Dose-Time Response Modeling of Rat RBC AChE Activity: Carbofuran Gavage Dosing

June 27, 2005

1 Preamble

Here is some code to set up the analysis: loading required libraries and datasets, and defining some functions.

First, `CarbamateData` loads the full dataset for this risk assessment, and causes the library `DRUtils` to be loaded.

```
> library(CarbamateData)

Loading required package: DRUtils
Loading required package: nlme
Loading required package: tcltk
```

Set up lattice to use B&W instead of color:

```
> library(lattice)
> ltheme <- canonical.theme(color = FALSE)
> ltheme$strip.background$col <- "transparent"
> lattice.options(default.theme = ltheme)
```

Use package `Hmisc` for some formatting support.

```
> library(Hmisc)

Hmisc library by Frank E Harrell Jr

Type library(help='Hmisc'), ?Overview, or ?Hmisc.Overview')
to see overall documentation.

NOTE:Hmisc no longer redefines [.factor to drop unused levels when
subsetting.  To get the old behavior of Hmisc type dropUnusedLevels().

Attaching package 'Hmisc':


        The following object(s) are masked from package:stats :

         ecdf
```

All the rat gavage data for this analysis are in a single study in `repeated_acute`: 45675701, and Padilla's acute study. The following code prints out documentation for the datasets in use:

```
> printDataDoc(repeated_acute)
```

```
----------------------------------------
Data set: repeated_acute

Dataset creation date: Wed Jun 22 12:07:28 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponsesFinal/Data/getdata.R
Script last modified: 2005-06-22 12:05:47
sysname: Linux
release: 2.4.24-openmosix2
version: #1 Wed Jul 28 14:33:52 CEST 2004
nodename: node24.cluster2.org
machine: i686
login: unknown
user: setzer
----------------------------------------

> printDataDoc(PadillaData)

----------------------------------------
Data set: PadillaData

Dataset creation date: Wed Jun 22 12:07:28 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponsesFinal/Data/getdata.R
Script last modified: 2005-06-22 12:05:47
sysname: Linux
release: 2.4.24-openmosix2
version: #1 Wed Jul 28 14:33:52 CEST 2004
nodename: node24.cluster2.org
machine: i686
login: unknown
user: setzer
----------------------------------------
```

The following function turns out to be quite useful on subsetted dataframes. It just eliminates unused levels of all factors in the data frame:

```
> CleanUp <- function(x) {
+     for (nm in names(x)) {
+         if (is.factor(x[, nm]))
+             x[, nm] <- factor(x[, nm])
+     }
+     x
+ }
```

To get starting values, we often have to extract values from a previously fit model. The following function simplifies that. The argument `what` is a regular expression:

```
> getParms <- function(what, Par) {
+     Par[grep(what, names(Par))]
+ }
```

This script is for modeling the dose-time response for rat red blood cells. via gavage dosing. It includes two acute studies.

Now, set up the analysis dataset.

```
> dta <- CleanUp(subset(repeated_acute, chemical %in% "Carobofuran" &
+     !is.na(rbc), select = c("id", "sex", "dose_mgkg", "rbc",
```

```
+     "time", "mrid")))
> names(dta) <- c("id", "sex", "dose", "cheact", "tmpstds", "mrid")
> Pdta <- subset(PadillaData, chemical %in% "carbofuran", select = c("dose",
+     "RBC.R", "TMPSTDS"))
> names(Pdta) <- c("dose", "cheact", "tmpstds")
> Pdta$sex <- factor(rep("M", nrow(Pdta)))
> Pdta$mrid <- factor(rep("Padilla", nrow(Pdta)))
> Pdta$id <- factor(seq(along = Pdta$dose))
> dta <- rbind(dta, Pdta[, names(dta)])
> dta <- dta[!is.na(dta$cheact), ]
```

Summary of the relevant variables in this dataset:

```
> by(dta, dta$mrid, summary)

dta$mrid: 45675701
       id      sex          dose          cheact          tmpstds
 216    : 13   F:319   Min.   :0.00   Min.   : 427.0   Min.   :0.000
 217    : 13   M:330   1st Qu.:0.00   1st Qu.: 676.0   1st Qu.:0.750
 218    : 13           Median :0.50   Median : 747.0   Median :1.500
 219    : 13           Mean   :0.52   Mean   : 785.2   Mean   :2.307
 220    : 13           3rd Qu.:1.00   3rd Qu.: 889.0   3rd Qu.:3.000
 221    : 13           Max.   :1.00   Max.   :1459.0   Max.   :8.000
 (Other):571
       mrid
 45675701:649
 Padilla :  0




------------------------------------------------------------
dta$mrid: Padilla
       id     sex         dose            cheact         tmpstds
 1      : 1   F: 0   Min.   :0.0000   Min.   :105.2   Min.   : 0.5000
 2      : 1   M:65   1st Qu.:0.3000   1st Qu.:251.0   1st Qu.: 0.6667
 3      : 1          Median :0.5000   Median :333.2   Median : 0.6667
 4      : 1          Mean   :0.4654   Mean   :327.3   Mean   : 3.4000
 5      : 1          3rd Qu.:0.5000   3rd Qu.:398.1   3rd Qu.: 4.0000
 6      : 1          Max.   :1.5000   Max.   :585.1   Max.   :24.0000
 (Other):59
       mrid
 45675701: 0
 Padilla :65

> unique(subset(dta, select = c("mrid", "dose", "tmpstds")))

         mrid dose    tmpstds
421  45675701 0.00  0.0000000
422  45675701 0.00  0.2500000
423  45675701 0.00  0.5000000
424  45675701 0.00  0.7500000
425  45675701 0.00  1.0000000
426  45675701 0.00  1.2500000
```

```
427  45675701 0.00  1.5000000
428  45675701 0.00  2.0000000
429  45675701 0.00  2.5000000
430  45675701 0.00  3.0000000
431  45675701 0.00  4.0000000
432  45675701 0.00  6.0000000
433  45675701 0.00  8.0000000
525  45675701 0.50  0.0000000
526  45675701 0.50  0.2500000
527  45675701 0.50  0.5000000
528  45675701 0.50  0.7500000
529  45675701 0.50  1.0000000
530  45675701 0.50  1.2500000
531  45675701 0.50  1.5000000
532  45675701 0.50  2.0000000
533  45675701 0.50  2.5000000
534  45675701 0.50  3.0000000
535  45675701 0.50  4.0000000
536  45675701 0.50  6.0000000
537  45675701 0.50  8.0000000
642  45675701 1.00  0.0000000
643  45675701 1.00  0.2500000
644  45675701 1.00  0.5000000
645  45675701 1.00  0.7500000
646  45675701 1.00  1.0000000
647  45675701 1.00  1.2500000
648  45675701 1.00  1.5000000
649  45675701 1.00  2.0000000
650  45675701 1.00  2.5000000
651  45675701 1.00  3.0000000
652  45675701 1.00  4.0000000
653  45675701 1.00  6.0000000
654  45675701 1.00  8.0000000
187   Padilla 0.00  0.6666667
192   Padilla 0.10  0.6666667
197   Padilla 0.30  0.6666667
202   Padilla 0.50  0.6666667
207   Padilla 0.75  0.6666667
212   Padilla 1.50  0.6666667
1881  Padilla 0.00  0.5000000
1891  Padilla 0.00  1.0000000
1901  Padilla 0.00  2.0000000
1911  Padilla 0.00 24.0000000
1921  Padilla 0.00  4.0000000
1931  Padilla 0.00  6.0000000
1941  Padilla 0.50  0.5000000
1991  Padilla 0.50  1.0000000
2041  Padilla 0.50  2.0000000
2091  Padilla 0.50  4.0000000
2141  Padilla 0.50  6.0000000
219   Padilla 0.50 24.0000000
```

```
> by(dta, dta$mrid, function(x) with(x, table(dose, tmpstds)))
```

```
dta$mrid: 45675701
```

```
     tmpstds
dose  0  0.25 0.5 0.75 1  1.25 1.5 2  2.5 3  4  6  8
  0   16 16   16  16   16 15   16  15 16  16 16 14 14
  0.5 17 17   17  17   17 17   17  17 17  17 17 17 15
  1   18 17   17  18   17 18   18  18 18  18 18 17 16
-------------------------------------------------------------
dta$mrid: Padilla
      tmpstds
dose   0.5 0.666666666666667 1 2 4 6 24
  0    1   5                 1 1 1 1 1
  0.1  0   5                 0 0 0 0 0
  0.3  0   5                 0 0 0 0 0
  0.5  5   5                 5 5 5 5 4
  0.75 0   5                 0 0 0 0 0
  1.5  0   5                 0 0 0 0 0
```

```
> with(CleanUp(subset(dta, mrid == "45675701")), table(id, tmpstds))
```

```
     tmpstds
id    0 0.25 0.5 0.75 1 1.25 1.5 2 2.5 3 4 6 8
  216 1 1    1   1    1 1    1   1 1   1 1 1 1
  217 1 1    1   1    1 1    1   1 1   1 1 1 1
  218 1 1    1   1    1 1    1   1 1   1 1 1 1
  219 1 1    1   1    1 1    1   1 1   1 1 1 1
  220 1 1    1   1    1 1    1   1 1   1 1 1 1
  221 1 1    1   1    1 1    1   1 1   1 1 1 1
  222 1 1    1   1    1 1    1   1 1   1 1 1 1
  223 1 1    1   1    1 1    1   1 1   1 1 1 1
  224 1 1    1   1    1 1    1   1 1   1 1 1 1
  225 1 1    1   1    1 1    1   1 1   1 1 1 1
  226 1 1    1   1    1 1    1   1 1   1 1 1 0
  227 1 1    1   1    1 1    1   1 1   1 1 1 1
  228 1 1    1   1    1 1    1   1 1   1 1 1 1
  230 1 1    1   1    1 1    1   1 1   1 1 1 1
  231 1 1    1   1    1 1    1   1 1   1 1 1 1
  232 1 1    1   1    1 1    1   1 1   1 1 1 1
  233 1 1    1   1    1 1    1   1 1   1 1 1 1
  234 1 1    1   1    1 1    1   1 1   1 1 1 1
  235 1 1    1   1    1 1    1   1 1   1 1 1 1
  236 1 1    1   1    1 1    1   1 1   1 1 0 0
  237 1 1    1   1    1 1    1   1 1   1 1 1 1
  238 1 1    1   1    1 1    1   1 1   1 1 1 1
  239 1 1    1   1    1 0    1   0 1   1 1 0 0
  240 1 1    1   1    1 1    1   1 1   1 1 1 1
  241 1 1    1   1    1 1    1   1 1   1 1 1 0
  242 1 1    1   1    1 1    1   1 1   1 1 1 1
  243 1 1    1   1    1 1    1   1 1   1 1 1 1
  244 1 1    1   1    1 1    1   1 1   1 1 1 1
  245 1 1    0   1    1 1    1   1 1   1 1 1 1
  246 1 1    1   1    1 1    1   1 1   1 1 1 1
  247 1 1    1   1    1 1    1   1 1   1 1 1 1
  248 1 1    1   1    1 1    1   1 1   1 1 1 1
  249 1 1    1   1    1 1    1   1 1   1 1 1 1
  250 1 1    1   1    1 1    1   1 1   1 1 0 0
  251 1 1    1   1    1 1    1   1 1   1 1 1 1
```

```
  252 1 0     1    1     0 1     1    1 1    1 1 1 1
  253 1 1     1    1     1 1     1    1 1    1 1 1 0
  254 1 1     1    1     1 1     1    1 1    1 1 1 1
  256 1 1     1    1     1 1     1    1 1    1 1 1 1
  258 1 1     1    1     1 1     1    1 1    1 1 1 1
  259 1 1     1    1     1 1     1    1 1    1 1 1 1
  260 1 1     1    1     1 1     1    1 1    1 1 1 1
  261 1 1     1    1     1 1     1    1 1    1 1 1 1
  262 1 1     1    1     1 1     1    1 1    1 1 1 1
  263 1 1     1    1     1 1     1    1 1    1 1 1 1
  264 1 1     1    1     1 1     1    1 1    1 1 1 1
  265 1 1     1    1     1 1     1    1 1    1 1 1 1
  266 1 1     1    1     1 1     1    1 1    1 1 1 1
  267 1 1     1    1     1 1     1    1 1    1 1 1 1
  268 1 1     1    1     1 1     1    1 1    1 1 1 1
  269 1 1     1    1     1 1     1    1 1    1 1 1 1
```

Mrid 45675701 has fairly finely divided time points, from 0.25 to 8 hours, and three dose levels (0, 0.5, and 1.0 mg/kg). Each subject in that study was observed at virtually every time point (there are very few missing time points). Padilla's data are all individual data, and are really two studies: a dose-response study at 0.67 hour, with doses from 0 to 1.5 mg/kg, and a time course study at 0.5 mg/kg, with times from 0.5 to 24 hours.

Create some new factors, for splitting up the background parameters and allowing groups to have different variances.

```
> dta$mridXsex <- with(dta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> dta$mridXsexXtmpstds <- with(dta, interaction(mrid, sex, tmpstds,
+     drop = TRUE, sep = ":"))
```

We can only estimate the time-course parameters (`ldT` and `lTmax`, or `lTr`) for positive doses. In particular, `ldT` and `lTr` tend to vary among doses, being greater for higher doses. We accomodate this by estimating a different value of `ldT` for different dose levels. We cannot just "factorize" `dose`, because that would leave a level for the control group, and would create a level for each dose in the dose-response study (most of which have no time course data).

