제 5회 제약산업 종사자를 위한 워크숍

R을 사용한 비구획분석 (NCA)

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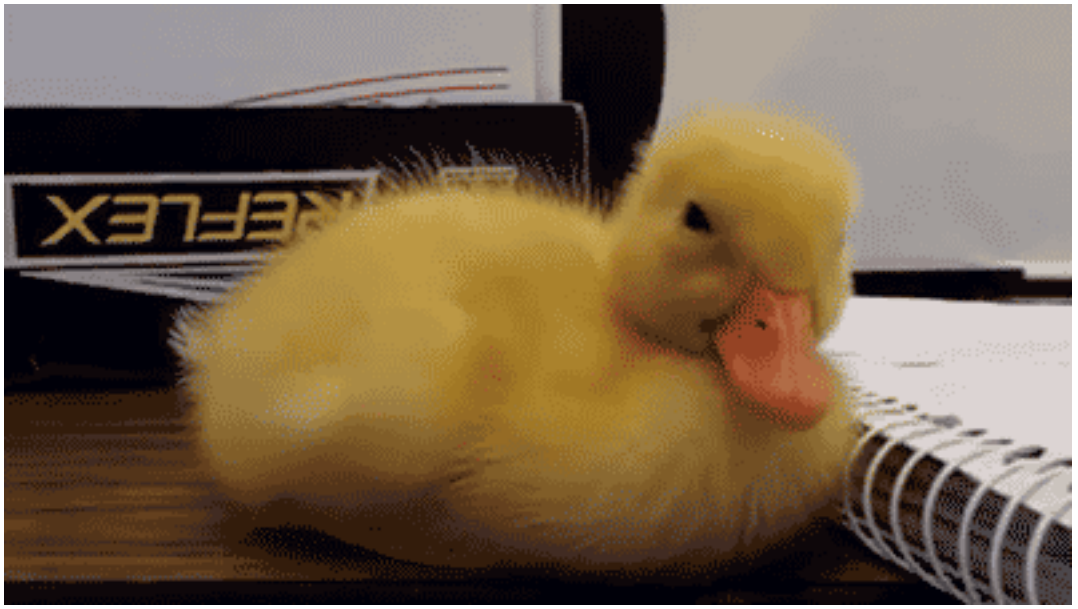
다운로드: bit.ly/shan-pkpd

앱: asan.shinyapps.io/pkrshiny

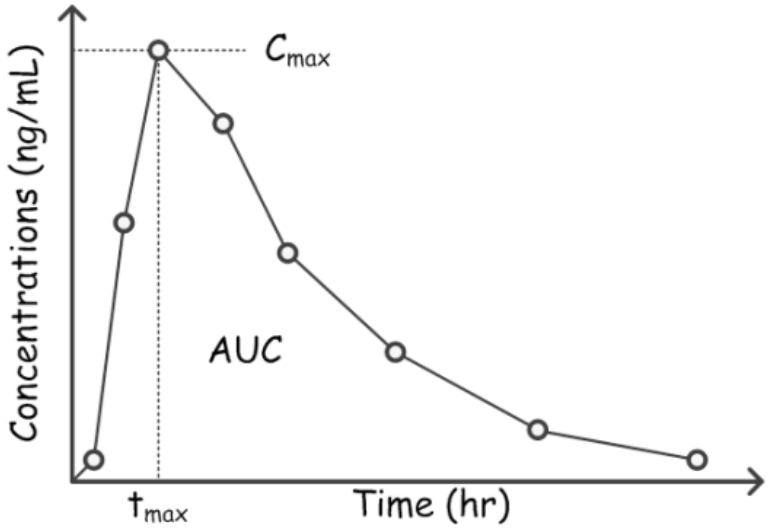
목적

- R을 사용하여 비구획분석을 수행할 수 있도록 안내할 것입니다.
- (프로그래밍..?)



비구획 분석이란

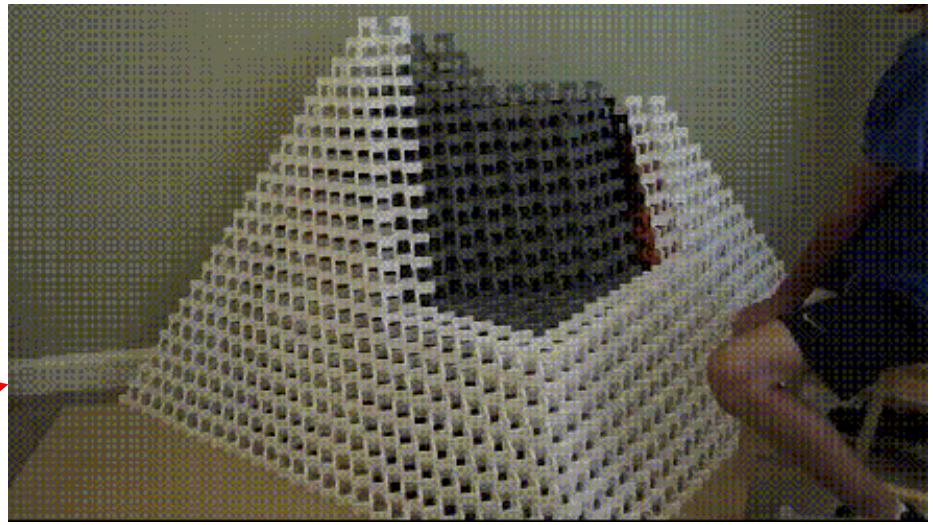
- 시간, 농도가 표현되어 있는 곡선에서 아무런 가정을 하지 않고 분석
- 최대농도 (C_{max}) 및 최대농도에 도달하는 시간 (T_{max}), 전체 시간-농도 곡선의 면적 (Area under the time-concentration curve, AUC)

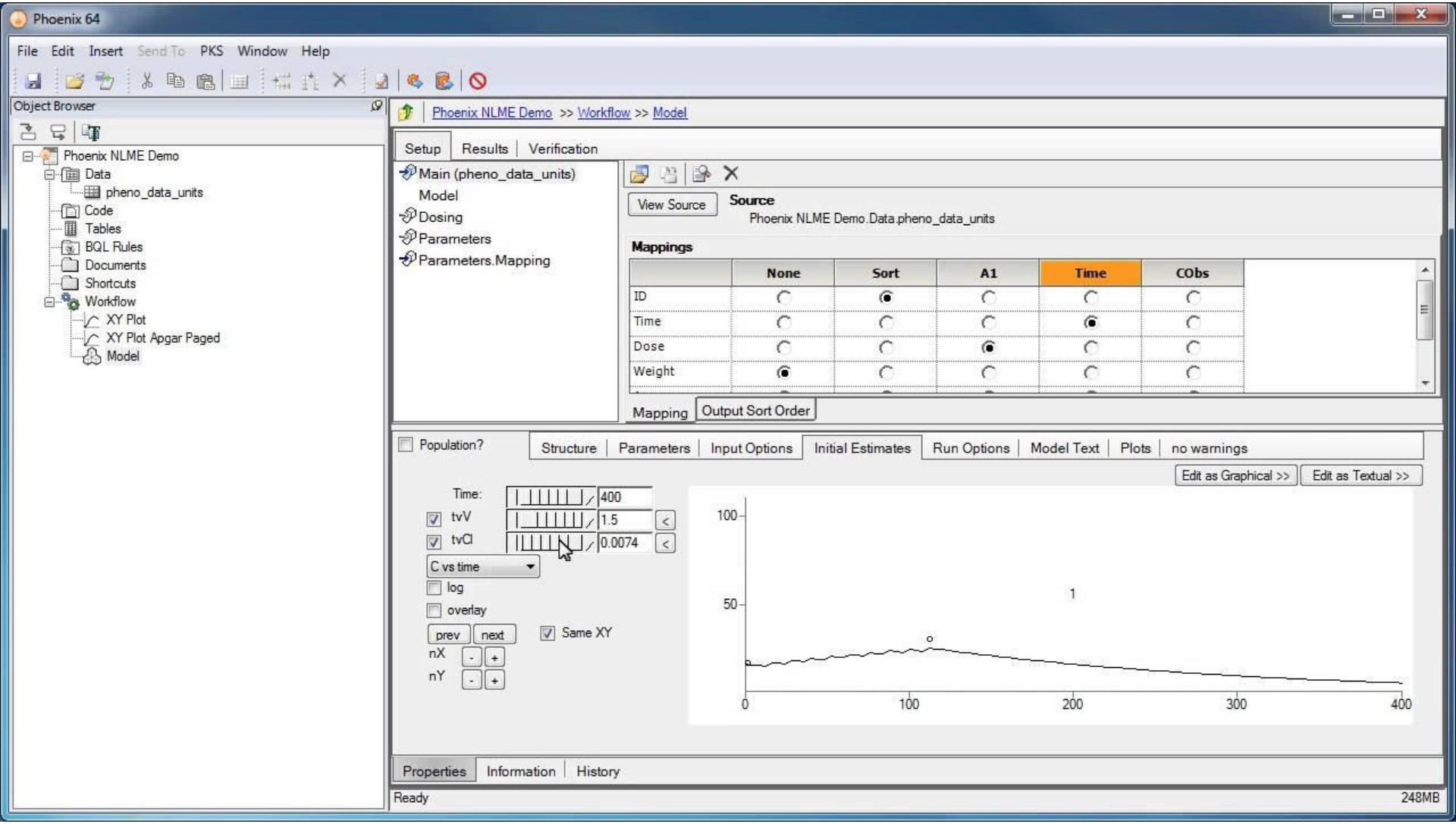


비구획 분석 작업 흐름

- WNL
  - 임상시험 자료
  - R에서 자료 변형
  - 파일 생성 (WNL용)
  - WNL에서 비구획분석
  - 파일 생성 (통계 용)
  - 통계분석 (R or SAS)
  - 보고서 작성
- R
  - 임상시험 자료
  - R에서 자료 변형 / 비구획분석 / 통계 분석/ 보고서 작성

임상시험 자료의 오류발견!




