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

June 23, 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.

```
> options(width = 80)
> 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 `AggData`. The following code prints out documentation for the datasets in use:

```
> printDataDoc(AggData)
```

```
----------------------------------------
Data set: AggData

Dataset creation date: Wed Jun 22 12:07:24 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.

All the data used for this DR model are in `repeated_acute`.

Now, set up the analysis dataset. Scale the response variable by 500.

```
> dta <- CleanUp(subset(repeated_acute, chemical %in% "Thiodicarb" &
+     !is.na(rbc), select = c("rbc", "dose_mgkg", "time", "sex",
+     "subset", "mrid", "id")))
> names(dta)[1:3] <- c("cheact", "dose", "tmpstds")
> dta$id <- interaction(dta$mrid, dta$id, drop = TRUE, sep = ":")
> dta$subset <- factor(dta$subset)
> dta$cheact <- dta$cheact/500
```

Summary of the relevant variables in this dataset:

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

dta$mrid: 45138702
     cheact           dose          tmpstds      sex    subset       mrid
 Min.   :0.350   Min.   : 0.00   Min.   :0.000   F:94    : 0   45138702:187
 1st Qu.:1.060   1st Qu.: 2.50   1st Qu.:0.000   M:93   A:92   45138703:  0
 Median :1.312   Median : 5.00   Median :1.000          B:95
 Mean   :1.360   Mean   :16.23   Mean   :2.578
 3rd Qu.:1.592   3rd Qu.:30.00   3rd Qu.:4.000
 Max.   :3.000   Max.   :40.00   Max.   :8.000
```

```
             id
 45138702:1003:  4
 45138702:1005:  4
 45138702:1008:  4
 45138702:1004:  4
 45138702:1007:  4
 45138702:1009:  4
 (Other)      :163
------------------------------------------------------------
dta$mrid: 45138703
     cheact           dose          tmpstds       sex     subset
 Min.   :0.124   Min.   : 0.00   Min.   : 0.000   F:119    :314
 1st Qu.:0.722   1st Qu.: 5.00   1st Qu.: 0.000   M:195   A:  0
 Median :0.952   Median :12.50   Median : 1.000           B:  0
 Mean   :1.006   Mean   :16.35   Mean   : 5.949
 3rd Qu.:1.262   3rd Qu.:40.00   3rd Qu.: 8.000
 Max.   :2.522   Max.   :40.00   Max.   :24.000

       mrid                 id
 45138702:  0   45138703:1013:  4
 45138703:314   45138703:1015:  4
                45138703:1018:  4
                45138703:1020:  4
                45138703:1022:  4
                45138703:1023:  4
                (Other)      :290
```

```
> by(dta, dta$mrid, function(x) sort(unique(x$tmpstds)))
```

```
dta$mrid: 45138702
[1] 0.0 0.5 1.0 2.0 4.0 6.0 8.0
------------------------------------------------------------
dta$mrid: 45138703
[1]  0  1  2  4  8 24
```

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

```
, , sex = F

          dose
mrid       0  5  20 40
  45138702 23 24 24 23
  45138703 30 29 30 30

, , sex = M

          dose
mrid       0  5  20 40
  45138702 24 23 22 24
  45138703 48 50 47 50
```

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

```
dta$mrid: 45138702
    tmpstds
```

```
dose 0  0.5 1  2  4  6  8
  0  12  6   6  6  6  6  5
  5  12  6   6  5  6  6  6
  20 12  6   6  6  6  6  4
  40 12  6   6  6  6  6  5
-------------------------------------------------------------
dta$mrid: 45138703
    tmpstds
dose 0  1  2  4  8  24
  0  25 20  4  9  5 15
  5  25 19  5 10  5 15
  20 25 19  3 10  5 15
  40 25 20  5 10  5 15
```

> by(dta, dta$mrid, function(x) with(CleanUp(x), table(id, tmpstds)))

```
dta$mrid: 45138702
                tmpstds
id               0 0.5 1 2 4 6 8
  45138702:1003 1 0   1 0 1 0 1
  45138702:1005 1 0   1 0 1 0 1
  45138702:1008 1 0   1 0 1 0 1
  45138702:1004 1 1   0 1 0 1 0
  45138702:1007 1 1   0 1 0 1 0
  45138702:1009 1 1   0 1 0 1 0
  45138702:2003 1 0   1 0 1 0 1
  45138702:2005 1 0   1 0 1 0 1
  45138702:2008 1 0   1 0 1 0 1
  45138702:2004 1 1   0 1 0 1 0
  45138702:2007 1 1   0 1 0 1 0
  45138702:2009 1 1   0 0 0 1 0
  45138702:3003 1 0   1 0 1 0 1
  45138702:3005 1 0   1 0 1 0 0
  45138702:3008 1 0   1 0 1 0 0
  45138702:3004 1 1   0 1 0 1 0
  45138702:3007 1 1   0 1 0 1 0
  45138702:3009 1 1   0 1 0 1 0
  45138702:4003 1 0   1 0 1 0 1
  45138702:4005 1 0   1 0 1 0 1
  45138702:4008 1 0   1 0 1 0 1
  45138702:4004 1 1   0 1 0 1 0
  45138702:4007 1 1   0 1 0 1 0
  45138702:4009 1 1   0 1 0 1 0
  45138702:1502 1 0   1 0 1 0 0
  45138702:1504 1 0   1 0 1 0 1
  45138702:1508 1 0   1 0 1 0 1
  45138702:1503 1 1   0 1 0 1 0
  45138702:1507 1 1   0 1 0 1 0
  45138702:1509 1 1   0 1 0 1 0
  45138702:2503 1 0   1 0 1 0 1
  45138702:2507 1 0   1 0 1 0 1
  45138702:2509 1 0   1 0 1 0 1
  45138702:2602 1 1   0 1 0 1 0
  45138702:2504 1 1   0 1 0 1 0
  45138702:2508 1 1   0 1 0 1 0
```

