

## Modeling

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## 1 Purpose

This script runs NONMEM models and diagnostics for sample phase1 data.

## 2 Model Development

### 2.1 Set up for NONMEM run.

Listing 1:

```
> #Be sure to set directory to the script directory that contains this file.
> library(metrumrg)
> #command <- '/opt/NONMEM/nm72/nmqual/autolog.pl'
> cat.cov='SEX'
> cont.cov=c('HEIGHT','WEIGHT','AGE')
> par.list=c('CL','Q','KA','V','V2','V3')
> eta.list=paste('ETA',1:10,sep='')
```

### 2.2 Run NONMEM.

Listing 2:

```
> NONR72(
+   run=1001:1005,                # 5 models, ctl pre-written
+   #command=command,             # this version will search for NONMEM
+   project='../nonmem',          # must specify, unless ctl in getwd()
+   grid=TRUE,                    # set to FALSE for better error
+   messaging (but slower)
+   nice=TRUE,                    # don't delete subversioned
+   directories
+   checkrunno=FALSE,            # TRUE auto-replaces conflicting run
+   numbers
+   cont.cov=cont.cov,            # see help for following
+   cat.cov=cat.cov,
+   par.list=par.list,
+   eta.list=eta.list,
+   grp='SEX',                    # separate diagnostic plots for each
+   level of SEX
+   grpnames=c('female','male'), # use these instead of 0, 1, when
+   plotting by SEX
+   include.all=TRUE,             # also show diagnostics with groups
+   combined
+   plotfile='../nonmem/*/*.pdf', # use the run dir and run name for the
+   plot file
+   streams='../nonmem/ctl'       # expect the control streams here, not
+   locally
+ )
```

Installing SIGCHLD signal handler...Done.

Listing 3:

```
> progress(1001:1005,project='../nonmem')

      queued      compiled      running      done indeterminate
         0             0             0          5             0
```

Listing 4:

```
> follow(1001:1005,project='../nonmem')

      queued      compiled      running      done indeterminate
         0             0             0          5             0
```

Listing 5:

```
> Sys.sleep(10)                                #wait briefly to ensure all processes
  complete
```

Covariance succeeded on model 1005. We confirm that we can get similar results with different initial estimates.

Listing 6:

```
> getwd()

[1] "/data/metrumrg/inst/example/project/script"
```

Listing 7:

```
> ctl <- read.nmctl('../nonmem/1005/1005.ctl',parse=TRUE)
> names(ctl)

[1] "prob"      "input"      "data"      "subroutine" "pk"
[6] "error"     "theta"      "omega"     "sigma"      "estimation"
[11] "cov"       "table"      "table"
```

Listing 8:

```
> ctl$theta[] <- lapply(ctl$theta,`comment<-`,value=NULL)
> writeLines(format(ctl$theta))

;
(0,10,50)
(0,10,100)
(0,0.2,5)
(0,10,50)
(0,100,1000)
(0,1,2)
(0,0.75,3)
```

Listing 9:

```
> set.seed(0)
> ctl$theta <- tweak(ctl$theta)
> writeLines(format(ctl$theta))

;
(0,11.6,50)
(0,9.58,100)
(0,0.235,5)
(0,11.7,50)
(0,105,1000)
(0,0.8,2)
(0,0.659,3)
```

Listing 10:

```
> ctl$prob

[1] "1005 phasel 2 CMT like 1004 but diff. initial on V3"
```

Listing 11:

```
> ctl$prob <- '1006 like 1005 with tweaked initial estimates'
```

We request some variants of PRED and CWRES.

Listing 12:

```
> ctl[[12]]

[1] "NOPRINT FILE=./1005.tab ONEHEADER ID AMT TIME EVID PRED IPRE CWRES"
```

Listing 13:

```
> preds <- c('NPRED','CPRED','CPREDI','EPRED')
> res <- c('RES','NRES','NWRES','CRES','RESI','WRESI','CRESI','CWRESI','ERES','
  EWRES','ECWRES')
> ctl[[12]] <- c(ctl[[12]],preds, res)
```

Listing 14:

```
> write.nmctl(ctl,file='../nonmem/ctl/1006.ctl')
> NONR72(
+   run=1006,
+   project='../nonmem',
+   grid=TRUE,
+   nice=TRUE,
+   mode='para',                                # For illustrative purposes, we
parallelize this run.
+   pe='orte 16',                                # orte is the parallelization
environment; we use 16 cores.
+   checkrunno=TRUE,                             # default
```

```
+      diag=TRUE,                                # default
+      streams='../nonmem/ctl',                  # software will look for 1006.pmn or
+      template.pmn
+      plotfile='../nonmem/*/*.pdf'
+ )
> Sys.sleep(5)
> qstat()
> follow(1006,project='../nonmem')
```

queued	compiled	running	done	indeterminate
1	0	0	0	0
queued	compiled	running	done	indeterminate
0	1	0	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	0	1	0

Listing 15:

```
> Sys.sleep(10)
```

We can make a quick run log using some simple tools. Table 1.

