# 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
+      concurrent=FALSE,
+      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
+ )
> progress(1001:1005,project='../nonmem')
```

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

Listing 3:

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

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

Listing 4:

```
> 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 5:

```
> getwd()
```

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

Listing 6:

```
> 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 7:

```
> 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 8:

```
> 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 9:

```
> ctl$prob
```

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

Listing 10:

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

We request some variants of PRED and CWRES.

Listing 11:

```
> ctl[[12]]
```

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

Listing 12:

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

Listing 13:

```
> 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'
+ )
```

```
Installing SIGCHLD signal handler...Done.
```

Listing 14:

```
> Sys.sleep(5)
> qstat()
> follow(1006,project='../nonmem')
```

```
      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 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 2526.39867230031
2  nm7 1001    THETA1 estimate          11.7167
3  nm7 1001    THETA1     prse             8.67
```

```
4   nm7 1001    THETA1        se           1.01636
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                              0.0676156
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/phase1.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                                     2526.39867230031
38                                                     0
39                                    1001 phase1 1CMT
40                                                     0
```

```
42                                                2525.96526753388
112                                                              1
113                                              1002 phase1 2 CMT
114                                                            134
116                                               2569.89393760215
153                                                              1
154 1003 phase1 2 CMT like 1002 but no eta on Q/v3 and no + err
155                                                              0
157                                               2570.45022637547
194                                                              0
195              1004 phase1 2 CMT like 1003 but better bounds
196                                                              0
198                                               2405.91625845151
247                                                              0
248        1005 phase1 2 CMT like 1004 but diff. initial on V3
249                                                              0
251                                               2405.91625869758
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$ofv <- signif(as.numeric(as.character(log$ofv,6)))
```

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 | 0 | 2569.89 |
| 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
            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             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.ctl')$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 0.72542   1
4    1 0.50 0.914 1.38320   1
5    1 1.00  1.12 2.06720   1
6    1 2.00  2.28 3.48570   1
7    1 3.00  1.63 5.44600   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 0.725 1.383 2.067 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 0.72542   1
4    1 0.50 0.914 1.38320   1
5    1 1.00 1.120 2.06720   1
6    1 2.00 2.280 3.48570   1
7    1 3.00 1.630 5.44600   1
8    1 4.00 2.040 2.99140   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  0.725420 3.4795  5.4460
3    1   2       DV  0.363000 1.6100  3.0900
4    1   2     PRED -0.085238 2.2941  4.6468
5    1   3       DV  0.363000 1.6100  3.0900
6    1   3     PRED -0.022407 4.8896 12.3770
```

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  0.725420
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 -0.022407
```

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 -0.61537
2    1   1    med 1.025  1.25865
3    1   1    max 2.530  2.17620
4    1   2    min 0.139 -0.35196
5    1   2    med 1.025  1.20926
6    1   2    max 2.530  2.42390
```

Listing 41:

```
> nrow(metr)
```

```
[1] 60000
```

Listing 42:

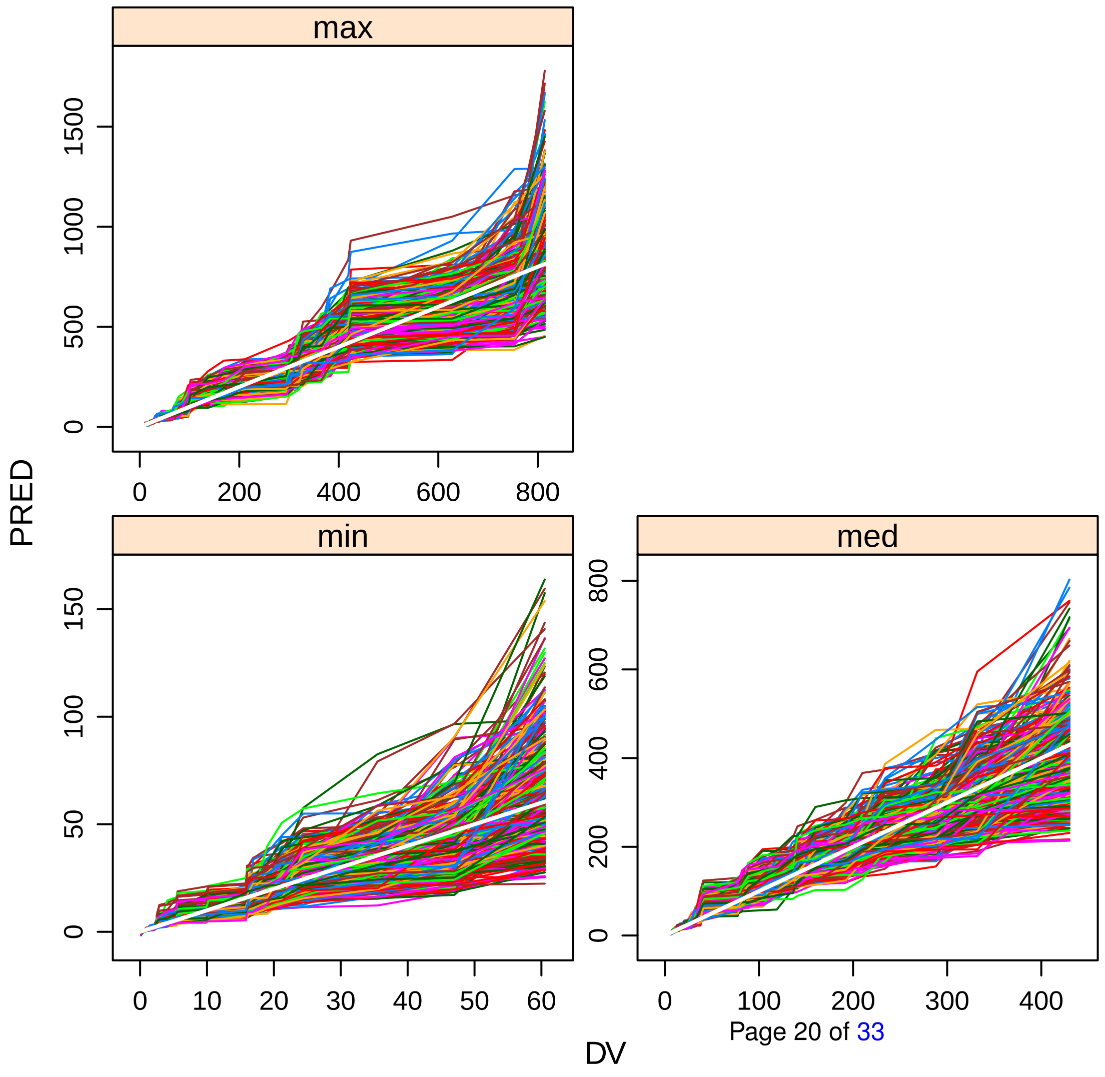
```
> metr <- metr[!is.na(metr$DV),]#maybe no NA
> nrow(metr)
```

```
[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)
+               }
+       )
+ )
```


max
min
med
PRED
DV
0
500
1000
1500
0
200
400
600
800
0
50
100
150
0
10
20
30
40
50
60
0
200
400
600
800
0
100
200
300
400

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

Listing 44:

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

```
   SUBJ SIM    DV    PRED
2     1   1 1.025 1.25865
5     1   2 1.025 1.20926
8     1   3 1.025 1.57990
11    1   4 1.025 0.88489
14    1   5 1.025 1.65875
17    1   6 1.025 0.95005
```

