

Mlfuns Sample Script

Phase I 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] "/Users/timb/project/metrum-mifuns/inst/sample/script"
```

Listing 2:

```
> library(Mifuns)

Mifuns 4.0.11 loaded
Installing SIGCHLD signal handler...Done.
```

Listing 3:

```
> command <- '/common/NONMEM/nm7_osx1/test/nm7_osx1.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.

To force a re-run of this model, delete 1005/diagnostics.pdf.

Listing 4:

```
> if(!file.exists('../nonmem/1005/diagnostics.pdf'))NONR(
+   run=1005,
+   command=command,
+   project='../nonmem',
+   grid=TRUE,
+   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'
+ )
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/sample/script"
```

Listing 5:

```
> while(!file.exists('../nonmem/1005/diagnostics.pdf')) {}
```

Covariance succeeded on model 1005.

3 Predictive Check

3.1 Create a simulation control stream.

Listing 6:

```
> t <- metaSub(  
+   as.filename('../nonmem/ctl/1005.ctl'),  
+   names=1105,  
+   pattern=c(  
+     '\\$THETA[^$]+',  
+     '\\$OMEGA[^$]+',  
+     '\\$SIGMA[^$]+',  
+     '\\$EST[^$]+',  
+     '\\$COV',  
+     '\\$TABLE.*'  
+   ),  
+   replacement=c(  
+     '$MSFI=../1005/1005.msf\\n',  
+     ';$OMEGA\\n',  
+     ';$SIGMA\\n',  
+     '$SIMULATION ONLYSIM (1968) SUBPROBLEMS=500\\n',  
+     ';$COV',  
+     '$TABLE DV NOHEADER NOPRINT FILE=/*.tab FORWARD NOAPPEND\\n'  
+   ),  
+   fixed=FALSE,  
+   out='../nonmem/ctl',  
+   suffix='.ctl'  
+ )
```

3.2 Run the simulation.

This run makes the predictions (simulations).

Listing 7:

```
> if(!file.exists('../nonmem/1105/1105.lst')) NONR(  
+   run=1105,  
+   command=command,  
+   project='../nonmem',
```

```
+ grid=TRUE,
+ nice=TRUE,
+ diag=FALSE,
+ streams='../nonmem/ctl'
+ )
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/sample/script"
```

Listing 8:

```
> while(!file.exists('../nonmem/1105/1105.lst')) {}
```

3.3 Recover and format the original dataset.

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

Listing 9:

```
> phasel1 <- read.csv('../data/derived/phasel.csv', na.strings='.')
> head(phasel1)
```

	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	1
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 10:

```
> phasel1 <- phasel1[is.na(phasel1$C), c('SUBJ', 'TIME', 'DV')]
> records <- nrow(phasel1)
> records
```

```
[1] 550
```

Listing 11:

```
> phasel1 <- phasel1[rep(1:records, 500), ]
> nrow(phasel1)
```

```
[1] 275000
```

Listing 12:

```
> 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 13:

```
> 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 14:

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

```
[1] 275000
```

Listing 15:

```
> length(pred)
```

```
[1] 275000
```

3.5 Combine the original data and the simulation data.

Listing 16:

```
> 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 17:

```
> 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 18:

```
> library(reshape)
> 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 19:

```
> 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 20:

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

Now we cast, ignoring time.

Listing 21:

```
> 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 22:

```
> 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

3.6.2 Aggregate data across subjects, within simulations.

Our predictions have central tendencies, which can vary by SIM. Thus, our metrics as well have central tendencies that vary by SIM. We want to represent the variability across SIMS by aggregating within SIM. That means aggregating across subjects, within SIMS. There are many aggregation strategies, but we choose quantiles for a non-parametric result. Quantiles that 'clip' the tails of the distribution offer robustness against number of SIMS (i.e., results less dependent on number of sims). Within each SIM, let's find for each metric the 5th, 50th, and 95th percentile. We also want to do this for the original data set (requires some minor rearrangement).

Listing 23:

```
> 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 24:

```
> quants <- data.frame(cast(metr, SIM + metric + variable ~ ., fun=quantile, probs=c
(0.05, 0.50, 0.95)))
> head(quants, 10)
```

	SIM	metric	variable		X5.	X50.	X95.
1	1	min	DV	0.3054500	2.1450	36.0750	
2	1	min	PRED	0.0976828	2.3129	29.6127	
3	1	med	DV	1.5860000	20.2500	290.2000	
4	1	med	PRED	2.2552400	22.8675	304.0180	
5	1	max	DV	3.0855000	40.7000	634.2500	
6	1	max	PRED	4.4729900	47.2865	579.6585	
7	2	min	DV	0.3054500	2.1450	36.0750	
8	2	min	PRED	0.0949232	2.8080	32.3266	
9	2	med	DV	1.5860000	20.2500	290.2000	
10	2	med	PRED	1.6609825	23.4225	263.8535	

Note, again, that DV quantiles are invariant across SIMS.

3.6.3 Reformat data for bivariate display.

We now have a lot of display options. The simplest is to plot DV PRED for each quantile and metric. Requires slight rearrangement.

Listing 25:

```
> molten <- melt(quants, measure.var=c('X5.', 'X50.', 'X95.'), variable_name='quant')
> head(molten)
```

	SIM	metric	variable	quant	value
1	1	min	DV	X5.	0.3054500
2	1	min	PRED	X5.	0.0976828
3	1	med	DV	X5.	1.5860000
4	1	med	PRED	X5.	2.2552400
5	1	max	DV	X5.	3.0855000
6	1	max	PRED	X5.	4.4729900

Listing 26:

```
> frozen <- data.frame(cast(molten, SIM + metric + quant ~ variable))
> head(frozen)
```

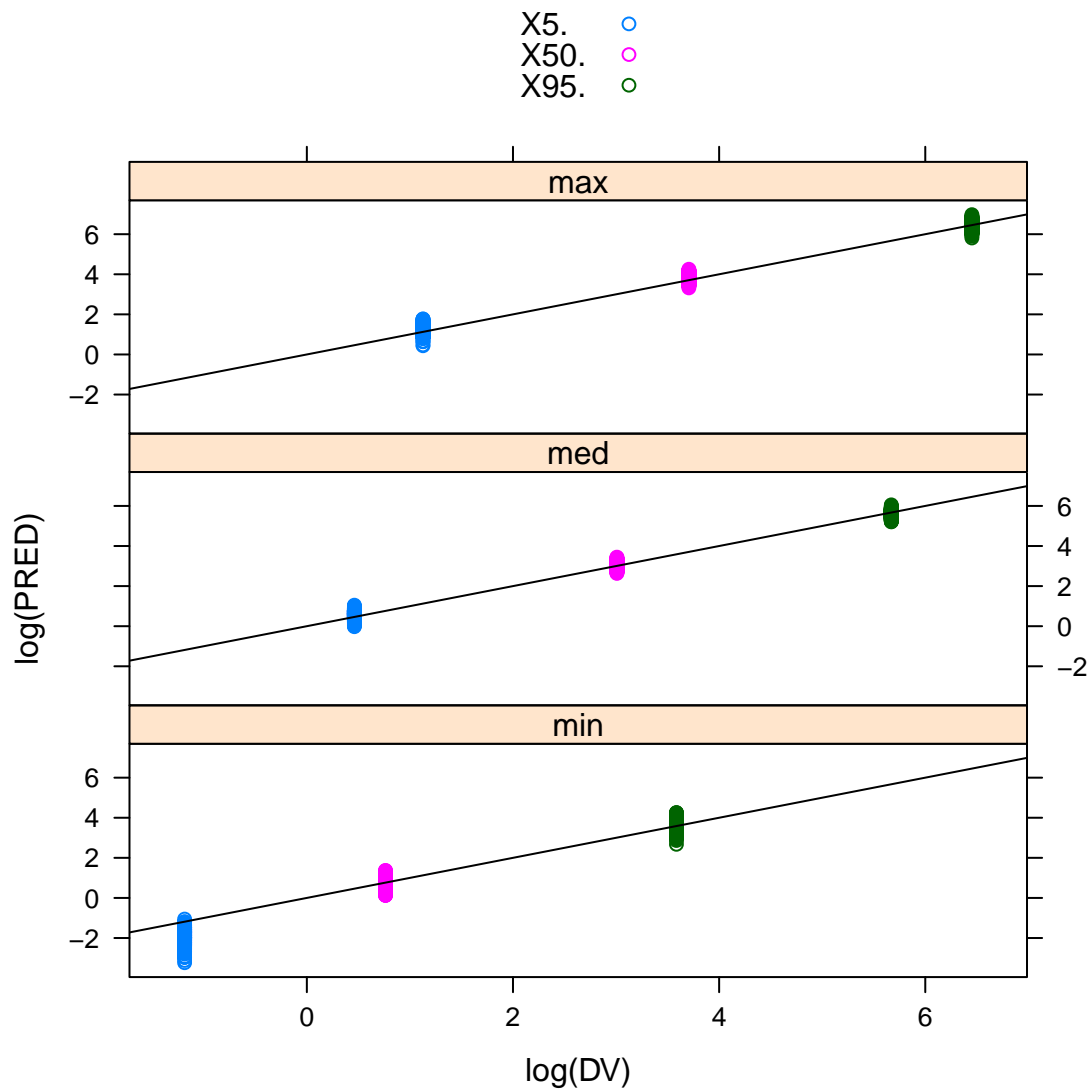
	SIM	metric	quant	DV	PRED
1	1	min	X5.	0.30545	0.0976828
2	1	min	X50.	2.14500	2.3129000
3	1	min	X95.	36.07500	29.6127000


```
4 1 med X5. 1.58600 2.2552400
5 1 med X50. 20.25000 22.8675000
6 1 med X95. 290.20000 304.0180000
```

3.6.4 Bivariate display of within-simulation aggregate metrics.

Listing 27:

```
> print(xyplot(
+   log(PRED) ~ log(DV) | metric,
+   frozen,
+   groups=quant,
+   layout=c(1,3),
+   auto.key=TRUE,
+   panel=function(...) {
+     panel.xyplot(...)
+     panel.abline(a=0,b=1)
+   })
```



3.6.5 Univariate displays.

For a better view of the distributions, however, we can work with single-axis plot functions, using the molten data. For faster and clearer plotting, we remove duplicates of DV.

3.6.6 Classic stripplot

Listing 28:

```
> head(molten)

  SIM metric variable quant      value
1   1    min        DV   X5. 0.3054500
2   1    min       PRED   X5. 0.0976828
3   1    med        DV   X5. 1.5860000
4   1    med       PRED   X5. 2.2552400
5   1    max        DV   X5. 3.0855000
6   1    max       PRED   X5. 4.4729900
```

Listing 29:

