Tests with NONMEM

Metrum Research Group, LLC

Contents

```
Sys.setenv(RSTUDIO_PANDOC = "/usr/lib/rstudio-server/bin/pandoc")
```

```
.libPaths("/data/Rlibs")
library(mrgsolve)
library(dplyr)
library(readr)
library(ggplot2)
```

```
carry <- c("cmt", "amt","ii", "addl", "rate", "evid", "ss")
```

1 Functions

1.1 Save `mrgsim` output as a `nonmem` input data set

```
to_data_set <- function(x,id = NULL) {
  x <- as.data.frame(x)
  x <- mutate(x, C = '.', DV = '.', cmt = if_else(cmt==0, 2, cmt))
  x <- dplyr::select(x, "C", everything())
  if(is.numeric(id)) x <- mutate(x,ID = id)
  x
}
```

1.2 Save the `nonmem` input data set

```
sv <- function(x,file) {
  write.csv(file = file, row.names = FALSE, quote = FALSE, x)
}
```

1.3 Run `nonmem`

```
run <- function(number) {
  metrumrg::NONR(number, project = "model",
                 command = "/opt/NONMEM/nm73/nmqual/autolog.pl",
                 checkrunno=FALSE)
  return(tabread(number))
}
```

1.4 Read in `nonmem` simulation results

```
tabread <- function(number) {
  tab <- file.path("model", number, "TAB")
  if(file.exists(tab)) return(read_table(tab, skip=1))
  stop("the run failed")
}
```

1.5 Simulate a scenario with `mrsim`

```
sim <- function(x, e,...) {
  mrgsim(x, events = e, carry.out = carry, digits = 5, ...)
}
```

2 The `mrgsim` model

```
code <- '
$SET req = ""
$PARAM CL = 1.1, V = 20, KA = 1.5
LAGT = 0, MODE = 0, DUR2 = 2, RAT2 = 10, BIOAV = 1

$PKMODEL cmt = "GUT CENT", depot = TRUE

$MAIN

F_CENT = BIOAV;
ALAG_CENT = LAGT;

if(MODE==1) R_CENT = RAT2;
if(MODE==2) D_CENT = DUR2;


$TABLE
capture DV = (CENT/(V/1000));
capture CP = DV;

$CAPTURE LAGT MODE DUR2 RAT2 BIOAV
'

mod <- mcode_cache("tests1", code)
```

```
. Compiling tests1 ... done.
```

```
mod <- update(mod, end=130, delta = 1)
```

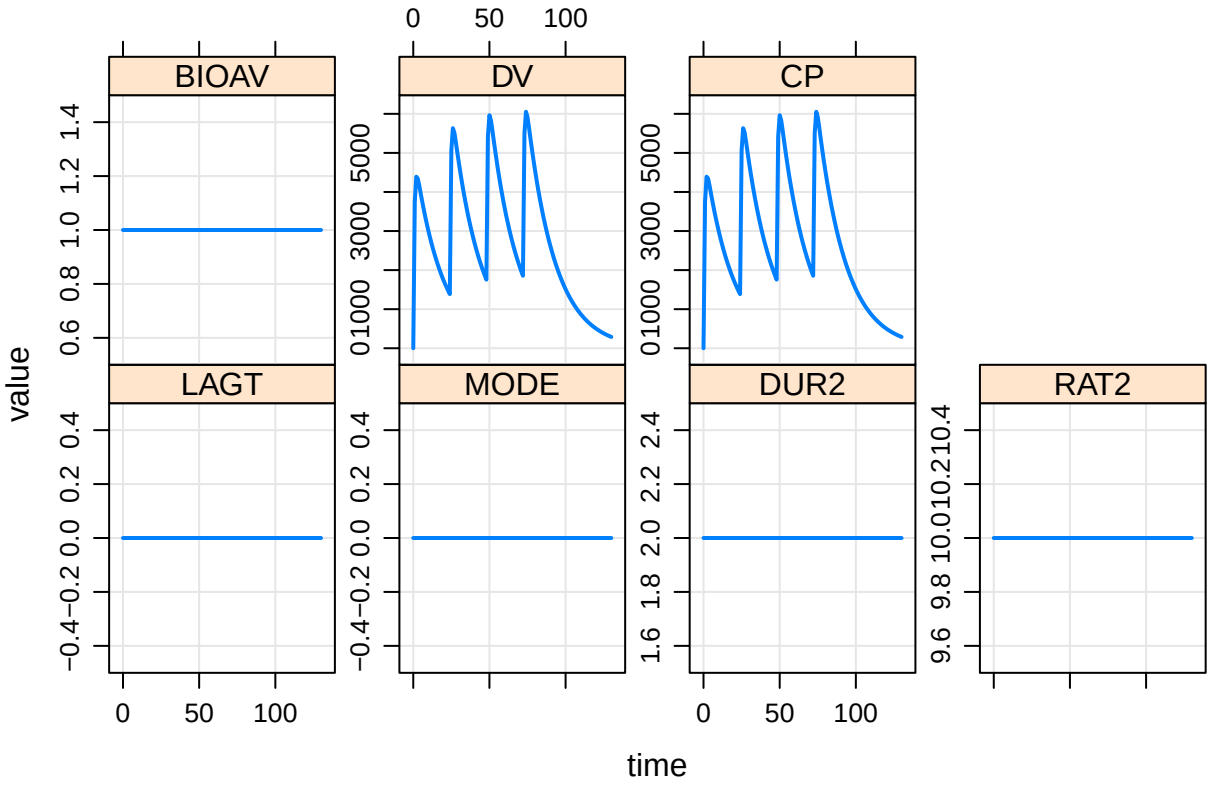
3 Scenarios

3.0.1 Bolus doses, with additional

```
ev <- ev(amt = 100, ii = 24, addl = 3)
ev
```

```
. Events:
.   time cmt amt ii addl evid
. 1    0   1 100 24    3    1
```

```
out1 <- sim(mod,ev)
plot(out1)
```



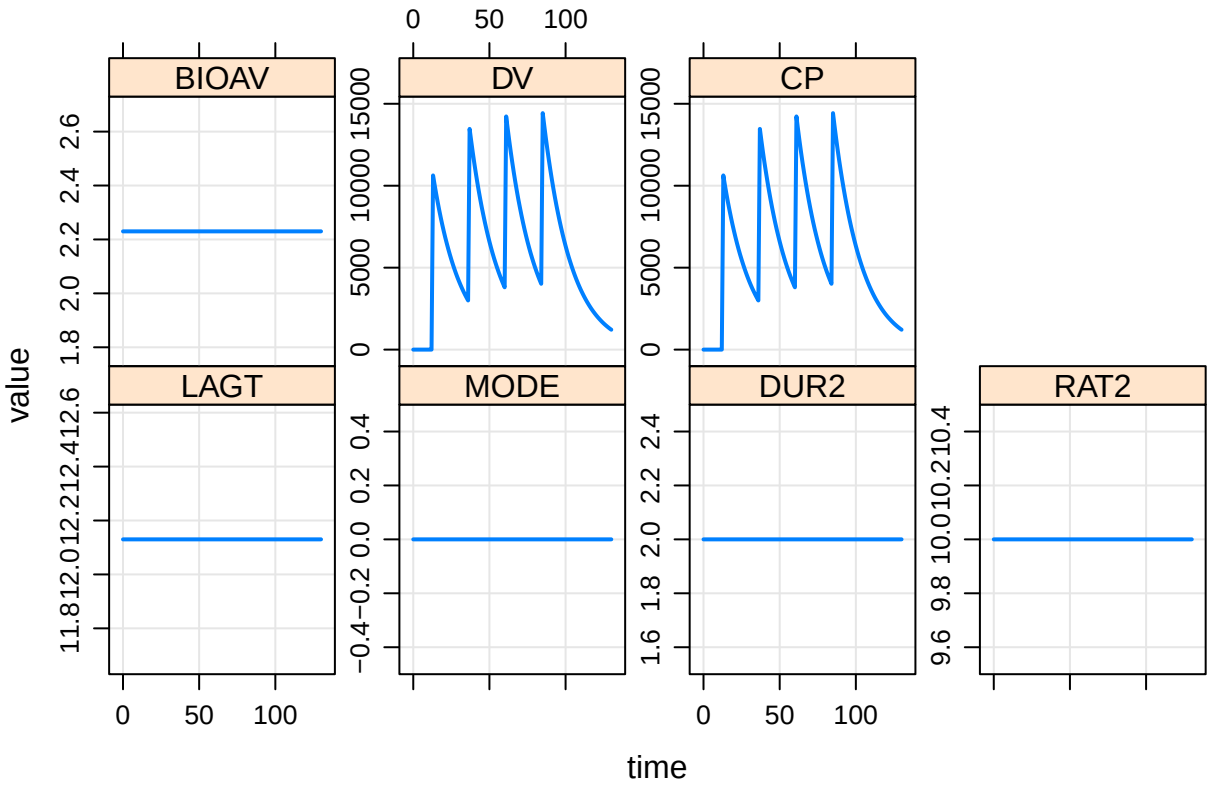

```
data1 <- to_data_set(out1, 1)
```

3.0.2 Bolus doses, lag time and bioav factor

```
ev <- ev(amt = 100, ii = 24, addl = 3, LAGT = 12.13, BIOAV = 2.23, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl  LAGT BIOAV evid
. 1    0   2 100 24    3 12.13  2.23    1
```

```
out1.1 <- sim(mod,ev)
plot(out1.1)
```