These are the doses available in the different mrids (non-zero entries indicate the presence of the dose-level in the corresponding study).

```
> with(dta, table(mrid, dose, sex))

, , sex = F

          dose
mrid       0   0.1 0.3 0.5 0.75 1   1.5
  45675701 102   0   0 104   0  113   0
  Padilla    0   0   0   0   0    0   0

, , sex = M

          dose
mrid       0   0.1 0.3 0.5 0.75 1   1.5
  45675701 100   0   0 115   0  115   0
  Padilla   11   5   5  34   5    0   5
```

Try creating `fdose` by cutting dose at:

```
> dta$fdose <- cut(dta$dose, c(0, 0.5, 1.5), include.lowest = TRUE)
```

How are the controls distributed among times post dosing?

```
> by(dta, dta$mrid, function(x) with(x, table(dose, tmpstds)))

dta$mrid: 45675701
     tmpstds
dose  0  0.25 0.5 0.75 1  1.25 1.5 2  2.5 3  4  6  8
  0   16 16   16  16   16 15   16  15 16  16 16 14 14
  0.5 17 17   17  17   17 17   17  17 17  17 17 17 15
  1   18 17   17  18   17 18   18  18 18  18 18 17 16
------------------------------------------------------------
dta$mrid: Padilla
      tmpstds
dose   0.5 0.666666666666667 1 2 4 6 24
  0    1   5                 1 1 1 1 1
  0.1  0   5                 0 0 0 0 0
  0.3  0   5                 0 0 0 0 0
  0.5  5   5                 5 5 5 5 4
  0.75 0   5                 0 0 0 0 0
  1.5  0   5                 0 0 0 0 0
```

There is a control group for each value of `tmpstds` in both mrids, so, initially, set up a separate control at each time. Later, see if we can collapse those to a single estimate of background for each study and sex.

2 Dose-Response Modeling

2.1 strategy

Use the model with simple exponential recovery (`tcmfn4()`), first. It looks as if the time to peak effect for all these chemicals is likely to be less than a half-hour, so the exponential recovery model is probably indistinguishable from the one with the more complex time course.

Fitting the model will follow these steps:

1. First, use `GetInitialValues()` to get starting values for the model against these data, and determine how finely we can estimate `lg` and `tz` of the dose-response parameters, and `lTr`, the log of the recovery half-life.

2. Next, fit `tcmfn4()` using the parameterizations determined in the previous step, and a constant variance model, allowing `lD` to vary among mrids.

   Try fitting with other variance models the same model for fixed and random effects, using AIC to identify the best variance model

3. Can we simplify the model for `lD`, that is, does `lD` differ among sexes? Use contrasts in the best model identified in the previous section.

4. Can we simplify the model for `lTr`, first between sexes, then among doses.

2.2 Initial Values

Save the initial values so that we do not need to go through all this to re-run the analysis. Also, set the argument `delta` to 0.25, the earliest non-zero time point.

```
> formals(tcmfn4)$delta <- min(dta$tmpstds[dta$tmpstds > 0])
> initfile <- paste("initvals-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
```

```
+         dose %in% 0)))
+     Start <- c(coef(lA.start), rep(log(0.15), nlevels(dta$mrid)),
+         0, c(-2, 0), c(log(1), 0), rep(log(1.5), nlevels(dta$fdose) *
+             2))
+     init1 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds,
+         lA = lA, tz = tz, lD = lD, lg = lg, lTr = lTr), data = dta,
+         params = list(lA ~ mridXsexXtmpstds - 1, lD ~ mrid +
+             sex - 1, tz ~ sex, lg ~ sex, lTr ~ fdose:sex - 1),
+         start = Start, weights = varComb(varIdent(form = ~1 |
+             mrid), varPower(value = 1)))
+     save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

```
                          [,1]  [,2]  [,3]  [,4] [,5] [,6] [,7]
CondIndex               75379226 51.32 43.21 11.57 6.39 6.07 4.63
mu                             0  0.05  0.05  0.20 0.37 0.39 0.51
lD.mrid45675701                1  0.00  0.00  0.00 0.00 0.00 0.00
lD.mridPadilla                 1  0.00  0.00  0.00 0.00 0.00 0.00
lD.sexM                        1  0.00  0.00  0.00 0.00 0.00 0.00
tz.(Intercept)                 1  0.00  0.00  0.00 0.00 0.00 0.00
tz.sexM                        1  0.00  0.00  0.00 0.00 0.00 0.00
lg.(Intercept)                 1  0.00  0.00  0.00 0.00 0.00 0.00
lg.sexM                        1  0.00  0.00  0.00 0.00 0.00 0.00
lTr.fdose[0,0.5]:sexF          0  0.27  0.02  0.00 0.31 0.12 0.01
lTr.fdose(0.5,1.5]:sexF        0  0.02  0.00  0.00 0.61 0.20 0.00
lTr.fdose[0,0.5]:sexM          0  0.02  0.12  0.23 0.09 0.33 0.03
lTr.fdose(0.5,1.5]:sexM        0  0.00  0.02  0.00 0.18 0.57 0.02
```

condition index is over 75 million (the matrix is computationally singular). Preliminary estimates of `tz` are small

```
> getParms("^tz", init1$start$beta)
```

```
tz.(Intercept)        tz.sexM
         -5.38          -3.99
```

suggesting that we can fix it to a small value rather than estimating it (that is, there is no data to support a value for a horizontal asymptote).

Try again with the simplified model:

```
> initfile <- paste("initvals-RBC-DR-2.RData", sep = "")
> formals(tcmfn4)$tz <- -10
> if (!file.exists(initfile)) {
+     Start <- init1$start$beta
+     Start <- Start[-grep("^tz", names(Start))]
+     init2 <- GetInitialValues(cheact ~ tcmfn4(dose, tmpstds,
+         lA = lA, lD = lD, lg = lg, lTr = lTr), data = dta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
+         lTr ~ fdose:sex - 1), start = Start, weights = varComb(varIdent(form = ~1 |
+         mrid), varPower(value = 1)))
+     save(init2, file = initfile)
+ } else load(initfile)
> tmp <- t(init2$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

```
                          [,1]  [,2] [,3] [,4] [,5] [,6] [,7]
CondIndex               111.07 20.06 8.03 5.69 4.42 4.21 3.49
mu                        0.02  0.11 0.27 0.38 0.49 0.52 0.62
lD.mrid45675701           0.98  0.02 0.00 0.00 0.00 0.00 0.00
lD.mridPadilla            0.90  0.07 0.00 0.00 0.01 0.01 0.00
lD.sexM                   0.98  0.02 0.00 0.00 0.00 0.00 0.00
lg.(Intercept)            0.97  0.02 0.01 0.00 0.00 0.00 0.00
lg.sexM                   0.90  0.10 0.01 0.00 0.00 0.00 0.00
lTr.fdose[0,0.5]:sexF     0.24  0.01 0.28 0.06 0.10 0.10 0.00
lTr.fdose(0.5,1.5]:sexF   0.04  0.00 0.53 0.09 0.08 0.07 0.00
lTr.fdose[0,0.5]:sexM     0.01  0.26 0.05 0.46 0.04 0.00 0.03
lTr.fdose(0.5,1.5]:sexM   0.00  0.02 0.07 0.69 0.02 0.00 0.03
```

There is still a single very large condition index (> 110) with strong loadings for all the dose-response parameters. Try fitting this model using gnls, first, and, if successful, use this to model the residual variance.

```
> Start <- init2$start$beta
> drmod1 <- gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD,
+     lg = lg, lTr = lTr), data = dta, params = list(lA ~ mridXsexXtmpstds -
+     1, lD ~ mrid + sex - 1, lg ~ sex, lTr ~ fdose:sex - 1), start = Start)
```

That converges successfully. Now, what about changing the variance model so that the standard deviation varies between mridXsex?

```
> Start <- Start0 <- coef(drmod1)
> itercnt <- 1
> maxcnt <- 20
> repeat {
+     drmod2 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = dta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
+         lTr ~ fdose:sex - 1), weights = varIdent(form = ~1 |
+         mridXsex), start = Start), silent = TRUE)
+     if (!inherits(drmod2, "try-error") || itercnt >= maxcnt)
+         break
+     else {
+         itercnt <- itercnt + 1
+         Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+     }
+ }
> if (itercnt >= maxcnt) {
+     writeLines("itercnt exceeded maxcnt")
+ } else {
+     writeLines(paste("Success in", itercnt, "iterations"))
+ }
```

```
Success in 2 iterations
```

Do we need to add `varPower()`?

```
> Start <- Start0 <- coef(drmod2)
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod3 <- try(gnls(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = dta, params = list(lA ~
```

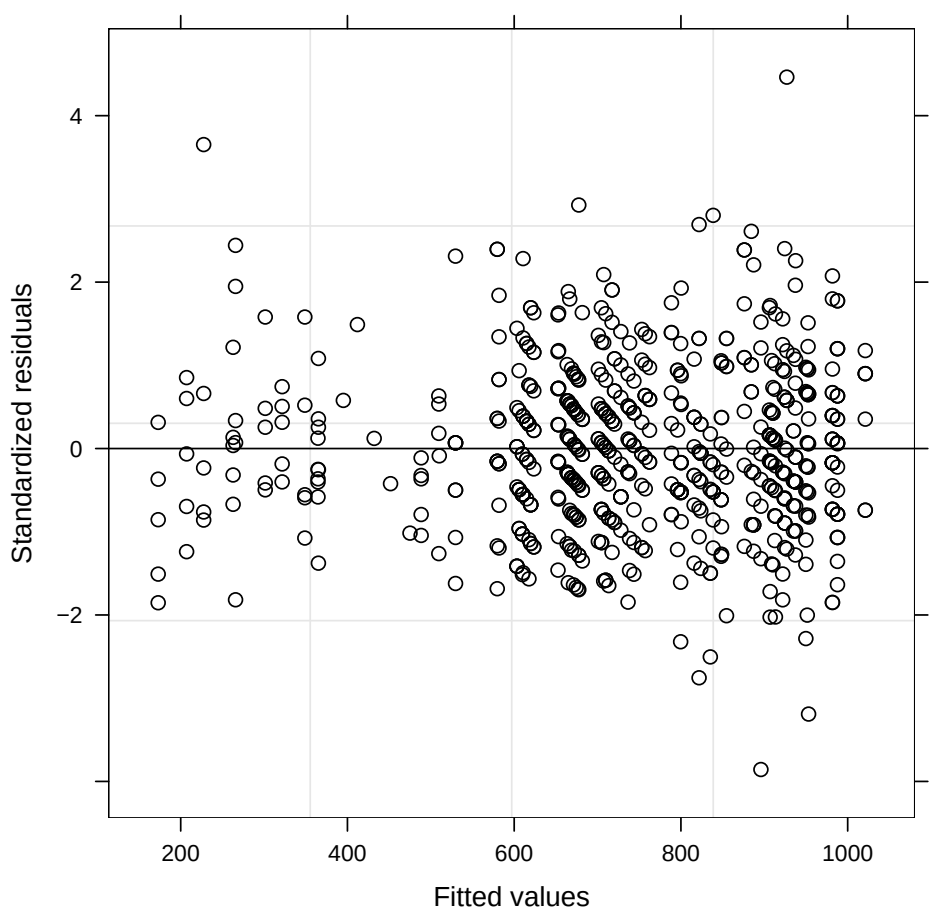
```
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, lg ~ sex,
+         lTr ~ fdose:sex - 1), weights = varComb(varIdent(form = ~1 |
+         mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod3, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+         break
+     }
+     Start <- Start0 * (1 + rnorm(length(Start0), sd = 0.2))
+     icnt <- icnt + 1
+ }

Success after 1 trie(s).

> anova(drmod1, drmod2, drmod3)

       Model df      AIC      BIC    logLik   Test  L.Ratio p-value
drmod1     1 43 8624.236 8820.784 -4269.118
drmod2     2 45 8610.984 8816.674 -4260.492 1 vs 2 17.25160   2e-04
drmod3     3 46 8563.851 8774.112 -4235.926 2 vs 3 49.13255  <.0001
```

Yes. Plot the model, to see if there looks to be any additional trend of residual magnitude versus fitted value:



Now, try plotting versus fraction of inhibition:

```
> local({
+     Pars <- nlme:::getParsGnls(drmod3$plist, drmod3$pmap, coef(drmod3),
+         length(drmod3$residuals))
+     BG <- exp(Pars[, "lA"])
+     Inh <- 1 - fitted(drmod3)/BG
+     plot(resid(drmod3, type = "p") ~ Inh, xlab = "Fractional Inhibition",
+         ylab = "Pearson Residual")
+ })
> abline(h = 0)
```

That looks pretty good. Hopefully, we'll be able to fit the more complicated mixed effects models with this weight function.

Fit the same model as above, except just allow `lD` to vary among sexes. We have random effects for `lD` varying among `mrid` and `lA` varying among `id` nested within `mrid`.

```
> Par <- coef(drmod3)
> lDpar <- getParms("^lD", Par)
> lD.sexF <- mean(lDpar[grep("mrid", names(lDpar))])
> Start0 <- c(getParms("^lA", Par), c(lD.sexF, getParms("lD\\.sexM",
+     Par)), getParms("^lg", Par), getParms("^lTr", Par))
> Start <- list(fixed = Start0)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+     drmod4 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ sex, lg ~ sex, lTr ~ fdose:sex -
+         1), random = list(mrid = lD ~ 1, id = lA ~ 1), weights = varComb(varIdent(form = ~1 |
+         mridXsex), varPower(value = 1)), start = Start), silent = TRUE)
+     if (!inherits(drmod4, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt,", Maxcnt, "exceeded"))
+         break
+     }
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)))
+     icnt <- icnt + 1
+ }
```

```
Success after 1 trie(s).
```

The interesting fitted values:

```
> nms <- names(fixed.effects(drmod4))
> summary(drmod4)$tTable[-grep("^lA", nms), ]
```

```
                            Value Std.Error  DF    t-value      p-value
lD.(Intercept)          -3.0078295 0.9816212 565 -3.0641448 2.287040e-03
lD.sexM                 -0.8282424 1.4100296 565 -0.5873936 5.571740e-01
lg.(Intercept)          -0.7272459 0.3340477 565 -2.1770724 2.988835e-02
lg.sexM                 -0.1383073 0.4279734 565 -0.3231679 7.466877e-01
lTr.fdose[0,0.5]:sexF    0.7769160 0.3143350 565  2.4716177 1.374397e-02
lTr.fdose(0.5,1.5]:sexF  1.2035100 0.2236498 565  5.3812256 1.085567e-07
```

```
lTr.fdose[0,0.5]:sexM    0.3581879 0.2275666 565  1.5739914 1.160492e-01
lTr.fdose(0.5,1.5]:sexM  1.1054481 0.1776659 565  6.2220623 9.561218e-10
```

Note, particularly, that neither of the "male" dose-response parameter effects are significant. Test for the effects jointly:

```
> L <- diag(2)
> dimnames(L) = list(NULL, c("lD.sexM", "lg.sexM"))
> anova(drmod4, L = L)

F-test for linear combination(s)
  lD.sexM lg.sexM
1       1       0
2       0       1
  numDF denDF  F-value p-value
1     2   565 0.881258  0.4148
```

There is no difference between the sexes in either `lg` or `lD`. Note that `lg` is negative, and significantly different from 0.