Listing 16:

```
> # intentionally including a bogus run, to test effect
> # don't want the 'wide' file, just the 'long' R object
> log <- rlog(1001:1007,'../nonmem',file=NULL)
> head(log)
```

	tool	run	parameter	moment	value
1	nm7	1001	ofv	minimum	2526.39867230153
2	nm7	1001	THETA1	estimate	11.7167
3	nm7	1001	THETA1	prse	8.67

```
4 nm7 1001 THETA1 se 1.01628
5 nm7 1001 THETA2 estimate 14.5657
6 nm7 1001 THETA2 prse 8.67
```

Listing 17:

```
> tail(log)

      tool run parameter      moment      value
299 nm7 1006 SIGMA2.2      se      0.0676642
300 nm7 1006      cov      status      0
301 nm7 1006      prob      text 1006 like 1005 with tweaked initial estimates
302 nm7 1006      min      status      0
303 nm7 1006      data filename      ../../data/derived/phasel.csv
304 nm7 1007      min      status      -1
```

Listing 18:

```
> sapply(log,class)

      tool      run      parameter      moment      value
"character" "integer" "character" "character" "character"
```

Listing 19:

```
> log$tool <- NULL
> log <- log[log$run!=1007,]
> unique(log$parameter)

[1] "ofv"      "THETA1"    "THETA2"    "THETA3"    "OMEGA1.1" "OMEGA2.1"
[7] "OMEGA2.2" "OMEGA3.1" "OMEGA3.2" "OMEGA3.3" "SIGMA1.1" "SIGMA2.1"
[13] "SIGMA2.2" "cov"       "prob"      "min"       "data"      "THETA4"
[19] "THETA5"    "OMEGA4.1" "OMEGA4.2" "OMEGA4.3" "OMEGA4.4" "OMEGA5.1"
[25] "OMEGA5.2" "OMEGA5.3" "OMEGA5.4" "OMEGA5.5" "THETA6"    "THETA7"
```

Listing 20:

```
> log <- log[log$parameter %in% c('ofv','prob','cov','min'),]
> log
```

```
      run parameter      moment
1   1001      ofv minimum
38  1001      cov      status
39  1001      prob      text
40  1001      min      status
42  1002      ofv minimum
112 1002      cov      status
113 1002      prob      text
114 1002      min      status
116 1003      ofv minimum
153 1003      cov      status
154 1003      prob      text
```

```

155 1003      min  status
157 1004      ofv minimum
194 1004      cov  status
195 1004      prob  text
196 1004      min  status
198 1005      ofv minimum
247 1005      cov  status
248 1005      prob  text
249 1005      min  status
251 1006      ofv minimum
300 1006      cov  status
301 1006      prob  text
302 1006      min  status

                                     value
1                                     2526.39867230153
38                                     0
39                                     1001 phase1 1CMT
40                                     0
42                                     2525.96522290374
112                                    1
113                                     1002 phase1 2 CMT
114                                     134
116                                     2570.47417423427
153                                    1
154 1003 phase1 2 CMT like 1002 but no eta on Q/v3 and no + err
155                                     136
157                                     2570.45022641404
194                                     0
195          1004 phase1 2 CMT like 1003 but better bounds
196                                     0
198                                     2405.91626347113
247                                     0
248          1005 phase1 2 CMT like 1004 but diff. initial on V3
249                                     0
251                                     2405.91625875217
300                                     0
301          1006 like 1005 with tweaked initial estimates
302                                     0

```

#### Listing 21:

```
> with(log, constant(moment,within=parameter))#i.e., moment is non-informative
here.
```

```
[1] TRUE
```

#### Listing 22:

```
> log <- data.frame(cast(log,run ~ parameter))
> log <- shuffle(log,'prob','run')
> log$ofv <- signif(digits=6,as.numeric(as.character(log$ofv)))
```

Table 1: Run Log

run	prob	cov	min	ofv
1001	1001 phase1 1CMT	0	0	2526.40
1002	1002 phase1 2 CMT	1	134	2525.97
1003	1003 phase1 2 CMT like 1002 but no eta on Q/v3 and no + err	1	136	2570.47
1004	1004 phase1 2 CMT like 1003 but better bounds	0	0	2570.45
1005	1005 phase1 2 CMT like 1004 but diff. initial on V3	0	0	2405.92
1006	1006 like 1005 with tweaked initial estimates	0	0	2405.92

### 3 Predictive Check

#### 3.1 Create a simulation control stream.

Convert control stream to R object.

Listing 23:

```
> ctl <- read.nmctl('../nonmem/ctl/1005.ctl')
```

Strip comments and view.

