

Covariate Plots

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1 Purpose

This script picks up after model.Rnw to process bootstrap results and make covariate plots.

1.1 Summarize bootstrap models.

Listing 1:

```
> #wait for bootstraps to finish
> getwd()

[1] "/data/metrumrg/inst/example/project/script"
```

Listing 2:

```
> require(metrumrg)
> boot <- read.csv('../nonmem/1005bootlog.csv', as.is=TRUE)
> head(boot)
```

	X	tool	run	parameter	moment	value
1	1	nm7	1	ofv	minimum	2459.17577376723
2	2	nm7	1	THETA1	estimate	9.90624
3	3	nm7	1	THETA1	prse	<NA>
4	4	nm7	1	THETA1	se	<NA>
5	5	nm7	1	THETA2	estimate	21.8851
6	6	nm7	1	THETA2	prse	<NA>

Listing 3:

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

```
[1] "ofv"      "THETA1"   "THETA2"   "THETA3"   "THETA4"   "THETA5"
[7] "THETA6"   "THETA7"   "OMEGA1.1" "OMEGA2.1" "OMEGA2.2" "OMEGA3.1"
[13] "OMEGA3.2" "OMEGA3.3" "SIGMA1.1" "SIGMA2.1" "SIGMA2.2" "cov"
[19] "prob"     "min"      "data"
```

Listing 4:

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

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

Listing 5:

```
> boot$X <- NULL
```

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

Listing 6:

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

	tool	run	parameter	moment	value
2	nm7	1	THETA1	estimate	9.90624
3	nm7	1	THETA1	prse	<NA>
4	nm7	1	THETA1	se	<NA>
5	nm7	1	THETA2	estimate	21.8851
6	nm7	1	THETA2	prse	<NA>
7	nm7	1	THETA2	se	<NA>

Listing 7:

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

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

Listing 8:

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

```
[1] NA
```

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

Listing 9:

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

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

Listing 10:

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

	run	parameter	value
2	1	THETA1	9.90624
5	1	THETA2	21.8851
8	1	THETA3	0.0708172
11	1	THETA4	3.36908
14	1	THETA5	94.6441
17	1	THETA6	0.972459

Listing 11:

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

[1]	"0.118664"	"0.00243903"	"-0.0290796"	"0.126793"	"0.00496538"
[6]	"-0.0348756"	"0.0793827"	"0.0126369"	"-0.0254598"	"0.0930785"
[11]	"-0.00800534"	"-0.0604644"	"0.0776862"	"-0.033206"	"-0.0431809"
[16]	"0.103253"	"-0.00112888"	"-0.0399964"	"0.124331"	"-0.00239167"
[21]	"-0.029284"	"0.0929814"	"0.00605676"	"-0.0318726"	"0.127233"
[26]	"0.0107017"	"-0.0244607"	"0.112805"	"0.0269056"	"-0.00833839"
[31]	"0.089781"	"0.00380984"	"-0.0419745"	"0.145258"	"-0.0511888"
[36]	"-0.034809"	"0.123498"	"0.0100472"	"-0.0206121"	"0.087605"
[41]	"-0.0100154"	"-0.0246587"	"0.0852641"	"-0.00160618"	"-0.0344951"
[46]	"0.130004"	"0.0285763"	"-0.0412472"	"0.0885414"	"-0.00653594"
[51]	"-0.0477025"	"0.128072"	"-0.043122"	"-0.0414366"	"0.0643089"
[56]	"-0.0278958"	"-0.0369344"	"0.190185"	"-0.0205086"	"-0.0254147"
[61]	"0.118594"	"-0.00752878"	"-0.0254214"	"0.0984033"	"-0.0268537"
[66]	"-0.0508149"	"0.128197"	"0.0232717"	"-0.0236485"	"0.167161"
[71]	"-0.0217378"	"-0.0381076"	"0.165581"	"0.0026395"	"-0.0201113"
[76]	"0.0947898"	"-0.0169356"	"-0.0396992"	"0.0463237"	"-0.00590113"
[81]	"-0.0567564"	"0.194381"	"-0.016843"	"-0.0245055"	"0.104522"
[86]	"0.00451787"	"-0.0224597"	"0.106576"	"-0.0108525"	"-0.0250716"
[91]	"0.108904"	"-0.011186"	"-0.0269199"	"0.099795"	"-0.0395158"
[96]	"-0.0396872"	"0.0850945"	"-0.0237444"	"-0.0408458"	"0.118145"
[101]	"-0.0351339"	"-0.0617783"	"0.11275"	"-0.0256919"	"-0.0452783"
[106]	"0.238867"	"0.0421175"	"-0.0113238"	"0.14246"	"-0.0102745"
[111]	"-0.024625"	"0.177373"	"0.0528303"	"0.00958209"	"0.106911"
[116]	"0.0084715"	"-0.0370734"	"0.0610869"	"-0.0328259"	"-0.047843"
[121]	"0.144278"	"0.00445557"	"-0.0430449"	"0.132424"	"-0.00549815"
[126]	"-0.0287111"	"0.0982603"	"-0.000319022"	"-0.0017437"	"0.171037"
[131]	"0.0245733"	"-0.000645002"	"0.0966426"	"-0.0427972"	"-0.0422852"
[136]	"0.104497"	"-0.00685035"	"-0.0241402"	"0.048328"	"-0.0161035"
[141]	"-0.0432615"	"0.10326"	"0.00876954"	"-0.0425963"	"0.0835945"
[146]	"-0.000345751"	"-0.0447939"	"0.112744"	"0.00295217"	"-0.038452"
[151]	"0.179544"	"0.0253114"	"-0.0173357"	"0.0567234"	"0.00397885"
[156]	"-0.0299795"	"0.180876"	"-0.00185961"	"-0.0249431"	"0.117222"
[161]	"0.0146515"	"-0.0264576"	"0.0867059"	"-0.0341638"	"-0.0468783"
[166]	"0.161077"	"0.016314"	"0.00365817"	"0.110393"	"-0.0199048"
[171]	"-0.0610041"	"0.0933731"	"0.00429235"	"-0.0585371"	"0.131606"
[176]	"-0.0273357"	"-0.0414518"	"0.0740837"	"-0.0393725"	"-0.0532824"
[181]	"0.114816"	"0.000498657"	"-0.0327203"	"0.166113"	"0.0260557"
[186]	"-0.0135421"	"0.202143"	"0.0177433"	"-0.0210063"	"0.0910233"
[191]	"0.0151667"	"-0.0408356"	"0.0869677"	"0.0132545"	"-0.0369345"
[196]	"0.121655"	"-0.0174125"	"-0.0312738"	"0.117305"	"-0.00249383"
[201]	"-0.0312059"	"0.0697088"	"-0.0238347"	"-0.0435523"	"0.157214"
[206]	"0.0276361"	"-0.0167383"	"0.103765"	"-0.0320889"	"-0.0491544"
[211]	"0.127115"	"0.00963291"	"-0.0315352"	"0.109701"	"-0.00298642"
[216]	"-0.0269827"	"0.16388"	"-0.0222152"	"-0.0279416"	"0.149759"
[221]	"-0.0606384"	"-0.0582305"	"0.156684"	"-0.00684425"	"-0.012883"
[226]	"0.132933"	"0.0117935"	"-0.0325854"	"0.0667252"	"-0.0396604"
[231]	"-0.0444942"	"0.16451"	"0.00956835"	"-0.0156386"	"0.09734"
[236]	"-0.00795721"	"-0.0377005"	"0.114314"	"-0.00645326"	"-0.0362318"
[241]	"0.130343"	"-0.0293751"	"-0.0610221"	"0.146619"	"-0.000407232"
[246]	"-0.0189186"	"0.137891"	"0.000284756"	"-0.0289554"	"0.0894687"