Phoenix 64
File Edit Insert Send To PKS Window Help
Object Browser
Phoenix NLME Demo
Data
pheno_data_units
Code
Tables
BQL Rules
Documents
Shortcuts
Workflow
XY Plot
XY Plot Apgar Paged
Model
Phoenix NLME Demo >> Workflow >> Model
Setup Results Verification
Main (pheno_data_units)
Model
Dosing
Parameters
Parameters.Mapping
View Source
Source
Phoenix NLME Demo.Data.pheno_data_units
Mappings
None Sort A1 Time CObs
ID
Time
Dose
Weight
Mapping Output Sort Order
Population?
Structure Parameters Input Options Initial Estimates Run Options Model Text Plots no warnings
Edit as Graphical >> Edit as Textual >>
Time: 400
tvV 1.5
tvCl 0.0074
C vs time
log
overlay
prev next
Same XY
nX
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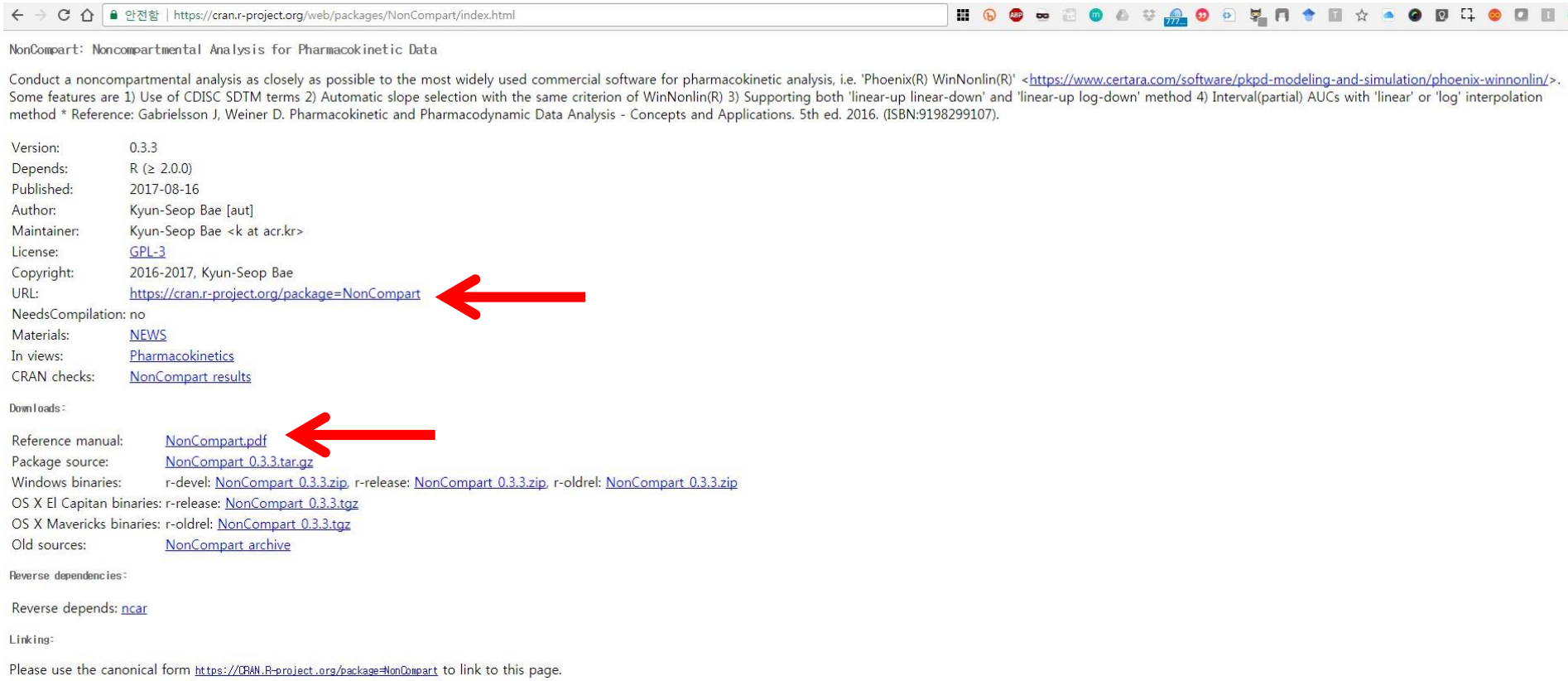
100
50
0
100
200
300
400
1
Properties Information History
Ready
248MB

NonCompart, ncar, pkr

- 비구획 약동학 분석을 쉽게 해 주는 프로그램
- 장점
  - **비용:** WinNonLin (~$5k/yr) 와 동일한 결과를 얻을 수 있음을 반복적으로 확인
  - **시각화:** 숫자 계산 뿐만 아니라 시각화 가능
    - 농도-시간 곡선, 용량군 별 파라메터의 forest plot 등의 유용한 그림도 쉽게 그릴 수 있습니다.-
  - **표준:** CDISC SDTM 표준을 따르는 용어를 사용
  - **속도:** R을 통한 빠른 계산
  - **연속성:** 재현가능한 연구

CRAN



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

NonCompart: Noncompartmental Analysis for Pharmacokinetic Data

Conduct a noncompartmental analysis as closely as possible to the most widely used commercial software for pharmacokinetic analysis, i.e. 'Phoenix(R) WinNonlin(R)' <https://www.certara.com/software/pkpd-modeling-and-simulation/phoenix-winnonlin/>. Some features are 1) Use of CDISC SDTM terms 2) Automatic slope selection with the same criterion of WinNonlin(R) 3) Supporting both 'linear-up linear-down' and 'linear-up log-down' method 4) Interval(partial) AUCs with 'linear' or 'log' interpolation method * Reference: Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications. 5th ed. 2016. (ISBN:9198299107).

Version:	0.3.3
Depends:	R (≥ 2.0.0)
Published:	2017-08-16
Author:	Kyun-Seop Bae [aut]
Maintainer:	Kyun-Seop Bae <k at acr.kr>
License:	GPL-3
Copyright:	2016-2017, Kyun-Seop Bae
URL:	https://cran.r-project.org/package=NonCompart
NeedsCompilation:	no
Materials:	NEWS
In views:	Pharmacokinetics
CRAN checks:	NonCompart results

Downloads:

Reference manual:	NonCompart.pdf
Package source:	NonCompart_0.3.3.tar.gz
Windows binaries:	r-devel: NonCompart_0.3.3.zip, r-release: NonCompart_0.3.3.zip, r-oldrel: NonCompart_0.3.3.zip
OS X El Capitan binaries:	r-release: NonCompart_0.3.3.tgz
OS X Mavericks binaries:	r-oldrel: NonCompart_0.3.3.tgz
Old sources:	NonCompart archive

Reverse dependencies:

Reverse depends: ncar

Linking:

Please use the canonical form https://CRAN.R-project.org/package=NonCompart to link to this page.

- https://cran.r-project.org/package=NonCompart

예시 자료

- R에는 theophylline과 Indomethacin의 약동학 데이터가 내장되어 있습니다.
- Theoph:
  - theophylline의 약동학 데이터,
  - 12명,
  - 320mg PO 단회투여,
  - 0~24시간 채혈,
  - NONMEM 의 run 폴더의 THEOPP 데이터와 동일
- Indometh:
  - Indomethacin의 약동학 데이터,
  - 6명,
  - 25mg IV bolus 단회투여,
  - 0~8시간 채혈(0, 0.25, 0.5, 0.75, 1, 1.25, 2, 3, 4, 5, 6, 8 h)

기초 작업

- 설치하기 & 불러오기

```r
install.packages('NonCompart')
install.packages('ncar')
install.packages('pkr')
```

```r
library(NonCompart)
library(ncar)
library(pkr)
```

- 도움 필요할때..

```r
?NonCompart
?tblNCA
```

tblNCA {NonCompart} R Documentation

Table output NCA

Description

Do multiple NCA and returns a result table.

