

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. Covariance succeeded on model 1005.

3 Predictive Check

3.1 Create a simulation control stream.

Listing 4:

```
> 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).

3.3 Recover and format the original dataset.

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

Listing 5:

```

> 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						
2	0	29.1	1000	1	0	0	83.5		0						
3	0	29.1	1000	1	0	0	83.5		0						
4	0	29.1	1000	1	0	0	83.5		0						
5	0	29.1	1000	1	0	0	83.5		0						
6	0	29.1	1000	1	0	0	83.5		0						

Listing 6:

```

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

```

```
> records <- nrow(phase1)
```

```
> records
```

```
[1] 550
```

Listing 7:

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

```
> nrow(phase1)
```

```
[1] 275000
```

Listing 8:

```
> 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 9:

```

> 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 10:

```

> 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 11:

```

> pred <- scan('../nonmem/1105/1105.tab')
> nrow(phase1)
[1] 27500

```

Listing 12:

```

> length(pred)
[1] 27500

```

3.5 Combine the original data and the simulation data.

Listing 13:

```
> 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 14:

```
> 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 15:

```
> 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 16:

```
> 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 17:

```
> subject <- melt(phase1,measure.var=c('DV','PRED'))
> head(subject)
```

SUBJ	TIME	SIM	variable	value
1	1	0.25	DV	0.363
2	1	0.50	DV	0.914
3	1	1.00	DV	1.120
4	1	2.00	DV	2.280
5	1	3.00	DV	1.630
6	1	4.00	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 18:

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

Now we cast, ignoring time.

Listing 19:

```
> subject <- data.frame(cast(subject, SUBJ + SIM + variable ~ .,fun=metrics))
> head(subject)
```

SUBJ	SIM	variable	min	med	max
1	1	DV	0.363000	1.6100	3.0900
2	1	PRED	0.179320	1.9653	5.0314
3	2	DV	0.363000	1.6100	3.0900
4	2	PRED	0.096462	3.0448	7.4728
5	3	DV	0.363000	1.6100	3.0900
6	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 20:

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

SUBJ	SIM	variable	metric	value
1	1		DV	min 0.363000
2	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 21:

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

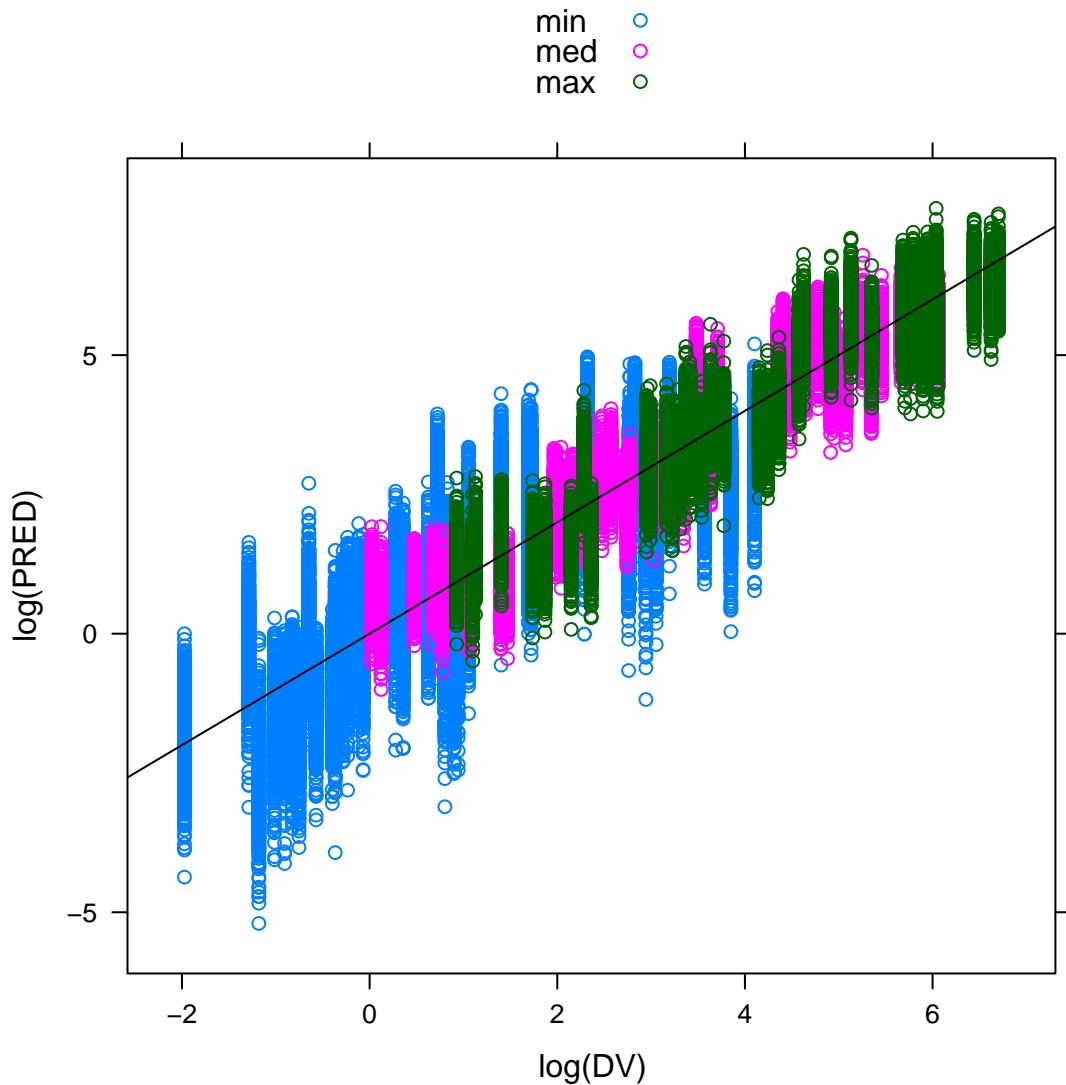
SUBJ	SIM	metric	DV	PRED
1	1	1	min 0.363	0.179320
2	1	1	med 1.610	1.965300
3	1	1	max 3.090	5.031400
4	1	2	min 0.363	0.096462
5	1	2	med 1.610	3.044800
6	1	2	max 3.090	7.472800

3.6.4 Simple bivariate plot.

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

Listing 22:

```
> 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 23:

```
> 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 24:

```
> 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 25:

```
> 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 26:

```
> 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 27:

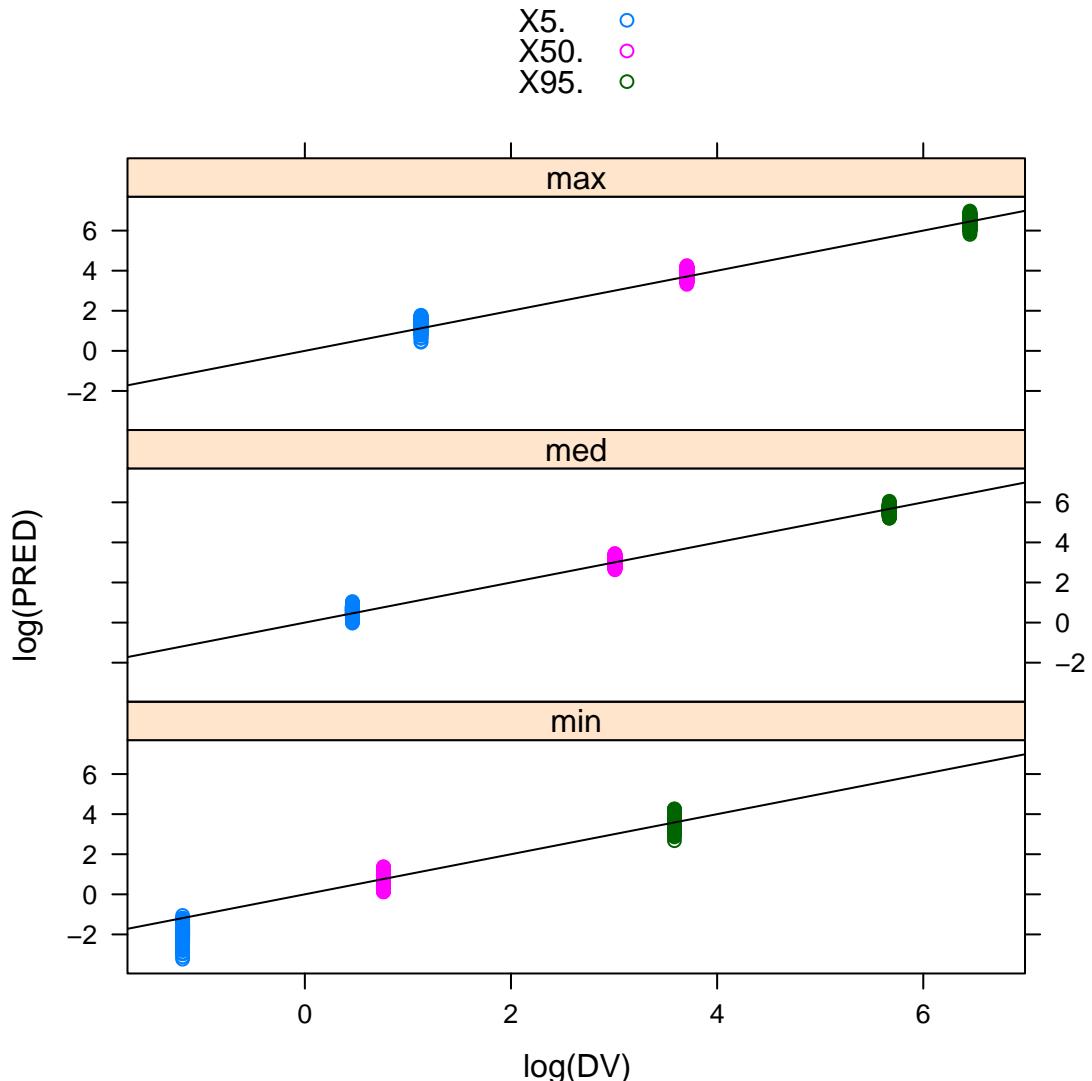
```
> frozen <- data.frame(cast(molten, SIM + metric + quant ~ variable))
> head(frozen)
```

	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 28:

```
> 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 29:

```
> 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 30:

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

  DV PRED
4500 4500
```

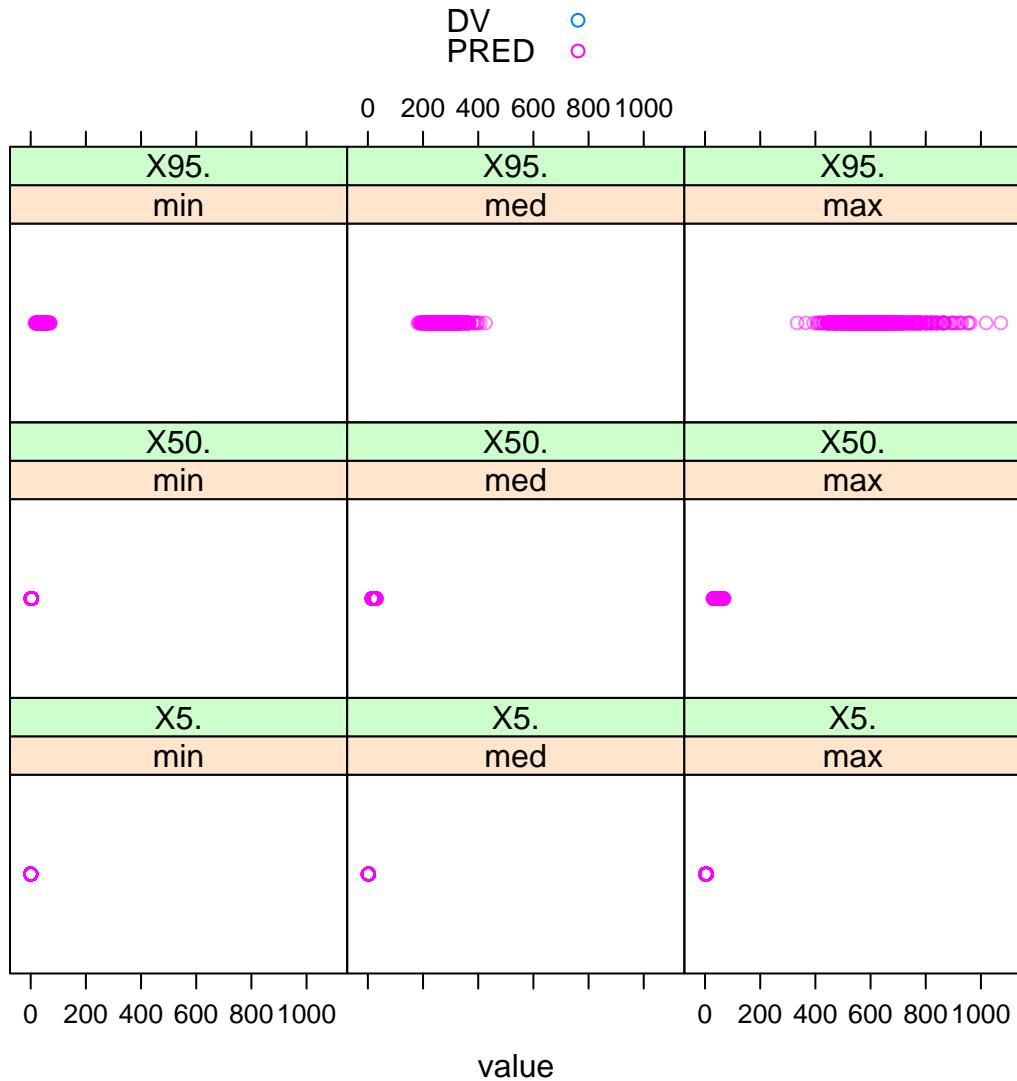
Listing 31:

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

  DV PRED
        9 4500
```

Listing 32:

```
> 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
+ ))
```

