

INFUSION TESTS

kyleb

Wed Nov 8 15:36:03 2017

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

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

```
##  
## Attaching package: 'dplyr'  
## The following objects are masked from 'package:stats':  
##  
##   filter, lag  
## The following objects are masked from 'package:base':  
##  
##   intersect, setdiff, setequal, union
```

```
library(readr)  
library(ggplot2)
```

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

Functions

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  
}
```

Save the nonmem input data set

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

Run nonmem

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

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")  
}
```

Simulate a scenario with mrsim

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

The mrgsim model

```
code <- '  
$SET req = ""  
$PARAM CL = 1, V = 30, 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)

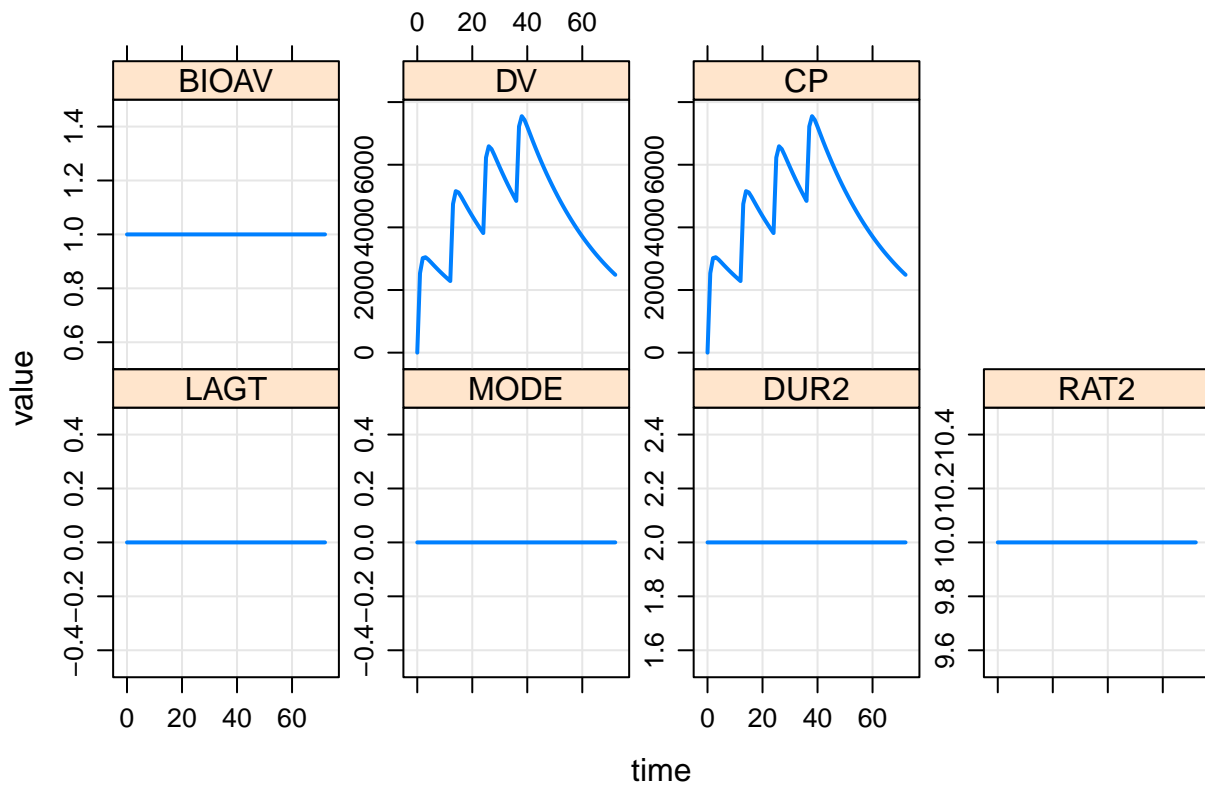
## Compiling tests1 ... done.

mod <- update(mod, end=72)
```

Scenarios

Bolus

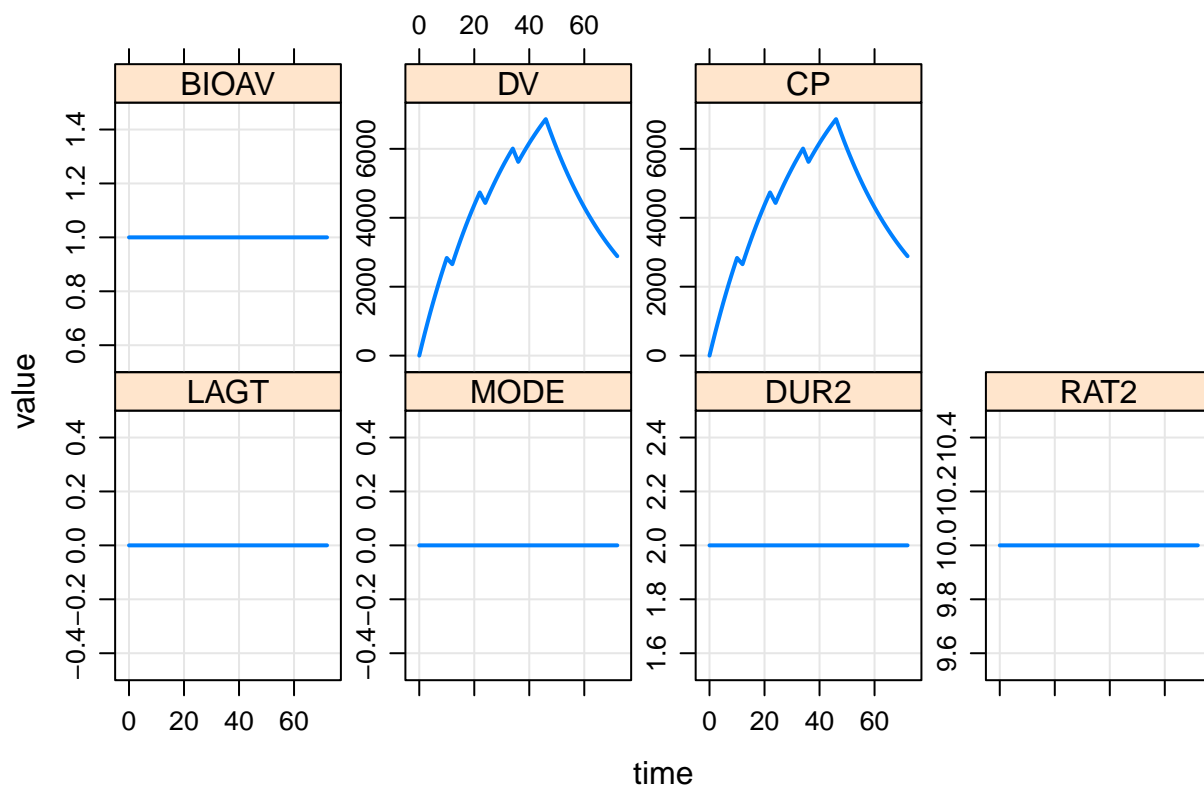
```
ev <- ev(amt = 100, ii = 12, addl = 3)
out1 <- sim(mod, ev)
plot(out1)
```