```
  45138702:3502 1 0   1 0 1 0 1
  45138702:3504 1 0   1 0 1 0 1
  45138702:3508 1 0   1 0 1 0 1
  45138702:3603 1 1   0 1 0 1 0
  45138702:3507 1 1   0 1 0 1 0
  45138702:3509 1 1   0 1 0 1 0
  45138702:4502 1 0   1 0 1 0 1
  45138702:4504 1 0   1 0 1 0 1
  45138702:4508 1 0   1 0 1 0 0
  45138702:4503 1 1   0 1 0 1 0
  45138702:4507 1 1   0 1 0 1 0
  45138702:4509 1 1   0 1 0 1 0
-------------------------------------------------------------
dta$mrid: 45138703
                tmpstds
id               0 1 2 4 8 24
  45138703:1011 1 1 0 0 0 0
  45138703:1012 1 1 0 0 0 0
  45138703:1013 1 1 0 1 0 1
  45138703:1014 1 0 0 0 1 1
  45138703:1015 1 0 1 0 1 1
  45138703:1016 1 1 0 0 0 0
  45138703:1017 1 1 0 0 0 0
  45138703:1018 1 1 0 1 0 1
  45138703:1019 1 1 0 0 0 1
  45138703:1020 1 0 1 0 1 1
  45138703:1021 1 1 0 0 0 0
  45138703:1022 1 1 0 1 0 1
  45138703:1023 1 1 0 1 0 1
  45138703:1024 1 0 1 0 1 1
  45138703:1025 1 0 1 0 1 1
  45138703:2011 1 1 0 0 0 0
  45138703:2012 1 1 0 0 0 0
  45138703:2013 1 1 0 1 0 1
  45138703:2014 1 0 1 0 1 1
  45138703:2015 1 0 1 0 1 1
  45138703:2016 1 1 0 0 0 0
  45138703:2017 1 1 0 0 0 0
  45138703:2018 1 1 0 1 0 1
  45138703:2019 1 1 0 1 0 1
  45138703:2020 1 0 1 0 1 1
  45138703:2021 1 1 0 0 0 0
  45138703:2022 1 1 0 1 0 1
  45138703:2023 1 1 0 1 0 1
  45138703:2024 1 0 1 0 1 1
  45138703:2025 1 0 1 0 1 1
  45138703:3011 1 1 0 0 0 0
  45138703:3012 1 1 0 0 0 0
  45138703:3013 1 0 0 1 0 1
  45138703:3014 1 0 0 0 1 1
  45138703:3015 1 0 0 0 1 1
  45138703:3016 1 1 0 0 0 0
  45138703:3017 1 1 0 0 0 0
  45138703:3018 1 1 0 1 0 1
```

```
45138703:3019 1 1 0 1 0 1
45138703:3020 1 0 1 0 1 1
45138703:3021 1 1 0 0 0 0
45138703:3022 1 1 0 1 0 1
45138703:3023 1 1 0 1 0 1
45138703:3024 1 0 1 0 1 1
45138703:3025 1 0 1 0 1 1
45138703:4011 1 1 0 0 0 0
45138703:4012 1 1 0 0 0 0
45138703:4013 1 1 0 1 0 1
45138703:4014 1 0 1 0 1 1
45138703:4015 1 0 1 0 1 1
45138703:4016 1 1 0 0 0 0
45138703:4017 1 1 0 0 0 0
45138703:4018 1 1 0 1 0 1
45138703:4019 1 1 0 1 0 1
45138703:4020 1 0 1 0 1 1
45138703:4021 1 1 0 0 0 0
45138703:4022 1 1 0 1 0 1
45138703:4023 1 1 0 1 0 1
45138703:4024 1 0 1 0 1 1
45138703:4025 1 0 1 0 1 1
45138703:1511 1 1 0 0 0 0
45138703:1512 1 1 0 0 0 0
45138703:1513 1 1 0 1 0 1
45138703:1514 1 1 0 0 0 0
45138703:1515 1 1 0 0 0 0
45138703:1516 1 1 0 1 0 1
45138703:1517 1 1 0 1 0 1
45138703:1518 1 1 0 0 0 0
45138703:1519 1 1 0 1 0 1
45138703:1520 1 1 0 1 0 1
45138703:2511 1 1 0 0 0 0
45138703:2512 1 1 0 0 0 0
45138703:2513 1 1 0 1 0 1
45138703:2514 1 1 0 0 0 0
45138703:2515 1 1 0 0 0 0
45138703:2516 1 0 0 1 0 1
45138703:2517 1 1 0 1 0 1
45138703:2518 1 1 0 0 0 0
45138703:2519 1 1 0 1 0 1
45138703:2520 1 1 0 1 0 1
45138703:3511 1 1 0 0 0 0
45138703:3512 1 1 0 0 0 0
45138703:3513 1 1 0 1 0 1
45138703:3514 1 1 0 0 0 0
45138703:3515 1 1 0 0 0 0
45138703:3516 1 1 0 1 0 1
45138703:3517 1 1 0 1 0 1
45138703:3518 1 1 0 0 0 0
45138703:3519 1 1 0 1 0 1
45138703:3520 1 1 0 1 0 1
45138703:4511 1 1 0 0 0 0
45138703:4512 1 1 0 0 0 0
```

