our newly-developed two R packages, *NonCompart* (NonCompartmental analysis for pharmacokinetic data) and *ncar* (NonCompartmental Analysis for pharmacokinetic Report), which can perform NCA and produce complete NCA reports in both pdf and rtf formats. These packages are compatible with CDISC (Clinical Data Interchange Standards Consortium) standard as well. We demonstrate how the results of WinNonlin® are reproduced and how NCA reports can be obtained. With these R packages, we aimed to help researchers carry out NCA and utilize the output for early stages of drug development process. These R packages are freely available for download from the CRAN repository.

## Introduction

The aim of pharmacokinetic (PK) studies is to examine the kinetics of a drug with regard to absorption, distribution, metabolism and elimination in the body. PK data analysis consists of noncompartmental analysis (NCA) and nonlinear regression analysis.[1,2] NCA uses the trapezoidal rule for measurement of area under the concentration-time curve (AUC), and requires fewer assumptions than model-based analysis.[2] NCA allows for estimation of various PK parameters such as AUC, peak observed drug concentration ( $C_{max}$ ), time of peak concentration ( $T_{max}$ ), and elimination half-life. Particularly, AUC and  $C_{max}$  are often accepted as the criteria for approval of bioequivalent drugs.

R, a widely-used computer language, is a suite of libraries of statistical and mathematical computations.[3] Despite its relatively small base system compared with other commercial softwares for NCA such as WinNonlin®[4] and Kinetica,[5] R has robust functions for scientific computation and numerous

add-in packages for use in various fields.[6] Therefore, many efforts are being made to replace commercial softwares with R packages.

In this article, we introduce two newly-developed R packages, *NonCompart* and *ncar*, that are compatible with SDTM (Study Data Tabulation Model)-formatted dataset of CDISC (Clinical Data Interchange Standards Consortium), which is the standard of documentation submitted to regulatory authorities,[7] while providing a practical method for producing complete NCA reports.

## Methods

### R packages (*NonCompart* and *ncar*)

Two R packages (*NonCompart* and *ncar*) for NCA were developed in the open-source R programming language in order to allow free public use. R packages can be installed and loaded using the following scripts.

#### R code

```
install.packages(c("NonCompart", "ncar"))  
  
library(NonCompart)  
  
library(ncar)
```

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#### Reviewer

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Detailed documentation and examples for each package can be found on the online user manual in the CRAN repository (<http://cran.r-project.org/web/packages/NonCompart/index.html>, <http://cran.r-project.org/web/packages/ncar/index.html>) or directly within the R console by entering ?function (e.g. ?NonCompart, ?ncar). These two packages are implemented in R and can accept a set of input arguments that allow for generation of NCA output. The names of most NCA metrics estimated by the function of these packages are consistent with those used in WinNonlin® (Table 1).

## Software

WinNonlin® (Pharsight, Mountain View, CA, USA)[4] in Mi-

crosoft-Windows 7 (64 bit) was used for the computation. R 3.4.2 in Microsoft-Windows 7 (64 bit) was used for the comparison of calculated values.

## Dataset

To compare the outputs generated by R packages and WinNonlin®, we used Theoph dataset obtained from the R software. The Theoph dataset has 132 observations from 12 subjects. A portion of the Theoph dataset (subject ID = 8) is shown in Table 2.

