MI210

Phase I Modeling

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1 Purpose

This script runs NONMEM models for the phase1 data.

2 Model Development

2.1 Set up for NONMEM run.

Listing 1:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/mi210/script"
```

Listing 2:

```
> library(MIfuns)
```

```
MIfuns 3.8.1 loaded
Installing SIGCHLD signal handler...Done.
```

Listing 3:

```
> command <- '/usr/local/nm7_osxi/test/nm7_osxi.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.

Here we comment out the NONMEM run so that it is not run accidentally if the file is sourced. Run it manually.

Listing 4:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/mi210/script"
```

Covariance succeeded on model 1005.

3 Predictive Check

3.1 Create a simulation control stream.

Listing 5:

```
> 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 6:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/mi210/script"
```

3.3 Recover and format the original dataset.

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

Listing 7:

```
> phase1 <- read.csv('../data/ph1/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      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 8:

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

```
[1] 550
```

Listing 9:

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

```
[1] 275000
```

Listing 10:

```
> phase1$SIM <- rep(1:500,each=records)
> head(phase1,300)
```

```
    SUBJ  TIME     DV SIM
2      1  0.00     NA   1
3      1  0.25  0.363   1
4      1  0.50  0.914   1
5      1  1.00  1.120   1
6      1  2.00  2.280   1
7      1  3.00  1.630   1
8      1  4.00  2.040   1
9      1  6.00  1.610   1
10     1  8.00  2.730   1
11     1 12.00  3.090   1
12     1 18.00  2.590   1
13     1 24.00  1.470   1
14     1 48.00  0.974   1
15     1 72.00  0.892   1
17     2  0.00     NA   1
```

18	2	0.25	1.550	1
19	2	0.50	3.510	1
20	2	1.00	11.400	1
21	2	2.00	19.100	1
22	2	3.00	13.300	1
23	2	4.00	19.100	1
24	2	6.00	14.100	1
25	2	8.00	6.820	1
26	2	12.00	7.290	1
27	2	18.00	8.410	1
28	2	24.00	4.370	1
29	2	48.00	1.900	1
30	2	72.00	0.933	1
32	3	0.00	NA	1
33	3	0.25	4.790	1
34	3	0.50	13.100	1
35	3	1.00	15.000	1
36	3	2.00	22.400	1
37	3	3.00	22.000	1
38	3	4.00	30.300	1
39	3	6.00	23.700	1
40	3	8.00	15.600	1
41	3	12.00	11.500	1
42	3	18.00	8.000	1
43	3	24.00	4.750	1
44	3	48.00	1.800	1
45	3	72.00	0.523	1
47	4	0.00	NA	1
48	4	0.25	38.300	1
49	4	0.50	61.400	1
50	4	1.00	76.000	1
51	4	2.00	148.000	1
52	4	3.00	200.000	1
53	4	4.00	142.000	1
54	4	6.00	142.000	1
55	4	8.00	211.000	1
56	4	12.00	136.000	1
57	4	18.00	88.400	1
58	4	24.00	79.300	1
59	4	48.00	24.300	1
60	4	72.00	19.000	1
62	5	0.00	NA	1
63	5	0.25	56.200	1
64	5	0.50	86.500	1
65	5	1.00	119.000	1
66	5	2.00	150.000	1
67	5	3.00	233.000	1
68	5	4.00	195.000	1
69	5	6.00	181.000	1
70	5	8.00	328.000	1

71	5	12.00	133.000	1
72	5	18.00	105.000	1
73	5	24.00	66.400	1
74	5	48.00	25.800	1
75	5	72.00	16.000	1
77	6	0.00	NA	1
78	6	0.25	0.818	1
79	6	0.50	1.190	1
80	6	1.00	2.470	1
81	6	2.00	3.540	1
82	6	3.00	3.200	1
83	6	4.00	0.438	1
84	6	6.00	1.970	1
85	6	8.00	2.340	1
86	6	12.00	4.080	1
87	6	18.00	1.590	1
88	6	24.00	2.400	1
89	6	48.00	0.455	1
90	6	72.00	0.676	1
92	7	0.00	NA	1
93	7	0.25	1.660	1
94	7	0.50	2.020	1
95	7	1.00	5.850	1
96	7	2.00	8.440	1
97	7	3.00	9.810	1
98	7	4.00	8.750	1
99	7	6.00	8.150	1
100	7	8.00	7.890	1
101	7	12.00	7.780	1
102	7	18.00	6.480	1
103	7	24.00	3.690	1
104	7	48.00	0.890	1
107	8	0.00	NA	1
108	8	0.25	5.190	1
109	8	0.50	11.600	1
110	8	1.00	18.000	1
111	8	2.00	33.800	1
112	8	3.00	43.600	1
113	8	4.00	32.900	1
114	8	6.00	21.500	1
115	8	8.00	29.100	1
116	8	12.00	27.600	1
117	8	18.00	20.600	1
118	8	24.00	12.000	1
119	8	48.00	4.720	1
120	8	72.00	2.470	1
122	9	0.00	NA	1
123	9	0.25	14.000	1
124	9	0.50	31.100	1
125	9	1.00	67.000	1

```
126    9  2.00  66.200   1
127    9  3.00  75.400   1
128    9  4.00  79.800   1
129    9  6.00  97.200   1
130    9  8.00  70.900   1
131    9 12.00  40.800   1
132    9 18.00  37.000   1
133    9 24.00  16.800   1
134    9 48.00   8.130   1
135    9 72.00   2.870   1
137   10  0.00      NA   1
138   10  0.25  62.400   1
139   10  0.50  83.200   1
140   10  1.00 156.000   1
141   10  2.00 197.000   1
142   10  3.00 294.000   1
143   10  4.00 209.000   1
144   10  6.00 237.000   1
145   10  8.00 139.000   1
146   10 12.00 104.000   1
147   10 18.00  69.800   1
148   10 24.00  73.600   1
149   10 48.00  17.400   1
150   10 72.00   5.590   1
152   11  0.00      NA   1
155   11  1.00   1.180   1
156   11  2.00   3.000   1
157   11  3.00   2.450   1
158   11  4.00   2.210   1
159   11  6.00   1.690   1
160   11  8.00   1.010   1
161   11 12.00   1.080   1
162   11 18.00   0.569   1
164   11 48.00   0.307   1
165   11 72.00   0.449   1
167   12  0.00      NA   1
168   12  0.25   2.260   1
169   12  0.50   2.830   1
170   12  1.00   8.730   1
171   12  2.00  19.300   1
172   12  3.00  15.200   1
173   12  4.00  16.200   1
174   12  6.00   8.830   1
175   12  8.00  12.900   1
176   12 12.00  12.700   1
177   12 18.00   7.140   1
178   12 24.00   5.740   1
179   12 48.00   1.980   1
180   12 72.00   0.791   1
182   13  0.00      NA   1
```

183	13	0.25	6.170	1
184	13	0.50	5.190	1
185	13	1.00	15.500	1
186	13	2.00	15.600	1
187	13	3.00	21.100	1
188	13	4.00	30.600	1
189	13	6.00	25.200	1
190	13	8.00	11.900	1
191	13	12.00	13.300	1
192	13	18.00	11.800	1
193	13	24.00	8.070	1
194	13	48.00	3.460	1
195	13	72.00	2.230	1
197	14	0.00	NA	1
198	14	0.25	27.400	1
199	14	0.50	29.900	1
200	14	1.00	74.200	1
201	14	2.00	82.800	1
202	14	3.00	102.000	1
203	14	4.00	67.600	1
204	14	6.00	50.700	1
205	14	8.00	45.700	1
206	14	12.00	32.500	1
207	14	18.00	27.500	1
208	14	24.00	11.200	1
209	14	48.00	5.900	1
210	14	72.00	2.060	1
212	15	0.00	NA	1
213	15	0.25	47.500	1
214	15	0.50	95.900	1
215	15	1.00	192.000	1
216	15	2.00	380.000	1
217	15	3.00	412.000	1
218	15	4.00	340.000	1
219	15	6.00	281.000	1
220	15	8.00	419.000	1
221	15	12.00	271.000	1
222	15	18.00	167.000	1
223	15	24.00	127.000	1
224	15	48.00	49.600	1
225	15	72.00	16.900	1
227	16	0.00	NA	1
228	16	0.25	1.020	1
230	16	1.00	0.683	1
231	16	2.00	1.730	1
232	16	3.00	2.320	1
233	16	4.00	2.530	1
234	16	6.00	2.280	1
235	16	8.00	0.565	1
236	16	12.00	0.704	1

