Modeling

September 27, 2012

Tim Bergsma

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
            5             0             0             0             0
```

Listing 4:

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

       queued      compiled       running          done indeterminate
            5             0             0             0             0
       queued      compiled       running          done indeterminate
            0             3             2             0             0
       queued      compiled       running          done indeterminate
            0             0             4             1             0
       queued      compiled       running          done indeterminate
            0             0             2             3             0
       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 phase1 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
           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             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
            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.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:

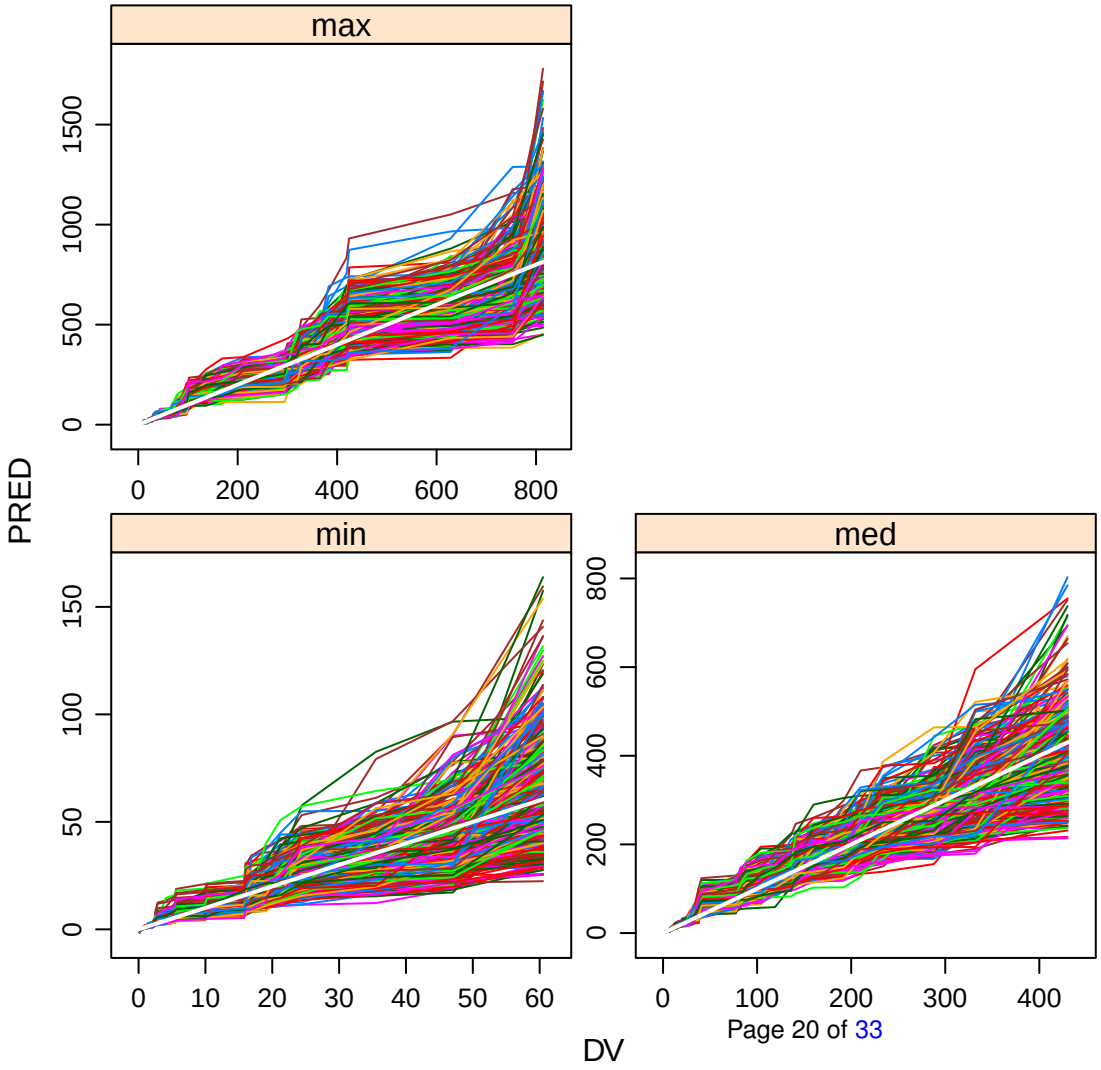
```
> metr <- metr[!is.na(metr$DV),]#maybe no NA
> nrow(metr)
```

```
[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
200
400
600
800
50
100
150
10
20
30
40
50
60
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:

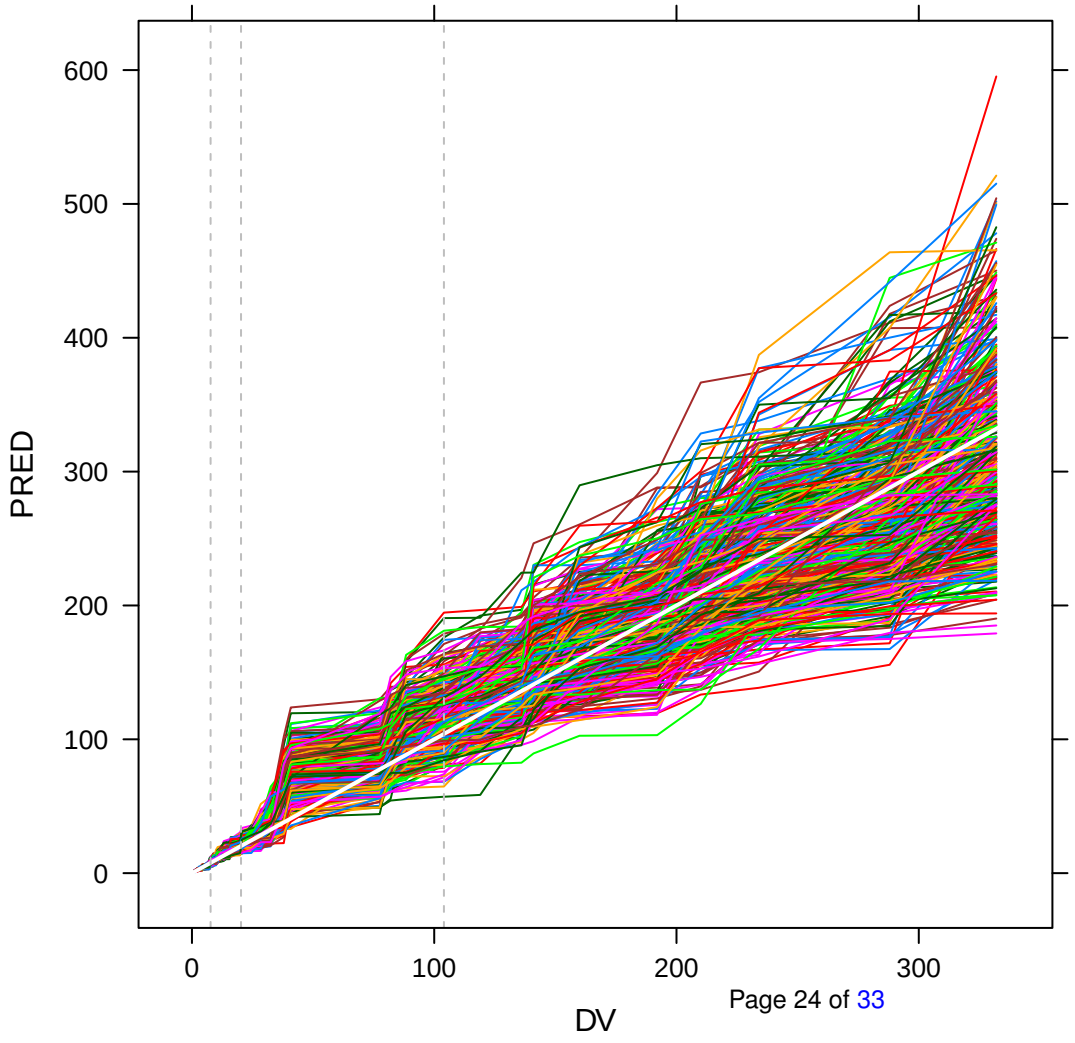
```
> head(trim)

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

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
```

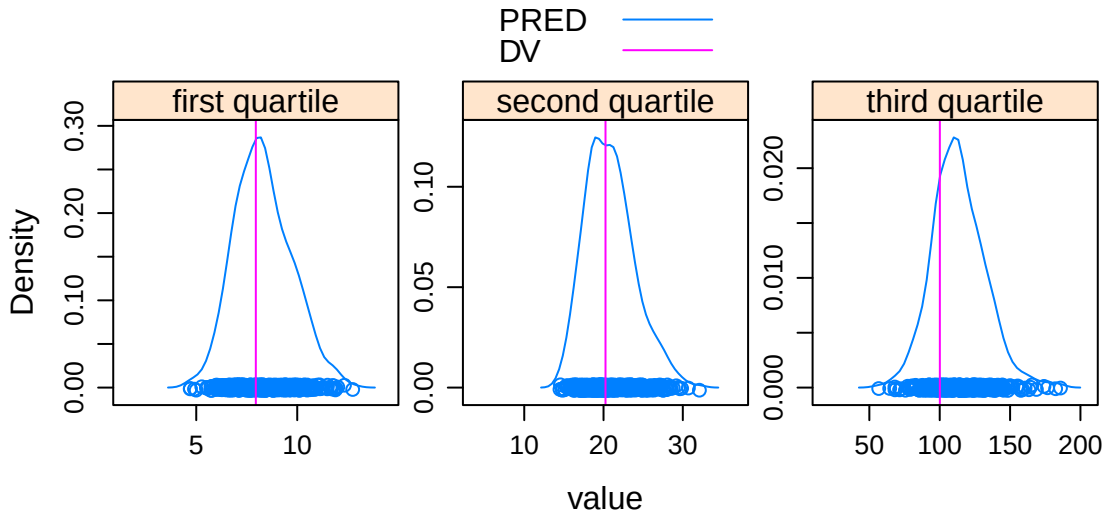
Listing 57:

```
> 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
0.00
0.10
0.20
0.30
0.05
0.020
0.010
0.000
5
10
20
30
50
100
150
200
value

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
         114            42            28           116             0
      queued      compiled       running          done indeterminate
          92            47            18           143             0
      queued      compiled       running          done indeterminate
          75            40            32           153             0
      queued      compiled       running          done indeterminate
          53            45            18           183             1
      queued      compiled       running          done indeterminate
          30            53            19           198             0
      queued      compiled       running          done indeterminate
          18            43            23           215             1
      queued      compiled       running          done indeterminate
           0            39            24           237             0
      queued      compiled       running          done indeterminate
           0            14            26           260             0
      queued      compiled       running          done indeterminate
           0             2             7           291             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)
```