Development & Use of R Package for Non-compartmental Analysis

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INTRODUCTION

- Non-compartmental Analysis (NCA) is the basic and essential analysis tool for pharmacokinetic (PK) data from phase 1 clinical studies.
- WinNonlin® is the most widely used commercial software for NCA, but has limited accessibility to some data scientists.
- R is the most widely used, open source statistical computing tool for data science.
- Authors developed a package for R as an open source tool for NCA: 'NonCompart.'

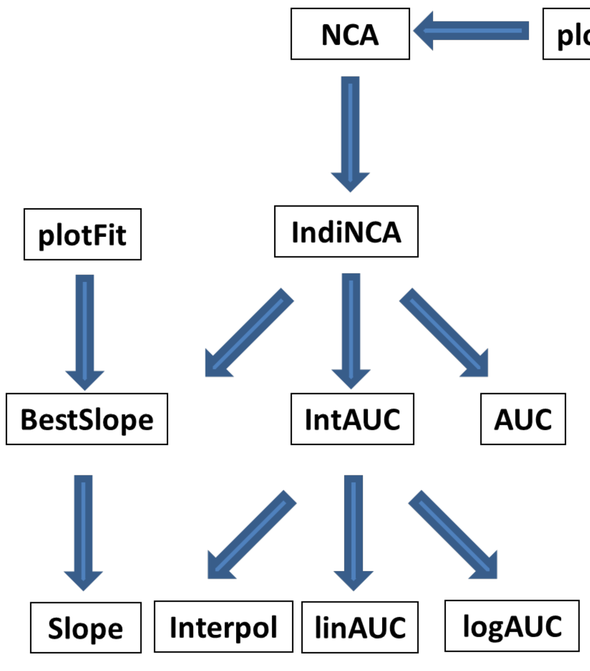
OBJECTIVES

- To develop an open source tool for NCA in R environment
- To provide an effective and efficient tool for writing an NCA report to PK scientists.

MAIN FEATURES

- CDISC SDTM based input and PP based output
- Automatic slope selection with the same criterion of WinNonlin®, 1e-4
- Supporting both 'linear-up linear-down' and 'linear-up log-down' method for AUC calculation
- Interval(partial) AUCs with 'linear' or 'log' interpolation

