

Hands-on: NCA using R

R을 사용한 비구획분석 (NCA)

가톨릭대학교 약리학교실
한성필 M.D, Ph.D

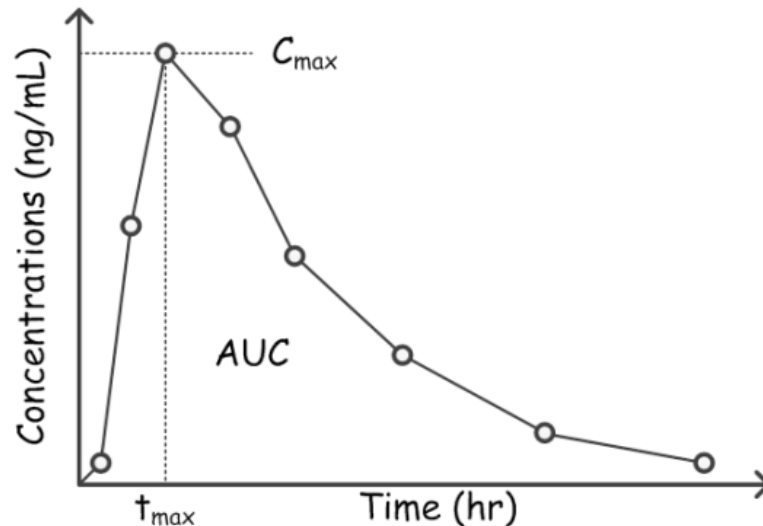
다운로드: bit.ly/shan-pkpd
앱: asan.shinyapps.io/pkrshiny

목적

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

비구획 분석이란

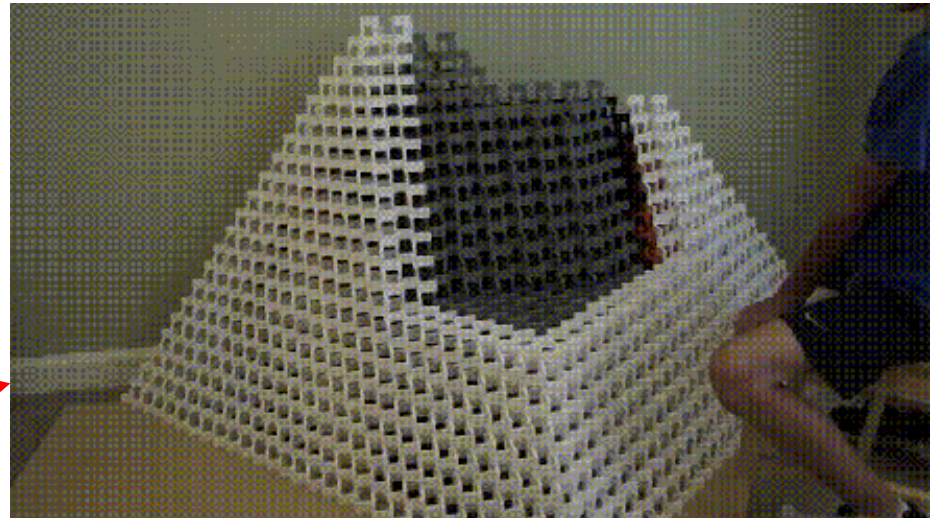
- 시간, 농도가 표현되어 있는 곡선에서 아무런 가정을 하지 않고 분석
- 최대농도 (C_{\max}) 및 최대농도에 도달하는 시간 (T_{\max}), 전체 시간-농도 곡선의 면적 (Area under the time-concentration curve, AUC)