Usage

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

Arguments

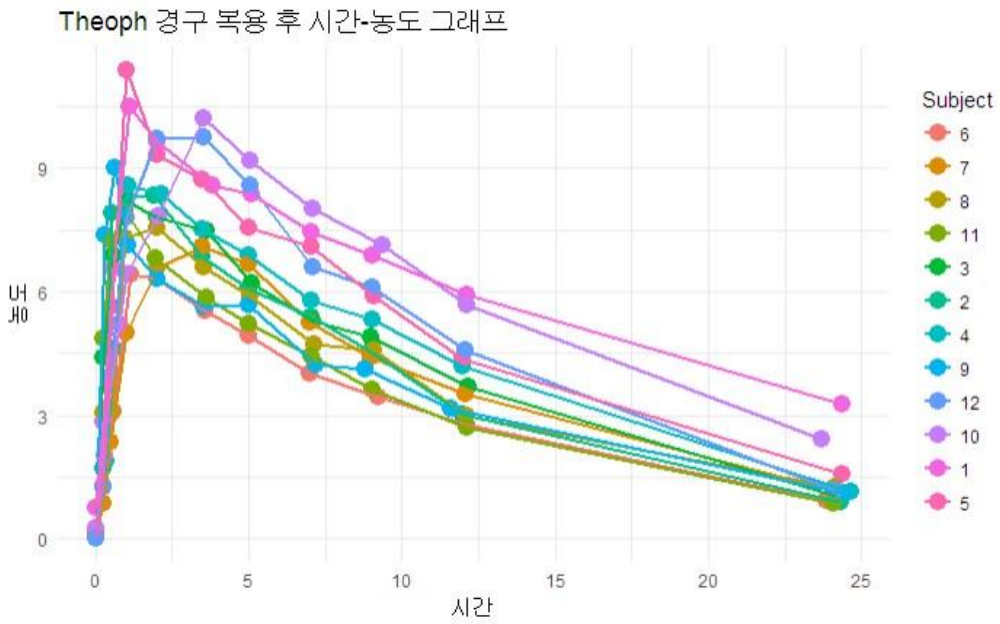
concData	concentration data table
key	column names of concData to be shown at the output table
colTime	column name for time
colConc	column name for concentration
dose	administered dose
adm	one of "Bolus" or "Infusion" or "Extravascular" to indicate drug administration mode
dur	duration of infusion
doseUnit	unit of dose
timeUnit	unit of time
concUnit	unit of concentration
down	method to calculate AUC, "Linear" or "Log"
MW	molecular weight of drug

기본 자료

```{r}
head(Theoph, n=20)
```

```
Grouped Data: conc ~ Time | Subject
   Subject   Wt Dose  Time  conc
1        1 79.6 4.02  0.00  0.74
2        1 79.6 4.02  0.25  2.84
3        1 79.6 4.02  0.57  6.57
4        1 79.6 4.02  1.12 10.50
5        1 79.6 4.02  2.02  9.66
6        1 79.6 4.02  3.82  8.58
7        1 79.6 4.02  5.10  8.36
8        1 79.6 4.02  7.03  7.47
9        1 79.6 4.02  9.05  6.89
10       1 79.6 4.02 12.12  5.94
11       1 79.6 4.02 24.37  3.28
12       2 72.4 4.40  0.00  0.00
13       2 72.4 4.40  0.27  1.72
14       2 72.4 4.40  0.52  7.91
15       2 72.4 4.40  1.00  8.31
16       2 72.4 4.40  1.92  8.33
17       2 72.4 4.40  3.50  6.85
18       2 72.4 4.40  5.02  6.08
19       2 72.4 4.40  7.03  5.40
20       2 72.4 4.40  9.00  4.55
```

```{r}
ggplot(Theoph, aes(Time, conc, group = Subject, color = Subject)) +
  geom_point(size = 4) + geom_line(size = 1) +
  theme_minimal() +
  labs(title = 'Theoph 경구 복용 후 시간-농도 그래프',
       x = '시간', y = '농도')
```



NonCompart

비구획 분석의 계산

tblNCA(): 전체 대상자 비구획분석

```
tblNCA(Theoph, key="Subject", dose=320, concUnit="mg/L")
```

```
tblNCA(Theoph, key="Subject", dose=320, concUnit="mg/L")
```

```
   Subject b0                CMAX    CMAXD       TMAX   TLAG CLST   CLSTP                TLST    LAMZHL               LAMZ                 LAMZLL LAMZUL  LAMZNPT CORRXY               R2
 [1,] "1"     "2.36878509420585" "10.5"  "0.0328125" "1.12" "0"  "3.28" "3.28014647414312"  "24.37" "14.304377571097"  "0.0484569969657749" "9.05" "24.37" "3"     "-0.99999986483748"  "0.999999729674979"
 [2,] "2"     "2.41123733696293" "8.33"  "0.02603125" "1.92" "0"  "0.9"  "0.888639849106919" "24.3"  "6.65934156262252"  "0.104086443688432"  "7.03" "24.3"  "4"     "-0.998596709529913" "0.99719538828397"
 [3,] "3"     "2.52971150145858" "8.2"   "0.025625"  "1.02" "0"  "1.05" "1.05509670837553"  "24.17" "6.76608737718236"  "0.102444314109434"  "9"    "24.17" "3"     "-0.999662423945811" "0.999324961849213"
 [4,] "4"     "2.59275546723663" "8.6"   "0.026875"  "1.07" "0"  "1.15" "1.15642160174997"  "24.65" "6.98124666099893"  "0.0992870205306231" "9.02" "24.65" "3"     "-0.999461923749821" "0.998924137025692"
 [5,] "5"     "2.55109229061238" "11.4"  "0.035625"  "1"    "0"  "1.57" "1.55569511595616"  "24.35" "8.0022640410078"   "0.0866188839818201" "7.02" "24.35" "4"     "-0.999323363372814" "0.998647184582752"
 [6,] "6"     "2.0334043955261"  "6.44"  "0.020125"  "1.15" "0"  "0.92" "0.941271173708175" "23.85" "7.89499786796582"  "0.0877957400561702" "2.03" "23.85" "7"     "-0.999120281624298" "0.998241337153017"
 [7,] "7"     "2.28854976005424" "7.09"  "0.02215625" "3.48" "0"  "1.15" "1.16071921229933"  "24.22" "7.84666826130148"  "0.0883364961379133" "6.98" "24.22" "4"     "-0.999334862622512" "0.998670167652754"
 [8,] "8"     "2.17040271754659" "7.56"  "0.023625"  "2.02" "0"  "1.25" "1.22852675835656"  "24.12" "8.51003788342506"  "0.0814505399453019" "3.53" "24.12" "6"     "-0.99549605294378S" "0.991012391426654"
 [9,] "9"     "2.12464810390587" "9.03"  "0.02821875" "0.63" "0"  "1.12" "1.11648311706515"  "24.43" "8.40599880716182"  "0.0824586341803179" "8.8"  "24.43" "3"     "-0.99972179371205"  "0.999443664822839"
[10,] "10"    "2.65770546248091" "10.21" "0.03190625" "3.55" "0"  "2.42" "2.41369227401111"  "23.7"  "9.24691582297898"  "0.0749598237757766" "9.38" "23.7"  "3"     "-0.999754311749369" "0.999508683861454"
[11,] "11"    "2.1475943307927"  "8"     "0.025"     "0.98" "0"  "0.86" "0.859806606884089" "24.08" "7.26123651504339"  "0.0954585598642772" "9.03" "24.08" "3"     "-0.999999127979356" "0.999998255959473"
[12,] "12"    "2.82449347826545" "9.75"  "0.03046875" "3.52" "0"  "1.17" "1.17553904959565"  "24.15" "6.28650816367189"  "0.110259489451627"  "9.03" "24.15" "3"     "-0.999698355328196" "0.9993968016459"
      R2ADJ                AUCLST          AUCALL          AUCIFO                AUCIFOD                AUCIFP                AUCIFPD                AUCPEO                AUCPEP                AUMCLST           AUMCIFO
 [1,] "0.999999459349959" "148.92305" "148.92305" "216.611933038226" "0.676912290744456" "216.614955803818" "0.67692173688693"  "31.2489169404534" "31.2498763313113" "1459.0711035" "4505.53481941065"
 [2,] "0.995793082425955" "91.5268"   "91.5268"   "100.173459143183" "0.313042059822447" "100.064317640308" "0.312700992625963" "8.63168669340252" "8.53203003991598" "706.586566"   "999.772287999786"
 [3,] "0.998649923698427" "99.2865"   "99.2865"   "109.535970740547" "0.342299908564208" "109.585721753278" "0.342455380478994" "9.3571734209797"  "9.39832451573008" "803.18587"    "1150.96476871455"
 [4,] "0.997848274051385" "106.7963"  "106.7963"  "118.378881427603" "0.369934004461258" "118.44355857992"  "0.370136120562249" "9.7843308603032"  "9.83359392402986" "901.0842105"  "1303.25240140958"
 [5,] "0.997970776874129" "121.2944"  "121.2944"  "139.419777837118" "0.435686805740995" "139.254630430615" "0.435170720095671" "13.0005786254328" "12.8974026752838" "1017.1143165" "1667.72161189007"
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 [9,] "0.998887329645677" "86.32615"  "86.32615"  "99.9087179279482" "0.312214743524838" "99.8660676588793" "0.312081461433998" "13.5949777052926" "13.5580763078894" "705.2296255"  "1201.77153812025"
[10,] "0.999017367722909" "138.3681"  "138.3681"  "170.652060635217" "0.533287689485054" "170.567912545332" "0.533024726704162" "18.9180022292417" "18.8780011813617" "1278.180042"  "2473.99342735889"
[11,] "0.999996511918946" "80.0936"   "80.0936"   "89.1027449234385" "0.278446077885745" "89.1007189855217" "0.278439746829755" "10.1109622730249" "10.1089184106194" "617.2422125"  "928.559971386069"
[12,] "0.998793603291801" "119.9775"  "119.9775"  "130.588831558118" "0.408090098619118" "130.639068046815" "0.408247087646298" "8.12575733430562" "8.16108703637935" "977.8807235"  "1330.38400236898"
      AUMCIFP            AUMCPEO           AUMCPEP           VZFO              VZFP              CLFO              CLFP              MRTEVLST          MRTEVIFO          MRTEVIFP
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 [7,] "1249.41106012833" "37.1599983764277" "37.376906210544"  "34.9084408430805" "34.8676684452056" "3.08368934971535" "3.08008765894795" "8.62138344128154" "11.9984271908357" "12.0259237101698"
 [8,] "1288.52011616077" "43.0301500208197" "42.605894256157"  "37.8105081118408" "37.9066861615621" "3.07968630131565" "3.08752005539633" "8.3506663903943"  "12.4930915850769" "12.4322865638375"
 [9,] "1200.2123597462"  "41.3174964516894" "41.2412628670872" "38.8427934436931" "38.8593822173436" "3.20292369511514" "3.20429158273309" "8.1693626496722"  "12.0286954236259" "12.0182198807093"
[10,] "2470.87654175199" "48.3353501320931" "48.2701777931124" "25.0155401378403" "25.0278813214113" "1.87516048038837" "1.87608557333405" "9.23753409926132" "14.4972959491374" "14.4861744795951"
[11,] "928.489963582081" "33.5269415524517" "33.5219295081337" "37.6221852019531" "37.6230406407462" "3.59135961832556" "3.59144127728081" "7.70651103833515" "10.4212274513421" "10.4206786898426"
[12,] "1332.05283411623" "26.4963558071417" "26.5884431567018" "22.2242935639128" "22.2157473419508" "2.45043926178O1"  "2.44949695970983" "8.15053425433936" "10.1875787270284" "10.1964355229393"
attr(,"units")
 [1] ""          ""          "mg/L"      "mg/L/mg"   "h"         "h"         "mg/L"      "mg/L"      "h"         "h"         "/h"        "h"         "h"         ""          ""          ""
[17] ""          "h*mg/L"    "h*mg/L"    "h*mg/L"    "h*mg/L/mg" "h*mg/L"    "h*mg/L/mg" "%"         "%"         "h2*mg/L"   "h2*mg/L"   "h2*mg/L"   "%"         "%"         "L"         "L"
[33] "L/h"       "L/h"       "h"         "h"         "h"
```