FUNCTIONS & CALLS

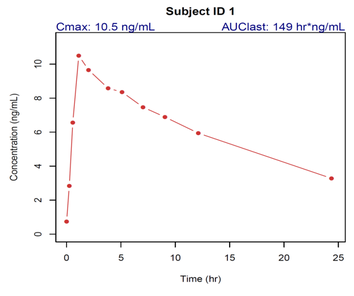


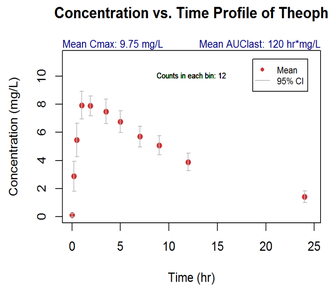
EXAMPLE OF OUTPUTS

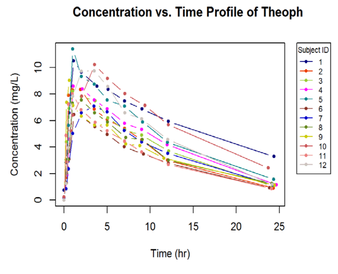
Output Data

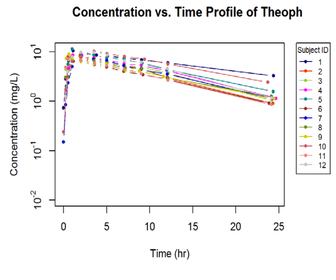
```
NCA REPORT
Subject=1
                        NONCOMPARTMENTAL ANALYSIS REPORT
                      Package version 0.2.7 (2017-01-30)
                         R version 3.3.2 (2016-10-31)

Date and Time: 2017-02-01 01:22:41 KST

Calculation Setting
-------------------
Drug Administration: Extravascular
Observation count excluding trailing zero: 11
dose at time 0: 320
AUC Calculation Method: Linear-up Linear-down fit
Weighting for lambda z: Uniform (Ordinary Least Square, OLS)
Lambda z selection criterion: Heighest adjusted R-squared value with
precision=1e-4


Fitting, AUC, AUMC Result
-------------------------
      Time          Conc.      Pred.   Residual          AUC         AUMC       Weight
-------------------------------------------------------------------------------------
    0.0000       0.7400                              0.0000      0.0000
    0.2500       2.8400                              0.4475      0.0888
    0.5700       6.5700                              1.9531      0.8015
    1.1200      10.5000                              6.6474      5.0654
    2.0200       9.6600                             15.7194     19.1383
    3.8200       8.5800                             32.1354     66.1982
    5.1000       8.3600                             42.9769    114.4617
    7.0300       7.4700                             58.2529    206.2815
    9.0500 *     6.8900      6.8912 -1.228e-03      72.7565    322.2988      1.0000
   12.1200 *     5.9400      5.9387 +1.324e-03      92.4505    528.5219      1.0000
   24.3700 *     3.2800      3.2801 -1.465e-04     148.9231   1459.0711      1.0000

*: Used for the calculation of Lambda z.


Calculated Values
-----------------
CMAX       Max Conc                                  10.5000 mg/L
CMAXD      Max Conc Norm by Dose                      0.0328 mg/L/mg
TMAX       Time of CMAX                               1.1200 h
TLAG       Time Until First Nonzero Conc              0.0000 h
CLST       Last Nonzero Conc                          3.2800 mg/L
CLSTP      Last Nonzero Conc Pred                     3.2801 mg/L
TLST       Time of Last Nonzero Conc                 24.3700 h
LAMZHL     Half-Life Lambda z                        14.3044 h
LAMZ       Lambda z                                   0.0485 /h
LAMZLL     Lambda z Lower Limit                       9.0500 h
LAMZUL     Lambda z Upper Limit                      24.3700 h
LAMZNPT    Number of Points for Lambda z              3
CORRXY     Correlation Between TimeX and Log ConcY   -1.0000
R2         R Squared                                  1.0000
R2ADJ      R Squared Adjusted                         1.0000
AUCLST     AUC to Last Nonzero Conc                 148.9231 h*mg/L
AUCALL     AUC All                                  148.9231 h*mg/L
AUCIFO     AUC Infinity Obs                         216.6119 h*mg/L
AUCIFOD    AUC Infinity Obs Norm by Dose              0.6769 h*mg/L/mg
AUCPEO     AUC %Extrapolation Obs                    31.2489 %
AUCIFP     AUC Infinity Pred                        216.6150 h*mg/L
AUCIFPD    AUC Infinity Pred Norm by Dose             0.6769 h*mg/L/mg
AUCPEP     AUC %Extrapolation Pred                   31.2499 %
AUMCLST    AUMC to Last Nonzero Conc               1459.0711 h2*mg/L
AUMCIFO    AUMC Infinity Obs                       4505.5348 h2*mg/L
AUMCPEO    AUMC %Extrapolation Obs                   67.6160 %
AUMCIFP    AUMC Infinity Pred                      4505.6709 h2*mg/L
AUMCPEP    AUMC % Extrapolation Pred                 67.6170 %
MRTEVLST   MRT Extravasc to Last Nonzero Conc         9.7975 h
MRTEVIFO   MRT Extravasc Infinity Obs                20.8000 h
MRTEVIFP   MRT Extravasc Infinity Pred               20.8004 h
VZFO       Vz Obs by F                               30.4867 L
VZFP       Vz Pred by F                              30.4863 L
CLFO       Total CL Obs by F                          1.4773 L/h
CLFP       Total CL Pred by F                         1.4773 L/h
```

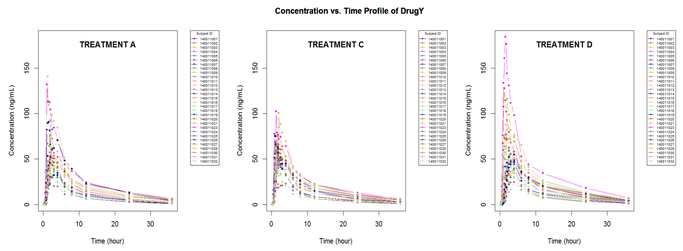
Output Figures

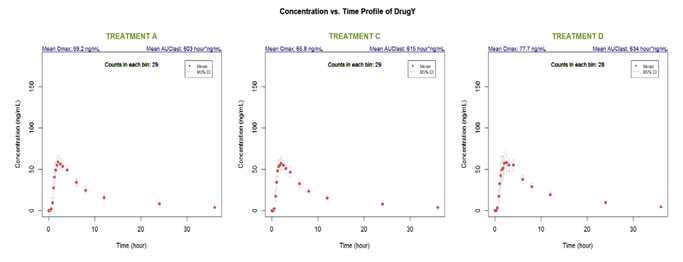




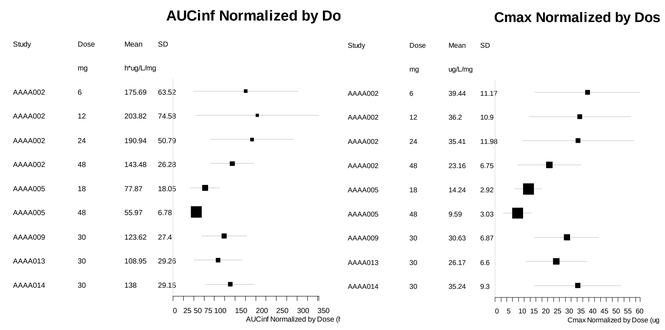








Forest Plots for Inter-Study and Inter-Treatment Comparisons



FUTURE DIRECTIONS

- To make urine data processing available
- To include more diverse graphical analyses
- To support NONMEM input data
- To produce full NCA report automatically
- To develop further based on feedback from end users in data science society

URL for NonCompart Package

https://cran.r-project.org/web/packages/NonCompart/index.html

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