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

Infusion

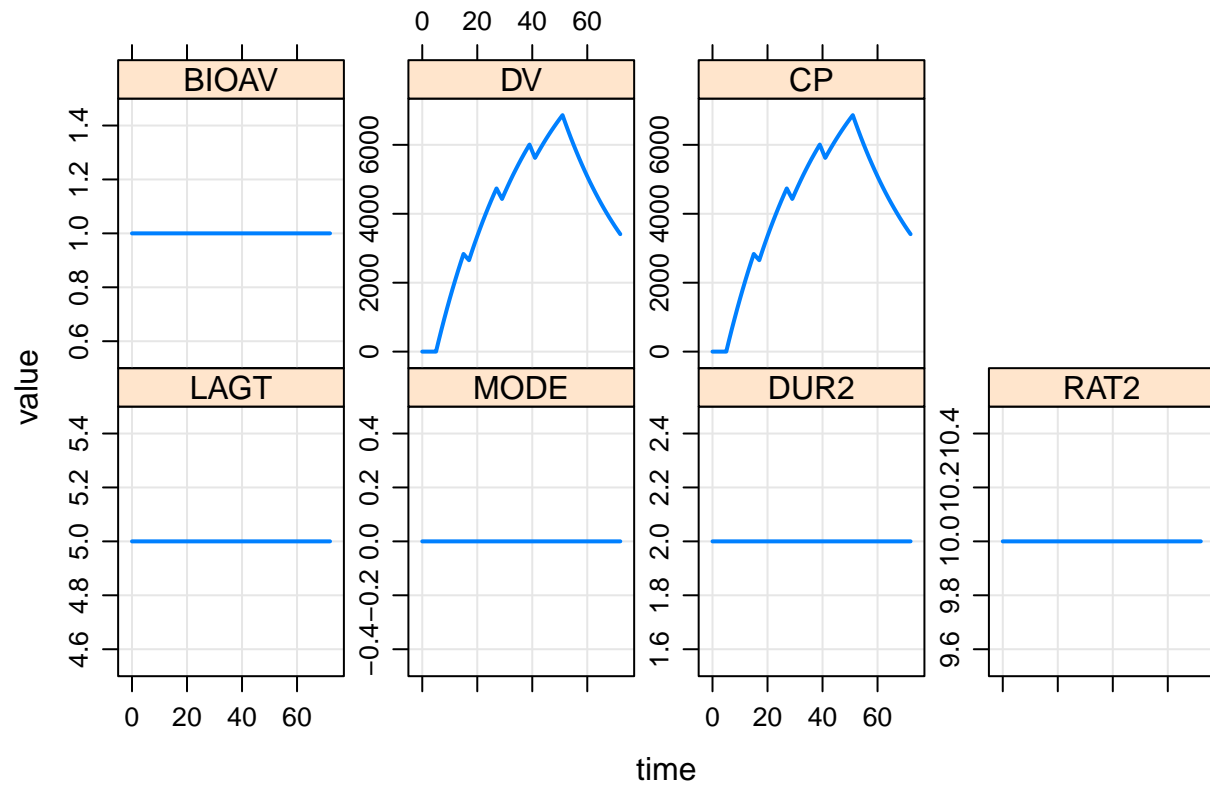
```
ev <- ev(amt = 100, ii = 12, addl = 3, rate = 100/10, cmt = 2)
out2 <- sim(mod, ev)
plot(out2)
```



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

Infusion, lag

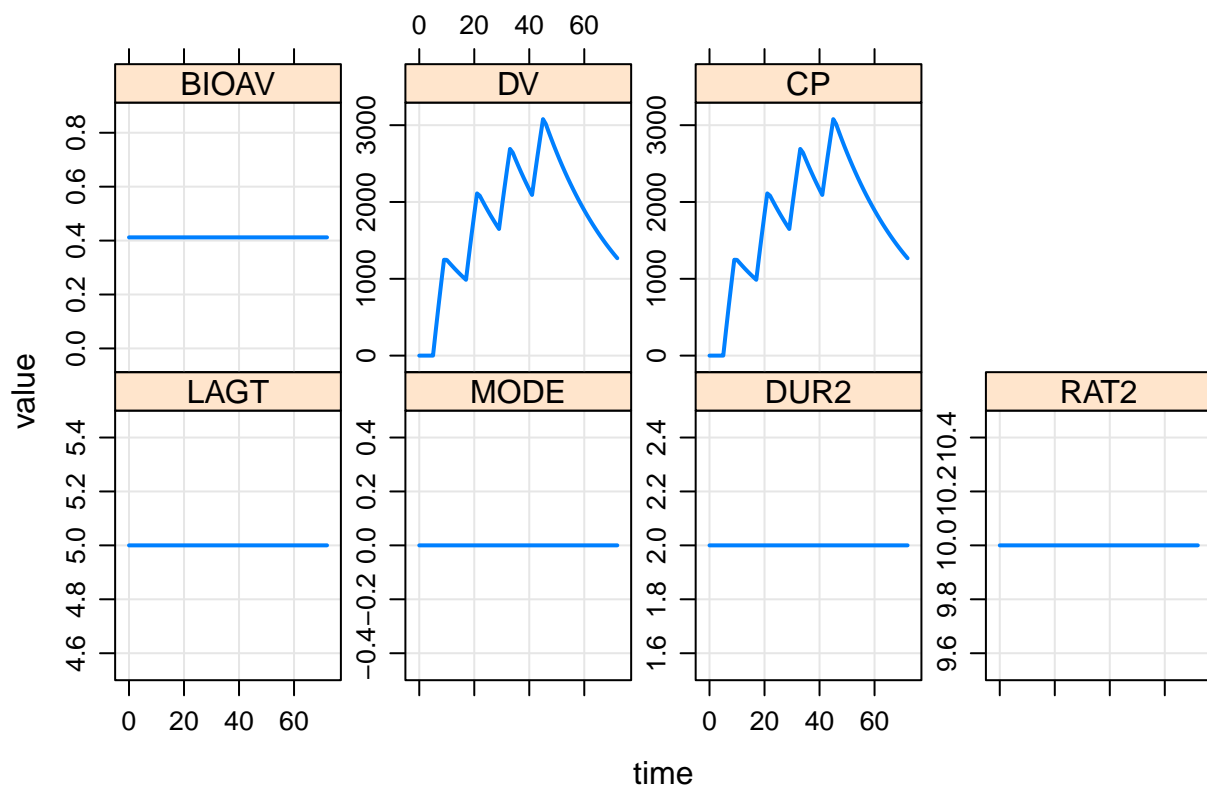
```
ev <- ev(amt = 100, ii = 12, addl=3, rate = 100/10, LAGT = 5, cmt = 2)
out3 <- sim(mod, ev)
plot(out3)
```