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
```

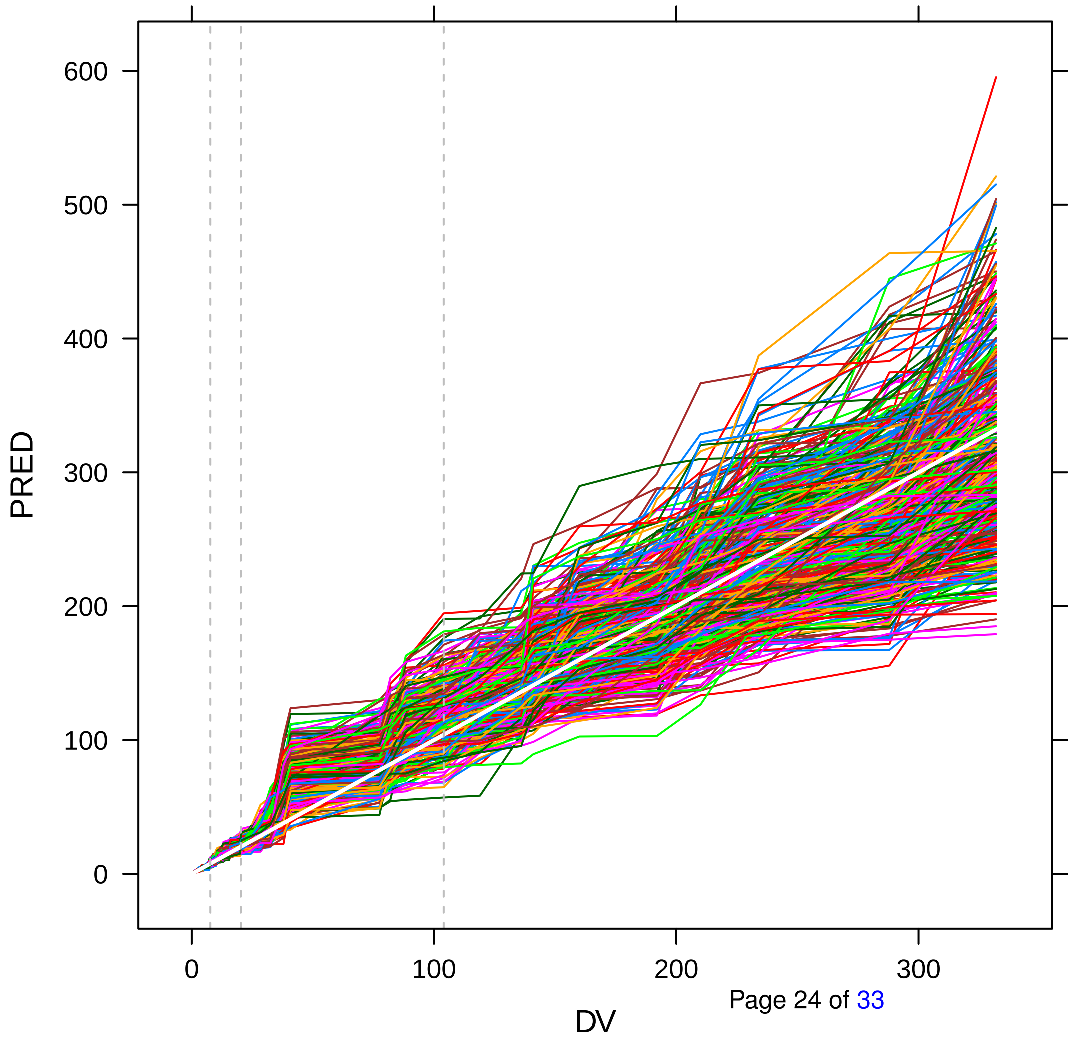
Listing 48:

```
> head(trim)
```

```
    SIM   DV    PRED
501   1 1.13 2.05880
502   2 1.13 2.00535
503   3 1.13 1.65480
504   4 1.13 1.06910
505   5 1.13 2.05960
506   6 1.13 0.98589
```

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
+                       )
+                              }
+               )
+  )
```


PRED
600
500
400
300
200
100
0
0
100
200
300
DV

We also show densityplots of predictions at those quartiles.

