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R packages for Noncompartmental Analysis

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Overview

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.

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1

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. PK data analysis consists of non-compartmental analysis (NCA) and nonlinear regression analysis. (Acharya et al., 2016; Gabrielsson, 2016) NCA uses the trapezoidal rule for measurement of area under the concentration-time curve (AUC), and requires fewer assumptions than model-based analysis. (Gabrielsson, 2016) 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. (R Core Team, 2017) 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 (Bae, 2017b) and ncar (Bae, 2017a), 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.

2

Methods

2.1 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.

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

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 2.1)

2.2 Software

WinNonlin® (Pharsight, Mountain View, CA, USA)[4] in Microsoft-Windows 7 (64 bit) was used for the computation. R

TABLE 2.1 Description of PK parameters of WinNonlin and the R packages

Parameter	WinNonlin	Description
b0	b0	Intercept
CMAX	Cmax	Max Concentration (Conc)
CMAXD	Cmax_D	Max Conc Norm by Dose
TMAX	Tmax_D	Time of Cmax
TLAG	Tlag	Time Until First Nonzero Conc
CLST	Clast	Last Nonzero Conc
CLSTP	Clast_pred	Last Nonzero Conc Pred
TLST	Tlast	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
R2	Rsq	R Squared
R2ADJ	Rsq_adjusted	R Squared Adjusted
AUCLST	AUClast	AUC to Last Nonzero Conc
AUCALL	AUCall	AUC All
AUCIFO	AUCINF_obs	AUC Infinity Obs
AUCIFOD	AUCINF_D_obs	AUC Infinity Obs Norm by Dose
AUCIFP	AUCINF_Pred	AUC Infinity Pred
AUCIFPD	AUCINF_D_pred	AUC Infinity Pred Norm by Dose
AUCPEO	AUC_Extrap_obs	AUC %Extrapolation Obs
AUCPEP	AUC_Extrap_pred	AUC %Extrapolation Pred
AUMCLST	AUMClast	AUMC to Last Nonzero Conc
AUMCIFO	AUMCINF_obs	AUMC Infinity Obs
AUMCIFP	AUMCINF_pred	AUMC Infinity Pred
AUMCPEO	AUMC_Extrap_obs	AUMC %Extrapolation Obs
AUMCPEP	AUMC_Extrap_pred	AUMC % Extrapolation Pred
VZFO	Vz_F_obs	Vz Obs by F
VZFP	Vz_F_p	Vz Pred by F
CLFO	Cl_F_obs	Total CL Obs by F
CLFP	Cl_F_pred	Total CL Pred by F
MRTEVLST	MRTlast	MRT Extravasc to Last Nonzero Conc
MRTEVIFO	MRTINF_obs	MRT Extravasc Infinity Obs
MRTEVIFP	MRTINF_pred	MRT Extravasc Infinity Pred

TABLE 2.2 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	0.00	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

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

2.3 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 2.2.

3

Results

3.1 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.

```
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.