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

Infusion, lag, bioav

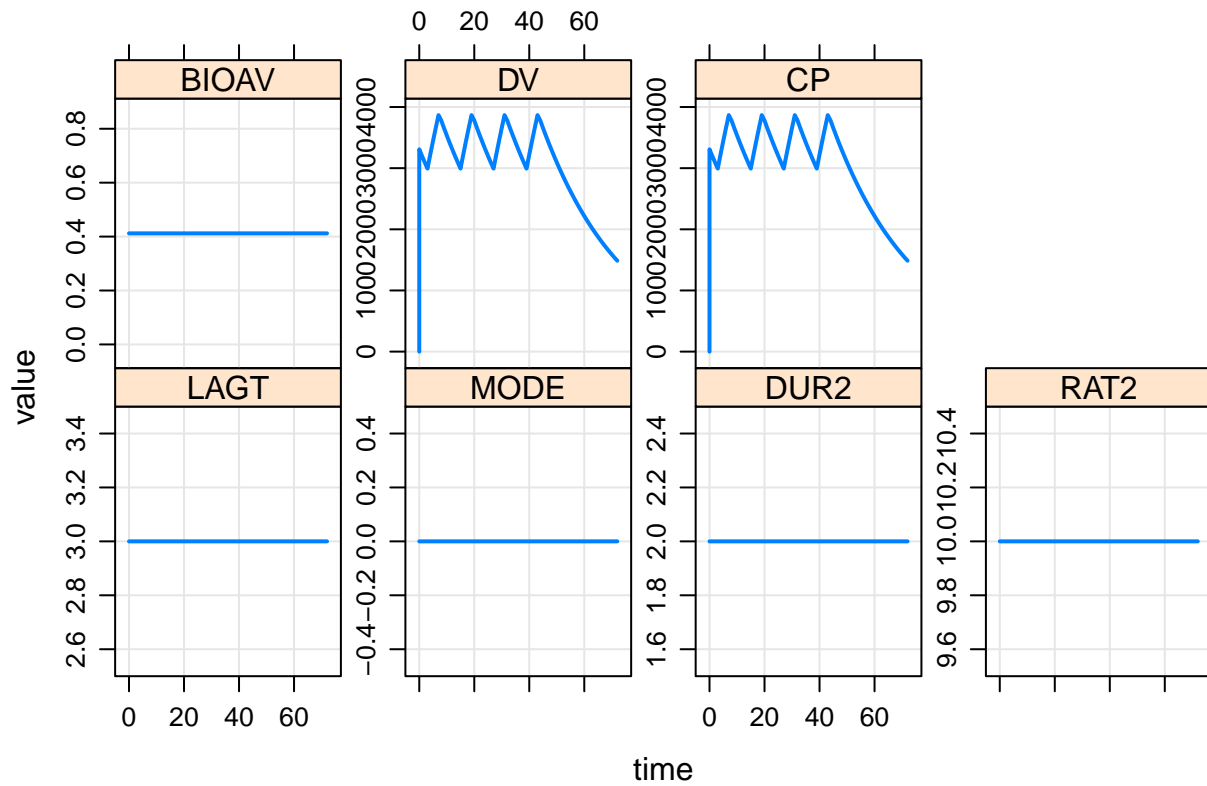
```
ev <- ev(amt = 100, ii = 12, addl=3, rate = 100/10, LAGT = 5, BIOAV = 0.412, cmt = 2)
out4 <- sim(mod, ev)
plot(out4)
```



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

Infusion, lag, bioav, ss

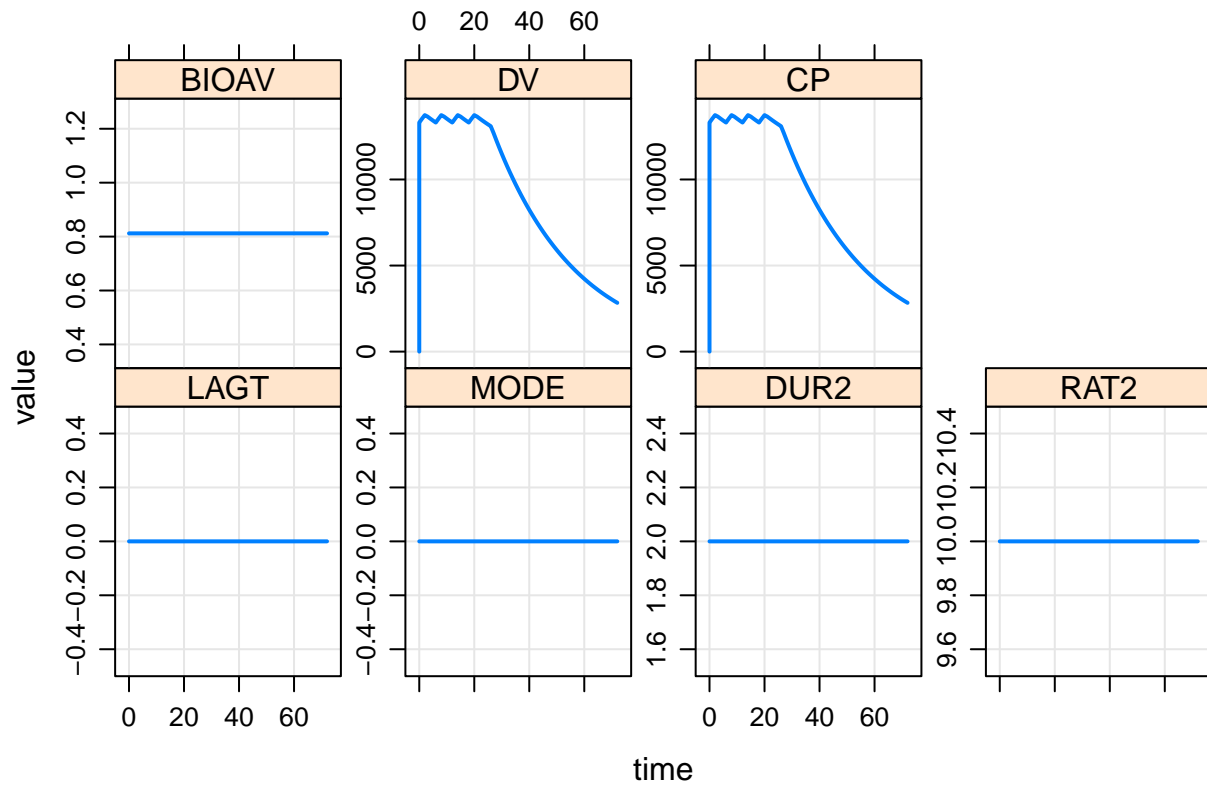
```
ev <- ev(amt = 100, ii = 12, addl=3, rate = 100/10, LAGT = 3, BIOAV = 0.412, ss = 1, cmt = 2)
out5 <- sim(mod, ev)
plot(out5)
```