[251]	"-0.045893"	"-0.0433736"	"0.146665"	"0.0142544"	"-0.0046038"
[256]	"0.128874"	"0.00757832"	"-0.0270146"	"0.173957"	"0.0191542"
[261]	"-0.0231056"	"0.105145"	"-0.0287821"	"-0.0461986"	"0.174007"
[266]	"-0.0250103"	"-0.0154687"	"0.157456"	"-0.024208"	"-0.0433639"
[271]	"0.11283"	"-0.0196416"	"-0.0358259"	"0.110391"	"-0.0343518"
[276]	"-0.0621958"	"0.119436"	"0.00084654"	"-0.0184177"	"0.0932988"
[281]	"-0.0145868"	"-0.0412257"	"0.11698"	"-0.0102802"	"-0.0421815"
[286]	"0.12102"	"-0.0340955"	"-0.0461667"	"0.204833"	"0.0048392"
[291]	"-0.0163318"	"0.102249"	"-0.0446726"	"-0.041768"	"0.100408"
[296]	"-0.018728"	"-0.0527315"	"0.105437"	"-0.0330352"	"-0.0412061"
[301]	"0.133189"	"-0.0168328"	"-0.0265733"	"0.0945628"	"-0.023821"
[306]	"-0.046713"	"0.115873"	"-0.0174054"	"-0.0383742"	"0.151988"
[311]	"-0.00223515"	"-0.0378195"	"0.111794"	"-0.0362"	"-0.0342003"
[316]	"0.115686"	"-0.0487321"	"-0.060517"	"0.0491857"	"-0.0400171"
[321]	"-0.0577105"	"0.0924036"	"-0.00301072"	"-0.0217227"	"0.120695"
[326]	"-0.0180271"	"-0.0419004"	"0.0841407"	"-0.0272724"	"-0.0373296"
[331]	"0.139445"	"-0.0562157"	"-0.0628584"	"0.133837"	"-0.00586549"
[336]	"-0.0465415"	"0.117258"	"0.00585337"	"-0.0212932"	"0.141695"
[341]	"-0.0128164"	"-0.0454878"	"0.0762841"	"-0.0419415"	"-0.0446022"
[346]	"0.115743"	"-0.0270675"	"-0.0334311"	"0.138236"	"0.0159711"
[351]	"-0.0182158"	"0.153652"	"-0.0133617"	"-0.0312735"	"0.129189"
[356]	"-0.00427277"	"-0.0375778"	"0.0784215"	"-0.0189919"	"-0.0278138"
[361]	"0.0859258"	"-0.0112918"	"-0.0467703"	"0.152543"	"-0.0117078"
[366]	"-0.0259285"	"0.146407"	"-0.00833509"	"-0.034062"	"0.117961"
[371]	"-0.0228667"	"-0.0302872"	"0.0998222"	"-0.0056598"	"-0.0270215"
[376]	"0.148139"	"-0.0358078"	"-0.0466091"	"0.154802"	"-0.00387405"
[381]	"-0.0344275"	"0.0821857"	"0.0179231"	"-0.0208862"	"0.159922"
[386]	"-0.00843248"	"-0.0361851"	"0.154326"	"-0.0204394"	"-0.0313897"
[391]	"0.0876006"	"0.0186169"	"-0.0384454"	"0.145707"	"-0.0513646"
[396]	"-0.0353279"	"0.0960684"	"-0.0153064"	"-0.0325897"	"0.11394"
[401]	"-0.034478"	"-0.0391465"	"0.120386"	"-0.0235295"	"-0.0403019"
[406]	"0.146429"	"-0.00908831"	"-0.0229428"	"0.097815"	"-0.0228671"
[411]	"-0.0477668"	"0.0527412"	"-0.0401556"	"-0.0404198"	"0.191292"
[416]	"0.0233172"	"0.00230111"	"0.0966339"	"-0.0101169"	"-0.0304393"
[421]	"0.10204"	"-0.0675111"	"-0.0323571"	"0.0669481"	"-0.00414325"
[426]	"-0.0350418"	"0.117326"	"0.0193662"	"-0.0293494"	"0.043366"
[431]	"-0.037891"	"-0.0554599"	"0.116669"	"-0.0318554"	"-0.0605897"
[436]	"0.0694246"	"-0.0246743"	"-0.0545532"	"0.0898996"	"-0.0190038"
[441]	"-0.0526655"	"0.115324"	"-0.0447849"	"-0.043447"	"0.121016"
[446]	"-0.00117652"	"-0.0408539"	"0.0741252"	"-0.018944"	"-0.0254045"
[451]	"0.104378"	"-0.00161247"	"-0.02001"	"0.157005"	"-0.00523794"
[456]	"-0.0247991"	"0.353326"	"0.0462137"	"0.00466421"	"0.118066"
[461]	"-0.0221416"	"-0.0276645"	"0.114712"	"-0.00405465"	"-0.0277673"
[466]	"0.12592"	"-0.0129521"	"-0.0347467"	"0.0982355"	"0.011252"
[471]	"-0.0208779"	"0.069048"	"-0.0578171"	"-0.0478397"	"0.116005"
[476]	"-0.0531913"	"-0.0461022"	"0.189958"	"0.023425"	"-0.00411602"
[481]	"0.0874002"	"-0.0666577"	"-0.0453464"	"0.2505"	"0.0077027"
[486]	"-0.020866"	"0.167599"	"0.0451788"	"-0.000658309"	"0.102168"
[491]	"-0.0143335"	"-0.0314068"	"0.0899941"	"-0.0436014"	"-0.0577496"
[496]	"0.0724949"	"-0.0250441"	"-0.0245517"	"0.105756"	"-0.0395233"