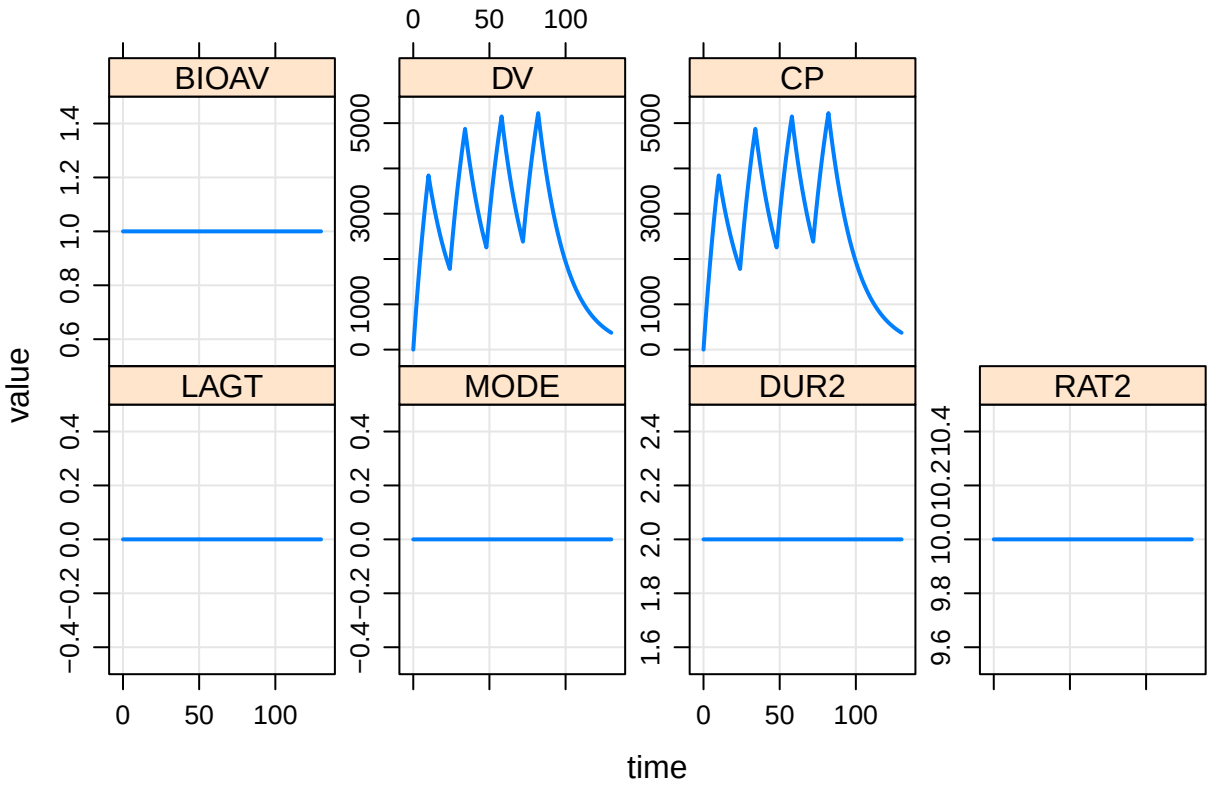

```
data1.1 <- to_data_set(out1.1, 1.1)
```

3.0.3 Infusion doses, with additional

```
ev <- ev(amt = 100, ii = 24, addl = 3, rate = 100/10, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate evid
. 1    0   2 100 24    3   10    1
```

```
out2 <- sim(mod,ev)
plot(out2)
```



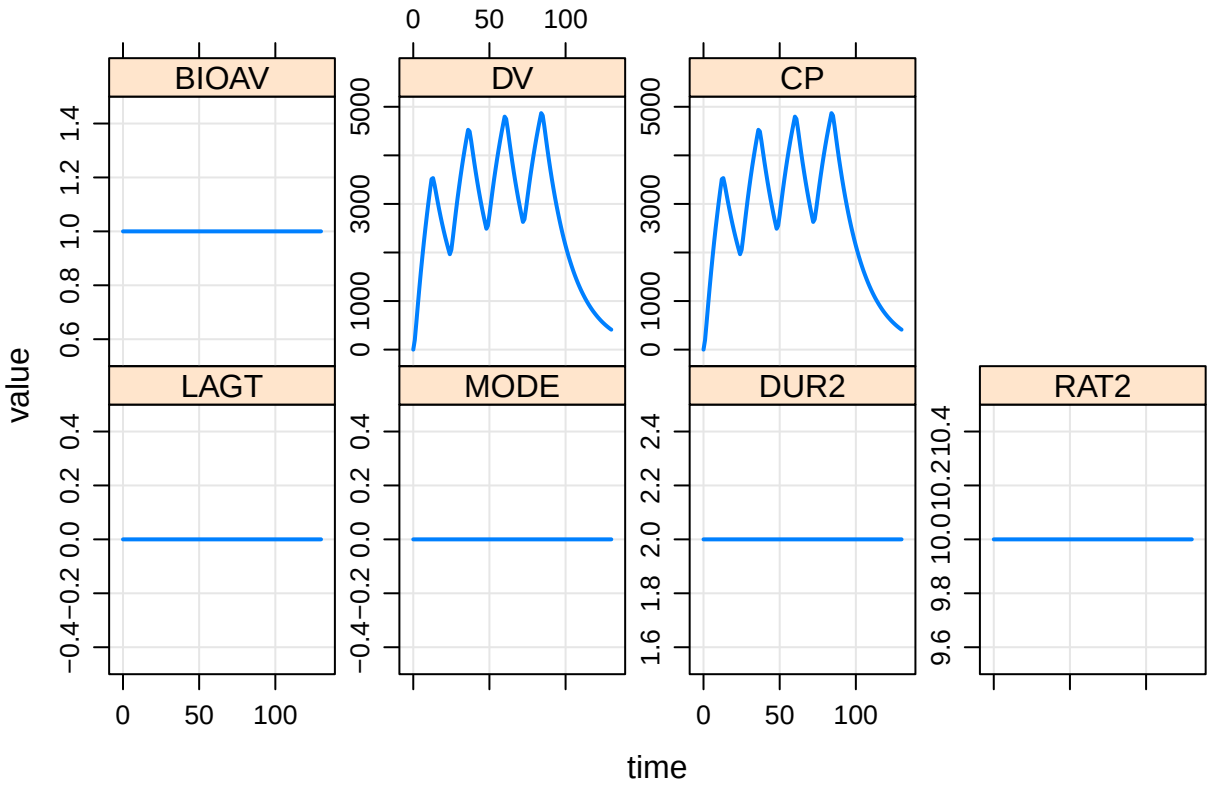

```
data2 <- to_data_set(out2, 2)
```

3.0.4 Infusion doses to depot, with additional

```
ev <- ev(amt = 100, ii = 24, addl = 3, rate = 100/12, cmt = 1)
ev
```

```
. Events:
.   time cmt amt ii addl     rate evid
. 1    0   1 100 24    3 8.333333    1
```

```
out2.1 <- sim(mod,ev)
plot(out2.1)
```



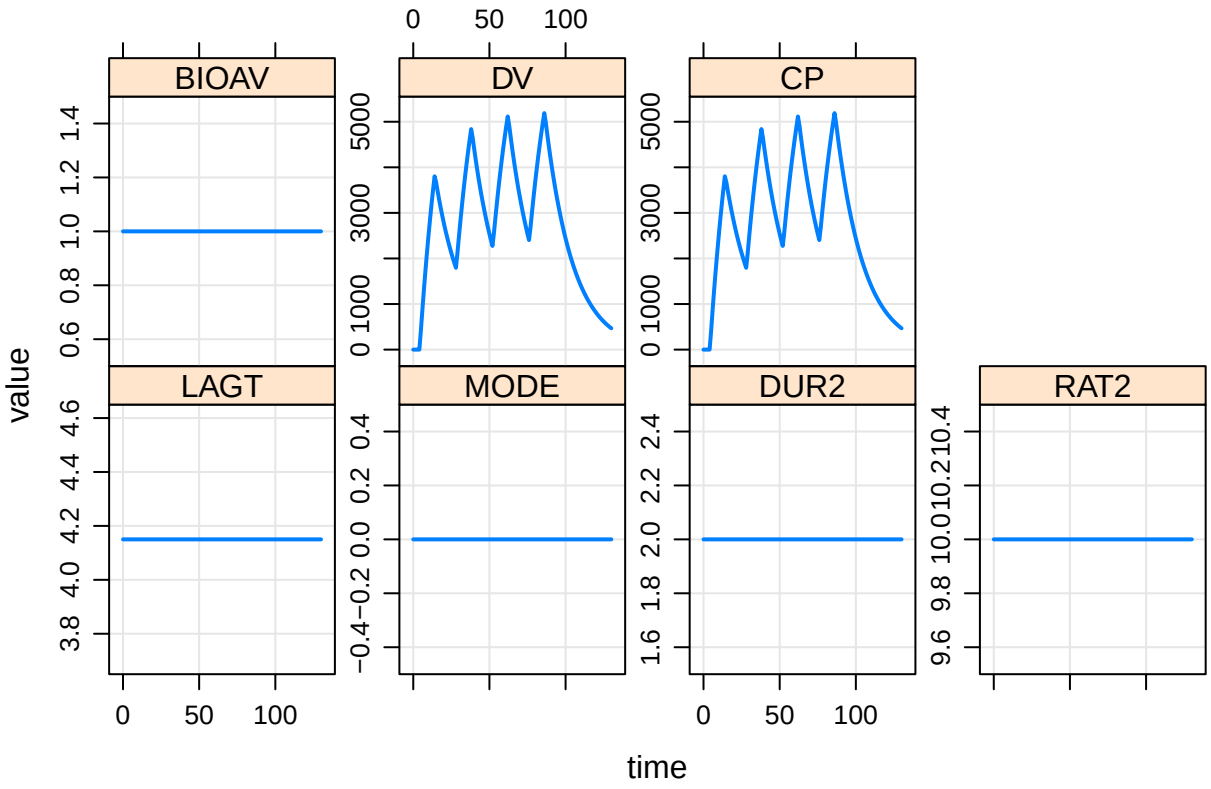

```
data2.1 <- to_data_set(out2.1, 2.1)
```

3.0.5 Infusion doses, with additional and lag time

```
ev <- ev(amt = 100, ii = 24, addl=3, rate = 100/10, LAGT = 4.15, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate LAGT evid
. 1    0   2 100 24    3   10 4.15    1
```

```
out3 <- sim(mod,ev)
plot(out3)
```



