Dept. of Clinical Pharmacology and Therapeutics

Manual for Clinical Trial

Noncompartmental Analysis

Implemented in `NonCompart` R package

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2026-11-15

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1 Formula

[1] Preparation

This is just for the prepartion of data for the subsequent R scripts.

```
Adm = c("BOLUS", "INFUSION", "EXTRAVASCULAR")[3] # Drug Administration Method
Dose = 320 # mg
x = x0 = Theoph[Theoph$Subject==1, "Time"] # h
y = y0 = Theoph[Theoph$Subject==1, "conc"] # ug/L

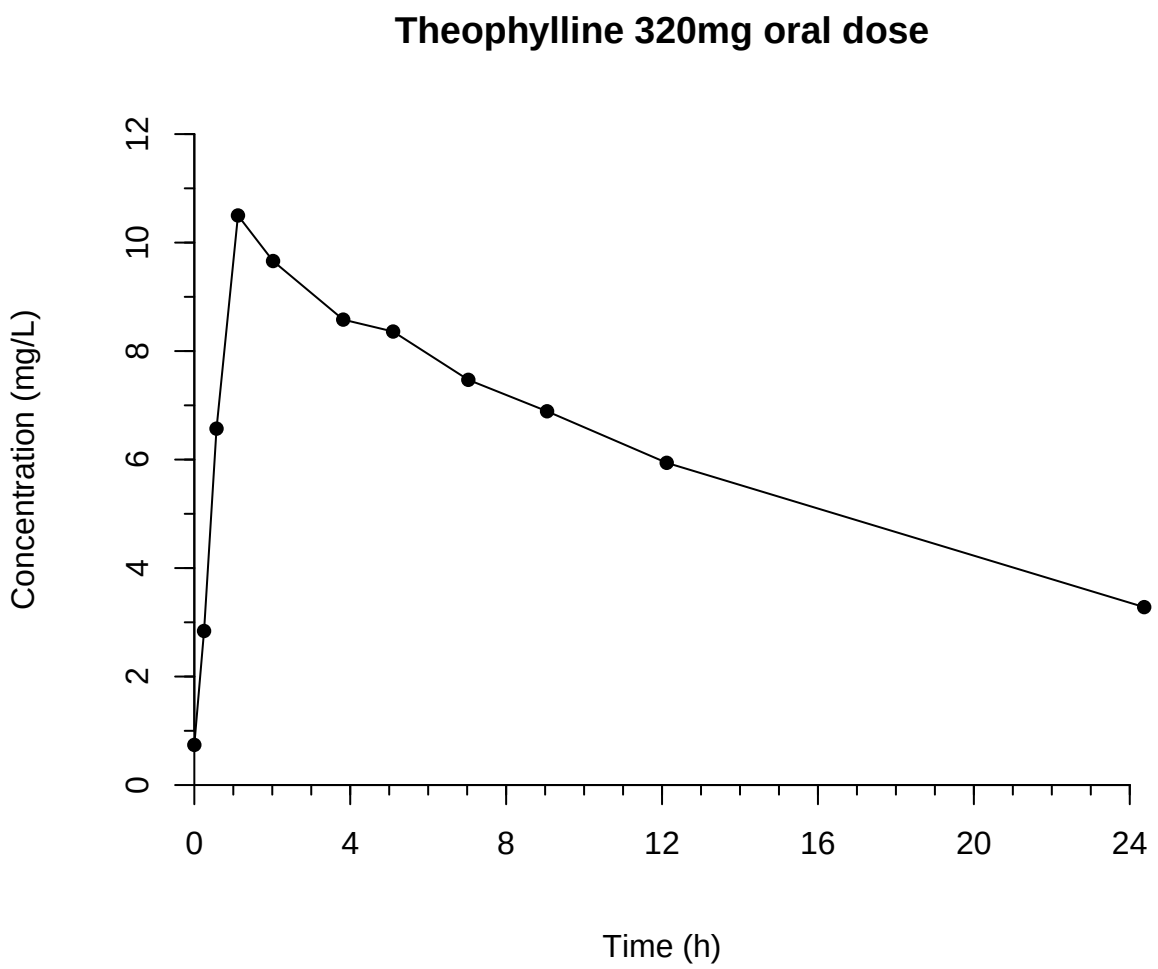
# For the calculation of AUClast
iLastNonZero = max(which(y > 0)) # index of last non-zero concentration
x1 = x0[1:iLastNonZero]
y1 = y0[1:iLastNonZero]

# For the log-concentration vs. time regression
x2 = x0[y0 > 0]
y2 = y0[y0 > 0]

# Print data
cbind(Time=x0, Conc=y0)
#        Time  Conc
#  [1,]  0.00  0.74
#  [2,]  0.25  2.84
#  [3,]  0.57  6.57
#  [4,]  1.12 10.50
#  [5,]  2.02  9.66
#  [6,]  3.82  8.58
#  [7,]  5.10  8.36
#  [8,]  7.03  7.47
```

```
#  [9,]  9.05  6.89
# [10,] 12.12  5.94
# [11,] 24.37  3.28
```

