**Noncompartmental analysis (NCA) using R packages : ‘*ncar’,* ‘pkr’, ‘NonCompart’**

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Running title: R packages for NCA

Key words: ncar, pkr, NonCompart, R, noncompartmental analysis (NCA)

**Abstract**

In this article, we introduce newly developed R packages, *pkr* (Pharmacokinetics in R)*, NonCompart* (NonCompartmental analysis for pharmacokinetic data)*,* and *ncar* (NonCompartmental Analysis for pharmacokinetic Report), which can perform a noncompartmental analysis (NCA), and produce a complete NCA report simultaneously in PDF and RTF format. We demonstrate how similarily results of WinNonlin® were reproduced and how easily an NCA report can be obtained by these packages. We hope that this article helps many researchers carry out NCA with these R packages and utilize the output for the early stage of drug discovery process. These R packages are freely available for download on CRAN repository ([http://cran.r-project.org/web/packages/ncar/index.html](http://cran.r-project.org/web/packages/ncar/%20index.html), <http://cran.r-project.org/web/packages/pkr/index.html>, [http://cran.r-project.org/web/packages/ NonCompart/index.html](http://cran.r-project.org/web/packages/%20NonCompart/index.html)).

**Introduction**

The aim of pharmacokinetics (PK) studies is to examine the kinetics of a drug with regard to absorption, distribution, metabolism and elimination in the body. When analyzing PK data, it can be classified into noncompartmental analysis (NCA) and nonlinear regression analysis. [1, 2] NCA, which uses the trapezoidal rule for measurements of the area under the concentration-time curve (AUC), requires fewer assumptions than model-based analysis. [2] In NCA, we can estimate various PK parameters such as AUC, peak observed drug concentration (Cmax), time of peak concentration (Tmax), elimination half-life and other metrics. In particular, AUC and Cmax are often accepted as the criteria of the approval for bioequivalent drugs.

R, widely-used computer language, is a suite of libraries for statistical and mathematical computation. [3] In spite of its relatively small base system compared with other commercial software for NCA such as WinNonlin®, [4] and Kinetica, [5] R has robust functions for scientific computation and many add-in packages for specific fields such as pharmacokinetics. [6] Until now, many efforts are being made to make an R package to replace commercial software.

In this article, we introduce *ncar, pkr,* and *NonCompart* packages written in R programming language that provides an easy-to-use and practical method to produce a complete NCA report. Thus, these packages can potentially facilitate the early stage of drug discovery process by performing NCA even for researchers who are not available for commercial software such as WinNonlin®.

**Methods**

**Software**

WinNonlin® (Pharsight, Mountain View, CA, USA) [4] under MS-Windows 7 (64 bit) was used for the computation. For the R software, R 3.4.1 under MS-Windows 7 was used for the comparison of calculated values.

**Dataset**

For the comparison of output between by Rpackage and by WinNonlin®, we used ‘Theoph’ dataset obtained from R software inside. The ‘Theoph’ dataset has 132 observations from 12 subjects.

**R packages (*ncar, pkr,* and *NonCompart*)**

Three R packages (ncar, pkr, and NonCompart) for NCA were developed in the open-source R programming language in order to allow public to use freely. R packages can be installed and loaded by the scripts below.

install.packages(“ncar”, “NonCompart”, “pkr”)

library(ncar)

library(pkr)

library(NonCompart)

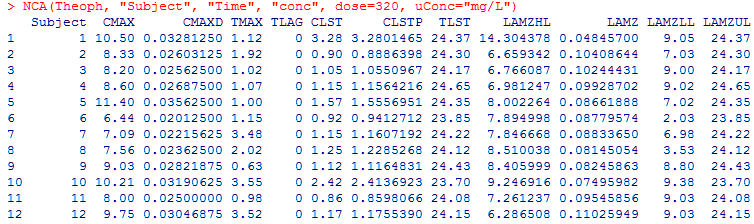
Detailed documentation and examples for each package can be found on the online user manual on the CRAN repository or directly within the R console by entering ?function (e.g. ?pkr, ?NonCompart, ?ncar) after installation. These three R packages are implemented in R and accept a set of input arguments, resulting in processing of data and output production. The names of most of NCA metrics estimated by the function of these packages are consistent with those used in WinNonlin® (Table 1).