Now, finally, do the half-lives differ between the sexes?

```
> L <- cbind(diag(2), -diag(2))
> dimnames(L) <- list(NULL, names(fixed.effects(drmod4))[grep("^lTr",
+     names(fixed.effects(drmod4)))])
> anova(drmod4, L = L)

F-test for linear combination(s)
  lTr.fdose[0,0.5]:sexF lTr.fdose(0.5,1.5]:sexF lTr.fdose[0,0.5]:sexM
1                     1                      0                    -1
2                     0                      1                     0
  lTr.fdose(0.5,1.5]:sexM
1                       0
2                      -1
  numDF denDF   F-value p-value
1     2   565 0.5994759  0.5494
```

No, so refit the data with the simpler term for `lD` and no sex differences in log half-life:

```
> Par <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Par), Par["lD.(Intercept)"], Par["lg.(Intercept)"],
+     getParms("^lTr.*sexF", Par))
> Start <- list(fixed = Start0)
> icnt <- 1
> Maxcnt <- 30
> repeat {
+     drmod5 <- try(nlme(cheact ~ tcmfn4(dose, tmpstds, lA = lA,
+         lD = lD, lg = lg, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ 1, lg ~ 1, lTr ~ fdose - 1),
+         random = list(mrid = lD ~ 1, id = lA ~ 1), weights = varComb(varIdent(form = ~1 |
+             mridXsex), varPower(value = 1)), start = Start),
+         silent = TRUE)
+     if (!inherits(drmod5, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Success after", icnt, "trie(s)."))
+         else writeLines(paste("Maxcnt", Maxcnt, "exceeded"))
+         break
```

```
+     }
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)))
+     icnt <- icnt + 1
+ }

Success after 2 trie(s).

> Ints <- intervals(drmod5, which = "fixed")$fixed
> Ints90 <- intervals(drmod5, which = "fixed", level = 0.9)$fixed
> tTab <- summary(drmod5)$tTable
> summary(drmod5)

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr)
 Data: dta
       AIC      BIC    logLik
  8422.645 8619.193 -4168.322

Random effects:
 Formula: lD ~ 1 | mrid
                  lD
StdDev: 3.903138e-07

 Formula: lA ~ 1 | id %in% mrid
        lA.(Intercept)  Residual
StdDev:     0.07070206 0.1148611

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXsex
 Parameter estimates:
45675701:M 45675701:F  Padilla:M
  1.000000   1.044625   2.219697
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
    power
0.9768942
Fixed effects: list(lA ~ mridXsexXtmpstds - 1, lD ~ 1, lg ~ 1, lTr ~ fdose -      1)
                                                   Value Std.Error  DF
lA.mridXsexXtmpstds45675701:M:0                 6.891853 0.0243303 569
lA.mridXsexXtmpstds45675701:M:0.25              6.770738 0.0295254 569
lA.mridXsexXtmpstds45675701:M:0.5               6.825715 0.0285789 569
lA.mridXsexXtmpstds45675701:M:0.75              6.787582 0.0282074 569
lA.mridXsexXtmpstds45675701:M:1                 6.832586 0.0280930 569
lA.mridXsexXtmpstds45675701:M:1.25              6.794241 0.0285320 569
lA.mridXsexXtmpstds45675701:M:1.5               6.824962 0.0281959 569
lA.mridXsexXtmpstds45675701:M:2                 6.886937 0.0286992 569
lA.mridXsexXtmpstds45675701:M:2.5               6.816513 0.0282882 569
lA.mridXsexXtmpstds45675701:M:3                 6.759456 0.0281589 569
lA.mridXsexXtmpstds45675701:M:4                 6.789115 0.0276156 569
lA.mridXsexXtmpstds45675701:M:6                 6.714829 0.0270412 569
lA.mridXsexXtmpstds45675701:M:8                 6.753995 0.0270264 569
lA.mridXsexXtmpstds45675701:F:0                 6.888435 0.0255468 569
```

```
lA.mridXsexXtmpstds45675701:F:0.25              6.873175 0.0305757 569
lA.mridXsexXtmpstds45675701:F:0.5               6.842640 0.0297692 569
lA.mridXsexXtmpstds45675701:F:0.75              6.804789 0.0291587 569
lA.mridXsexXtmpstds45675701:F:1                 6.795350 0.0293643 569
lA.mridXsexXtmpstds45675701:F:1.25              6.766744 0.0290929 569
lA.mridXsexXtmpstds45675701:F:1.5               6.801995 0.0291432 569
lA.mridXsexXtmpstds45675701:F:2                 6.782632 0.0292545 569
lA.mridXsexXtmpstds45675701:F:2.5               6.804929 0.0292400 569
lA.mridXsexXtmpstds45675701:F:3                 6.776699 0.0291281 569
lA.mridXsexXtmpstds45675701:F:4                 6.686618 0.0286932 569
lA.mridXsexXtmpstds45675701:F:6                 6.789926 0.0279386 569
lA.mridXsexXtmpstds45675701:F:8                 6.779375 0.0274306 569
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  5.929227 0.0468983 108
lA.mridXsexXtmpstdsPadilla:M:0.5                5.719674 0.1007752 108
lA.mridXsexXtmpstdsPadilla:M:1                  5.866256 0.1001865 108
lA.mridXsexXtmpstdsPadilla:M:2                  5.956966 0.1000657 108
lA.mridXsexXtmpstdsPadilla:M:24                 6.231614 0.1064648 108
lA.mridXsexXtmpstdsPadilla:M:4                  5.941093 0.0991650 108
lA.mridXsexXtmpstdsPadilla:M:6                  5.944992 0.0983134 108
lD                                             -3.456819 0.7176866 569
lg                                             -0.808144 0.2113734 569
lTr.fdose[0,0.5]                                0.472971 0.1852148 569
lTr.fdose(0.5,1.5]                              1.123909 0.1389514 569
                                                 t-value p-value
lA.mridXsexXtmpstds45675701:M:0                283.26261  0.0000
lA.mridXsexXtmpstds45675701:M:0.25             229.31926  0.0000
lA.mridXsexXtmpstds45675701:M:0.5              238.83734  0.0000
lA.mridXsexXtmpstds45675701:M:0.75             240.63141  0.0000
lA.mridXsexXtmpstds45675701:M:1                243.21310  0.0000
lA.mridXsexXtmpstds45675701:M:1.25             238.12734  0.0000
lA.mridXsexXtmpstds45675701:M:1.5              242.05535  0.0000
lA.mridXsexXtmpstds45675701:M:2                239.96965  0.0000
lA.mridXsexXtmpstds45675701:M:2.5              240.96663  0.0000
lA.mridXsexXtmpstds45675701:M:3                240.04721  0.0000
lA.mridXsexXtmpstds45675701:M:4                245.84387  0.0000
lA.mridXsexXtmpstds45675701:M:6                248.31858  0.0000
lA.mridXsexXtmpstds45675701:M:8                249.90386  0.0000
lA.mridXsexXtmpstds45675701:F:0                269.63935  0.0000
lA.mridXsexXtmpstds45675701:F:0.25             224.79201  0.0000
lA.mridXsexXtmpstds45675701:F:0.5              229.85674  0.0000
lA.mridXsexXtmpstds45675701:F:0.75             233.37067  0.0000
lA.mridXsexXtmpstds45675701:F:1                231.41533  0.0000
lA.mridXsexXtmpstds45675701:F:1.25             232.59071  0.0000
lA.mridXsexXtmpstds45675701:F:1.5              233.39898  0.0000
lA.mridXsexXtmpstds45675701:F:2                231.84946  0.0000
lA.mridXsexXtmpstds45675701:F:2.5              232.72642  0.0000
lA.mridXsexXtmpstds45675701:F:3                232.65178  0.0000
lA.mridXsexXtmpstds45675701:F:4                233.03808  0.0000
lA.mridXsexXtmpstds45675701:F:6                243.03049  0.0000
lA.mridXsexXtmpstds45675701:F:8                247.14655  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667 126.42723  0.0000
lA.mridXsexXtmpstdsPadilla:M:0.5                56.75677  0.0000
lA.mridXsexXtmpstdsPadilla:M:1                  58.55333  0.0000
lA.mridXsexXtmpstdsPadilla:M:2                  59.53057  0.0000
```

```
lA.mridXsexXtmpstdsPadilla:M:24                 58.53216  0.0000
lA.mridXsexXtmpstdsPadilla:M:4                  59.91121  0.0000
lA.mridXsexXtmpstdsPadilla:M:6                  60.46979  0.0000
lD                                              -4.81661  0.0000
lg                                              -3.82330  0.0001
lTr.fdose[0,0.5]                                 2.55364  0.0109
lTr.fdose(0.5,1.5]                               8.08851  0.0000
 Correlation:
                                               lA.mXX45675701:M:0
lA.mridXsexXtmpstds45675701:M:0.25              0.282
lA.mridXsexXtmpstds45675701:M:0.5               0.292
lA.mridXsexXtmpstds45675701:M:0.75              0.296
lA.mridXsexXtmpstds45675701:M:1                 0.297
lA.mridXsexXtmpstds45675701:M:1.25              0.292
lA.mridXsexXtmpstds45675701:M:1.5               0.296
lA.mridXsexXtmpstds45675701:M:2                 0.290
lA.mridXsexXtmpstds45675701:M:2.5               0.295
lA.mridXsexXtmpstds45675701:M:3                 0.296
lA.mridXsexXtmpstds45675701:M:4                 0.302
lA.mridXsexXtmpstds45675701:M:6                 0.308
lA.mridXsexXtmpstds45675701:M:8                 0.308
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.000
lA.mridXsexXtmpstds45675701:F:0.5               0.000
lA.mridXsexXtmpstds45675701:F:0.75              0.000
lA.mridXsexXtmpstds45675701:F:1                 0.000
lA.mridXsexXtmpstds45675701:F:1.25              0.000
lA.mridXsexXtmpstds45675701:F:1.5               0.000
lA.mridXsexXtmpstds45675701:F:2                 0.000
lA.mridXsexXtmpstds45675701:F:2.5               0.000
lA.mridXsexXtmpstds45675701:F:3                 0.000
lA.mridXsexXtmpstds45675701:F:4                 0.000
lA.mridXsexXtmpstds45675701:F:6                 0.000
lA.mridXsexXtmpstds45675701:F:8                 0.000
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                0.000
lA.mridXsexXtmpstdsPadilla:M:1                  0.000
lA.mridXsexXtmpstdsPadilla:M:2                  0.000
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.000
lA.mridXsexXtmpstdsPadilla:M:6                  0.000
lD                                              0.000
lg                                              0.000
lTr.fdose[0,0.5]                                0.000
lTr.fdose(0.5,1.5]                              0.000
                                               lA.XX45675701:M:0.2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5               0.521
lA.mridXsexXtmpstds45675701:M:0.75              0.492
lA.mridXsexXtmpstds45675701:M:1                 0.463
lA.mridXsexXtmpstds45675701:M:1.25              0.432
lA.mridXsexXtmpstds45675701:M:1.5               0.412
lA.mridXsexXtmpstds45675701:M:2                 0.368
lA.mridXsexXtmpstds45675701:M:2.5               0.346
```

```
lA.mridXsexXtmpstds45675701:M:3                 0.325
lA.mridXsexXtmpstds45675701:M:4                 0.300
lA.mridXsexXtmpstds45675701:M:6                 0.271
lA.mridXsexXtmpstds45675701:M:8                 0.262
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.292
lA.mridXsexXtmpstds45675701:F:0.5               0.262
lA.mridXsexXtmpstds45675701:F:0.75              0.236
lA.mridXsexXtmpstds45675701:F:1                 0.203
lA.mridXsexXtmpstds45675701:F:1.25              0.183
lA.mridXsexXtmpstds45675701:F:1.5               0.161
lA.mridXsexXtmpstds45675701:F:2                 0.125
lA.mridXsexXtmpstds45675701:F:2.5               0.099
lA.mridXsexXtmpstds45675701:F:3                 0.078
lA.mridXsexXtmpstds45675701:F:4                 0.049
lA.mridXsexXtmpstds45675701:F:6                 0.014
lA.mridXsexXtmpstds45675701:F:8                 0.003
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.179
lA.mridXsexXtmpstdsPadilla:M:0.5                0.096
lA.mridXsexXtmpstdsPadilla:M:1                  0.071
lA.mridXsexXtmpstdsPadilla:M:2                  0.040
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.014
lA.mridXsexXtmpstdsPadilla:M:6                  0.005
lD                                             -0.259
lg                                             -0.173
lTr.fdose[0,0.5]                               -0.018
lTr.fdose(0.5,1.5]                             -0.071
                                               lA.XX45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75              0.503
lA.mridXsexXtmpstds45675701:M:1                 0.487
lA.mridXsexXtmpstds45675701:M:1.25              0.465
lA.mridXsexXtmpstds45675701:M:1.5               0.453
lA.mridXsexXtmpstds45675701:M:2                 0.420
lA.mridXsexXtmpstds45675701:M:2.5               0.402
lA.mridXsexXtmpstds45675701:M:3                 0.385
lA.mridXsexXtmpstds45675701:M:4                 0.360
lA.mridXsexXtmpstds45675701:M:6                 0.322
lA.mridXsexXtmpstds45675701:M:8                 0.302
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.263
lA.mridXsexXtmpstds45675701:F:0.5               0.250
lA.mridXsexXtmpstds45675701:F:0.75              0.239
lA.mridXsexXtmpstds45675701:F:1                 0.218
lA.mridXsexXtmpstds45675701:F:1.25              0.207
lA.mridXsexXtmpstds45675701:F:1.5               0.192
lA.mridXsexXtmpstds45675701:F:2                 0.166
lA.mridXsexXtmpstds45675701:F:2.5               0.144
lA.mridXsexXtmpstds45675701:F:3                 0.126
lA.mridXsexXtmpstds45675701:F:4                 0.098
lA.mridXsexXtmpstds45675701:F:6                 0.056
lA.mridXsexXtmpstds45675701:F:8                 0.034
```

```
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.174
lA.mridXsexXtmpstdsPadilla:M:0.5                0.090
lA.mridXsexXtmpstdsPadilla:M:1                  0.078
lA.mridXsexXtmpstdsPadilla:M:2                  0.057
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.031
lA.mridXsexXtmpstdsPadilla:M:6                  0.016
lD                                             -0.203
lg                                             -0.124
lTr.fdose[0,0.5]                                0.100
lTr.fdose(0.5,1.5]                              0.031
                                               lA.XX45675701:M:0.7
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1                 0.497
lA.mridXsexXtmpstds45675701:M:1.25              0.485
lA.mridXsexXtmpstds45675701:M:1.5               0.479
lA.mridXsexXtmpstds45675701:M:2                 0.455
lA.mridXsexXtmpstds45675701:M:2.5               0.442
lA.mridXsexXtmpstds45675701:M:3                 0.426
lA.mridXsexXtmpstds45675701:M:4                 0.403
lA.mridXsexXtmpstds45675701:M:6                 0.359
lA.mridXsexXtmpstds45675701:M:8                 0.331
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.233
lA.mridXsexXtmpstds45675701:F:0.5               0.235
lA.mridXsexXtmpstds45675701:F:0.75              0.236
lA.mridXsexXtmpstds45675701:F:1                 0.225
lA.mridXsexXtmpstds45675701:F:1.25              0.221
lA.mridXsexXtmpstds45675701:F:1.5               0.213
lA.mridXsexXtmpstds45675701:F:2                 0.195
lA.mridXsexXtmpstds45675701:F:2.5               0.178
lA.mridXsexXtmpstds45675701:F:3                 0.163
lA.mridXsexXtmpstds45675701:F:4                 0.136
lA.mridXsexXtmpstds45675701:F:6                 0.089
lA.mridXsexXtmpstds45675701:F:8                 0.058
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.165
lA.mridXsexXtmpstdsPadilla:M:0.5                0.083
lA.mridXsexXtmpstdsPadilla:M:1                  0.081
lA.mridXsexXtmpstdsPadilla:M:2                  0.069
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.043
lA.mridXsexXtmpstdsPadilla:M:6                  0.025
lD                                             -0.154
lg                                             -0.082
lTr.fdose[0,0.5]                                0.192
lTr.fdose(0.5,1.5]                              0.115
                                               lA.mXX45675701:M:1
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25              0.494
```

```
lA.mridXsexXtmpstds45675701:M:1.5                0.494
lA.mridXsexXtmpstds45675701:M:2                  0.477
lA.mridXsexXtmpstds45675701:M:2.5                0.468
lA.mridXsexXtmpstds45675701:M:3                  0.456
lA.mridXsexXtmpstds45675701:M:4                  0.434
lA.mridXsexXtmpstds45675701:M:6                  0.386
lA.mridXsexXtmpstds45675701:M:8                  0.352
lA.mridXsexXtmpstds45675701:F:0                  0.000
lA.mridXsexXtmpstds45675701:F:0.25               0.206
lA.mridXsexXtmpstds45675701:F:0.5                0.220
lA.mridXsexXtmpstds45675701:F:0.75               0.230
lA.mridXsexXtmpstds45675701:F:1                  0.227
lA.mridXsexXtmpstds45675701:F:1.25               0.229
lA.mridXsexXtmpstds45675701:F:1.5                0.226
lA.mridXsexXtmpstds45675701:F:2                  0.215
lA.mridXsexXtmpstds45675701:F:2.5                0.203
lA.mridXsexXtmpstds45675701:F:3                  0.190
lA.mridXsexXtmpstds45675701:F:4                  0.164
lA.mridXsexXtmpstds45675701:F:6                  0.114
lA.mridXsexXtmpstds45675701:F:8                  0.077
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.155
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.077
lA.mridXsexXtmpstdsPadilla:M:1                   0.082
lA.mridXsexXtmpstdsPadilla:M:2                   0.078
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lA.mridXsexXtmpstdsPadilla:M:4                   0.053
lA.mridXsexXtmpstdsPadilla:M:6                   0.031
lD                                              -0.112
lg                                              -0.047
lTr.fdose[0,0.5]                                 0.261
lTr.fdose(0.5,1.5]                               0.183
                                                lA.XX45675701:M:1.2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5                0.498
lA.mridXsexXtmpstds45675701:M:2                  0.490
lA.mridXsexXtmpstds45675701:M:2.5                0.482
lA.mridXsexXtmpstds45675701:M:3                  0.472
lA.mridXsexXtmpstds45675701:M:4                  0.451
lA.mridXsexXtmpstds45675701:M:6                  0.402
lA.mridXsexXtmpstds45675701:M:8                  0.364
lA.mridXsexXtmpstds45675701:F:0                  0.000
lA.mridXsexXtmpstds45675701:F:0.25               0.181
lA.mridXsexXtmpstds45675701:F:0.5                0.204
lA.mridXsexXtmpstds45675701:F:0.75               0.221
lA.mridXsexXtmpstds45675701:F:1                  0.226
lA.mridXsexXtmpstds45675701:F:1.25               0.233
lA.mridXsexXtmpstds45675701:F:1.5                0.233
lA.mridXsexXtmpstds45675701:F:2                  0.228
lA.mridXsexXtmpstds45675701:F:2.5                0.219
lA.mridXsexXtmpstds45675701:F:3                  0.208
```

```
lA.mridXsexXtmpstds45675701:F:4                 0.184
lA.mridXsexXtmpstds45675701:F:6                 0.133
lA.mridXsexXtmpstds45675701:F:8                 0.091
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.146
lA.mridXsexXtmpstdsPadilla:M:0.5                0.070
lA.mridXsexXtmpstdsPadilla:M:1                  0.082
lA.mridXsexXtmpstdsPadilla:M:2                  0.083
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.059
lA.mridXsexXtmpstdsPadilla:M:6                  0.035
lD                                             -0.077
lg                                             -0.019
lTr.fdose[0,0.5]                                0.312
lTr.fdose(0.5,1.5]                              0.236
                                               lA.XX45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2                 0.500
lA.mridXsexXtmpstds45675701:M:2.5               0.497
lA.mridXsexXtmpstds45675701:M:3                 0.488
lA.mridXsexXtmpstds45675701:M:4                 0.469
lA.mridXsexXtmpstds45675701:M:6                 0.417
lA.mridXsexXtmpstds45675701:M:8                 0.376
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.160
lA.mridXsexXtmpstds45675701:F:0.5               0.190
lA.mridXsexXtmpstds45675701:F:0.75              0.213
lA.mridXsexXtmpstds45675701:F:1                 0.222
lA.mridXsexXtmpstds45675701:F:1.25              0.233
lA.mridXsexXtmpstds45675701:F:1.5               0.237
lA.mridXsexXtmpstds45675701:F:2                 0.237
lA.mridXsexXtmpstds45675701:F:2.5               0.231
lA.mridXsexXtmpstds45675701:F:3                 0.221
lA.mridXsexXtmpstds45675701:F:4                 0.199
lA.mridXsexXtmpstds45675701:F:6                 0.147
lA.mridXsexXtmpstds45675701:F:8                 0.102
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.137
lA.mridXsexXtmpstdsPadilla:M:0.5                0.064
lA.mridXsexXtmpstdsPadilla:M:1                  0.081
lA.mridXsexXtmpstdsPadilla:M:2                  0.086
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.063
lA.mridXsexXtmpstdsPadilla:M:6                  0.038
lD                                             -0.050
lg                                              0.003
lTr.fdose[0,0.5]                                0.347
lTr.fdose(0.5,1.5]                              0.277
                                               lA.mXX45675701:M:2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
```

```
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5                0.505
lA.mridXsexXtmpstds45675701:M:3                  0.499
lA.mridXsexXtmpstds45675701:M:4                  0.483
lA.mridXsexXtmpstds45675701:M:6                  0.432
lA.mridXsexXtmpstds45675701:M:8                  0.388
lA.mridXsexXtmpstds45675701:F:0                  0.000
lA.mridXsexXtmpstds45675701:F:0.25               0.123
lA.mridXsexXtmpstds45675701:F:0.5                0.163
lA.mridXsexXtmpstds45675701:F:0.75               0.194
lA.mridXsexXtmpstds45675701:F:1                  0.212
lA.mridXsexXtmpstds45675701:F:1.25               0.228
lA.mridXsexXtmpstds45675701:F:1.5                0.237
lA.mridXsexXtmpstds45675701:F:2                  0.243
lA.mridXsexXtmpstds45675701:F:2.5                0.242
lA.mridXsexXtmpstds45675701:F:3                  0.236
lA.mridXsexXtmpstds45675701:F:4                  0.216
lA.mridXsexXtmpstds45675701:F:6                  0.165
lA.mridXsexXtmpstds45675701:F:8                  0.116
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.119
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.054
lA.mridXsexXtmpstdsPadilla:M:1                   0.077
lA.mridXsexXtmpstdsPadilla:M:2                   0.089
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lA.mridXsexXtmpstdsPadilla:M:4                   0.068
lA.mridXsexXtmpstdsPadilla:M:6                   0.042
lD                                              -0.007
lg                                               0.036
lTr.fdose[0,0.5]                                 0.391
lTr.fdose(0.5,1.5]                               0.335
                                                lA.XX45675701:M:2.
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3                  0.505
lA.mridXsexXtmpstds45675701:M:4                  0.492
lA.mridXsexXtmpstds45675701:M:6                  0.441
lA.mridXsexXtmpstds45675701:M:8                  0.396
lA.mridXsexXtmpstds45675701:F:0                  0.000
lA.mridXsexXtmpstds45675701:F:0.25               0.099
lA.mridXsexXtmpstds45675701:F:0.5                0.144
lA.mridXsexXtmpstds45675701:F:0.75               0.178
lA.mridXsexXtmpstds45675701:F:1                  0.200
lA.mridXsexXtmpstds45675701:F:1.25               0.219
lA.mridXsexXtmpstds45675701:F:1.5                0.230
```

```
lA.mridXsexXtmpstds45675701:F:2                 0.241
lA.mridXsexXtmpstds45675701:F:2.5               0.243
lA.mridXsexXtmpstds45675701:F:3                 0.239
lA.mridXsexXtmpstds45675701:F:4                 0.221
lA.mridXsexXtmpstds45675701:F:6                 0.172
lA.mridXsexXtmpstds45675701:F:8                 0.122