sNCA(): 한명만 비구획분석

```r
head(Theoph, n=20)
```

```
Grouped Data: conc ~ Time | Subject
   Subject   Wt Dose  Time  conc
1        1 79.6 4.02  0.00  0.74
2        1 79.6 4.02  0.25  2.84
3        1 79.6 4.02  0.57  6.57
4        1 79.6 4.02  1.12 10.50
5        1 79.6 4.02  2.02  9.66
6        1 79.6 4.02  3.82  8.58
7        1 79.6 4.02  5.10  8.36
8        1 79.6 4.02  7.03  7.47
9        1 79.6 4.02  9.05  6.89
10       1 79.6 4.02 12.12  5.94
11       1 79.6 4.02 24.37  3.28
12       2 72.4 4.40  0.00  0.00
13       2 72.4 4.40  0.27  1.72
14       2 72.4 4.40  0.52  7.91
15       2 72.4 4.40  1.00  8.31
16       2 72.4 4.40  1.92  8.33
17       2 72.4 4.40  3.50  6.85
18       2 72.4 4.40  5.02  6.08
19       2 72.4 4.40  7.03  5.40
20       2 72.4 4.40  9.00  4.55
```

```r
# For one subject
x = Theoph[Theoph$Subject=="1","Time"]
y = Theoph[Theoph$Subject=="1","conc"]

sNCA(x, y, dose=320, doseUnit="mg", concUnit="mg/L", timeUnit="h")
```

```
        b0         CMAX         CMAXD         TMAX         TLAG         CLST
 2.3687851   10.5000000    0.0328125    1.1200000    0.0000000    3.2800000
      CLSTP         TLST       LAMZHL         LAMZ       LAMZLL       LAMZUL
 3.2801465   24.3700000   14.3043776    0.0484570    9.0500000   24.3700000
    LAMZNPT       CORRXY           R2        R2ADJ        AUCLST       AUCALL
 3.0000000   -0.9999999    0.9999997    0.9999995  148.9230500  148.9230500
      AUCIFO       AUCIFOD       AUCIFP       AUCIFPD       AUCPEO       AUCPEP
216.6119330    0.6769123  216.6149558    0.6769217   31.2489169   31.2498763
     AUMCLST       AUMCIFO       AUMCIFP       AUMCPEO       AUMCPEP          VZFO
1459.0711035 4505.5348194 4505.6708646   67.6160287   67.6170065   30.4867482
         VZFP         CLFO         CLFP       MRTEVLST       MRTEVIFO       MRTEVIFP
  30.4863228    1.4772963    1.4772757    9.7974834   20.8000305   20.8003683
attr(,"units")
 [1] ""           "mg/L"       "mg/L/mg"    "h"          "h"          "mg/L"       "mg/L"
 [8] "h"          "h"          "/h"         "h"          "h"          ""           ""
[15] ""           ""           "h*mg/L"     "h*mg/L"     "h*mg/L"     "h*mg/L/mg"  "h*mg/L"
[22] "h*mg/L/mg"  "%"          "%"          "h2*mg/L"    "h2*mg/L"    "h2*mg/L"    "%"
[29] "%"          "L"          "L"          "L/h"        "L/h"        "h"          "h"
[36] "h"
```

```r
ggplot(Theoph %>% filter(Subject == 1), aes(Time, conc, group = Subject, color = Subject)) +
  geom_point(size = 4) + geom_line(size = 1) +
  theme_minimal() +
  labs(title = 'Theoph 경구 복용 후 시간-농도 그래프 (Subject 1)',
       x = '시간', y = '농도')
```

각 파라메터의 의미를 알고싶으면?

```
?ncar::txtNCA()
```

Value

CMAX	maximum concentration, Cmax
CMAXD	dose normalized Cmax, CMAX / Dose, Cmax / Dose
TMAX	time of maximum concentration, Tmax
TLAG	time to observe the first non-zero concentration, for extravascular administration only
CLST	last positive concentration observed, Clast
CLSTP	last positive concentration predicted, Clast_pred
TLST	time of last positive concentration, Tlast
LAMZHL	half-life by lambda z, ln(2)/LAMZ
LAMZ	lambda_z negative of best fit terminal slope
LAMZLL	earliest time for LAMZ
LAMZUL	last time for LAMZ
LAMZNPT	number of points for LAMZ
CORRXY	correlation of log(concentration) and time
R2	R-squared
R2ADJ	R-squared adjusted

...

```
ncar::RptCfg
```

PPTESTCD <chr>	SYNONYM <chr>	NCI <chr>
b0	Intercept	Intercept of regression
TLAG	Time Until First Nonzero Conc	Time until First Nonzero Concentration
MRTEVLST	MRT Extravasc to Last Nonzero Conc	Mean Residence Time to Last Nonzero Concentration by Extravascular
MRTEVIFO	MRT Extravasc Infinity Obs	Mean Residence Time Infinity Observed by Extravascular Dose
MRTEVIFP	MRT Extravasc Infinity Pred	Mean Residence Time Infinity Predicted by Extravascular Dose
VZFO	Vz Obs by F	Observed Volume of Distribution of Absorbed Fraction
VZFP	Vz Pred by F	Predicted Volume of Distribution of Absorbed Fraction
CLFO	Total CL Obs by F	Observed Total Body Clearance by Fraction of Dose Absorbed

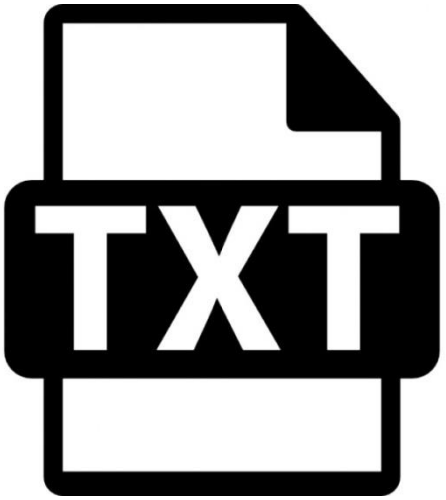
...