```
> molten$SIM <- NULL
> table(molten$variable)
```

```
 DV PRED
4500 4500
```

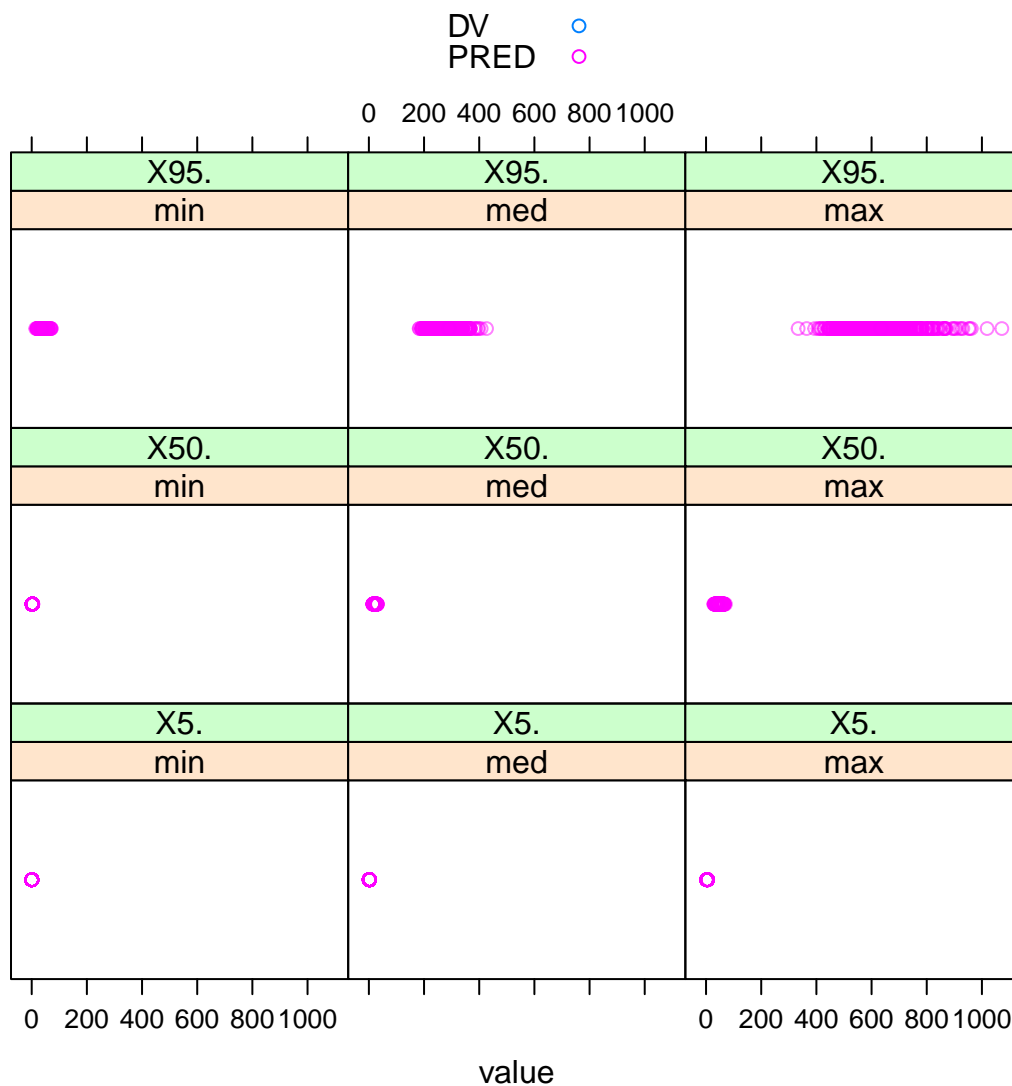
Listing 30:

```
> molten <- molten[!(duplicated(molten[,c('metric','variable','quant')]) &
  molten$variable=='DV'),]
> table(molten$variable)
```

```
 DV PRED
  9 4500
```

Listing 31:

```
> library(grid)
> print(stripplot(
+   ~ value|metric+quant,
+   molten,
+   groups=variable,
+   horizontal=TRUE,
+   auto.key=TRUE,
+   panel=panel.superpose,
+   alpha=0.5,
+   panel.groups=panel.stripplot
+ ))
```



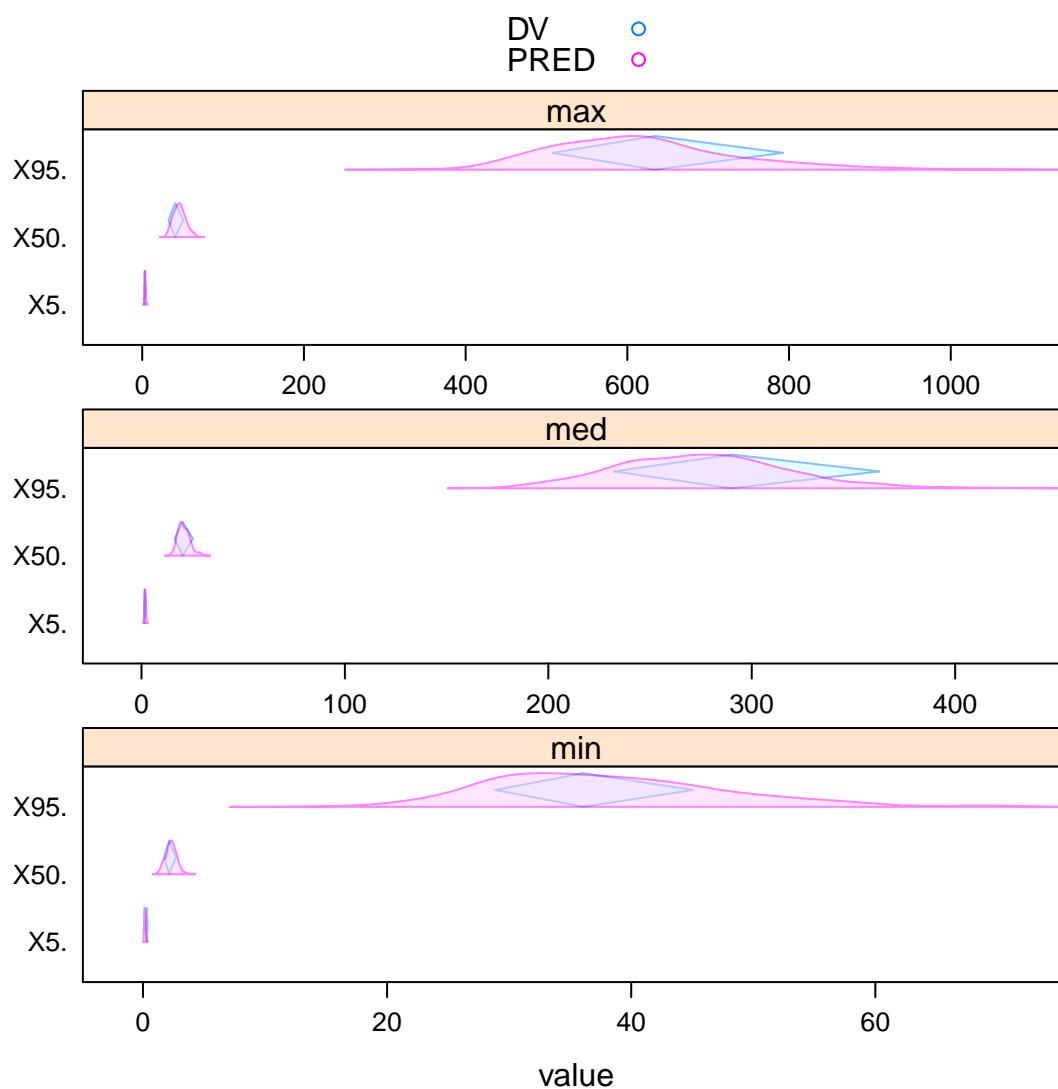
3.6.7 Diamondback: reference regions on density strips

Here we show the distribution data as density strips, and indicate reference regions around the point estimates. Here is one option. Also try swapping 'quant' and 'metric'.

Listing 32:

```
> print(stripplot(
+   quant ~ value | metric,
+   molten,
+   groups=variable,
```

```
+     auto.key=TRUE,
+     panel=panel.stratify,
+     alpha=0.5,
+     layout=c(1,3),
+     scales=list(relation='free'),
+     panel.levels = function(x,y,group.number,col,col.line,fill,font,...){
+         if(group.number==1)for(d in seq(length.out=length(x))) panel.
+         polygon(
+             x=x[[d]]*c(0.8,1,1.25,1),
+             y=y[[d]] + c(0.25,0,0.25,0.5),
+             border=col.line,
+             col=fill,
+             ...
+         )
+         else panel.densitystrip(x=x,y=y,col=fill,border=col.line,...)
+     }
+ ) )
```



4 Bootstrap Estimates of Parameter Uncertainty

4.1 Create directories.

Listing 33:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/sample/script"
```

Listing 34:

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

4.2 Create replicate control streams.

Listing 35:

```
> t <- metaSub(
+   clear(readLines('../nonmem/ctl/1005.ctl'), ';.+', fixed=FALSE),
+   names=1:300,
+   pattern=c(
+     '1005',
+     '../data/derived/phasel.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 36:

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

4.4 Run bootstrap models.

To force a re-run of bootstraps, delete log.csv.

Listing 37:

```
> if(!file.exists('../nonmem/1005.boot/CombRunLog.csv'))NONR(
+   run=1:300,
+   command=command,
+   project='../nonmem/1005.boot/',
+   boot=TRUE,
+   nice=TRUE,
+   streams='../nonmem/1005.boot/ctl1'
+ )
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/sample/script"
```

4.5 Summarize bootstrap models.

When the bootstraps are complete, we return here and summarize. If you do not have time for bootstraps, use `read.csv()` on `../nonmem/1005.boot/log.csv`.

Listing 38:

```
> #boot <- read.csv('../nonmem/1005.boot/log.csv',as.is=TRUE)
> #wait for bootstraps to finish
> while(!(all(file.exists(paste(sep=' ', '../nonmem/1005.boot/', 1:300, '.boot
/ ', 1:300, '.lst'))))){}
> if(file.exists('../nonmem/1005.boot/log.csv')){
+   boot <- read.csv('../nonmem/1005.boot/log.csv',as.is=TRUE)
+ }else{
+   boot <- rlog(
+     run=1:300,
+     project='../nonmem/1005.boot',
+     boot=TRUE,
+     append=FALSE,
+     tool='nm7'
+   )
+   write.csv(boot, '../nonmem/1005.boot/log.csv')
+ }
> head(boot)
```

	X	tool	run	parameter	moment	
1	1	nm7	1	prob	text	
2	2	nm7	1	min	status	
3	3	nm7	1	ofv	estimate	
4	4	nm7	1	OMEGA1.1	estimate	
5	5	nm7	1	OMEGA1.1	prse	
6	6	nm7	1	OMEGA2.1	estimate	
						value
1	1	phase1	2	CMT	like 1004 but diff. initial on V3	
2						0
3						2760.84241850239


```
4 0.188595
5 <NA>
6 0
```

Listing 39:

```
> unique(boot$parameter)