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

Infusion, bioav, ss, II < DUR

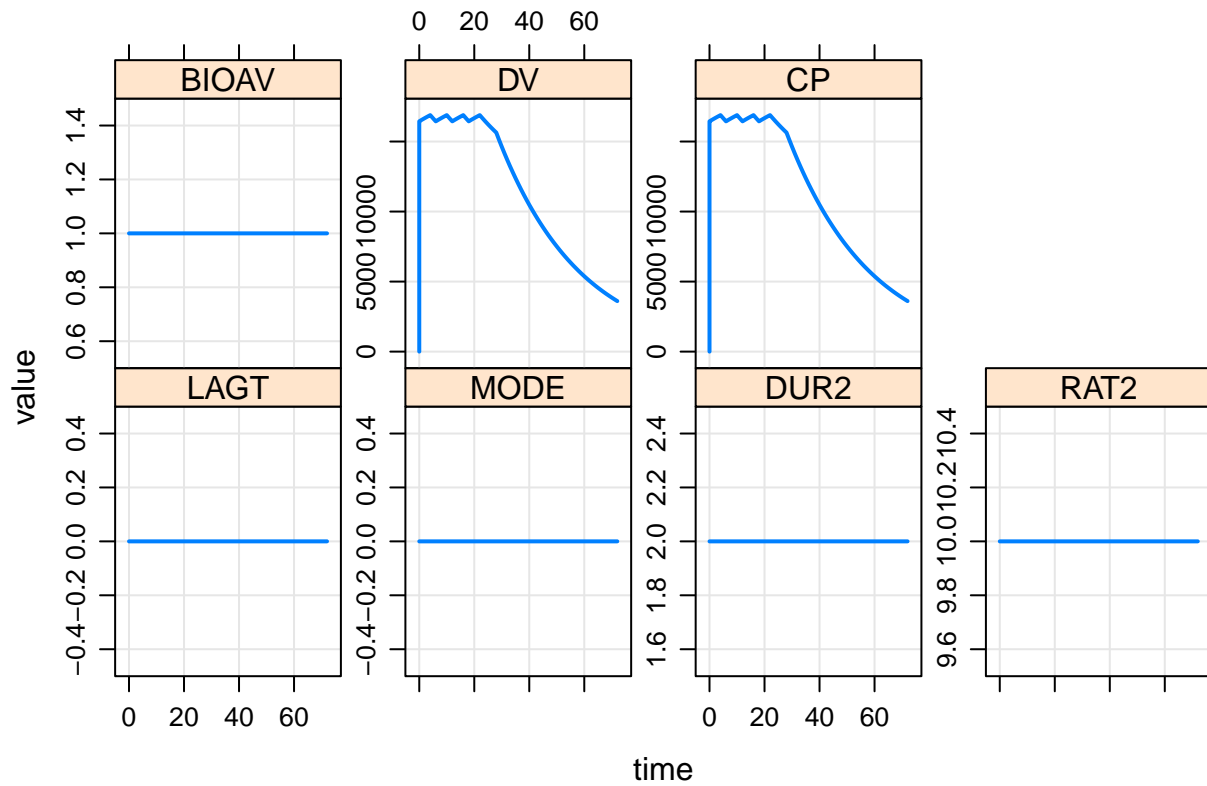
```
ev <- ev(amt = 100, ii = 6, addl = 3, rate = 100/10, BIOAV = 0.812, ss = 1, cmt = 2)
out6 <- sim(mod, ev)
plot(out6)
```



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

Infusion, ss, II < DUR

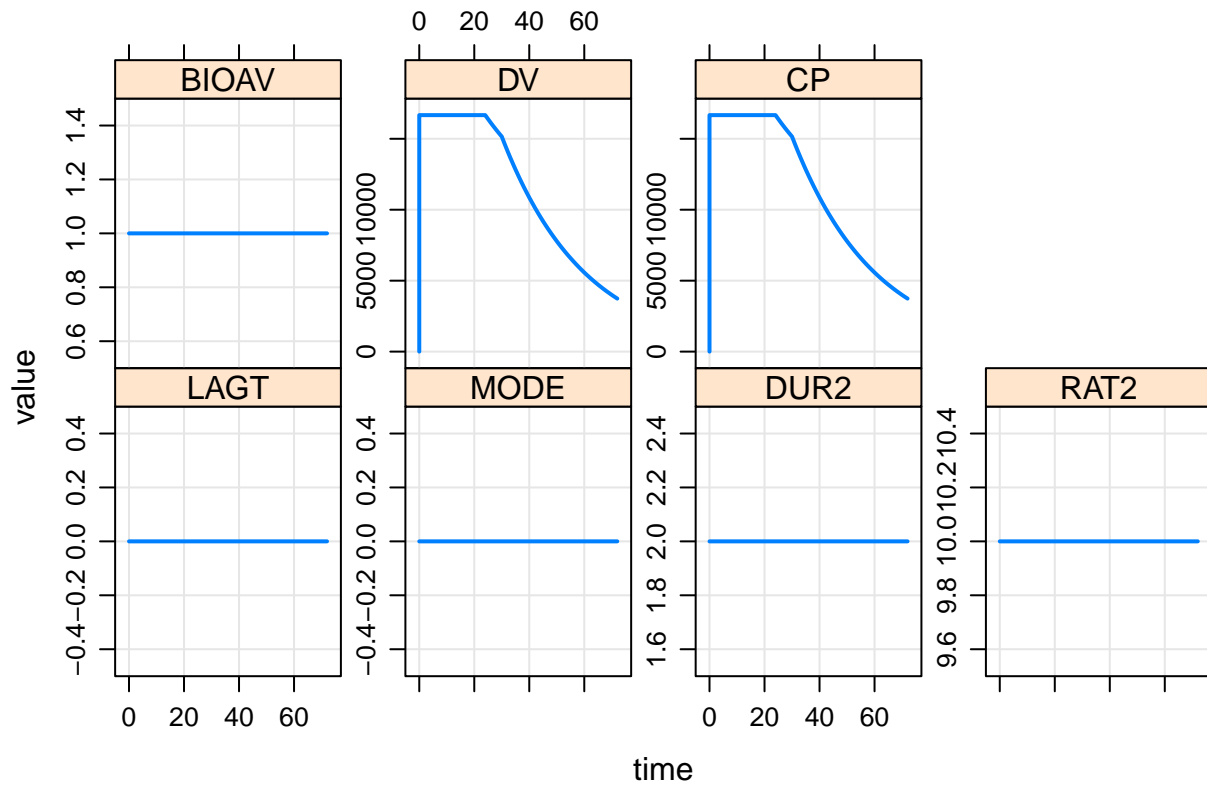
```
ev <- ev(amt = 100, ii = 6, addl = 3, rate = 100/10, ss = 1, cmt = 2)
out6.1 <- sim(mod, ev)
plot(out6.1)
```

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

Infusion, ss, II multiple of DUR

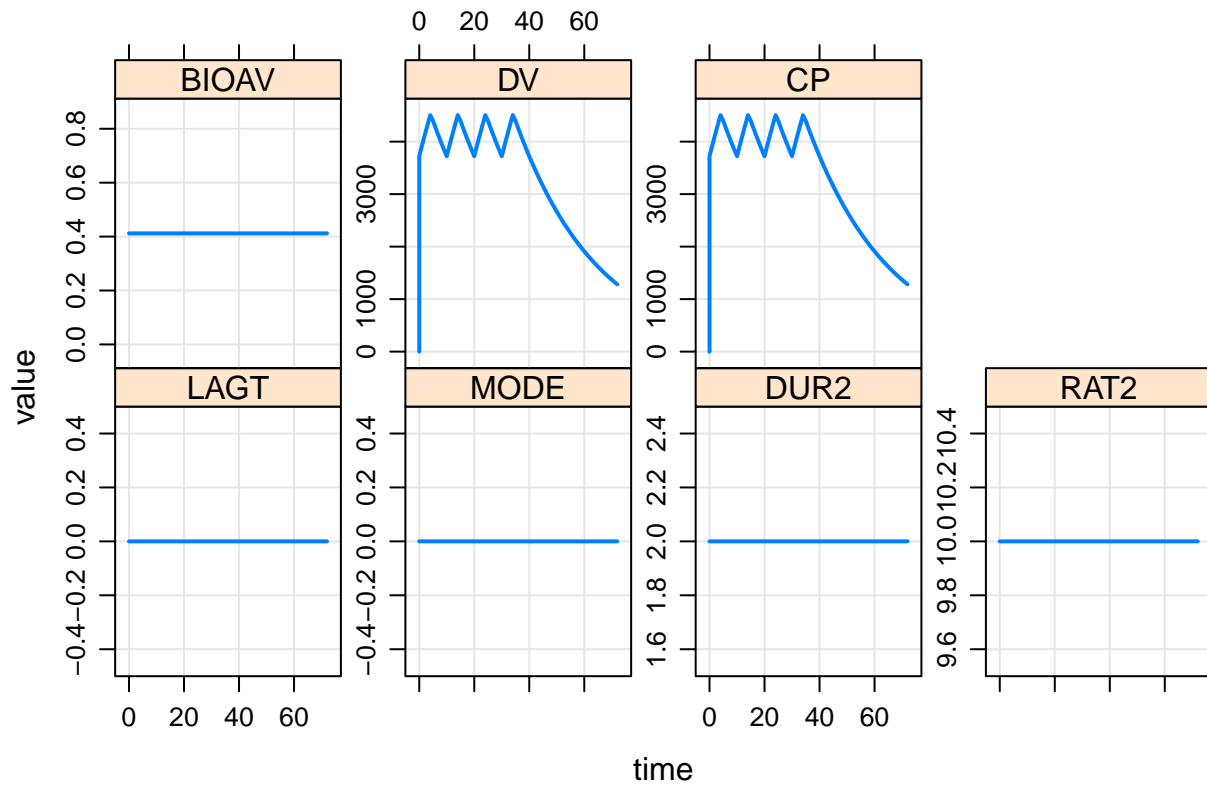
```
ev <- ev(amt = 100, ii = 6, addl = 3, rate = signif(100/12,5), ss = 1, cmt = 2)
out6.2 <- sim(mod, ev)
plot(out6.2)
```