ncar

비구획 분석 보고서 작성

ncar 소개

- 보고서를 통해 다른 사람/기관과 정보 공유
- pdf, rtf, text 형식 지원



txtNCA()

```
txtNCA(Theoph[Theoph$Subject=="1","Time"], Theoph[Theoph$Subject=="1","conc"],
       dose=320, doseUnit="mg", concUnit="mg/L", timeUnit="h")
```

```
                    NONCOMPARTMENTAL ANALYSIS REPORT
                    Package version 0.3.7 (2017-08-16 KST)
                      R version 3.4.2 (2017-09-28)

Date and Time: 2017-11-01 18:00:30 Asia/Seoul

Calculation Setting
-------------------
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: Heighest adjusted R-squared value with precision=1e-


Fitting, AUC, AUMC Result
-------------------------
      Time         Conc.      Pred.    Residual       AUC       AUMC
------------------------------------------------------------------------
     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
    12.1200 *     5.9400     5.9387 +1.324e-03    92.4505   528.5219
    24.3700 *     3.2800     3.2801 -1.465e-04   148.9231  1459.0711

*: 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
AUCIFP     AUC Infinity Pred                      216.6150 h*mg/L
AUCIFPD    AUC Infinity Pred Norm by Dose           0.6769 h*mg/L/mg
AUCPEO     AUC %Extrapolation Obs                  31.2489 %
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
AUMCIFP    AUMC Infinity Pred                    4505.6709 h2*mg/L
AUMCPEO    AUMC %Extrapolation Obs                 67.6160 %
AUMCPEP    AUMC % Extrapolation Pred               67.6170 %
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
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
```

pdfNCA()

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

Subject ID = 1

NONCOMPARTMENTAL ANALYSIS REPORT
Package version 0.3.7 (2017-08-16 KST)
R version 3.4.2 (2017-09-28)

Date and Time: 2017-11-01 18:04:59 Asia/Seoul

Calculation Setting

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: Heighest adjusted R-squared value with precision=1e-4

Fitting, AUC, AUMC Result

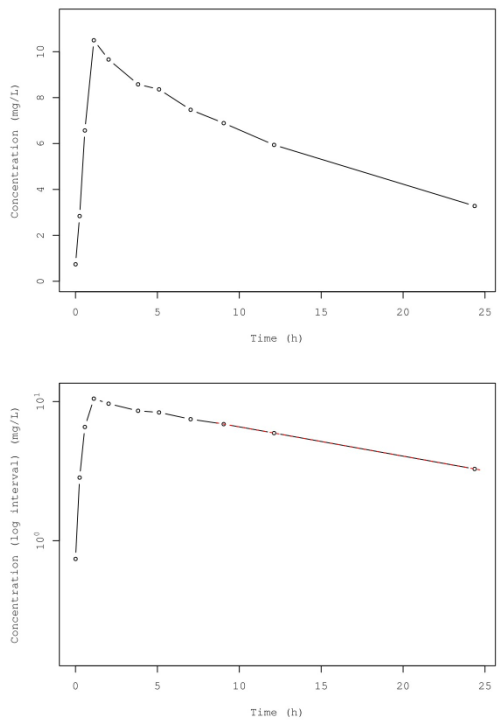
	Time	Conc.	Pred.	Residual	AUC	AUMC
	0.0000	0.7400			0.0000	0.0000
	0.2500	2.8400			0.4475	0.0888
	0.5700	6.5700			1.9531	0.8015
	1.1200	10.5000			6.6474	5.0654
	2.0200	9.6600			15.7194	19.1383
	3.8200	8.5800			32.1354	66.1982
	5.1000	8.3600			42.9769	114.4617
	7.0300	7.4700			58.2529	206.2815
	9.0500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

*: 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

Subject ID = 1

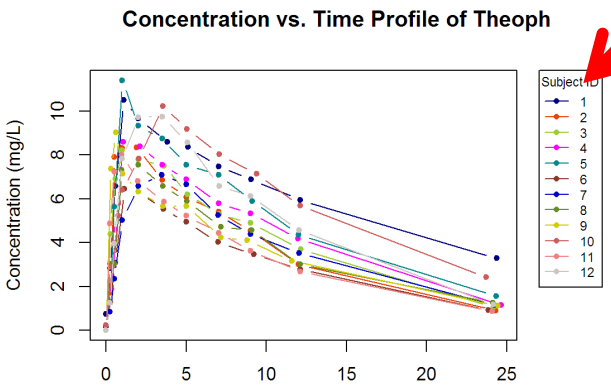


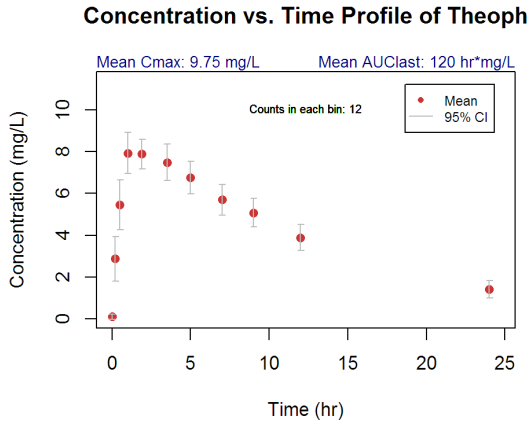
pkr

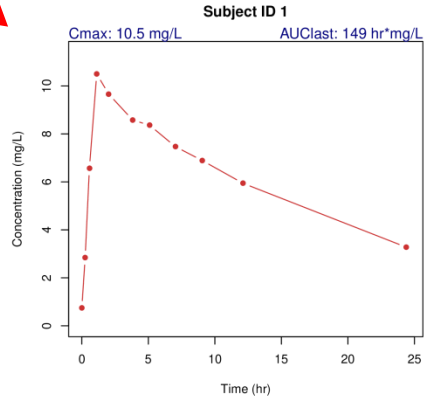
비구획 분석 시각화 & SDTM

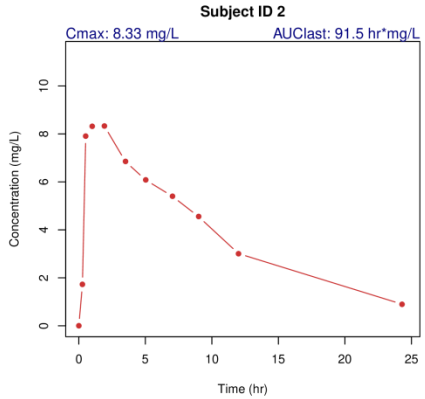
plotPK()

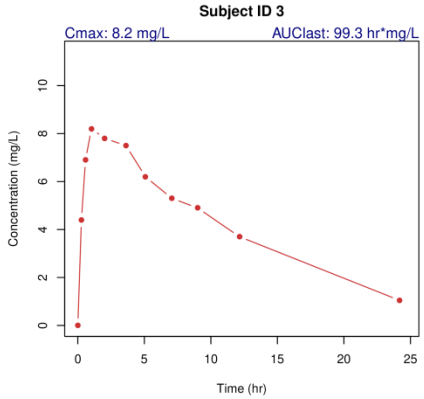
```
plotPK(Theoph, "Subject", "Time", "conc", unitTime="hr", unitConc="mg/L", dose=320)
```