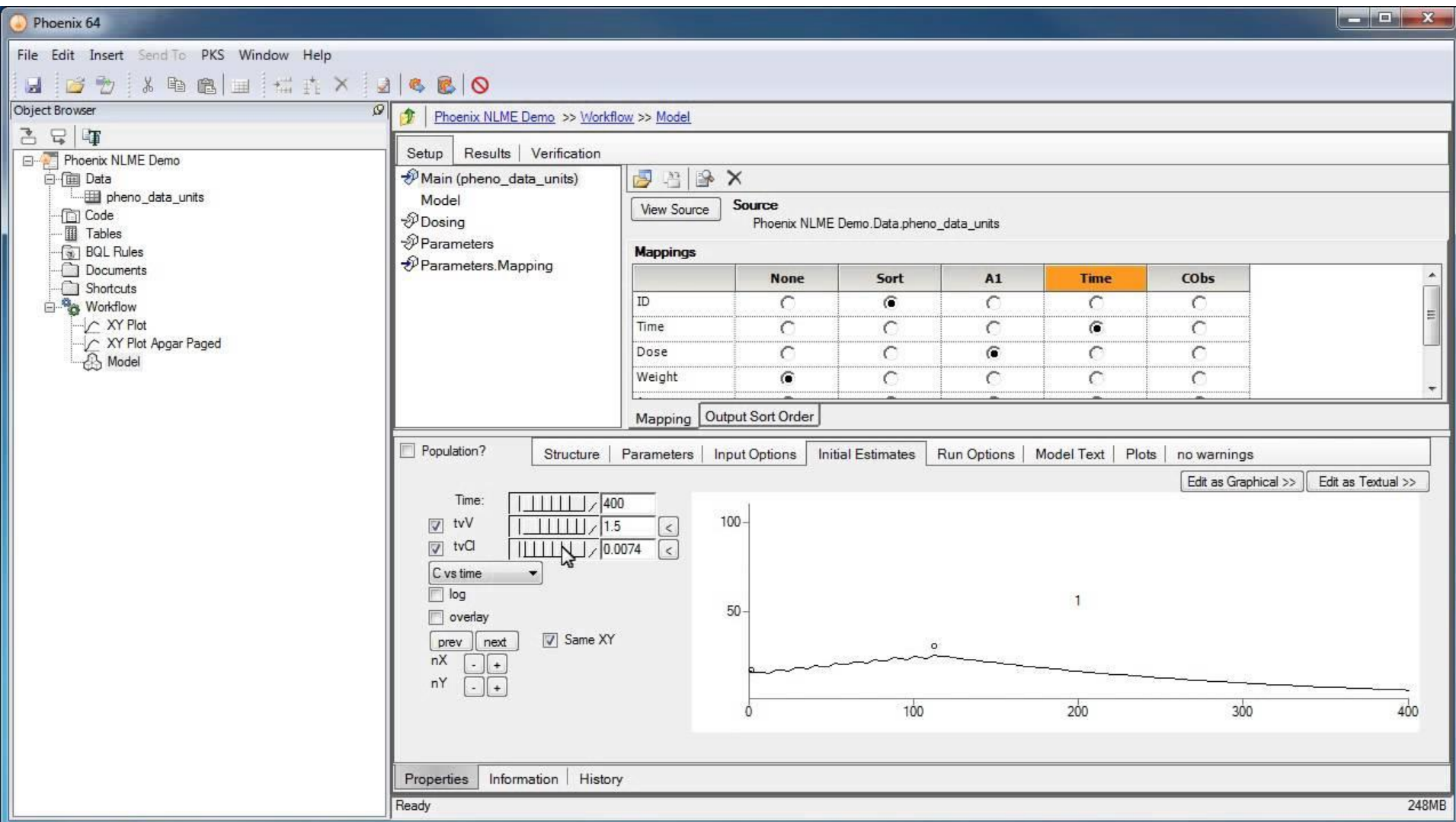


비구획 분석 작업 흐름

- 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!





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 파라미터의 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 eval = FALSE}
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 |

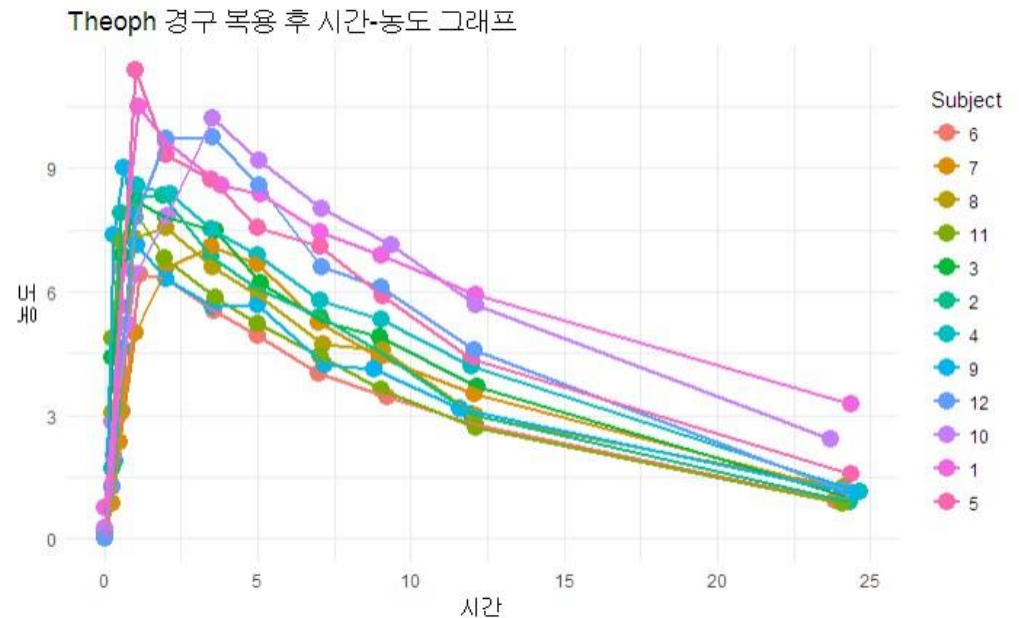
기본 자료

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

...

