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:

```
> getwd()
```

```
[1] "/home/timb/metrumrg/inst/sample/script"
```

Listing 2:

```
> library(metrumrg)
```

```
metrumrg 5.0
```

Listing 3:

```
> 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 4:

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

```
[1] "/home/timb/metrumrg/inst/sample/script"
```

Covariance succeeded on model 1005.

3 Predictive Check

3.1 Create a simulation control stream.

Convert control stream to R object.

Listing 5:

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

Strip comments and view.

Listing 6:

```
> 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*EXP(ERR(1))"
[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 0.09 0.09 0.09"
[27] ""
[28] ""
[29] ""
[30] ""
```

```
[31] ""
[32] "$SIGMA 0.09"
[33] ""
[34] ""
[35] ""
[36] "$ESTIMATION MAXEVAL=9999 PRINT=5 NOABORT METHOD=1 INTER MSFO=./1005.msf"
[37] "$COV PRINT=E"
[38] "$TABLE NOPRINT FILE=./1005.tab ONEHEADER ID AMT TIME EVID PRED IPRE CWRES"
[39] "$TABLE NOPRINT FILE=./1005par.tab ONEHEADER ID TIME CL Q V2 V3 KA ETA1 ETA2 ETA3"
[40] ""
[41] ""
[42] ""
[43] ""
[44] ""
[45] ""
[46] ""
[47] ""
[48] ""
[49] ""
[50] ""
[51] ""
[52] ""
```

Fix records of interest.

Listing 7:

```
> ctl$prob
```

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

Listing 8:

```
> 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 9:

```
> 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 10:

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

```
+ )
> getwd()
```

```
[1] "/home/timb/metrumrg/inst/sample/script"
```

3.3 Recover and format the original dataset.

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

Listing 11:

```
> 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 12:

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

```
[1] 550
```

Listing 13:

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

```
[1] 275000
```

Listing 14:

```
> 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 15:

```
> 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 16:

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

```
[1] 275000
```

Listing 17:

```
> length(pred)

[1] 275000
```

3.5 Combine the original data and the simulation data.

Listing 18:

```
> 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 0.17932
4    1 0.50 0.914   1 0.53642
5    1 1.00 1.120   1 0.78983
6    1 2.00 2.280   1 1.84990
7    1 3.00 1.630   1 1.96530
```

Listing 19:

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

  SUBJ TIME    DV SIM    PRED
3    1 0.25 0.363   1 0.17932
4    1 0.50 0.914   1 0.53642
5    1 1.00 1.120   1 0.78983
6    1 2.00 2.280   1 1.84990
7    1 3.00 1.630   1 1.96530
8    1 4.00 2.040   1 2.01810
```

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 20:

```
> head(phase1)
```

```
  SUBJ TIME    DV SIM    PRED
3    1 0.25 0.363   1 0.17932
4    1 0.50 0.914   1 0.53642
5    1 1.00 1.120   1 0.78983
6    1 2.00 2.280   1 1.84990
7    1 3.00 1.630   1 1.96530
8    1 4.00 2.040   1 2.01810
```

Listing 21:

```
> 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 22:

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

Now we cast, ignoring time.

Listing 23:

```
> 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 0.179320 1.9653 5.0314
3    1   2       DV 0.363000 1.6100 3.0900
4    1   2     PRED 0.096462 3.0448 7.4728
5    1   3       DV 0.363000 1.6100 3.0900
6    1   3     PRED 0.450430 5.5284 8.7665
```

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

Now we melt the metrics.

Listing 24:

```
> 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 0.179320
3    1   2       DV    min 0.363000
4    1   2     PRED    min 0.096462
5    1   3       DV    min 0.363000
6    1   3     PRED    min 0.450430
```

Listing 25:

```
> 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 0.064213
2    1   1    med 1.025 1.943600
3    1   1    max 2.530 3.945400
4    1   2    min 0.139 0.016162
5    1   2    med 1.025 1.476300
6    1   2    max 2.530 3.463200
```

Listing 26:

```
> nrow(metr)
```

```
[1] 60000
```

Listing 27:

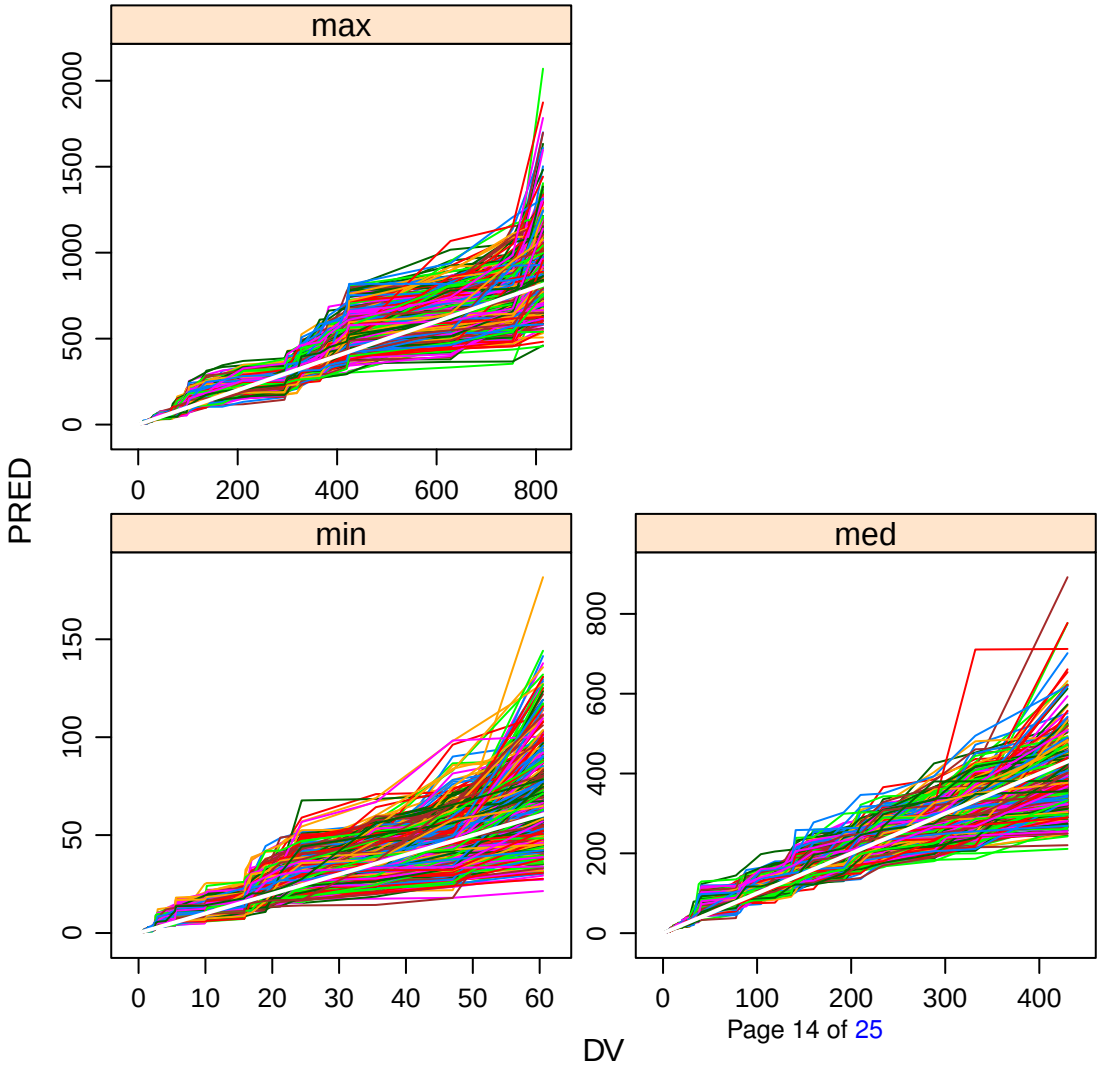
```
> metr <- metr[!is.na(metr$DV),]#maybe no NA
> nrow(metr)
```

```
[1] 60000
```

We plot using lattice.