[501]	"-0.031799"	"0.11358"	"0.0199425"	"-0.0149443"	"0.0744656"
[506]	"-0.067681"	"-0.0450863"	"0.0890981"	"-0.0412376"	"-0.0493254"
[511]	"0.114138"	"-0.0385923"	"-0.0430469"	"0.0888011"	"-0.0233544"
[516]	"-0.0528061"	"0.0437555"	"-0.0220735"	"-0.0363112"	"0.108748"
[521]	"-0.00845016"	"-0.0437129"	"0.0888528"	"-0.027201"	"-0.0455558"
[526]	"0.109073"	"0.0282737"	"-0.0144904"	"0.129467"	"-0.00760702"
[531]	"-0.0198483"	"0.124009"	"0.0141844"	"-0.0382784"	"0.0587984"
[536]	"-0.0244563"	"-0.0366547"	"0.151268"	"-0.00472393"	"-0.0293829"
[541]	"0.174939"	"-0.00865166"	"-0.0339589"	"0.156336"	"-0.0134474"
[546]	"-0.0319209"	"0.146133"	"-0.0145848"	"-0.020574"	"0.146571"
[551]	"-0.014698"	"-0.0412586"	"0.164571"	"-0.0107431"	"-0.0206866"
[556]	"0.080354"	"-0.021482"	"-0.0432427"	"0.112315"	"-0.0225172"
[561]	"-0.0452995"	"0.182548"	"-0.0240036"	"-0.0307118"	"0.148057"
[566]	"-0.00531287"	"-0.0421696"	"0.10471"	"0.00909549"	"-0.0103994"
[571]	"0.141531"	"-0.0117441"	"-0.0268305"	"0.0559151"	"-0.0145141"
[576]	"-0.0399355"	"0.28593"	"0.0647187"	"0.0090289"	"0.226196"
[581]	"0.0465617"	"-0.0167024"	"0.0863951"	"-0.0242882"	"-0.0445673"
[586]	"0.106766"	"0.00711912"	"-0.0384497"	"0.128791"	"0.00935973"
[591]	"-0.0255152"	"0.151827"	"0.0441323"	"0.00135172"	"0.112872"
[596]	"-0.00344834"	"-0.022351"	"0.0481444"	"-0.0179546"	"-0.055449"
[601]	"0.0818587"	"-0.0253594"	"-0.0342839"	"0.0963877"	"-0.00883704"
[606]	"-0.0304148"	"0.139391"	"-0.0187507"	"-0.0402836"	"0.155405"
[611]	"-0.010436"	"-0.0216516"	"0.0635618"	"-0.00394322"	"-0.0362427"
[616]	"0.134236"	"0.0036363"	"-0.00675133"	"0.0945227"	"-0.0698679"
[621]	"-0.0602625"	"0.0923165"	"-0.0150991"	"-0.03504"	"0.081674"
[626]	"-0.00441006"	"-0.0490822"	"0.128433"	"-0.0261758"	"-0.0399649"
[631]	"0.109765"	"-0.0263731"	"-0.0386598"	"0.0884195"	"0.0352562"
[636]	"-0.0224681"	"0.125047"	"-0.0162158"	"-0.0186845"	"0.0836961"
[641]	"0.00447476"	"-0.0381655"	"0.113755"	"0.0275129"	"-0.00949459"
[646]	"0.0651323"	"-0.0287285"	"-0.0593339"	"0.12926"	"-0.0386841"
[651]	"-0.0235969"	"0.1418"	"0.00185295"	"-0.0213206"	"0.113659"
[656]	"-0.0188672"	"-0.0347941"	"0.0657834"	"-0.0261605"	"-0.0511768"
[661]	"0.119641"	"-0.0109612"	"-0.0345783"	"0.107459"	"-0.0279097"
[666]	"-0.0412287"	"0.128837"	"-0.00841091"	"-0.0275248"	"0.0641978"
[671]	"-0.0448828"	"-0.0548623"	"0.105479"	"-0.00756979"	"-0.0405812"
[676]	"0.171147"	"0.00200281"	"-0.0121898"	"0.0862844"	"-0.0229536"
[681]	"-0.0273754"	"0.183258"	"0.00836453"	"-0.0156531"	"0.0791151"
[686]	"-0.0363597"	"-0.04549"	"0.233874"	"0.00370539"	"-0.0186613"
[691]	"0.142951"	"-0.0015608"	"-0.0336835"	"0.0595705"	"-0.0238448"
[696]	"-0.0408746"	"0.0778225"	"-0.0396712"	"-0.0301179"	"0.0918823"
[701]	"-0.0157737"	"-0.0291893"	"0.112115"	"0.0144137"	"-0.0306044"
[706]	"0.138055"	"-0.0309795"	"-0.043204"	"0.138132"	"0.00912759"
[711]	"-0.033212"	"0.138767"	"-0.0134388"	"-0.0507434"	"0.124444"
[716]	"-0.047932"	"-0.0479316"	"0.171497"	"-0.0121706"	"-0.0242095"
[721]	"0.0539906"	"-0.0110564"	"-0.0497779"	"0.0957407"	"-0.0272087"