[2] Plot of raw data



[3] Cmax (CMAX)

Maximum concentration. At steady state (SS=TRUE) only the samples within the dosing interval, $0 \leq t \leq \tau$, are searched; the same holds for Tmax. Up to NonCompart 0.8.4 the whole profile was searched.

```
CMAX = NA
CMAX = max(y, na.rm=TRUE) ; CMAX
# [1] 10.5
```

[4] Cmax_D (CMAXD)

Dose normalized Cmax.

```
CMAXD = NA
CMAXD = CMAX/Dose ; CMAXD
# [1] 0.0328125
```

[5] Tmax (TMAX)

Time of maximum concentration.

```
TMAX = NA
if (CMAX > 0) TMAX = x[which.max(y)]
TMAX
# [1] 1.12
```

[6] Tlag (TLAG)

Time until first non-zero concentration.

```
TLAG = NA
if (CMAX > 0) TLAG = x[max(1, min(which(y > 0)) - 1)]
TLAG
# [1] 0
```

[7] Clast (CLST)

Last non-zero concentration.

```
CLST = y[iLastNonZero] ; CLST
# [1] 3.28
```

[8] Tlast (TLST)

Time of last non-zero concentration.

```
TLST = x[iLastNonZero] ; TLST
# [1] 24.37
```

[9] Rsq (R2)

R-squared value from the log concentration and time regression.

[10] Rsq_adjusted (R2ADJ)

Adujsted R-squared value.

$$R^2_{\text{adj}} = 1 - (1 - R^2)\frac{n-1}{n-2}$$

[11] Corr_XY (CORRXY)

Correlation value of the regression

[12] b0

Intercept of the simple linear regression of log(y) vs x

[13] Lambda_z (LAMZ)

Terminal slope as a positive value

[14] No_points_Lambda_z (LAMZNPT)

Number of points used for the regression

[15] Lambda_z_lower (LAMZLL)

First time point used for the regression

[16] Lambda_z_upper (LAMZUL)