**Results**

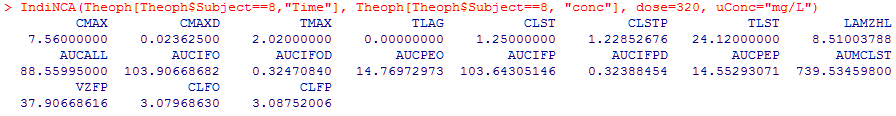
***pkr* package**

This package conducts a NCA as closely as possible to the most widely used commercial PK analysis software. The main functions are NCA and IndNCA to perfom NCA for many subjects and for to perform for one subject, respectively. An example of these two functions is below.

NCA(Theoph, "Subject", "Time", "conc", dose=320, uConc="mg/L")



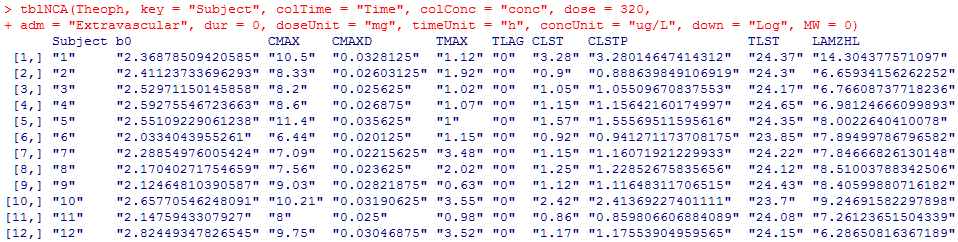
IndiNCA(Theoph[Theoph$Subject==8,"Time"], Theoph[Theoph$Subject==8, "conc"], dose=320, uConc="mg/L")

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***NonCompart* package**

This package also conducts a NCA as closely as *pkr*, however, this package gives a tablular form in contrast to *pkr* package. In this package, there are two main functions which are tblNCA and sNCA for many subjects and for one subject, respectively.

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

****

One can input several keys such as subject demographics, information regarding dose, period, or sequence and the result of tblNCA( ) will print the keys 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'. The down argument can be 'Linear' or 'Log'.

***ncar* package**

Particularly, this package can produce a complete NCA report (PDF and rtf file format). Two main functions are pdfNCA and rtfNCA, which can generate a PDF file format and rtf file format, respectively. If you enter pdfNCA instead of rtfNCA, you can generate a PDF file.

rtfNCA(fileName="rtfNCA-Theoph.rtf", Theoph, colSubj="Subject", colTime="Time", colConc="conc", dose=320, doseUnit="mg", timeUnit="h", concUnit="mg/L")

(Subject ID = 8)

NONCOMPARTMENTAL ANALYSIS REPORT

Package version 0.3.7 (2017-08-16 KST)

R version 3.4.1 (2017-06-30)

Date and Time: 2017-09-19 15:42:56 KST

Calculation Setting

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Drug Administration: Extravascular

Observation count excluding trailing zero: 11

Dose at time 0: 320 mg

AUC Calculation Method: Linear-up Linear-down

Weighting for lambda z: Uniform (Ordinary Least Square, OLS)

Lambda z selection criterion: Highest adjusted R-squared value with precision=1e-4

Fitting, AUC, AUMC Result

-------------------------

Time Conc. Pred. Residual AUC AUMC

---------------------------------------------------------------------

0.0000 0.0000 0.0000 0.0000

0.2500 3.0500 0.3813 0.0953

0.5200 3.0500 1.2048 0.4124

0.9800 7.3100 3.5875 2.4248

2.0200 7.5600 11.3200 14.0910

3.5300 \* 6.5900 6.5724 +1.758e-02 22.0032 43.1841

5.0500 \* 5.8800 5.8071 +7.292e-02 31.4804 83.4312

7.1500 \* 4.7300 4.8941 -1.641e-01 42.6209 150.1204

9.0700 \* 4.5700 4.1856 +3.844e-01 51.5489 222.3790

12.1000 \* 3.0000 3.2702 -2.702e-01 63.0175 340.1701

24.1200 \* 1.2500 1.2285 +2.147e-02 88.5600 739.5346

\*: Used for the calculation of Lambda z.