| Subject b0 | | CMAX | CMAXD | TMAX | TLAG | CLST | CLSTP | TLST | LAMZHL | LAMZ | LAMZLL | LAMZUL | LAMZNP | CORRY | R2 |
|---------------|---------------------|--------------------|--------------------|---------------------|---------------------|---------------------|---------------------|--------------------|---------------------|----------------------|--------------------|----------|----------|----------------------|---------------------|
| [1,] | "1" | "2.36878509420585" | "10.5" | "0.0328125" | "1.12" | "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" | "0.88639849106919" | "24.3" | "6.65934156262252" | "0.104086443688432" | "7.03" | "24.17" | "4" | "-0.998596709529913" | "0.99719538828397" |
| [3,] | "3" | "2.52971150145858" | "8.2" | "0.025625" | "1.02" | "0" | "1.05509670837553" | "24.17" | "6.76608737718236" | "0.102444314109434" | "9" | "24.17" | "3" | "-0.99966249354811" | "0.999324961849213" |
| [4,] | "4" | "2.59275546733663" | "8.6" | "0.026875" | "1.07" | "0" | "1.15642160174993" | "24.65" | "6.981246660989893" | "0.0992870205306231" | "9.02" | "24.65" | "3" | "-0.999461923749821" | "0.998924137025692" |
| [5,] | "5" | "2.55109229605128" | "11.4" | "0.035625" | "1.01" | "0" | "1.55569511595616" | "24.35" | "8.0022640410078" | "0.0866188839818201" | "7.02" | "24.35" | "4" | "-0.99932363732814" | "0.998647184582752" |
| [6,] | "6" | "2.0334043955621" | "6.44" | "0.020125" | "1.15" | "0" | "0.9217173708175" | "23.85" | "7.89499786796582" | "0.0877547400561702" | "2.03" | "23.85" | "7" | "-0.999120281624298" | "0.998241337153017" |
| [7,] | "7" | "2.28854976005454" | "7.09" | "0.02215625" | "3.48" | "0" | "1.16071921229933" | "24.22" | "7.84666826130148" | "0.0883364913791333" | "6.98" | "24.22" | "4" | "-0.999334862622512" | "0.998670167652754" |
| [8,] | "8" | "2.17040271754529" | "7.56" | "0.023625" | "2.02" | "0" | "1.28526758235656" | "24.12" | "8.51003788342506" | "0.0814505399453019" | "3.53" | "24.12" | "6" | "-0.99549602943785" | "0.991021391426654" |
| [9,] | "9" | "2.12464810390587" | "9.03" | "0.02821875" | "0.63" | "0" | "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" | "2.41369227401111" | "23.7" | "9.24691582297898" | "0.0749589327757766" | "9.38" | "23.7" | "3" | "-0.999754311749369" | "0.999508683861454" |
| [11,] | "11" | "2.1475943307927" | "8" | "0.025" | "0.98" | "0" | "0.859806606884089" | "24.08" | "7.26123651504393" | "0.095458598642772" | "9.03" | "24.08" | "3" | "-0.99999171793956" | "0.999988255959473" |
| [12,] | "12" | "2.82449437826545" | "9.75" | "0.03046875" | "3.52" | "0" | "1.1753904959565" | "24.15" | "6.28650816367189" | "0.110259489451627" | "9.03" | "24.15" | "3" | "-0.999669355328196" | "0.9993968016459" |
| R2ADJ | | AUCLST | AUALL | AUCIFO | AUCIFD | AUCIFP | AUCIFPD | AUCPEO | AUCPEP | AUMCLST | AUMCIFO | | | | |
| [1,] | "0.999999459349959" | "148.92305" | "148.92305" | "216.6119333038226" | "0.67691229074454" | "216.614955803818" | "0.67692173688693" | "31.248916940534" | "31.2498763313113" | "1459.0711035" | "4505.53481941065" | | | | |
| [2,] | "0.99579308242595" | "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" | "9.35713430809397" | "9.39832451573008" | "803.18587" | "1150.96476871455" | | | | |
| [4,] | "0.997482740501385" | "106.7963" | "106.7963" | "118.378881427603" | "0.369934004461258" | "118.443558579901" | "0.370136120562429" | "9.8733408603032" | "9.83359392402986" | "901.0842105" | "1303.25240140958" | | | | |
| [5,] | "0.997970776874129" | "121.2944" | "121.2944" | "139.419777837118" | "0.435686805740995" | "139.254630430615" | "0.435107209095671" | "13.0005786254328" | "12.8974026752838" | "1017.1143165" | "1667.72161189007" | | | | |
| [6,] | "0.99788960458362" | "73.77555" | "73.77555" | "84.2544183301878" | "0.263295057281837" | "84.4966985785753" | "0.264052183058048" | "12.437136674055" | "12.688245527848" | "609.1523875" | "978.428485741731" | | | | |
| [7,] | "0.998005215479131" | "90.7534" | "90.7534" | "103.771801796293" | "0.324286880613414" | "103.893147024686" | "0.32466084452144" | "12.5452290792812" | "12.6473664538854" | "782.41986" | "1245.09840831465" | | | | |
| [8,] | "0.998765489283318" | "88.55995" | "88.55995" | "103.906686815243" | "0.324708396297635" | "103.643051464786" | "0.323884535827455" | "14.7697297311878" | "15.529307094073" | "739.534598" | "1298.11575468474" | | | | |
| [9,] | "0.998887329645677" | "86.32615" | "86.32615" | "99.9087179279482" | "0.312124743524838" | "99.8660676588793" | "0.312081147433398" | "13.5949777052926" | "13.5580763078894" | "705.2296255" | "1201.77153812025" | | | | |
| [10,] | "0.99901736772909" | "138.3681" | "138.3681" | "170.652060635217" | "0.533287689485054" | "170.567912545332" | "0.533024726704162" | "18.9180022292417" | "18.8780011813617" | "1278.180042" | "2473.99342735889" | | | | |
| [11,] | "0.99996511979486" | "80.0936" | "80.0936" | "89.1027449234385" | "0.278442777885745" | "89.100718955217" | "0.278439746829755" | "10.1109622730249" | "10.1089184106194" | "617.2422125" | "928.559971386069" | | | | |
| [12,] | "0.998793603291801" | "119.9775" | "119.9775" | "130.588831558118" | "0.408090098619118" | "130.639068406815" | "0.408247087646298" | "8.12575733430562" | "8.16108703637935" | "977.8807235" | "1330.38400236898" | | | | |
| AUMCIPF | | AUMCPEO | AUMCPEP | VZFO | VZFP | CLFO | CLFP | MRTVELST | MRTVEVIF | | | | | | |
| [1,] | "45095.67086458209" | "67.6160286851127" | "67.6170064935417" | "30.4867482345887" | "30.4863228055444" | "1.47729626669981" | "1.47727565168591" | "9.79748335465867" | "20.8000305256292" | "20.8003683211179" | | | | | |
| [2,] | "096.0715835091064" | "29.3252499112927" | "29.0626720309864" | "30.6904415765423" | "30.7239160557228" | "3.1944589189298" | "3.1979415842211" | "7.17999639449866" | "9.98041094468705" | "9.9543135455675" | | | | | |
| [3,] | "1152.65209626304" | "30.2162940315685" | "30.318495985664" | "28.5170999496524" | "28.5041534217657" | "2.92141474473231" | "2.92008844565826" | "8.08957783787323" | "10.5067420187191" | "10.518276217325" | | | | | |
| [4,] | "1305.4981091996" | "30.8588106551429" | "30.9777467963968" | "27.2259641330176" | "27.2110971545992" | "2.70318485984093" | "2.70170876184947" | "8.43741038313125" | "11.0091630001303" | "11.022115006327" | | | | | |
| [5,] | "1661.7936736228" | "39.011744571429" | "38.7941877387202" | "26.49799465056136" | "26.5294196385914" | "2.295222742438806" | "2.29794872178016" | "8.38540103302378" | "11.9618752389051" | "11.9334895308224" | | | | | |
| [6,] | "986.966459689532" | "37.7417566662348" | "38.280335514986" | "43.2957344953234" | "43.135694392041" | "3.79802044056035" | "3.78713021198604" | "8.25683288704727" | "11.612785479182" | "11.6805328053438" | | | | | |
| [7,] | "1249.41106012833" | "37.1559983764277" | "37.376906210544" | "34.9084408430805" | "34.8676645452056" | "3.08368934971535" | "3.080087159804795" | "8.26138344128154" | "11.998427190837" | "12.052937101698" | | | | | |
| [8,] | "1288.52001616077" | "41.0301500280197" | "42.605894256157" | "37.8105087118408" | "37.90668611615621" | "3.07968630131565" | "3.08752005539633" | "8.056663903944" | "12.4930915850769" | "12.432865638375" | | | | | |
| [9,] | "1200.2123597462" | "41.3174964516894" | "41.2412628670872" | "38.8472934436931" | "38.8593822173436" | "3.20292369511514" | "3.20429158273309" | "8.1693626469722" | "12.0286954236259" | "12.0182198807093" | | | | | |
| [10,] | "2470.87654175199" | "48.3353501320931" | "48.2701777931124" | "25.0155401378403" | "25.0278813214113" | "1.87516048038837" | "1.87608557333405" | "9.23753409926132" | "14.497595491374" | "14.4861744795951" | | | | | |
| [11,] | "928.489963582081" | "33.5269415524517" | "33.521925081337" | "37.6221852019531" | "37.6230406407462" | "3.59135961832556" | "3.59144127728081" | "7.70651103833515" | "10.4212274513421" | "10.4026786898426" | | | | | |
| [12,] | "1332.05283411623" | "26.4963558071417" | "26.5884431567018" | "22.2249305693128" | "22.2157473419508" | "2.4504392617801" | "2.44949659970983" | "8.15053425433936" | "10.1875787270284" | "10.1964355292939" | | | | | |
| attr("units") | | "mg/L" | "mg/L/mg" | "h" | "mg/L" | "mg/L" | "h" | "h" | "h2*mg/L" | "h2/mg/L" | "h2*mg/L" | "h" | "h" | "h" | "L" |
| [17] | "L/h" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L/mg" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" | "h*mg/L" |
| [33] | "L/h" | "h" | "h" | "h" | "h" | "h" | "h" | "h" | "h" | "h" | "h" | "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	RZADJ	AUCCLST	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	AUMCIPF	AUMCPEO	AUMCPEP	VZF0
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" "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')
```
```