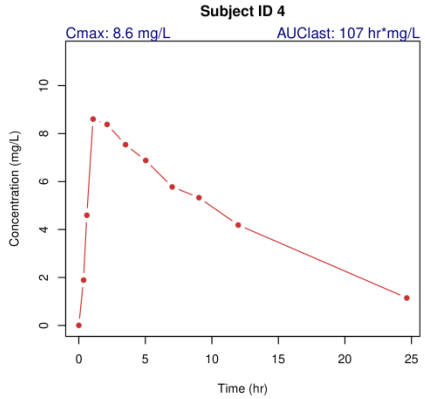






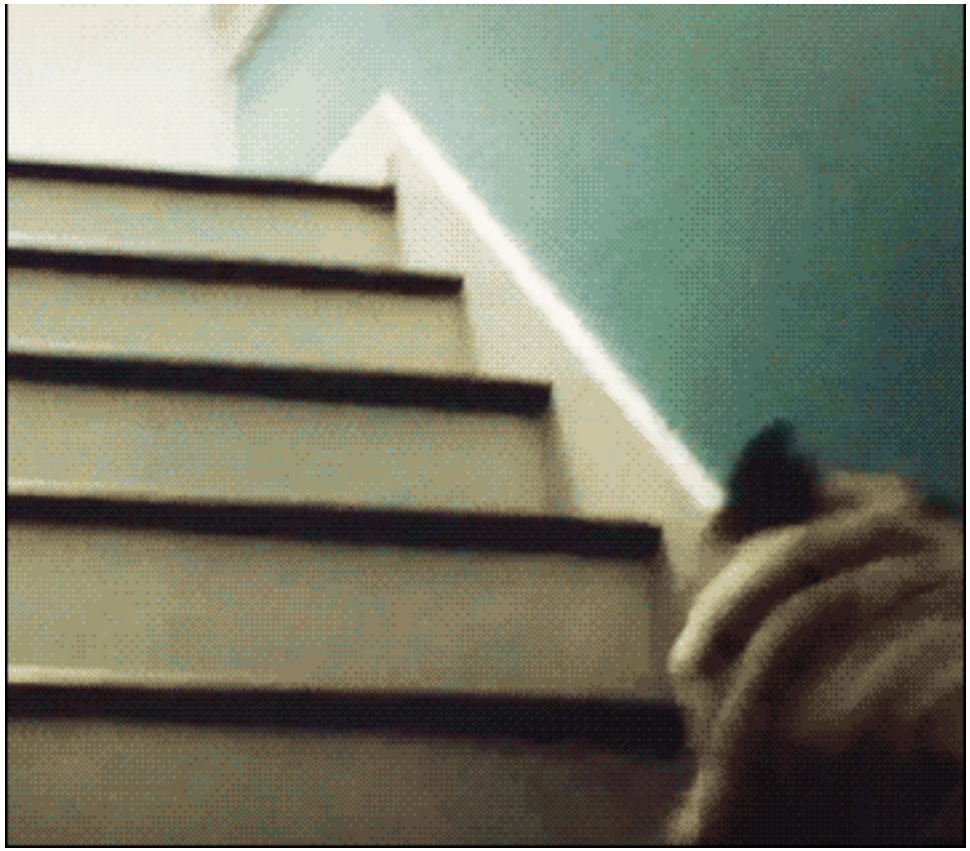






인터넷 웹브라우져를 통한 비구획분석

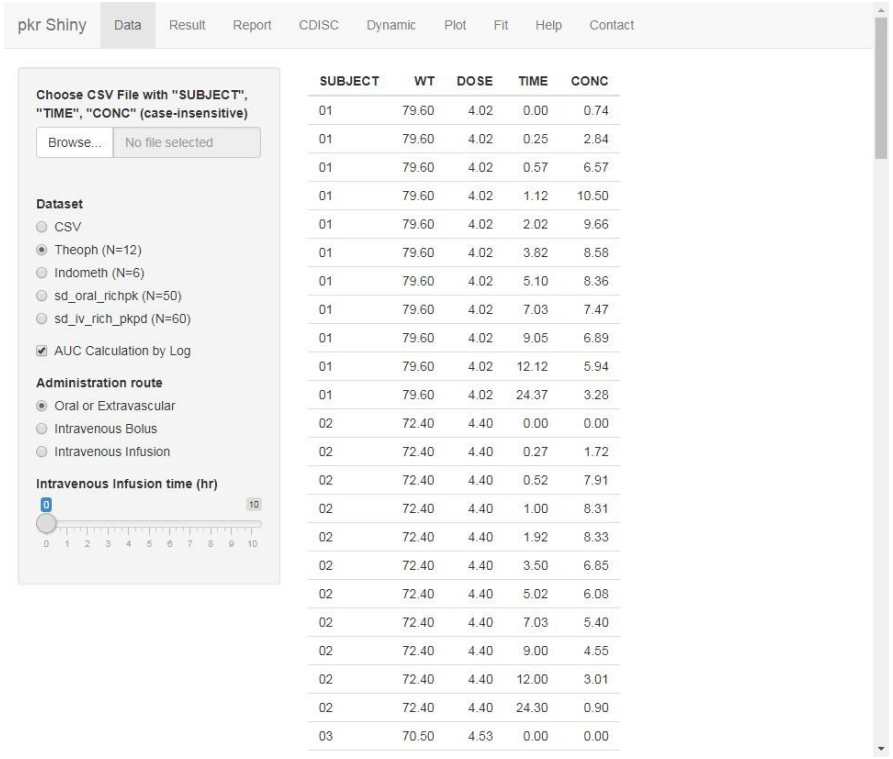
https://asan.shinyapps.io/pkrshiny



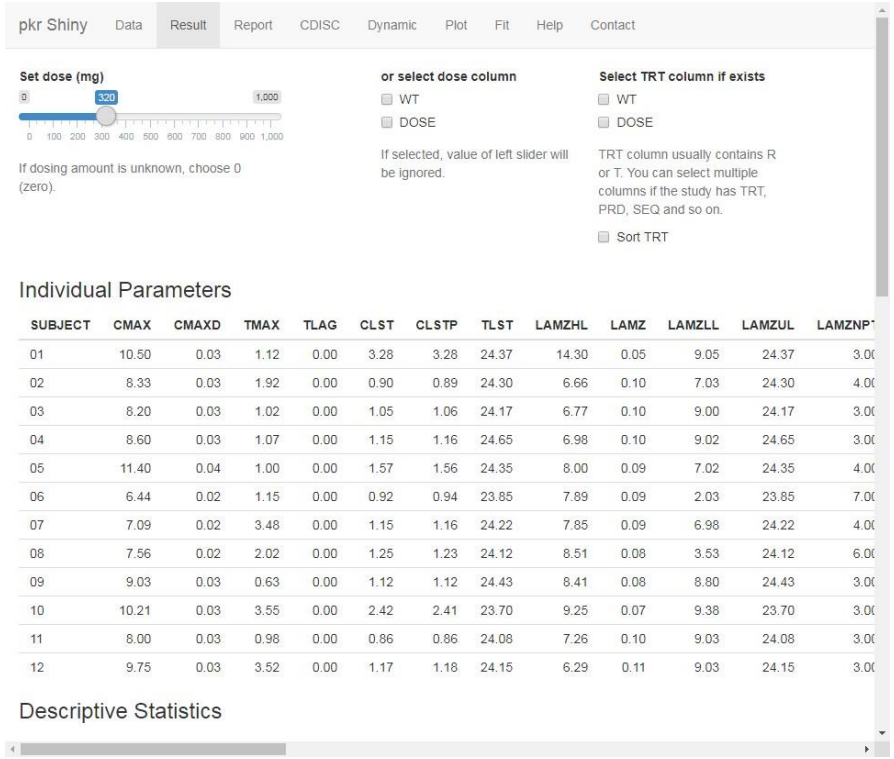
pkrshiny

- Shiny를 이용한 간편한 비구획분석
  - Csv 업로드 하여 NonCompart, ncar, pkr의 핵심 기능을 클릭하여 수행.
  - R이 설치되어 있지 않은 PC, Mac, Linux, 혹은 휴대폰으로도 접속 가능
- http://asan.shinyapps.io/pkrshiny

예시



SUBJECT	WT	DOSE	TIME	CONC
01	79.60	4.02	0.00	0.74
01	79.60	4.02	0.25	2.84
01	79.60	4.02	0.57	6.57
01	79.60	4.02	1.12	10.50
01	79.60	4.02	2.02	9.66
01	79.60	4.02	3.82	8.58
01	79.60	4.02	5.10	8.36
01	79.60	4.02	7.03	7.47
01	79.60	4.02	9.05	6.89
01	79.60	4.02	12.12	5.94
01	79.60	4.02	24.37	3.28
02	72.40	4.40	0.00	0.00
02	72.40	4.40	0.27	1.72
02	72.40	4.40	0.52	7.91
02	72.40	4.40	1.00	8.31
02	72.40	4.40	1.92	8.33
02	72.40	4.40	3.50	6.85
02	72.40	4.40	5.02	6.08
02	72.40	4.40	7.03	5.40
02	72.40	4.40	9.00	4.55
02	72.40	4.40	12.00	3.01
02	72.40	4.40	24.30	0.90
03	70.50	4.53	0.00	0.00



SUBJECT	CMAX	CMAXD	TMAX	TLAG	CLST	CLSTP	TLST	LAMZHL	LAMZ	LAMZLL	LAMZUL	LAMZNP
01	10.50	0.03	1.12	0.00	3.28	3.28	24.37	14.30	0.05	9.05	24.37	3.0
02	8.33	0.03	1.92	0.00	0.90	0.89	24.30	6.66	0.10	7.03	24.30	4.0
03	8.20	0.03	1.02	0.00	1.05	1.06	24.17	6.77	0.10	9.00	24.17	3.0
04	8.60	0.03	1.07	0.00	1.15	1.16	24.65	6.98	0.10	9.02	24.65	3.0
05	11.40	0.04	1.00	0.00	1.57	1.56	24.35	8.00	0.09	7.02	24.35	4.0
06	6.44	0.02	1.15	0.00	0.92	0.94	23.85	7.89	0.09	2.03	23.85	7.0
07	7.09	0.02	3.48	0.00	1.15	1.16	24.22	7.85	0.09	6.98	24.22	4.0
08	7.56	0.02	2.02	0.00	1.25	1.23	24.12	8.51	0.08	3.53	24.12	6.0
09	9.03	0.03	0.63	0.00	1.12	1.12	24.43	8.41	0.08	8.80	24.43	3.0
10	10.21	0.03	3.55	0.00	2.42	2.41	23.70	9.25	0.07	9.38	23.70	3.0
11	8.00	0.03	0.98	0.00	0.86	0.86	24.08	7.26	0.10	9.03	24.08	3.0
12	9.75	0.03	3.52	0.00	1.17	1.18	24.15	6.29	0.11	9.03	24.15	3.0

pkr Shiny | Data | Result | Report | CDISC | Dynamic | Plot | Fit | Help | Contact

Study ID

Drug

PP

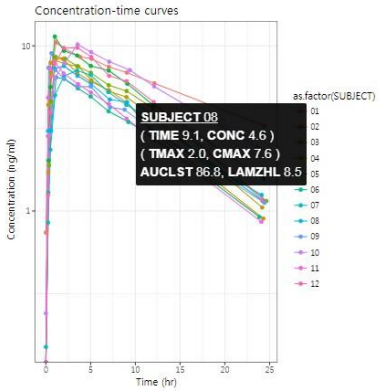
STUDYID	DOMAIN	USUBJID	PPSEQ	PPGRPID	PPTESTCD	PPTEST	PPSCAT	PPORRES
	PP	01	1		CMAX	Max Conc	NON-COMPARTMENTAL	10.50
	PP	01	2		CMAXD	Max Conc Norm by Dose	NON-COMPARTMENTAL	0.03
	PP	01	3		TMAX	Time of CMAX	NON-COMPARTMENTAL	1.12
	PP	01	4		TLAG	Time Until First Nonzero Conc	NON-COMPARTMENTAL	0.00
	PP	01	5		CLST	Last Nonzero Conc	NON-COMPARTMENTAL	3.28
	PP	01	6		CLSTP	Last Nonzero Conc Pred	NON-COMPARTMENTAL	3.28
	PP	01	7		TLST	Time of Last Nonzero Conc	NON-COMPARTMENTAL	24.37
	PP	01	8		LAMZHL	Half-Life Lambda z	NON-COMPARTMENTAL	14.30
	PP	01	9		LAMZ	Lambda z	NON-COMPARTMENTAL	0.05
	PP	01	10		LAMZLL	Lambda z Lower Limit	NON-COMPARTMENTAL	9.05
	PP	01	11		LAMZUL	Lambda z Upper Limit	NON-	24.37

pkr Shiny | Data | Result | Report | CDISC | Dynamic | Plot | Fit | Help | Contact

Hovering a cursor over a plot shows dynamic results.