```
  45138703:4513 1 1 0 1 0 1
  45138703:4514 1 1 0 0 0 0
  45138703:4515 1 1 0 0 0 0
  45138703:4516 1 1 0 1 0 1
  45138703:4517 1 1 0 1 0 1
  45138703:4518 1 1 0 0 0 0
  45138703:4519 1 1 0 1 0 1
  45138703:4520 1 1 0 1 0 1
```

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

```
dta$mrid: 45138702
   tmpstds
sex 0  0.5 1  2  4  6  8
  F 24 12  12 12 12 12 10
  M 24 12  12 11 12 12 10
------------------------------------------------------------
dta$mrid: 45138703
   tmpstds
sex 0  1  2  4  8  24
  F 40 39  0 20  0 20
  M 60 39 17 19 20 40
```

Both studies involve repeated measures; not every animal was observed at each time point, but there is a time 0 (predosing) observation for each animal. In 45138702, the observations are pretty much balanced, with about half the animals contributing to every time point (except for the pre-dosing point, to which each animal contributes). In 45138703, most of the animals contribute to the one hour and 24 hour time points, with varying numbers of animals contributing to the others. There are fewer observations on female animals, for which there are no 2 and 8 hour time points.

Create a new dose variable that is 0 at the pre-dosing time point:

```
> dta$dose2 <- with(dta, ifelse(tmpstds > 0, dose, 0))
```

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 = ":"))
```

Both studies use the same dose levels, and there is a time course at each dose

Try creating `fdose` by cutting dose at:

```
> dta$fdose <- cut(dta$dose, c(0, 5, 20, 40), include.lowest = TRUE)
```

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 (the earliest time point in this dataset), 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 and between sexes.

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

3. Use `nlme()` to fit a nested random effects model, with `lD` varying among mrids, and `lA` varying among subjects.

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

5. Can we simplify the model for `lTr`.

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 0.5, the earliest non-zero time point.

```
> formals(tcmfn4)$delta <- 0.5
> initfile <- paste("initvals-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
+         dose2 %in% 0)))
+     Start <- c(coef(lA.start), rep(log(10), nlevels(dta$mrid)),
+         0, c(-2, 0), c(log(1), 0), rep(log(1.5), nlevels(dta$fdose) *
+             2))
+     init1 <- GetInitialValues(cheact ~ tcmfn4(dose2, tmpstds,
+         lA = lA, tz = tz, lD = lD, lg = lg, lTr = lTr), data = dta,
+         params = list(lA ~ mridXsexXtmpstds - 1, lD ~ mrid +
+             sex - 1, tz ~ sex, lg ~ sex, lTr ~ fdose:sex - 1),
+         start = Start, weights = varComb(varIdent(form = ~1 |
+             mrid), varPower(value = 1)))
+     save(init1, file = initfile)
+ } else load(initfile)
> tmp <- t(init1$Redundancy[[1]]$Eigens)
> tmp <- tmp[-grep("^lA", rownames(tmp)), ]
> round(tmp[, 1:7], digits = 2)
```

```
                        [,1]  [,2]  [,3]  [,4] [,5] [,6] [,7]
CondIndex             351.69 42.44 20.38 11.50 6.13 5.36 4.09
mu                      0.01  0.05  0.10  0.18 0.34 0.39 0.51
lD.mrid45138702         0.00  0.86  0.00  0.09 0.00 0.00 0.03
lD.mrid45138703         0.00  0.71  0.00  0.28 0.00 0.00 0.00
lD.sexM                 0.96  0.00  0.04  0.00 0.00 0.00 0.00
tz.(Intercept)          0.00  0.86  0.00  0.13 0.00 0.00 0.00
tz.sexM                 1.00  0.00  0.00  0.00 0.00 0.00 0.00
lg.(Intercept)          0.00  1.00  0.00  0.00 0.00 0.00 0.00
lg.sexM                 1.00  0.00  0.00  0.00 0.00 0.00 0.00
lTr.fdose[0,5]:sexF     0.00  0.13  0.00  0.24 0.00 0.33 0.01
lTr.fdose(5,20]:sexF    0.00  0.00  0.00  0.20 0.00 0.49 0.00
lTr.fdose(20,40]:sexF   0.00  0.01  0.00  0.00 0.00 0.64 0.00
lTr.fdose[0,5]:sexM     0.01  0.00  0.23  0.00 0.48 0.00 0.01
```