Last time point used for the regression

[17] R2, R2ADJ, CORRXY, b0, LAMZ, LAMZNPT, LAMZLL, LAMZUL

Only positive concentrations are used. In case of oral administration, the first possible point is next to `Tmax` point. In case of intravascular administration, the first point can be `Tmax` point. If the difference of `R2ADJ` (R2-squared adjusted) is less than 1e-4, the longer slope is chosen. Regression points should be at least 3.

```
x = x2 ; y = y2

if (toupper(Adm) == "EXTRAVASCULAR") {
  iFirst = which.max(y) + 1 # for oral administration
} else {
  iFirst = which.max(y)     # for intravenous administration
}
iLast = iLastNonZero

ColNames = c("R2", "R2ADJ", "CORRXY", "b0", "LAMZ", "LAMZNPT", "LAMZLL", "LAMZUL")
mRes = matrix(nrow = iLast - iFirst + 1 - 2, ncol=length(ColNames))
colnames(mRes) = ColNames
for (i in iFirst:(iLast - 2)) {
  Res = lm(log(y[i:iLast]) ~ x[i:iLast])
  mRes[i - iFirst + 1, "R2"]      = summary(Res)$r.squared
  mRes[i - iFirst + 1, "R2ADJ"]   = summary(Res)$adj.r.squared
  mRes[i - iFirst + 1, "CORRXY"]  = cor(log(y[i:iLast]), x[i:iLast])
  mRes[i - iFirst + 1, "b0"]      =  Res$coefficients[1]
  mRes[i - iFirst + 1, "LAMZ"]    = -Res$coefficients[2]
  mRes[i - iFirst + 1, "LAMZNPT"] = iLast - i + 1
  mRes[i - iFirst + 1, "LAMZLL"]  = x[i]
  mRes[i - iFirst + 1, "LAMZUL"]  = x[iLast]
} ; mRes
```

```
#             R2     R2ADJ     CORRXY       b0       LAMZ LAMZNPT LAMZLL LAMZUL
# [1,] 0.9988013 0.9985615 -0.9994005 2.355187 0.04778625       7   2.02  24.37
# [2,] 0.9987305 0.9984131 -0.9993650 2.350845 0.04751440       6   3.82  24.37
# [3,] 0.9995671 0.9994229 -0.9997836 2.362429 0.04817356       5   5.10  24.37
# [4,] 0.9996109 0.9994164 -0.9998054 2.356834 0.04787556       4   7.03  24.37
# [5,] 0.9999997 0.9999995 -0.9999999 2.368785 0.04845700       3   9.05  24.37

OKs = abs(max(mRes[,"R2ADJ"]) - mRes[,"R2ADJ"]) < 1e-4
resNCA = as.data.frame(mRes[which(OKs)[1],,drop=FALSE]) ; resNCA
#          R2     R2ADJ     CORRXY       b0     LAMZ LAMZNPT LAMZLL LAMZUL
# 1 0.9999997 0.9999995 -0.9999999 2.368785 0.048457       3   9.05  24.37
attach(resNCA, warn.conflicts=FALSE)
```

If you want to manually omit some points, use an R package for convenience.

[18] HL_Lambda_z (LAMZHL)

Terminal half-life calculated by $\ln(2)/\lambda_Z$

```
LAMZHL = NA
if (LAMZ > 0) LAMZHL = log(2)/LAMZ
LAMZHL
# [1] 14.30438
```

[19] Clast_pred (CLSTP)

Predicted Clast, predicted concentration at Tlast.

$C_{\text{last,pred}} = \exp(\beta_0 - \lambda \cdot T_{\text{last}})$

```
CLSTP = NA
if (LAMZ > 0) CLSTP = exp(b0 - LAMZ*x[iLast])
CLSTP
# [1] 3.280146
```

[20] C0 (C0)

Concentration at time 0, intial concentration. This is calculated only for BOLUS administration.

$$C_0 = \exp\left(\log(C_1) - t_1\frac{\log(C_2) - \log(C_1)}{t_2 - t_1}\right)$$

```
x = x0 ; y = y0
if (toupper(Adm) == "BOLUS") {
  if (y[1] > y[2] & y[2] > 0) {
    C0 = exp(log(y[1]) - x[1]*(log(y[2]) - log(y[1]))/(x[2] - x[1]))
  } else {
    C0 = y[x==min(x[y > 0])]
  }
} else {
  C0 = NA
}
```

[21] AUClast (AUCLST)

Area under the time-concentration curve from dosing to the last positive concentration.

For linear trapezoidal method,

$$\text{AUC}_{\text{last}} = \sum_{i=2} \frac{(t_i - t_{i-1}) \times (C_i + C_{i-1})}{2}$$

```
n = length(x1)
AUCLST = sum((y1[-1] + y1[-n]) * (x1[-1] - x1[-n]))/2 ; AUCLST
# [1] 148.923
```

For 'linear-up log-down' method,

```
AUCLST = 0
for (i in 2:n) {
  if (y1[i] < y1[i-1] & y1[i] > 0) {
    k = (log(y1[i - 1]) - log(y1[i]))/(x1[i] - x1[i - 1]) # slope in log
    AUCLST = AUCLST + (y1[i - 1] - y1[i])/k
  } else {
    AUCLST = AUCLST + (x1[i] - x1[i - 1])*(y1[i] + y1[i - 1])/2
  }
} ; AUCLST
```

[22] AUCall (AUCALL)

AUC values including all zero concentrations.