Y axis

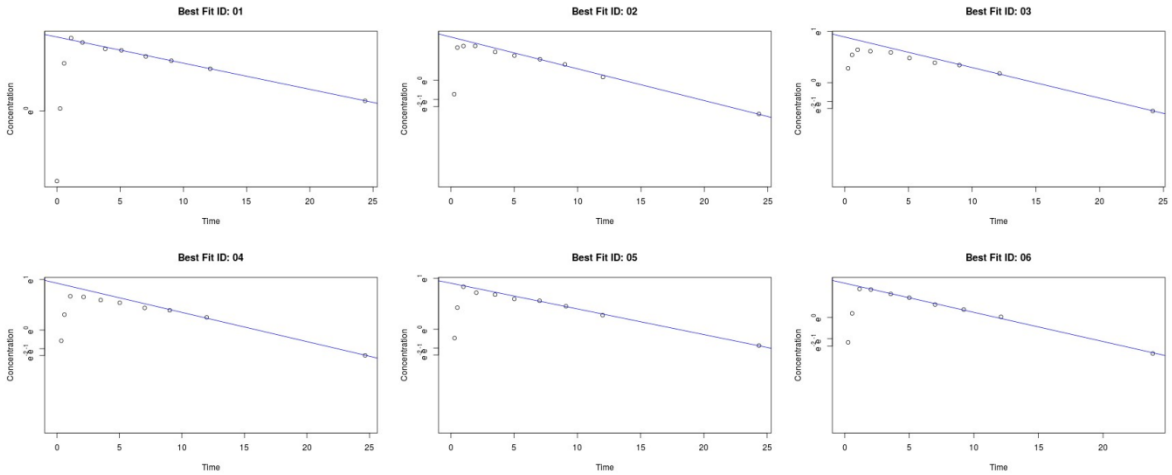
- (•) Log
- ( ) Linear



pkr Shiny | Data | Result | Report | CDISC | Dynamic | Plot | Fit | Help | Contact

Generating plots takes a while. Please wait.

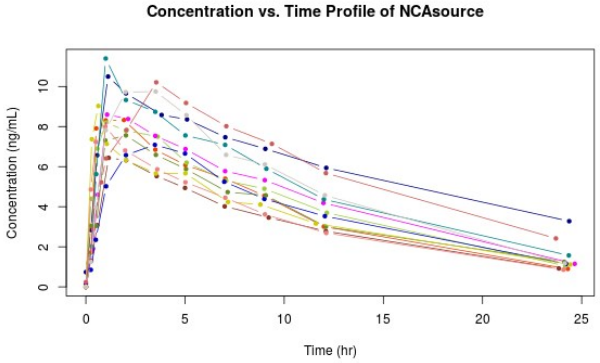
Individual Plots

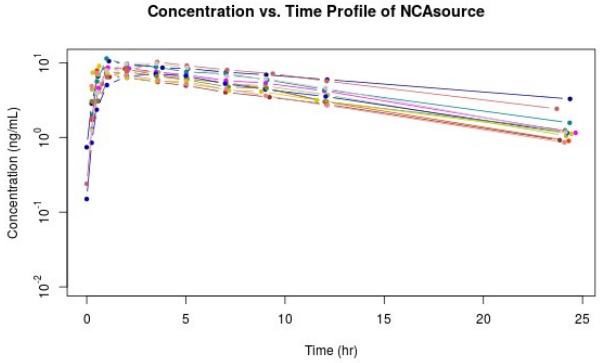


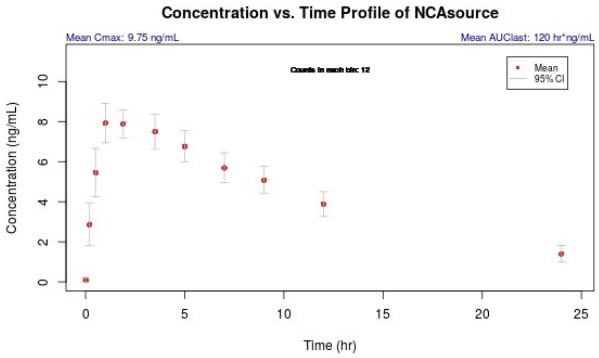
Generating plots takes a while. Please wait.