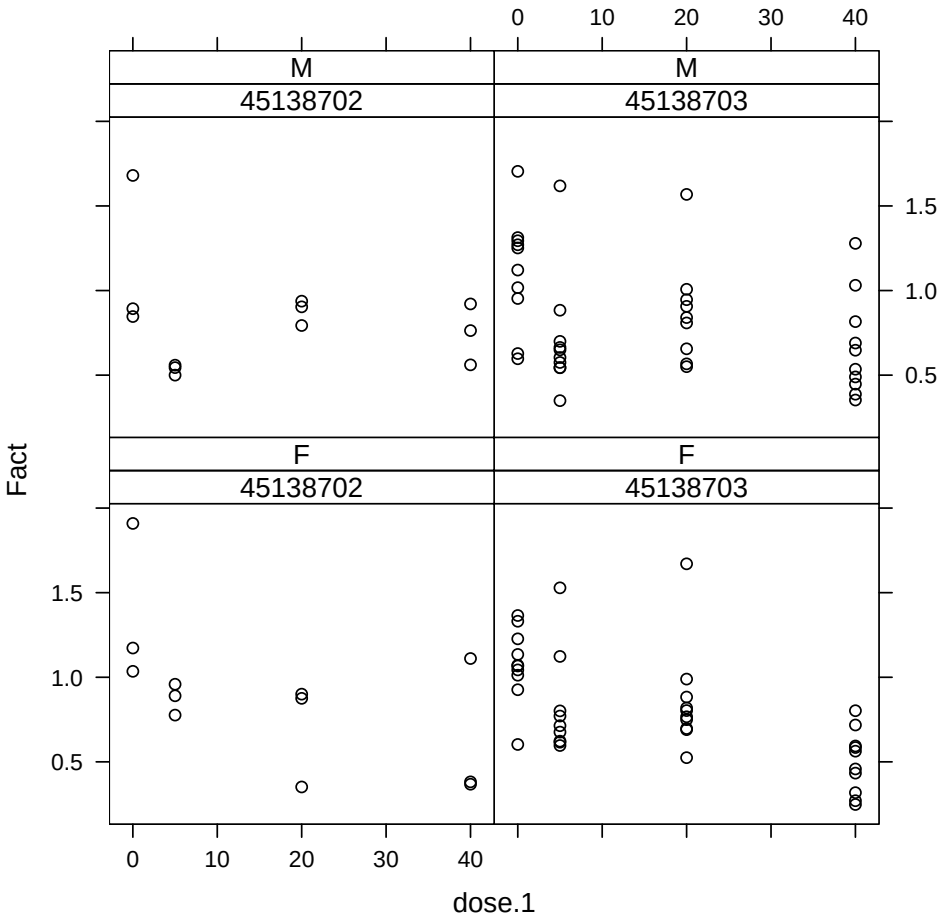
```
lTr.fdose(5,20]:sexM    0.03  0.00  0.01  0.00 0.65 0.00 0.00
lTr.fdose(20,40]:sexM   0.01  0.00  0.02  0.00 0.73 0.00 0.00
```

From the above redundancy analysis, it is clear that we cannot estimate the effects of sex on both `lD` and `lg` at the same time. Furthermore, there are probably going to be problems estimating jointly `lD`, `tz`, and `lg`. First try simplifying the model by fixing `lg` to 0, and eliminate sex differences for `tz`, and try again:

```
> formals(tcmfn4)$delta <- 0.5
> formals(tcmfn4)$lg <- 0
> initfile <- paste("initvals-RBC-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+     lA.start <- lm(I(log(cheact)) ~ mridXsexXtmpstds - 1, data = CleanUp(subset(dta,
+         dose2 %in% 0)))
+     Start <- c(coef(lA.start), rep(log(10), nlevels(dta$mrid)),
+         0, -2, rep(log(1.5), nlevels(dta$fdose) * 2))
+     init2 <- GetInitialValues(cheact ~ tcmfn4(dose2, tmpstds,
+         lA = lA, tz = tz, lD = lD, lTr = lTr), data = dta, params = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, tz ~ 1, 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             4.92 4.24 3.47 3.31 3.24 2.67 1.80
mu                    0.33 0.39 0.47 0.50 0.51 0.62 0.91
lD.mrid45138702       0.38 0.08 0.19 0.26 0.01 0.00 0.00
lD.mrid45138703       0.20 0.07 0.14 0.37 0.13 0.00 0.00
lD.sexM               0.00 0.00 0.10 0.01 0.11 0.64 0.00
tz                    0.05 0.48 0.14 0.02 0.24 0.01 0.00
lTr.fdose[0,5]:sexF   0.67 0.04 0.00 0.00 0.05 0.00 0.00
lTr.fdose(5,20]:sexF  0.71 0.00 0.01 0.00 0.00 0.00 0.00
lTr.fdose(20,40]:sexF 0.40 0.06 0.18 0.00 0.00 0.00 0.01
lTr.fdose[0,5]:sexM   0.01 0.41 0.15 0.01 0.08 0.14 0.01
lTr.fdose(5,20]:sexM  0.02 0.52 0.01 0.00 0.00 0.04 0.20
lTr.fdose(20,40]:sexM 0.02 0.49 0.05 0.00 0.01 0.08 0.08
```

Interestingly, it may not be possible to estimate sex differences in `lD`. Although this does not turn up in the redundance analysis, above, preliminary optimization drives `lD` to a small value, with an extremely large standard error. What does this dose-response look like? Just look at the 1 hour timepoint relative to control.