Listing 50:

```
> head(trim)
```

```
    SIM   DV    PRED
501   1 1.13 2.05880
502   2 1.13 2.00535
503   3 1.13 1.65480
504   4 1.13 1.06910
505   5 1.13 2.05960
506   6 1.13 0.98589
```

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 100.10000
2   1     PRED 11.92825 22.16750 103.96500
3   2       DV  7.95000 20.25000 100.10000
4   2     PRED  7.23495 20.27050 105.20875
5   3       DV  7.95000 20.25000 100.10000
6   3     PRED  7.82690 14.50425  98.27575
```

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. 11.92825
3       DV     X25.  7.95000
4     PRED     X25.  7.23495
5       DV     X25.  7.95000
6     PRED     X25.  7.82690
```

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 11.92825
3       DV first quartile  7.95000
4     PRED first quartile  7.23495
5       DV first quartile  7.95000
6     PRED first quartile  7.82690
```

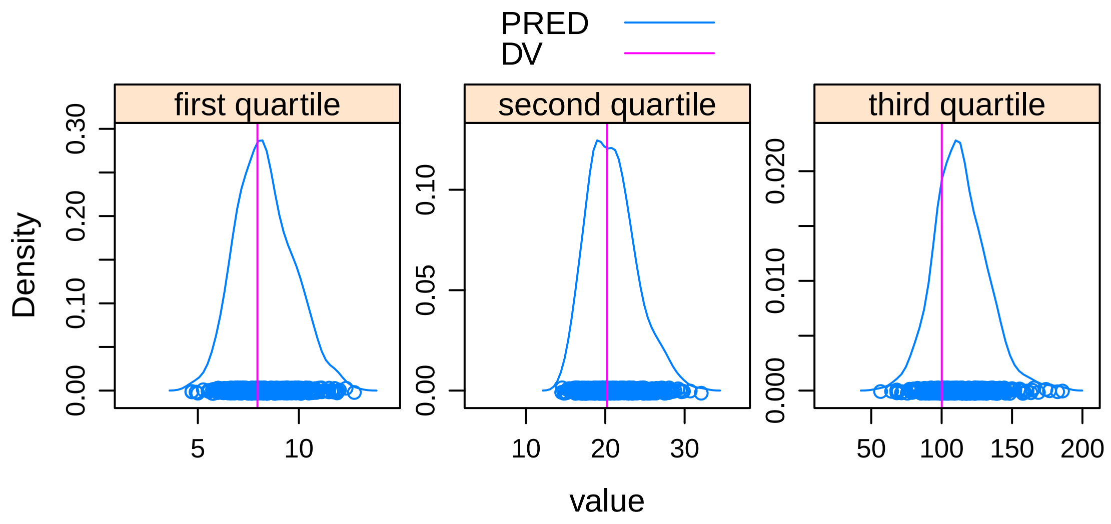
Listing 57:

```
> 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
+       )
+ )
```


PRED
DV
first quartile
second quartile
third quartile
Density
value
0.00
0.10
0.20
0.30
0.00
0.05
0.10
0.000
0.010
0.020
5
10
10
20
30
50
100
150
200

## 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$table <- NULL
> ctl$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/phase1.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.ctl 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
          112            52            22           114             0
       queued      compiled       running          done indeterminate
          104            33            33           130             0
       queued      compiled       running          done indeterminate
           79            33            29           159             0
       queued      compiled       running          done indeterminate
           53            50            13           184             0
       queued      compiled       running          done indeterminate
           35            58            15           192             0
       queued      compiled       running          done indeterminate
           25            41            28           205             1
       queued      compiled       running          done indeterminate
           10            26            38           226             0
       queued      compiled       running          done indeterminate
            0            19            22           259             0
       queued      compiled       running          done indeterminate
            0             0            17           283             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)
```