For linear trapezoidal method,

```
AUCALL = sum((y0[-1] + y0[-n]) * (x0[-1] - x0[-n]))/2 ; AUCALL
# [1] 148.923
```

For 'linear-up log-down' method,

```
AUCALL = 0
for (i in 2:n) {
  if (y0[i] < y0[i-1] & y0[i] > 0) {
    k = (log(y0[i - 1]) - log(y0[i]))/(x0[i] - x0[i - 1]) # slope in log
    AUCALL = AUCALL + (y0[i - 1] - y0[i])/k
  } else {
    AUCALL = AUCALL + (x0[i] - x0[i - 1])*(y0[i] + y0[i - 1])/2
  }
} ; AUCALL
```

A segment that comes down to a zero concentration cannot take the log rule, because the logarithm of zero is not finite, and is calculated by the linear trapezoidal rule. Up to `NonCompart` 0.8.4 such a segment was left out of `AUCLST`, `AUCALL` and `AUMCLST` under the log-down method.

[23] AUCtau (AUCTAU)

Area under the curve over one dosing interval, from dosing (time 0) to τ, the dosing interval. This is calculated only at steady state (`SS=TRUE`), when `tau` is required; its unit `unitTau` defaults to `"h"` and is converted into the unit of time. Available since `NonCompart` 0.8.4.

$$\mathrm{AUC}_{\mathrm{tau}} = \int_0^{\tau} C(t)\,dt$$

The same trapezoidal rules as for `AUClast` (linear, or linear-up log-down) are applied over $0 \le t \le \tau$. When τ is not a sampling time, the concentration at τ is interpolated between the two neighboring samples (linearly, or log-linearly for a descending segment under the log-down method). When τ is later than T_{last}, the concentration at τ is predicted from the terminal regression, $\exp(\beta_0 - \lambda_z \tau)$,

and the segment after T_{last} is integrated by the log trapezoidal rule; without a terminal slope `AUCTAU` is `NA`. This is the interval AUC that `iAUC` with `Start=0` and `End=tau` gives. Without a sample at time 0, the lowest concentration observed within the dosing interval is inserted there for extravascular administration and infusion (0 after a single dose; up to `NonCompart` 0.8.4, 0 at steady state too).

For a steady-state profile sampled over one 12 h dosing interval (pre-dose trough 2 mg/L, then 6, 10, 8, 4 and 2 mg/L at 1, 2, 4, 8 and 12 h), the linear trapezoidal method gives

```
tau = 12
xs = c(0, 1, 2, 4, 8, 12)
ys = c(2, 6, 10, 8, 4, 2)
ns = length(xs)
AUCTAU = sum((ys[-1] + ys[-ns]) * (xs[-1] - xs[-ns]))/2 ; AUCTAU
# [1] 66
```

[24] Cavg (CAVG)

Average concentration over the dosing interval at steady state. This is calculated only at steady state (`SS=TRUE`).

$$C_{\text{avg}} = \frac{\text{AUC}_{\text{tau}}}{\tau}$$

```
CAVG = AUCTAU/tau ; CAVG
# [1] 5.5
```

[25] AUCinf_obs (AUCIFO)

AUCinf observed.

$$\text{AUC}_{\text{inf,obs}} = \text{AUC}_{\text{last}} + \frac{C_{\text{last}}}{\lambda_z}$$

[26] AUC_%Extrap_obs (AUCPEO)

AUC percent extrapolated observed.

$$\text{AUC}_{\%\text{Extrap,obs}} = \left(1 - \frac{\text{AUC}_{\text{last}}}{\text{AUC}_{\text{inf,obs}}}\right) \times 100$$

[27] AUCinf_D_obs (AUCIFOD)

Dose normalized AUCinf observed.

$$\text{AUC}_{\text{dose,inf,obs}} = \frac{\text{AUC}_{\text{inf,obs}}}{\text{Dose}}$$

[28] AUCinf_pred (AUCIFP)

AUCinf predicted.

$$\text{AUC}_{\text{inf,pred}} = \text{AUC}_{\text{last}} + \frac{C_{\text{last,pred}}}{\lambda_z}$$

[29] AUC_%Extrap_pred (AUCPEP)

AUC percent extrapolated predicted.

$$\text{AUC}_{\%\text{Extrap,pred}} = \left(1 - \frac{\text{AUC}_{\text{last}}}{\text{AUC}_{\text{inf,pred}}}\right) \times 100$$

[30] AUCinf_D_pred (AUCIFPD)