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

Infusion, bioav, ss, II == DUR

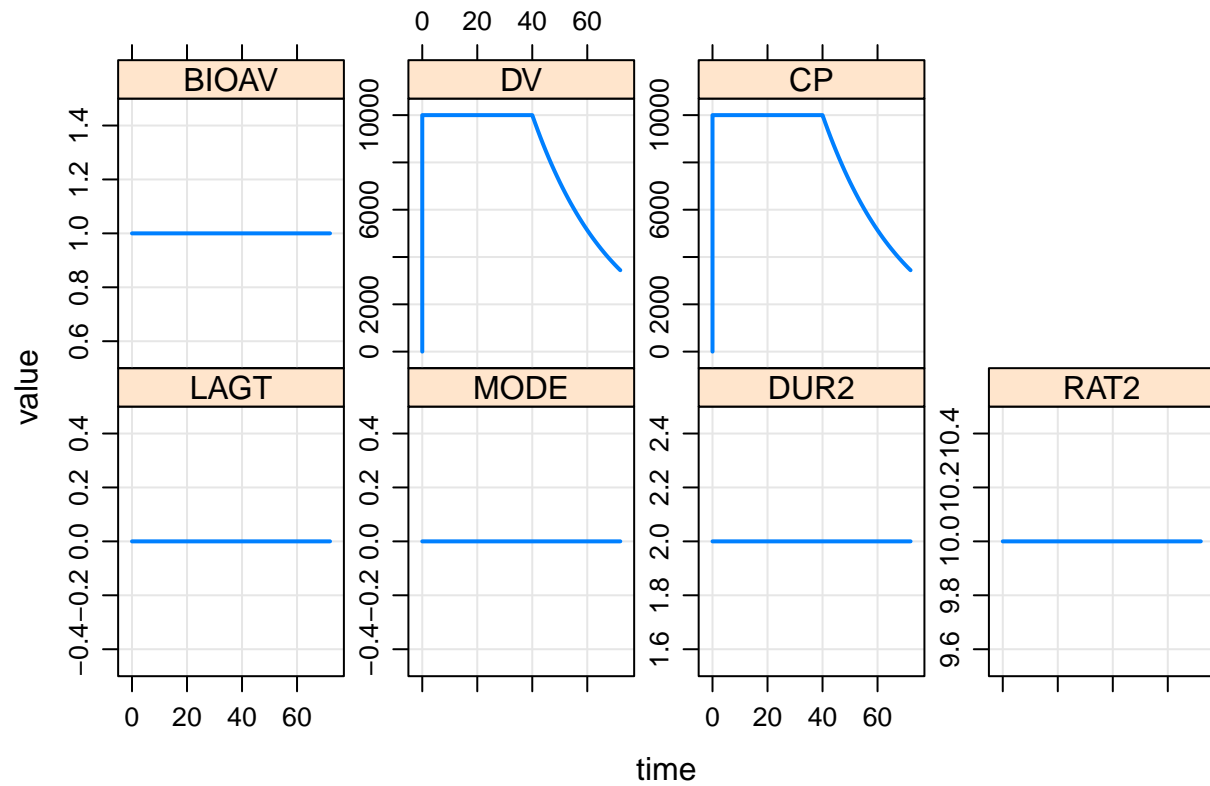
```
ev <- ev(amt = 100, ii = 10, addl=3, rate = 100/10, LAGT = 0, BIOAV = 0.412, ss = 1, cmt = 2)
out7 <- sim(mod, ev)
plot(out7)
```



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

Infusion,, ss, II == DUR

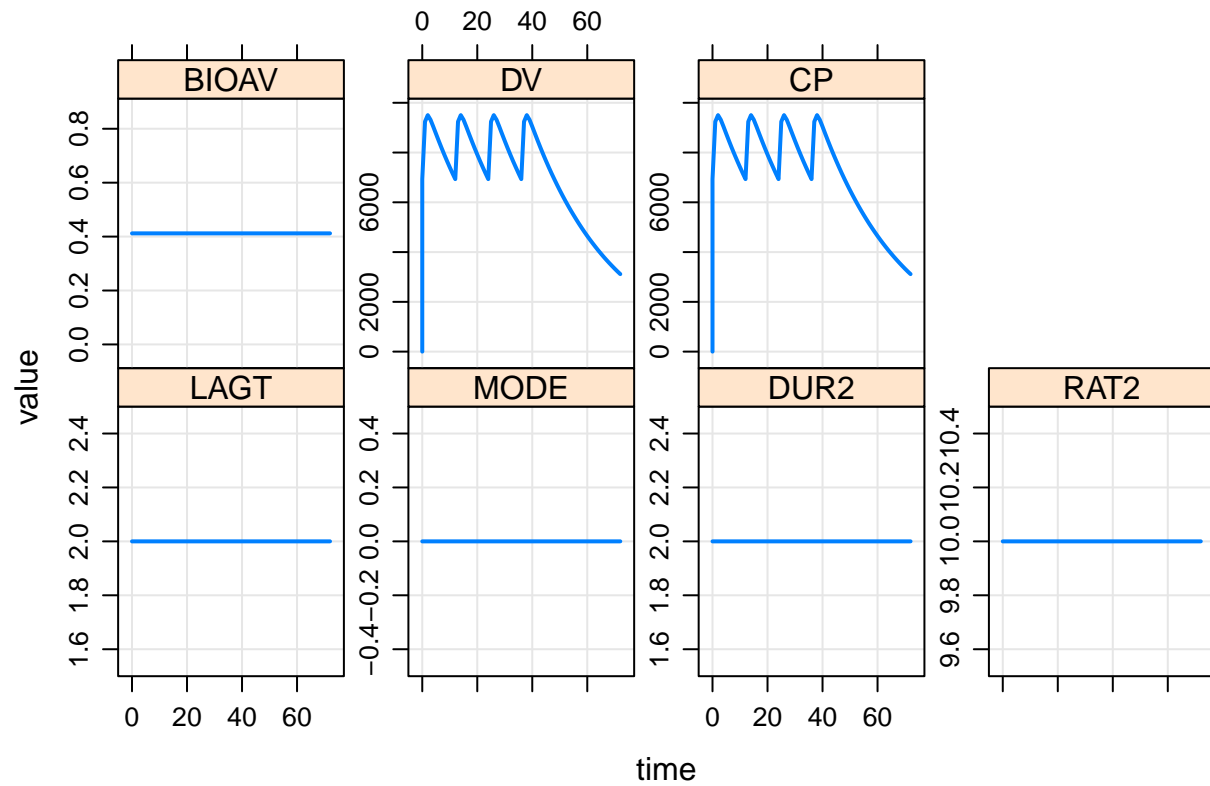
```
ev <- ev(amt = 100, ii = 10, addl=3, rate = 100/10, LAGT = 0, ss = 1, cmt = 2)
out7.1 <- sim(mod, ev)
plot(out7.1)
```