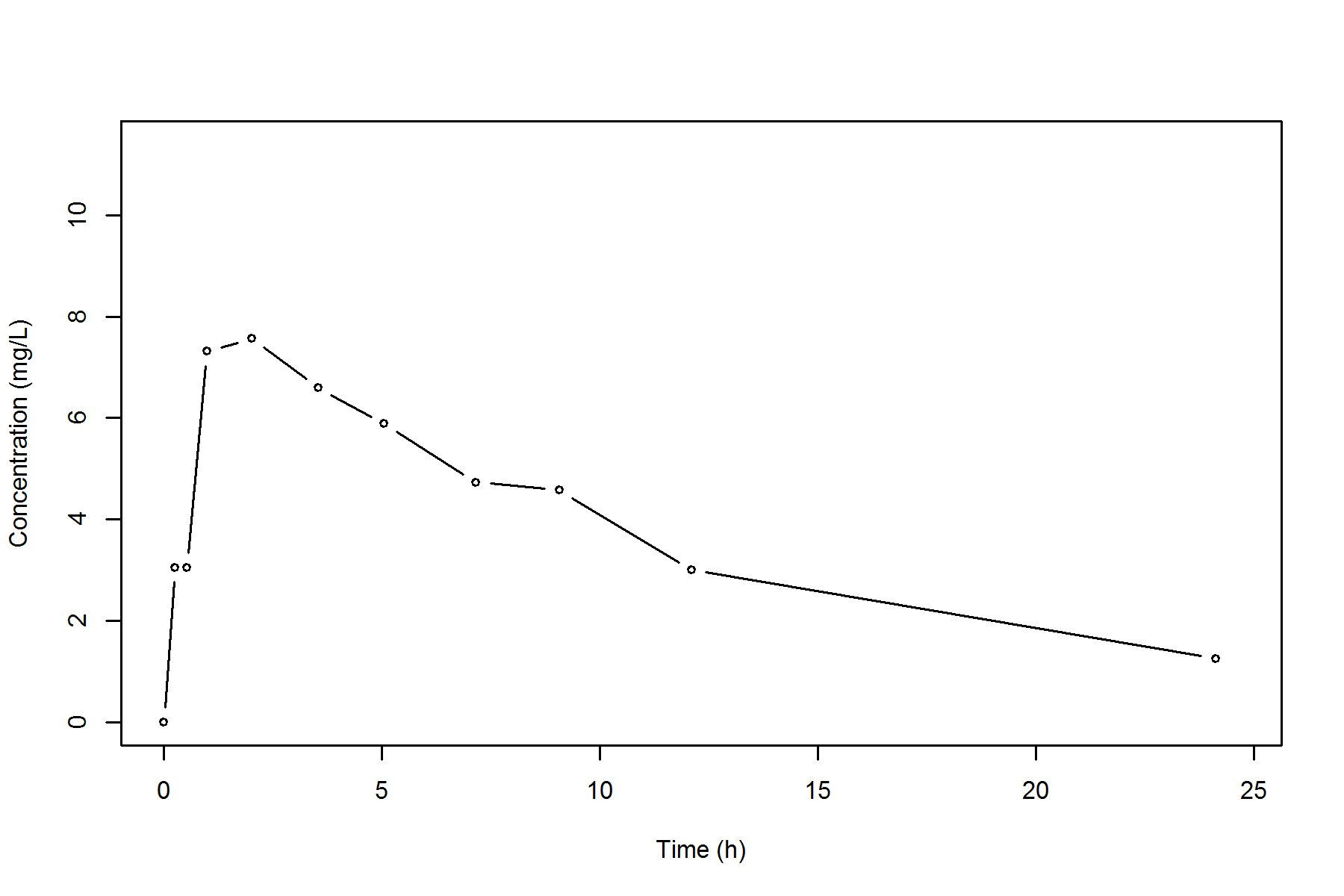
Calculated Values

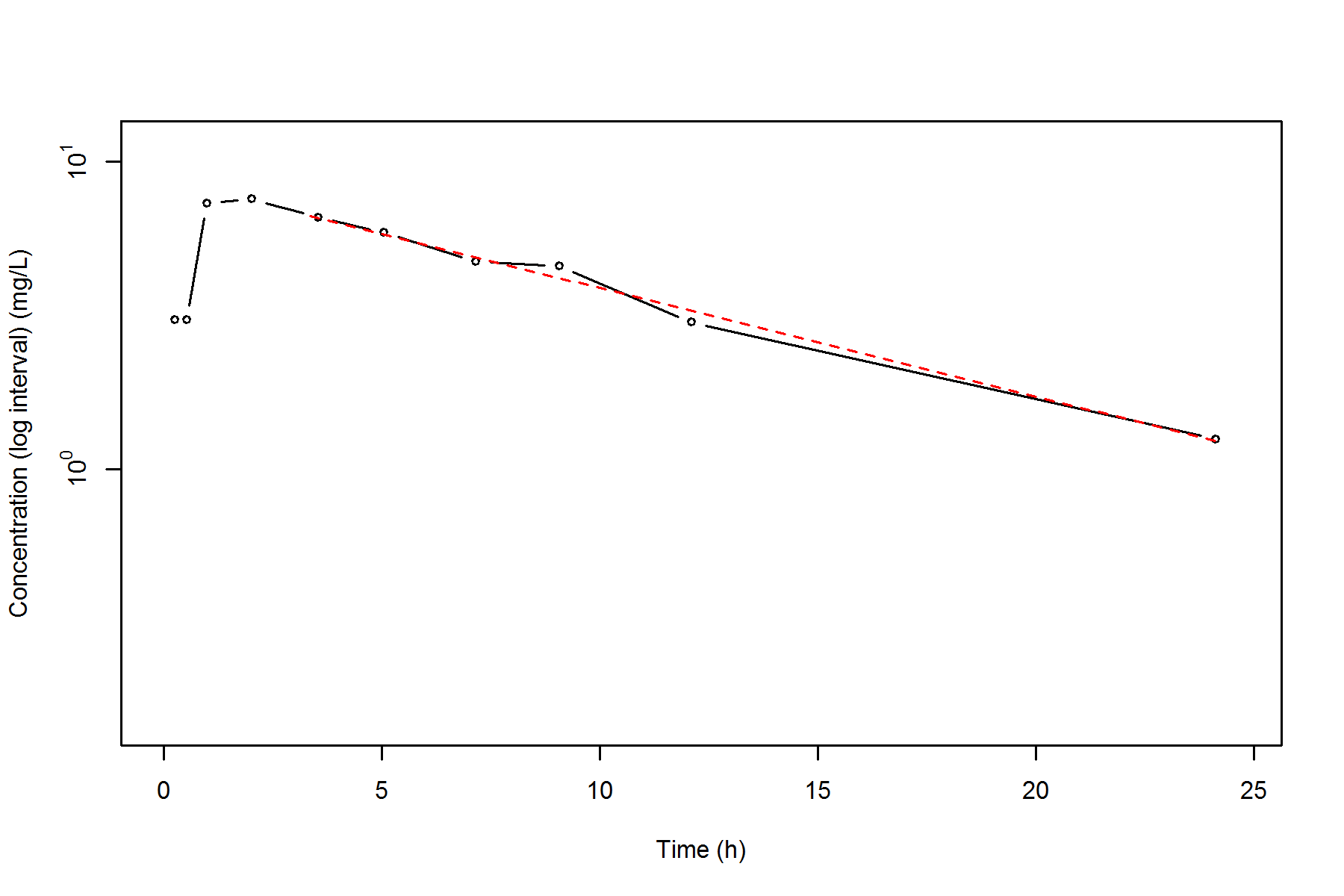
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|  |  |  |
| --- | --- | --- |
| CMAX  CMAXD  TMAX  TLAG  CLST  CLSTP  TLST  LAMZHL  LAMZ  LAMZLL  LAMZUL  LAMZNPT  CORRXY  R2  R2ADJ  AUCLST  AUCALL  AUCIFO  AUCIFOD  AUCIFP  AUCIFPD  AUCPEO  AUCPEP  AUMCLST  AUMCIFO  AUMCIFP  AUMCPEO  AUMCPEP  VZFO  VZFP  CLFO  CLFP  MRTEVLST  MRTEVIFO  MRTEVIFP | Max Conc  Max Conc Norm by Dose  Time of CMAX  Time Until First Nonzero Conc  Last Nonzero Conc  Last Nonzero Conc Pred  Time of Last Nonzero Conc  Half-Life Lambda z  Lambda z  Lambda z Lower Limit  Lambda z Upper Limit  Number of Points for Lambda z  Correlation Between TimeX and Log ConcY  R Squared  R Squared Adjusted  AUC to Last Nonzero Conc  AUC All  AUC Infinity Obs  AUC Infinity