237	16	18.00	0.644	1
239	16	48.00	1.030	1
242	17	0.00	NA	1
243	17	0.25	2.100	1
244	17	0.50	5.400	1
245	17	1.00	10.600	1
246	17	2.00	17.100	1
247	17	3.00	14.000	1
248	17	4.00	25.200	1
249	17	6.00	22.000	1
250	17	8.00	15.600	1
251	17	12.00	11.800	1
252	17	18.00	6.020	1
253	17	24.00	4.630	1
254	17	48.00	2.770	1
255	17	72.00	0.693	1
257	18	0.00	NA	1
258	18	0.25	2.470	1
259	18	0.50	8.210	1
260	18	1.00	13.300	1
261	18	2.00	15.000	1
262	18	3.00	29.100	1
263	18	4.00	22.600	1
264	18	6.00	23.100	1
265	18	8.00	16.100	1
266	18	12.00	9.970	1
267	18	18.00	7.750	1
268	18	24.00	6.210	1
269	18	48.00	2.160	1
270	18	72.00	1.320	1
272	19	0.00	NA	1
273	19	0.25	15.300	1
274	19	0.50	35.200	1
275	19	1.00	88.400	1
276	19	2.00	129.000	1
277	19	3.00	137.000	1
278	19	4.00	123.000	1
279	19	6.00	129.000	1
280	19	8.00	83.700	1
281	19	12.00	77.500	1
282	19	18.00	70.100	1
283	19	24.00	35.200	1
284	19	48.00	8.860	1
285	19	72.00	4.060	1
287	20	0.00	NA	1
288	20	0.25	26.200	1
289	20	0.50	70.700	1
290	20	1.00	111.000	1
291	20	2.00	119.000	1
292	20	3.00	156.000	1

```
293   20  4.00 117.000   1
294   20  6.00 162.000   1
295   20  8.00 169.000   1
296   20 12.00  81.400   1
297   20 18.00  82.000   1
298   20 24.00  52.900   1
299   20 48.00  17.100   1
300   20 72.00   5.440   1
302   21  0.00      NA   1
303   21  0.25   0.841   1
304   21  0.50   3.530   1
305   21  1.00   5.630   1
306   21  2.00   4.350   1
307   21  3.00   8.570   1
308   21  4.00   6.260   1
309   21  6.00   6.810   1
310   21  8.00   5.150   1
311   21 12.00   4.770   1
312   21 18.00   3.950   1
313   21 24.00   4.260   1
314   21 48.00   0.933   1
315   21 72.00   0.404   1
317   22  0.00      NA   1
318   22  0.25   6.700   1
319   22  0.50  10.900   1
320   22  1.00  19.400   1
321   22  2.00  25.500   1
322   22  3.00  34.400   1
323   22  4.00  27.100   1
324   22  6.00  23.400   1
325   22  8.00  17.600   1
326   22 12.00  14.400   1
327   22 18.00   6.130   1
328   22 24.00   6.660   1
329   22 48.00   1.360   1
```

Listing 11:

```
> 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 12:

```
> 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 13:

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

```
[1] 275000
```

Listing 14:

```
> length(pred)
```

```
[1] 275000
```

3.5 Combine the original data and the simulation data.

Listing 15:

```
> 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 16:

```
> 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.

We take a quick look at the predictions. These are commented out because they take a very long time to render. But you could try them manually.

3.6.1 First look.

Listing 17:

```
> library(lattice)
```

3.6.2 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.

3.6.3 Format for bivariate plot.

Now we can repeat earlier plots using aggregated data. We need DV and PRED in separate columns, with min/med/max as the variable.

Listing 22:

```
> dvpred <- melt(subject,measure.var=c('min','med','max'),variable_name='metric')
> head(dvpred)
```

```
  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 23:

```
> dvpred <- data.frame(cast(dvpred, SUBJ + SIM + metric ~ variable))
> head(dvpred)
```

```
  SUBJ SIM metric    DV     PRED
1    1   1    min 0.363 0.179320
2    1   1    med 1.610 1.965300
3    1   1    max 3.090 5.031400
4    1   2    min 0.363 0.096462
5    1   2    med 1.610 3.044800
6    1   2    max 3.090 7.472800
```

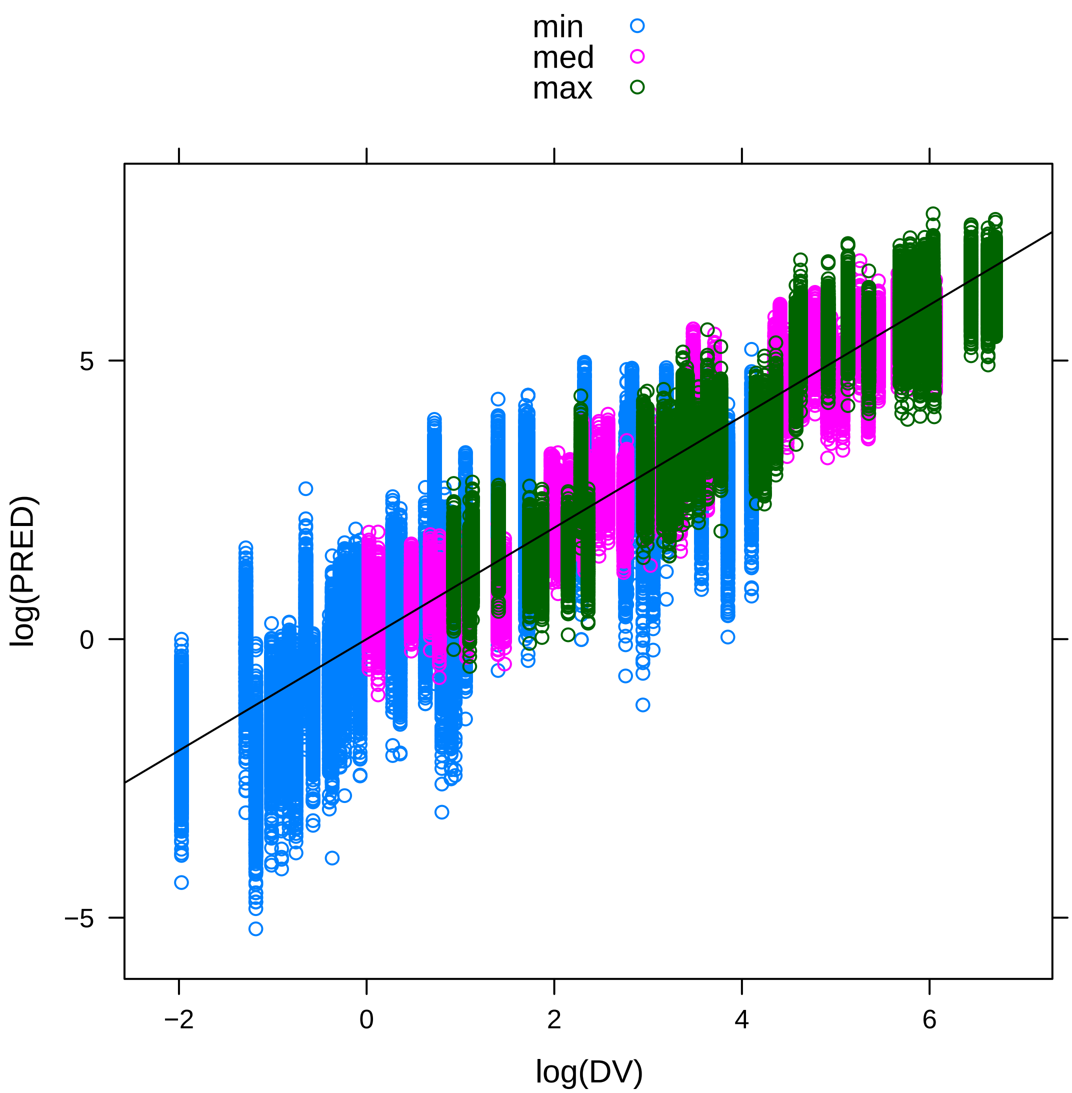
3.6.4 Simple bivariate plot.

Now we can do seperate-axis comparisons of DV and PRED.

Listing 24:

```
> print(xyplot(
+       log(PRED) ~ log(DV),
```

```
+         dvpred,
+         groups=metric,
+         auto.key=TRUE,
+         panel=function(...){
+                 panel.xyplot(...)
+                 panel.abline(a=0,b=1)
+         }
+ ))
```



3.6.5 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 25:

```
> head(dvpred)
```

```
  SUBJ SIM metric    DV     PRED
1    1   1    min 0.363 0.179320
2    1   1    med 1.610 1.965300
3    1   1    max 3.090 5.031400
4    1   2    min 0.363 0.096462
5    1   2    med 1.610 3.044800
6    1   2    max 3.090 7.472800
```

Listing 26:

```
> quants <- melt(dvpred,measure.var=c('DV','PRED'))
> head(quants)
```

```
  SUBJ SIM metric variable value
1    1   1    min       DV 0.363
2    1   1    med       DV 1.610
3    1   1    max       DV 3.090
4    1   2    min       DV 0.363
5    1   2    med       DV 1.610
6    1   2    max       DV 3.090
```

Listing 27:

```
> quants <- data.frame(cast(quants,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.

3.6.6 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 28:

```
> 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 29:

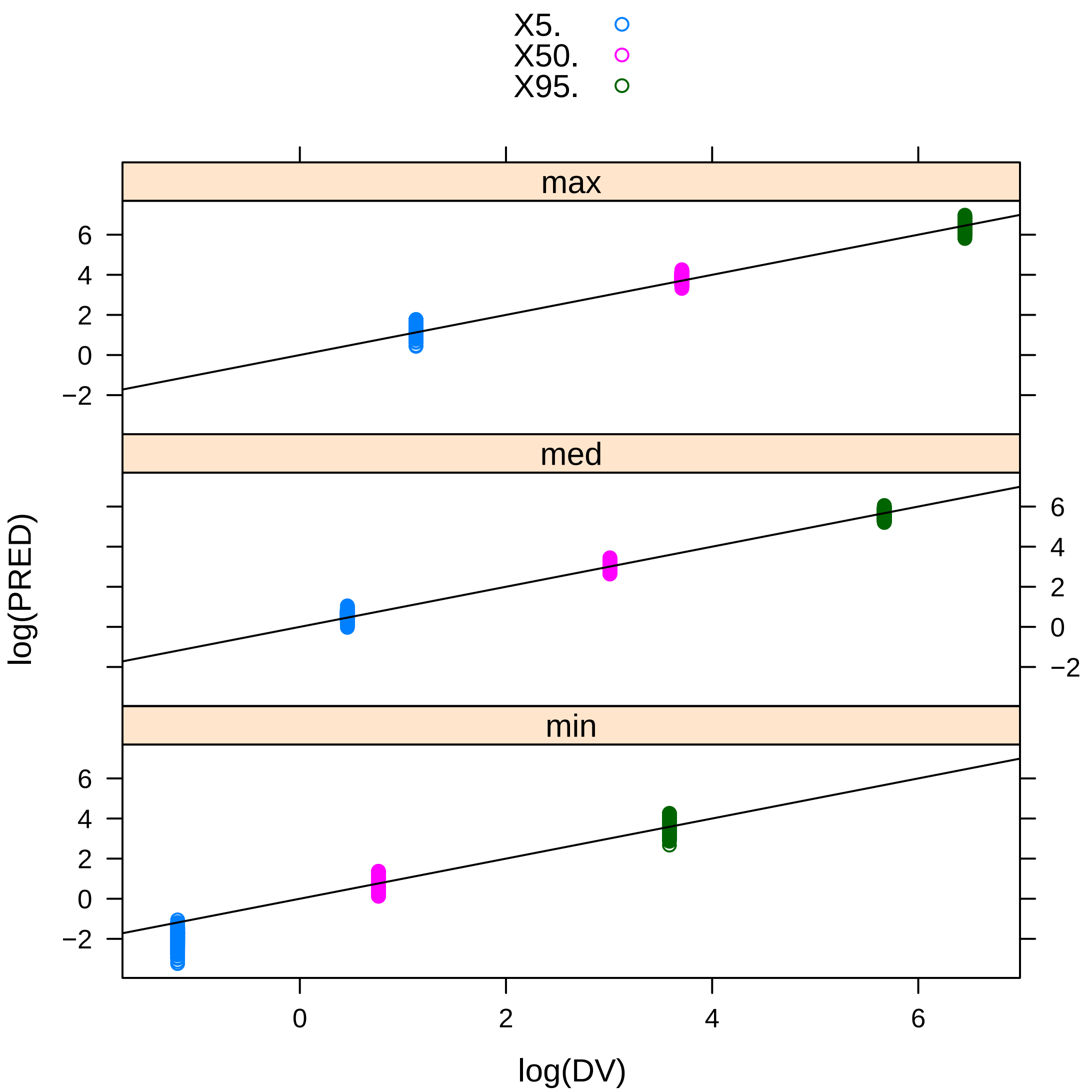
```
> frozen <- data.frame(cast(molten, SIM + metric + quant  ~  variable))
> head(frozen)

  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
```

3.6.7 Bivariate display of within-simulation aggregate metrics.

Listing 30:

```
> 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)
+       }
+ ))
```



3.6.8 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.

3.6.9 Classic stripplot

Listing 31:

```
> 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 32:

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

  DV PRED
4500 4500
```

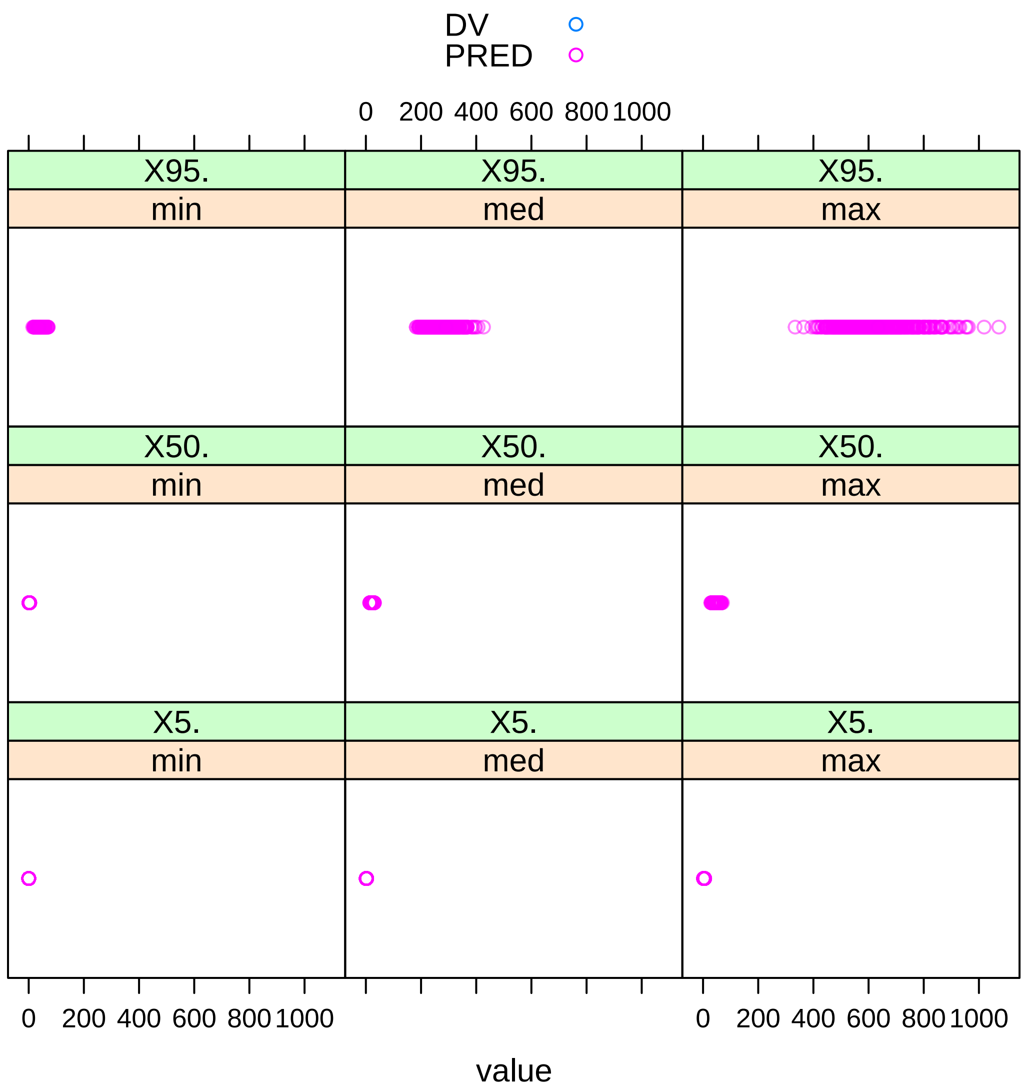
Listing 33:

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

  DV PRED
   9 4500
```

Listing 34:

```
> 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
+ ))
```

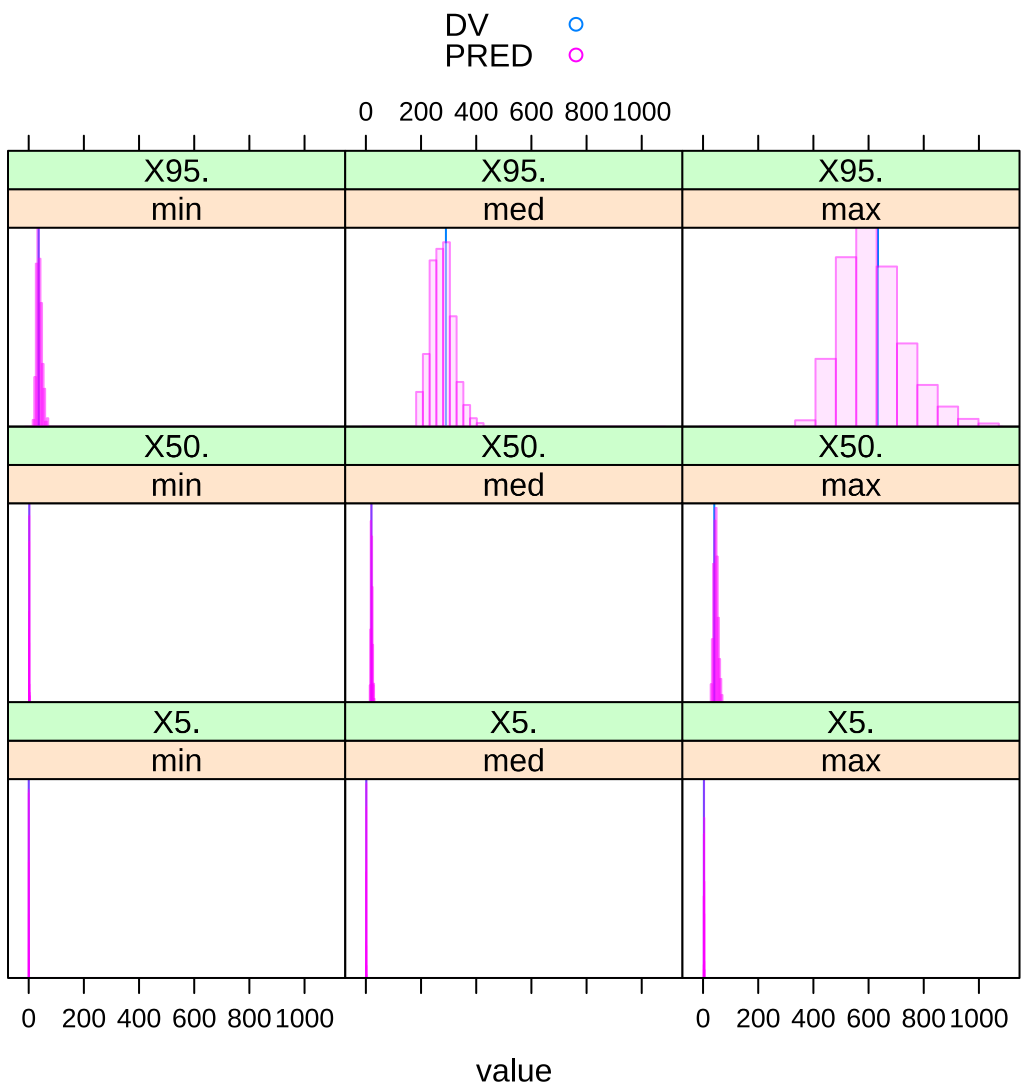


3.6.10 Needle-in-the-haystack

Listing 35:

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

```
+       alpha=0.5,
+       panel.groups=function(x,type,group.number,col.line,fill,col,...){
+               #browser()
+               view <- viewport(xscale=current.viewport()$xscale,yscale=c(0,max(
    hist(x,plot=FALSE)$density)))
+               pushViewport(view)
+               if(group.number==1) panel.abline(v=x,col=col.line)
+               else panel.histogram(x,breaks=NULL,col=fill,border=col.line,...)
+               popViewport()
+       }
+ ))
```

