

Supplementary

```

library(pmxTools)
library(PKconverter)

calc_derived_1cpt(CL=16, V=25)

## $k10
## [1] 0.64
##
## $Vss
## [1] 25
##
## $thalf
## [1] 1.083
##
## $alpha
## [1] 0.64
##
## $trueA
## [1] 0.04
##
## $fracA
## [1] 1

OneComp_Volume_Clearance(V1=25, C11=16, V1.sd=1, C11.sd=0.1)

##      Parameter Estimate Std.err
## Vdss      Vdss 25.000000 1.00000000
## V1         V1 25.000000 1.00000000
## C11        C11 16.000000 0.10000000
## k10        k10 0.640000 0.02591062
## alpha      alpha 0.640000 0.02591062
## t_alpha    t_alpha 1.083042 0.04384734
## True_A     True_A 0.040000 0.00160000
## Frac_A     Frac_A 1.000000 0.00000000

calc_derived_3cpt(CL=29.4, V1=23.4, V2=114, V3=4614, Q2=270, Q3=73)

## $k10
## [1] 1.2564
##
## $k12
## [1] 11.538
##
## $k21
## [1] 2.3684
##
## $k13
## [1] 3.1197
##
## $k31
## [1] 0.015821
##
## $Vss
## [1] 4751.4
##
## $thalf_alpha
## [1] 0.039161
##
## $thalf_beta
## [1] 1.1659
##
## $thalf_gamma
## [1] 154.92
##
## $alpha
## [1] 17.7
##
## $beta

```

```

## [1] 0.59449
##
## $gamma
## [1] 0.0044742
##
## $trueA
## [1] 0.038279
##
## $trueB
## [1] 0.0043467
##
## $trueC
## [1] 0.0001098
##
## $fracA
## [1] 0.89572
##
## $fracB
## [1] 0.10171
##
## $fracC
## [1] 0.0025692

ThreeComp_Volume_Clearance(V1=23.4, V2=114, V3=4614,
  C11=29.4, C12=270, C13=73, V1.sd=1, V2.sd=12,
  V3.sd=23, C11.sd=1.5, C12.sd=13, C13.sd=21)

##      Parameter Estimate Std.err
## Vdss      Vdss 4.751400e+03 2.596151e+01
## V1         V1 2.340000e+01 1.000000e+00
## V2         V2 1.140000e+02 1.200000e+01
## V3         V3 4.614000e+03 2.300000e+01
## C11        C11 2.940000e+01 1.500000e+00
## C12        C12 2.700000e+02 1.300000e+01
## C13        C13 7.300000e+01 2.100000e+01
## k10        k10 1.256410e+00 8.361848e-02
## k12        k12 1.153846e+01 7.428232e-01
## k21        k21 2.368421e+00 2.741500e-01
## k13        k13 3.119658e+00 9.072844e-01
## k31        k31 1.582141e-02 4.552049e-03
## alpha      alpha 1.769980e+01 1.260304e+00
## beta       beta 5.944938e-01 1.114723e-01
## gamma      gamma 4.474246e-03 3.951601e-04
## t_alpha    t_alpha 3.916129e-02 2.788456e-03
## t_beta     t_beta 1.165945e+00 2.186240e-01
## t_gamma    t_gamma 1.549193e+02 1.368229e+01
## True_A     True_A 3.827859e-02 1.920848e-03
## True_B     True_B 4.346657e-03 6.320372e-04
## True_C     True_C 1.097954e-04 1.798302e-05
## Frac_A     Frac_A 8.957190e-01 1.512419e-02
## Frac_B     Frac_B 1.017118e-01 1.536039e-02
## Frac_C     Frac_C 2.569213e-03 4.348749e-04

library(nlme)
library(nlmeODE)
keep.p<-NULL
TheophODE<-Theoph
TheophODE$Dose<-320
TheophODE$Dose[TheophODE$Time!=0] <- 0
TheophODE$Cmt <- rep(1,dim(TheophODE)[1])

OneComp2 <- list(
  DiffEq = list(dy1dt = ~-ka*y1,
               dy2dt = ~ka*y1-CL/V*y2),
  ObsEq = list(SC ~0, Cp ~ y2/V),
  Parms = c("ka", "V", "CL"),
  States = c("y1", "y2"),
  Init = list(0,0))

TheophModel2 <- nlmeODE(OneComp2, TheophODE,
  LogParms=TRUE, JAC=TRUE,
  SEQ=FALSE, rtol=0.000001,
  atol=0.000001)