Dose normalized AUCinf predicted.

$$\text{AUC}_{\text{dose,inf,pred}} = \frac{\text{AUC}_{\text{inf,pred}}}{\text{Dose}}$$

[31] AUMClast (AUMCLST)

$$\text{AUMC}_{\text{last}} = \int_0^{t_{\text{last}}} t\,C(t)\,dt$$

For linear trapezoidal method;

$$\text{AUMC}_{\text{last}} \approx \sum_{i=2} \frac{(t_i - t_{i-1}) \times (t_i C_i + t_{i-1} C_{i-1})}{2}$$

```
AUMCLST = sum((x1[-1] - x1[-n])*(x1[-1]*y1[-1] + x1[-n]*y1[-n]))/2
```

For 'linear-up log-down' method;

```
AUMCLST = 0
for (i in 2:n) {
  if (y1[i] < y1[i-1] & y1[i] > 0) {
    k = (log(y1[i-1]) - log(y1[i]))/(x1[i] - x1[i-1]) # slope in log
    AUMCLST = AUMCLST + (x1[i-1]*y1[i-1] - x1[i]*y1[i])/k + (y1[i-1] - y1[i])/k/k
  } else {
    AUMCLST = AUMCLST + (x1[i] - x1[i-1])*(x1[i]*y1[i] + x1[i-1]*y1[i-1])/2
  }
}
```

[32] AUMCinf_obs (AUMCIFO)

AUMC infinity observed.

$$\text{AUMC}_{\text{inf,obs}} = \text{AUMC}_{\text{last}} + \frac{C_{\text{last}}\,T_{\text{last}}}{\lambda_z} + \frac{C_{\text{last}}}{\lambda_z^2}$$

[33] AUMC_%Extrap_obs (AUMCPEO)

AUMC percent extrapolated observed.

$$\text{AUMC}_{\%Extrap,obs} = \left(1 - \frac{\text{AUMC}_{\text{last}}}{\text{AUMC}_{\text{inf,obs}}}\right) \times 100$$

[34] AUMCinf_pred (AUMCIFP)

AUMC infinity predicted.

$$\text{AUMC}_{\text{inf,pred}} = \text{AUMC}_{\text{last}} + \frac{C_{\text{last,pred}}\, T_{\text{last}}}{\lambda_z} + \frac{C_{\text{last,pred}}}{\lambda_z^2}$$

[35] AUMC_%Extrap_pred (AUMCPEP)

AUMC percent extrapolated predicted.

$$\text{AUMC}_{\%\text{Extrap,pred}} = \left(1 - \frac{\text{AUMC}_{\text{last}}}{\text{AUMC}_{\text{inf,pred}}}\right) \times 100$$

[36] AUC_Back_Ext_obs (AUCBEO)

AUC back extrapolated observed. This is only for BOLUS administration.

For trapezoidal method;

$$\text{AUC}_{\text{backextrap}} = \frac{t_1 \times (C_0 + C_1)}{2}$$

For log-down method;

$$\text{AUC}_{\text{backextrap}} = \frac{t_1 \times (C_0 - C_1)}{\log(C_0) - \log(C_1)}$$

[37] AUC_%Back_Ext_obs (AUCPBEO)

AUC percent back extrapolated observed. This is only for BOLUS administration.

$$\text{AUC}_{\%\text{backextrap,obs}} = \frac{\text{AUC}_{\text{backextrap}}}{\text{AUC}_{\text{inf,obs}}} \times 100$$

[38] AUC_%Back_Ext_pred (AUCPBEP)

AUC percent back extrapolated predicted. This is only for BOLUS administration.

$$\mathrm{AUC}_{\%\mathrm{backextrap,pred}} = \frac{\mathrm{AUC}_{\mathrm{backextrap}}}{\mathrm{AUC}_{\mathrm{inf,pred}}} \times 100$$

[39] MRTlast (MRTEVLST, MRTIVLST)

Mean Residence Time (MRT) from 0 to Tlast.

$$\mathrm{MRT}_{\mathrm{EV,last}} = \frac{\mathrm{AUMC}_{\mathrm{last}}}{\mathrm{AUC}_{\mathrm{last}}}$$

$$\mathrm{MRT}_{\mathrm{IV,last}} = \frac{\mathrm{AUMC}_{\mathrm{last}}}{\mathrm{AUC}_{\mathrm{last}}} - \frac{\mathrm{Dur}}{2}$$

