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:

```
> library(metrumrg)

metrumrg 5.4
enter "?metrumrg" for help
```

Listing 2:

```
> 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 3:

```
> NONR72(
+      run=1001:1005,
+      command=command,
+      project='../nonmem',
+       grid=FALSE,
+       nice=TRUE,
+       checkrunno=FALSE,
+       cont.cov=cont.cov,
+       cat.cov=cat.cov,
+       par.list=par.list,
+       eta.list=eta.list,
+       plotfile='../nonmem/*/diagnostics.pdf',
+       streams='../nonmem/ctl',
+       checksum=FALSE
+ )
```

Covariance succeeded on model 1005. We can make a quick run log using some simple tools. Table 1.

Listing 4:

```
> log <- rlog(1001:1005,'../nonmem',tool='nm7')
> 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 5:

```
> tail(log)
```

```
    tool  run parameter   moment
245  nm7 1005  SIGMA2.2     prse
246  nm7 1005  SIGMA2.2       se
247  nm7 1005       cov   status
```

```
248  nm7 1005       prob     text
249  nm7 1005        min   status
250  nm7 1005       data filename
                                                  value
245                                                33.5
246                                           0.0676412
247                                                   0
248 1005 phase1 2 CMT like 1004 but diff. initial on V3
249                                                   0
250                          ../../data/derived/phase1.csv
```

Listing 6:

```
> sapply(log,class)
```

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

Listing 7:

```
> log$tool <- NULL
> unique(log$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 8:

```
> 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
                                                               value
1                                                   2526.39867230031
38                                                                 0
39                                                  1001 phase1 1CMT
40                                                                 0
42                                                  2525.96526753388
112                                                                1
113                                                1002 phase1 2 CMT
114                                                                1
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
```

Listing 9:

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

```
[1] TRUE
```

Listing 10:

```
> 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	1	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

3 Predictive Check

3.1 Create a simulation control stream.

Convert control stream to R object.

Listing 11:

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

Strip comments and view.

Listing 12:

```
> ctl[] <- lapply(ctl,function(rec)sub(' *;.*','',rec))
> ctl
```

```
 [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 13:

```
> ctl$prob
```

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

Listing 14:

```
> ctl$prob <- sub('1005','1105',ctl$prob)
> names(ctl)
```

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

Listing 15:

```
> names(ctl)[names(ctl)=='theta'] <- 'msfi'
> ctl$msfi <- '=../1005/1005.msf'
> ctl$omega <- NULL
> ctl$sigma <- NULL
> names(ctl)[names(ctl)=='estimation'] <- 'simulation'
> ctl$simulation <- 'ONLYSIM (1968) SUBPROBLEMS=500'
> ctl$cov <- NULL
> ctl$table <- NULL
> ctl$table <- NULL
> ctl$table <- 'DV NOHEADER NOPRINT FILE=./1105.tab FORWARD NOAPPEND'
> write.nmctl(ctl,'../nonmem/ctl/1105.ctl')
```

3.2 Run the simulation.

This run makes the predictions (simulations).

Listing 16:

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

3.3 Recover and format the original dataset.

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

Listing 17:

```
> phase1 <- read.csv('../data/derived/phase1.csv',na.strings='.')
> head(phase1)
```

```
     C ID TIME SEQ EVID  AMT    DV SUBJ HOUR TAFD  TAD LDOS MDV HEIGHT WEIGHT
1    C  1 0.00   0    0   NA 0.000    1 0.00 0.00   NA   NA   0    174   74.2
2 <NA>  1 0.00   1    1 1000    NA    1 0.00 0.00 0.00 1000   1    174   74.2
3 <NA>  1 0.25   0    0   NA 0.363    1 0.25 0.25 0.25 1000   0    174   74.2
4 <NA>  1 0.50   0    0   NA 0.914    1 0.50 0.50 0.50 1000   0    174   74.2
5 <NA>  1 1.00   0    0   NA 1.120    1 1.00 1.00 1.00 1000   0    174   74.2
6 <NA>  1 2.00   0    0   NA 2.280    1 2.00 2.00 2.00 1000   0    174   74.2
  SEX  AGE DOSE FED SMK DS CRCN predose zerodv
1   0 29.1 1000   1   0  0 83.5       1      0
2   0 29.1 1000   1   0  0 83.5       0      0
3   0 29.1 1000   1   0  0 83.5       0      0
4   0 29.1 1000   1   0  0 83.5       0      0
5   0 29.1 1000   1   0  0 83.5       0      0
6   0 29.1 1000   1   0  0 83.5       0      0
```

Listing 18:

```
> phase1 <- phase1[is.na(phase1$C),c('SUBJ','TIME','DV')]
> records <- nrow(phase1)
> records
```

```
[1] 550
```

Listing 19:

```
> phase1 <- phase1[rep(1:records,500),]
> nrow(phase1)
```

```
[1] 275000
```

Listing 20:

```
> phase1$SIM <- rep(1:500,each=records)
> #head(phase1,300)
> with(phase1,DV[SIM==1 & SUBJ==12])
```

```
 [1]     NA  2.260  2.830  8.730 19.300 15.200 16.200  8.830 12.900 12.700
[11]  7.140  5.740  1.980  0.791
```

Listing 21:

```
> with(phase1,DV[SIM==2 & SUBJ==12])
```

```
 [1]     NA  2.260  2.830  8.730 19.300 15.200 16.200  8.830 12.900 12.700
[11]  7.140  5.740  1.980  0.791
```

3.4 Recover and format the simulation results.

Listing 22:

```
> pred <- scan('../nonmem/1105/1105.tab')
> nrow(phase1)
```

```
[1] 275000
```

Listing 23:

```
> length(pred)
```

```
[1] 275000
```

3.5 Combine the original data and the simulation data.

Listing 24:

```
> phase1$PRED <- pred
> head(phase1)
```

```
  SUBJ TIME    DV SIM    PRED
2    1 0.00    NA   1 0.00000
3    1 0.25 0.363   1 0.72542
4    1 0.50 0.914   1 1.38320
5    1 1.00 1.120   1 2.06720
6    1 2.00 2.280   1 3.48570
7    1 3.00 1.630   1 5.44600
```

Listing 25:

```
> phase1 <- phase1[!is.na(phase1$DV),]
> head(phase1)
```

```
  SUBJ TIME    DV SIM    PRED
3    1 0.25 0.363   1 0.72542
4    1 0.50 0.914   1 1.38320
5    1 1.00 1.120   1 2.06720
6    1 2.00 2.280   1 3.48570
7    1 3.00 1.630   1 5.44600
8    1 4.00 2.040   1 2.99140
```

3.6 Plot predictive checks.

3.6.1 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 26:

```
> head(phase1)
```

```
  SUBJ TIME    DV SIM    PRED
3    1 0.25 0.363   1 0.72542
4    1 0.50 0.914   1 1.38320
5    1 1.00 1.120   1 2.06720
6    1 2.00 2.280   1 3.48570
7    1 3.00 1.630   1 5.44600
8    1 4.00 2.040   1 2.99140
```

Listing 27:

```
> subject <- melt(phase1,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 28:

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

Now we cast, ignoring time.

Listing 29:

```
> 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 30:

```
> 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 31:

```
> 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 32:

```
> nrow(metr)
```

```
[1] 60000
```

Listing 33:

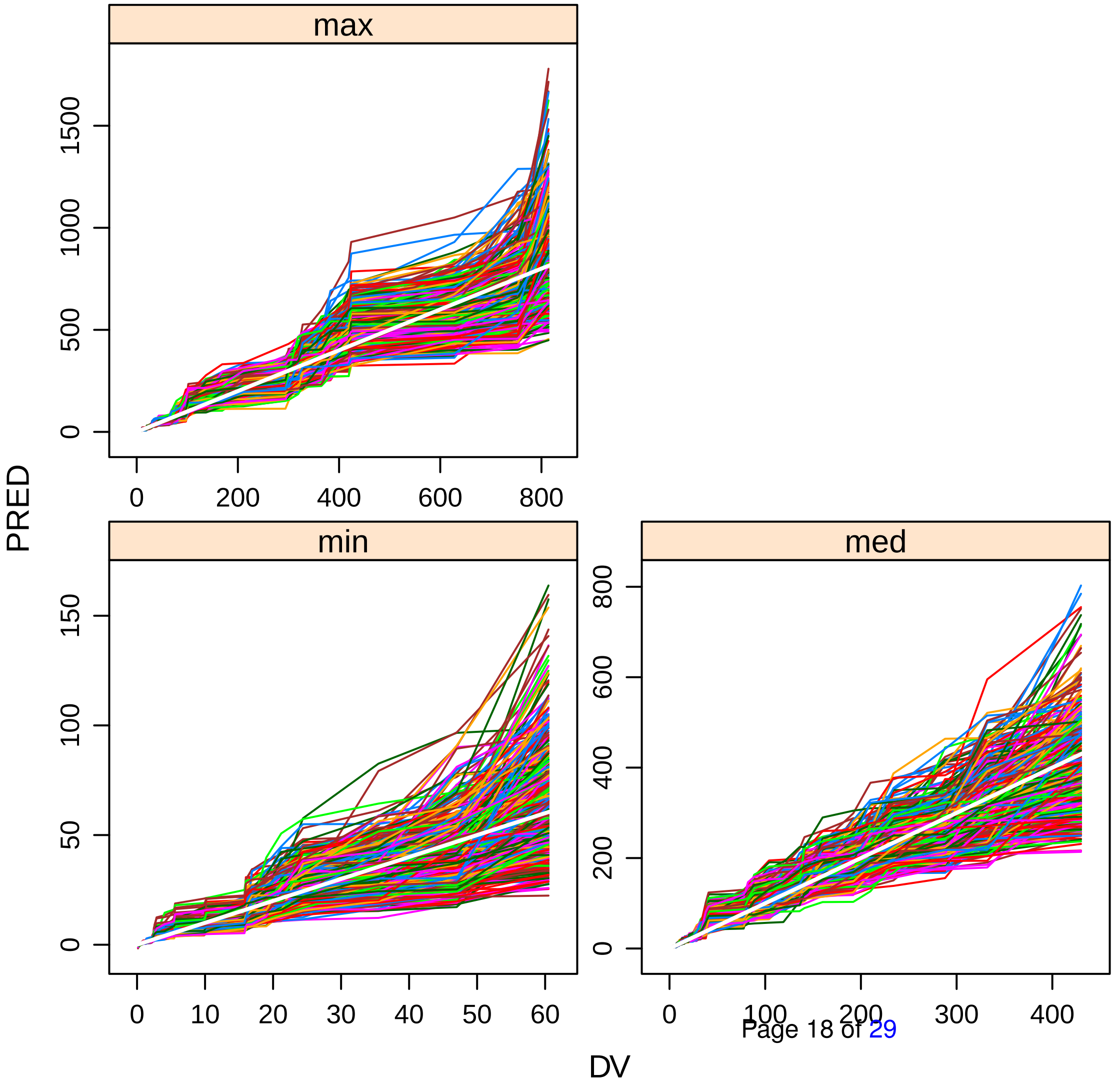
```
> metr <- metr[!is.na(metr$DV),]#maybe no NA
> nrow(metr)
```

```
[1] 60000
```

We plot using lattice.

Listing 34:

```
> 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.