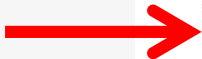




# 각 파라미터의 의미를 알고싶으면?

?ncar::txtNCA()

Value




|                    |                                                                                         |
|--------------------|-----------------------------------------------------------------------------------------|
| C <sub>MAX</sub>   | maximum concentration, C <sub>max</sub>                                                 |
| C <sub>MAXD</sub>  | dose normalized C <sub>max</sub> , C <sub>MAX</sub> / Dose, C <sub>max</sub> / Dose     |
| T <sub>MAX</sub>   | time of maximum concentration, T <sub>max</sub>                                         |
| T <sub>LAG</sub>   | time to observe the first non-zero concentration, for extravascular administration only |
| C <sub>LST</sub>   | last positive concentration observed, C <sub>last</sub>                                 |
| C <sub>LSTP</sub>  | last positive concentration predicted, C <sub>last_pred</sub>                           |
| T <sub>LST</sub>   | time of last positive concentration, T <sub>last</sub>                                  |
| 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                                              |
| R <sup>2</sup>     | R-squared                                                                               |
| R <sup>2</sup> ADJ | R-squared adjusted                                                                      |
| ...                |                                                                                         |

ncar::RptCfg

PPTSTCD  
<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")
```



```

1 NONCOMPARTMENTAL ANALYSIS REPORT
2 Package version 0.3.7 (2017-08-16 KST)
3 R version 3.4.2 (2017-09-28)
4
5 Date and Time: 2017-11-01 18:00:30 Asia/Seoul
6
7 Calculation Setting
8 -----
9 Drug Administration: Extravascular
10 Observation count excluding trailing zero: 11
11 Dose at time 0: 320 mg
12 AUC Calculation Method: Linear-up Linear-down
13 Weighting for lambda z: Uniform (Ordinary Least Square, OLS)
14 Lambda z selection criterion: Heighest adjusted R-squared value with precision=1e-
15
16
17 Fitting, AUC, AUMC Result
18 -----
19 Time Conc. Pred. Residual AUC AUMC
20 -----
21 0.0000 0.7400 0.0000 0.0000
22 0.2500 2.8400 0.4475 0.0888
23 0.5700 6.5700 1.9531 0.8015
24 1.1200 10.5000 6.6474 5.0654
25 2.0200 9.6600 15.7194 19.1383
26 3.8200 8.5800 32.1354 66.1982
27 5.1000 8.3600 42.9769 114.4617
28 7.0300 7.4700 58.2529 206.2815
29 9.0500 * 6.8900 6.8912 -1.228e-03 72.7565 322.2988
30 12.1200 * 5.9400 5.9387 +1.324e-03 92.4505 528.5219
31 24.3700 * 3.2800 3.2801 -1.465e-04 148.9231 1459.0711
32
33 *: Used for the calculation of Lambda z.
34
```