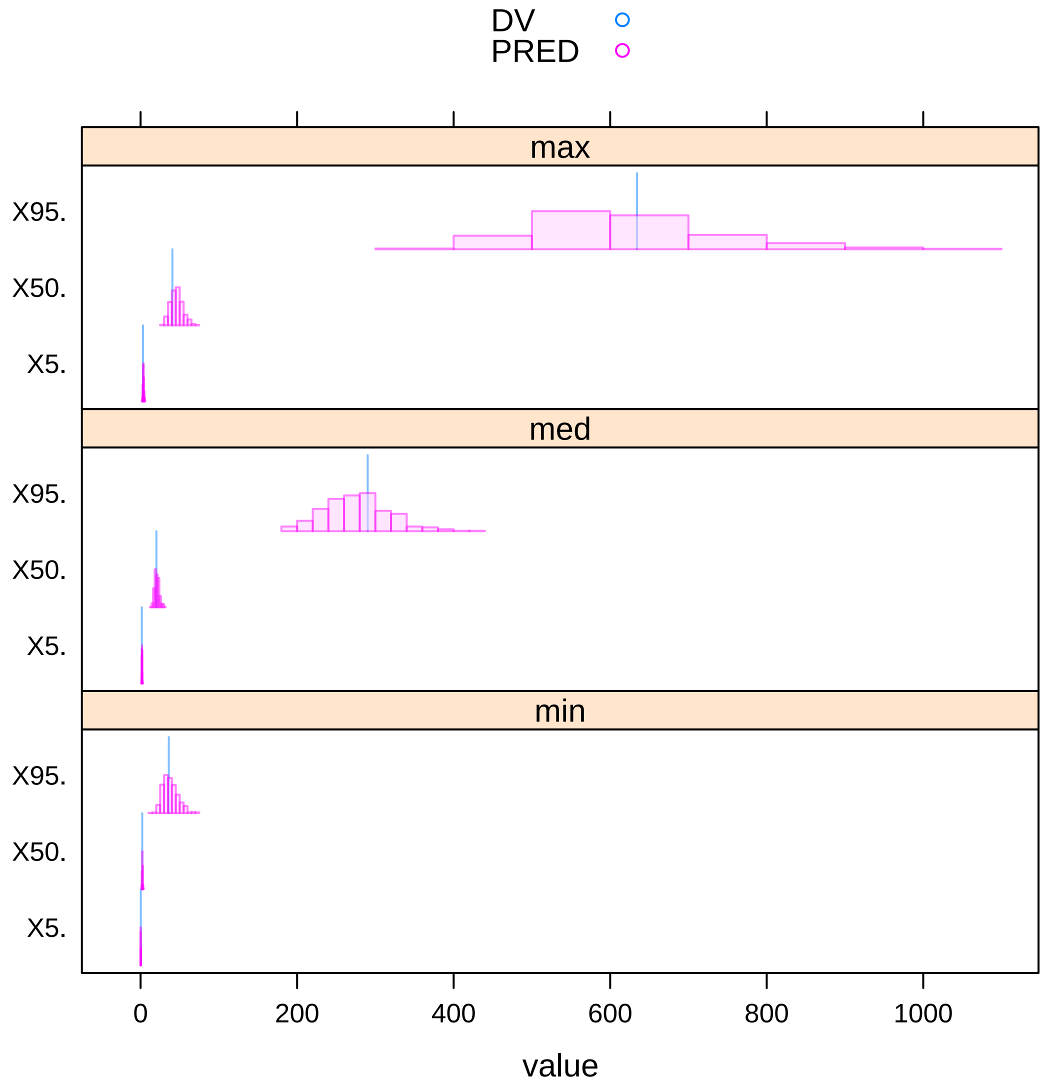


3.6.11 Haystacks in strips

Listing 36:

```
> print(stripplot(
+       quant ~ value|metric,
+       molten,
+       groups=variable,
+       auto.key=TRUE,
+       layout=c(1,3),
+       panel=panel.stratify,
```

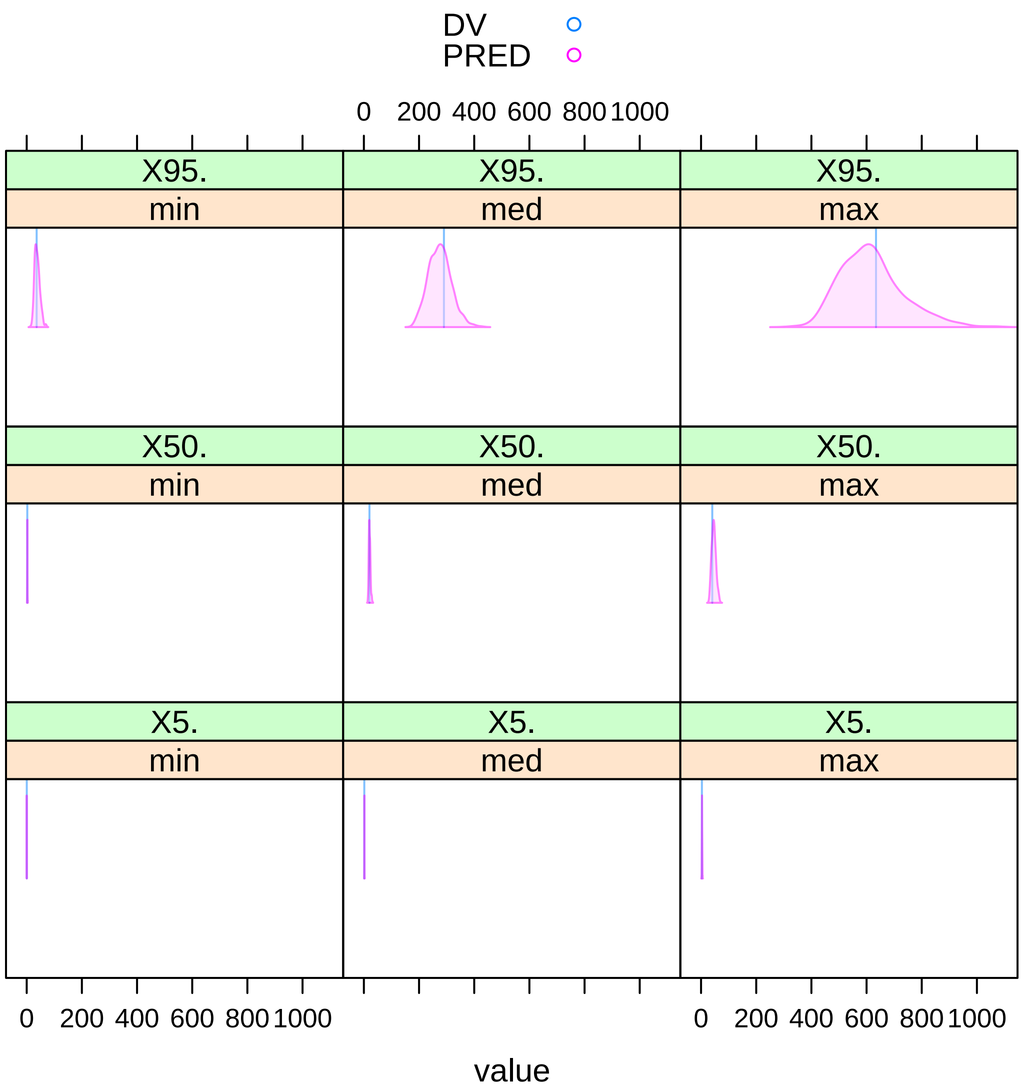
```
+         alpha=0.5,
+         panel.levels=function(group.number,...){
+                 if(group.number==1)panel.bar(...)
+                 else panel.hist(...)
+         }
+ ))
```



3.6.12 Density stripplot

Listing 37:

```
> print(stripplot(
+        ~ value|metric+quant,
+       molten,
+       groups=variable,
+       auto.key=TRUE,
+       panel=panel.stratify,
+       alpha=0.5,
+       panel.levels = function(group.number,x,y,font,col,col.line,...){
+               if(group.number==1)panel.segments(x0=x,x1=x,y0=y,y1=y+1,col=col.
   line,...)
+               else panel.densitystrip(x=x,y=y,col.line=col.line,...)
+       }
+ ))
```