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.106
lA.mridXsexXtmpstdsPadilla:M:0.5                0.046
lA.mridXsexXtmpstdsPadilla:M:1                  0.072
lA.mridXsexXtmpstdsPadilla:M:2                  0.087
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.068
lA.mridXsexXtmpstdsPadilla:M:6                  0.042
lD                                              0.018
lg                                              0.053
lTr.fdose[0,0.5]                                0.403
lTr.fdose(0.5,1.5]                              0.365
                                               lA.XX45675701:M:3
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4                 0.492
lA.mridXsexXtmpstds45675701:M:6                 0.444
lA.mridXsexXtmpstds45675701:M:8                 0.399
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.079
lA.mridXsexXtmpstds45675701:F:0.5               0.126
lA.mridXsexXtmpstds45675701:F:0.75              0.163
lA.mridXsexXtmpstds45675701:F:1                 0.187
lA.mridXsexXtmpstds45675701:F:1.25              0.208
lA.mridXsexXtmpstds45675701:F:1.5               0.221
lA.mridXsexXtmpstds45675701:F:2                 0.235
lA.mridXsexXtmpstds45675701:F:2.5               0.239
lA.mridXsexXtmpstds45675701:F:3                 0.236
lA.mridXsexXtmpstds45675701:F:4                 0.221
lA.mridXsexXtmpstds45675701:F:6                 0.174
lA.mridXsexXtmpstds45675701:F:8                 0.124
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.094
lA.mridXsexXtmpstdsPadilla:M:0.5                0.039
lA.mridXsexXtmpstdsPadilla:M:1                  0.067
lA.mridXsexXtmpstdsPadilla:M:2                  0.084
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.067
lA.mridXsexXtmpstdsPadilla:M:6                  0.042
lD                                              0.035
lg                                              0.065
lTr.fdose[0,0.5]                                0.401
lTr.fdose(0.5,1.5]                              0.382
```

```
                                                lA.XX45675701:M:4
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6                 0.442
lA.mridXsexXtmpstds45675701:M:8                 0.400
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.051
lA.mridXsexXtmpstds45675701:F:0.5               0.099
lA.mridXsexXtmpstds45675701:F:0.75              0.136
lA.mridXsexXtmpstds45675701:F:1                 0.162
lA.mridXsexXtmpstds45675701:F:1.25              0.184
lA.mridXsexXtmpstds45675701:F:1.5               0.199
lA.mridXsexXtmpstds45675701:F:2                 0.215
lA.mridXsexXtmpstds45675701:F:2.5               0.221
lA.mridXsexXtmpstds45675701:F:3                 0.221
lA.mridXsexXtmpstds45675701:F:4                 0.209
lA.mridXsexXtmpstds45675701:F:6                 0.168
lA.mridXsexXtmpstds45675701:F:8                 0.121
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.075
lA.mridXsexXtmpstdsPadilla:M:0.5                0.029
lA.mridXsexXtmpstdsPadilla:M:1                  0.057
lA.mridXsexXtmpstdsPadilla:M:2                  0.075
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.061
lA.mridXsexXtmpstdsPadilla:M:6                  0.038
lD                                              0.053
lg                                              0.074
lTr.fdose[0,0.5]                                0.374
lTr.fdose(0.5,1.5]                              0.387
                                                lA.XX45675701:M:6
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8                 0.385
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.019
lA.mridXsexXtmpstds45675701:F:0.5               0.058
lA.mridXsexXtmpstds45675701:F:0.75              0.089
```

```
lA.mridXsexXtmpstds45675701:F:1                 0.112
lA.mridXsexXtmpstds45675701:F:1.25              0.131
lA.mridXsexXtmpstds45675701:F:1.5               0.144
lA.mridXsexXtmpstds45675701:F:2                 0.161
lA.mridXsexXtmpstds45675701:F:2.5               0.168
lA.mridXsexXtmpstds45675701:F:3                 0.170
lA.mridXsexXtmpstds45675701:F:4                 0.164
lA.mridXsexXtmpstds45675701:F:6                 0.135
lA.mridXsexXtmpstds45675701:F:8                 0.099
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.045
lA.mridXsexXtmpstdsPadilla:M:0.5                0.014
lA.mridXsexXtmpstdsPadilla:M:1                  0.037
lA.mridXsexXtmpstdsPadilla:M:2                  0.053
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.044
lA.mridXsexXtmpstdsPadilla:M:6                  0.028
lD                                              0.063
lg                                              0.073
lTr.fdose[0,0.5]                                0.278
lTr.fdose(0.5,1.5]                              0.332
                                               lA.XX45675701:M:8
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0                 0.000
lA.mridXsexXtmpstds45675701:F:0.25              0.009
lA.mridXsexXtmpstds45675701:F:0.5               0.039
lA.mridXsexXtmpstds45675701:F:0.75              0.062
lA.mridXsexXtmpstds45675701:F:1                 0.080
lA.mridXsexXtmpstds45675701:F:1.25              0.095
lA.mridXsexXtmpstds45675701:F:1.5               0.105
lA.mridXsexXtmpstds45675701:F:2                 0.119
lA.mridXsexXtmpstds45675701:F:2.5               0.125
lA.mridXsexXtmpstds45675701:F:3                 0.127
lA.mridXsexXtmpstds45675701:F:4                 0.124
lA.mridXsexXtmpstds45675701:F:6                 0.104
lA.mridXsexXtmpstds45675701:F:8                 0.077
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.032
lA.mridXsexXtmpstdsPadilla:M:0.5                0.010
lA.mridXsexXtmpstdsPadilla:M:1                  0.026
lA.mridXsexXtmpstdsPadilla:M:2                  0.037
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.031
lA.mridXsexXtmpstdsPadilla:M:6                  0.020
lD                                              0.038
```

```
lg                                                0.043
lTr.fdose[0,0.5]                                  0.197
lTr.fdose(0.5,1.5]                                0.266
                                                 lA.mXX45675701:F:0
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25                0.270
lA.mridXsexXtmpstds45675701:F:0.5                 0.277
lA.mridXsexXtmpstds45675701:F:0.75                0.283
lA.mridXsexXtmpstds45675701:F:1                   0.281
lA.mridXsexXtmpstds45675701:F:1.25                0.284
lA.mridXsexXtmpstds45675701:F:1.5                 0.283
lA.mridXsexXtmpstds45675701:F:2                   0.282
lA.mridXsexXtmpstds45675701:F:2.5                 0.282
lA.mridXsexXtmpstds45675701:F:3                   0.283
lA.mridXsexXtmpstds45675701:F:4                   0.288
lA.mridXsexXtmpstds45675701:F:6                   0.295
lA.mridXsexXtmpstds45675701:F:8                   0.301
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667    0.000
lA.mridXsexXtmpstdsPadilla:M:0.5                  0.000
lA.mridXsexXtmpstdsPadilla:M:1                    0.000
lA.mridXsexXtmpstdsPadilla:M:2                    0.000
lA.mridXsexXtmpstdsPadilla:M:24                   0.000
lA.mridXsexXtmpstdsPadilla:M:4                    0.000
lA.mridXsexXtmpstdsPadilla:M:6                    0.000
lD                                                0.000
lg                                                0.000
lTr.fdose[0,0.5]                                  0.000
lTr.fdose(0.5,1.5]                                0.000
                                                 lA.XX45675701:F:0.2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
```

```
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5                0.477
lA.mridXsexXtmpstds45675701:F:0.75               0.459
lA.mridXsexXtmpstds45675701:F:1                  0.428
lA.mridXsexXtmpstds45675701:F:1.25               0.410
lA.mridXsexXtmpstds45675701:F:1.5                0.389
lA.mridXsexXtmpstds45675701:F:2                  0.356
lA.mridXsexXtmpstds45675701:F:2.5                0.331
lA.mridXsexXtmpstds45675701:F:3                  0.313
lA.mridXsexXtmpstds45675701:F:4                  0.290
lA.mridXsexXtmpstds45675701:F:6                  0.263
lA.mridXsexXtmpstds45675701:F:8                  0.256
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.168
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.089
lA.mridXsexXtmpstdsPadilla:M:1                   0.066
lA.mridXsexXtmpstdsPadilla:M:2                   0.037
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lA.mridXsexXtmpstdsPadilla:M:4                   0.013
lA.mridXsexXtmpstdsPadilla:M:6                   0.005
lD                                              -0.237
lg                                              -0.156
lTr.fdose[0,0.5]                                -0.016
lTr.fdose(0.5,1.5]                              -0.058
                                                lA.XX45675701:F:0.5
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75               0.467
lA.mridXsexXtmpstds45675701:F:1                  0.446
lA.mridXsexXtmpstds45675701:F:1.25               0.438
lA.mridXsexXtmpstds45675701:F:1.5                0.424
lA.mridXsexXtmpstds45675701:F:2                  0.399
lA.mridXsexXtmpstds45675701:F:2.5                0.379
lA.mridXsexXtmpstds45675701:F:3                  0.364
lA.mridXsexXtmpstds45675701:F:4                  0.341
lA.mridXsexXtmpstds45675701:F:6                  0.308
lA.mridXsexXtmpstds45675701:F:8                  0.291
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.162
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.083
lA.mridXsexXtmpstdsPadilla:M:1                   0.072
lA.mridXsexXtmpstdsPadilla:M:2                   0.053
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
```

```
lA.mridXsexXtmpstdsPadilla:M:4                  0.029
lA.mridXsexXtmpstdsPadilla:M:6                  0.015
lD                                             -0.184
lg                                             -0.109
lTr.fdose[0,0.5]                                0.094
lTr.fdose(0.5,1.5]                              0.037
                                               lA.XX45675701:F:0.7
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1                 0.461
lA.mridXsexXtmpstds45675701:F:1.25              0.459
lA.mridXsexXtmpstds45675701:F:1.5               0.451
lA.mridXsexXtmpstds45675701:F:2                 0.433
lA.mridXsexXtmpstds45675701:F:2.5               0.417
lA.mridXsexXtmpstds45675701:F:3                 0.404
lA.mridXsexXtmpstds45675701:F:4                 0.382
lA.mridXsexXtmpstds45675701:F:6                 0.344
lA.mridXsexXtmpstds45675701:F:8                 0.319
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.156
lA.mridXsexXtmpstdsPadilla:M:0.5                0.078
lA.mridXsexXtmpstdsPadilla:M:1                  0.076
lA.mridXsexXtmpstdsPadilla:M:2                  0.065
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.041
lA.mridXsexXtmpstdsPadilla:M:6                  0.023
lD                                             -0.135
lg                                             -0.066
lTr.fdose[0,0.5]                                0.180
lTr.fdose(0.5,1.5]                              0.113
                                               lA.mXX45675701:F:1
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
```

```
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25              0.461
lA.mridXsexXtmpstds45675701:F:1.5               0.458
lA.mridXsexXtmpstds45675701:F:2                 0.447
lA.mridXsexXtmpstds45675701:F:2.5               0.436
lA.mridXsexXtmpstds45675701:F:3                 0.425
lA.mridXsexXtmpstds45675701:F:4                 0.405
lA.mridXsexXtmpstds45675701:F:6                 0.365
lA.mridXsexXtmpstds45675701:F:8                 0.335
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.145
lA.mridXsexXtmpstdsPadilla:M:0.5                0.071
lA.mridXsexXtmpstdsPadilla:M:1                  0.076
lA.mridXsexXtmpstdsPadilla:M:2                  0.072
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.049
lA.mridXsexXtmpstdsPadilla:M:6                  0.028
lD                                             -0.100
lg                                             -0.038
lTr.fdose[0,0.5]                                0.242
lTr.fdose(0.5,1.5]                              0.178
                                               lA.XX45675701:F:1.2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5               0.470
lA.mridXsexXtmpstds45675701:F:2                 0.465
lA.mridXsexXtmpstds45675701:F:2.5               0.456
lA.mridXsexXtmpstds45675701:F:3                 0.447
lA.mridXsexXtmpstds45675701:F:4                 0.428
lA.mridXsexXtmpstds45675701:F:6                 0.387
lA.mridXsexXtmpstds45675701:F:8                 0.351
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.138
lA.mridXsexXtmpstdsPadilla:M:0.5                0.066
```

```
lA.mridXsexXtmpstdsPadilla:M:1                  0.077
lA.mridXsexXtmpstdsPadilla:M:2                  0.077
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.055
lA.mridXsexXtmpstdsPadilla:M:6                  0.033
lD                                             -0.066
lg                                             -0.010
lTr.fdose[0,0.5]                                0.289
lTr.fdose(0.5,1.5]                              0.228
                                               lA.XX45675701:F:1.5
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2                 0.472
lA.mridXsexXtmpstds45675701:F:2.5               0.467
lA.mridXsexXtmpstds45675701:F:3                 0.459
lA.mridXsexXtmpstds45675701:F:4                 0.441
lA.mridXsexXtmpstds45675701:F:6                 0.399
lA.mridXsexXtmpstds45675701:F:8                 0.361
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.129
lA.mridXsexXtmpstdsPadilla:M:0.5                0.060
lA.mridXsexXtmpstdsPadilla:M:1                  0.075
lA.mridXsexXtmpstdsPadilla:M:2                  0.080
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.059
lA.mridXsexXtmpstdsPadilla:M:6                  0.035
lD                                             -0.041
lg                                              0.010
lTr.fdose[0,0.5]                                0.322
lTr.fdose(0.5,1.5]                              0.268
                                               lA.mXX45675701:F:2
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
```

```
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5                0.476
lA.mridXsexXtmpstds45675701:F:3                  0.471
lA.mridXsexXtmpstds45675701:F:4                  0.456
lA.mridXsexXtmpstds45675701:F:6                  0.415
lA.mridXsexXtmpstds45675701:F:8                  0.373
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.114
lA.mridXsexXtmpstdsPadilla:M:0.5                 0.051
lA.mridXsexXtmpstdsPadilla:M:1                   0.072
lA.mridXsexXtmpstdsPadilla:M:2                   0.082
lA.mridXsexXtmpstdsPadilla:M:24                  0.000
lA.mridXsexXtmpstdsPadilla:M:4                   0.063
lA.mridXsexXtmpstdsPadilla:M:6                   0.038
lD                                              -0.004
lg                                               0.038
lTr.fdose[0,0.5]                                 0.361
lTr.fdose(0.5,1.5]                               0.323
                                                lA.XX45675701:F:2.
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3                  0.475
lA.mridXsexXtmpstds45675701:F:4                  0.462
lA.mridXsexXtmpstds45675701:F:6                  0.423
```

```
lA.mridXsexXtmpstds45675701:F:8                 0.380
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.101
lA.mridXsexXtmpstdsPadilla:M:0.5                0.043
lA.mridXsexXtmpstdsPadilla:M:1                  0.067
lA.mridXsexXtmpstdsPadilla:M:2                  0.081
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.064
lA.mridXsexXtmpstdsPadilla:M:6                  0.039
lD                                              0.020
lg                                              0.055
lTr.fdose[0,0.5]                                0.375
lTr.fdose(0.5,1.5]                              0.355
                                               lA.XX45675701:F:3
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4                 0.463
lA.mridXsexXtmpstds45675701:F:6                 0.426
lA.mridXsexXtmpstds45675701:F:8                 0.384
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.090
lA.mridXsexXtmpstdsPadilla:M:0.5                0.037
lA.mridXsexXtmpstdsPadilla:M:1                  0.063
lA.mridXsexXtmpstdsPadilla:M:2                  0.078
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.063
lA.mridXsexXtmpstdsPadilla:M:6                  0.039
lD                                              0.036
lg                                              0.065
lTr.fdose[0,0.5]                                0.374
lTr.fdose(0.5,1.5]                              0.371
                                               lA.XX45675701:F:4
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
```

```
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6                 0.425
lA.mridXsexXtmpstds45675701:F:8                 0.385
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.071
lA.mridXsexXtmpstdsPadilla:M:0.5                0.027
lA.mridXsexXtmpstdsPadilla:M:1                  0.053
lA.mridXsexXtmpstdsPadilla:M:2                  0.070
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.057
lA.mridXsexXtmpstdsPadilla:M:6                  0.036
lD                                              0.052
lg                                              0.072
lTr.fdose[0,0.5]                                0.349
lTr.fdose(0.5,1.5]                              0.377
                                               lA.XX45675701:F:6
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
```

```
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8                 0.376
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.043
lA.mridXsexXtmpstdsPadilla:M:0.5                0.013
lA.mridXsexXtmpstdsPadilla:M:1                  0.035
lA.mridXsexXtmpstdsPadilla:M:2                  0.050
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.042
lA.mridXsexXtmpstdsPadilla:M:6                  0.027
lD                                              0.058
lg                                              0.067
lTr.fdose[0,0.5]                                0.266
lTr.fdose(0.5,1.5]                              0.337
                                               lA.XX45675701:F:8 lA.XXP:M:0.6
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667  0.026
lA.mridXsexXtmpstdsPadilla:M:0.5                0.006             0.066
lA.mridXsexXtmpstdsPadilla:M:1                  0.022             0.058
lA.mridXsexXtmpstdsPadilla:M:2                  0.033             0.044
lA.mridXsexXtmpstdsPadilla:M:24                 0.000             0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.028             0.024
lA.mridXsexXtmpstdsPadilla:M:6                  0.018             0.013
lD                                              0.051            -0.200
lg                                              0.056            -0.155
lTr.fdose[0,0.5]                                0.179             0.085
lTr.fdose(0.5,1.5]                              0.259             0.043
                                               lA.XXP:M:0.5 lA.XXP:M:1
lA.mridXsexXtmpstds45675701:M:0.25
```

```
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1                  0.033
lA.mridXsexXtmpstdsPadilla:M:2                  0.023        0.035
lA.mridXsexXtmpstdsPadilla:M:24                 0.000        0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.012        0.024
lA.mridXsexXtmpstdsPadilla:M:6                  0.006        0.014
lD                                             -0.149       -0.093
lg                                             -0.127       -0.076
lTr.fdose[0,0.5]                                0.036        0.120
lTr.fdose(0.5,1.5]                             -0.003        0.040
                                               lA.mXXP:M:2 lA.XXP:M:24
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
```

```
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1
lA.mridXsexXtmpstdsPadilla:M:2
lA.mridXsexXtmpstdsPadilla:M:24                 0.000
lA.mridXsexXtmpstdsPadilla:M:4                  0.031       0.000
lA.mridXsexXtmpstdsPadilla:M:6                  0.019       0.000
lD                                             -0.032       0.000
lg                                             -0.021       0.000
lTr.fdose[0,0.5]                                0.182       0.000
lTr.fdose(0.5,1.5]                              0.074       0.000
                                               lA.XXP:M:4 lA.XXP:M:6 lD
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1
lA.mridXsexXtmpstdsPadilla:M:2
lA.mridXsexXtmpstdsPadilla:M:24
lA.mridXsexXtmpstdsPadilla:M:4
lA.mridXsexXtmpstdsPadilla:M:6                  0.016
lD                                              0.005      0.009
lg                                              0.010      0.012      0.986
lTr.fdose[0,0.5]                                0.156      0.099      0.208
```

```
lTr.fdose(0.5,1.5]                                0.067      0.044      0.144
                                                 lg     lT.[0,
lA.mridXsexXtmpstds45675701:M:0.25
lA.mridXsexXtmpstds45675701:M:0.5
lA.mridXsexXtmpstds45675701:M:0.75
lA.mridXsexXtmpstds45675701:M:1
lA.mridXsexXtmpstds45675701:M:1.25
lA.mridXsexXtmpstds45675701:M:1.5
lA.mridXsexXtmpstds45675701:M:2
lA.mridXsexXtmpstds45675701:M:2.5
lA.mridXsexXtmpstds45675701:M:3
lA.mridXsexXtmpstds45675701:M:4
lA.mridXsexXtmpstds45675701:M:6
lA.mridXsexXtmpstds45675701:M:8
lA.mridXsexXtmpstds45675701:F:0
lA.mridXsexXtmpstds45675701:F:0.25
lA.mridXsexXtmpstds45675701:F:0.5
lA.mridXsexXtmpstds45675701:F:0.75
lA.mridXsexXtmpstds45675701:F:1
lA.mridXsexXtmpstds45675701:F:1.25
lA.mridXsexXtmpstds45675701:F:1.5
lA.mridXsexXtmpstds45675701:F:2
lA.mridXsexXtmpstds45675701:F:2.5
lA.mridXsexXtmpstds45675701:F:3
lA.mridXsexXtmpstds45675701:F:4
lA.mridXsexXtmpstds45675701:F:6
lA.mridXsexXtmpstds45675701:F:8
lA.mridXsexXtmpstdsPadilla:M:0.666666666666667
lA.mridXsexXtmpstdsPadilla:M:0.5
lA.mridXsexXtmpstdsPadilla:M:1
lA.mridXsexXtmpstdsPadilla:M:2
lA.mridXsexXtmpstdsPadilla:M:24
lA.mridXsexXtmpstdsPadilla:M:4
lA.mridXsexXtmpstdsPadilla:M:6
lD
lg
lTr.fdose[0,0.5]                                  0.217
lTr.fdose(0.5,1.5]                                0.130  0.453

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-4.65134237 -0.62235709  0.01292931  0.59758541  3.37870083

Number of Observations: 714
Number of Groups:
        mrid id %in% mrid
           2          116
```