```

36 Calculated Values
37 -----
38 CMAX Max Conc 10.5000 mg/L
39 CMAXD Max Conc Norm by Dose 0.0328 mg/L/mg
40 TMAX Time of CMAX 1.1200 h
41 TLAG Time Until First Nonzero Conc 0.0000 h
42 CLST Last Nonzero Conc 3.2800 mg/L
43 CLSTP Last Nonzero Conc Pred 3.2801 mg/L
44 TLST Time of Last Nonzero Conc 24.3700 h
45 LAMZHL Half-Life Lambda z 14.3044 h
46 LAMZ Lambda z 0.0485 /h
47 LAMZLL Lambda z Lower Limit 9.0500 h
48 LAMZUL Lambda z Upper Limit 24.3700 h
49 LAMZNPT Number of Points for Lambda z 3
50 CORRX Correlation Between TimeX and Log ConcY -1.0000
51 R2 R Squared 1.0000
52 R2ADJ R Squared Adjusted 1.0000
53 AUCCLST AUC to Last Nonzero Conc 148.9231 h*mg/L
54 AUCALL AUC All 148.9231 h*mg/L
55 AUCIFO AUC Infinity Obs 216.6119 h*mg/L
56 AUCIFOD AUC Infinity Obs Norm by Dose 0.6769 h*mg/L/mg
57 AUCIFP AUC Infinity Pred 216.6150 h*mg/L
58 AUCIFPD AUC Infinity Pred Norm by Dose 0.6769 h*mg/L/mg
59 AUCPEO AUC %Extrapolation Obs 31.2489 %
60 AUCPEP AUC %Extrapolation Pred 31.2499 %
61 AUMCLST AUMC to Last Nonzero Conc 1459.0711 h2*mg/L
62 AUMCIFO AUMC Infinity Obs 4505.5348 h2*mg/L
63 AUMCIPF AUMC Infinity Pred 4505.6709 h2*mg/L
64 AUMCPEO AUMC %Extrapolation Obs 67.6160 %
65 AUMCPEP AUMC % Extrapolation Pred 67.6170 %
66 VZFO Vz Obs by F 30.4867 L
67 VZFP Vz Pred by F 30.4863 L
68 CLFO Total CL Obs by F 1.4773 L/h
69 CLFP Total CL Pred by F 1.4773 L/h
70 MRTEVLST MRT Extravasc to Last Nonzero Conc 9.7975 h
71 MRTEVIFO MRT Extravasc Infinity Obs 20.8000 h
72 MRTEVIFP MRT Extravasc Infinity Pred 20.8004 h
73
```

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

#### Fitting, AUC, AUMC Result

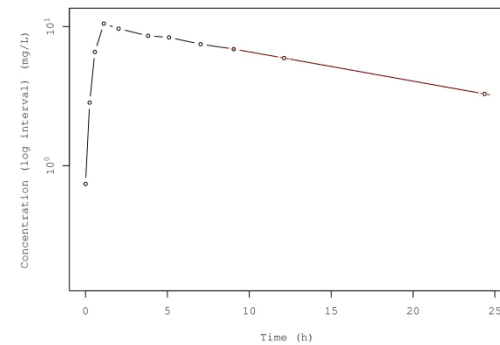
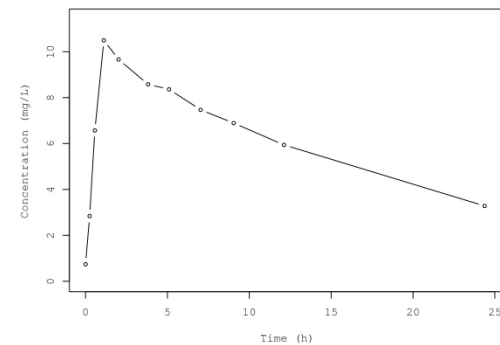
| Time      | Conc.   | Pred.  | Residual   | AUC      | AUMC      |
|-----------|---------|--------|------------|----------|-----------|
| 0.0000    | 0.7400  |        |            | 0.0000   | 0.0000    |
| 0.2500    | 2.8400  |        |            | 0.4475   | 0.0888    |
| 0.5700    | 6.5700  |        |            | 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   |
| 5.1800    | 8.3600  |        |            | 42.9769  | 114.4517  |
| 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       |
| LAMNPT | Number of Points for Lambda z           | 3               |
| CORRKY | Correlation Between TimeX and Log ConcY | -1.0000         |
| R2     | R Squared                               | 1.0000          |
| READJ  | R Squared Adjusted                      | 1.0000          |