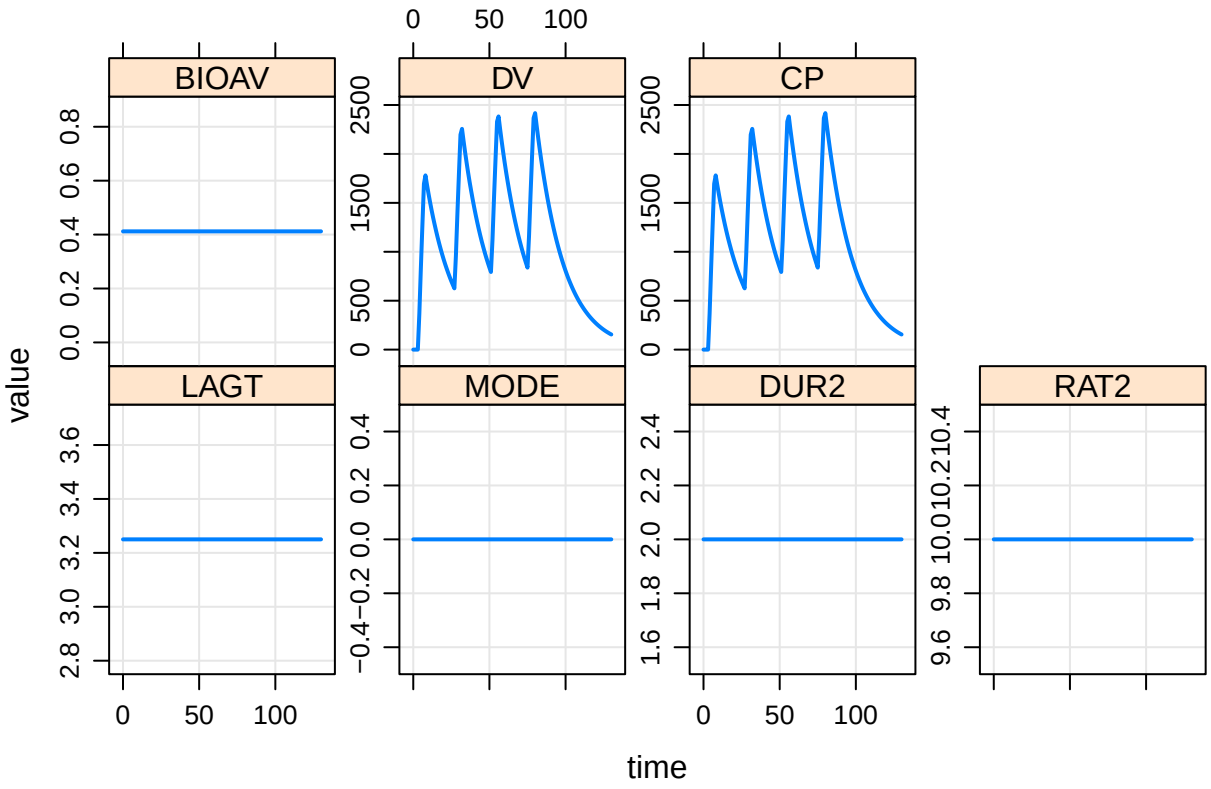

```
data3 <- to_data_set(out3, 3)
```

3.0.6 Infusion doses, with lag time and bioav factor

```
ev <- ev(amt = 100, ii = 24, addl = 3, rate = 100/10, LAGT = 3.25, BIOAV = 0.412, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate LAGT BIOAV evid
. 1    0   2 100 24    3   10 3.25 0.412    1
```

```
out4 <- sim(mod,ev)
plot(out4)
```



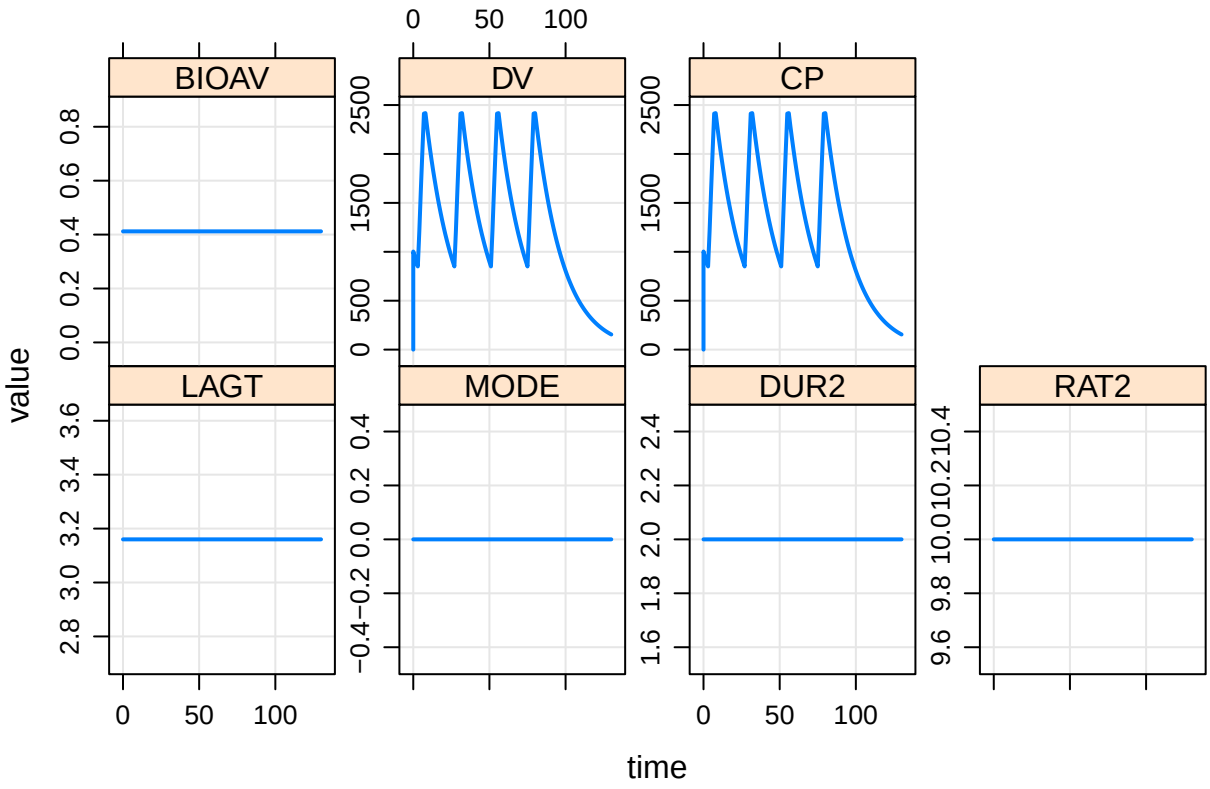

```
data4 <- to_data_set(out4, 4)
```

3.0.7 Infusion doses at steady-state, with lag time and bioav factor

```
ev <- ev(amt = 100, ii = 24, addl = 3, rate = 100/10, LAGT = 3.16, BIOAV = 0.412, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate LAGT BIOAV ss evid
. 1    0   2 100 24    3   10 3.16 0.412  1    1
```

```
out5 <- sim(mod,ev)
plot(out5)
```



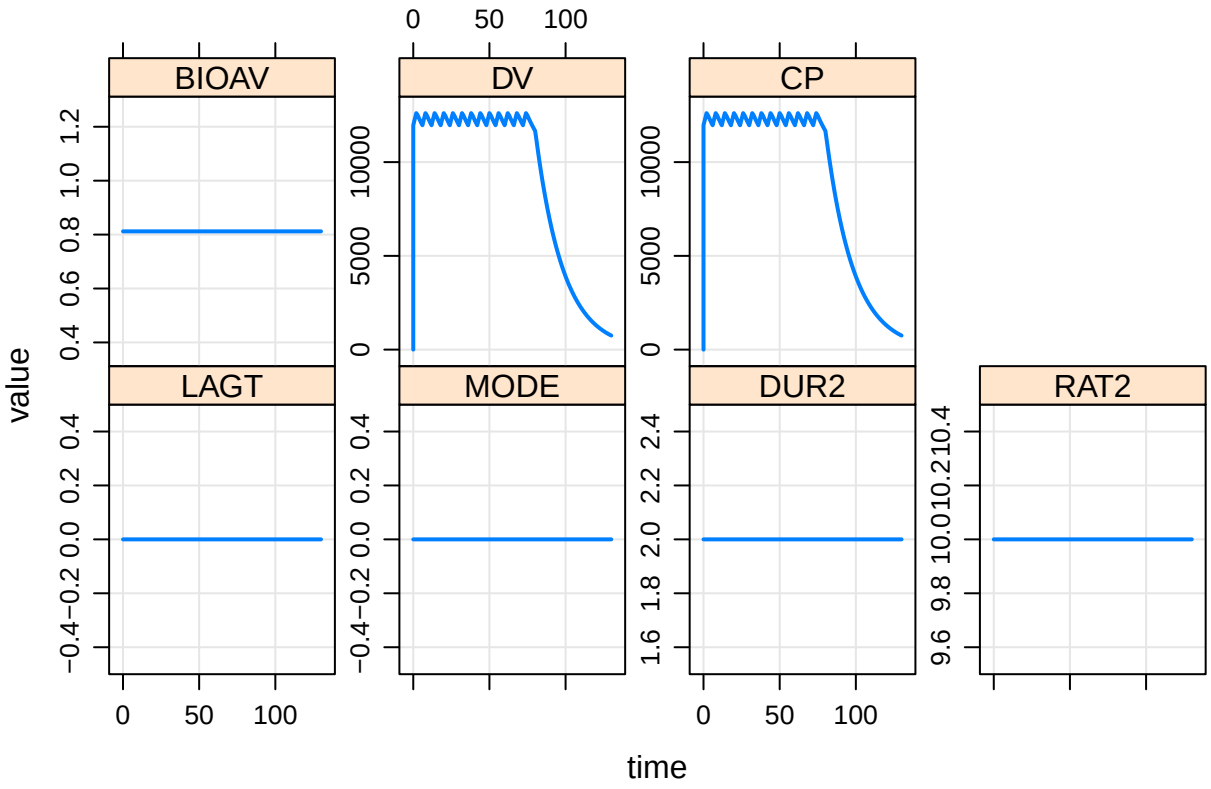

```
data5 <- to_data_set(out5, 5)
```

3.0.8 Infusion doses at steady state, II < DUR, with bioav factor

```
ev <- ev(amt = 100, ii = 6, addl = 12, rate = 100/10, BIOAV = 0.812, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate BIOAV ss evid
. 1    0   2 100  6   12   10 0.812  1    1
```

```
out6 <- sim(mod,ev)
plot(out6)
```