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

Bolus, bioav, lag, ss

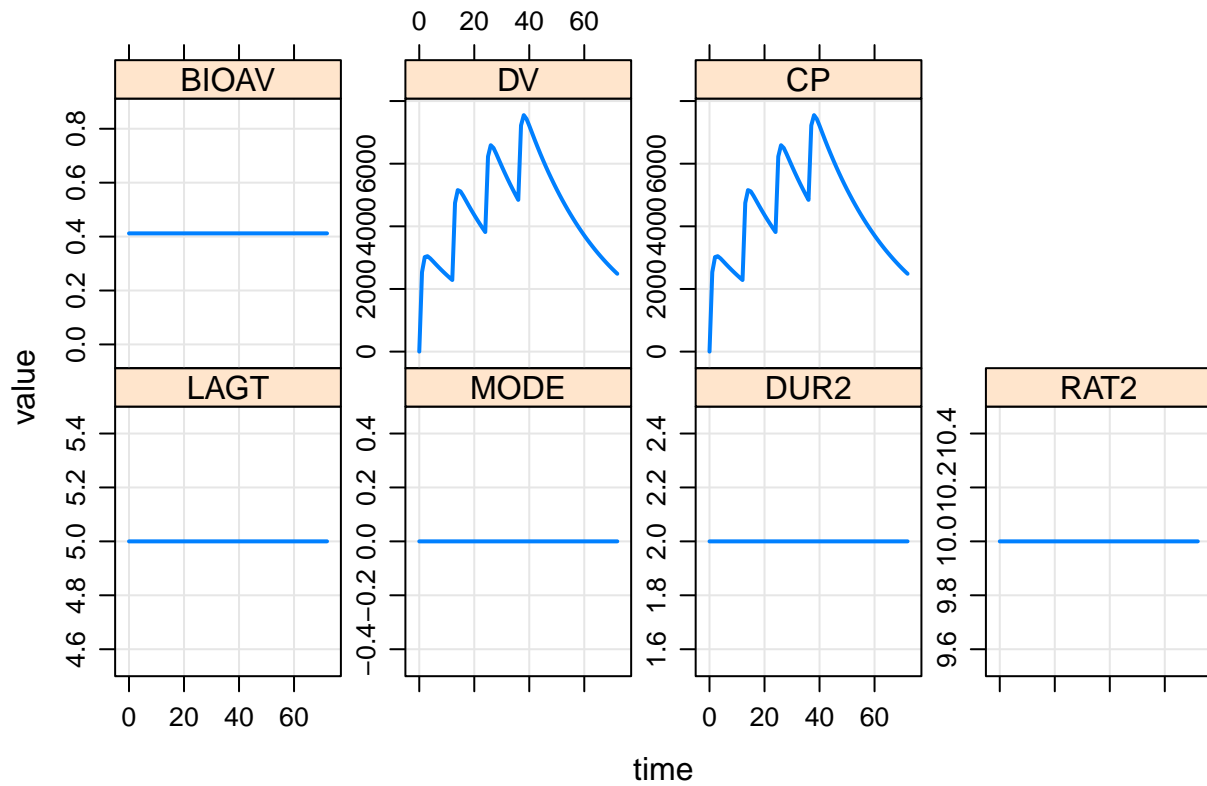
```
ev <- ev(amt = 100, ii = 12, addl=3, LAGT = 2, BIOAV = 0.412, ss = 1)
out8 <- sim(mod, ev)
plot(out8)
```



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

Bolus, lag, bioav

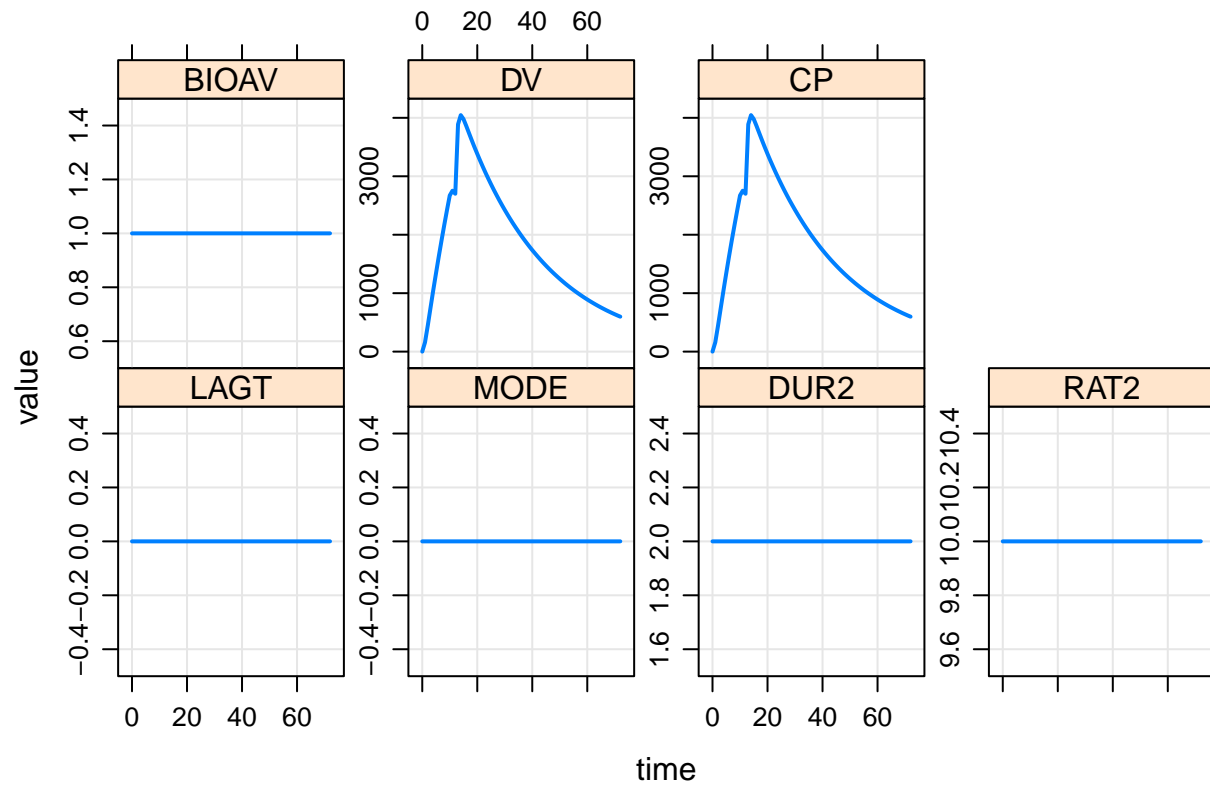
```
ev <- ev(amt = 100, ii = 12, addl=3, LAGT = 5, BIOAV = 0.412)
out9 <- sim(mod, ev)
plot(out9)
```