Obs Norm by Dose  AUC Infinity Pred  AUC Infinity Pred Norm by Dose  AUC %Extrapolation Obs  AUC %Extrapolation Pred  AUMC to Last Nonzero Conc  AUMC Infinity Obs  AUMC Infinity Pred  AUMC %Extrapolation Obs  AUMC % Extrapolation Pred  Vz Obs by F  Vz Pred by F  Total CL Obs by F  Total CL Pred by F  MRT Extravasc to Last Nonzero Conc  MRT Extravasc Infinity Obs  MRT Extravasc Infinity Pred | 7.5600 mg/L  0.0236 mg/L/mg  2.0200 h  0.0000 h  1.2500 mg/L  1.2285 mg/L  24.1200 h  8.5100 h  0.0815 h  3.5300 h  24.1200 h  6  -0.9955  0.9910  0.9888  88.5600 h\*mg/L  88.5600 h\*mg/L  103.9067 h\*mg/L  0.3247 h\*mg/L/mg  103.6431 h\*mg/L  0.3239 h\*mg/L/mg  14.7697 %  14.5529 %  739.5346 h2\*mg/L  1298.1158 h2\*mg/L  1288.5201 h2\*mg/L  43.0302 %  42.6059 %  37.8105 L  37.9067 L  3.0797 L/h  3.0875 L/h  8.3507 h  12.4931 h  12.4323 h |