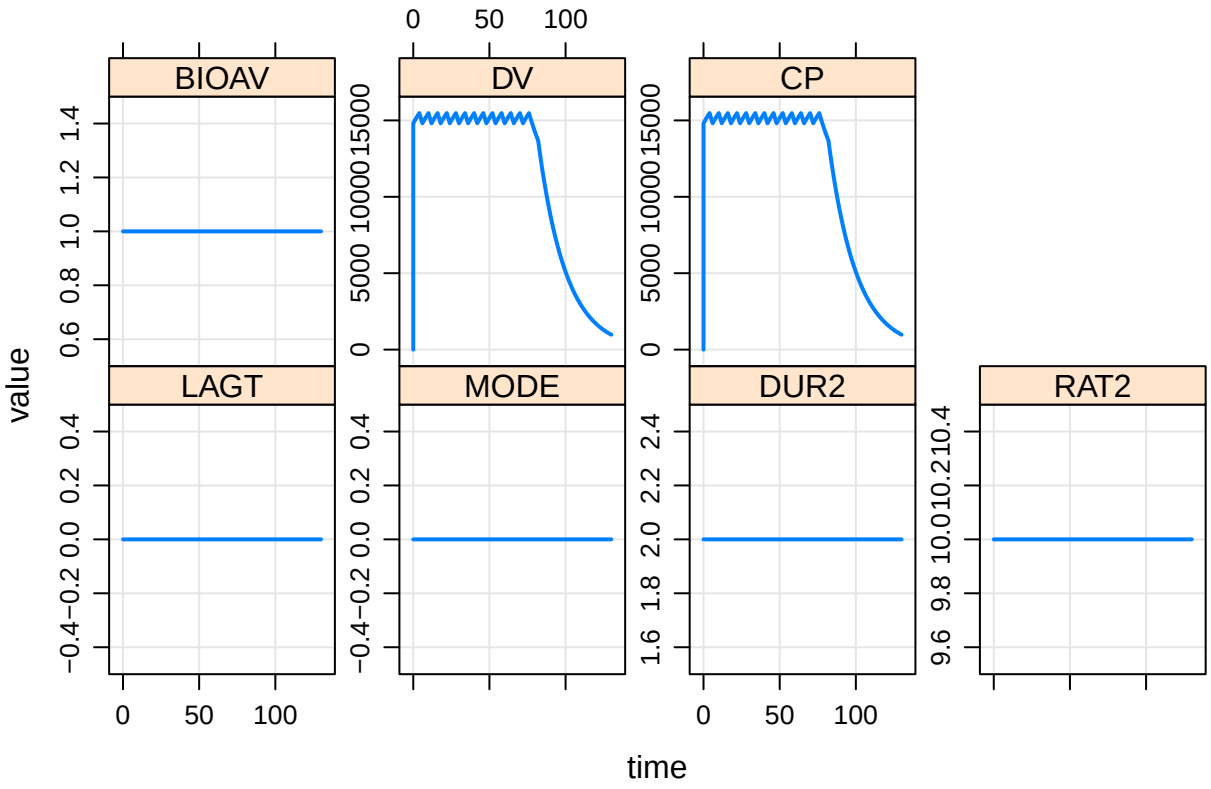

```
data6 <- to_data_set(out6, 6)
```

3.0.9 Infusion doses at steady state, II < DUR, no bioav factor

```
ev <- ev(amt = 100, ii = 6, addl = 12, rate = 100/10, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate ss evid
. 1    0   2 100  6   12   10  1    1
```

```
out6.1 <- sim(mod,ev)
plot(out6.1)
```



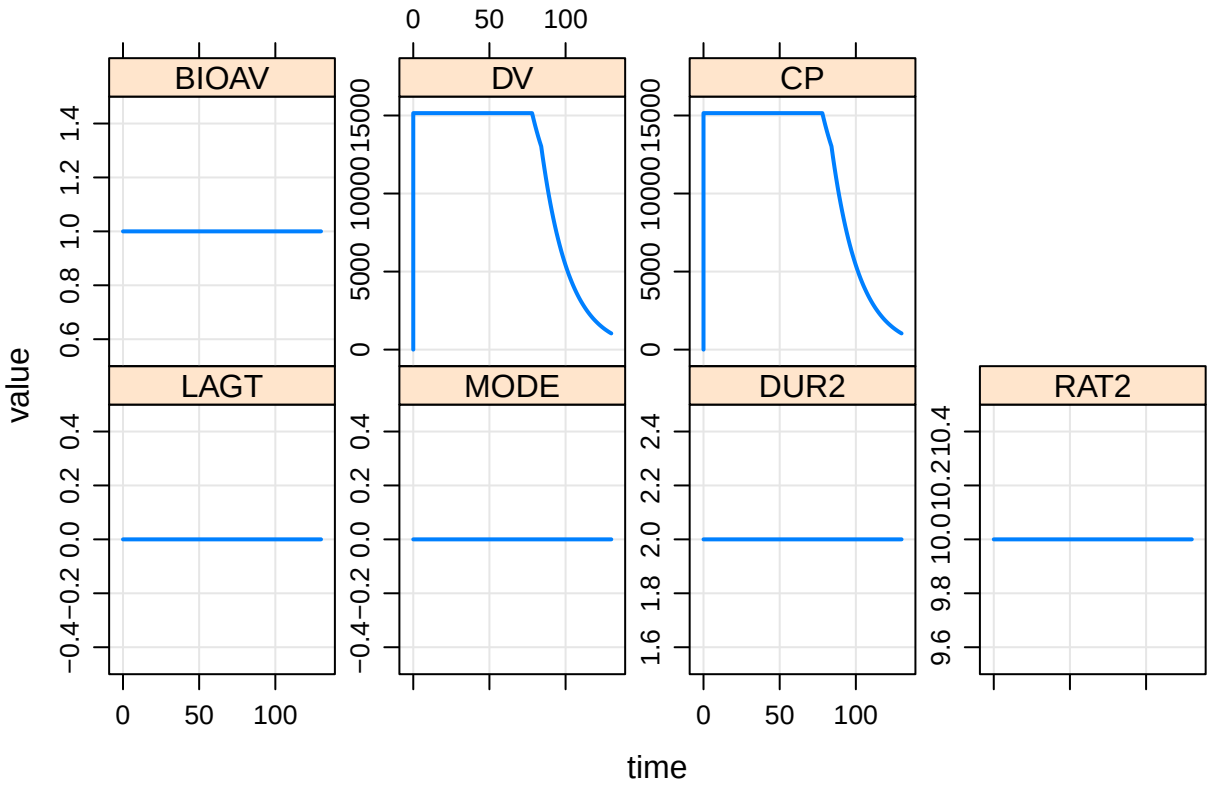

```
data6.1 <- to_data_set(out6.1, 6.1)
```

3.0.10 Infusion doses at steady state where II is a multiple of DUR

```
ev <- ev(amt = 100, ii = 6, addl = 12, rate = signif(100/12,5), ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl   rate ss evid
. 1    0   2 100  6   12 8.3333  1    1
```

```
out6.2 <- sim(mod,ev)
plot(out6.2)
```



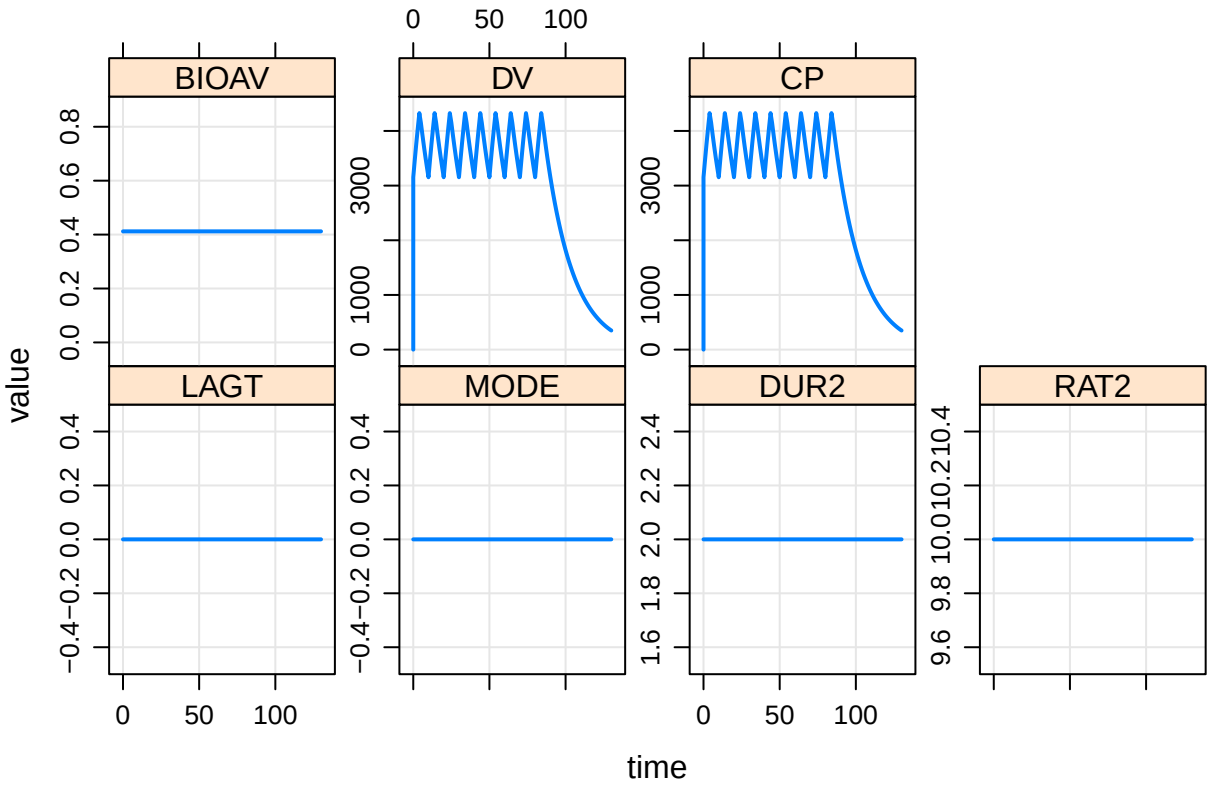

```
data6.2 <- to_data_set(out6.2, 6.2)
```

3.0.11 Infusion doses at steady state where II == DUR, with bioav factor

```
ev <- ev(amt = 100, ii = 10, addl = 8, rate = 100/10, LAGT = 0, BIOAV = 0.412, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate LAGT BIOAV ss evid
. 1    0   2 100 10    8   10    0 0.412  1    1
```

```
out7 <- sim(mod,ev)
plot(out7)
```