**Table 1.** Description of PK parameters of WinNonlin® and the R packages

Parameter	WinNonlin®	Description
b0	b0	Intercept
C <sub>MAX</sub>	C <sub>max</sub>	Max Concentration (Conc)
C <sub>MAXD</sub>	C <sub>max_D</sub>	Max Conc Norm by Dose
T <sub>MAX</sub>	T <sub>max_D</sub>	Time of C <sub>max</sub>
T <sub>LAG</sub>	T <sub>lag</sub>	Time Until First Nonzero Conc
CL <sub>ST</sub>	C <sub>last</sub>	Last Nonzero Conc
CL <sub>STP</sub>	C <sub>last_pred</sub>	Last Nonzero Conc Pred
TL <sub>ST</sub>	T <sub>last</sub>	Time of Last Nonzero Conc
LAMZHL	HL_Lambda_z	Half-Life Lambda z
LAMZ	Lambda_z	Lambda z
LAMZLL	Lambda_z lower	Lambda z Lower Limit
LAMZUL	Lambda_z upper	Lambda z Upper Limit
LAMZNPT	No_points_Lambda_z	Number of Points for Lambda z
CORRXY	Corr_XY	Correlation Between Time X and Log Conc Y
R <sup>2</sup>	Rs <sub>q</sub>	R Squared
R <sup>2</sup> ADJ	Rs <sub>q_adjusted</sub>	R Squared Adjusted
AUC <sub>CLST</sub>	AUC <sub>last</sub>	AUC to Last Nonzero Conc
AUC <sub>CALL</sub>	AUC <sub>all</sub>	AUC All
AUC <sub>IFO</sub>	AUC <sub>INF_obs</sub>	AUC Infinity Obs
AUC <sub>IFOD</sub>	AUC <sub>INF_D_obs</sub>	AUC Infinity Obs Norm by Dose
AUC <sub>IFP</sub>	AUC <sub>INF_Pred</sub>	AUC Infinity Pred
AUC <sub>IFPD</sub>	AUC <sub>INF_D_pred</sub>	AUC Infinity Pred Norm by Dose
AUC <sub>PEO</sub>	AUC_Ext <sub>rap_obs</sub>	AUC %Extrapolation Obs
AUC <sub>PEP</sub>	AUC_Ext <sub>rap_pred</sub>	AUC %Extrapolation Pred
AUM <sub>CLST</sub>	AUM <sub>last</sub>	AUMC to Last Nonzero Conc
AUM <sub>IFO</sub>	AUM <sub>CINF_obs</sub>	AUMC Infinity Obs
AUM <sub>IFP</sub>	AUM <sub>CINF_Pred</sub>	AUMC Infinity Pred
AUM <sub>CPEO</sub>	AUMC_Ext <sub>rap_obs</sub>	AUMC %Extrapolation Obs
AUM <sub>CPEP</sub>	AUMC_Ext <sub>rap_pred</sub>	AUMC % Extrapolation Pred
VZ <sub>FO</sub>	Vz_F_obs	Vz Obs by F
VZ <sub>FP</sub>	Vz_F_p	Vz Pred by F
CL <sub>FO</sub>	Cl_F_obs	Total CL Obs by F
CL <sub>FP</sub>	Cl_F_pred	Total CL Pred by F
MRT <sub>EV<sub>LST</sub></sub>	MRT <sub>last</sub>	MRT Extravasc to Last Nonzero Conc
MRT <sub>EV<sub>IFO</sub></sub>	MRT <sub>INF_obs</sub>	MRT Extravasc Infinity Obs
MRT <sub>EV<sub>IFP</sub></sub>	MRT <sub>INF_pred</sub>	MRT Extravasc Infinity Pred

**Table 2.** Part of Theoph dataset with information on key (subject), time, and concentration

Subject	Weight (kg)	Dose (mg)	Time (h)	Concentration (mg/ml)
8	70.5	4.53	0	0.00
8	70.5	4.53	0.25	3.05
8	70.5	4.53	0.52	3.05
8	70.5	4.53	0.98	7.31
8	70.5	4.53	2.02	7.56
8	70.5	4.53	3.53	6.59
8	70.5	4.53	5.05	5.88
8	70.5	4.53	7.15	4.73
8	70.5	4.53	9.05	4.57
8	70.5	4.53	12.10	3.00
8	70.5	4.53	24.12	1.25

## Results

### NonCompart package: performance of NCA

This package conducts NCA as similarly as possible to the most widely used commercial PK analysis software. The *NonCompart* package has two main functions, `tblNCA` and `sNCA`, for use in multiple subjects and one subject, respectively. Figure 1 shows an example of output by `tblNCA`. The input data for `tblNCA()` should be in a long format as exemplified by the Theoph dataset.

It is possible to input several keys such as subject demographics and information regarding dose, period, or sequence; the result of `tblNCA()` will print the key columns and the carried keys can be further used for additional statistical analysis (i.e. descriptive statistics, bioequivalence test, t-test, or ANOVA). The `adm` argument can be 'Extravascular', 'Bolus', or 'Infusion' and the `down` argument can be either 'Linear' or 'Log'. The greatest advantage of this package is that the outputs produced by this package are compatible with those of pharmacokinetic parameter (PP) TESTCD of CDISC SDTM.

### R code

```
tblNCA(Theoph, key = "Subject", colTime =
"Time", colConc = "conc", dose = 320,
adm = "Extravascular", dur = 0, doseUnit
= "mg", timeUnit = "h", concUnit = "mg/
L", down = "Linear")
```

`IntAUC()` function calculates interval (partial) AUC (from  $t_1$  and  $t_2$ ) with the given series of time and concentration. The interval AUC (0.5–11 hour) of the subject 8 can be calculated using the Theoph dataset with the following R script.