```
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
```

3.2 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 PPTESTCD of CDISC SDTM. ncar produces NCA reports through NonCompart and converts them into Microsoft Word format when using rtfNCA( ), which is convenient for editing. Re- ports 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 for- mat and an individual concentration-time plot.

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

3.3 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 ob- tained 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 2.2 (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 any discrepancy between outputs generated by the R packages and WinNonlin®.

TABLE 3.1 Comparison of NCA results generated from WinNonlin and ncar package

Parameter	WinNonlin	ncar
CMAX	7.56 mg/L	7.5600 mg/L
CMAXD	0.023625 mg/L/mg	0.0236 mg/L/mg
TMAX	2.02 h	2.0200 h
TLAG	0 h	0.0000 h
CLST	1.25 mg/L	1.2500 mg/L
TLST	24.12 h	24.1200 h
LAMZHL	8.510037883 h	8.5100 h
LAMZ	0.08145054 /h	0.0815 /h
LAMZLL	3.53 h	3.5300 h
LAMZUL	24.12 h	24.1200 h
LAMZNPT	6	6
CORRXY	-0.995496053	-0.9955
R2	0.991012391	0.991
R2ADJ	0.988765489	0.9888
AUCLST	88.55995 h*mg/L	88.5600 h*mg/L
AUCALL	88.55995 h*mg/L	88.5600 h*mg/L
AUCIFO	103.906687 h*mg/L	103.9067 h*mg/L
AUCIFOD	0.324708 h*mg/L/mg	0.3247 h*mg/L/mg
AUCIFP	103.643051 h*mg/L	103.6431 h*mg/L
AUCIFP	0.323884 h*mg/L/mg	0.3239 h*mg/L/mg
AUCPEO	14.77%	14.77%
AUCPEP	14.55%	14.55%
AUMCLST	739.534598 h2*mg/L	739.5346 h2*mg/L
AUMCIFO	1298.115755 h2*mg/L	1298.1158 h2*mg/L
AUMCIFP	1288.520116 h2*mg/L	1288.5201 h2*mg/L
AUMCPEO	43.03%	43.03%
AUMCPEP	42.61%	42.61%
VZFO	37.81050811 L	37.8105 L
VZFP	37.90668616 L	37.9067 L
CLFO	3.079686301 L/h	3.0797 L/h
CLFP	3.087520055 L/h	3.0875 L/h
MRTEVLST	8.35066639 h	8.3507 h
MRTEVIFO	12.49309159 h	12.4931 h
MRTEVIFP	12.43228656 h	12.4323 h

4

Discussion

We developed two R packages - NonCompart and ncar for NCA. Through these packages, we aimed to imple ment 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 prepara- tion of data and NCA as well as generation of reports includ- ing 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 ter- minal 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 re- sult, 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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Environment

Package	Version
tidyverse	1.2.1
NonCompart	0.3.3
ncar	0.3.7
knitr	1.20

```
##  setting  value
##  version  R version 3.4.3 (2017-11-30)
##  system   x86_64, mingw32
##  ui       RTerm
##  language (EN)
##  collate  Korean_Korea.949
##  tz       Asia/Seoul
##  date     2018-03-08
##
##  package     * version    date       source
##  assertthat    0.2.0      2017-04-11 CRAN (R 3.4.0)
##  backports     1.1.2      2017-12-13 CRAN (R 3.4.3)
##  base        * 3.4.3      2017-11-30 local
##  bindr         0.1.0.9000 2018-02-08 Github (krlmlr/bindr@4b20179)
##  bindrcpp      0.2.0.9000 2018-02-08 Github (krlmlr/bindrcpp@7553d4f)
##  bookdown      0.7        2018-02-18 CRAN (R 3.4.3)
##  broom         0.4.3      2017-11-20 CRAN (R 3.4.2)
##  cellranger    1.1.0      2016-07-27 CRAN (R 3.4.0)
##  cli           1.0.0      2017-11-05 CRAN (R 3.4.2)
##  colorspace    1.3-2      2016-12-14 CRAN (R 3.4.0)
##  compiler      3.4.3      2017-11-30 local
##  crayon        1.3.4      2018-03-02 Github (gaborcsardi/crayon@95b3eae)
##  datasets    * 3.4.3      2017-11-30 local
##  devtools      1.13.5     2018-02-18 CRAN (R 3.4.3)
```