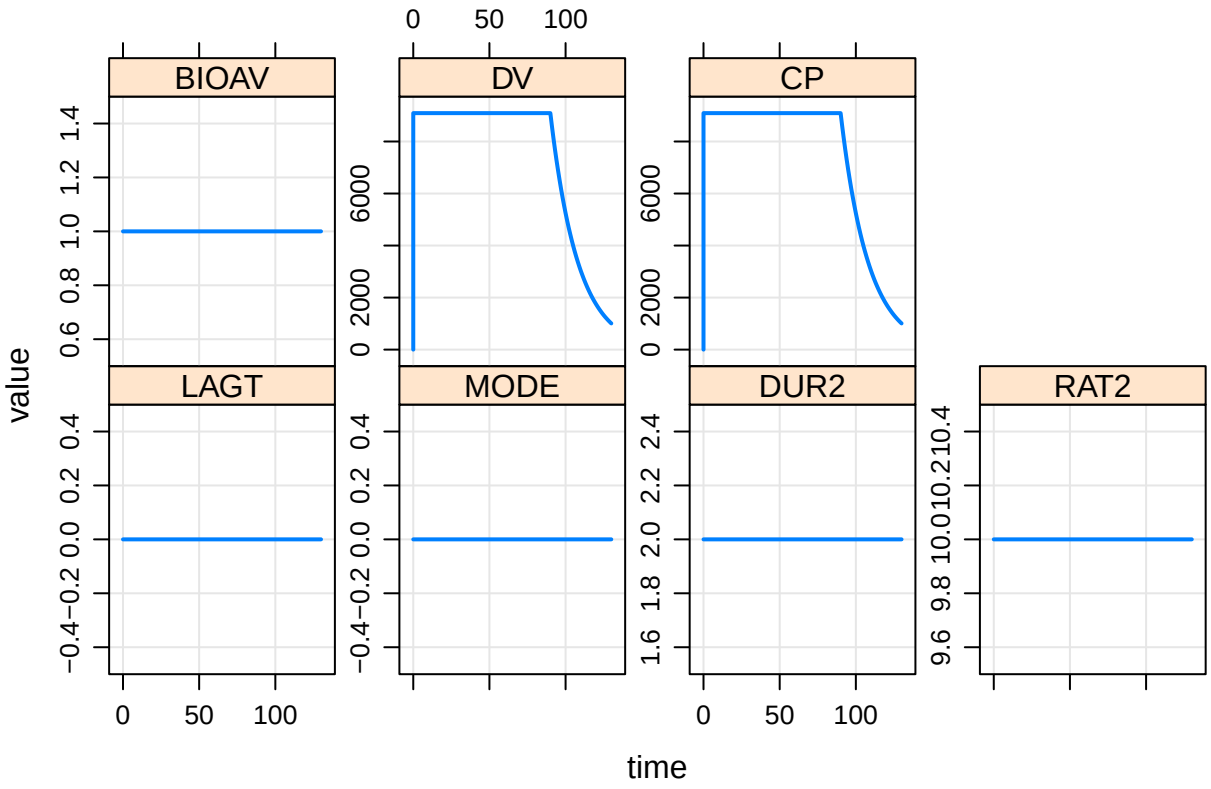

```
data7 <- to_data_set(out7, 7)
```

3.0.12 Infusion doses at steady state, where II == DUR

```
ev <- ev(amt = 100, ii = 10, addl = 8, rate = 100/10, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate ss evid
. 1    0   2 100 10    8   10  1    1
```

```
out7.1 <- sim(mod,ev)
plot(out7.1)
```



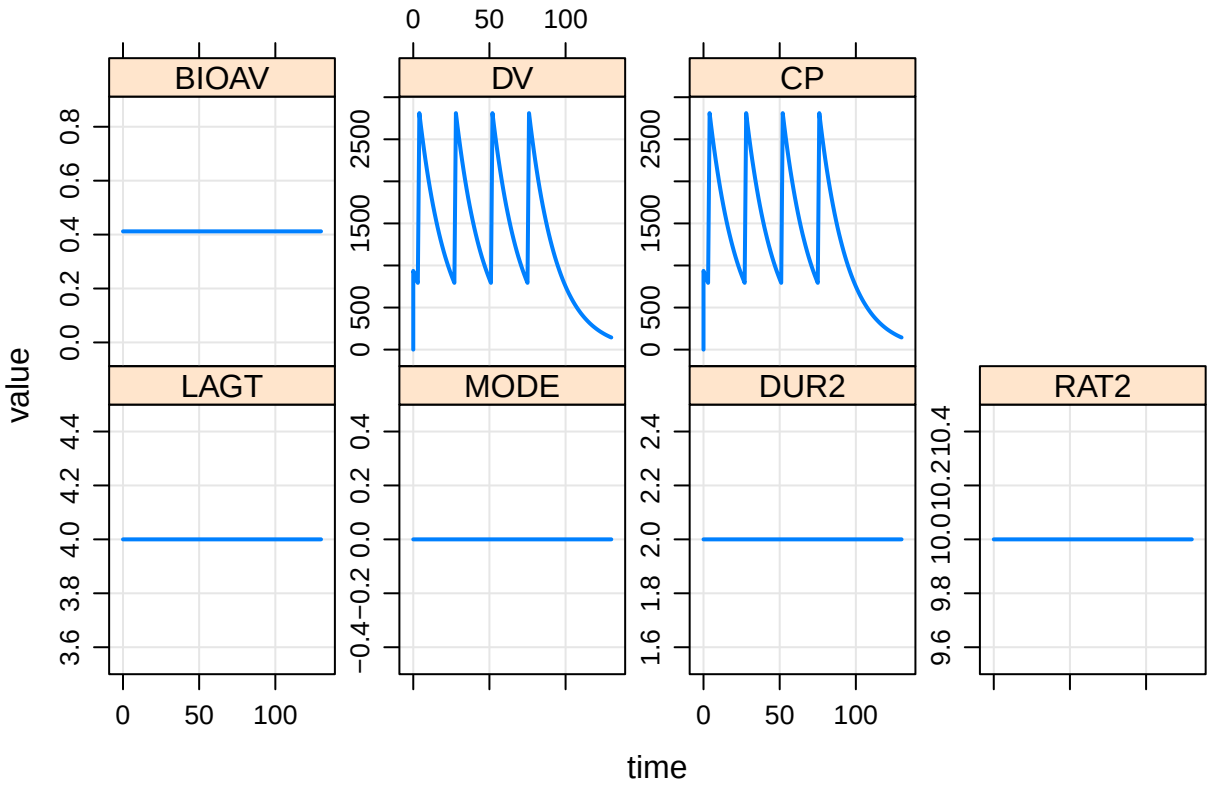

```
data7.1 <- to_data_set(out7.1, 7.1)
```

3.0.13 Bolus doses at steady state, with bioav factor and lag time

```
ev <- ev(amt = 100, ii = 24, addl=3,  LAGT = 4, BIOAV = 0.412, ss = 1, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl LAGT BIOAV ss evid
. 1    0   2 100 24    3    4 0.412  1    1
```

```
out8 <- sim(mod,ev)
plot(out8)
```



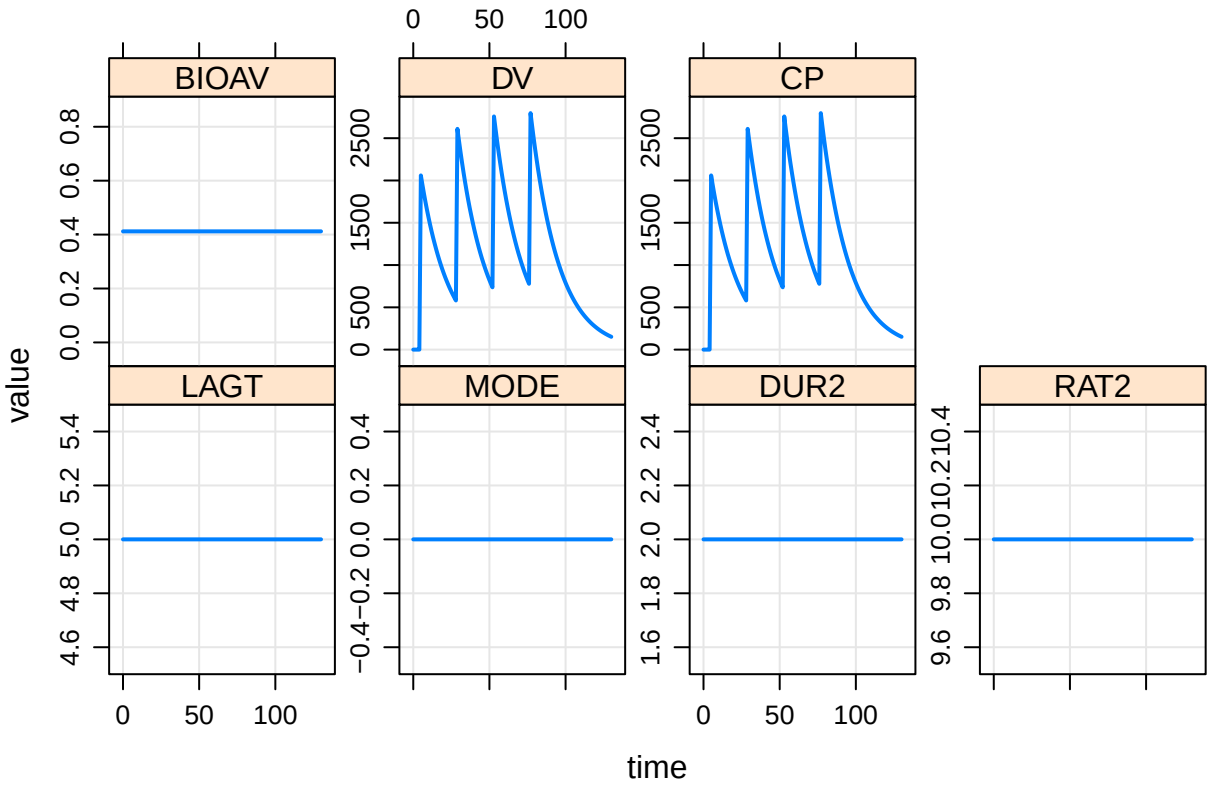

```
data8 <- to_data_set(out8, 8)
```

3.0.14 Bolus doses with lag time and bioavability factor

```
ev <- ev(amt = 100, ii = 24, addl=3,  LAGT = 5, BIOAV = 0.412, cmt = 2)
ev
```

```
. Events:
.   time cmt amt ii addl LAGT BIOAV evid
. 1    0   2 100 24    3    5 0.412    1
```

```
out9 <- sim(mod,ev)
plot(out9)
```