[1] "prob"      "min"      "ofv"      "OMEGA1.1" "OMEGA2.1" "OMEGA2.2"
[7] "OMEGA3.1" "OMEGA3.2" "OMEGA3.3" "SIGMA1.1" "THETA1"   "THETA2"
[13] "THETA3"   "THETA4"   "THETA5"   "THETA6"   "THETA7"
```

Listing 40:

```
> text2decimal(unique(boot$parameter))

[1] NA NA NA 1.1 2.1 2.2 3.1 3.2 3.3 1.1 1.0 2.0 3.0 4.0 5.0 6.0 7.0
```

It looks like we have 14 estimated parameters. We will map them to the original control stream.

Listing 41:

```
> boot <- boot[!is.na(text2decimal(boot$parameter)),]
> head(boot)

  X tool run parameter  moment  value
4 4 nm7 1 OMEGA1.1 estimate 0.188595
5 5 nm7 1 OMEGA1.1 prse      <NA>
6 6 nm7 1 OMEGA2.1 estimate 0
7 7 nm7 1 OMEGA2.1 prse      <NA>
8 8 nm7 1 OMEGA2.2 estimate 0.112992
9 9 nm7 1 OMEGA2.2 prse      <NA>
```

Listing 42:

```
> unique(boot$moment)

[1] "estimate" "prse"
```

Listing 43:

```
> unique(boot$value[boot$moment=='prse'])

[1] NA
```

prse, and therefore moment, is noninformative for these bootstraps.

Listing 44:

```
> boot <- boot[boot$moment=='estimate',]
> boot$moment <- NULL
> unique(boot$tool)
```

```
[1] "nm7"
```

Listing 45:

```
> boot$tool <- NULL
> head(boot)

      X run parameter      value
4    4    1  OMEGA1.1  0.188595
6    6    1  OMEGA2.1      0.00
8    8    1  OMEGA2.2  0.112992
10  10    1  OMEGA3.1      0.00
12  12    1  OMEGA3.2      0.00
14  14    1  OMEGA3.3  0.0854714
```

Listing 46:

```
> unique(boot$value[boot$parameter %in% c('OMEGA2.1','OMEGA3.1','OMEGA3.2')])

[1] "0"
```

Listing 47:

```
> unique(boot$parameter[boot$value=='0'])

[1] "OMEGA2.1" "OMEGA3.1" "OMEGA3.2"
```

Off-diagonals (and only off-diagonals) are noninformative.

Listing 48:

```
> boot <- boot[!boot$value=='0',]
> any(is.na(as.numeric(boot$value)))

[1] FALSE
```

Listing 49:

```
> boot$value <- as.numeric(boot$value)
> head(boot)

      X run parameter      value
4    4    1  OMEGA1.1  0.1885950
8    8    1  OMEGA2.2  0.1129920
14  14    1  OMEGA3.3  0.0854714
16  16    1  SIGMA1.1  0.0640717
18  18    1   THETA1  7.9889300
20  20    1   THETA2 19.8920000
```

4.6 Restrict data to 95 percentiles.

We did 300 runs. Min and max are strongly dependent on number of runs, since with an unbounded distribution, (almost) any value is possible with enough sampling. We clip to the 95 percentiles, to give distributions that are somewhat more scale independent.

Listing 50:

```
> boot$upper <- with(boot, reapply(value, INDEX=parameter, FUN=quantile, probs=0.975))
> boot$lower <- with(boot, reapply(value, INDEX=parameter, FUN=quantile, probs=0.025))
> nrow(boot)
```

```
[1] 3300
```

Listing 51:

```
> boot <- boot[with(boot, value < upper & value > lower),]
> nrow(boot)
```

```
[1] 3124
```

Listing 52:

```
> head(boot)
```

	X	run	parameter	value	upper	lower
4	4	1	OMEGA1.1	0.1885950	0.28599012	0.10657525
8	8	1	OMEGA2.2	0.1129920	0.19930930	0.05290951
14	14	1	OMEGA3.3	0.0854714	0.16658800	0.05277859
16	16	1	SIGMA1.1	0.0640717	0.08328707	0.05422743
18	18	1	THETA1	7.9889300	10.18006750	6.90182250
20	20	1	THETA2	19.8920000	26.29300250	17.74395750

Listing 53:

```
> boot$upper <- NULL
> boot$lower <- NULL
> head(boot)
```

	X	run	parameter	value
4	4	1	OMEGA1.1	0.1885950
8	8	1	OMEGA2.2	0.1129920
14	14	1	OMEGA3.3	0.0854714
16	16	1	SIGMA1.1	0.0640717
18	18	1	THETA1	7.9889300
20	20	1	THETA2	19.8920000

4.7 Recover parameter metadata from a specially-marked control stream.

We want meaningful names for our parameters. Harvest these from a reviewed control stream.

Listing 54:

```
> stream <- readLines('../nonmem/ctl/1005.ctl')
> tail(stream)

[1] ";<parameter name='SIGMA1.1' label='$\\sigma^{1.1}prop$'>proportional error</parameter>"
[2] ""
[3] "$ESTIMATION MAXEVAL=9999 PRINT=5 NOABORT METHOD=1 INTER MSFO=./1005.msf"
[4] "$COV PRINT=E"
[5] "$TABLE NOPRINT FILE=./1005.tab ONEHEADER ID AMT TIME EVID PRED IPRE CWRES"
[6] "$TABLE NOPRINT FILE=./1005par.tab ONEHEADER ID TIME CL Q V2 V3 KA ETA1 ETA2 ETA3"
```

Listing 55:

```
> doc <- ctl2xml(stream)
> doc

[1] "<document>"
[2] "<parameter name='THETA1' latex='$\\theta_1$' unit='$L/h$' label='CL/F' model='$CL/F \\sim \\theta_6^{MALE} * (WT/70)^{\\theta_7}$'>clearance</parameter>"
[3] "<parameter name='THETA2' latex='$\\theta_2$' unit='$L$' label='Vc/F' model='$Vc/F \\sim (WT/70)^{1}$'>central volume</parameter>"
[4] "<parameter name='THETA3' latex='$\\theta_3$' unit='$h^{-1}$' label='Ka'>absorption constant</parameter>"
[5] "<parameter name='THETA4' latex='$\\theta_4$' unit='$L/h$' label='Q/F'>intercompartmental clearance</parameter>"
[6] "<parameter name='THETA5' latex='$\\theta_5$' unit='$L$' label='Vp/F'>peripheral volume</parameter>"
[7] "<parameter name='THETA6' latex='$\\theta_6$' label='Male.CL'>male effect on clearance</parameter>"
[8] "<parameter name='THETA7' latex='$\\theta_7$' label='WT.CL'>weight effect on clearance</parameter>"
[9] "<parameter name='OMEGA1.1' label='$\\Omega^{1.1}CL/F$'>interindividual variability on clearance</parameter>"
[10] "<parameter name='OMEGA2.2' label='$\\Omega^{2.2}Vc/F$'>interindividual variability on central volume</parameter>"
[11] "<parameter name='OMEGA3.3' label='$\\Omega^{3.3}Ka$'>interindividual variability on Ka</parameter>"
[12] "<parameter name='SIGMA1.1' label='$\\sigma^{1.1}prop$'>proportional error</parameter>"
[13] "</document>"
```

Listing 56:

```
> params <- unique(boot[, 'parameter', drop=FALSE])
```

```
> params$defs <- lookup(params$parameter,within=doc)
> params$labels <- lookup(params$parameter,within=doc,as='label')
> params
```

	parameter	defs	labels
4	OMEGA1.1	interindividual variability on clearance	$\Omega^{1.1}CL/F$
8	OMEGA2.2	interindividual variability on central volume	$\Omega^{2.2}Vc/F$
14	OMEGA3.3	interindividual variability on Ka	$\Omega^{3.3}Ka$
16	SIGMA1.1	proportional error	$\sigma^{1.1}prop$
18	THETA1	clearance	CL/F
20	THETA2	central volume	Vc/F
22	THETA3	absorption constant	Ka
24	THETA4	intercompartmental clearance	Q/F
26	THETA5	peripheral volume	Vp/F
28	THETA6	male effect on clearance	Male.CL
30	THETA7	weight effect on clearance	WT.CL

Listing 57:

```
> boot$parameter <- lookup(boot$parameter,within=doc,as='label')
> head(boot)
```

	X	run	parameter	value
4	4	1	$\Omega^{1.1}CL/F$	0.1885950
8	8	1	$\Omega^{2.2}Vc/F$	0.1129920
14	14	1	$\Omega^{3.3}Ka$	0.0854714
16	16	1	$\sigma^{1.1}prop$	0.0640717
18	18	1	CL/F	7.9889300
20	20	1	Vc/F	19.8920000

4.8 Create covariate plot.

Now we make a covariate plot for clearance. We will normalize clearance by its median (we also could have used the model estimate). We need to take cuts of weight, since we can only really show categorically-constrained distributions. Male effect is already categorical. I.e, the reference individual has median clearance, is female, and has median weight.

4.8.1 Recover original covariates for guidance.

Listing 58:

```
> covariates <- read.csv('../data/derived/phases1.csv',na.strings='.')
> head(covariates)
```

	C	ID	TIME	SEQ	EVID	AMT	DV	SUBJ	HOURL	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 1
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 59:

```
> with(covariates, constant(WEIGHT, within=ID))
```

```
[1] TRUE
```

Listing 60:

```
> covariates <- unique(covariates[,c('ID', 'WEIGHT')])
> head(covariates)
```

```

ID WEIGHT
1 1 74.2
16 2 80.3
31 3 94.2
46 4 85.2
61 5 82.8
76 6 63.9

```

Listing 61:

```
> covariates$WT <- as.numeric(covariates$WEIGHT)
> wt <- median(covariates$WT)
> wt
```

```
[1] 81
```

Listing 62:

```
> range(covariates$WT)
```

```
[1] 61 117
```

4.8.2 Reproduce the control stream submodel for selective cuts of a continuous covariate.

In the model we normalized by 70 kg, so that cut will have null effect. Let's try 65, 75, and 85 kg. We have to make a separate column for each cut, which is a bit of work. Basically, we make two more copies of our weight effect columns, and raise our normalized cuts to those powers, effectively reproducing the submodel from the control stream.

Listing 63:

```
> head(boot)
```

	X	run	parameter	value
4	4	1	$\Omega^{1.1}$ CL/F\$	0.1885950
8	8	1	$\Omega^{2.2}$ Vc/F\$	0.1129920
14	14	1	$\Omega^{3.3}$ Ka\$	0.0854714
16	16	1	$\sigma^{1.1}$ prop\$	0.0640717
18	18	1	CL/F	7.9889300
20	20	1	Vc/F	19.8920000

Listing 64:

```
> unique(boot$parameter)
```

```
[1] "$\\Omega^{1.1}CL/F$" "$\\Omega^{2.2}Vc/F$" "$\\Omega^{3.3}Ka$"
[4] "$\\sigma^{1.1}prop$" "CL/F" "Vc/F"
[7] "Ka" "Q/F" "Vp/F"
[10] "Male.CL" "WT.CL"
```

Listing 65:

```
> clearance <- boot[boot$parameter %in% c('CL/F', 'WT.CL', 'Male.CL'),]
> head(clearance)
```

	X	run	parameter	value
18	18	1	CL/F	7.988930
28	28	1	Male.CL	1.182580
30	30	1	WT.CL	1.308790
49	49	2	CL/F	7.636730
59	59	2	Male.CL	0.956565
61	61	2	WT.CL	2.369810

Listing 66:

```
> frozen <- data.frame(cast(clearance, run ~ parameter), check.names=FALSE)
> head(frozen)
```

	run	CL/F	Male.CL	WT.CL
1	1	7.98893	1.182580	1.30879
2	2	7.63673	0.956565	2.36981
3	3	9.15198	0.937231	1.88593
4	4	9.56138	1.028670	1.47186
5	5	8.36964	0.914796	1.97656
6	6	9.09701	1.079030	1.16319

Listing 67:

```
> frozen$WT.CL65 <- (65/70)**frozen$WT.CL
> frozen$WT.CL75 <- (75/70)**frozen$WT.CL
> frozen$WT.CL85 <- (85/70)**frozen$WT.CL
```

4.8.3 Normalize key parameter

Listing 68:

```
> cl <- median(boot$value[boot$parameter=='CL/F'])
> cl
```

```
[1] 8.56139
```

Listing 69:

```
> head(frozen)
```

	run	CL/F	Male.CL	WT.CL	WT.CL65	WT.CL75	WT.CL85
1	1	7.98893	1.182580	1.30879	0.9075635	1.094499	1.289313
2	2	7.63673	0.956565	2.36981	0.8389352	1.177625	1.584253
3	3	9.15198	0.937231	1.88593	0.8695648	1.138960	1.442193
4	4	9.56138	1.028670	1.47186	0.8966618	1.106883	1.330787
5	5	8.36964	0.914796	1.97656	0.8637440	1.146104	1.467795
6	6	9.09701	1.079030	1.16319	0.9174092	1.083560	1.253376

Listing 70:

```
> frozen[['CL/F']] <- frozen[['CL/F']]/cl
> head(frozen)
```

	run	CL/F	Male.CL	WT.CL	WT.CL65	WT.CL75	WT.CL85
1	1	0.9331347	1.182580	1.30879	0.9075635	1.094499	1.289313
2	2	0.8919965	0.956565	2.36981	0.8389352	1.177625	1.584253
3	3	1.0689830	0.937231	1.88593	0.8695648	1.138960	1.442193
4	4	1.1168023	1.028670	1.47186	0.8966618	1.106883	1.330787
5	5	0.9776029	0.914796	1.97656	0.8637440	1.146104	1.467795
6	6	1.0625623	1.079030	1.16319	0.9174092	1.083560	1.253376

Listing 71:

```
> frozen$WT.CL <- NULL
> molten <- melt(frozen,id.var='run',na.rm=TRUE)
> head(molten)
```

	run	variable	value
1	1	CL/F	0.9331347
2	2	CL/F	0.8919965
3	3	CL/F	1.0689830
4	4	CL/F	1.1168023
5	5	CL/F	0.9776029
6	6	CL/F	1.0625623

4.8.4 Plot.

Now we plot. We reverse the variable factor to give us top-down layout of strips.

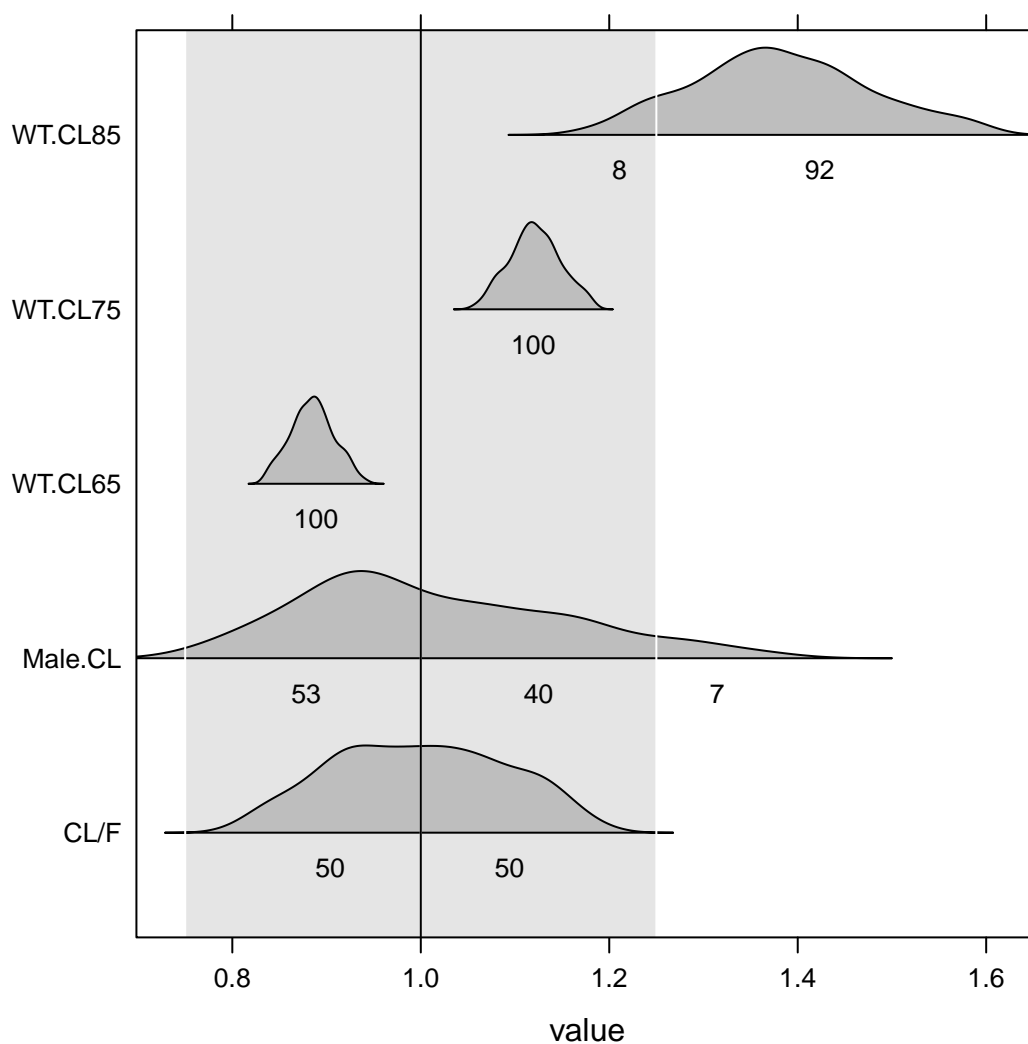
Listing 72:

```
> levels(molten$variable)
```

```
[1] "CL/F"      "Male.CL" "WT.CL65" "WT.CL75" "WT.CL85"
```

Listing 73:

```
> molten$variable <- factor(molten$variable, levels=rev(levels(molten$variable)))
> print(stripplot(variable ~ value, molten, panel=panel.covplot))
```



4.8.5 Summarize

We see that clearance is estimated with good precision. Ignoring outliers, there is not much effect on clearance of being male, relative to female. Increasing weight is associated with increasing clearance. There is a 79 percent probability that an 85 kg person will have at least 25 percent greater clearance than a 70 kg person.

5 Parameter Table

Listing 74:

```
> library(Hmisc)
> tab <- partab(1005,'../nonmem',tool='nm7',as=c('label','latex','model','estimate',
  'unit','prse'))
> tab$estimate <- as.character(signif(as.numeric(tab$estimate),3))
> tab$estimate <- ifelse(is.na(tab$unit),tab$estimate,paste(tab$estimate, tab$unit
  ))
> tab$unit <- NULL
> tab$label <- ifelse(is.na(tab$latex),tab$label,paste(tab$label, ' (' ,tab$latex
  ,') ',sep=''))
> tab$latex <- NULL
> names(tab)[names(tab)=='label'] <- 'parameter'
> tab$root <- signif(sqrt(exp(as.numeric(tab$estimate))-1),3)
> tab$estimate <- ifelse(contains('Omega|sigma',tab$parameter),paste(tab$estimate
  , ' (\\%CV=',tab$root*100,') ',sep=''),tab$estimate)
> tab$root <- NULL
> #offdiag <- contains('2.1',tab$parameter)
> #tab$estimate[offdiag] <- text2decimal(tab$estimate[offdiag])
> #omegablock <- text2decimal(tab$estimate[contains('Omega..(1|2)',tab$parameter)
  ])
> #cor <- signif(half(cov2cor(as.matrix(as.halfmatrix(omegablock))))[[2]],3)
> #tab$estimate[offdiag] <- paste(sep=' ',tab$estimate[offdiag], ' (COR=',cor,') ')
> tab$model[is.na(tab$model)] <- ''
> #boot <- rlog(1:300,project='../nonmem/1005.boot',tool='nm7',boot=TRUE)
> boot <- read.csv('../nonmem/1005.boot/log.csv',as.is=TRUE)
> boot <- boot[boot$moment=='estimate',]
> boot <- data.frame(cast(boot,... ~ moment))
> boot[] <- lapply(boot,as.character)
> boot <- boot[contains('THETA|OMEGA|SIGMA',boot$parameter),c('parameter','
  estimate')]
> boot$estimate <- as.numeric(boot$estimate)
> boot <- data.frame(cast(boot,parameter ~ .,value='estimate',fun=function(x)list(
  lo=as.character(signif(quantile(x,probs=0.05),3)),hi=as.character(signif(
  quantile(x,probs=0.95),3)))))
> boot$CI <- with(boot, paste(sep=' ', '(',lo,',',hi,') '))
> names(boot)[names(boot)=='parameter'] <- 'name'
> tab <- stableMerge(tab,boot[,c('name','CI')])
> tab$name <- NULL
```

Table 1: Parameter Estimates from Population Pharmacokinetic Model Run 1005

parameter	model	estimate	prse	CI
CL/F (θ_1)	$CL/F \sim \theta_6^{MALE} * (WT/70)^{\theta_7}$	8.58 L/h	9.51	(7.14,9.89)
Vc/F (θ_2)	$Vc/F \sim (WT/70)^1$	21.6 L	9.33	(18.5,25.4)
Ka (θ_3)		0.0684 h ⁻¹	8.04	(0.0586,0.0793)
Q/F (θ_4)		3.78 L/h	13.5	(3.03,4.83)
Vp/F (θ_5)		107 L	15.7	(85.7,148)
Male.CL (θ_6)		0.999	13.7	(0.799,1.31)
WT.CL (θ_7)		1.67	21.9	(1.03,2.34)
$\Omega^{1.1}CL/F$		0.196 (%CV=46.5)	23.1	(0.115,0.26)
$\Omega^{2.2}Vc/F$		0.129 (%CV=37.1)	30.4	(0.0623,0.181)
$\Omega^{3.3}Ka$		0.107 (%CV=33.6)	25.2	(0.0638,0.157)
$\sigma^{1.1}prop$		0.0671 (%CV=26.3)	11.4	(0.055,0.0796)