Listing 24:

```
> ctl[] <- lapply(ctl,function(rec)sub(' *;.*',' ',rec))      # read control
  stream into a list
> ctl                                                         # print it like
  text

[1] "$PROB 1005 phase1 2 CMT like 1004 but diff. initial on V3"
[2] "$INPUT C ID TIME SEQ=DROP EVID AMT DV SUBJ HOUR TAFD TAD LDOS MDV HEIGHT WT
SEX AGE DOSE FED"
[3] "$DATA ../../data/derived/phase1.csv IGNORE=C"
[4] "$SUBROUTINE ADVAN4 TRANS4"
[5] "$PK"
[6] " CL=THETA(1)*EXP(ETA(1)) * THETA(6)**SEX * (WT/70)**THETA(7) "
[7] " V2 =THETA(2)*EXP(ETA(2)) "
[8] " KA=THETA(3)*EXP(ETA(3)) "
[9] " Q =THETA(4) "
[10] " V3=THETA(5) "
[11] " S2=V2 "
[12] " "
[13] "$ERROR"
[14] " Y=F*(1+ERR(1)) + ERR(2) "
[15] " IPRE=F"
[16] ""
[17] "$THETA"
[18] "(0,10,50) "
```



```
[19] "(0,10,100)"
[20] "(0,0.2, 5)"
[21] "(0,10,50)"
[22] "(0,100,1000)"
[23] "(0,1,2)"
[24] "(0,0.75,3)"
[25] ""
[26] "$OMEGA BLOCK(3)"
[27] ".1"
[28] ".01 .1"
[29] ".01 .01 .1"
[30] ""
[31] ""
[32] ""
[33] ""
[34] ""
[35] ""
[36] ""
[37] ""
[38] "$SIGMA 0.1 0.1"
[39] ""
[40] ""
[41] ""
[42] ""
[43] "$ESTIMATION MAXEVAL=9999 PRINT=5 NOABORT METHOD=1 INTER MSFO=./1005.msf"
[44] "$COV PRINT=E"
[45] "$TABLE NOPRINT FILE=./1005.tab ONEHEADER ID AMT TIME EVID PRED IPRE CWRES"
[46] "$TABLE NOPRINT FILE=./1005par.tab ONEHEADER ID TIME CL Q V2 V3 KA ETA1 ETA2
ETA3"
[47] ""
[48] ""
[49] ""
[50] ""
[51] ""
[52] ""
[53] ""
[54] ""
[55] ""
[56] ""
[57] ""
[58] ""
[59] ""
[60] ""
[61] ""
[62] ""
[63] ""
```

Fix records of interest.

Listing 25:

```
> ctl$prob                                     # problem
  statement
```

```
[1] "1005 phase1 2 CMT like 1004 but diff. initial on V3"
```

Listing 26:

```
> ctl$prob <- sub('1005','1105',ctl$prob)      # substitute new
  run number
> names(ctl)
```

```
[1] "prob"      "input"      "data"        "subroutine" "pk"
[6] "error"     "theta"      "omega"       "sigma"      "estimation"
[11] "cov"       "table"      "table"
```

Listing 27:

```
> names(ctl)[names(ctl)=='theta'] <- 'msfi'    # replace theta
  with final msfi
> ctl$msfi <- '../1005/1005.msf'
> ctl$omega <- NULL                            # drop omega,
  sigma
> ctl$sigma <- NULL
> names(ctl)[names(ctl)=='estimation'] <- 'simulation' # simulate
  instead of estimate
> ctl$simulation <- 'ONLYSIM (1968) SUBPROBLEMS=500'
> ctl$cov <- NULL                             # drop covariance
  step
> ctl$table <- NULL                            # replace
  multiple tables with one
> ctl$table <- NULL
> ctl$table <- 'DV NOHEADER NOPRINT FILE=../1105.tab FORWARD NOAPPEND' # only
  really need DV, save file space
> write.nmctl(ctl,'../nonmem/ctl/1105.ctl')
```

## 3.2 Run the simulation.

This run makes the predictions (simulations).

Listing 28:

```
> NONR72 (
+   run=1105,
+   #command=command,
+   project='../nonmem',
+   grid=TRUE,
+   nice=TRUE,
+   diag=FALSE,
```

```
+ streams='../nonmem/ctl'
+ )
> follow(1105,project='../nonmem')
```

queued	compiled	running	done	indeterminate
0	0	0	0	1
queued	compiled	running	done	indeterminate
0	1	0	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	1	0	0
queued	compiled	running	done	indeterminate
0	0	0	1	0

Listing 29:

```
> Sys.sleep(5) # let all processes complete
```

### 3.3 Combine the original data and the simulation data.

Now we fetch the results and integrate them with the other data.