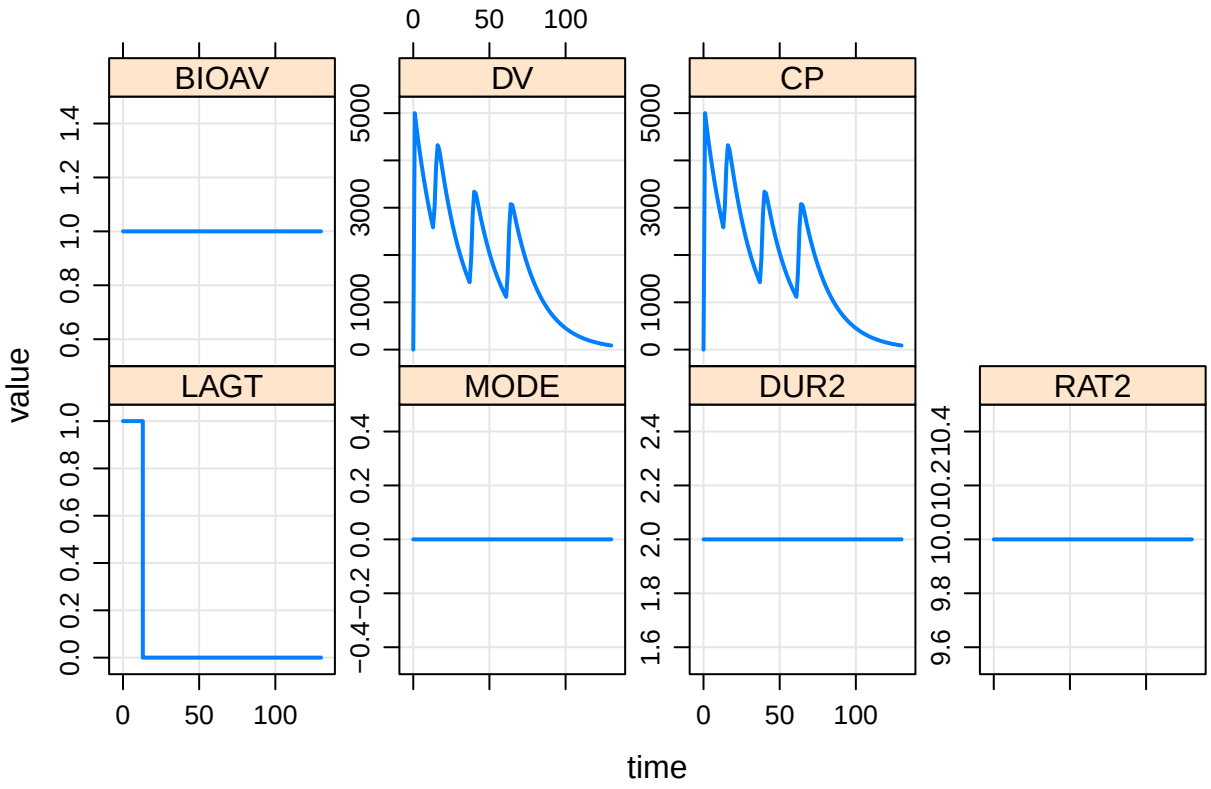

```
data9 <- to_data_set(out9, 9)
```

3.0.15 Bolus / infusion

```
ev <- ev(amt = 100, cmt = 2, LAGT = 1) + ev(time = 13, amt = 50, ii = 24, addl = 2, rate = 24)
ev
```

```
. Events:
.   time cmt amt LAGT evid ii addl rate
. 1    0   2 100    1    1  0    0    0
. 2   13   1  50    0    1 24    2   24
```

```
out10 <- sim(mod,ev)
plot(out10)
```



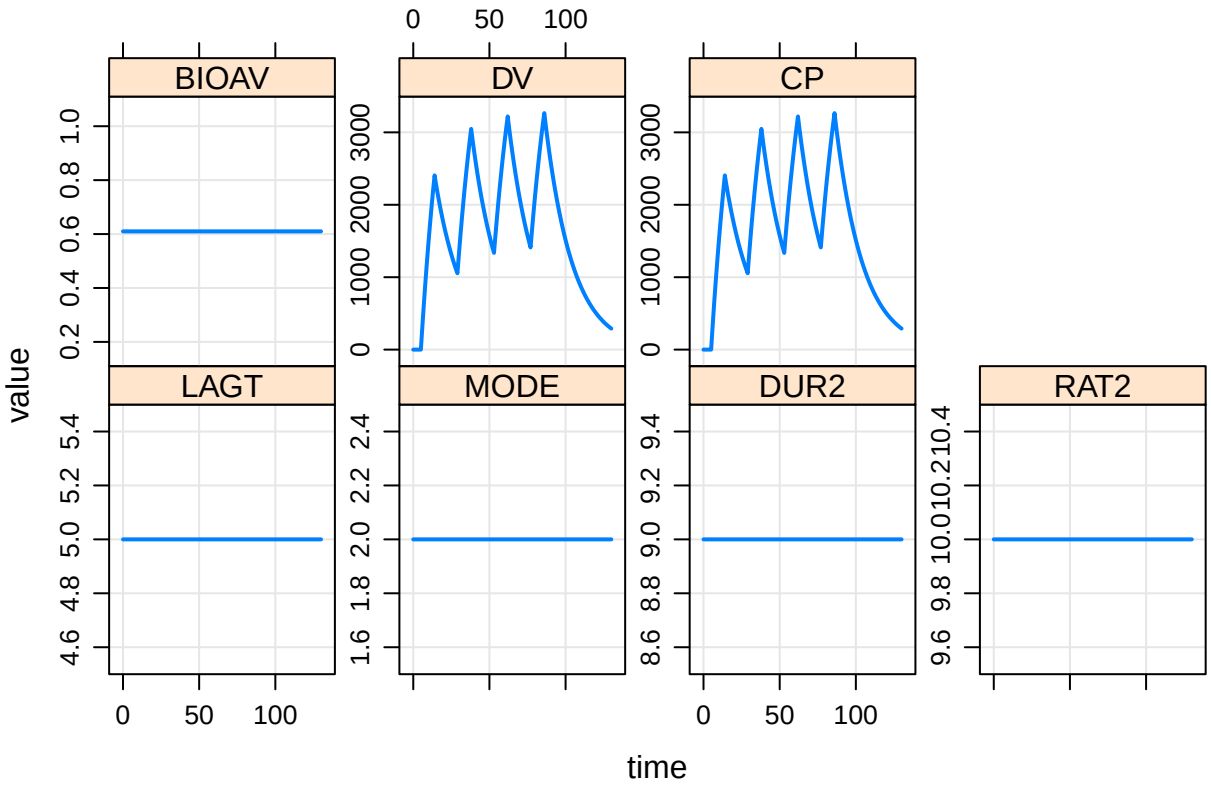

```
data10 <- to_data_set(out10, 10)
```

3.0.16 Infusion with modeled duration, lag time, and bioav factor

```
ev <- ev(amt = 100, rate = -2, DUR2 = 9, MODE = 2, cmt = 2, ii = 24, addl = 3, LAGT = 5, BIOAV = 0.61)
ev
```

```
. Events:
.   time cmt amt rate DUR2 MODE ii addl LAGT BIOAV evid
. 1    0   2 100   -2    9    2 24    3    5  0.61    1
```

```
out11 <- sim(mod,ev)
plot(out11)
```



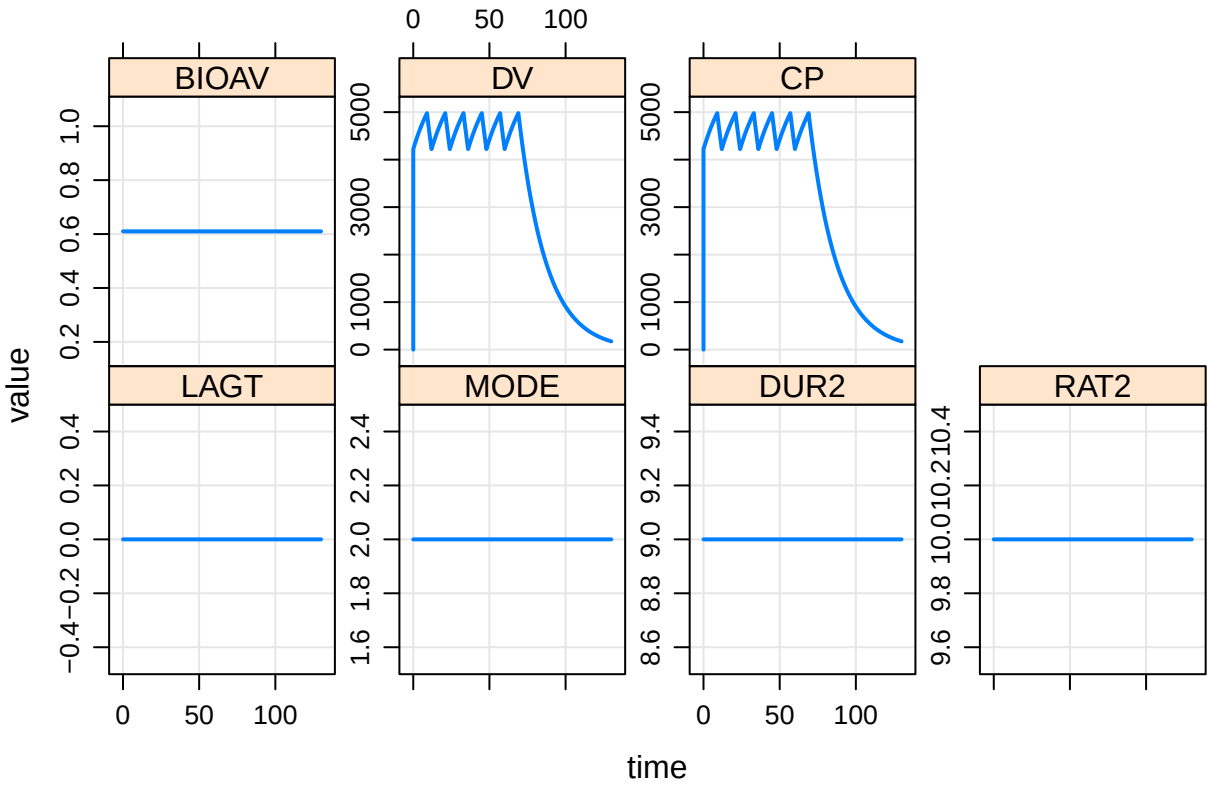

```
data11 <- to_data_set(out11,11)
```