Listing 28:

```
> 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
2000
200
400
600
800
150
100
50
10
20
30
40
60
100
300

For detail, we show one endpoint, tossing the outer 5 percent of values, and indicating quartiles.

Listing 29:

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

```
   SUBJ SIM    DV     PRED
2     1   1 1.025 1.943600
5     1   2 1.025 1.476300
8     1   3 1.025 1.466300
11    1   4 1.025 1.342400
14    1   5 1.025 1.362350
17    1   6 1.025 0.625815
```

Listing 30:

```
> 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 31:

```
> nrow(trim)
```

```
[1] 20000
```

Listing 32:

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

[1] 19000
```

Listing 33:

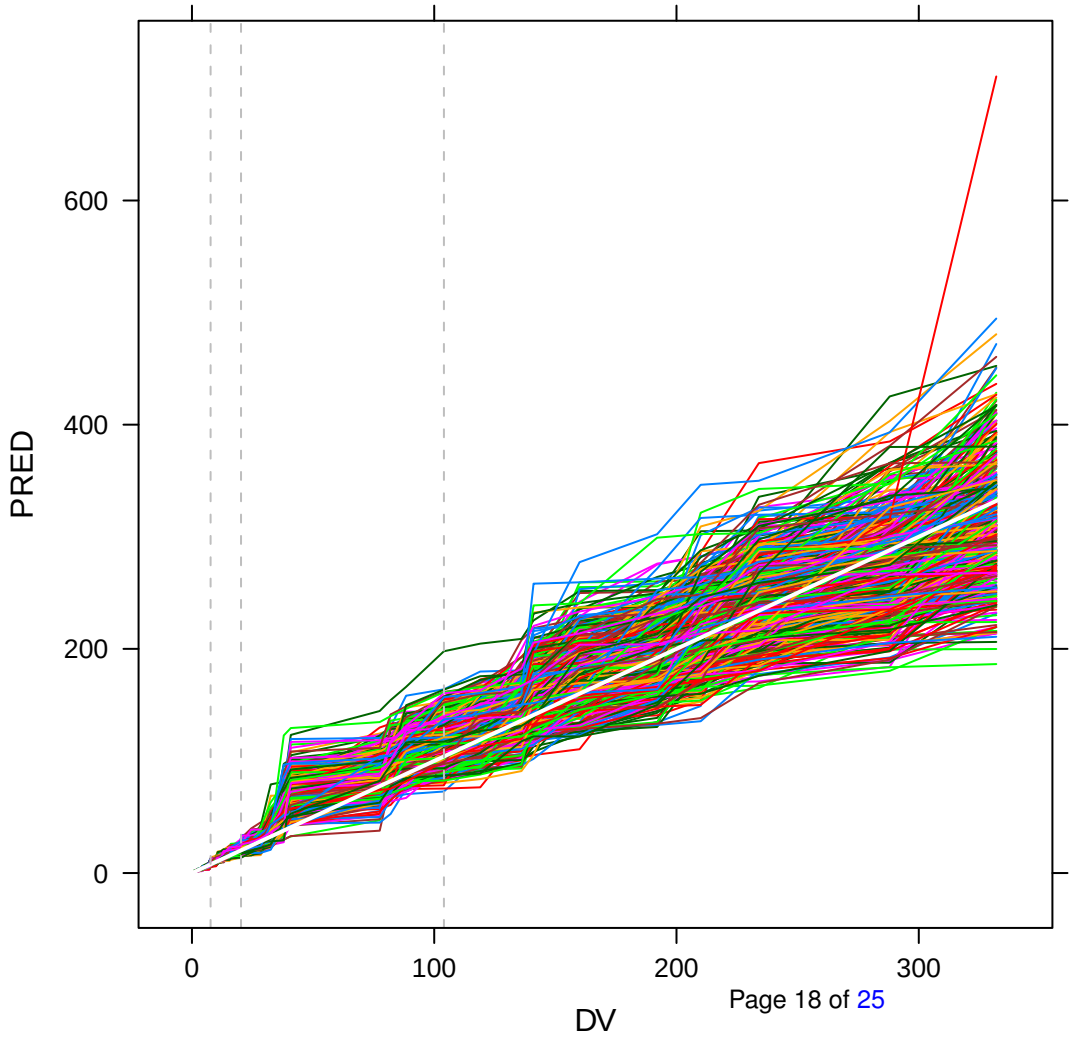
```
> head(trim)

    SIM   DV   PRED
501   1 1.13 1.9653
502   2 1.13 1.5989
503   3 1.13 1.4754
504   4 1.13 1.4074
505   5 1.13 1.3787
506   6 1.13 1.4753
```

Listing 34:

```
> 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
400
200
0
0
100
200
300
DV

We also show densityplots of predictions at those quartiles.