Listing 30:

```
> x <- superset(
+ run=1105,
+ project='../nonmem',
+ read.output=list(read.table,header=FALSE)
+ )
> x <- x[,c('SUBJ','TIME','DV','V1','1105')]
> read.nmctl('../nonmem/1105/1105.ct1')$simulation
```

```
[1] "ONLYSIM (1968) SUBPROBLEMS=500"
```

Listing 31:

```
> x$SIM <- rep(1:500,each=nrow(x)/500)
> colname(x) <- c(V1='PRED')
> x <- x[x$`1105`==1,]
> x$`1105` <- NULL
> head(x)
```

	SUBJ	TIME	DV	PRED	SIM
2	1	0.00	.	0.00000	1
3	1	0.25	0.363	0.72558	1

```
4    1 0.50 0.914 1.38350 1
5    1 1.00 1.12 2.06760 1
6    1 2.00 2.28 3.48620 1
7    1 3.00 1.63 5.44660 1
```

Listing 32:

```
> nrow(x)
```

```
[1] 275000
```

Listing 33:

```
> str(x)
```

```
'data.frame': 275000 obs. of 5 variables:
 $ SUBJ: int 1 1 1 1 1 1 1 1 1 1 ...
 $ TIME: num 0 0.25 0.5 1 2 3 4 6 8 12 ...
 $ DV : chr "." "0.363" "0.914" "1.12" ...
 $ PRED: num 0 0.726 1.383 2.068 3.486 ...
 $ SIM : int 1 1 1 1 1 1 1 1 1 1 ...
```

Listing 34:

```
> x <- x[x$DV != '.',]
> x$DV <- as.numeric(x$DV)
```

## 3.4 Plot predictive checks.

### 3.4.1 Aggregate data within subject.

Since subjects may contribute differing numbers of observations, it may be useful to look at predictions from a subject-centric perspective. Therefore, we wish to calculate summary statistics for each subject, (observed and predicted) and then make obspred comparisons therewith.

Listing 35:

```
> head(x)
```

```
  SUBJ TIME    DV    PRED SIM
3    1 0.25 0.363 0.72558 1
4    1 0.50 0.914 1.38350 1
5    1 1.00 1.120 2.06760 1
6    1 2.00 2.280 3.48620 1
7    1 3.00 1.630 5.44660 1
8    1 4.00 2.040 2.99170 1
```

Listing 36:

```
> subject <- melt(x,measure.var=c('DV','PRED'))
> head(subject)
```

```

SUBJ TIME SIM variable value
1     1 0.25  1      DV 0.363
2     1 0.50  1      DV 0.914
3     1 1.00  1      DV 1.120
4     1 2.00  1      DV 2.280
5     1 3.00  1      DV 1.630
6     1 4.00  1      DV 2.040

```

We are going to aggregate each subject's DV and PRED values using `cast()`. `cast()` likes an aggregation function that returns a list. We write one that grabs min med max for each subject, sim, and variable.

Listing 37:

```
> metrics <- function(x) list(min=min(x), med=median(x), max=max(x))
```

Now we cast, ignoring time.

Listing 38:

```
> subject <- data.frame(cast(subject, SUBJ + SIM + variable ~ ., fun=metrics))
> head(subject)
```

```

SUBJ SIM variable      min      med      max
1     1  1      DV 0.363000 1.6100  3.0900
2     1  1     PRED 0.725580 3.4797  5.4466
3     1  2      DV 0.363000 1.6100  3.0900
4     1  2     PRED -0.085238 2.2940  4.6461
5     1  3      DV 0.363000 1.6100  3.0900
6     1  3     PRED -0.022438 4.8888 12.3760

```

Note that regardless of SIM, DV (observed) is constant.

Now we melt the metrics.

Listing 39:

```
> metr <- melt(subject, measure.var=c('min', 'med', 'max'), variable_name='metric')
> head(metr)
```

```

SUBJ SIM variable metric      value
1     1  1      DV     min 0.363000
2     1  1     PRED     min 0.725580
3     1  2      DV     min 0.363000
4     1  2     PRED     min -0.085238
5     1  3      DV     min 0.363000
6     1  3     PRED     min -0.022438

```

Listing 40:

```
> metr$value <- reapply(
+   metr$value,
+   INDEX=metr[,c('SIM', 'variable', 'metric')],
+   FUN=sort,
```

```
+      na.last=FALSE
+ )
> metr <- data.frame(cast(metr))
> head(metr)
```

	SUBJ	SIM	metric	DV	PRED
1	1	1	min	0.139	-0.615480
2	1	1	med	1.025	1.258600
3	1	1	max	2.530	2.176200
4	1	2	min	0.139	-0.351970
5	1	2	med	1.025	1.209335
6	1	2	max	2.530	2.424000

Listing 41:

```
> nrow(metr)
```

```
[1] 60000
```

Listing 42:

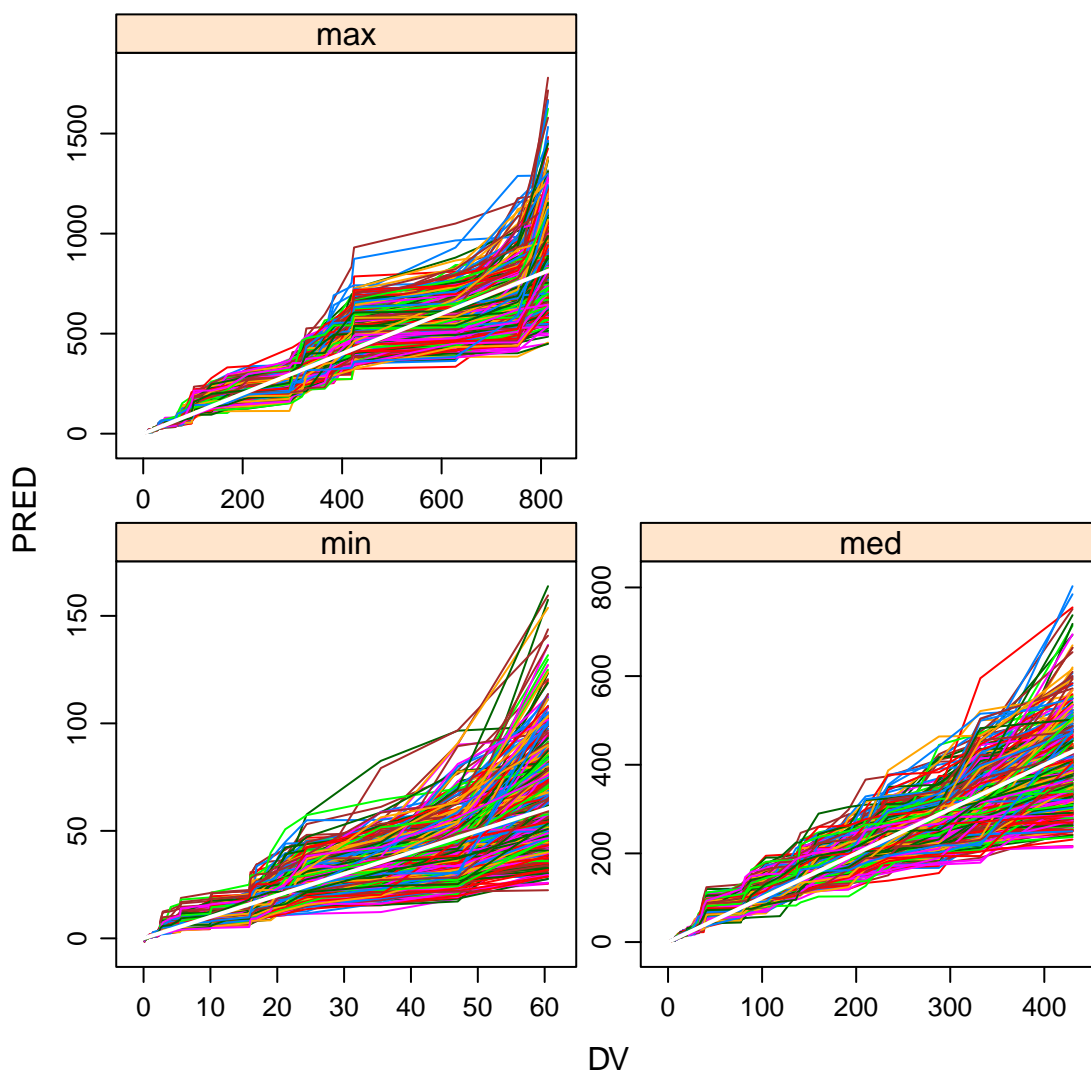
```
> metr <- metr[!is.na(metr$DV),]#maybe no NA
> nrow(metr)
```

```
[1] 60000
```

We plot using lattice.

Listing 43:

```
> print(
+   xyplot(
+     PRED ~ DV|metric,
+     metr,
+     groups=SIM,
+     scales=list(relation='free'),
+     type='l',
+     panel=function(...) {
+       panel.superpose(...)
+       panel.abline(0,1,col='white',lwd=2)
+     }
+   )
+ )
```



For detail, we show one endpoint, tossing the outer 5 percent of values, and indicating quartiles. Technically, though, one may want to calculate quartiles before trimming the data.