### R code

```
Time = Theoph[Theoph$Subject == 8,
"Time"]

Concentration = Theoph[Theoph$Subject
== 8, "conc"]

Res = sNCA(Time, Concentration, dose
= 320, concUnit = "mg/L")

IntAUC(Time, Concentration, t1 = 0.5,
t2 = 11, Res)

[1] 58.26022
```

### ncar package: generation of NCA reports

This package generates complete NCA reports including plots with both linear and logarithmic scale. Its two main functions are `pdfNCA` and `rtfNCA`, which produce pdf file format and rtf file format, respectively. The generated reports are similar to those generated from commercial softwares, but like *NonCompart*, this package has the advantage of using PPT-

```
> tblNCA(Theoph, key = "Subject", colTime = "Time", colConc = "conc", dose = 320,
+ adm = "Extravascular", dur = 0, doseUnit = "mg", timeUnit = "h", concUnit = "mg/L", down = "Linear")
  Subject b0          CMAX      CMAXD      TMAX      TLAG      CLST      CLSTP      TLST      LAMZHL
[1,] "1"      "2.36878509420585" "10.5" "0.0328125" "1.12" "0" "3.28" "3.28014647414312" "24.37" "14.304377571097"
[2,] "2"      "2.41123733696293" "8.33" "0.02603125" "1.92" "0" "0.9" "0.888639849106919" "24.3" "6.65934156262252"
[3,] "3"      "2.52971150145858" "8.2" "0.025625" "1.02" "0" "1.05" "1.05509670837553" "24.17" "6.76608737718236"
[4,] "4"      "2.59275546723663" "8.6" "0.026875" "1.07" "0" "1.15" "1.15642160174997" "24.65" "6.98124666099893"
[5,] "5"      "2.55109229061238" "11.4" "0.035625" "1" "0" "1.57" "1.55569511595616" "24.35" "8.0022640410078"
[6,] "6"      "2.0334043955261" "6.44" "0.020125" "1.15" "0" "0.92" "0.941271173708175" "23.85" "7.89499786796582"
[7,] "7"      "2.28854976005424" "7.09" "0.02215625" "3.48" "0" "1.15" "1.16071921229933" "24.22" "7.84666826130148"
[8,] "8"      "2.17040271754659" "7.56" "0.023625" "2.02" "0" "1.25" "1.22852675835656" "24.12" "8.51003788342506"
[9,] "9"      "2.12464810390587" "9.03" "0.02821875" "0.63" "0" "1.12" "1.11648311706515" "24.43" "8.40599880716182"
[10,] "10"     "2.65770546248091" "10.21" "0.03190625" "3.55" "0" "2.42" "2.41369227401111" "23.7" "9.24691582297898"
[11,] "11"     "2.1475943307927" "8" "0.025" "0.98" "0" "0.86" "0.859806606884089" "24.08" "7.26123651504339"
[12,] "12"     "2.82449347826545" "9.75" "0.03046875" "3.52" "0" "1.17" "1.17553904959565" "24.15" "6.28650816367189"
```

**Figure 1.** Example of *NonCompart* package functions. Example by `tblNCA`.

ESTCD of CDISC SDTM. *ncar* produces NCA reports through *NonCompart* and converts them into Microsoft Word format when using `rtfNCA()`, which is convenient for editing. Reports generated by `pdfNCA()` function show individual plots with trend lines that joins the dots used for calculating terminal slopes. Figure 2 shows an example of an NCA report in pdf format and an individual concentration-time plot.

#### R code

```
pdfNCA(fileName = "pdfNCA-Theoph.pdf",
Theoph, colSubj = "Subject", colTime =
"Time", colConc = "conc", dose = 320,
doseUnit = "mg", timeUnit = "h", concU-
nit = "mg/L", down = "Linear")
```