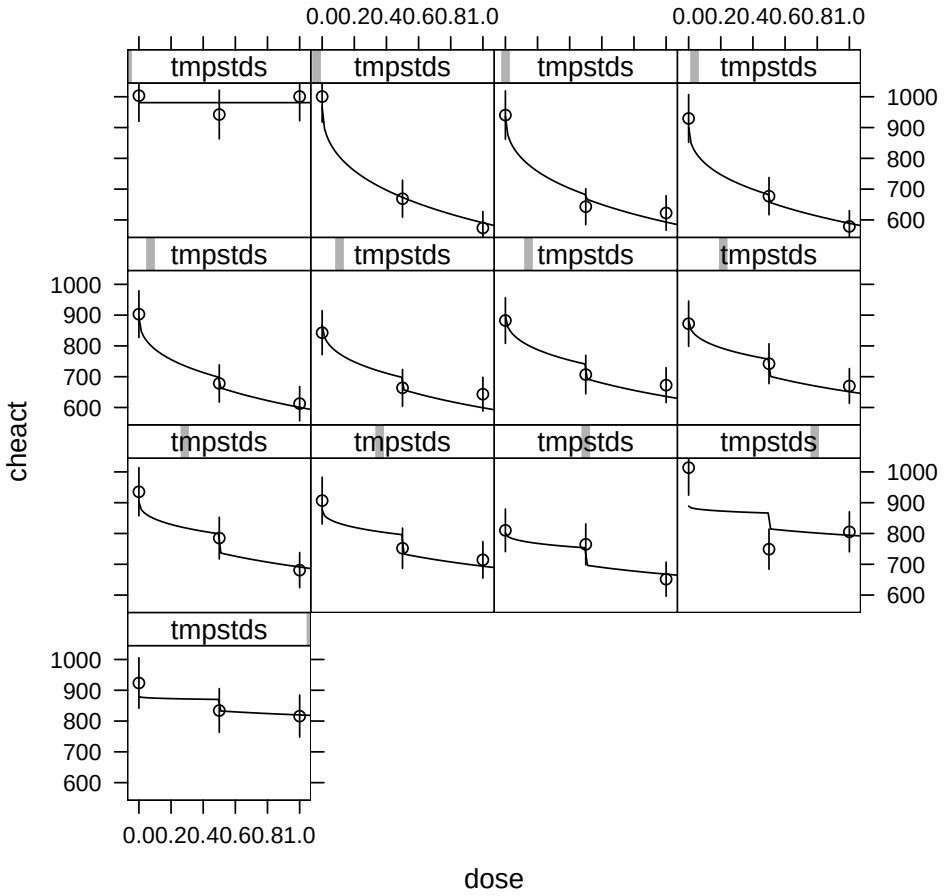
Diagnostic plots for this model: Dose-response curves at different times after dosing for mrid 45675701, males and females separately, and the dose-response curve at 2/3 hour, and recovery curve at 0.5 mg/kg in the Padilla data set (males only). First, set up the datasets for the plots:

```
> tmpd <- dta
> tmpd$mridXsexXtmpstdsXdose <- with(tmpd, interaction(mridXsexXtmpstds,
+     dose, drop = TRUE, sep = ":"))
```