(B)

(Subject ID = 8)





**Comparison of NCA results between R package (*ncar*) and WinNonlin®**

A comparison of NCA metrics obtained by *ncar* package and WinNonlin® showed no discrepancies as shown in Table 2 (a randomized subject, Subject ID = 8).

Table 2. Comparison of NCA results between WinNonlin® and *ncar* package (Theoph dataset, subject ID = 8)

|  |  |  |
| --- | --- | --- |
| Parameter | WinNonlin® | *ncar* |
| CMAX  CMAXD  TMAX  TLAG  CLST  CLSTP  TLST  LAMZHL  LAMZ  LAMZLL  LAMZUL  LAMZNPT  CORRXY  R2  R2ADJ  AUCLST  AUCALL  AUCIFO  AUCIFOD  AUCIFP  AUCIFPD  AUCPEO  AUCPEP  AUMCLST  AUMCIFO  AUMCIFP  AUMCPEO  AUMCPEP  VZFO  VZFP  CLFO  CLFP  MRTEVLST  MRTEVIFO  MRTEVIFP | 7.56 mg/L  -  2.02 h  0 h  1.25 mg/L  -  24.12 h  8.5100379 h  0.08145054 h  3.53 h  24.12 h  6  -0.99549605  0.99101239  0.98876549  88.55995 h\*mg/L  88.55995 h\*mg/L  103.906687 h\*mg/L  -  103.643051 h\*mg/L  -  14.769730 %  14.552931 %  739.534598 h2\*mg/L  1298.115755 h2\*mg/L  1288.520116 h2\*mg/L  42.479491 %  42.056657 %  37.81051 L  37.90669 L  3.079686 L  3.087520 L  8.350066 h  12.493092 h  12.432287 h | 7.5600 mg/L  0.0236 mg/L/mg  2.0200 h  0.0000 h  1.2500 mg/L  1.2285 mg/L  24.1200 h  8.5100 h  0.0815 h  3.5300 h  24.1200 h  6  -0.9955  0.9910  0.9888  88.5600 h\*mg/L  88.5600 h\*mg/L  103.9067 h\*mg/L  0.3247 h\*mg/L/mg  103.6431 h\*mg/L  0.3239 h\*mg/L/mg  14.7697 %  14.5529 %  739.5346 h2\*mg/L  1298.1158 h2\*mg/L  1288.5201 h2\*mg/L  43.0302 %  42.6059 %  37.8105 L  37.9067 L  3.0797 L/h  3.0875 L/h  8.3507 h  12.4931 h  12.4323 h |