[726]	"-0.0377266"	"0.105232"	"-0.0423657"	"-0.0309091"	"0.0727366"
[731]	"-0.00618372"	"-0.042519"	"0.140173"	"-0.0588466"	"-0.0585394"
[736]	"0.1177"	"-0.0279011"	"-0.0488746"	"0.141545"	"0.0282797"
[741]	"-0.00360611"	"0.150651"	"0.0033684"	"-0.0222497"	"0.141123"
[746]	"-0.0345764"	"-0.0358508"	"0.126262"	"0.00663914"	"-0.0317031"

```
[751] "0.127498"      "-0.0124166"      "-0.0283863"      "0.131374"      "-0.0134399"
[756] "-0.036174"      "0.148283"        "-0.0190479"      "-0.017962"      "0.121113"
[761] "-0.0326466"      "-0.0519758"      "0.115299"        "-0.0400513"     "-0.0586101"
[766] "0.153765"        "-0.00778942"     "-0.0310329"      "0.0721597"      "-0.0137686"
[771] "-0.0349912"      "0.106628"        "0.00160757"      "-0.0459419"     "0.13816"
[776] "-0.0181902"      "-0.0264274"      "0.0938884"       "-0.0191998"     "-0.0385028"
[781] "0.146527"        "-0.00176887"     "-0.0262183"      "0.0941695"      "0.00247702"
[786] "-0.0389381"      "0.153674"        "0.0248971"       "0.00316929"     "0.135013"
[791] "-0.0159761"      "-0.0366188"      "0.150773"        "-0.0121322"     "-0.0210345"
[796] "0.100948"        "-0.0100324"      "-0.0380679"      "0.0781693"      "-0.0131155"
[801] "-0.0260249"      "0.183728"        "0.0471509"       "-0.00331759"     "0.122793"
[806] "0.0128808"       "-0.022205"       "0.0961981"       "0.00881522"     "-0.0339731"
[811] "0.0988059"       "0.0129752"       "-0.0250672"      "0.106903"       "-0.0307499"
[816] "-0.0488798"      "0.199369"        "-0.0026988"      "-0.034997"      "0.103321"
[821] "0.0245504"       "-0.00192493"     "0.106192"        "0.00493618"     "-0.0361149"
[826] "0.0844764"       "0.00496454"      "-0.0254247"      "0.058592"       "-0.00590223"
[831] "-0.0442436"      "0.0701997"       "-0.00732918"     "-0.0466255"     "0.0715442"
[836] "-0.0347355"      "-0.0415529"      "0.0926783"       "-0.0344959"     "-0.0327224"
[841] "0.121309"        "-0.0321942"      "-0.0385079"      "0.099353"       "0.000595448"
[846] "-0.0240711"      "0.149399"        "-0.0155101"      "-0.041984"      "0.158858"
[851] "0.0105719"       "-0.00492554"     "0.067364"        "-0.0108857"     "-0.0470531"
[856] "0.127813"        "0.00669009"      "-0.0184069"      "0.14897"        "0.0134118"
[861] "-0.0248284"      "0.135642"        "0.0179566"       "-0.00793688"     "0.060602"
[866] "0.00193913"      "-0.0211142"      "0.0592927"       "-0.0327238"     "-0.0356362"
[871] "0.136618"        "-0.0223643"      "-0.0262968"      "0.106394"       "-0.0196676"
[876] "-0.0533358"      "0.0742905"       "-0.00833212"     "-0.0373445"     "0.0998197"
[881] "-0.00384365"     "-0.025143"       "0.170587"        "-0.0143729"     "-0.0394337"
[886] "0.0868"          "-0.0287056"      "-0.0297065"      "0.100429"       "0.00791036"
[891] "-0.0297891"      "0.059776"        "-0.0391323"      "-0.0377099"     "0.112937"
[896] "0.00219594"      "-0.0172751"      "0.174089"        "0.0131627"      "-0.0141584"
```