It looks as if the response actually saturates somewhere below 5 mg/kg, with maximum inhibition less than 50%. This may be due to bad assay conditions using the Ellman assay (which can produce apparent dose-response curves that look like this). Fit a model, and see what happens.

```
> Start0 <- init2$start$beta
> RE <- log(subset(dta, tmpstds == 0)$cheact)
> RE <- RE - mean(RE)
> Start <- list(fixed = Start0, random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+     NULL)))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod1 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid + sex - 1, tz ~ 1, lTr ~
+         fdose:sex - 1), random = lA ~ 1 | id, start = Start),
+         silent = TRUE)
+     if (!inherits(drmod1, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
```

```
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }
```

The final try fails with the error:

```
Error: Singularity in backsolve at level 0, block 1
```

Try fitting the same curve jointly to both sexes:

```
> Start0 <- init2$start$beta
> Start0 <- Start0[-grep("^lD.sexM", names(Start0))]
> RE <- log(subset(dta, tmpstds == 0)$cheact)
> RE <- RE - mean(RE)
> Start <- list(fixed = Start0, random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+     NULL)))
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod1 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid - 1, tz ~ 1, lTr ~ fdose:sex -
+         1), random = lA ~ 1 | id, start = Start), silent = TRUE)
+     if (!inherits(drmod1, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }
```

```
Successful in  1 try
```

That does it!

Now, do we need to allow the standard deviation to vary with study, and do we need to add `varPower()` to the variance model?

```
> Start0 <- fixed.effects(drmod1)
> RE <- data.matrix(random.effects(drmod1))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 20
> repeat {
```

```
+     drmod2 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid - 1, tz ~ 1, lTr ~ fdose:sex -
+         1), random = lA ~ 1 | id, weights = varIdent(form = ~1 |
+         mridXsex), start = Start), silent = TRUE)
+     if (!inherits(drmod2, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }
```

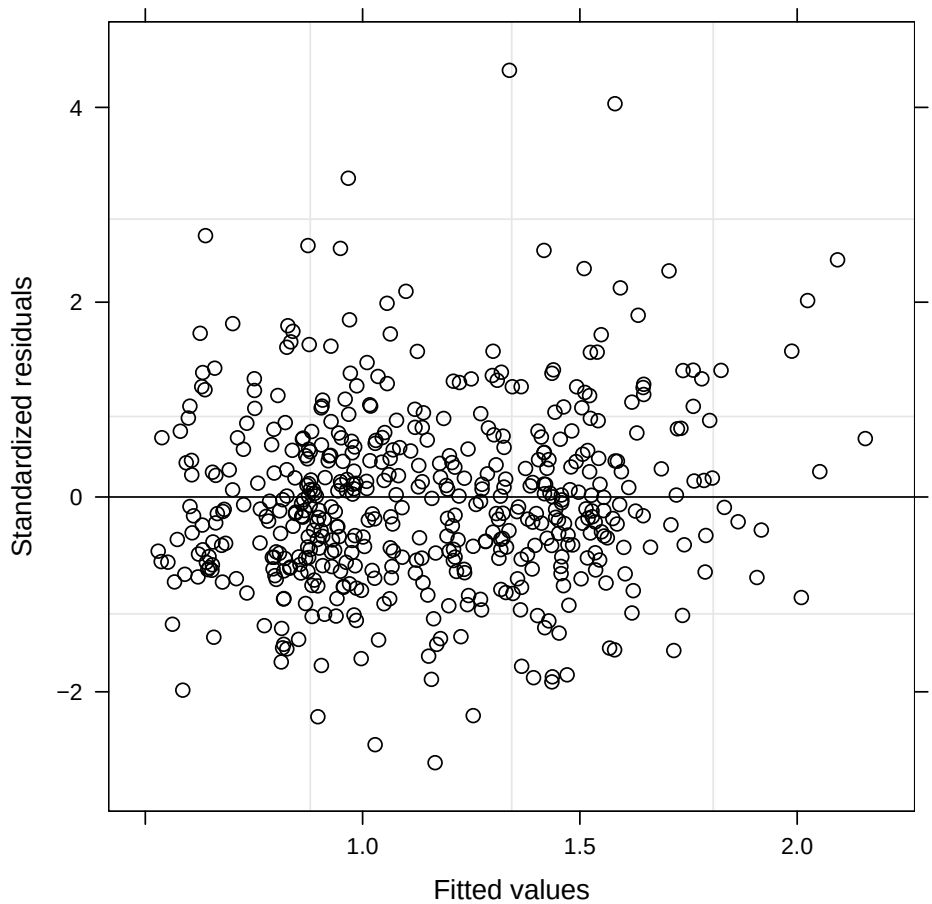
```
Successful in  1 try
```

```
> Start0 <- fixed.effects(drmod2)
> RE <- data.matrix(random.effects(drmod2))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod3 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ mrid - 1, tz ~ 1, lTr ~ fdose:sex -
+         1), random = lA ~ 1 | id, 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("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }
```

That fails with the error:

```
Error: Singularity in backsolve at level 0, block 1
```

Try plotting `drmod2` to see if there looks to be any additional trend of residual magnitude versus fitted value:



There does not seem to be any trend in magnitude of residual with predicted value, so stick with the model in drmod2. It is superior to the fit in drmod1:

```
> anova(drmod1, drmod2)

       Model df      AIC      BIC     logLik   Test  L.Ratio p-value
drmod1     1 35 295.7345 443.3157 -112.86725
drmod2     2 38 265.8208 426.0519  -94.91042 1 vs 2 35.91366  <.0001
```

Do the two mrids differ in their estimate of `lD`?

```
> L <- matrix(c(1, -1), nrow = 1, ncol = 2)
> colnames(L) <- c("lD.mrid45138702", "lD.mrid45138703")
> anova(drmod2, L = L)

F-test for linear combination(s)
lD.mrid45138702 lD.mrid45138703
               1              -1
  numDF denDF   F-value p-value
1     1   321 0.4087283  0.5231
```