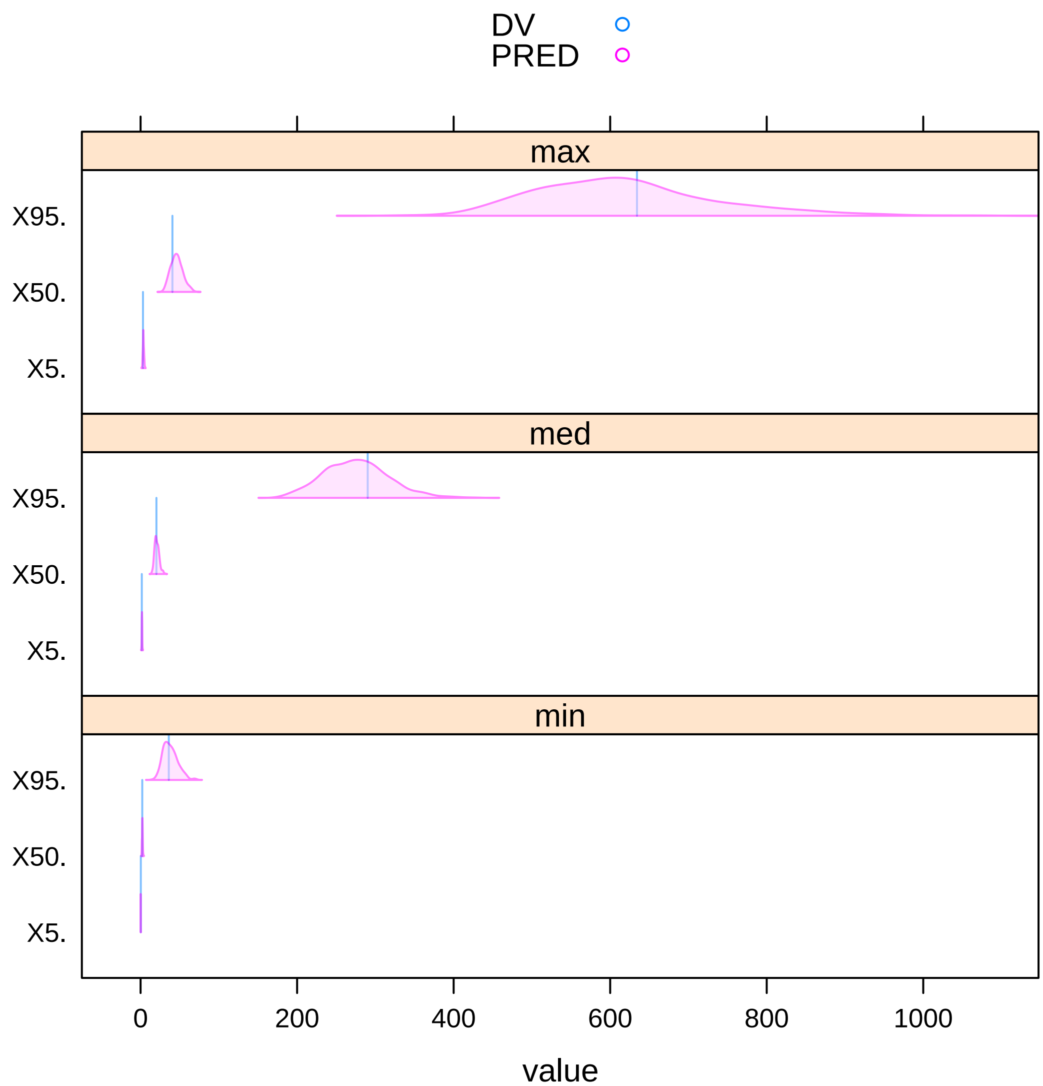


3.6.13 Density variant: multistrip panels

Listing 38:

```
> 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)panel.segments(x0=x,x1=x,y0=y,y1=y+1,col=col.
    line,...)
+               else panel.densitystrip(x=x,y=y,col=fill,border=col.line,...)
+       }
+ ))
```

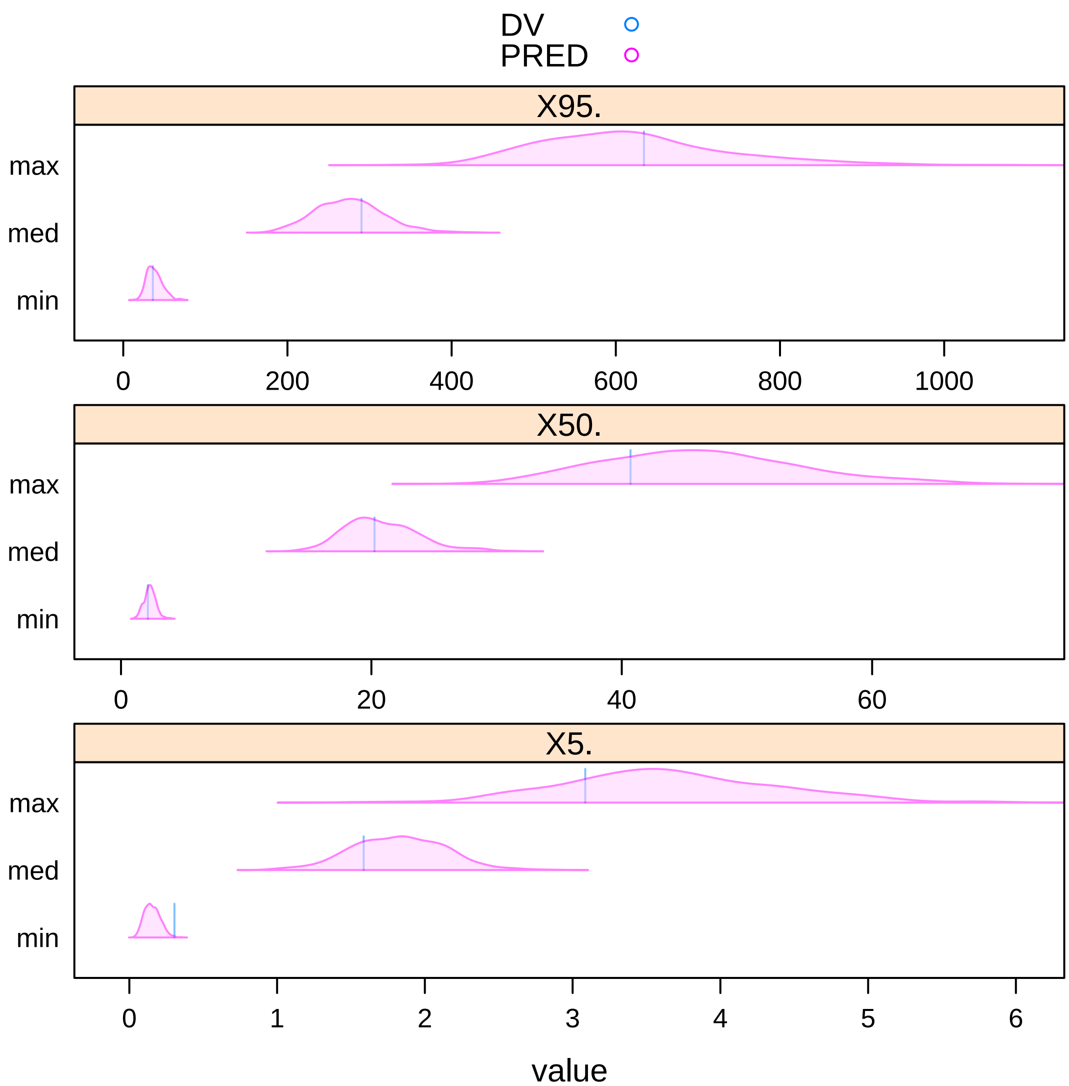


3.6.14 Density variant: interchanging the ordinal and the conditional

Listing 39:

```
> print(stripplot(
+       metric ~ value|quant,
+       molten,
+       groups=variable,
+       horizontal=TRUE,
+       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)panel.segments(x0=x,x1=x,y0=y,y1=y+0.5,col=col.
    line,...)
+                else panel.densitystrip(x=x,y=y,col=fill,border=col.line,...)
+        }
+ ))
```