**Discussion**

We developed three R packages: *ncar, pkr,* and *NonCompart* for NCA. In these packages, we aimed to imple­ment the following functionalities to perform NCA: 1) automatic slope selection with the same criterion of WinNonlin®; 2) supporting both 'linear-up linear-down' and 'linear-up log-down' method; 3) interval (partial) AUCs with 'linear' or 'log' interpolation method. Based on our results, we think that the *ncar* package meets the objectives described above.

As shown in Table 2, comparison of NCA metrics obtained by *ncar* package and WinNonlin® showed no discrepancies. These three Rpackage are fast and easy-to-use tool-set written in R programming language that successfully perform NCA with the concentration–time data. Especially, *ncar* package can produce a comprehensive set of graphical and tabular output to summarize NCA results, which is a complete report in PDF or RTF format. We hope that our newly-developed *ncar, pkr, and NonCompart* packages enable many researchers to use NCA easily without any cost and can contribute to facilitation for the drug discovery process.

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**Conflicts of interests**

* Authors: The authors declare that they have no conflict of interests
* Reviewers: Nothing to declare
* Editors: Nothing to declare

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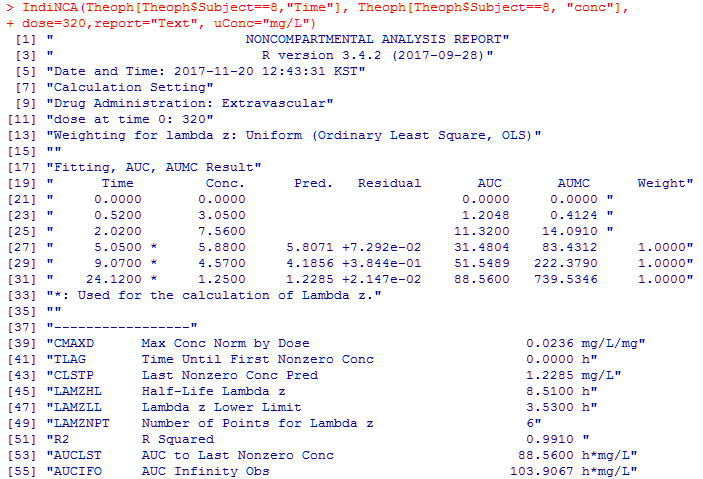
Table 1. Description of the *ncar* arguments