EV: extravascular

IV: intravascular

Dur: duration of infusion

[40] MRTinf_obs (MRTEVIFO, MRTIVIFO)

MRT infinity observed.

$$\mathrm{MRT}_{\mathrm{EV,inf,obs}} = \frac{\mathrm{AUMC}_{\mathrm{inf,obs}}}{\mathrm{AUC}_{\mathrm{inf,obs}}}$$

$$\mathrm{MRT}_{\mathrm{IV,inf,obs}} = \frac{\mathrm{AUMC}_{\mathrm{inf,obs}}}{\mathrm{AUC}_{\mathrm{inf,obs}}} - \frac{\mathrm{Dur}}{2}$$

At steady state (`SS=TRUE`) the first moment of one dosing interval is used, together with the area that lies beyond the interval:

$$\mathrm{MRT}_{\mathrm{EV,inf,obs}} = \frac{\mathrm{AUMC}_{\mathrm{tau}} + \tau\left(\mathrm{AUC}_{\mathrm{inf,obs}} - \mathrm{AUC}_{\mathrm{tau}}\right)}{\mathrm{AUC}_{\mathrm{tau}}}$$

$$\mathrm{MRT}_{\mathrm{IV,inf,obs}} = \frac{\mathrm{AUMC}_{\mathrm{tau}} + \tau\left(\mathrm{AUC}_{\mathrm{inf,obs}} - \mathrm{AUC}_{\mathrm{tau}}\right)}{\mathrm{AUC}_{\mathrm{tau}}} - \frac{\mathrm{Dur}}{2}$$

$\mathrm{AUMC}_{\mathrm{tau}}$ is the AUMC from 0 to τ, calculated by the same rules as $\mathrm{AUC}_{\mathrm{tau}}$. Up to `NonCompart` 0.8.4 this was not calculated (`NA`) at steady state.

[41] MRTinf_pred (MRTEVIFP, MRTIVIFP)

MRT infinity predicted.

$$\mathrm{MRT}_{\mathrm{EV,inf,pred}} = \frac{\mathrm{AUMC}_{\mathrm{inf,pred}}}{\mathrm{AUC}_{\mathrm{inf,pred}}}$$

$$\mathrm{MRT}_{\mathrm{IV,inf,pred}} = \frac{\mathrm{AUMC}_{\mathrm{inf,pred}}}{\mathrm{AUC}_{\mathrm{inf,pred}}} - \frac{\mathrm{Dur}}{2}$$

At steady state (`SS=TRUE`), $\mathrm{AUC}_{\mathrm{inf,pred}}$ takes the place of $\mathrm{AUC}_{\mathrm{inf,obs}}$ in the steady-state formulas of `MRTinf_obs`. Up to `NonCompart` 0.8.4 this was not calculated (`NA`) at steady state.

[42] Vz_obs (VZO) or Vz_F_obs (VZFO)

Volume of distribution by AUCIFO. VZO is for intravascular administration and VZFO for extravascular administration.

$$\mathrm{V}_{\mathrm{z,obs}} = \frac{\mathrm{Dose}}{\mathrm{AUC}_{\mathrm{inf,obs}} \times \lambda_z}$$

At steady state (`SS=TRUE`) the area over one dosing interval takes the place of $\mathrm{AUC}_{\mathrm{inf,obs}}$:

$$\mathrm{V}_{\mathrm{z,obs}} = \frac{\mathrm{Dose}}{\mathrm{AUC}_{\mathrm{tau}} \times \lambda_z}$$

Up to `NonCompart` 0.8.3, $\mathrm{AUC}_{\mathrm{last}}$ was used here at steady state; it equals $\mathrm{AUC}_{\mathrm{tau}}$ only when the last sample falls exactly at τ.