Listing 35:

```
> 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 36:

```
> 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 37:

```
> nrow(trim)
```

```
[1] 20000
```

Listing 38:

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

```
[1] 19000
```

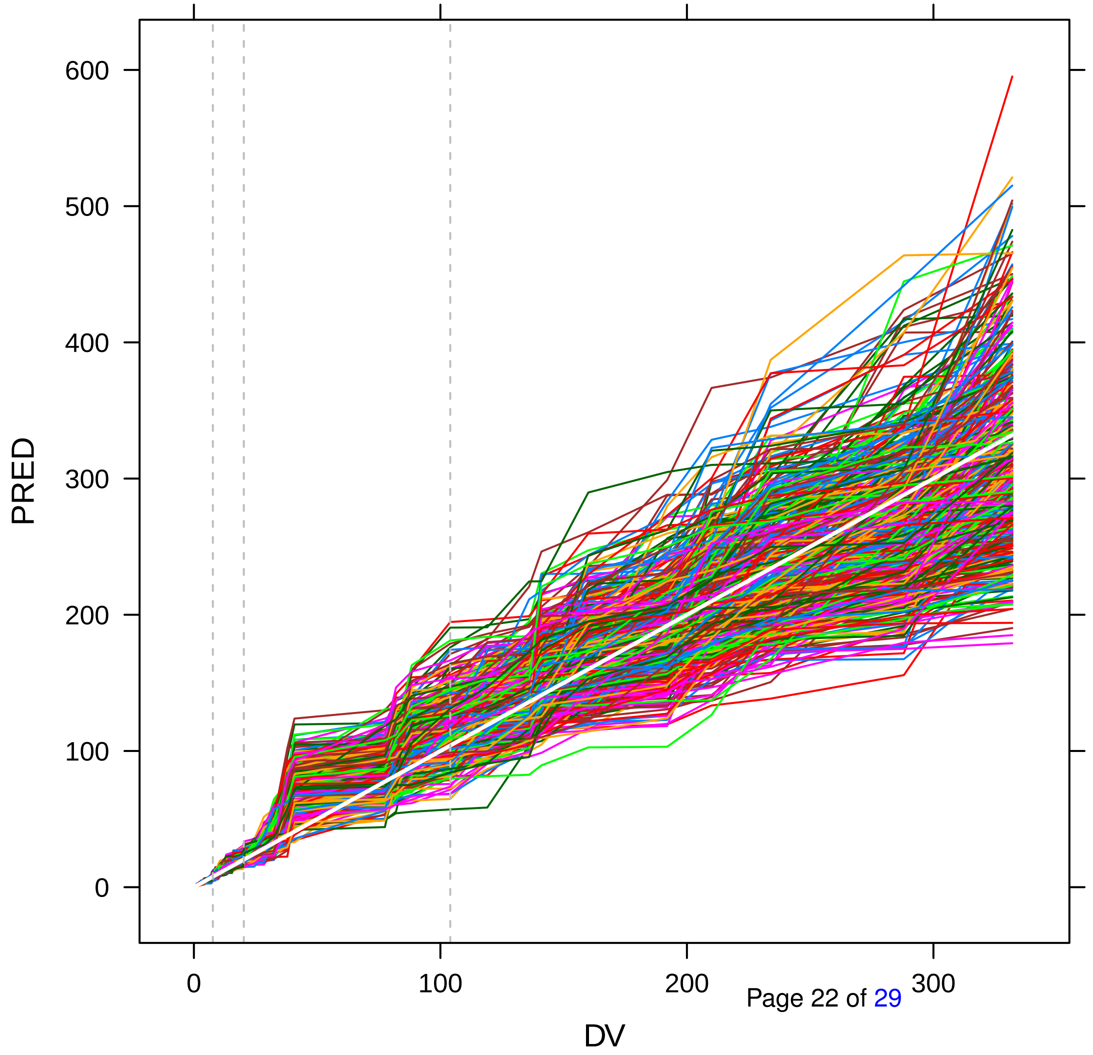
Listing 39:

```
> 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 40:

```
> print(
+       xplot(
+               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
600
500
400
300
200
100
0
0
100
200
300

We also show densityplots of predictions at those quartiles.