Listing 12:

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

```
[1] "SIGMA2.1"
```

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

Listing 13:

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

```
[1] FALSE
```

Listing 14:

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

```

run parameter      value
2      1      THETA1  9.9062400
5      1      THETA2 21.8851000
8      1      THETA3  0.0708172
11     1      THETA4  3.3690800
14     1      THETA5 94.6441000
17     1      THETA6  0.9724590

```

1.2 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 15:

```

> boot <- inner(
+   boot,
+   preserve='run',
+   id.var='parameter',
+   measure.var='value'
+ )
> head(boot)

```

```

run parameter      value
1      1      THETA1  9.9062400
2      1      THETA2 21.8851000
3      1      THETA3  0.0708172
4      1      THETA4  3.3690800
5      1      THETA5 94.6441000
6      1      THETA6  0.9724590

```

Listing 16:

```

> any(is.na(boot$value))

```

```

[1] TRUE

```

Listing 17:

```

> boot <- boot[!is.na(boot$value),]

```

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

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

Listing 18:

```

> wiki <- wikipar(1005, '../nonmem')
> wiki

```


parameter	description	
1 THETA1	apparent oral clearance	
2 THETA2	central volume of distribution	
3 THETA3	absorption rate constant	
4 THETA4	intercompartmental clearance	
5 THETA5	peripheral volume of distribution	
6 THETA6	male effect on clearance	
7 THETA7	weight effect on clearance	
8 OMEGA1.1	interindividual variability of clearance	
9 OMEGA2.1	interindividual clearance-volume covariance	
10 OMEGA2.2	interindividual variability of central volume	
11 OMEGA3.1	interindividual clearance-Ka covariance	
12 OMEGA3.2	interindividual volume-Ka covariance	
13 OMEGA3.3	interindividual variability of Ka	
14 SIGMA1.1	proportional error	
15 SIGMA2.2	additive error	
	model	tool run
1 CL/F (L/h) ~ theta_1 * theta_6 ^MALE * (WT/70)^theta_7	* e^eta_1	nm7 1005
2 V_c /F (L) ~ theta_2 * (WT/70)^1	* e^eta_2	nm7 1005
3 K_a (h^-1) ~ theta_3	* e^eta_3	nm7 1005
4 Q/F (L/h) ~ theta_4		nm7 1005
5 V_p /F (L) ~ theta_5		nm7 1005
6 MALE_CL/F ~ theta_6		nm7 1005
7 WT_CL/F ~ theta_7		nm7 1005
8 IIV_CL/F ~ Omega_1.1		nm7 1005
9 cov_CL,V ~ Omega_2.1		nm7 1005
10 IIV_V_c /F ~ Omega_2.2		nm7 1005
11 cov_CL,Ka ~ Omega_3.1		nm7 1005
12 cov_V,Ka ~ Omega_3.2		nm7 1005
13 IIV_K_a ~ Omega_3.3		nm7 1005
14 err_prop ~ Sigma_1.1		nm7 1005
15 err_add ~ Sigma_2.2		nm7 1005
	estimate	prse se
1 9.5079	9.72	0.923845
2 22.7899	9.56	2.17804
3 0.0714253	7.34	0.00524566
4 3.4739	15.4	0.535313
5 113.258	20.9	23.6434
6 1.02445	11	0.112909
7 1.19194	28.3	0.337219
8 0.213815	22.8	0.0488441
9 0.120753	26.4	0.0319031
10 0.0945159	33.2	0.0313359
11 -0.0115975	173	0.0200682
12 -0.0371806	36.1	0.0134303
13 0.0465513	34.8	0.016184
14 0.0491672	10.9	0.0053805
15 0.201823	33.5	0.0675911

Listing 19:

```
> wiki$name <- wiki2label(wiki$model)
> wiki$estimate <- as.numeric(wiki$estimate)
> unique(wiki$parameter)

[1] "THETA1"    "THETA2"    "THETA3"    "THETA4"    "THETA5"    "THETA6"
[7] "THETA7"    "OMEGA1.1"  "OMEGA2.1"  "OMEGA2.2"  "OMEGA3.1"  "OMEGA3.2"
[13] "OMEGA3.3"  "SIGMA1.1"  "SIGMA2.2"
```

Listing 20:

```
> unique(boot$parameter)

[1] "THETA1"    "THETA2"    "THETA3"    "THETA4"    "THETA5"    "THETA6"
[7] "THETA7"    "OMEGA1.1"  "OMEGA2.1"  "OMEGA2.2"  "OMEGA3.1"  "OMEGA3.2"
[13] "OMEGA3.3"  "SIGMA1.1"  "SIGMA2.2"
```

Listing 21:

```
> boot <- stableMerge(boot, wiki[,c('parameter','name')])
> head(boot)
```

	run	parameter	value	name
1	1	THETA1	9.9062400	CL/F
2	1	THETA2	21.8851000	V _c /F
3	1	THETA3	0.0708172	K _a
4	1	THETA4	3.3690800	Q/F
5	1	THETA5	94.6441000	V _p /F
6	1	THETA6	0.9724590	MALE_CL/F

1.4 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.