[43] Vz_pred (VZP) or Vz_F_pred (VZFP)

Volume of distribution by AUCIFP. VZP is for intravascular administration and VZFP for extravascular administration. Not calculated (`NA`) at steady state.

$$V_{z,\text{pred}} = \frac{\text{Dose}}{AUC_{\text{inf,pred}} \times \lambda_z}$$

[44] CL_obs (CLO) or CL_F_obs (CLFO)

Clearance observed. CLO is for intravascular administration and CLFO for extravascular administration.

$$CL_{\text{obs}} = \frac{\text{Dose}}{AUC_{\text{inf,obs}}}$$

At steady state (`SS=TRUE`) the dose given in one dosing interval is cleared over that interval, so

$$CL_{\text{obs}} = \frac{\text{Dose}}{AUC_{\text{tau}}}$$

Up to `NonCompart` 0.8.3, AUC_{last} was used here at steady state; it equals AUC_{tau} only when the last sample falls exactly at τ.

[45] CL_pred (CLP) or CL_F_pred (CLFP)

Clearance predicted. CLP is for intravascular administration and CLFP for extravascular administration. Not calculated (`NA`) at steady state.

$$CL_{\text{pred}} = \frac{\text{Dose}}{AUC_{\text{inf,pred}}}$$

[46] Vss_obs (VSSO)

Volume of distribution at steady state, observed. This is for intravascular administration only.

$$V_{ss,obs} = MRT_{IV,inf,obs} \times CL_{obs}$$

With `SS=TRUE` the same product is taken with the steady-state $MRT_{IV,inf,obs}$ and $CL_{obs} = Dose/AUC_{tau}$. Up to `NonCompart` 0.8.4, $MRT_{IV,last}$ was used here at steady state.

[47] Vss_pred (VSSP)

Volume of distribution at steady state, predicted. This is for intravascular administration only.

$$V_{ss,pred} = MRT_{IV,inf,pred} \times CL_{pred}$$

With `SS=TRUE` there is one clearance, $Dose/AUC_{tau}$, so

$$V_{ss,pred} = MRT_{IV,inf,pred} \times CL_{obs}$$

Up to `NonCompart` 0.8.4 this was not calculated (`NA`) at steady state.

[48] AmtRecLast (RCAMLST)

Amount recovered in urine.

$$Ae_{last} = \sum_{i=1} Vol_i \, Conc_i$$

[49] CLrenal (RENALCL)

Renal clearance.

$$CL_R = \frac{Ae_{last}}{AUC_{last}}$$

[50] fe (FE)

Fraction excreted unchanged.

$$\mathrm{fe} = \frac{\mathrm{CL_R}}{\mathrm{CL_{obs}}} = \frac{\mathrm{Ae_{last}}/\mathrm{AUC_{last}}}{\mathrm{Dose}/\mathrm{AUC_{inf,obs}}} = \frac{\mathrm{Ae_{last}}}{\mathrm{Dose}} \times \frac{\mathrm{AUC_{inf,obs}}}{\mathrm{AUC_{last}}}$$

[51] AI (ARCMAX, ARAUC, ARCMIN)

Accumulation index, accumulation ratio.

$$\mathrm{R_{ac}} = \frac{C_{\mathrm{max,ss}}}{C_{\mathrm{max,1}}} = \frac{\mathrm{AUC_{tau,ss}}}{\mathrm{AUC_{tau,1}}} = \frac{\mathrm{AUC_{inf,ss}}}{\mathrm{AUC_{inf,1}}} = \frac{C_{\mathrm{min,ss}}}{C_{\mathrm{min,1}}}$$