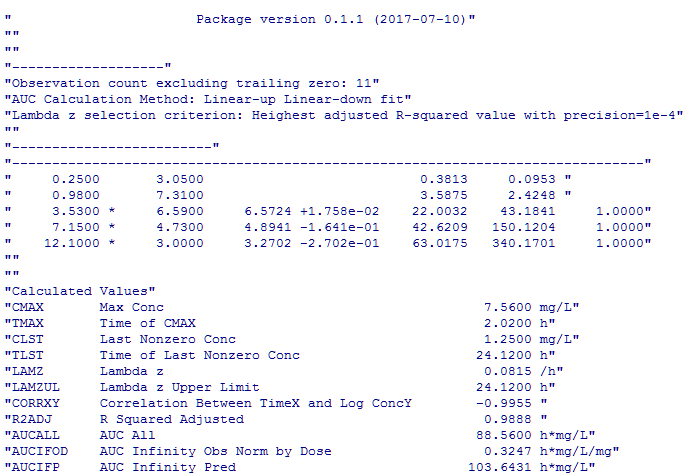
|  |  |
| --- | --- |
| **Name** | **Description** |
| CMAX | Max Conc |
| CMAXD | Max Conc Norm by Dose |
| TMAX | Time of CMAX |
| TLAG | Time Until First Nonzero Conc |
| CLST | Last Nonzero Conc |
| CLSTP | Last Nonzero Conc Pred |
| TLST | Time of Last Nonzero Conc |
| LAMZHL | Half-Life Lambda z |
| LAMZ | Lambda z |
| LAMZLL | Lambda z Lower Limit |
| LAMZUL | Lambda z Upper Limit |
| LAMZNPT | Number of Points for Lambda z |
| CORRXY | Correlation Between TimeX and Log ConcY |
| R2 | R Squared |
| R2ADJ | R Squared Adjusted |
| AUCLST | AUC to Last Nonzero Conc |
| AUCALL | AUC All |
| AUCIFO | AUC Infinity Obs |
| AUCIFOD | AUC Infinity Obs Norm by Dose |
| AUCIFP | AUC Infinity Pred |
| AUCIFPD | AUC Infinity Pred Norm by Dose |
| AUCPEO | AUC %Extrapolation Obs |
| AUCPEP | AUC %Extrapolation Pred |
| AUMCLST | AUMC to Last Nonzero Conc |
| AUMCIFO | AUMC Infinity Obs |
| AUMCIFP | AUMC Infinity Pred |
| AUMCPEO | AUMC %Extrapolation Obs |
| AUMCPEP | AUMC % Extrapolation Pred |
| VZFO | Vz Obs by F |
| VZFP | Vz Pred by F |
| CLFO | Total CL Obs by F |
| CLFP | Total CL Pred by F |
| MRTEVLST | MRT Extravasc to Last Nonzero Conc |
| MRTEVIFO | MRT Extravasc Infinity Obs |
| MRTEVIFP | MRT Extravasc Infinity Pred |

Table 2. Comparison of NCA parameter results between WinNonlin® and *ncar* package

|  |  |  |
| --- | --- | --- |
| parameter | WinNonlin® | ncar |
| CMAX  CMAXD  TMAX  TLAG  CLST  CLSTP  TLST  LAMZHL  LAMZ  LAMZLL  LAMZUL  LAMZNPT  CORRXY  R2  R2ADJ  AUCLST  AUCALL  AUCIFO  AUCIFOD  AUCIFP  AUCIFPD  AUCPEO  AUCPEP  AUMCLST  AUMCIFO  AUMCIFP  AUMCPEO  AUMCPEP  VZFO  VZFP  CLFO  CLFP  MRTEVLST  MRTEVIFO  MRTEVIFP | 7.56 mg/L  -  2.02 h  0 h  1.25 mg/L  -  24.12 h  8.5100379 h  0.08145054 h  3.53 h  24.12 h  6  -0.99549605  0.99101239  0.98876549  88.55995 h\*mg/L  88.55995 h\*mg/L  103.906687 h\*mg/L  -  103.643051 h\*mg/L  -  14.769730 %  14.552931 %  739.534598 h2\*mg/L  1298.115755 h2\*mg/L  1288.520116 h2\*mg/L  42.479491 %  42.056657 %  37.81051 L  37.90669 L  3.079686 L  3.087520 L  8.350066 h  12.493092 h  12.432287 h | 7.5600 mg/L  0.0236 mg/L/mg  2.0200 h  0.0000 h  1.2500 mg/L  1.2285 mg/L  24.1200 h  8.5100 h  0.0815 h  3.5300 h  24.1200 h  6  -0.9955  0.9910  0.9888  88.5600 h\*mg/L  88.5600 h\*mg/L  103.9067 h\*mg/L  0.3247 h\*mg/L/mg  103.6431 h\*mg/L  0.3239 h\*mg/L/mg  14.7697 %  14.5529 %  739.5346 h2\*mg/L  1298.1158 h2\*mg/L  1288.5201 h2\*mg/L  43.0302 %  42.6059 %  37.8105 L  37.9067 L  3.0797 L/h  3.0875 L/h  8.3507 h  12.4931 h  12.4323 h |

**Supplementary**

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