```

```

M2.1.ML <- nlme(
  conc ~TheophODE12(ka,V,CL,Time,Subject),
  data = TheophODE, fixed = list(ka+V+CL~1),
  random = pdDiag(ka+V+CL~1),
  start = c(ka = 0.5,V = 3,CL = 0.5),
  control = list(returnObject = T, msVerbose = F),
                verbose = F,method="ML")

M2.1.ML.fixed<-cbind(exp(fixef(M2.1.ML)),
  sqrt(diag(M2.1.ML$varFix))*exp(fixef(M2.1.ML)))
colnames(M2.1.ML.fixed)<-c("Value","Std.Error")

M2.1.ML.fixed
##          Value Std.Error
## ka  1.570314 0.2956111
## V  32.067292 1.5856184
## CL  2.804855 0.2384023

OneComp_Volume_Clearance(V1=M2.1.ML.fixed[2,1],
  C11=M2.1.ML.fixed[3,1],
  V1.sd=M2.1.ML.fixed[2,2],
  C11.sd=M2.1.ML.fixed[3,2])

##          Parameter Estimate Std.err
## Vdss      Vdss 32.06729246 1.585618408
## V1         V1 32.06729246 1.585618408
## C11        C11 2.80485468 0.238402332
## k10        k10 0.08746777 0.008600952
## alpha      alpha 0.08746777 0.008600952
## t_alpha    t_alpha 7.92460069 0.779248214
## True_A     True_A 0.03118442 0.001224545
## Frac_A     Frac_A 1.00000000 0.000000000

OneComp_Volume_Clearance(V1=32.067292 ,
  C11=2.804855 ,
  V1.sd=1.5856184,
  C11.sd=0.2384023)

##          Parameter Estimate Std.err
## Vdss      Vdss 32.06729200 1.585618400
## V1         V1 32.06729200 1.585618400
## C11        C11 2.80485500 0.238402300
## k10        k10 0.08746778 0.008600951
## alpha      alpha 0.08746778 0.008600951
## t_alpha    t_alpha 7.92459968 0.779247970
## True_A     True_A 0.03118442 0.001224545
## Frac_A     Frac_A 1.00000000 0.000000000

### MODEL WITH v AND K10

OneComp3 <- list(
  DiffEq = list(dy1dt = ~-ka*y1,
                dy2dt = ~ka*y1-k10*y2),
  ObsEq = list(SC ~0, Cp ~ y2/V),
  Parms = c("ka","k10","V"),
  States = c("y1","y2"),
  Init = list(0,0))

TheophODE13 <- nlmeODE(OneComp3,TheophODE,
  LogParms=TRUE,JAC=TRUE,
  SEQ=FALSE,rtol=0.0000001,
  atol=0.0000001)

M3.1.ML <- nlme(
  conc ~TheophODE13(ka,k10,V,Time,Subject),
  data = TheophODE, fixed = list(ka+k10+V~1),
  random = pdDiag(ka+k10+V~1),
  start = c(ka = 0.5,k10 = -2.5,V = 3),
  control = list(returnObject = T, msVerbose = F),
                verbose = F,method="ML")

```

```

M3.1.ML.fixed<-cbind(exp(fixef(M3.1.ML)),
  sqrt(diag(M3.1.ML$varFix))*exp(fixef(M3.1.ML)))
colnames(M3.1.ML.fixed)<-c("Value","Std.Error")

M3.1.ML.fixed
##          Value Std.Error
## ka  1.58789927 0.298354631
## k10  0.08668555 0.005581171
## V  32.26109850 1.663936996

OneComp_Volume_Exponent(V1=M3.1.ML.fixed[3,1],
  alpha=M3.1.ML.fixed[2,1],
  V1.sd=M2.1.ML.fixed[3,2],
  alpha.sd=M3.1.ML.fixed[2,2])

##          Parameter Estimate Std.err
## Vdss      Vdss 32.26109850 0.2384023325
## V1         V1 32.26109850 0.2384023325
## C11        C11 2.79657117 0.1812368106
## k10        k10 0.08668555 0.0055811709
## alpha      alpha 0.08668555 0.0055811709
## t_alpha    t_alpha 7.99610956 0.5148222782
## True_A     True_A 0.03099708 0.0002290616
## Frac_A     Frac_A 1.00000000 0.0000000000

OneComp_Volume_Exponent(V1=32.26109850,
  alpha=0.08668555,
  V1.sd=1.663936996,
  alpha.sd=0.005581171)

##          Parameter Estimate Std.err
## Vdss      Vdss 32.26109850 1.663936996
## V1         V1 32.26109850 1.663936996
## C11        C11 2.79657107 0.230704728
## k10        k10 0.08668555 0.005581171
## alpha      alpha 0.08668555 0.005581171
## t_alpha    t_alpha 7.99610985 0.514822325
## True_A     True_A 0.03099708 0.001598743
## Frac_A     Frac_A 1.00000000 0.000000000

```