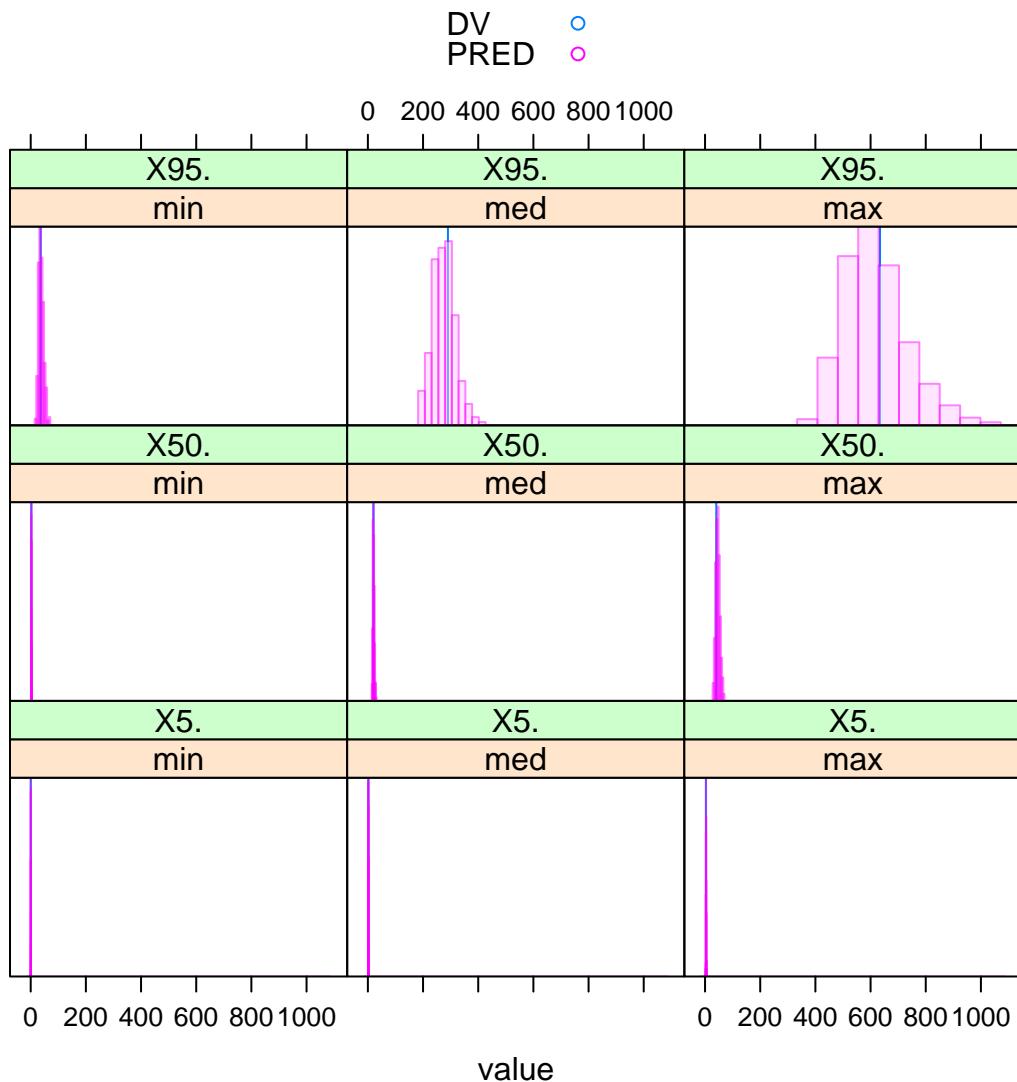


3.6.10 Needle-in-the-haystack

Listing 33:

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

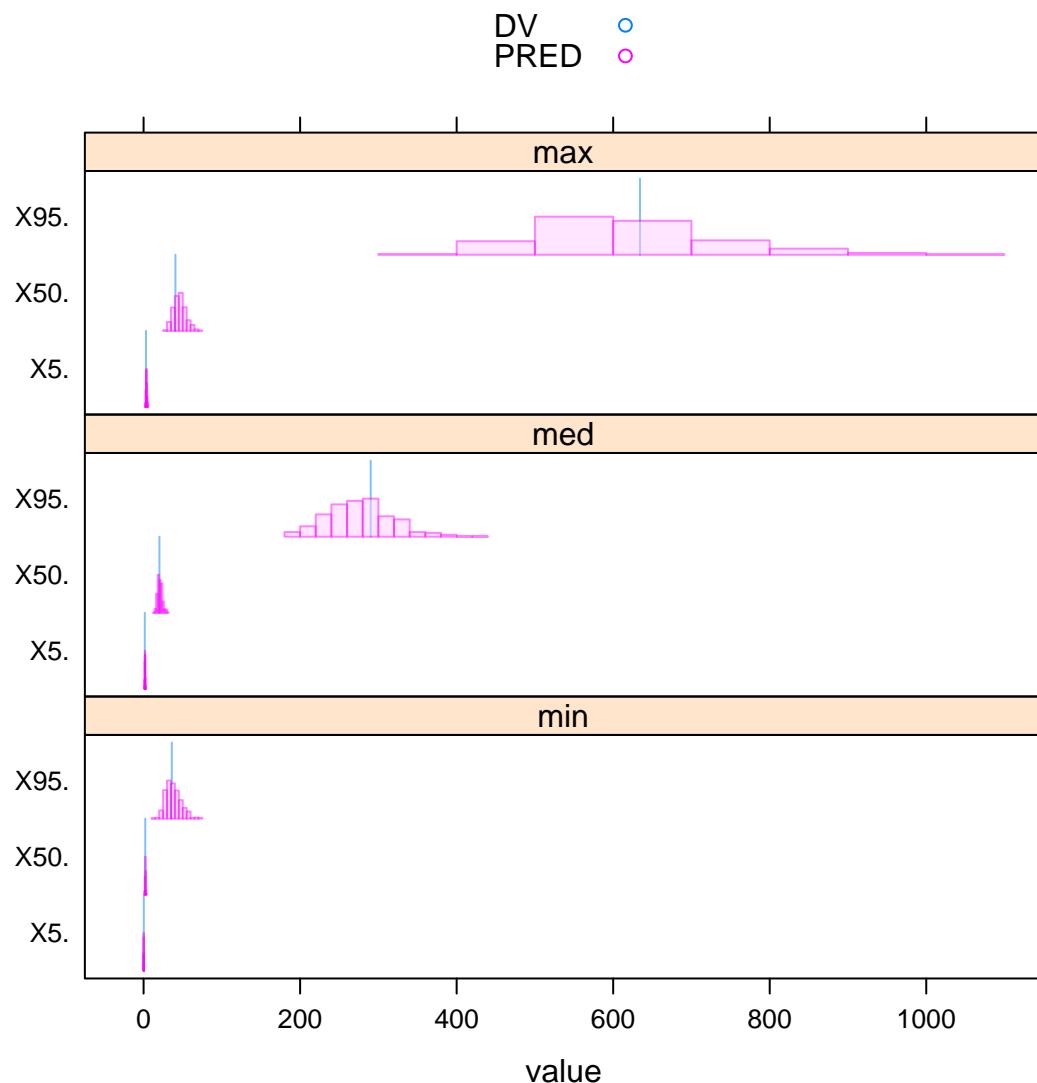


3.6.11 Haystacks in strips

Listing 34:

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

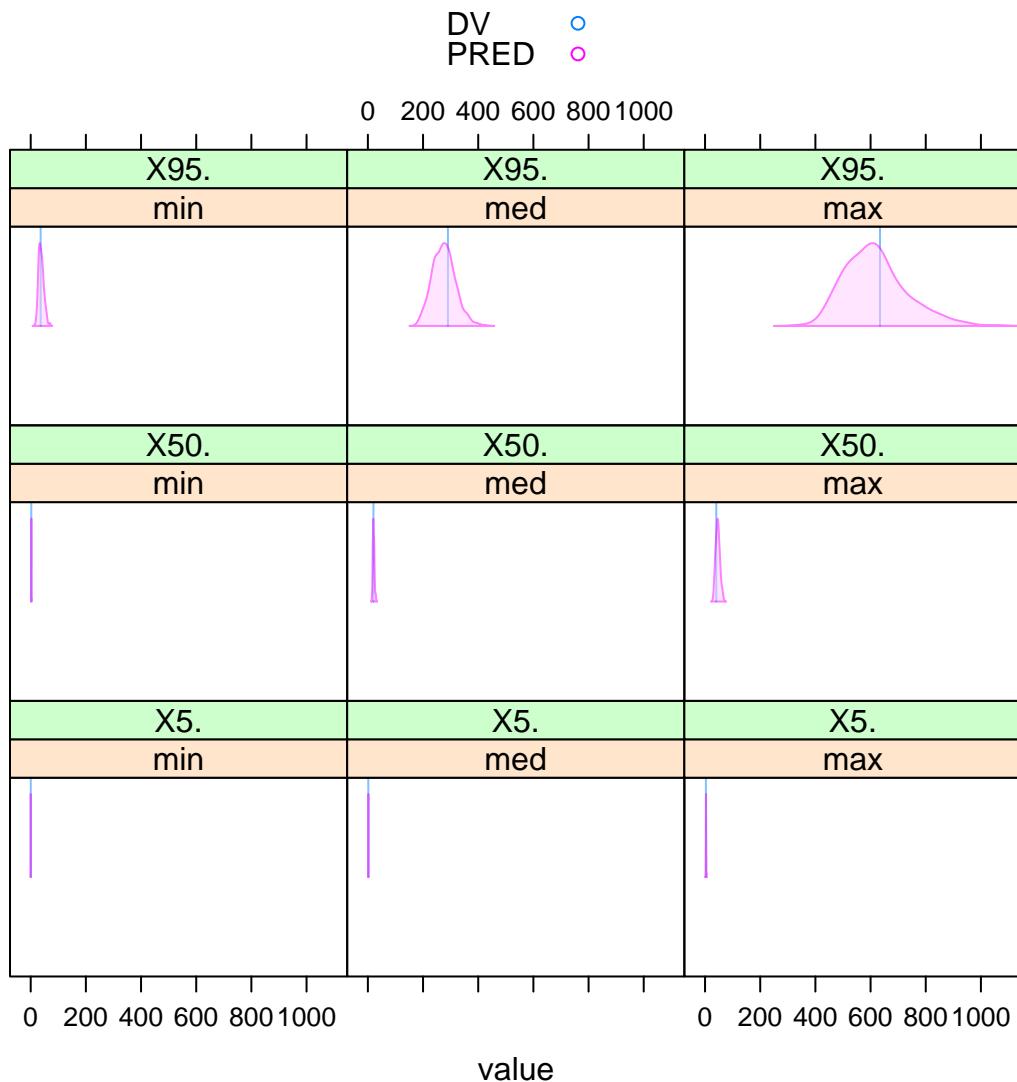
```
+     alpha=0.5,
+     panel.levels=function(group.number,...){
+       if(group.number==1)panel.bar(...)
+       else panel.hist(...)
+     }
+   ))
```



3.6.12 Density stripplot

Listing 35:

```
> 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,...)
+   }
+ ))
```