Listing 44:

```
> med <- metr[metr$metric=='med',]
> med$metric <- NULL
> head(med)
```

```
  SUBJ SIM  DV  PRED
2     1  1 1.025 1.258600
```

```
5      1    2 1.025 1.209335
8      1    3 1.025 1.579650
11     1    4 1.025 0.884860
14     1    5 1.025 1.658650
17     1    6 1.025 0.950105
```

Listing 45:

```
> trim <- inner(med, id.var=c('SIM'),measure.var=c('PRED','DV'))
> head(trim)
```

```
      SIM DV PRED
1      1 NA   NA
2      2 NA   NA
3      3 NA   NA
4      4 NA   NA
5      5 NA   NA
6      6 NA   NA
```

Listing 46:

```
> nrow(trim)
```

```
[1] 20000
```

Listing 47:

```
> trim <- trim[!is.na(trim$DV),]
> nrow(trim)
```

```
[1] 19000
```

Listing 48:

```
> head(trim)
```

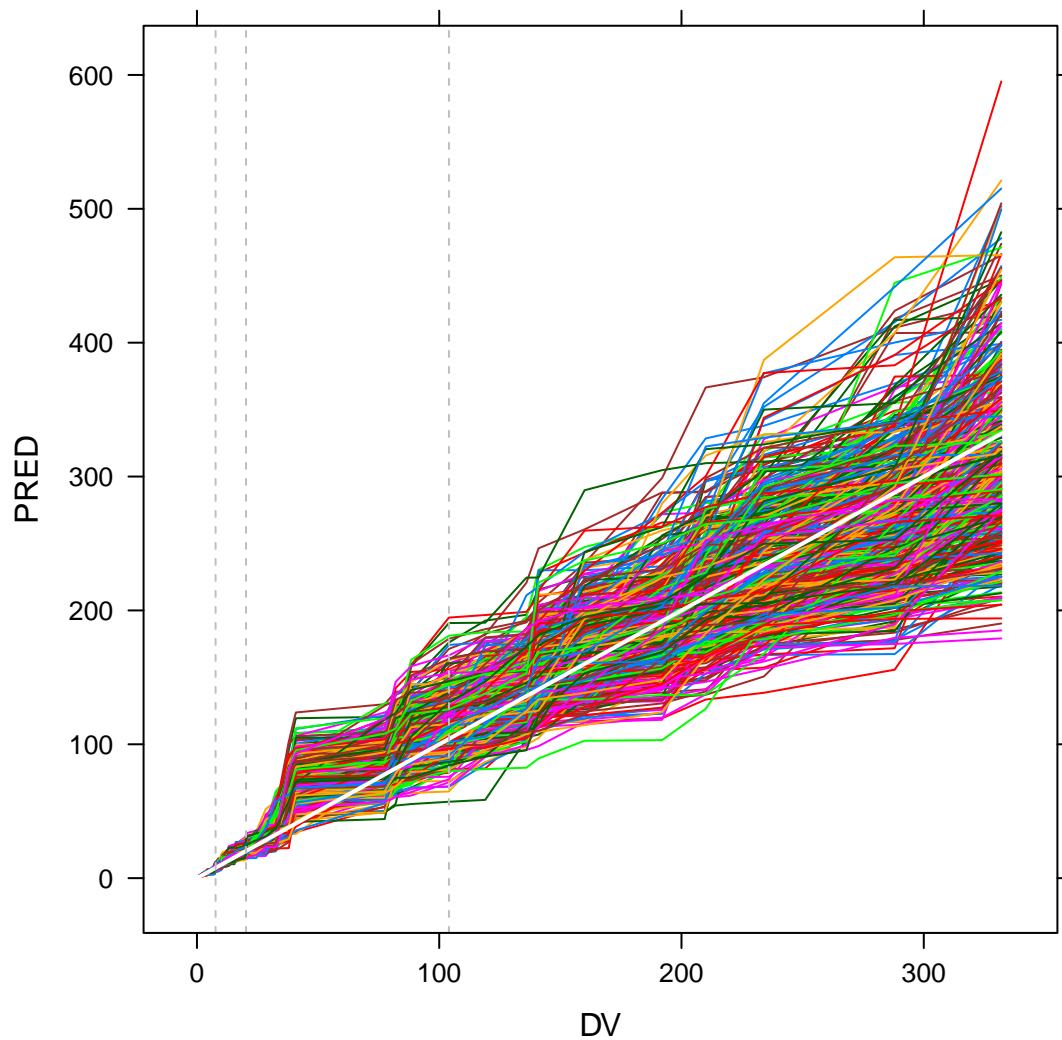
```
      SIM    DV    PRED
501    1 1.13 2.05870
502    2 1.13 2.00520
503    3 1.13 1.65485
504    4 1.13 1.06910
505    5 1.13 2.05965
506    6 1.13 0.98596
```

Listing 49:

```
> print(
+   xyplot(
+     PRED ~ DV,
+     trim,
+     groups=SIM,
+     type='l',
```



```
+         panel=function(x,y,...){  
+             panel.xyplot(x=x,y=y,...)  
+             panel.abline(0,1,col='white',lwd=2)  
+             panel.abline(  
+                 v=quantile(x,probs=c(0.25,0.5,0.75)),  
+                 col='grey',  
+                 lty=2  
+             )  
+         }  
+     )  
+ )
```



We also show densityplots of predictions at those quartiles.