| ADCLST | AUC to Last Nonzero Conc                | 148.9231 h*mg/L |
| AUCALL | AUC All                                 | 148.9231 h*mg/L |

Subject ID = 1



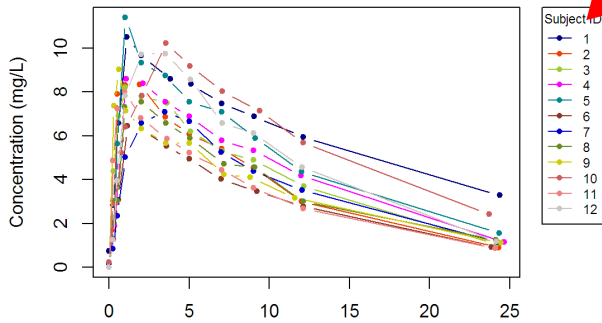
pk<sub>r</sub>

비구획 분석 시각화 & SDTM

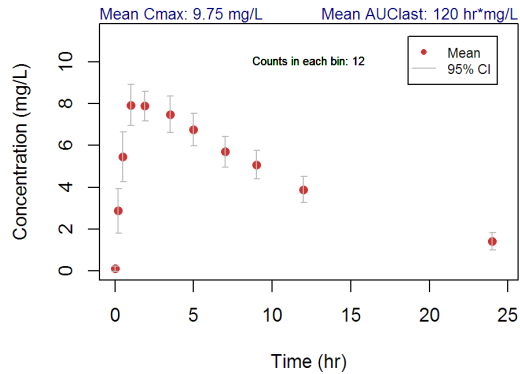
# plotPK()

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

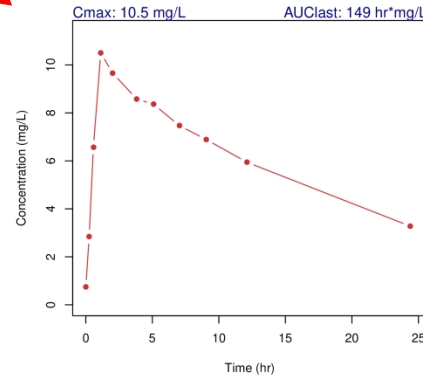
Concentration vs. Time Profile of Theoph



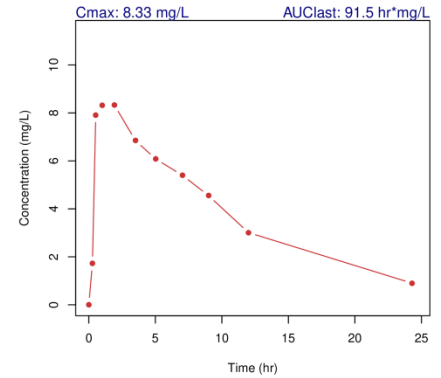
Concentration vs. Time Profile of Theoph



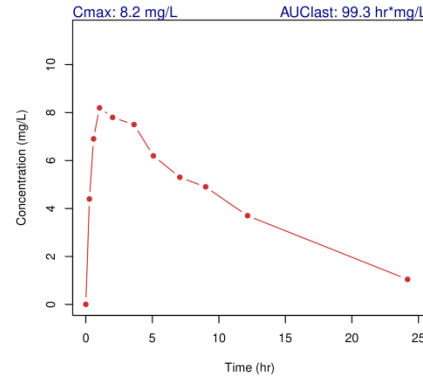
Subject ID 1



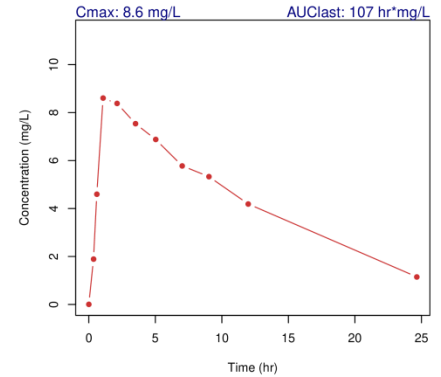
Subject ID 2



Subject ID 3



Subject ID 4



# 인터넷 웹브라우저를 통한 비구획분석

<https://asan.shinyapps.io/pkrshiny>

# pkrrshiny

- 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/pkrrshiny>

# 예시

pkR Shiny

DataResultReportCDISCDynamicPlotFitHelpContact

Choose CSV File with "SUBJECT", "TIME", "CONC" (case-insensitive)

Browse...

No file selected

Dataset

☐ CSV

☒ Theoph (N=12)

☐ Indometh (N=6)

☐ sd\_oral\_richpk (N=50)

☐ sd\_iv\_rich\_pkpd (N=60)

☒ AUC Calculation by Log

Administration route

☒ Oral or Extravascular

☐ Intravenous Bolus

☐ Intravenous Infusion

Intravenous Infusion time (hr)

0

10

| 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  |

pkR Shiny

DataResultReportCDISCDynamicPlotFitHelpContact

Set dose (mg)

0

320

1,000

or select dose column

☐ WT

☒ DOSE

Select TRT column if exists

☐ WT

☒ DOSE

If dosing amount is unknown, choose 0 (zero).

If selected, value of left slider will be ignored.

TRT column usually contains R or T. You can select multiple columns if the study has TRT, PRD, SEQ and so on.

☐ Sort TRT

Individual Parameters

| SUBJECT | C <sub>MAX</sub> | C <sub>MAXD</sub> | T <sub>MAX</sub> | T <sub>LAG</sub> | CL <sub>ST</sub> | CL <sub>STP</sub> | T <sub>LST</sub> | LAM <sub>ZHL</sub> | LAM <sub>Z</sub> | LAM <sub>ZLL</sub> | LAM <sub>ZUL</sub> | LAM <sub>ZNP</sub> |
|---------|------------------|-------------------|------------------|------------------|------------------|-------------------|------------------|--------------------|------------------|--------------------|--------------------|--------------------|
| 01      | 10.50            | 0.03              | 1.12             | 0.00             | 3.28             | 3.28              | 24.37            | 14.30              | 0.05             | 9.05               | 24.37              | 3.00               |