No. Refit the model, pooling the estimate of `lD` over studies. (It is still apparently impossible to estimate the difference between sexes with these data).

```
> Parm <- fixed.effects(drmod2)
> Start0 <- c(getParms("^lA", Parm), mean(getParms("^lD", Parm)),
+     getParms("^tz", Parm), getParms("^lTr", Parm))
> RE <- data.matrix(random.effects(drmod2))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod4 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ 1, tz ~ 1, lTr ~ fdose:sex -
+         1), random = lA ~ 1 | id, weights = varIdent(form = ~1 |
+         mridXsex), start = Start), silent = TRUE)
+     if (!inherits(drmod4, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }

Successful in  1 try
```

Do the half-lives differ between the sexes?

```
> L <- cbind(diag(3), -diag(3))
> 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[0,5]:sexF lTr.fdose(5,20]:sexF lTr.fdose(20,40]:sexF
1                   1                    0                     0
2                   0                    1                     0
3                   0                    0                     1
  lTr.fdose[0,5]:sexM lTr.fdose(5,20]:sexM lTr.fdose(20,40]:sexM
1                  -1                    0                     0
2                   0                   -1                     0
3                   0                    0                    -1
  numDF denDF  F-value p-value
1     3   322 1.503380  0.2136
```

Do the half-lives differ from one another at all?

```
> L <- diag(6) - matrix(1, nrow = 6, ncol = 6)/6
> L <- L[-6, ]
> colnames(L) <- names(fixed.effects(drmod4))[grep("^lTr", names(fixed.effects(drmod4)))]
> anova(drmod4, L = L)
```

```
F-test for linear combination(s)
  lTr.fdose[0,5]:sexF lTr.fdose(5,20]:sexF lTr.fdose(20,40]:sexF
1           0.8333333           -0.1666667            -0.1666667
2          -0.1666667            0.8333333            -0.1666667
3          -0.1666667           -0.1666667             0.8333333
4          -0.1666667           -0.1666667            -0.1666667
5          -0.1666667           -0.1666667            -0.1666667
  lTr.fdose[0,5]:sexM lTr.fdose(5,20]:sexM lTr.fdose(20,40]:sexM
1          -0.1666667           -0.1666667            -0.1666667
2          -0.1666667           -0.1666667            -0.1666667
3          -0.1666667           -0.1666667            -0.1666667
4           0.8333333           -0.1666667            -0.1666667
5          -0.1666667            0.8333333            -0.1666667
  numDF denDF  F-value p-value
1     5   322 1.155526   0.331
```