Listing 35:

```
> head(trim)
```

```
    SIM   DV   PRED
501   1 1.13 1.9653
502   2 1.13 1.5989
503   3 1.13 1.4754
504   4 1.13 1.4074
505   5 1.13 1.3787
506   6 1.13 1.4753
```

Listing 36:

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

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

Listing 37:

```
> 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 38:

```
> 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  7.950000 20.2500 100.10000
2   1     PRED 10.329750 22.8675  91.61825
3   2       DV  7.950000 20.2500 100.10000
4   2     PRED 10.241500 23.4225  97.26175
5   3       DV  7.950000 20.2500 100.10000
6   3     PRED  8.081437 20.0330 106.59750
```

Listing 39:

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

```
  variable quartile     value
1       DV     X25.  7.950000
2     PRED     X25. 10.329750
3       DV     X25.  7.950000
4     PRED     X25. 10.241500
5       DV     X25.  7.950000
6     PRED     X25.  8.081437
```

Listing 40:

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

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

Listing 41:

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

```
  variable       quartile     value
1       DV first quartile  7.950000
2     PRED first quartile 10.329750
3       DV first quartile  7.950000
4     PRED first quartile 10.241500
5       DV first quartile  7.950000
6     PRED first quartile  8.081437
```

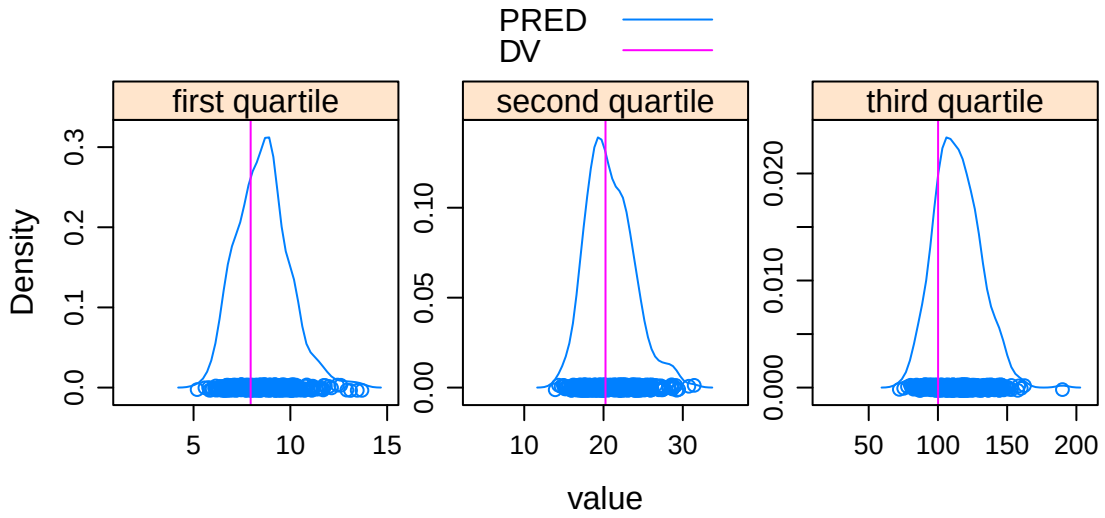
Listing 42:

```
> levels(molt$variable)

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

Listing 43:

```
> 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
0.0
0.1
0.2
0.3
0.00
0.05
0.10
0.000
0.010
0.020
5
10
15
10
20
30
50
100
150
200
value

4 Bootstrap Estimates of Parameter Uncertainty

4.1 Create directories.

Listing 44:

```
> getwd()
```

```
[1] "/home/timb/metrumrg/inst/sample/script"
```

Listing 45:

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

4.2 Create replicate control streams.

Listing 46:

```
> 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 47:

```
> 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 48:

```
> 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 49:

```
> 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')
```