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

Infusion / bolus

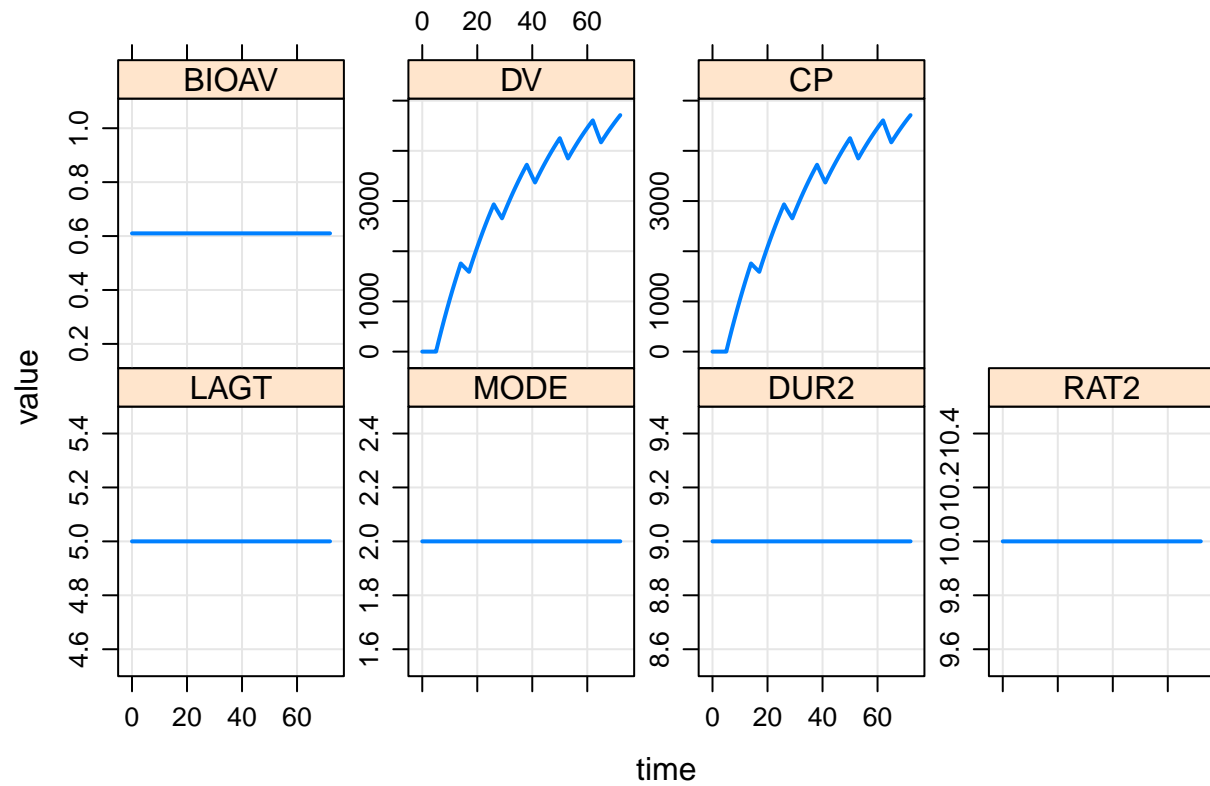
```
ev <- ev(amt = 100, rate = 10) + ev(time = 12, amt = 50)
out10 <- sim(mod, ev)
plot(out10)
```



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

Infusion (D_) lag, BIOAV

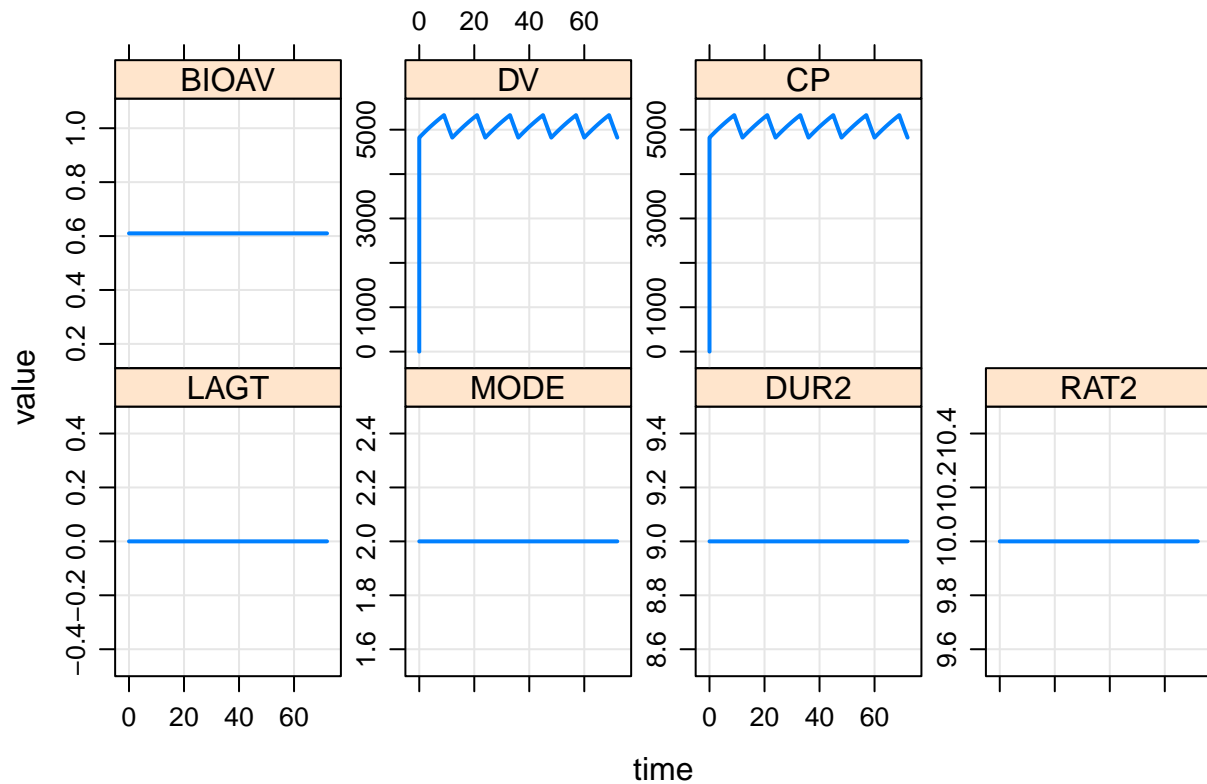
```
ev <- ev(amt = 100, rate = -2, DUR2 = 9, MODE = 2, cmt = 2, ii = 12, addl = 5, LAGT = 5, BIOAV = 0.61)
out11 <- sim(mod, ev)
plot(out11)
```



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

Infusion (D_) ss, BIOAV

```
ev <- ev(amt = 100, rate = -2, DUR2 = 9, MODE = 2, cmt = 2, ii = 12, addl = 5, ss = 1, BIOAV = 0.61)
out12 <- sim(mod, ev)
plot(out12)
```

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

Collect mrgsim output

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

Create a single data set for nonmem

```
data <- bind_rows(data1,data2,data3,data4,data5,data6,data6.1,data6.2,data7,data7.1,
                  data8,data9,data10,data11,data12)
sv(data, "data/101.csv")
```

Simulate with nonmem

```
out <- run(101)

## Run 101 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()
## )
```

Overall Summary

This is the nonmem minus mrgsim summary

```
dim(out)

## [1] 1111    6

dim(sims)

## [1] 1111   16

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
```