No, so refit the data with a single half-life term:

```
> Parm <- fixed.effects(drmod4)
> Start0 <- c(getParms("^lA", Parm), getParms("^lD", Parm), getParms("^tz",
+     Parm), mean(getParms("^lTr", Parm)))
> RE <- data.matrix(random.effects(drmod4))
> Start <- list(fixed = Start0, random = RE)
> icnt <- 1
> Maxcnt <- 20
> repeat {
+     drmod5 <- try(nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA,
+         tz = tz, lD = lD, lTr = lTr), data = dta, fixed = list(lA ~
+         mridXsexXtmpstds - 1, lD ~ 1, tz ~ 1, lTr ~ 1), random = lA ~
+         1 | id, weights = varIdent(form = ~1 | mridXsex), start = Start),
+         silent = TRUE)
+     if (!inherits(drmod5, "try-error") || icnt > Maxcnt) {
+         if (icnt <= Maxcnt)
+             writeLines(paste("Successful in ", icnt, if (icnt >
+                 1)
+                 "tries"
+             else "try"))
+         else writeLines("Maxcnt exceeded")
+         break
+     }
+     icnt <- icnt + 1
+     Start <- list(fixed = Start0 * (1 + rnorm(length(Start0),
+         sd = 0.2)), random = matrix(RE, ncol = 1, dimnames = list(levels(dta$id),
+         NULL)))
+ }

Successful in  1 try

> 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(dose2, tmpstds, lA = lA, tz = tz, lD = lD, lTr = lTr)
```

```
 Data: dta
       AIC      BIC    logLik
  258.8345 393.7659 -97.41727

Random effects:
 Formula: lA ~ 1 | id
        lA.(Intercept)  Residual
StdDev:      0.1246713 0.2351974

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXsex
 Parameter estimates:
45138703:M 45138703:F 45138702:M 45138702:F
 1.0000000  0.9448035  1.6184046  1.2808097
Fixed effects: list(lA ~ mridXsexXtmpstds - 1, lD ~ 1, tz ~ 1, lTr ~ 1)
                                      Value Std.Error  DF   t-value p-value
lA.mridXsexXtmpstds45138703:M:0   -0.1093768 0.0384151 327 -2.847232  0.0047
lA.mridXsexXtmpstds45138703:M:1   -0.0604993 0.0629683 327 -0.960789  0.3374
lA.mridXsexXtmpstds45138703:M:4    0.0703226 0.0762560 327  0.922191  0.3571
lA.mridXsexXtmpstds45138703:M:24  -0.1014301 0.0616536 327 -1.645161  0.1009
lA.mridXsexXtmpstds45138703:M:8    0.1965402 0.0656916 327  2.991860  0.0030
lA.mridXsexXtmpstds45138703:M:2   -0.0898521 0.0908509 327 -0.989006  0.3234
lA.mridXsexXtmpstds45138703:F:0    0.3310430 0.0328183 327 10.087162  0.0000
lA.mridXsexXtmpstds45138703:F:1    0.3887876 0.0458825 327  8.473546  0.0000
lA.mridXsexXtmpstds45138703:F:4    0.5046644 0.0517972 327  9.743079  0.0000
lA.mridXsexXtmpstds45138703:F:24   0.4228655 0.0565456 327  7.478309  0.0000
lA.mridXsexXtmpstds45138702:M:0    0.4451644 0.0573617 327  7.760651  0.0000
lA.mridXsexXtmpstds45138702:M:1    0.5193588 0.0978364 327  5.308442  0.0000
lA.mridXsexXtmpstds45138702:M:4    0.4914326 0.0960304 327  5.117470  0.0000
lA.mridXsexXtmpstds45138702:M:8    0.3158894 0.1143663 327  2.762084  0.0061
lA.mridXsexXtmpstds45138702:M:0.5  0.3680237 0.1121666 327  3.281045  0.0011
lA.mridXsexXtmpstds45138702:M:2    0.6018288 0.0932895 327  6.451193  0.0000
lA.mridXsexXtmpstds45138702:M:6    0.3703555 0.1049583 327  3.528596  0.0005
lA.mridXsexXtmpstds45138702:F:0    0.4304083 0.0484692 327  8.880042  0.0000
lA.mridXsexXtmpstds45138702:F:1    0.5085777 0.0813181 327  6.254173  0.0000
lA.mridXsexXtmpstds45138702:F:4    0.5236272 0.0773409 327  6.770379  0.0000
lA.mridXsexXtmpstds45138702:F:8    0.4549794 0.0888233 327  5.122297  0.0000
lA.mridXsexXtmpstds45138702:F:0.5  0.5529014 0.0835002 327  6.621560  0.0000
lA.mridXsexXtmpstds45138702:F:2    0.6842746 0.0737921 327  9.273010  0.0000
lA.mridXsexXtmpstds45138702:F:6    0.6201903 0.0748777 327  8.282715  0.0000
lD                                 0.3291198 0.2719753 327  1.210109  0.2271
tz                                 0.7841507 0.1694808 327  4.626783  0.0000
lTr                                2.5529396 0.4045264 327  6.310935  0.0000
 Correlation:
                                  lA.XX45138703:M:0 lA.XX45138703:M:1
lA.mridXsexXtmpstds45138703:M:1    0.113
lA.mridXsexXtmpstds45138703:M:4    0.093             0.183
lA.mridXsexXtmpstds45138703:M:24   0.118             0.047
lA.mridXsexXtmpstds45138703:M:8    0.114             0.084
lA.mridXsexXtmpstds45138703:M:2    0.079             0.119
lA.mridXsexXtmpstds45138703:F:0    0.000             0.003
lA.mridXsexXtmpstds45138703:F:1    0.000             0.225
lA.mridXsexXtmpstds45138703:F:4    0.001             0.148
```

```
lA.mridXsexXtmpstds45138703:F:24   0.001            -0.006
lA.mridXsexXtmpstds45138702:M:0    0.000             0.000
lA.mridXsexXtmpstds45138702:M:1    0.000             0.109
lA.mridXsexXtmpstds45138702:M:4    0.000             0.080
lA.mridXsexXtmpstds45138702:M:8    0.000             0.040
lA.mridXsexXtmpstds45138702:M:0.5  0.000             0.099
lA.mridXsexXtmpstds45138702:M:2    0.000             0.098
lA.mridXsexXtmpstds45138702:M:6    0.000             0.057
lA.mridXsexXtmpstds45138702:F:0    0.000            -0.002
lA.mridXsexXtmpstds45138702:F:1    0.000             0.133
lA.mridXsexXtmpstds45138702:F:4    0.000             0.100
lA.mridXsexXtmpstds45138702:F:8    0.001             0.055
lA.mridXsexXtmpstds45138702:F:0.5  0.000             0.148
lA.mridXsexXtmpstds45138702:F:2    0.000             0.142
lA.mridXsexXtmpstds45138702:F:6    0.001             0.086
lD                                -0.002            -0.279
tz                                 0.001            -0.347
lTr                                0.002            -0.085
                                  lA.XX45138703:M:4 lA.XX45138703:M:24
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24   0.202
lA.mridXsexXtmpstds45138703:M:8    0.155             0.356
lA.mridXsexXtmpstds45138703:M:2    0.098             0.113