Concentration-time curve

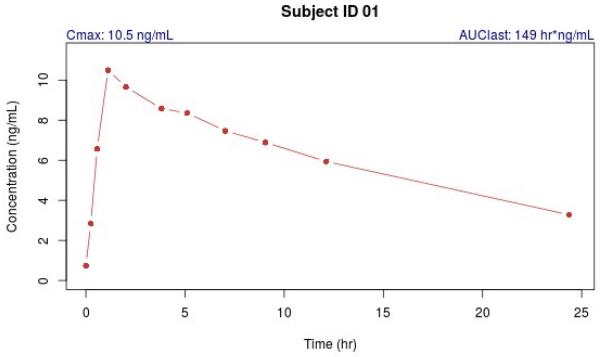
Group

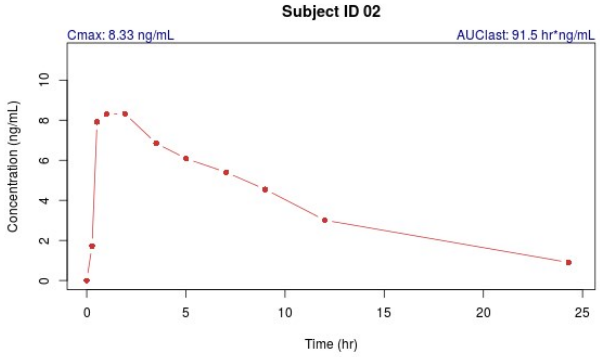


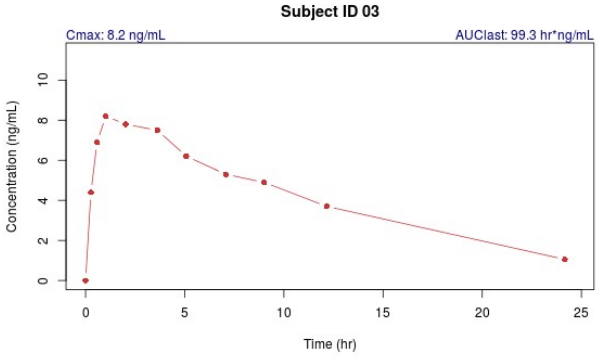


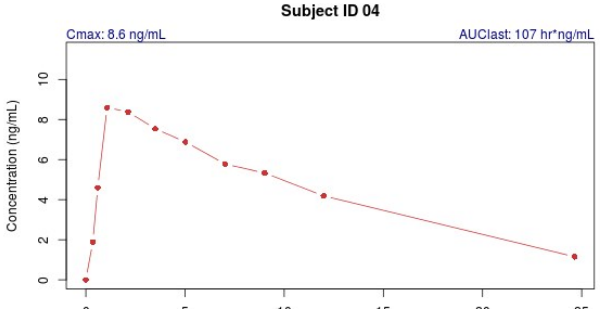


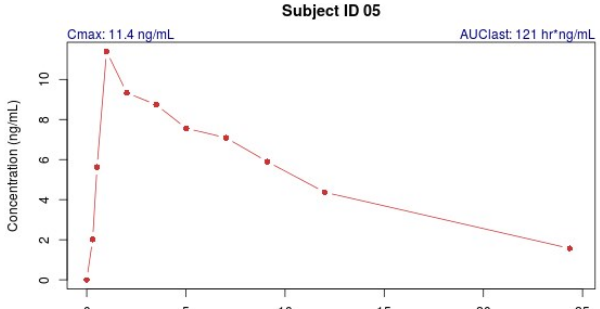
Individual

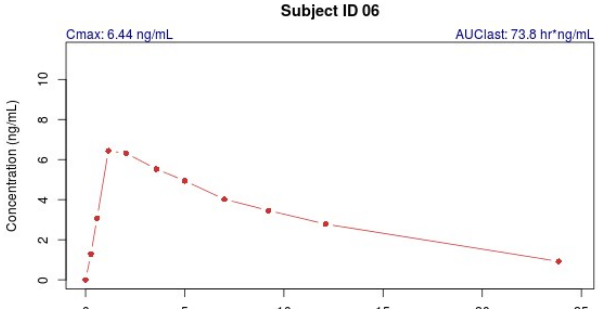










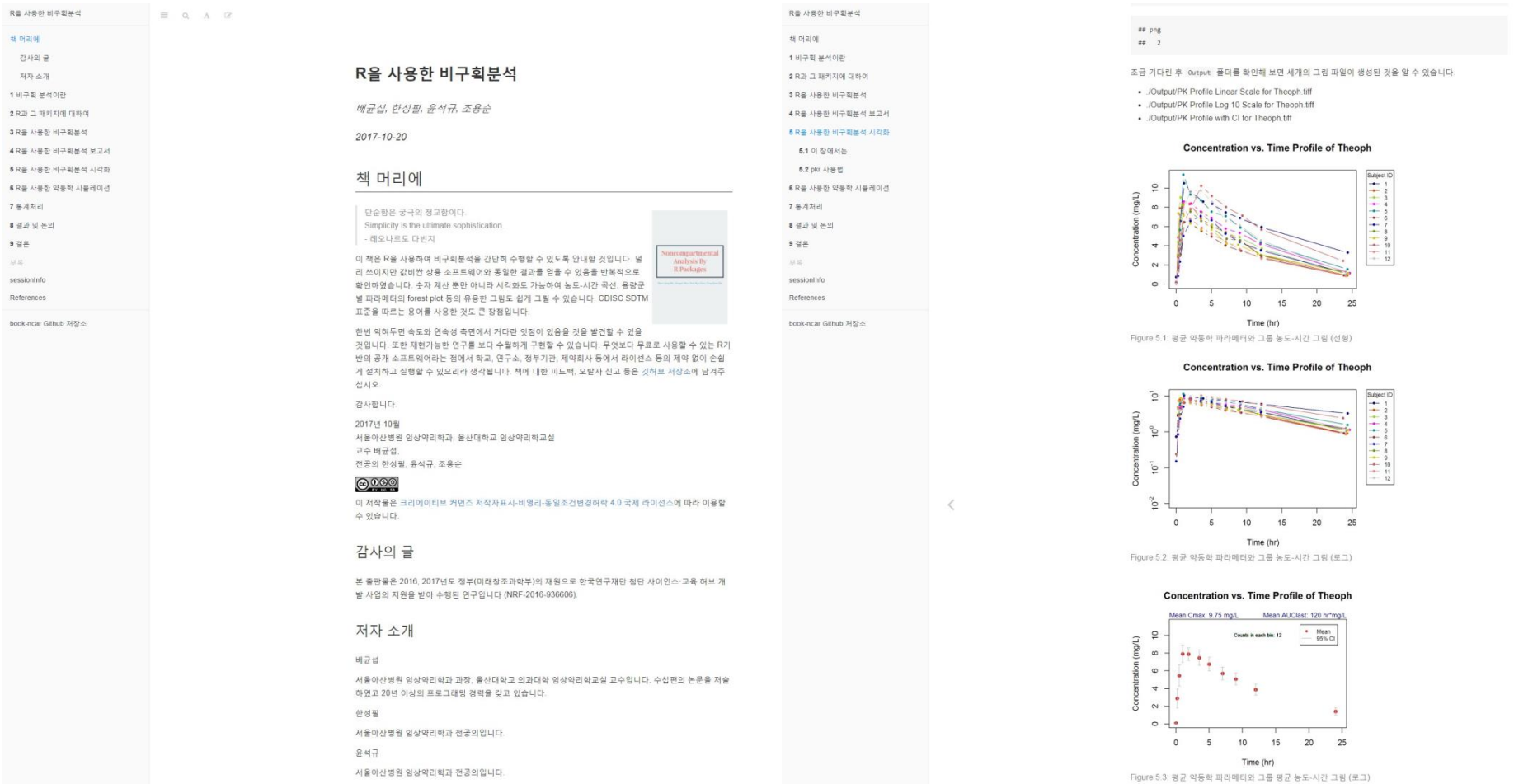


결론

- 무료 소프트웨어인 R과 그 패키지를 통해서 상용 소프트웨어와 동일한 결과를 얻을 수 있음. ($0)
- R을 사용하여 이후 여러 통계 분석을 연속적으로 행할 수 있음. (Bioequivalence, ANOVA, linear regression, glm, nlme 등)
- 자료의 오류가 있을 때 재분석을 쉽게 할 수 있고 보고서와 그림의 수정도 한번에 행할 수 있음 → Continuous Integration & Reproducible Research

매뉴얼 책

- Gitbook: https://asancpt.github.io/book-ncar/



R을 사용한 비구획분석

책 머리에
감사의 글
저자 소개
1 비구획 분석이란
2 R과 그 패키지에 대하여
3 R을 사용한 비구획분석
4 R을 사용한 비구획분석 보고서
5 R을 사용한 비구획분석 시각화
6 R을 사용한 약동학 시뮬레이션
7 통계처리
8 결과 및 논의
9 결론
부록
sessionInfo
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R을 사용한 비구획분석

배균섭, 한성필, 윤석규, 조용순

2017-10-20

책 머리에

단순함은 궁극의 정교함이다.
Simplicity is the ultimate sophistication.
- 레오나르도 다빈치

이 책은 R을 사용하여 비구획분석을 간단히 수행할 수 있도록 안내할 것입니다. 널리 쓰이지만 값비싼 상용 소프트웨어와 동일한 결과를 얻을 수 있음을 반복적으로 확인하였습니다. 숫자 계산 뿐만 아니라 시각화도 가능하여 농도-시간 곡선, 용량군별 파라메터의 forest plot 등의 유용한 그림도 쉽게 그릴 수 있습니다. CDISC SDTM 표준을 따르는 용어를 사용한 것도 큰 장점입니다.

한번 익혀두면 속도와 연속성 측면에서 커다란 잇점이 있음을 것을 발견할 수 있을 것입니다. 또한 재현가능한 연구를 보다 수월하게 구현할 수 있습니다. 무엇보다 무료로 사용할 수 있는 R기반의 공개 소프트웨어라는 점에서 학교, 연구소, 정부기관, 제약회사 등에서 라이센스 등의 제약 없이 손쉽게 설치하고 실행할 수 있으리라 생각됩니다. 책에 대한 피드백, 오탈자 신고 등은 깃허브 저장소에 남겨주십시오.

감사합니다.

2017년 10월
서울아산병원 임상약리학과, 울산대학교 임상약리학교실
교수 배균섭,
전공의 한성필, 윤석규, 조용순

이 저작물은 크리에이티브 커먼즈 저작자표시-비영리-동일조건변경허락 4.0 국제 라이선스에 따라 이용할 수 있습니다.

감사의 글

본 출판물은 2016, 2017년도 정부(미래창조과학부)의 재원으로 한국연구재단 첨단 사이언스 교육 허브 개발 사업의 지원을 받아 수행된 연구입니다 (NRF-2016-936606).

저자 소개

배균섭

서울아산병원 임상약리학과 과장, 울산대학교 의과대학 임상약리학교실 교수입니다. 수십편의 논문을 저술하였고 20년 이상의 프로그래밍 경력을 갖고 있습니다.

한성필

서울아산병원 임상약리학과 전공의입니다.

윤석규

서울아산병원 임상약리학과 전공의입니다.

R을 사용한 비구획분석

책 머리에
1 비구획 분석이란
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5 R을 사용한 비구획분석 시각화
5.1 이 장에서는
5.2 pkr 사용법
6 R을 사용한 약동학 시뮬레이션
7 통계처리
8 결과 및 논의
9 결론
부록
sessionInfo
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```
## png
##   2
```

조금 기다린 후 `Output` 폴더를 확인해 보면 세개의 그림 파일이 생성된 것을 알 수 있습니다.

- ./Output/PK Profile Linear Scale for Theoph.tiff
- ./Output/PK Profile Log 10 Scale for Theoph.tiff
- ./Output/PK Profile with CI for Theoph.tiff

Figure 5.1: 평균 약동학 파라메터와 그룹 농도-시간 그림 (선형)

Figure 5.2: 평균 약동학 파라메터와 그룹 농도-시간 그림 (로그)

Figure 5.3: 평균 약동학 파라메터와 그룹 평균 농도-시간 그림 (로그)

감사합니다.

사용후 궁금한 점이 있다면 shan@catholic.ac.kr 로 알려주세요.

Reference

-Bae, Kyun-Seop. 2017a. *Ncar: Noncompartmental Analysis for Pharmacokinetic Report*. https://CRAN.R-project.org/package=ncar.

-Bae, Kyun-Seop. 2017b. *NonCompart: Noncompartmental Analysis for Pharmacokinetic Data*. https://CRAN.R-project.org/package=NonCompart.

-Bae, Kyun-Seop, and Jee Eun Lee. 2017. *Pkr: Pharmacokinetics in R*. https://CRAN.R-project.org/package=pkr.

-Gabrielsson J, Weiner D. Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications. 5th ed. 2016. (ISBN:9198299107).