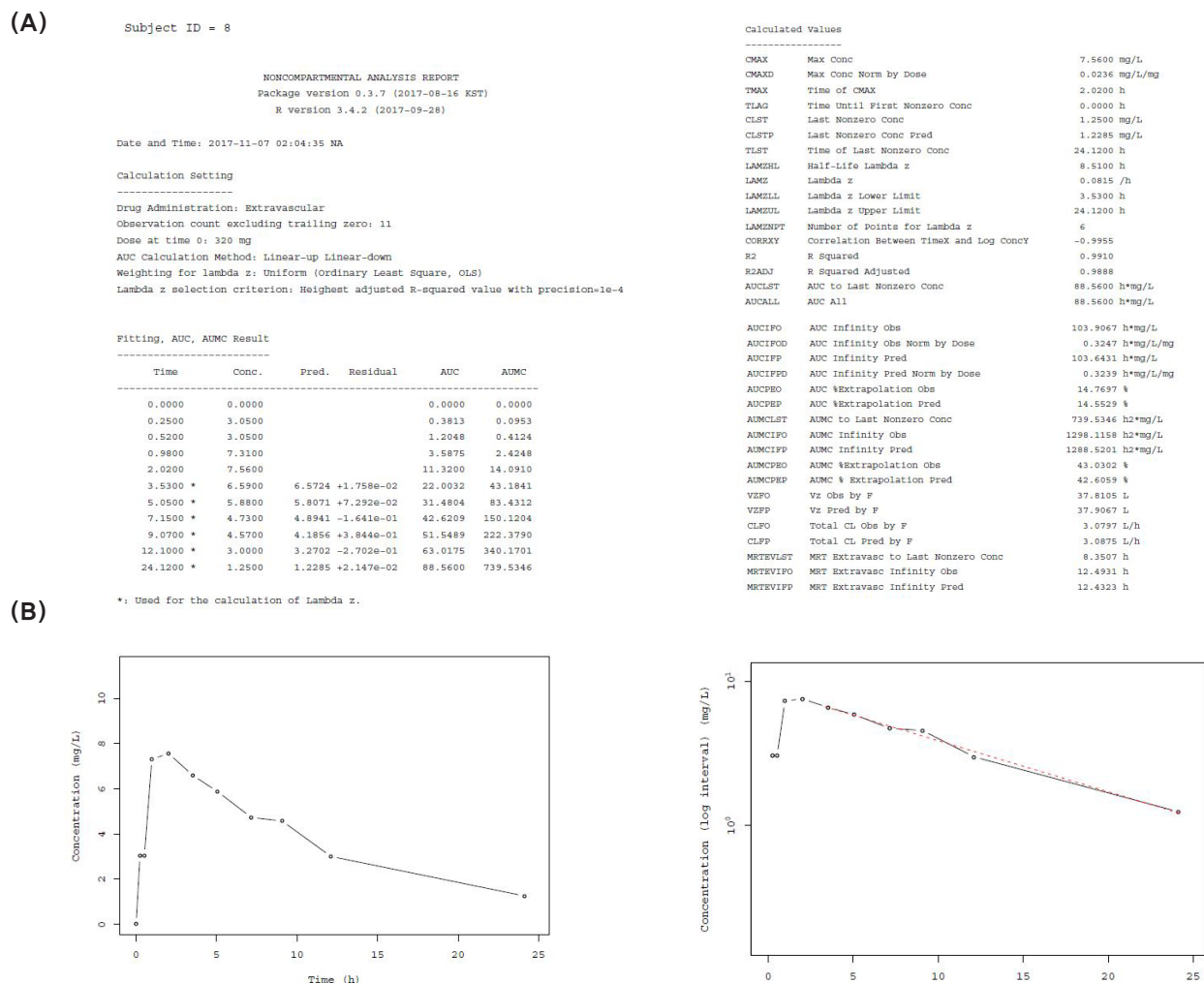
#### Validation of NCA results between R packages and WinNonlin®

To demonstrate the accordance of outputs by *ncar* package and WinNonlin®, we performed NCA using *Theoph* dataset obtained from the R software. For comparison of the NCA results, we selected the following conditions: extravascular, linear-up linear-down, and best fit. We found no discrepancy between the two results as shown in Table 3 (a randomized subject, Subject ID = 8).

In order to further validate these packages, we compared NCA results using *Indometh*, another available dataset of the R software as well as other datasets of a number of subjects from several phase 1 clinical trials with different dosing routes such as infusion, bolus, and oral route. As a result, we could not find