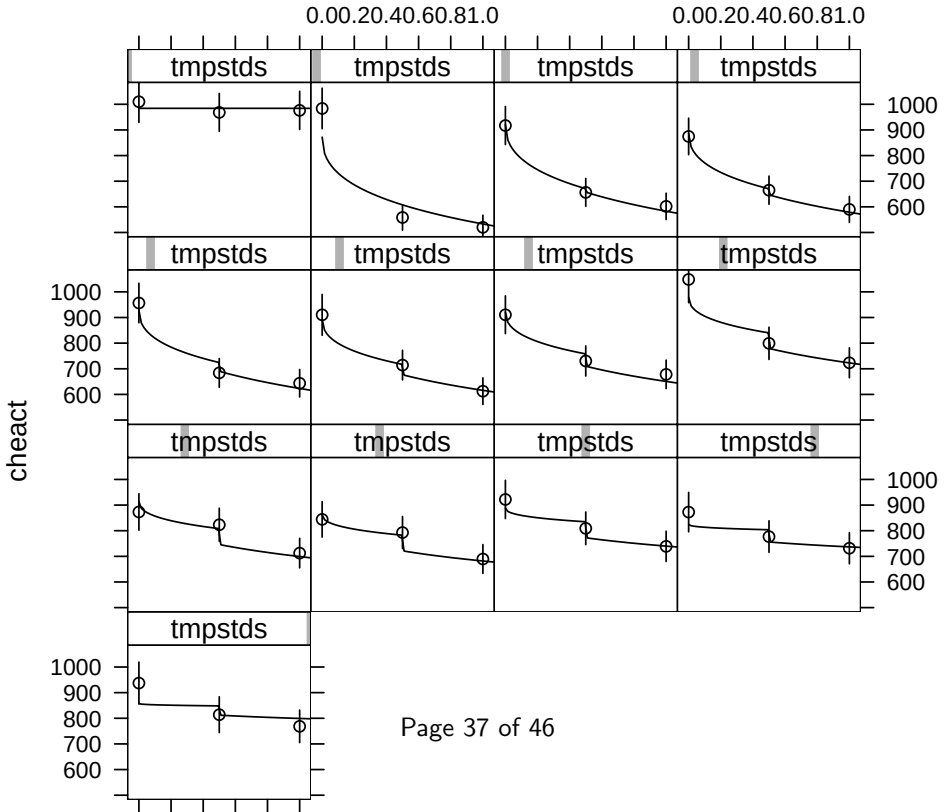
```
> out <- lme(cheact ~ mridXsexXtmpstdsXdose - 1, random = ~1 |
+     id, weights = varComb(varIdent(form = ~1 | mridXsex), varPower(value = 1)),
+     data = tmpd)
> Ints2 <- intervals(out, which = "fixed")$fixed
> sstr <- strsplit(gsub("mridXsexXtmpstdsXdose", "", rownames(Ints2)),
+     ":")
> tdta <- data.frame(cheact = Ints2[, "est."], llim = Ints2[, "lower"],
+     ulim = Ints2[, "upper"], mrid = factor(sapply(sstr, function(x) x[1])),
+     sex = factor(sapply(sstr, function(x) x[2])), tmpstds = as.numeric(sapply(sstr,
+         function(x) x[3])), dose = as.numeric(sapply(sstr, function(x) x[4])))
> ndta <- with(dta, expand.grid(dose = seq(0, max(dose), length = 101),
+     mridXsexXtmpstds = mridXsexXtmpstds))
> sstr <- strsplit(as.character(ndta$mridXsexXtmpstds), ":")
> ndta$mrid <- factor(sapply(sstr, function(x) x[1]))
> ndta$sex <- factor(sapply(sstr, function(x) x[2]))
> ndta$tmpstds <- as.numeric(sapply(sstr, function(x) x[3]))
> ndta$mridXsex <- with(ndta, interaction(mrid, sex, drop = TRUE,
+     sep = ":"))
> ndta$fdose <- cut(ndta$dose, c(0, 0.5, 1.5), include.lowest = TRUE)
> tmp <- drmod5
> tmp$contrasts <- NULL
> ndta$pred <- predict(tmp, newdata = ndta, level = 0)
```

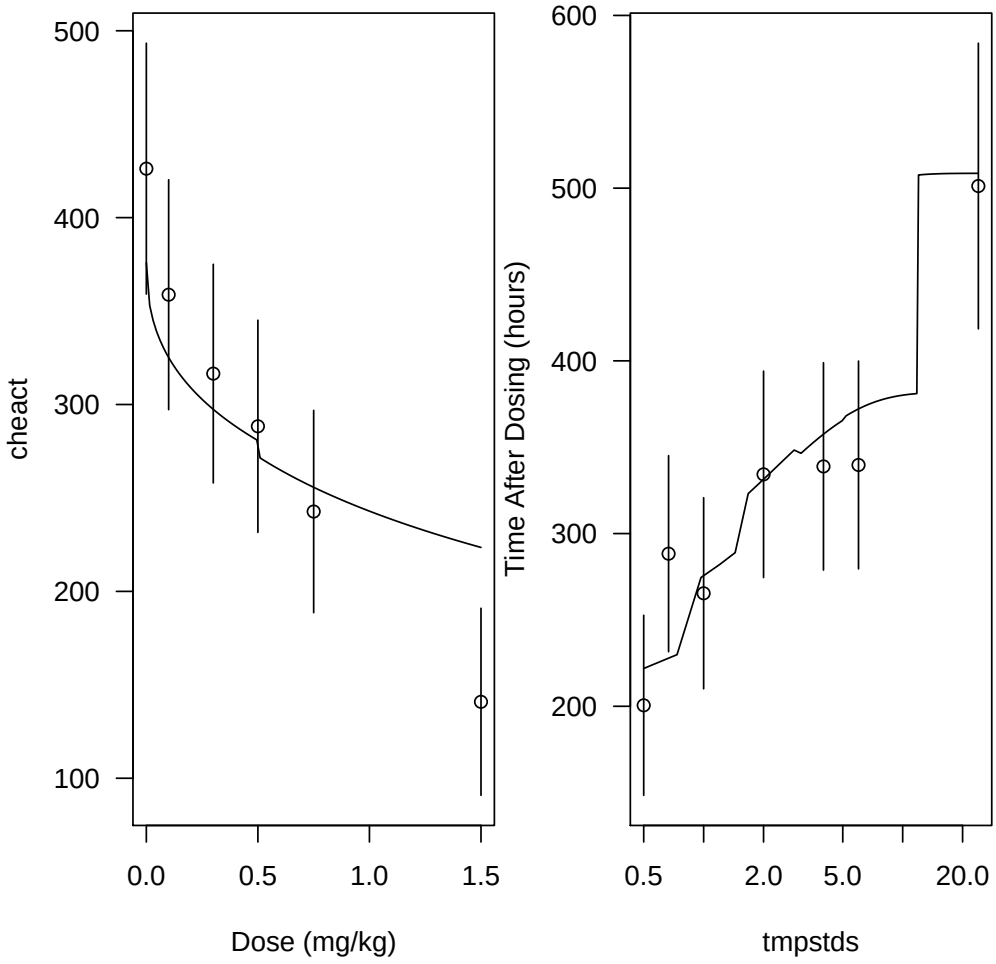
The dose-response plots will look "funny", because `lTr` changes with dose, but there were not enough doses to model it as a smooth function of dose, so, in the predicted values, `lTr` jumps abruptly just above 0.5 mg/kg.