| 02      | 8.33             | 0.03              | 1.92             | 0.00             | 0.90             | 0.89              | 24.30            | 6.66               | 0.10             | 7.03               | 24.30              | 4.00               |
| 03      | 8.20             | 0.03              | 1.02             | 0.00             | 1.05             | 1.06              | 24.17            | 6.77               | 0.10             | 9.00               | 24.17              | 3.00               |
| 04      | 8.60             | 0.03              | 1.07             | 0.00             | 1.15             | 1.16              | 24.65            | 6.98               | 0.10             | 9.02               | 24.65              | 3.00               |
| 05      | 11.40            | 0.04              | 1.00             | 0.00             | 1.57             | 1.56              | 24.35            | 8.00               | 0.09             | 7.02               | 24.35              | 4.00               |
| 06      | 6.44             | 0.02              | 1.15             | 0.00             | 0.92             | 0.94              | 23.85            | 7.89               | 0.09             | 2.03               | 23.85              | 7.00               |
| 07      | 7.09             | 0.02              | 3.48             | 0.00             | 1.15             | 1.16              | 24.22            | 7.85               | 0.09             | 6.98               | 24.22              | 4.00               |
| 08      | 7.56             | 0.02              | 2.02             | 0.00             | 1.25             | 1.23              | 24.12            | 8.51               | 0.08             | 3.53               | 24.12              | 6.00               |
| 09      | 9.03             | 0.03              | 0.63             | 0.00             | 1.12             | 1.12              | 24.43            | 8.41               | 0.08             | 8.80               | 24.43              | 3.00               |
| 10      | 10.21            | 0.03              | 3.55             | 0.00             | 2.42             | 2.41              | 23.70            | 9.25               | 0.07             | 9.38               | 23.70              | 3.00               |
| 11      | 8.00             | 0.03              | 0.98             | 0.00             | 0.86             | 0.86              | 24.08            | 7.26               | 0.10             | 9.03               | 24.08              | 3.00               |