**Table 3.** Comparison of NCA results generated from WinNonlin® and *ncar* package

Parameter	WinNonlin®	ncar
C <sub>MAX</sub>	7.56 mg/L	7.5600 mg/L
C <sub>MAXD</sub>	0.023625 mg/L/mg	0.0236 mg/L/mg
T <sub>MAX</sub>	2.02 h	2.0200 h
T <sub>LAG</sub>	0 h	0.0000 h
CL <sub>ST</sub>	1.25 mg/L	1.2500 mg/L
T <sub>LST</sub>	24.12 h	24.1200 h
LAM <sub>ZHL</sub>	8.510037883 h	8.5100 h
LAM <sub>Z</sub>	0.08145054 /h	0.0815 /h
LAM <sub>ZLL</sub>	3.53 h	3.5300 h
LAM <sub>ZUL</sub>	24.12 h	24.1200 h
LAM <sub>ZNPT</sub>	6	6
COR <sub>XY</sub>	-0.995496053	-0.9955
R <sup>2</sup>	0.991012391	0.991
R <sup>2</sup> <sub>ADJ</sub>	0.988765489	0.9888
AUC <sub>LST</sub>	88.55995 h*mg/L	88.5600 h*mg/L
AUC <sub>ALL</sub>	88.55995 h*mg/L	88.5600 h*mg/L
AUC <sub>IFO</sub>	103.906687 h*mg/L	103.9067 h*mg/L
AUC <sub>IFOD</sub>	0.324708 h*mg/L/mg	0.3247 h*mg/L/mg
AUC <sub>IFP</sub>	103.643051 h*mg/L	103.6431 h*mg/L
AUC <sub>IFP</sub>	0.323884 h*mg/L/mg	0.3239 h*mg/L/mg
AUC <sub>PEO</sub>	14.77%	14.77%
AUC <sub>PEP</sub>	14.55%	14.55%
AUM <sub>CLST</sub>	739.534598 h <sup>2</sup> *mg/L	739.5346 h <sup>2</sup> *mg/L
AUM <sub>CIFO</sub>	1298.115755 h <sup>2</sup> *mg/L	1298.1158 h <sup>2</sup> *mg/L
AUM <sub>CIFP</sub>	1288.520116 h <sup>2</sup> *mg/L	1288.5201 h <sup>2</sup> *mg/L
AUM <sub>CPEO</sub>	43.03%	43.03%
AUM <sub>CPEP</sub>	42.61%	42.61%
VZ <sub>FO</sub>	37.81050811 L	37.8105 L
VZ <sub>FP</sub>	37.90668616 L	37.9067 L
CL <sub>FO</sub>	3.079686301 L/h	3.0797 L/h
CL <sub>FP</sub>	3.087520055 L/h	3.0875 L/h
MRTE <sub>VLST</sub>	8.35066639 h	8.3507 h
MRTE <sub>VIFO</sub>	12.49309159 h	12.4931 h
MRTE <sub>VIFP</sub>	12.43228656 h	12.4323 h



**Figure 2.** Examples of *ncar* package functions. (A) Example of a NCA report in pdf format by pdfNCA, (B) Individual concentration-time plots (left: linear scale, right: log-linear scale).

any discrepancy between outputs generated by the R packages and WinNonlin®.

## Discussion

We developed two R packages—*NonCompart* and *ncar* for NCA. Through these packages, we aimed to implement the following functionalities for performing NCA: 1) CDISC SDTM terms; 2) automatic slope selection with the same criterion of WinNonlin®; 3) supporting both 'linear-up linear-down' and 'linear-up log-down' method; and 4) interval (partial) AUCs with 'linear' or 'log' interpolation method. These packages are convenient and efficient because they enable preparation of data and NCA as well as generation of reports including plots together in R software. As shown in Figure 2B, the

NCA plot allows for automatic slope selection, however, it is not possible to manually choose the points used for calculating terminal slope. In addition, any error or change can easily be fixed, and users may choose calculation methods between linear and logarithmic, which support 'linear-up linear-down' and 'linear-up log-down' method, respectively. Our results showed that our R packages meet the aforementioned objectives.

Since the PPTESTCD of SDTM is used in the R packages, it is helpful to construct PP domain. In the present practice, one has to change variables from WinNonlin® one by one, which is an especially difficult task for those without specific knowledge on SDTM. A number of packages can perform NCA, but no package—even commercial softwares—can give outputs in the format of SDTM or receive SDTM-formatted input data. It is

important to ensure that the reports are legible to sponsors and regulatory bodies by generating a consistent and systematic result, as well as the exact results of NCA.

As shown in Table 3, comparison of NCA results obtained by WinNonlin® and *ncar* package (including another package) showed no significant discrepancies. These two R packages are fast and easy-to-use tool-set that can successfully perform NCA with concentration–time data. Specifically, the *ncar* package can produce a comprehensive set of graphical and tabular outputs that summarize the NCA results, which is a complete report in pdf or rtf format. Our two newly-developed packages are free and open-source, so they can be used to develop other useful packages as well. We hope that *NonCompart* and *ncar* packages will enable researchers to easily perform NCA, and contribute to facilitation of drug discovery process.

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### Conflicts of interests

- Authors: The authors declare that they have no conflict of interests
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