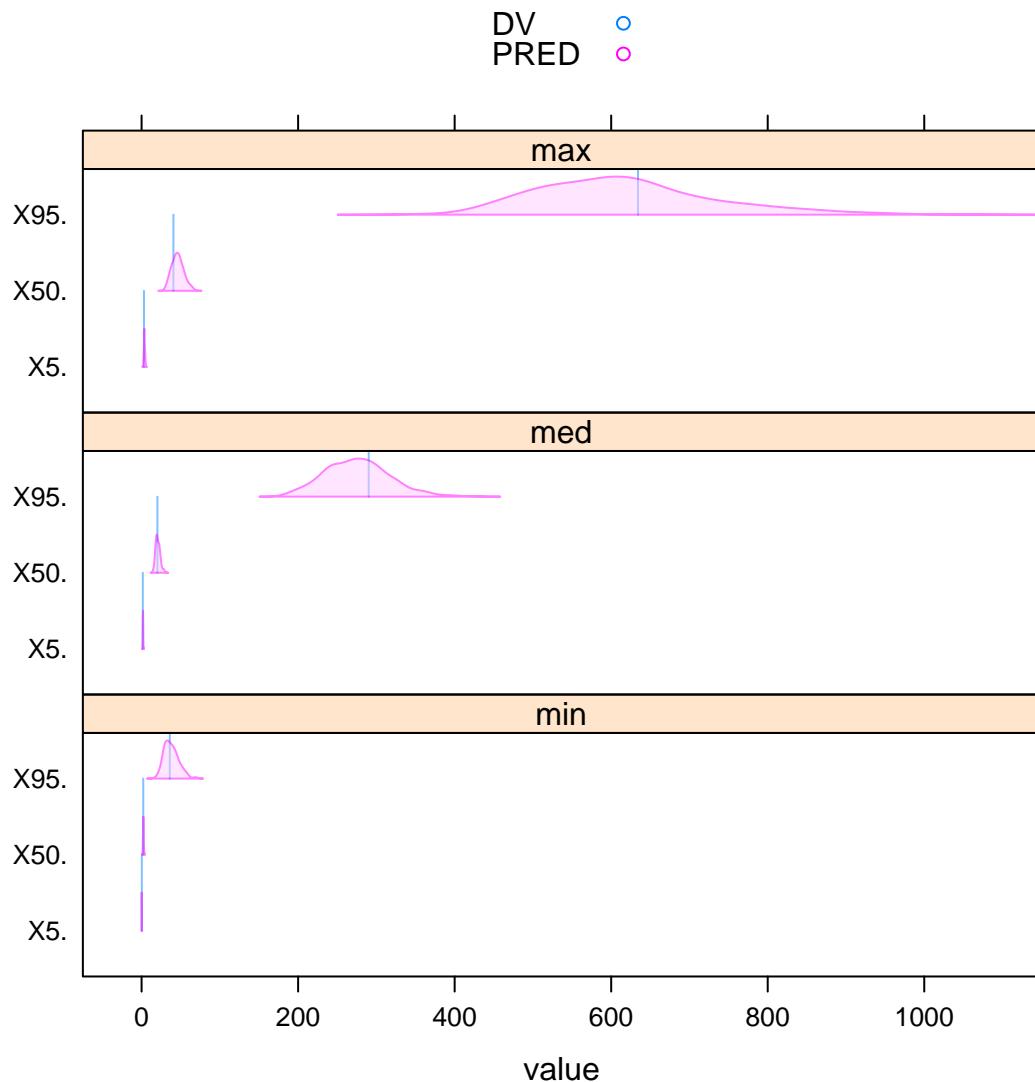


3.6.13 Density variant: multistrip panels

Listing 36:

```
> 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,...)
+     }
+   ))
```