| 12      | 9.75             | 0.03              | 3.52             | 0.00             | 1.17             | 1.18              | 24.15            | 6.29               | 0.11             | 9.03               | 24.15              | 3.00               |

Descriptive Statistics

Study ID

Drug

PP

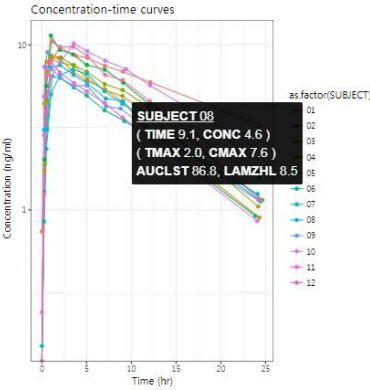
| STUDYID | DOMAIN | USUBJID | PPSEQ | PPGRPID | PPTTESTCD | PPTTEST                       | PPSCAT            | PPORRES |
|---------|--------|---------|-------|---------|-----------|-------------------------------|-------------------|---------|
| PP      | PP     | 01      | 1     |         | CMAx 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

Hovering a cursor over a plot shows dynamic results.

Y axis

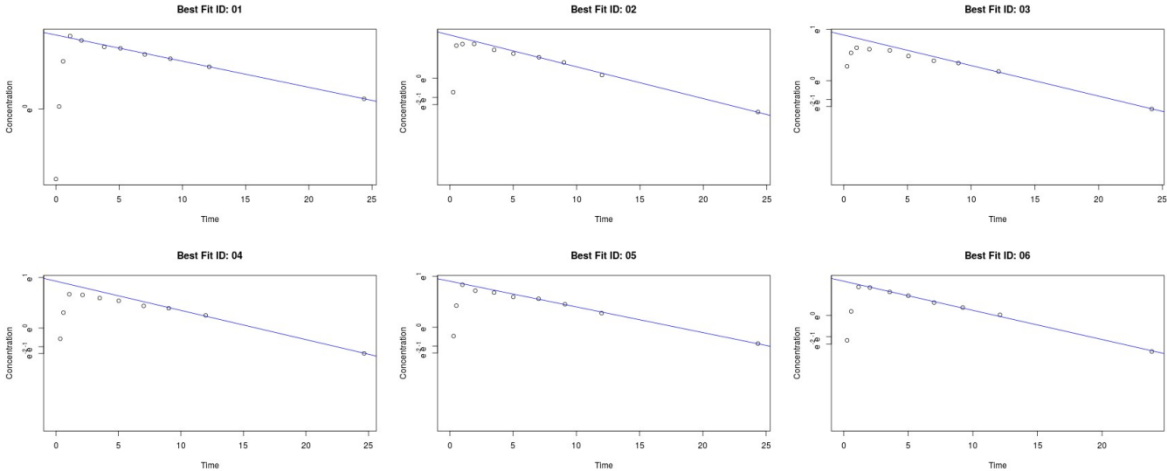
☒ Log

☐ Linear



Generating plots takes a while. Please wait.

Individual Plots

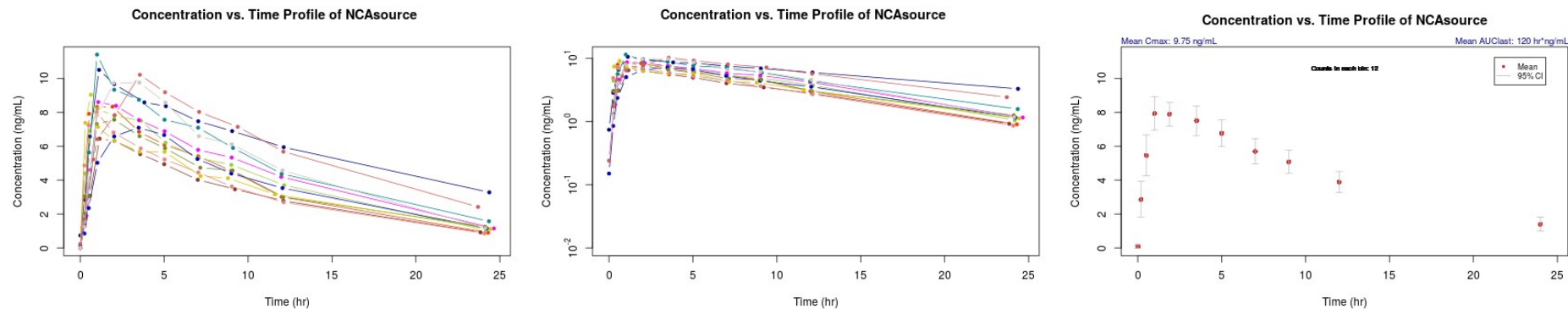




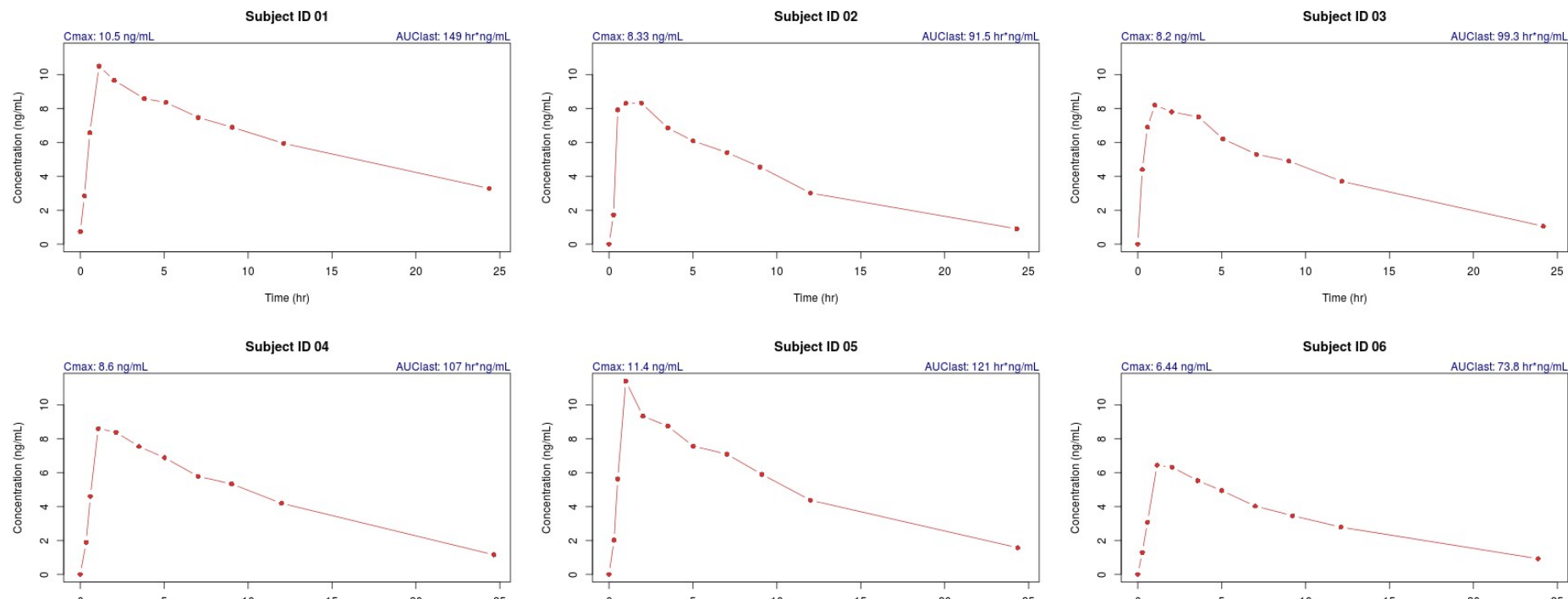
Generating plots takes a while. Please wait.

# 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

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R을 사용한 비구획분석

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 가능하며 농도-시간 곡선, 용량군 별 파라미터의 forest plot 등의 유용한 그림도 쉽게 그릴 수 있습니다. CDISC SDTM 표준을 따르는 용어를 사용한 것도 큰 장점입니다.

한번 익히두면 속도와 연속성 측면에서 커다란 이점이 있음을 발견할 수 있을 것입니다. 또한 재현가능한 연구를 보다 수월하게 구현할 수 있습니다. 무엇보다 무료로 사용할 수 있는 R 기반의 공개 소프트웨어라는 점에서 학교, 연구소, 정부기관, 제약회사 등에서 라이선스 등의 제약 없이 손쉽게 설치하고 실행할 수 있으리라 생각합니다. 책에 대한 피드백, 오탈자 신고 등은 깃허브 저장소에 남겨주세요.

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 경험을 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 pkc 사용법

6 R을 사용한 약동학 시뮬레이션

7 통계처리

8 결과 및 논의

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```
png
2
```

조금 기다린 후 ./output: 폴더를 확인해 보면 새개의 그림 파일이 생성된 것을 알 수 있습니다.

- ./Output/PPK Profile Linear Scale for Theoph.tif
- ./Output/PPK Profile Log 10 Scale for Theoph.tif
- ./Output/PPK Profile with CI for Theoph.tif

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

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

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

# 감사합니다.

사용후 궁금한 점이 있다면 [shan@catholic.ac.kr](mailto:shan@catholic.ac.kr) 로 알려주세요.

## Reference

- Bae, Kyun-Seop. 2017a. *Ncar: Noncompartmental Analysis for Pharmacokinetic Report*. <https://CRAN.R-project.org/package=ncar>.
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- Gabrielsson J, Weiner D. *Pharmacokinetic and Pharmacodynamic Data Analysis – Concepts and Applications*. 5th ed. 2016. (ISBN:9198299107).