2

Example using NonCompart::sNCA

```
require(NonCompart)
x = Theoph[Theoph$Subject==1, "Time"]
y = Theoph[Theoph$Subject==1, "conc"]
r1 = sNCA(x, y, dose=320, concUnit="mg/L") ; r1
#           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"
# attr(,"UsedPoints")
# [1]  9 10 11
```

```
r2 = data.frame(VALUE=r1, UNIT=attr(r1, "units")) ; r2
#                 VALUE      UNIT
# b0          2.3687851
# CMAX       10.5000000      mg/L
# CMAXD       0.0328125   mg/L/mg
# TMAX        1.1200000         h
# TLAG        0.0000000         h
# CLST        3.2800000      mg/L
# CLSTP       3.2801465      mg/L
# TLST       24.3700000         h
# LAMZHL     14.3043776         h
# LAMZ        0.0484570        /h
# LAMZLL      9.0500000         h
# LAMZUL     24.3700000         h
# LAMZNPT     3.0000000
# CORRXY     -0.9999999
# R2          0.9999997
# R2ADJ       0.9999995
# AUCLST    148.9230500    h*mg/L
# AUCALL    148.9230500    h*mg/L
# AUCIFO    216.6119330    h*mg/L
# AUCIFOD     0.6769123 h*mg/L/mg
# AUCIFP    216.6149558    h*mg/L
# AUCIFPD     0.6769217 h*mg/L/mg
# AUCPEO     31.2489169         %
# AUCPEP     31.2498763         %
# AUMCLST  1459.0711035   h2*mg/L
# AUMCIFO  4505.5348194   h2*mg/L
# AUMCIFP  4505.6708646   h2*mg/L
# AUMCPEO    67.6160287         %
# AUMCPEP    67.6170065         %
# VZFO       30.4867482         L
# VZFP       30.4863228         L
# CLFO        1.4772963       L/h
# CLFP        1.4772757       L/h
# MRTEVLST    9.7974834         h
# MRTEVIFO   20.8000305         h
# MRTEVIFP   20.8003683         h
```

[1] Steady state

One dosing interval of a q12h regimen at steady state, sampled from the pre-dose trough to the next dose. `tau` is the dosing interval; `AUCTAU`, `CAVG`, `CLFO` and `VZFO` are derived over it, the MRT to infinity follows the steady-state formula, and the `Pred` twins of Vz and CL are `NA`.

```
xs = c(0, 1, 2, 4, 8, 12)
ys = c(2, 6, 10, 8, 4, 2)
r3 = sNCA(xs, ys, dose=100, concUnit="mg/L", SS=TRUE, tau=12)
data.frame(VALUE=r3, UNIT=attr(r3, "units"))
#                VALUE      UNIT
# b0         2.7725887
# CMAX      10.0000000      mg/L
# CMAXD      0.1000000   mg/L/mg
# TMAX       2.0000000         h
# TLAG       0.0000000         h
# CLST       2.0000000      mg/L
# CLSTP      2.0000000      mg/L
# TLST      12.0000000         h
# LAMZHL     4.0000000         h
# LAMZ       0.1732868        /h
# LAMZLL     4.0000000         h
# LAMZUL    12.0000000         h
# LAMZNPT    3.0000000
# CORRXY    -1.0000000
# R2         1.0000000
# R2ADJ      1.0000000
# AUCLST    66.0000000    h*mg/L
# AUCALL    66.0000000    h*mg/L
# AUCIFO    77.5415603    h*mg/L
# AUCIFOD    0.7754156 h*mg/L/mg
# AUCIFP    77.5415603    h*mg/L
# AUCIFPD    0.7754156 h*mg/L/mg
# AUCPEO    14.8843540         %
# AUCPEP    14.8843540         %
# AUMCLST  308.0000000   h2*mg/L
# AUMCIFO  513.1025313   h2*mg/L
# AUMCIFP  513.1025313   h2*mg/L
# AUMCPEO   39.9730110         %
# AUMCPEP   39.9730110         %
# AUCTAU    66.0000000    h*mg/L
# CAVG       5.5000000      mg/L
```

```
# VZFO       8.7436063         L
# VZFP              NA         L
# CLFO       1.5151515       L/h
# CLFP              NA       L/h
# MRTEVLST   4.6666667         h
# MRTEVIFO   6.7651322         h
# MRTEVIFP   6.7651322         h
```

Session Information

Compile Time

```
# [1] "2026-11-15 09:55:42 KST"
```

Session Information

```
# R version 4.6.2 (2026-10-29 ucrt)
# Platform: x86_64-w64-mingw32/x64
# Running under: Windows 11 x64 (build 26100)
#
# Matrix products: default
#   LAPACK version 3.12.1
#
# locale:
# [1] LC_COLLATE=Korean_Korea.utf8  LC_CTYPE=Korean_Korea.utf8
# [3] LC_MONETARY=Korean_Korea.utf8 LC_NUMERIC=C
# [5] LC_TIME=Korean_Korea.utf8
#
# time zone: Asia/Seoul
# tzcode source: internal
#
# attached base packages:
# [1] stats     graphics  grDevices utils     datasets  methods   base
#
# other attached packages:
# [1] NonCompart_0.8.5 knitr_1.52       rmarkdown_2.32
```