Listing 50:

```
> head(trim)
```

	SIM	DV	PRED
501	1	1.13	2.05870
502	2	1.13	2.00520
503	3	1.13	1.65485
504	4	1.13	1.06910

```
505 5 1.13 2.05965
506 6 1.13 0.98596
```

Listing 51:

```
> quantile(trim$DV)

 0%    25%    50%    75%   100%
1.13   7.69  20.25 104.00 332.00
```

Listing 52:

```
> molt <- melt(trim, id.var='SIM')
> head(molt)

SIM variable value
1 1         DV  1.13
2 2         DV  1.13
3 3         DV  1.13
4 4         DV  1.13
5 5         DV  1.13
6 6         DV  1.13
```

Listing 53:

```
> quart <- data.frame(cast(molt, SIM+variable ~ ., fun=quantile, probs=c
  (0.25,0.5,0.75)))
> head(quart)

SIM variable    X25.    X50.    X75.
1 1         DV  7.95000 20.25000 100.1000
2 1        PRED 11.92750 22.16550 103.9625
3 2         DV  7.95000 20.25000 100.1000
4 2        PRED  7.23535 20.27100 105.2067
5 3         DV  7.95000 20.25000 100.1000
6 3        PRED  7.82700 14.50425  98.2655
```

Listing 54:

```
> molt <- melt(quart, id.var='variable', measure.var=c('X25.', 'X50.', 'X75.'),
  variable_name='quartile')
> head(molt)

variable quartile  value
1      DV      X25.  7.95000
2     PRED      X25. 11.92750
3      DV      X25.  7.95000
4     PRED      X25.  7.23535
5      DV      X25.  7.95000
6     PRED      X25.  7.82700
```

Listing 55:

```
> levels(molt$quartile)
```

```
[1] "X25." "X50." "X75."
```

Listing 56:

```
> levels(molt$quartile) <- c('first quartile','second quartile','third quartile')
> head(molt)
```

	variable	quartile	value
1	DV	first quartile	7.95000
2	PRED	first quartile	11.92750
3	DV	first quartile	7.95000
4	PRED	first quartile	7.23535
5	DV	first quartile	7.95000
6	PRED	first quartile	7.82700

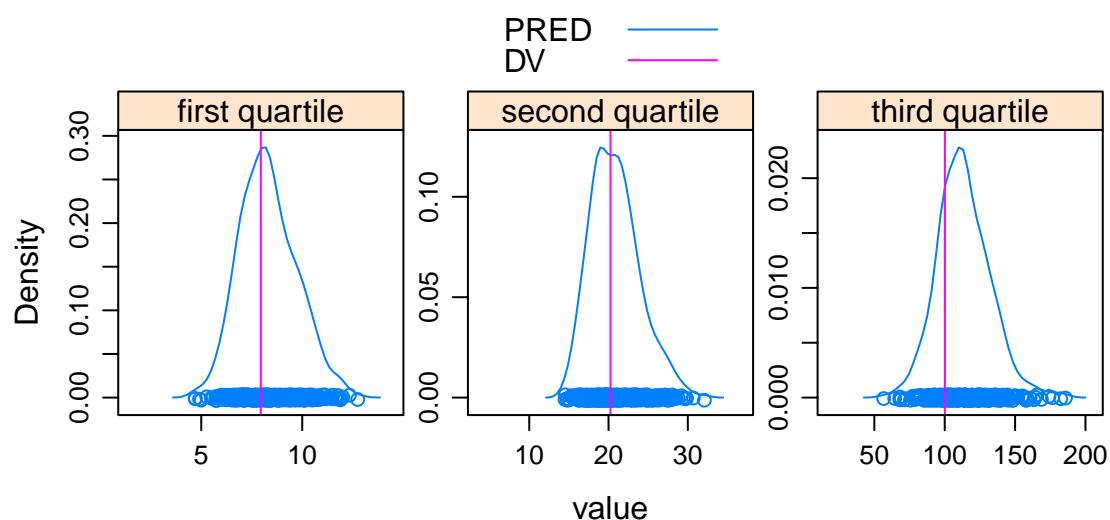
Listing 57:

```
> levels(molt$variable)
```

```
[1] "DV" "PRED"
```

Listing 58:

```
> molt$variable <- factor(molt$variable, levels=c('PRED', 'DV'))
> print(
+   densityplot(
+     ~ value|quartile,
+     molt,
+     groups=variable,
+     layout=c(3,1),
+     scales=list(relation='free'),
+     aspect=1,
+     panel=panel.superpose,
+     panel.groups=function(x,...,group.number){
+       if(group.number==1)panel.densityplot(x,...)
+       if(group.number==2)panel.abline(v=unique(x),...)
+     },
+     auto.key=TRUE
+   )
+ )
```