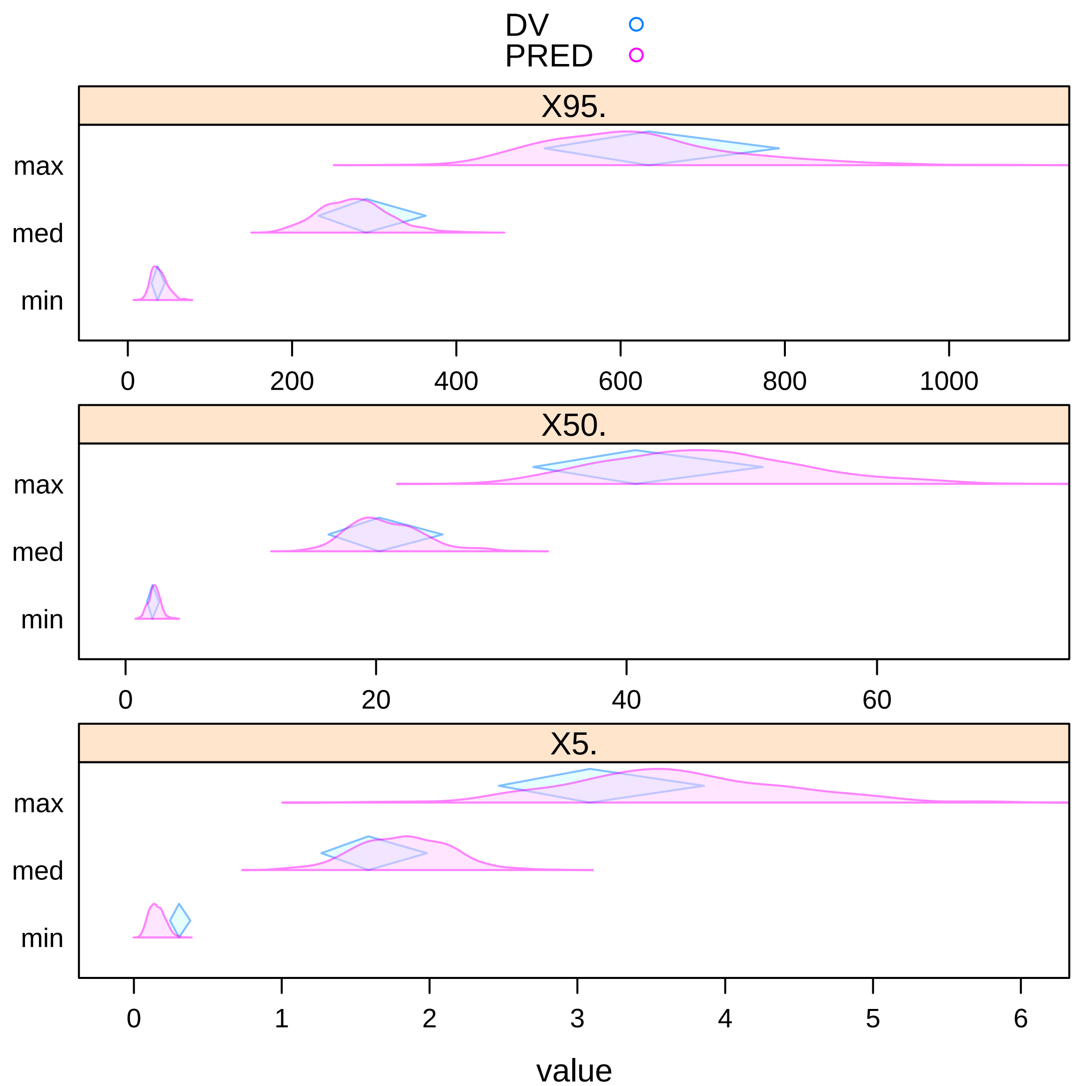
3.6.15 Diamondback: indicating reference regions

It is often useful to show some reference region around a reference point estimate. Here is one option.

Listing 40:

```
> print(stripplot(
+       metric ~ value|quant,
+       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 41:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/mi210/script"
```

Listing 42:

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

4.2 Create replicate control streams.

Listing 43:

```
> t <- metaSub(
+       as.filename('../nonmem/ctl/1005.ctl'),
+       names=1:300,
+       pattern=c(
+           '1005',
+           '../../data/ph1/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 44:

```
>  bootset <- read.csv('../data/ph1/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.

Again, model step is commented for safety. Run manually.

Listing 45:

```
> getwd()
```

```
[1] "/Users/timb/project/metrum-mifuns/inst/mi210/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 46:

```
> #boot <- read.csv('../nonmem/1005.boot/log.csv',as.is=TRUE)
> boot <- rlog(
+       run=1:300,
+       project='../nonmem/1005.boot',
+       boot=TRUE,
+       append=FALSE,
+       tool='nm7'
+ )
> head(boot)
```

```
  tool run parameter   moment                                            value
1  nm7   1      prob     text 1 phase1 2 CMT like 1004 but diff. initial on V3
2  nm7   1       min   status                                                0
3  nm7   1        P1 estimate                                          7.98893
4  nm7   1        P2 estimate                                           19.892
5  nm7   1        P3 estimate                                        0.0650249
6  nm7   1        P4 estimate                                          3.35627
```

Listing 47:

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

```
 [1] "prob" "min"  "P1"   "P2"   "P3"   "P4"   "P5"   "P6"   "P7"   "P8"  
[11] "P9"   "P10"  "P11"  "P12"  "P13"  "P14"  "ofv" 
```

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

Listing 48:

```
> pars <- paste('P',1:14,sep='')
> pars
```

```
 [1] "P1"  "P2"  "P3"  "P4"  "P5"  "P6"  "P7"  "P8"  "P9"  "P10" "P11" "P12"
[13] "P13" "P14"
```

Listing 49:

```
> boot <- boot[boot$parameter %in% pars,]
> head(boot)
```

```
  tool run parameter   moment     value
3  nm7   1        P1 estimate   7.98893
4  nm7   1        P2 estimate    19.892
5  nm7   1        P3 estimate 0.0650249
6  nm7   1        P4 estimate   3.35627
7  nm7   1        P5 estimate   123.566
8  nm7   1        P6 estimate   1.18258
```

Listing 50:

```
> unique(boot$moment)
```

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

Listing 51:

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

```
[1] "Inf"
```

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

Listing 52:

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

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

Listing 53:

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

```
  run parameter     value
3   1        P1   7.98893
4   1        P2    19.892
5   1        P3 0.0650249
6   1        P4   3.35627
7   1        P5   123.566
8   1        P6   1.18258
```

Listing 54:

```
> unique(boot$value[boot$parameter %in% c('P10','P12','P13')])
```

```
[1] "0"
```

Listing 55:

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

```
[1] "P10" "P12" "P13"
```

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

Listing 56:

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

```
[1] FALSE
```

Listing 57:

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

```
  run parameter       value
3   1        P1   7.9889300
4   1        P2  19.8920000
5   1        P3   0.0650249
6   1        P4   3.3562700
7   1        P5 123.5660000
8   1        P6   1.1825800
```

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 58:

```
> 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 59:

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

```
[1] 3124
```

Listing 60:

```
> head(boot)
```

```
  run parameter       value        upper       lower
3   1         P1   7.9889300  10.18006750  6.90182250
4   1         P2  19.8920000  26.29300250 17.74395750
5   1         P3   0.0650249   0.08202897  0.05760593
6   1         P4   3.3562700   5.12041500  2.78587675
7   1         P5 123.5660000 165.65365000 82.14751500
8   1         P6   1.1825800   1.38279825  0.75346095
```

Listing 61:

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

```
  run parameter       value
3   1         P1   7.9889300
4   1         P2  19.8920000
5   1         P3   0.0650249
6   1         P4   3.3562700
7   1         P5 123.5660000
8   1         P6   1.1825800
```

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 62:

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

```
[1] "$SIGMA 0.09 ;0.1"
[2] ";<parameter name='P14' label='ERR'>proportional error</parameter>"
[3] "$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 63:

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

```
 [1] "<document>"
 [2] "<parameter name='P1' label='CL'>clearance</parameter>"
 [3] "<parameter name='P2' label='V2'>central volume</parameter>"
 [4] "<parameter name='P3' label='Ka'>absorption constant</parameter>"
 [5] "<parameter name='P4' label='Q' >intercompartmental clearance</parameter>"
 [6] "<parameter name='P5' label='V3'>peripheral volume</parameter>"
```

```
 [7] "<parameter name='P6' label='Male.CL'>male effect on clearance</parameter>"
 [8] "<parameter name='P7' label='WT.CL'>weight effect on clearance</parameter>"
 [9] "<parameter name='P8' label='IIV.CL'>interindividual variability on clearance
     </parameter>"
[10] "<parameter name='P9' label='CL.V2'>covariance of clearance and central
    volume</parameter>"
[11] "<parameter name='P10' label='IIV.V2'>interindividual variability on central
    volume</parameter>"
[12] "<parameter name='P11' label='CL.Ka'>covariance of clearance and Ka</
    parameter>"
[13] "<parameter name='P12' label='V2.Ka'>covariance of central volume and Ka</
    parameter>"
[14] "<parameter name='P13' label='IIV.Ka'>interindividual variability on Ka</
    parameter>"
[15] "<parameter name='P14' label='ERR'>proportional error</parameter>"
[16] "</document>"
```

Listing 64:

```
> pars
```

```
 [1] "P1"  "P2"  "P3"  "P4"  "P5"  "P6"  "P7"  "P8"  "P9"  "P10" "P11" "P12"
[13] "P13" "P14"
```

Listing 65:

```
> defs <- lookup(pars,within=doc)
> defs
```

```
                                              P1
                                     "clearance"
                                              P2
                                "central volume"
                                              P3
                           "absorption constant"
                                              P4
                  "intercompartmental clearance"
                                              P5
                             "peripheral volume"
                                              P6
                      "male effect on clearance"
                                              P7
                    "weight effect on clearance"
                                              P8
      "interindividual variability on clearance"
                                              P9
    "covariance of clearance and central volume"
                                             P10
"interindividual variability on central volume"
                                             P11
                  "covariance of clearance and Ka"
```

```
                                              P12
          "covariance of central volume and Ka"
                                              P13
            "interindividual variability on Ka"
                                              P14
                           "proportional error"
```

Listing 66:

```
> labels <- lookup(pars,within=doc,as='label')
> labels
```

```
 P1.label  P2.label  P3.label  P4.label  P5.label  P6.label  P7.label  P8.label
     "CL"      "V2"      "Ka"       "Q"      "V3" "Male.CL"   "WT.CL"  "IIV.CL"
 P9.label P10.label P11.label P12.label P13.label P14.label
  "CL.V2"  "IIV.V2"   "CL.Ka"   "V2.Ka"  "IIV.Ka"     "ERR"
```

Listing 67:

```
> boot$parameter <- as.character(factor(boot$parameter,levels=pars,labels=labels))
> head(boot)
```

```
  run parameter       value
3   1        CL   7.9889300
4   1        V2  19.8920000
5   1        Ka   0.0650249
6   1         Q   3.3562700
7   1        V3 123.5660000
8   1   Male.CL   1.1825800
```

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 68:

```
> covariates <- read.csv('../data/ph1/derived/phase1.csv',na.strings='.')
> head(covariates)
```

```
     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 69:

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

```
[1] TRUE
```

Listing 70:

```
> 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 71:

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

```
[1] 81
```

Listing 72:

```
> 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 73:

```
> head(boot)

  run parameter       value
3   1        CL   7.9889300
4   1        V2  19.8920000
5   1        Ka   0.0650249
6   1         Q   3.3562700
7   1        V3 123.5660000
8   1   Male.CL   1.1825800
```

Listing 74:

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

   run parameter    value
3    1        CL 7.988930
8    1   Male.CL 1.182580
9    1     WT.CL 1.308790
34   2        CL 7.636730
39   2   Male.CL 0.956565
40   2     WT.CL 2.369810
```

Listing 75:

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

  run      CL  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 76:

```
> frozen$WT.CL65 <- (60/70)**frozen$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 77:

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

```
[1] 8.56139
```

Listing 78:

```
> frozen$CL <- frozen$CL/cl
> head(frozen)
```

```
  run        CL  Male.CL   WT.CL   WT.CL65  WT.CL75  WT.CL85
1   1 0.9331347 1.182580 1.30879 0.8172985 1.094499 1.289313
2   2 0.8919965 0.956565 2.36981 0.6939830 1.177625 1.584253
3   3 1.0689830 0.937231 1.88593 0.7477270 1.138960 1.442193
4   4 1.1168023 1.028670 1.47186 0.7970099 1.106883 1.330787
5   5 0.9776029 0.914796 1.97656 0.7373533 1.146104 1.467795
6   6 1.0625623 1.079030 1.16319 0.8358496 1.083560 1.253376
```

Listing 79:

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

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

4.8.4 Plot.

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

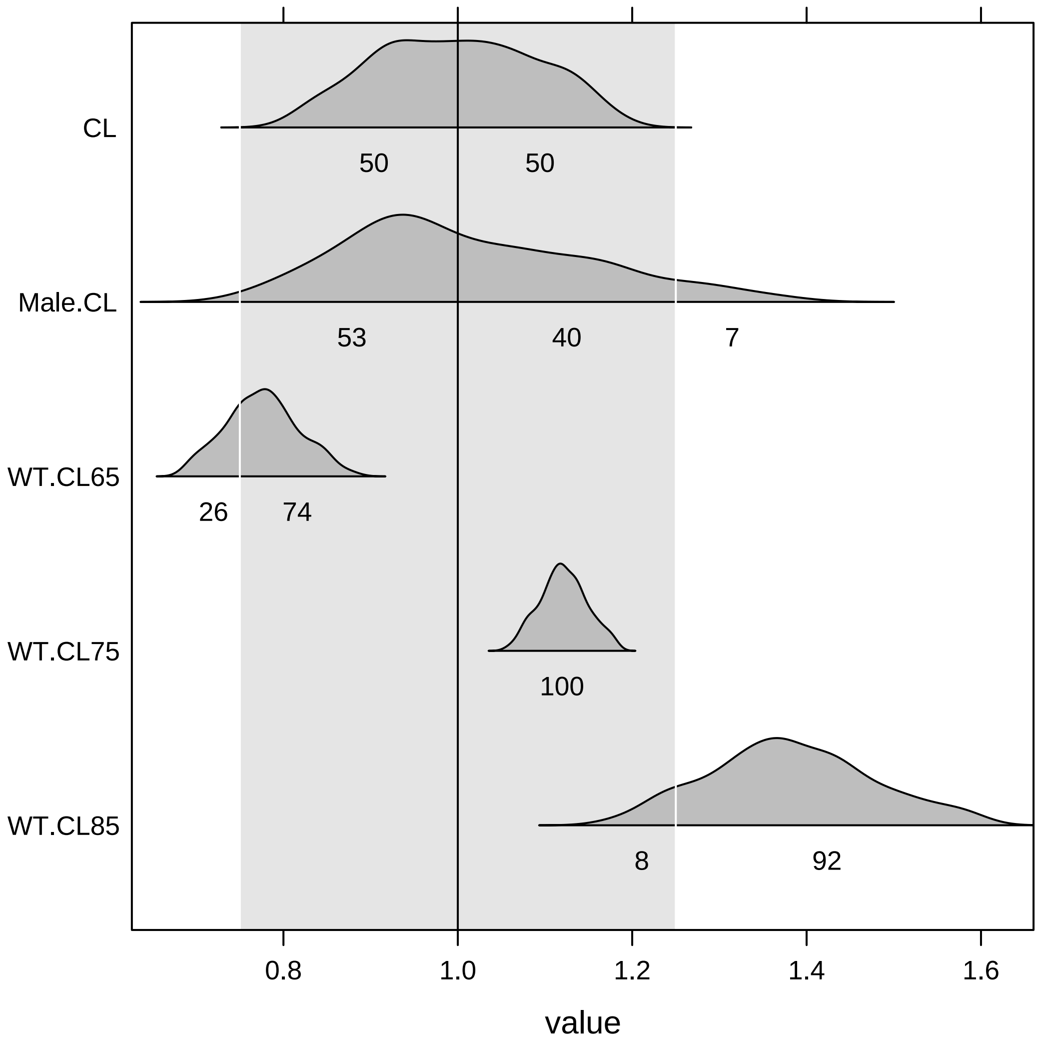
Listing 80:

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

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

Listing 81:

```
> print(stripplot(
+       factor(
+               variable,levels= c(
+                       "WT.CL85",
+                       "WT.CL75",
+                       "WT.CL65",
+                       "Male.CL",
+                       "CL"
+               )
+       ) ~ 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.