45675701 F

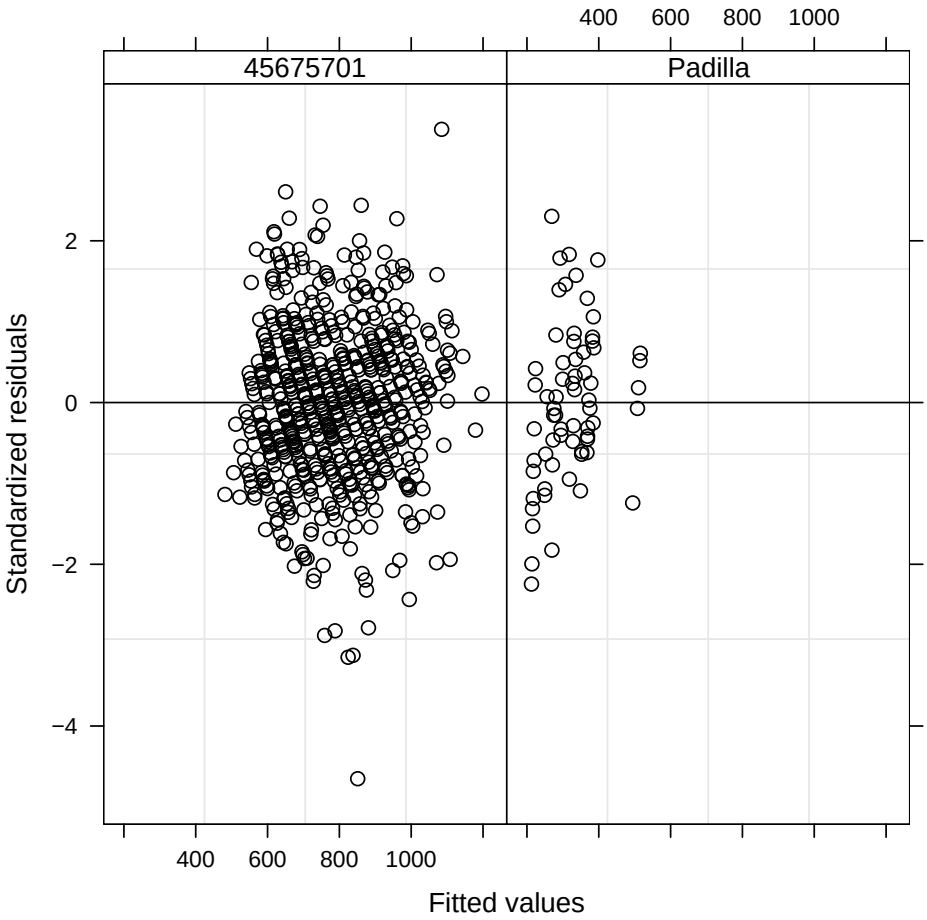


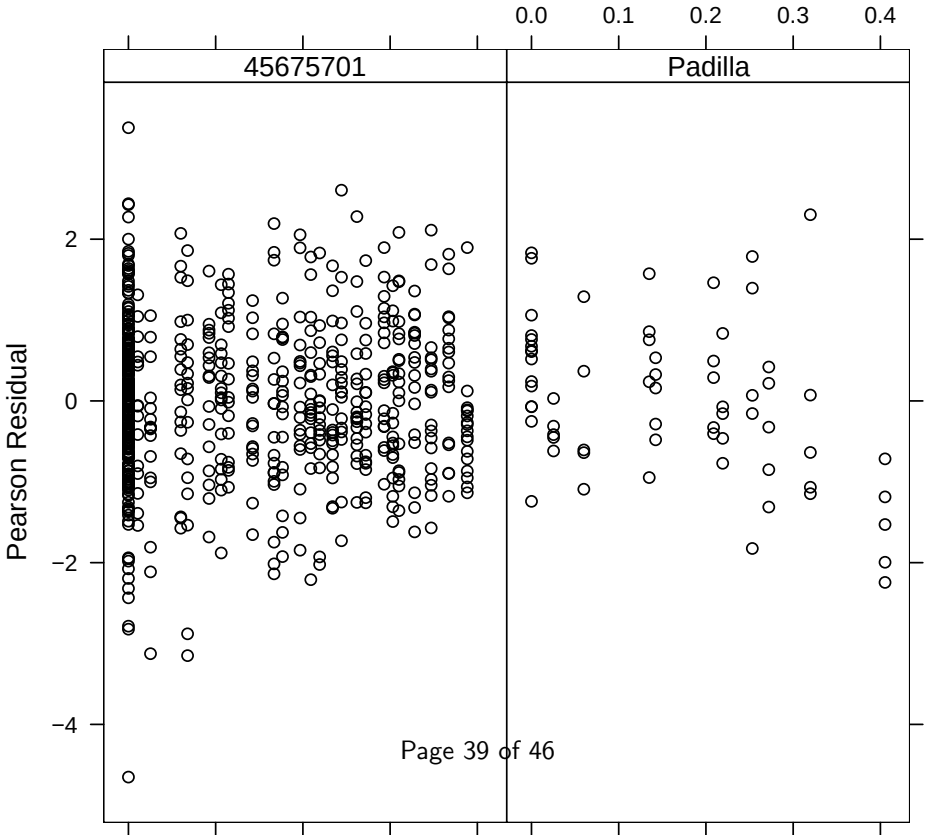
45675701 M

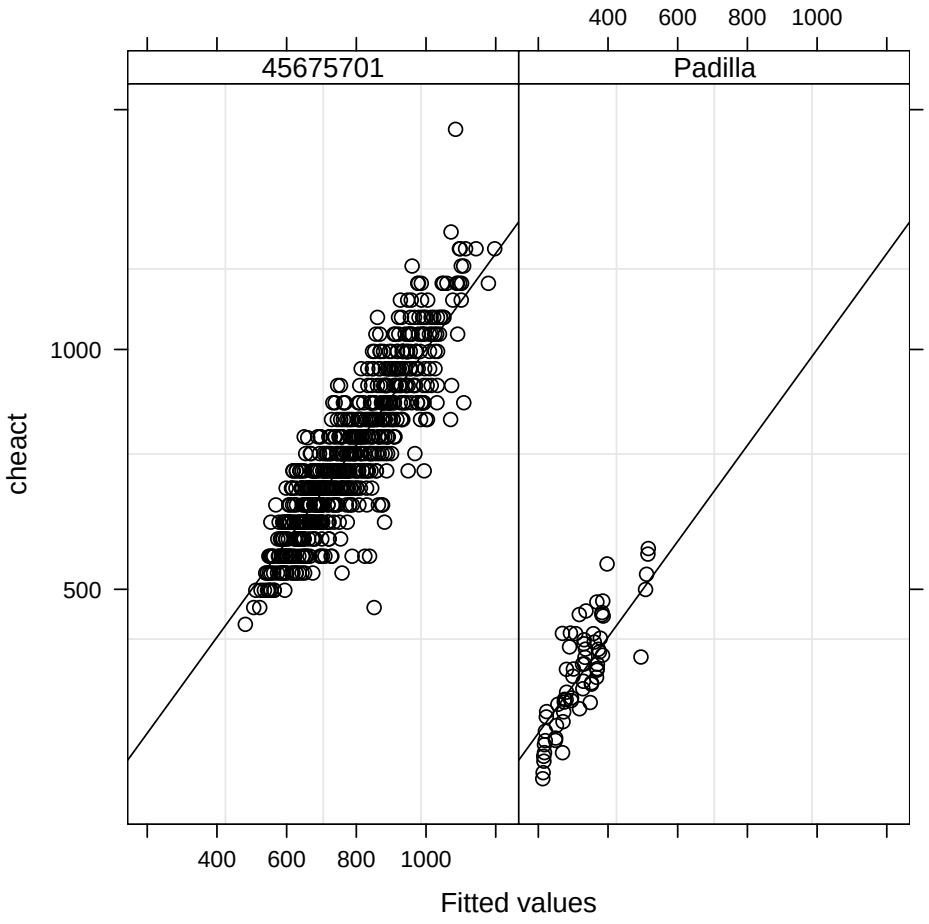


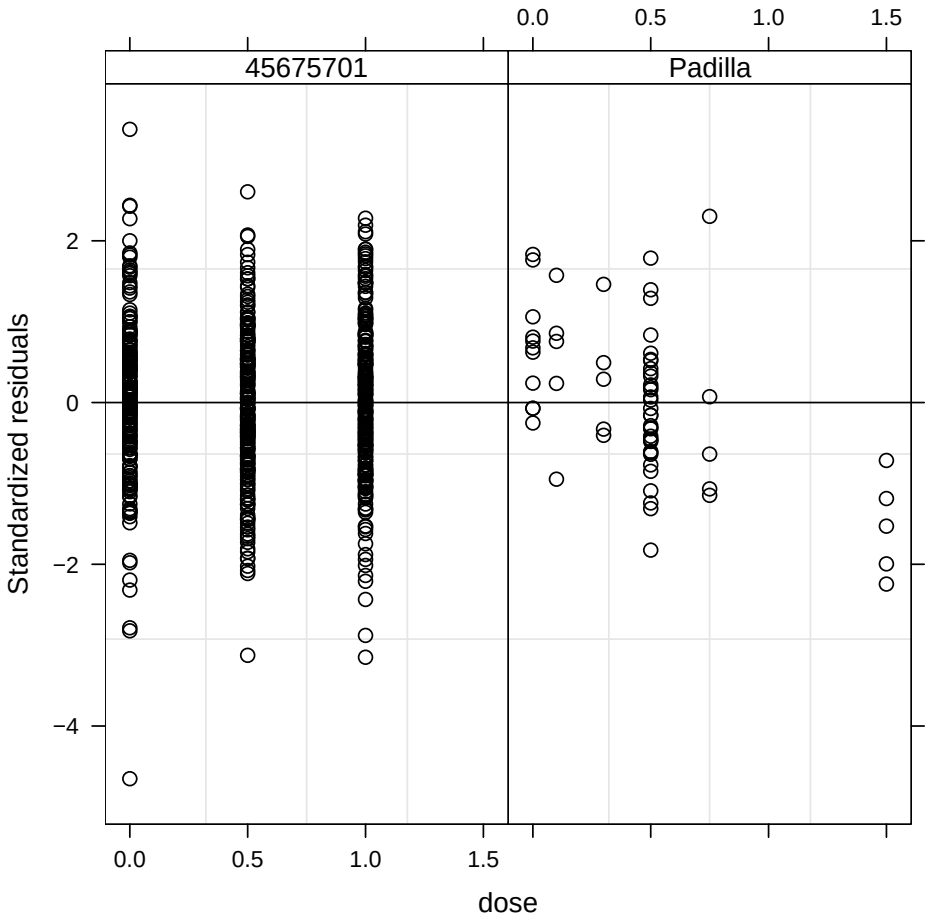


(Jagged recovery curves result from heterogeneity in background levels of AChE activity.)