```
##  digest        0.6.15     2018-01-28 CRAN (R 3.4.3)
##  dplyr       * 0.7.4.9000 2018-02-08 Github (tidyverse/dplyr@0a2c208)
##  evaluate      0.10.1     2017-06-24 CRAN (R 3.4.1)
##  forcats     * 0.3.0      2018-02-19 CRAN (R 3.4.3)
##  foreign       0.8-69     2017-06-22 CRAN (R 3.4.3)
##  ggplot2     * 2.2.1      2016-12-30 CRAN (R 3.4.0)
##  glue          1.2.0      2017-10-29 CRAN (R 3.4.2)
##  graphics    * 3.4.3      2017-11-30 local
##  grDevices   * 3.4.3      2017-11-30 local
##  grid          3.4.3      2017-11-30 local
##  gtable        0.2.0      2016-02-26 CRAN (R 3.4.0)
##  haven         1.1.1      2018-01-18 CRAN (R 3.4.3)
##  hms           0.4.1      2018-01-24 CRAN (R 3.4.3)
##  htmltools     0.3.6      2017-04-28 CRAN (R 3.4.0)
##  httr          1.3.1      2017-08-20 CRAN (R 3.4.1)
##  jsonlite      1.5        2017-06-01 CRAN (R 3.4.0)
##  knitr       * 1.20       2018-02-20 CRAN (R 3.4.3)
##  lattice       0.20-35    2017-03-25 CRAN (R 3.4.3)
##  lazyeval      0.2.1      2017-10-29 CRAN (R 3.4.2)
##  lubridate     1.7.3      2018-02-27 CRAN (R 3.4.3)
##  magrittr      1.5        2014-11-22 CRAN (R 3.4.0)
##  memoise       1.1.0      2017-04-21 CRAN (R 3.4.0)
##  methods       3.4.3      2017-11-30 local
##  mnormt        1.5-5      2016-10-15 CRAN (R 3.4.0)
##  modelr        0.1.1      2017-07-24 CRAN (R 3.4.1)
##  munsell       0.4.3      2016-02-13 CRAN (R 3.4.0)
##  ncar        * 0.3.7      2017-08-16 CRAN (R 3.4.1)
##  nlme          3.1-131.1  2018-02-16 CRAN (R 3.4.3)
##  NonCompart  * 0.3.3      2017-08-16 CRAN (R 3.4.1)
##  parallel      3.4.3      2017-11-30 local
##  pillar        1.2.1      2018-02-27 CRAN (R 3.4.3)
##  pkgconfig     2.0.1      2017-03-21 CRAN (R 3.4.0)
##  plyr          1.8.4      2016-06-08 CRAN (R 3.4.0)
##  psych         1.7.8      2017-09-09 CRAN (R 3.4.1)
##  purrr       * 0.2.4.9000 2018-03-02 Github (tidyverse/purrr@84ce1ad)
##  R.methodsS3   1.7.1      2016-02-16 CRAN (R 3.4.0)
##  R.oo          1.21.0     2016-11-01 CRAN (R 3.4.0)
```

```
##  R6            2.2.2      2017-06-17 CRAN (R 3.4.1)
##  Rcpp          0.12.15    2018-01-20 CRAN (R 3.4.3)
##  readr       * 1.1.1      2017-05-16 CRAN (R 3.4.0)
##  readxl        1.0.0      2017-04-18 CRAN (R 3.4.0)
##  reshape2      1.4.3      2017-12-11 CRAN (R 3.4.3)
##  rlang         0.2.0      2018-02-20 CRAN (R 3.4.3)
##  rmarkdown     1.9        2018-03-01 CRAN (R 3.4.3)
##  rprojroot     1.3-2      2018-01-03 CRAN (R 3.4.3)
##  rstudioapi    0.7        2017-09-07 CRAN (R 3.4.1)
##  rtf         * 0.4-11     2013-11-12 CRAN (R 3.4.0)
##  rvest         0.3.2      2016-06-17 CRAN (R 3.4.0)
##  scales        0.5.0      2017-08-24 CRAN (R 3.4.1)
##  stats       * 3.4.3      2017-11-30 local
##  stringi       1.1.6      2017-11-17 CRAN (R 3.4.2)
##  stringr     * 1.3.0      2018-02-19 CRAN (R 3.4.3)
##  tibble      * 1.4.2      2018-01-22 CRAN (R 3.4.3)
##  tidyr       * 0.8.0      2018-01-29 CRAN (R 3.4.3)
##  tidyselect    0.2.4      2018-02-26 CRAN (R 3.4.3)
##  tidyverse   * 1.2.1      2017-11-14 Github (tidyverse/tidyverse@3769ff2)
##  tools         3.4.3      2017-11-30 local
##  utils       * 3.4.3      2017-11-30 local
##  withr         2.1.1.9000 2018-03-02 Github (r-lib/withr@5d05571)
##  xfun          0.1        2018-01-22 CRAN (R 3.4.3)
##  xml2          1.2.0      2018-01-24 CRAN (R 3.4.3)
##  yaml          2.1.17     2018-02-27 CRAN (R 3.4.3)
```

B

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