3.0.17 Infusion with modeled duration, at steady state with bioav factor

```
ev <- ev(amt = 100, rate = -2, DUR2 = 9, MODE = 2, cmt = 2, ii = 12, addl = 5, ss = 1, BIOAV = 0.61)
ev
```

```
. Events:
.   time cmt amt rate DUR2 MODE ii addl ss BIOAV evid
. 1    0   2 100   -2    9    2 12    5  1  0.61    1
```

```
out12 <- sim(mod,ev)
plot(out12)
```



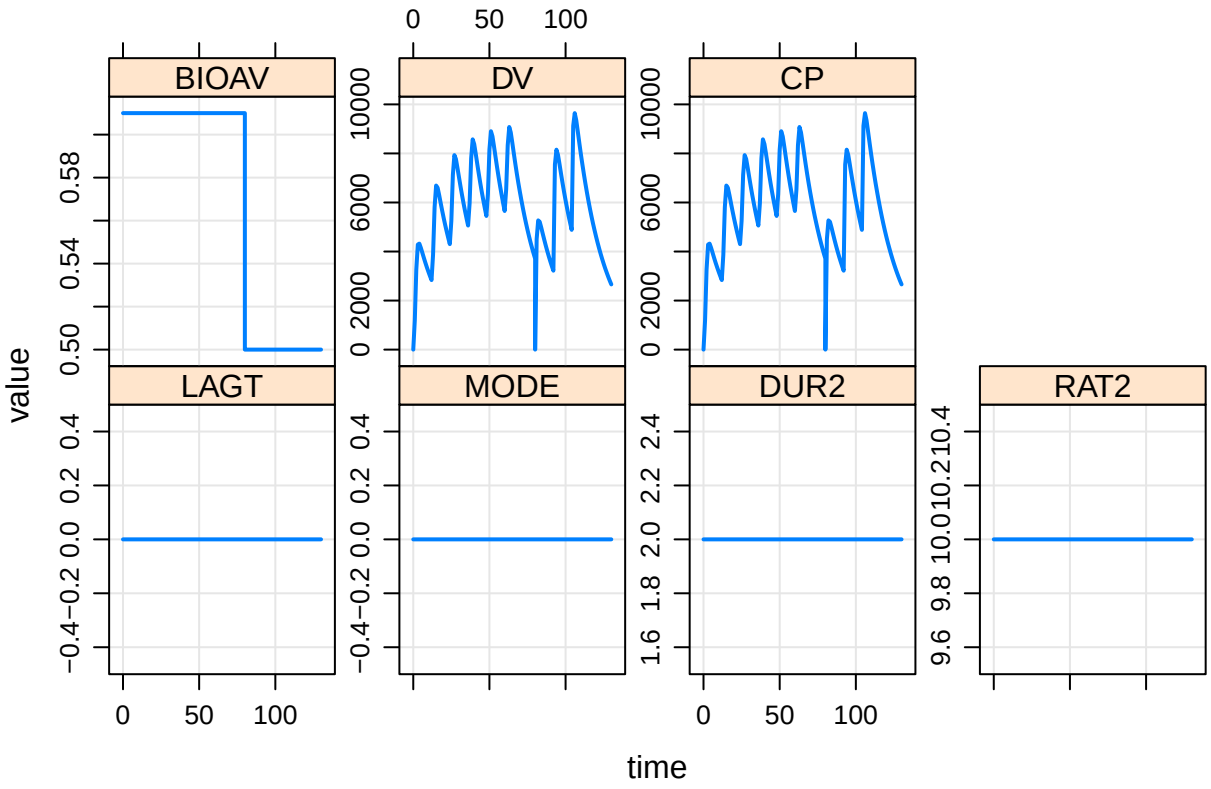

```
data12 <- to_data_set(out12,12)
```

3.0.18 Reset and dose (EVID 4) with additional

```
ev <-
  ev(amt = 100, ii = 12, addl = 5, rate = 50, BIOAV = 0.61) +
  ev(amt = 120, evid = 4, time = 80, BIOAV = 0.5, ii = 12, addl = 2)
ev
```

```
. Events:
.   time cmt amt ii addl rate BIOAV evid
. 1    0   1 100 12    5   50  0.61    1
. 2   80   1 120 12    2    0  0.50    4
```

```
out13 <- sim(mod,ev)
plot(out13)
```



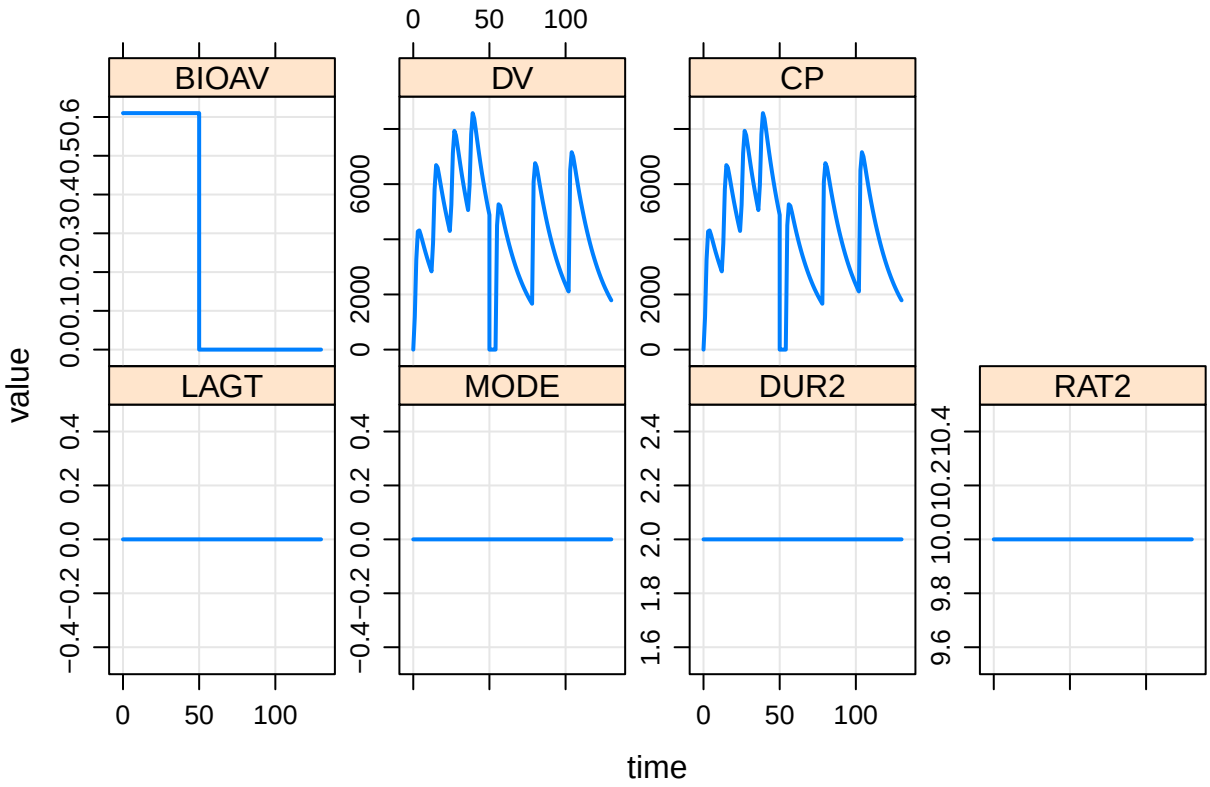

```
data13 <- to_data_set(out13,13)
```

3.0.19 Reset (EVID 3) with additional

```
ev <-
  ev(amt = 100, ii = 12, addl = 3, rate = 50, BIOAV = 0.61) +
  ev(amt = 0, evid = 3, time = 50, cmt = 2) +
  ev(amt = 120, ii = 24, addl = 2, time = 54)
ev
```

```
. Events:
.   time cmt amt ii addl rate BIOAV evid
. 1    0   1 100 12    3   50  0.61    1
. 2   50   2   0  0    0    0  0.00    3
. 3   54   1 120 24    2    0  0.00    1
```

```
out14 <- sim(mod,ev)
plot(out14)
```




```
data14 <- to_data_set(out14,14)
```

4 Collect `mrgsim` output

```
sims <- list(out1,out1.1,out2,out2.1,out3,out4,out5,out6,out6.1,out6.2,out7,out7.1,
             out8,out9,out10,out11,out12,out13,out14)
sims <- lapply(sims, as.data.frame)
sims <- bind_rows(sims)
```

5 Create a single data set for `nonmem`

```
data <- bind_rows(data1,data1.1,data2,data2.1,data3,data4,data5,data6,data6.1,data6.2,data7,data7.1,
                  data8,data9,data10,data11,data12,data13,data14)

sv(data, "data/1001.csv")
```

6 Simulate with `nonmem`

```
out <- run(1001)
```

```
. Run 1001 complete.
```

```
. NONR complete.
```

```
. Parsed with column specification:
. cols(
.   TIME = col_double(),
.   EVID = col_double(),
.   CP = col_double(),
.   IPRED = col_double(),
.   PRED = col_double(),
.   DV = col_double()
. )
```

7 Overall Summary

Dimensions for mrgsim and nonmem output

```
dim(out)
```

```
. [1] 2512    6
```

```
dim(sims)
```

```
. [1] 2512   16
```

This is the `nonmem` minus `mrgsim` summary

```
summary(out$CP - sims$CP)
```

```
.    Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
.       0       0       0       0       0       0
```

```
data$NM <- out$CP
data$MRGSIM <- sims$CP
```