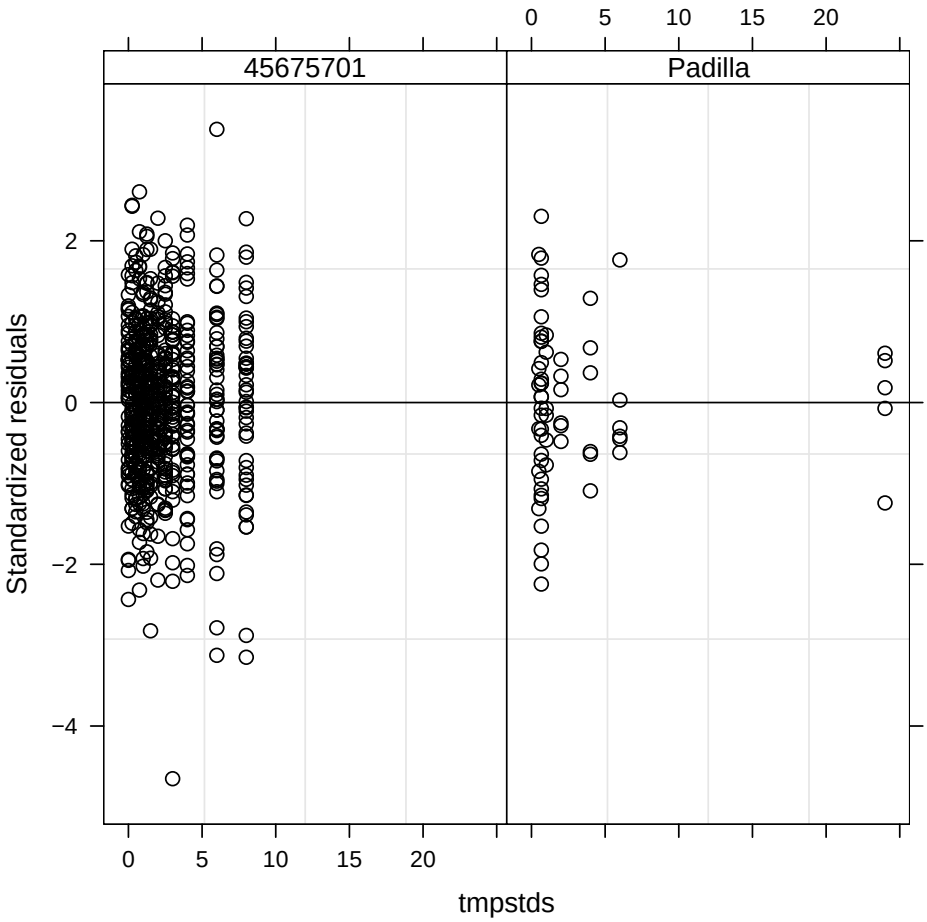

45675701
Padilla
Standardized residuals
Fitted values
400
600
800
1000
2
0
−2
−4


45675701
Padilla
Pearson Residual
0.0
0.1
0.2
0.3
0.4
2
0
−2
−4


45675701
Padilla
cheact
1000
500
400
600
800
1000
Fitted values

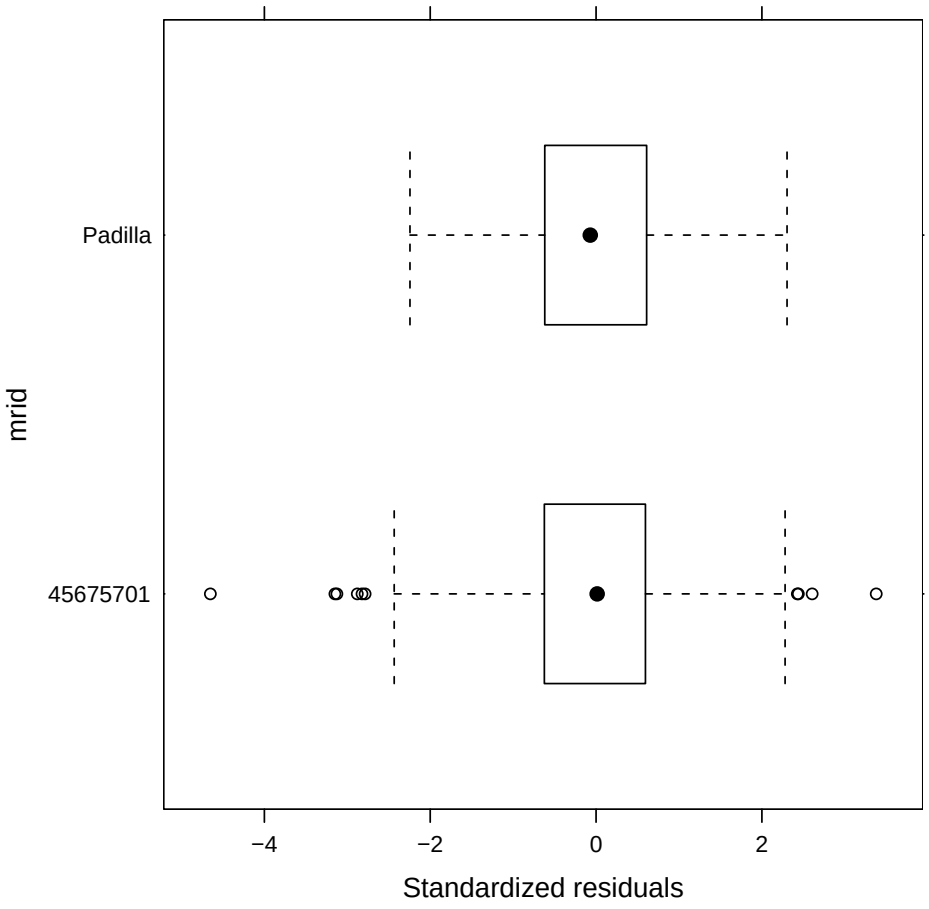


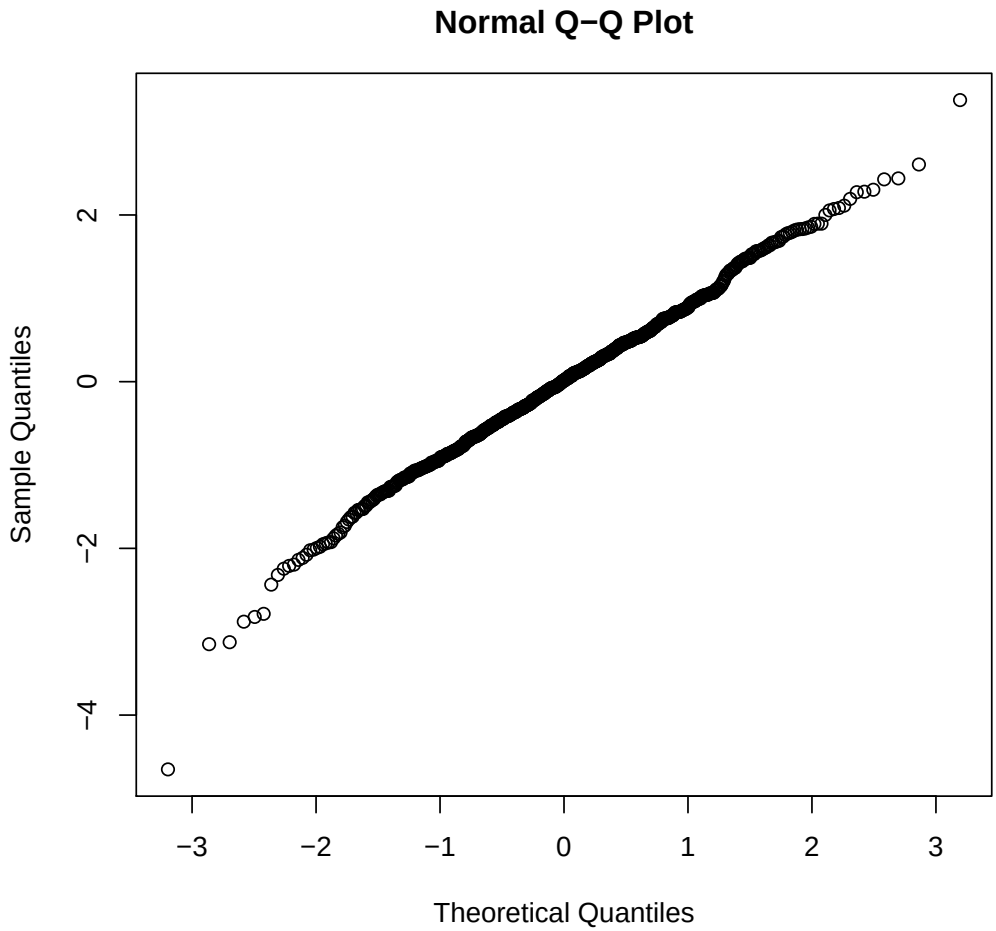
It looks like we may be getting the high dose group (1.5 mg/kg) wrong.

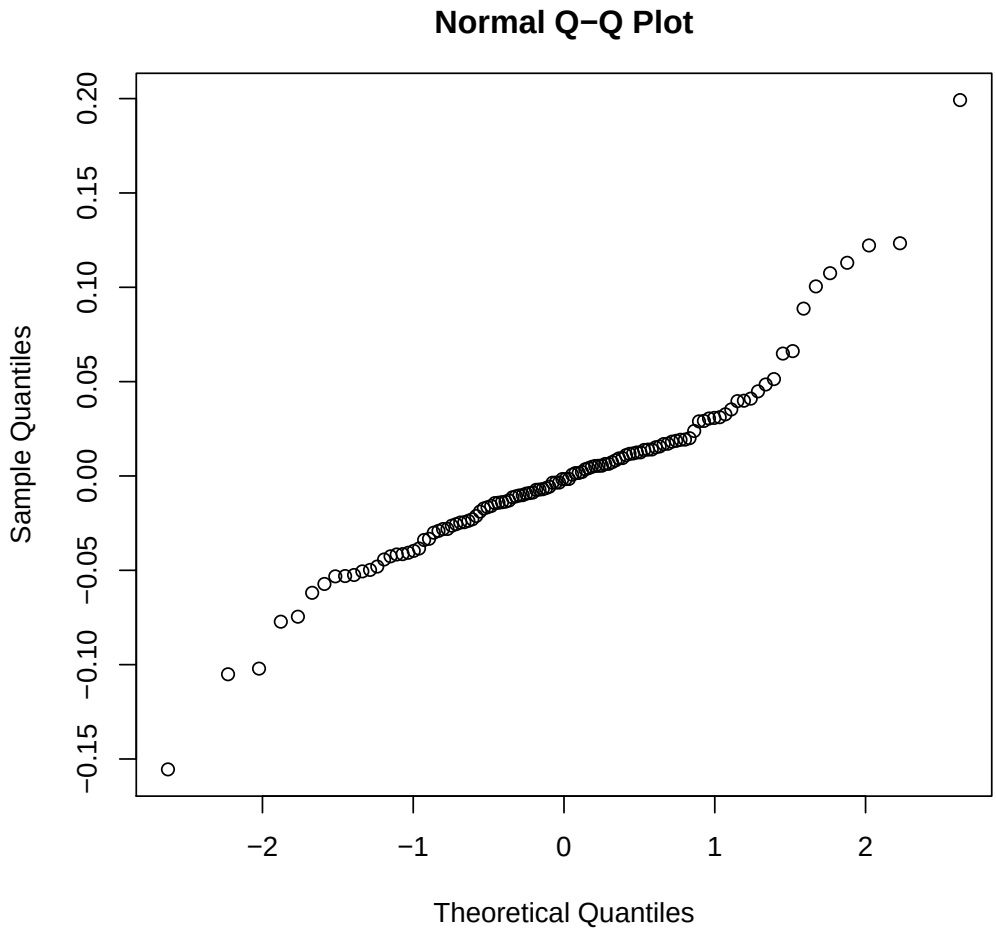


Some more graphs:

Pearson residuals split by mrid and sex, and QQ plots for the Pearson residuals and random effects:


Padilla
45675701
mrid
−4
−2
0
2
Standardized residuals


Normal Q−Q Plot
Sample Quantiles
Theoretical Quantiles
−4
−2
0
2
−3
−2
−1
0
1
2
3



3 Summary

The critical estimates from this analysis are listed below. They are printed with greater than usual precision, in case they are to be used in further computation. For reporting, round to two or three significant digits. In these data, the BMD differs between sexes, and only a single value for recovery half life, pooled over doses and sexes, was estimated. BMD has units mg/kg, and times are in hours.

species RAT

mrid `[1] "45675701" "Padilla"`

`lD` **(se)** -3.45681898065219 (0.717686586040141)

BMD (95% CI) 0.031529899885251 (0.00799093751268408, 0.124407753808105)

BMDL, the one-sided lower 95% CL 0.00996985597909544

`lTr dose: [0, 0.5] (standard error)` 0.472971264637763 (0.185214758883357)

`lTr dose: (0.5, 1.5] (standard error)` 1.12390913367463 (0.138951376226746)

Recovery Half-life dose: [0, 0.5 (95% CI)] 1.60475526908975 (1.12607086184997, 2.28692488272061)

Recovery Half-life dose: (0.5, 1.5 (95% CI)] 3.07685857612907 (2.35880336109952, 4.01350059679671)

Save the results:

```
> save.image(file = "RatRBCDR.RData")
```

Save the results for incorporating into a database:

```
> carbofuran.oral.rbc <- list(mrid = levels(dta$mrid), species = "RAT",
+     BMDs = list(combined = list(lD = tTab["lD", "Value"], lD.se = tTab["lD",
+         "Std.Error"], BMD = exp(Ints["lD", "est."]), BMD.CI = exp(Ints["lD",
+         c("lower", "upper")]), BMDL = exp(Ints90["lD", "lower"]))),
+     HalfLives = list("[0, 0.5]" = list(lTr = tTab["lTr.fdose[0,0.5]",
+         "Value"], lTr.se = tTab["lTr.fdose[0,0.5]", "Std.Error"],
+         Tr = exp(Ints["lTr.fdose[0,0.5]", "est."]), Tr.CI = exp(Ints["lTr.fdose[0,0.5]",
+             c("lower", "upper")])), "(0.5, 1.5]" = list(lTr = tTab["lTr.fdose(0.5,1.5]",
+         "Value"], lTr.se = tTab["lTr.fdose(0.5,1.5]", "Std.Error"],
+         Tr = exp(Ints["lTr.fdose(0.5,1.5]", "est."]), Tr.CI = exp(Ints["lTr.fdose(0.5,1.5]",
+             c("lower", "upper")]))))
> save(carbofuran.oral.rbc, file = file.path("..", "..", "01Summaries",
+     "carbofuran.oral.rbc.RData"))
```