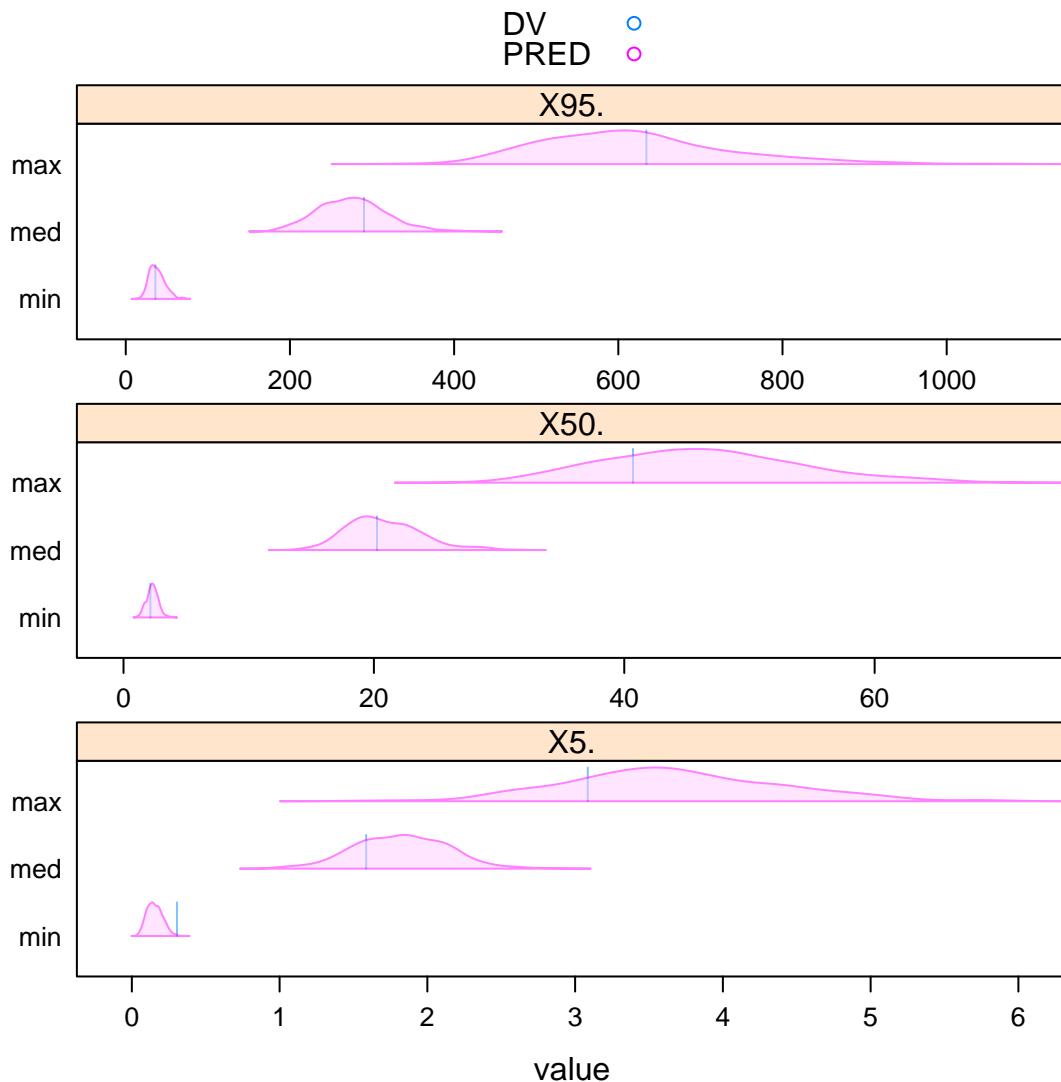


3.6.14 Density variant: interchanging the ordinal and the conditional

Listing 37:

```
> 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,...)
+     }
+   ))
```



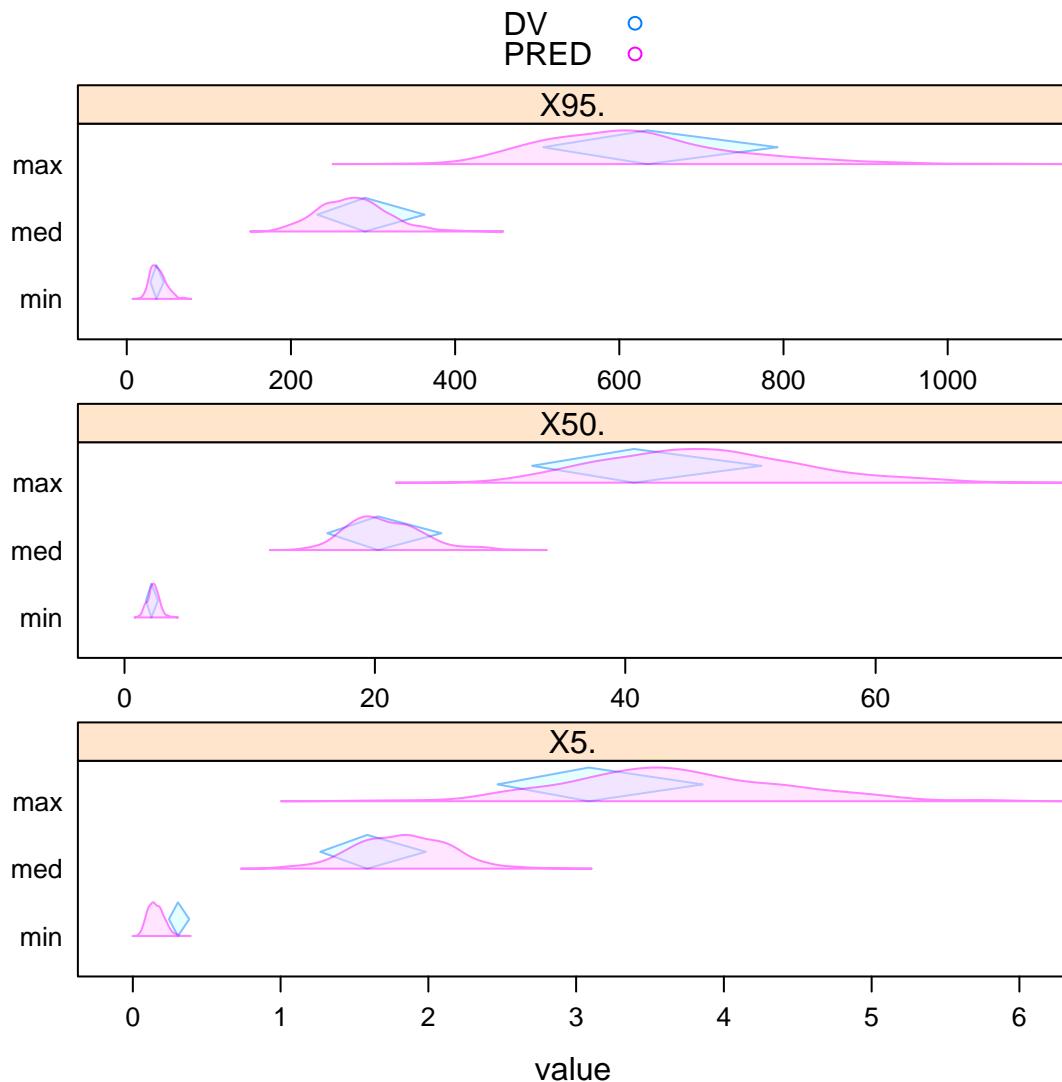
3.6.15 Diamondback: indicating reference regions

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

Listing 38:

```
> 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 39:

```
> getwd()
```

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

Listing 40:

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

4.2 Create replicate control streams.

Listing 41:

```
> 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 42:

```
> 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.

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 43:

```
> #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 phasel 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 44:

```
> 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 45:

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

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

Listing 46:

```
> 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 47:

```
> unique(boot$moment)
[1] "estimate" "prse"
```

Listing 48:

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

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

Listing 49:

```
> boot <- boot[boot$moment=='estimate',]
> boot$moment <- NULL
> unique(boot$tool)
[1] "nm7"
```

Listing 50:

```
> 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 51:

```
> unique(boot$value[boot$parameter %in% c('P10','P12','P13')])
[1] "0"
```

Listing 52:

```
> unique(boot$parameter[boot$value=='0'])
[1] "P10" "P12" "P13"
```

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

Listing 53:

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

```
[1] FALSE
```

Listing 54:

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

run	parameter	value
3	P1	7.9889300
4	P2	19.8920000
5	P3	0.0650249
6	P4	3.3562700
7	P5	123.5660000
8	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 55:

```
> 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 56:

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

```
[1] 3124
```

Listing 57:

```
> head(boot)
```

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

Listing 58:

```
> 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 59:

```
> 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 60:

```
> 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 61:

```
> pars
```

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

Listing 62:

```
> 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 63:

```
> 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 64:

```
> 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 65:

```
> covariates <- read.csv('../data/ph1/derived/phasel1.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															
2															
3															

```
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 66:

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

```
[1] TRUE
```

Listing 67:

```
> 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 68:

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

```
[1] 81
```

Listing 69:

```
> 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 70:

```
> 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 71:

```

> clearance <- 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 72:

```

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

```

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

Listing 73:

```

> 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 74:

```

> cl <- median(boot$value[boot$parameter=='CL'])
> cl
[1] 8.56139

```

Listing 75:

```
> 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 76:

```
> 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.

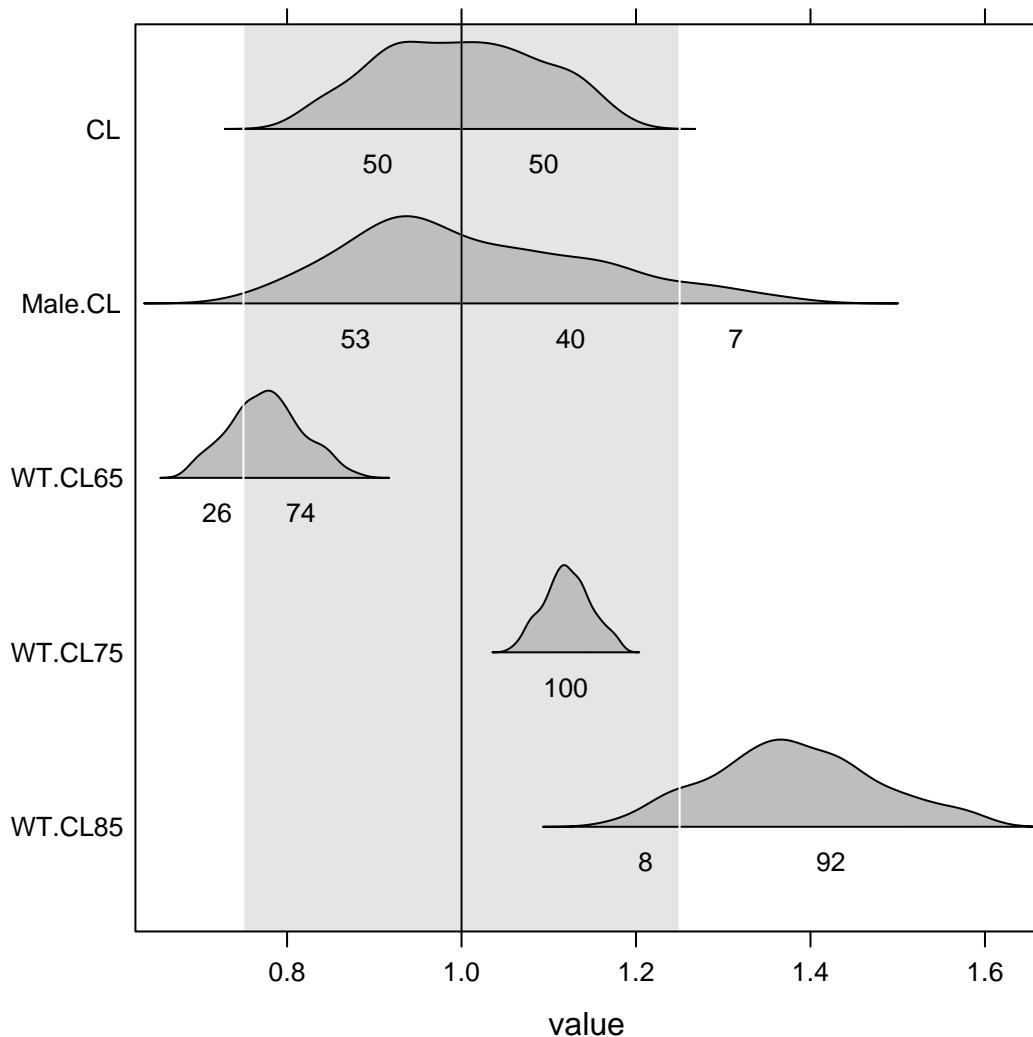
Listing 77:

```
> levels(molten$variable)

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

Listing 78:

```
> 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.