Summary by RUN

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

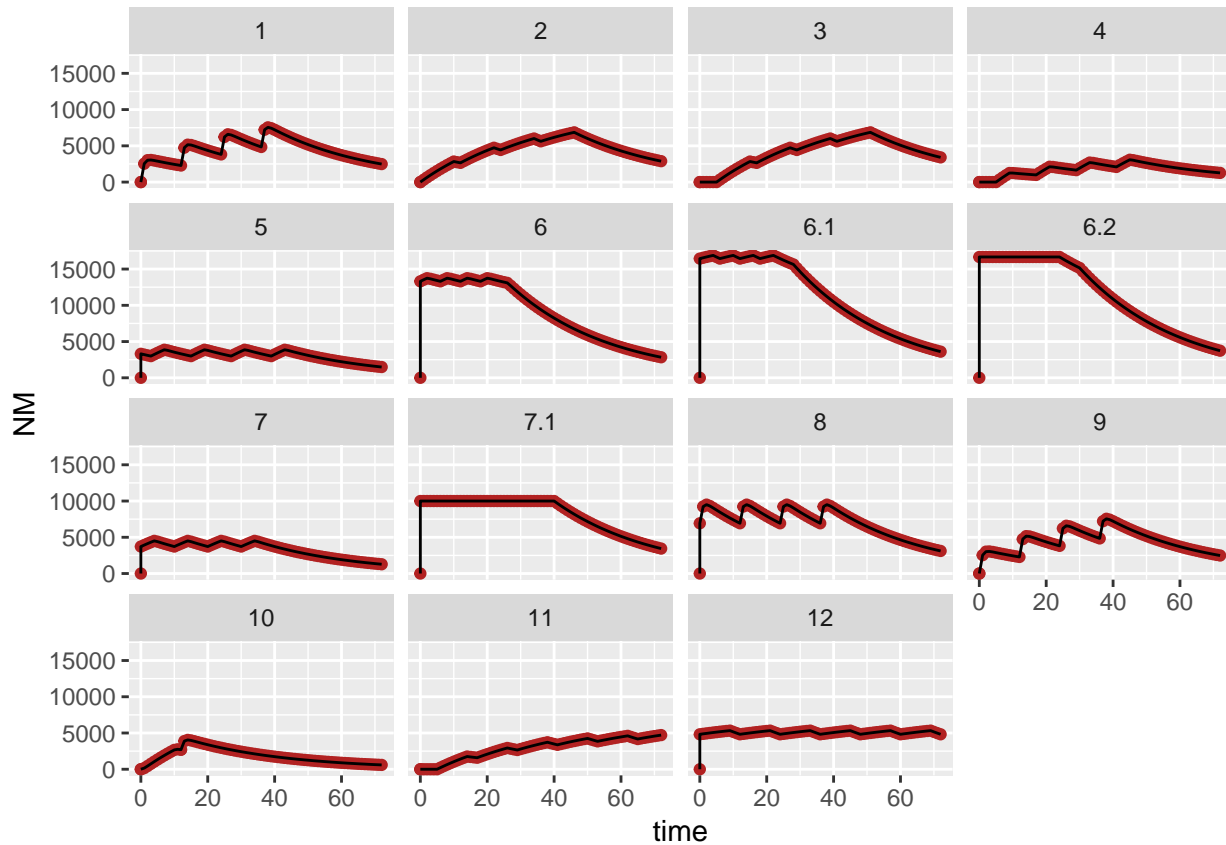
```
group_by(data, ID) %>%
  mutate(diff = NM - MRGSIM) %>%
  summarise(mean = mean(diff), max = max(diff), min = min(diff))
```

```
## # A tibble: 15 x 4
##       ID mean  max  min
##   <dbl> <dbl> <dbl> <dbl>
## 1  1.0    0    0    0
## 2  2.0    0    0    0
## 3  3.0    0    0    0
## 4  4.0    0    0    0
## 5  5.0    0    0    0
## 6  6.0    0    0    0
## 7  6.1    0    0    0
## 8  6.2    0    0    0
## 9  7.0    0    0    0
## 10 7.1    0    0    0
## 11 8.0    0    0    0
## 12 9.0    0    0    0
## 13 10.0   0    0    0
```

```
## 14 11.0 0 0 0
## 15 12.0 0 0 0
```

Plot

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



Control stream

```
writeLines(readLines("model/101.ct1"))
```

```
$PROB RUN# 101
```

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

```
$DATA ../../data/101.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, FIX) ;; CL
(30, 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
```

```
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 2017-11-08
```

```
## Packages -----
```

```
## package * version date
## assertthat 0.1 2013-12-06
```

##	backports	1.0.4	2016-10-24
##	base	* 3.3.3	2017-03-06
##	bindr	0.1	2016-11-13
##	bindrcpp	* 0.2	2017-06-17
##	colorspace	1.3-2	2016-12-14
##	datasets	* 3.3.3	2017-03-06
##	devtools	1.13.3	2017-08-02
##	digest	0.6.10	2016-08-02
##	dplyr	* 0.7.4	2017-09-28
##	evaluate	0.10	2016-10-11
##	ggplot2	* 2.2.1	2016-12-30
##	glue	1.1.1	2017-06-21
##	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	0.3	2016-11-22
##	htmltools	0.3.5	2016-03-21
##	knitr	1.17	2017-08-10
##	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	7.3-47	2017-04-21
##	memoise	1.0.0	2016-01-29
##	methods	* 3.3.3	2017-03-06
##	metrumrg	5.57	2017-10-14
##	mrgsolve	* 0.8.10	2017-11-08
##	munsell	0.4.3	2016-02-13
##	pkgconfig	2.0.1	2017-03-21
##	plyr	1.8.4	2016-06-08
##	R6	2.2.0	2016-10-05
##	Rcpp	0.12.13	2017-09-28
##	RcppArmadillo	0.8.100.1.0	2017-10-11
##	readr	* 1.1.1	2017-05-16
##	reshape	0.8.7	2017-08-06
##	rlang	0.1.2	2017-08-09
##	rmarkdown	1.6	2017-06-15
##	rprojroot	1.1	2016-10-29
##	scales	0.4.1	2016-11-09
##	stats	* 3.3.3	2017-03-06
##	stringi	1.1.2	2016-10-01
##	stringr	1.2.0	2017-02-18
##	tibble	1.3.4	2017-08-22
##	tools	3.3.3	2017-03-06
##	utils	* 3.3.3	2017-03-06
##	withr	1.0.2	2016-06-20
##	XML	3.98-1.9	2017-06-19
##	yaml	2.1.14	2016-11-12
##	source		
##	CRAN (R 3.3.2)		
##	CRAN (R 3.3.2)		
##	local		
##	CRAN (R 3.3.3)		

```

## CRAN (R 3.3.3)
## CRAN (R 3.3.2)
## local
## CRAN (R 3.3.3)
## CRAN (R 3.3.2)
## CRAN (R 3.3.3)
## CRAN (R 3.3.2)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## local
## local
## local
## 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)
## 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)
## Github (metrumresearchgroup/mrgsolve@86e326b)
## CRAN (R 3.3.2)
## CRAN (R 3.3.3)
## CRAN (R 3.3.2)
## CRAN (R 3.3.2)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## cran (@0.8.7)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## CRAN (R 3.3.2)
## CRAN (R 3.3.2)
## local
## CRAN (R 3.3.2)
## CRAN (R 3.3.3)
## CRAN (R 3.3.3)
## local
## local
## CRAN (R 3.3.2)
## cran (@3.98-1.)
## CRAN (R 3.3.2)

```