8 Summary by RUN

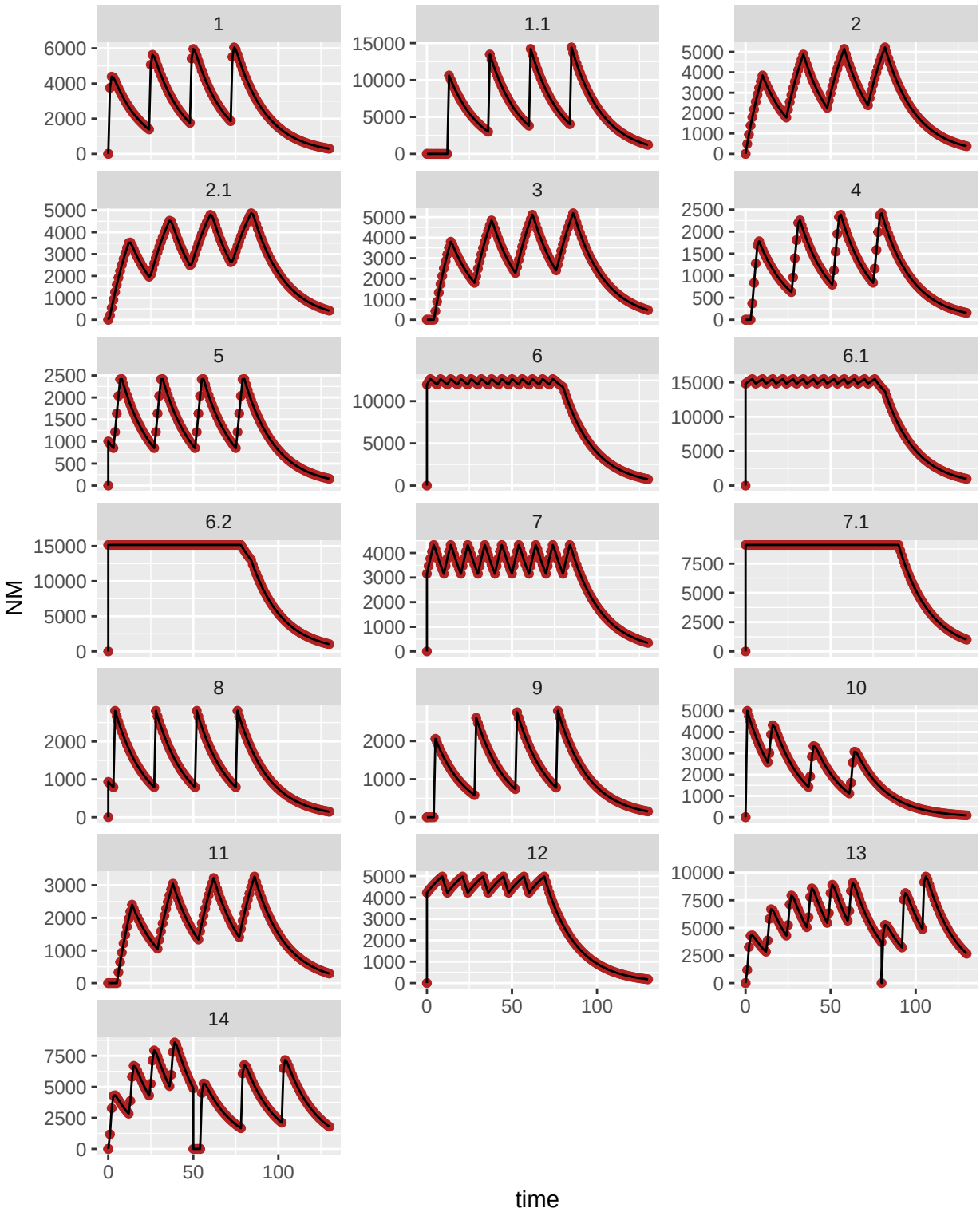
`diff` is the simulated `CP` from `nonmem` minus the simulated `CP` from `mrgsim`

```
group_by(data,ID) %>%
  mutate(diff = NM - MRGSIM) %>%
  summarise(mean = mean(diff), max = max(diff), min = min(diff))
```

```
. # A tibble: 19 x 4
.       ID  mean   max   min
.    <dbl> <dbl> <dbl> <dbl>
.  1  1.00    0.    0.    0.
.  2  1.10    0.    0.    0.
.  3  2.00    0.    0.    0.
.  4  2.10    0.    0.    0.
.  5  3.00    0.    0.    0.
.  6  4.00    0.    0.    0.
.  7  5.00    0.    0.    0.
.  8  6.00    0.    0.    0.
.  9  6.10    0.    0.    0.
. 10  6.20    0.    0.    0.
. 11  7.00    0.    0.    0.
. 12  7.10    0.    0.    0.
. 13  8.00    0.    0.    0.
. 14  9.00    0.    0.    0.
. 15 10.0     0.    0.    0.
. 16 11.0     0.    0.    0.
. 17 12.0     0.    0.    0.
. 18 13.0     0.    0.    0.
. 19 14.0     0.    0.    0.
```

9 Plot

```
ggplot(data = data) +
  geom_point(aes(time,NM),color = "firebrick") +
  geom_line(aes(time,MRGSIM,group = ID)) +
  facet_wrap(~ID, scales = "free_y", ncol = 3)
```


1
1.1
2
2.1
3
4
5
6
6.1
6.2
7
7.1
8
9
10
11
12
13
14
NM
time
0
50
100

10 Control stream

```
writeLines(readLines("model/1001.ctl"))
```

```
$PROB RUN# 101

$INPUT C ID TIME EVID AMT CMT SS II ADDL RATE LAGT MODE DUR2 RAT2 BIOAV DV

$DATA ../../data/1001.csv IGNORE=C

$SUBROUTINES ADVAN2 TRANS2

$PK

TVCL=THETA(1)
CL=TVCL*EXP(ETA(1))

TVV2=THETA(2)
V=TVV2*EXP(ETA(2))

TVKA=THETA(3)
KA=TVKA*EXP(ETA(3))

ALAG2 = LAGT
F2 = BIOAV

IF(MODE.EQ.1) R2 = RAT2
IF(MODE.EQ.2) D2 = DUR2

$ERROR
IPRED=A(2)/(V/1000)
Y=IPRED*EXP(ERR(1))

CP = IPRED

$THETA
(1.1,   FIX) ;; CL
(20,  FIX) ;; V
(1.5, FIX) ;; KA

$OMEGA
0.0 FIX
0.0 FIX
0.0 FIX

$SIGMA
0.00 FIX

$TABLE FILE=TAB TIME EVID CP IPRED PRED DV NOPRINT ONEHEADER NOAPPEND

$SIMULATION (2674474) ONLYSIMULATION
```

11 Session Info

```
devtools::session_info()
```

```
. Session info -------------------------------------------------------------
.  setting  value
.  version  R version 3.3.3 (2017-03-06)
.  system   x86_64, linux-gnu
.  ui       X11
.  language (EN)
.  collate  en_US.UTF-8
.  tz       Etc/UTC
.  date     2018-04-26
. Packages -----------------------------------------------------------------
.  package       * version     date
.  assertthat      0.2.0       2017-04-11
.  backports       1.1.2       2017-12-13
.  base          * 3.3.3       2017-03-06
.  bindr           0.1.1       2018-03-13
.  bindrcpp      * 0.2.2       2018-03-29
.  cli             1.0.0       2017-11-05
.  colorspace      1.3-2       2016-12-14
.  crayon          1.3.4       2017-09-16
.  datasets      * 3.3.3       2017-03-06
.  devtools        1.13.5      2018-02-18
.  digest          0.6.15      2018-01-28
.  dplyr         * 0.7.4       2017-09-28
.  evaluate        0.10.1      2017-06-24
.  ggplot2       * 2.2.1       2016-12-30
.  glue            1.2.0       2017-10-29
.  graphics      * 3.3.3       2017-03-06
.  grDevices     * 3.3.3       2017-03-06
.  grid            3.3.3       2017-03-06
.  gtable          0.2.0       2016-02-26
.  hms             0.4.2       2018-03-10
.  htmltools       0.3.6       2017-04-28
.  knitr           1.20        2018-02-20
.  labeling        0.3         2014-08-23
.  lattice         0.20-34     2016-09-06
.  lazyeval        0.2.1       2017-10-29
.  magrittr        1.5         2014-11-22
.  MASS            7.3-49      2018-02-23
.  memoise         1.0.0       2016-01-29
.  methods       * 3.3.3       2017-03-06
.  metrumrg        5.57        2017-10-14
.  mrgsolve      * 0.8.11      2018-04-26
.  munsell         0.4.3       2016-02-13
.  pillar          1.2.1       2018-02-27
.  pkgconfig       2.0.1       2017-03-21
.  plyr            1.8.4       2016-06-08
.  R6              2.2.2       2017-06-17
.  Rcpp            0.12.16     2018-03-13
```

```
.  RcppArmadillo   0.8.400.0.0 2018-03-01
.  readr         * 1.1.1       2017-05-16
.  reshape         0.8.7       2017-08-06
.  rlang           0.2.0       2018-02-20
.  rmarkdown       1.9         2018-03-01
.  rprojroot       1.3-2       2018-01-03
.  rstudioapi      0.7         2017-09-07
.  scales          0.5.0       2017-08-24
.  stats         * 3.3.3       2017-03-06
.  stringi         1.1.7       2018-03-12
.  stringr         1.3.0       2018-02-19
.  tibble          1.4.2       2018-01-22
.  tools           3.3.3       2017-03-06
.  utf8            1.1.3       2018-01-03
.  utils         * 3.3.3       2017-03-06
.  withr           2.1.2       2018-03-15
.  XML             3.98-1.11   2018-04-16
.  yaml            2.1.18      2018-03-08
.  source
.  CRAN (R 3.3.3)
.  cran (@1.1.2)
.  local
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  cran (@1.0.0)
.  CRAN (R 3.3.2)
.  cran (@1.3.4)
.  local
.  CRAN (R 3.3.3)
.  cran (@0.6.15)
.  CRAN (R 3.3.3)
.  cran (@0.10.1)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  local
.  local
.  local
.  CRAN (R 3.3.2)
.  CRAN (R 3.3.3)
.  cran (@0.3.6)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.2)
.  CRAN (R 3.3.2)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.2)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.2)
.  local
.  Github (metrumresearchgroup/metrumrg@2e5a541)
.  local
.  CRAN (R 3.3.2)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.2)
```

```
.  cran (@2.2.2)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  cran (@1.3-2)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  local
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  cran (@1.4.2)
.  local
.  cran (@1.1.3)
.  local
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
.  CRAN (R 3.3.3)
```