1.4.1 Recover original covariates for guidance.

Listing 22:

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

```

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

```

Listing 23:

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

```
[1] TRUE
```

Listing 24:

```
> 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 25:

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

```
[1] 81
```

Listing 26:

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

```
[1] 61 117
```

1.4.2 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 27:

```
> head(boot)

  run parameter      value      name
1   1   THETA1  9.9062400    CL/F
2   1   THETA2 21.8851000   V_c/F
3   1   THETA3  0.0708172    K_a
4   1   THETA4  3.3690800    Q/F
5   1   THETA5 94.6441000   V_p/F
6   1   THETA6  0.9724590 MALE_CL/F
```

Listing 28:

```
> unique(boot$name)

[1] "CL/F"      "V_c/F"      "K_a"      "Q/F"      "V_p/F"      "MALE_CL/F"
[7] "WT_CL/F"   "IIV_CL/F"   "cov_CL,V"  "IIV_V_c/F" "cov_CL,Ka"  "cov_V,Ka"
[13] "IIV_K_a"   "err_prop"   "err_add"
```

Listing 29:

```
> clearance <- boot[boot$name %in% c('CL/F','WT_CL/F','MALE_CL/F'),]
> head(clearance)

  run parameter      value      name
1   1   THETA1  9.906240    CL/F
6   1   THETA6 0.972459 MALE_CL/F
7   1   THETA7 1.469340   WT_CL/F
16  2   THETA1  9.030570    CL/F
21  2   THETA6 1.038960 MALE_CL/F
22  2   THETA7 0.999512   WT_CL/F
```

Listing 30:

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

  run      CL/F MALE_CL/F WT_CL/F
1   1  9.90624  0.972459 1.469340
2   2  9.03057  1.038960 0.999512
3   3  9.33144  0.846678 1.909720
4   4  9.25626  0.940994 1.697690
5   5 10.27090  1.252490 1.159250
6   6  9.42006  0.967176 1.484520
```

Listing 31:

```
> frozen$`WT_CL/F:65` <- (65/70)**frozen$`WT_CL/F`
> frozen$`WT_CL/F:75` <- (75/70)**frozen$`WT_CL/F`
> frozen$`WT_CL/F:85` <- (85/70)**frozen$`WT_CL/F`
```

1.4.3 Normalize key parameter

Listing 32:

```
> #cl <- median(boot$value[boot$name=='CL/F'])
> cl <- with(wiki, estimate[name=='CL/F'])
> cl
```

```
[1] 9.5079
```

Listing 33:

```
> head(frozen)
```

run	CL/F	MALE_CL/F	WT_CL/F	WT_CL/F:65	WT_CL/F:75	WT_CL/F:85	
1	1	9.90624	0.972459	1.469340	0.8968292	1.106690	1.330136
2	2	9.03057	1.038960	0.999512	0.9286050	1.071392	1.214171
3	3	9.33144	0.846678	1.909720	0.8680331	1.140831	1.448870
4	4	9.25626	0.940994	1.697690	0.8817803	1.124264	1.390435
5	5	10.27090	1.252490	1.159250	0.9176771	1.083265	1.252417
6	6	9.42006	0.967176	1.484520	0.8958209	1.107850	1.334062

Listing 34:

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

run	CL/F	MALE_CL/F	WT_CL/F	WT_CL/F:65	WT_CL/F:75	WT_CL/F:85	
1	1	1.0418957	0.972459	1.469340	0.8968292	1.106690	1.330136
2	2	0.9497965	1.038960	0.999512	0.9286050	1.071392	1.214171
3	3	0.9814407	0.846678	1.909720	0.8680331	1.140831	1.448870
4	4	0.9735336	0.940994	1.697690	0.8817803	1.124264	1.390435
5	5	1.0802491	1.252490	1.159250	0.9176771	1.083265	1.252417
6	6	0.9907614	0.967176	1.484520	0.8958209	1.107850	1.334062

Listing 35:

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

run	variable	value
1	1	CL/F 1.0418957
2	2	CL/F 0.9497965
3	3	CL/F 0.9814407
4	4	CL/F 0.9735336
5	5	CL/F 1.0802491
6	6	CL/F 0.9907614

1.4.4 Plot.

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

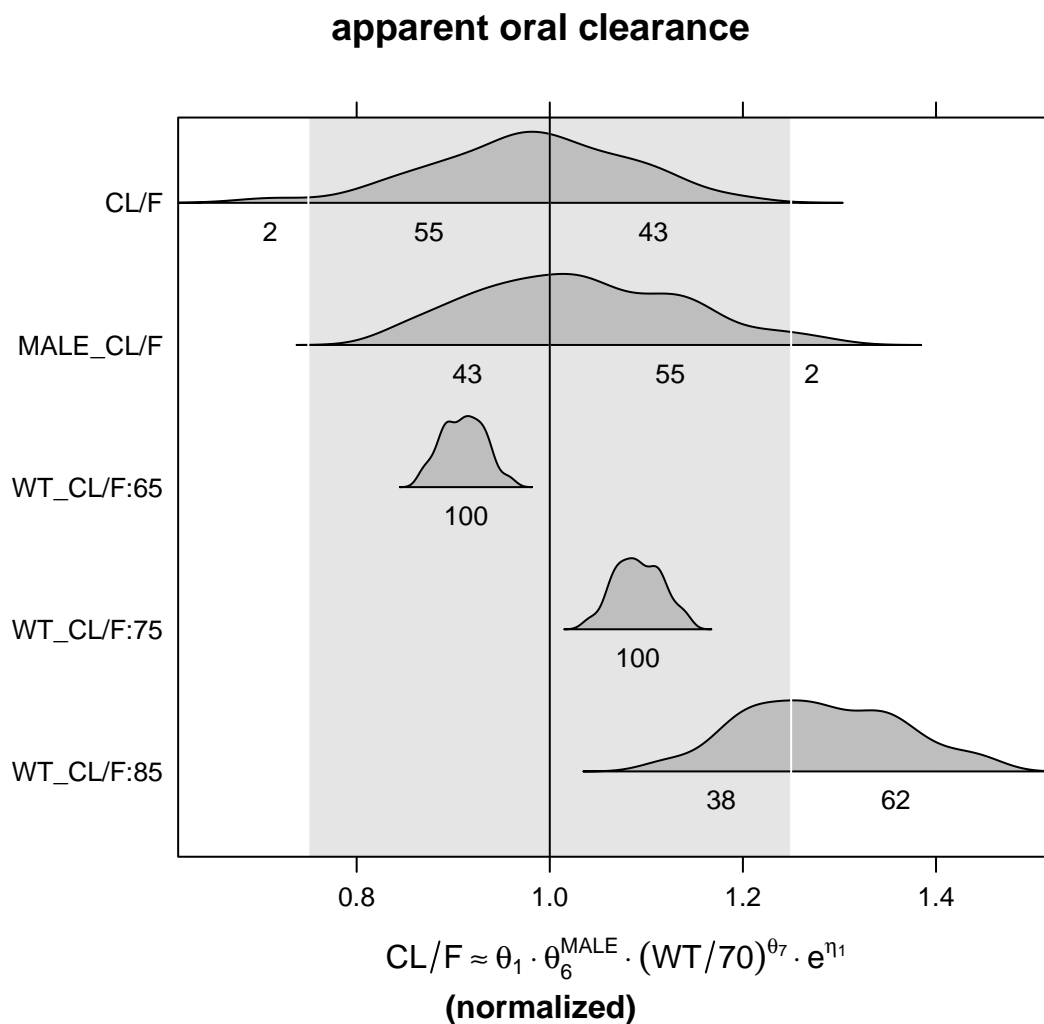
Listing 36:

```
> levels(molten$variable)

[1] "CL/F"      "MALE_CL/F" "WT_CL/F:65" "WT_CL/F:75" "WT_CL/F:85"
```

Listing 37:

```
> molten$variable <- factor(molten$variable, levels=rev(levels(molten$variable)))
> print(
+   stripplot(
+     variable ~ value,
+     data=molten,
+     panel=panel.covplot,
+     xlab=parse(text=with(wiki, wiki2plotmath(noUnits(model[name=='CL/F'])))),
+     main=with(wiki, description[name=='CL/F']),
+     sub=(' (normalized) \n\n\n'),
+   )
+ )
```



1.4.5 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 93 percent probability that an 85 kg person will have at least 25 percent greater clearance than a 70 kg person.