Listing 41:

```
> 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 42:

```
> quantile(trim$DV)
```

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

Listing 43:

```
> 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 44:

```
> 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 45:

```
> 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 46:

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

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

Listing 47:

```
> 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
```

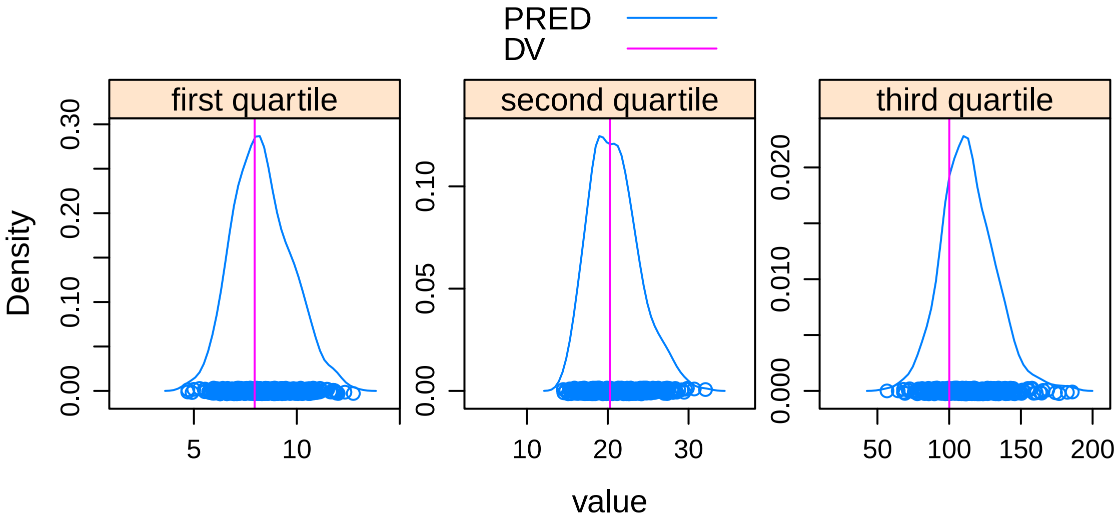
Listing 48:

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

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

Listing 49:

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

4 Bootstrap Estimates of Parameter Uncertainty

4.1 Create directories.

Listing 50:

```
> getwd()

[1] "/data/metsvn/wiki/inst/sample/script"
```

Listing 51:

```
> dir.create('../nonmem/1005.boot')
> dir.create('../nonmem/1005.boot/data')
> dir.create('../nonmem/1005.boot/ctl')
```

4.2 Create replicate control streams.

Listing 52:

```
> t <- metaSub(
+       clear(readLines('../nonmem/ctl/1005.ctl'),';.+',fixed=FALSE),
+       names=1:300,
+       pattern=c(
+           '1005',
+           '../../data/derived/phase1.csv',
+           '$COV',
+           '$TABLE'
+       ),
+       replacement=c(
+           '*',
+           '../data/*.csv',
+           ';$COV',
+           ';$TABLE'
+     ),
+     fixed=TRUE,
+     out='../nonmem/1005.boot/ctl',
+     suffix='.ctl'
+   )
```

4.3 Create replicate data sets by resampling original.

Listing 53:

```
>  bootset <- read.csv('../data/derived/phase1.csv')
>  r <- resample(
+       bootset,
+       names=1:300,
+       key='ID',
+       rekey=TRUE,
+       out='../nonmem/1005.boot/data',
+       stratify='SEX'
+   )
```

4.4 Run bootstrap models.

Listing 54:

```
> NONR72(
+       run=1:300,
+       command=command,
+       project='../nonmem/1005.boot/',
+       boot=TRUE,
+       nice=TRUE,
+       grid=TRUE,
+       #concurrent=TRUE,
+       streams='../nonmem/1005.boot/ctl',
+       checksum=FALSE
+ )
```

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

Listing 55:

```
> nms <- paste('../nonmem/1005.boot/',1:300,'.boot/',1:300,'.log.xml',sep='')
> while(!(all(file.exists(nms))))Sys.sleep(10)
> boot <- rlog(
+       run=1:300,
+       project='../nonmem/1005.boot',
+       boot=TRUE,
+       append=FALSE,
+       tool='nm7'
+ )
> write.csv(boot, '../nonmem/1005.boot/log.csv')
```