## 4 Bootstrap Estimates of Parameter Uncertainty

### 4.1 Create directories.

Listing 59:

```
> getwd()
```

```
[1] "/data/metrumrg/inst/example/project/script"
```

Listing 60:

```
> dir.create('../nonmem/1005boot')
> dir.create('../nonmem/1005bootdata')
> dir.create('../nonmem/1005bootctl')
```

## 4.2 Create replicate control streams.

Listing 61:

```
> ctl <- clear(readLines('../nonmem/ctl/1005.ctl'),';.+',fixed=FALSE)
> #ctl <- read.nmctl('../nonmem/1005/1005.ctl')
> ctl <- as.nmctl(ctl)
> names(ctl)
```

```
[1] "prob"      "input"      "data"      "subroutine" "pk"
[6] "error"     "theta"      "omega"     "sigma"      "estimation"
[11] "cov"       "table"      "table"
```

Listing 62:

```
> ctl$cov <- NULL
> ctl$table <- NULL
> ctl$theta <- NULL
> ctl$prob
```

```
[1] "1005 phase1 2 CMT like 1004 but diff. initial on V3"
```

Listing 63:

```
> ctl$data
```

```
[1] ".././data/derived/phase1.csv IGNORE=C"
```

Listing 64:

```
> #makes nice padded run directories like 001 instead of 1 (better directory
  sorting) to be used below
> RUN <- padded(1:300)
> invisible(
+   lapply(
+     RUN,
+     function(i,ctl){
+       ctl$prob <- sub('1005',i,ctl$prob)
+       ctl$data <- sub(
+         '.././data/derived/phase1.csv',
+         sub('\\*',i,'.././1005bootdata/*.csv'),
+         ctl$data
+       )
+       write.nmctl(ctl,file=glue('../nonmem/1005bootctl/',i,'.ctl'))
+     })
+ )
```

```
+ },
+   ctl=ctl
+ )
+ )
```

### 4.3 Create replicate data sets by resampling original.

Listing 65:

```
> bootset <- read.csv('../data/derived/phasel.csv')
> r <- resample(
+   bootset,
+   names=RUN,
+   key='ID',
+   rekey=TRUE,
+   out='../nonmem/1005bootdata',
+   stratify='SEX'
+ )
```

### 4.4 Run bootstrap models.

Listing 66:

```
> #intentionally trying a non-existent run ... 1 should be 001 per above.
> #Parentheses force display of invisible NONR result.
> (NONR72(
+   run=1,
+   wait=FALSE,
+   grid=TRUE,
+   project='../nonmem/1005boot',
+   streams='../nonmem/1005bootctl'
+ ))
```

```
[[1]]
[1] "../nonmem/1005bootctl/1.ct1 not found"
```

Listing 67:

```
> NONR72(
+   run=RUN,
+   wait=FALSE,
+   grid=TRUE,
+   project='../nonmem/1005boot',
+   streams='../nonmem/1005bootctl'
+ )
> qstat()
> follow(RUN,project='../nonmem/1005boot')
```

queued	compiled	running	done	indeterminate
156	46	17	81	0

queued	compiled	running	done	indeterminate
134	52	20	94	0
queued	compiled	running	done	indeterminate
119	49	20	112	0
queued	compiled	running	done	indeterminate
104	46	20	130	0
queued	compiled	running	done	indeterminate
88	41	25	146	0
queued	compiled	running	done	indeterminate
67	45	19	169	0
queued	compiled	running	done	indeterminate
41	53	19	187	0
queued	compiled	running	done	indeterminate
35	36	25	203	1
queued	compiled	running	done	indeterminate
9	38	26	226	1
queued	compiled	running	done	indeterminate
0	35	22	243	0
queued	compiled	running	done	indeterminate
0	15	15	270	0
queued	compiled	running	done	indeterminate
0	3	9	288	0
queued	compiled	running	done	indeterminate
0	0	1	299	0
queued	compiled	running	done	indeterminate
0	0	0	300	0

Listing 68:

```
> Sys.sleep(5)
> boot <- rlog(
+   run=RUN,
+   project='../nonmem/1005boot',
+   append=FALSE,
+   tool='nm7',
+   file=NULL
+ )
> write.csv(boot, '../nonmem/1005bootlog.csv')
```

## 5 File Disposition

Predictive checks and bootstraps make huge files that need not be retained.

Listing 69:

```
> unlink('../nonmem/1105',recursive=TRUE)
> unlink('../nonmem/1005boot',recursive=TRUE)
> unlink('../nonmem/1005bootdata',recursive=TRUE)
> unlink('../nonmem/1005bootctl',recursive=TRUE)
```