lA.mridXsexXtmpstds45138703:F:0    0.002             0.000
lA.mridXsexXtmpstds45138703:F:1    0.146            -0.001
lA.mridXsexXtmpstds45138703:F:4    0.161             0.179
lA.mridXsexXtmpstds45138703:F:24   0.135             0.384
lA.mridXsexXtmpstds45138702:M:0    0.000             0.000
lA.mridXsexXtmpstds45138702:M:1    0.070            -0.003
lA.mridXsexXtmpstds45138702:M:4    0.085             0.091
lA.mridXsexXtmpstds45138702:M:8    0.073             0.129
lA.mridXsexXtmpstds45138702:M:0.5  0.057            -0.020
lA.mridXsexXtmpstds45138702:M:2    0.074             0.029
lA.mridXsexXtmpstds45138702:M:6    0.081             0.120
lA.mridXsexXtmpstds45138702:F:0   -0.002            -0.001
lA.mridXsexXtmpstds45138702:F:1    0.087            -0.001
lA.mridXsexXtmpstds45138702:F:4    0.108             0.117
lA.mridXsexXtmpstds45138702:F:8    0.106             0.194
lA.mridXsexXtmpstds45138702:F:0.5  0.086            -0.029
lA.mridXsexXtmpstds45138702:F:2    0.108             0.043
lA.mridXsexXtmpstds45138702:F:6    0.123             0.184
lD                                -0.180            -0.003
tz                                -0.177             0.142
lTr                                0.157             0.587
                                  lA.XX45138703:M:8 lA.mXX45138703:M:2
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2    0.193
lA.mridXsexXtmpstds45138703:F:0    0.001             0.002
lA.mridXsexXtmpstds45138703:F:1    0.096             0.145
lA.mridXsexXtmpstds45138703:F:4    0.194             0.119
```

```
lA.mridXsexXtmpstds45138703:F:24   0.276             0.047
lA.mridXsexXtmpstds45138702:M:0    0.000             0.000
lA.mridXsexXtmpstds45138702:M:1    0.045             0.071
lA.mridXsexXtmpstds45138702:M:4    0.100             0.064
lA.mridXsexXtmpstds45138702:M:8    0.111             0.043
lA.mridXsexXtmpstds45138702:M:0.5  0.028             0.061
lA.mridXsexXtmpstds45138702:M:2    0.063             0.067
lA.mridXsexXtmpstds45138702:M:6    0.112             0.053
lA.mridXsexXtmpstds45138702:F:0   -0.001            -0.002
lA.mridXsexXtmpstds45138702:F:1    0.057             0.086
lA.mridXsexXtmpstds45138702:F:4    0.128             0.080
lA.mridXsexXtmpstds45138702:F:8    0.165             0.062
lA.mridXsexXtmpstds45138702:F:0.5  0.043             0.092
lA.mridXsexXtmpstds45138702:F:2    0.092             0.097
lA.mridXsexXtmpstds45138702:F:6    0.171             0.080
lD                                -0.122            -0.192
tz                                -0.046            -0.198
lTr                                0.389             0.023
                                  lA.XX45138703:F:0 lA.XX45138703:F:1
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1    0.285
lA.mridXsexXtmpstds45138703:F:4    0.250             0.389
lA.mridXsexXtmpstds45138703:F:24   0.226             0.164
lA.mridXsexXtmpstds45138702:M:0    0.000             0.001
lA.mridXsexXtmpstds45138702:M:1    0.002             0.149
lA.mridXsexXtmpstds45138702:M:4    0.002             0.111
lA.mridXsexXtmpstds45138702:M:8    0.001             0.058
lA.mridXsexXtmpstds45138702:M:0.5  0.002             0.135
lA.mridXsexXtmpstds45138702:M:2    0.002             0.134
lA.mridXsexXtmpstds45138702:M:6    0.001             0.081
lA.mridXsexXtmpstds45138702:F:0    0.000            -0.003
lA.mridXsexXtmpstds45138702:F:1    0.003             0.182
lA.mridXsexXtmpstds45138702:F:4    0.002             0.139
lA.mridXsexXtmpstds45138702:F:8    0.001             0.080
lA.mridXsexXtmpstds45138702:F:0.5  0.003             0.201
lA.mridXsexXtmpstds45138702:F:2    0.003             0.194
lA.mridXsexXtmpstds45138702:F:6    0.002             0.122
lD                                -0.007            -0.373
tz                                -0.006            -0.474
lTr                               -0.001            -0.102
                                  lA.XX45138703:F:4 lA.XX45138703:F:2
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
```

```
lA.mridXsexXtmpstds45138703:F:24   0.408
lA.mridXsexXtmpstds45138702:M:0    0.000             0.000
lA.mridXsexXtmpstds45138702:M:1    0.099            -0.002
lA.mridXsexXtmpstds45138702:M:4    0.121             0.099
lA.mridXsexXtmpstds45138702:M:8    0.104             0.140
lA.mridXsexXtmpstds45138702:M:0.5  0.081            -0.020
lA.mridXsexXtmpstds45138702:M:2    0.105             0.033
lA.mridXsexXtmpstds45138702:M:6    0.115             0.130
lA.mridXsexXtmpstds45138702:F:0   -0.002            -0.001
lA.mridXsexXtmpstds45138702:F:1    0.122             0.001
lA.mridXsexXtmpstds45138702:F:4    0.153             0.128
lA.mridXsexXtmpstds45138702:F:8    0.152             0.210
lA.mridXsexXtmpstds45138702:F:0.5  0.120            -0.029
lA.mridXsexXtmpstds45138702:F:2    0.152             0.048
lA.mridXsexXtmpstds45138702:F:6    0.175             0.200
lD                                -0.256            -0.008
tz                                -0.245             0.150
lTr                                0.228             0.633
                                  lA.mXX45138702:M:0 lA.XX45138702:M:1
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1    0.124
lA.mridXsexXtmpstds45138702:M:4    0.127              0.196
lA.mridXsexXtmpstds45138702:M:8    0.107              0.150
lA.mridXsexXtmpstds45138702:M:0.5  0.107              0.079
lA.mridXsexXtmpstds45138702:M:2    0.130              0.081
lA.mridXsexXtmpstds45138702:M:6    0.114              0.053
lA.mridXsexXtmpstds45138702:F:0    0.000             -0.002
lA.mridXsexXtmpstds45138702:F:1    0.000              0.088
lA.mridXsexXtmpstds45138702:F:4    0.000              0.067
lA.mridXsexXtmpstds45138702:F:8    0.000              0.038
lA.mridXsexXtmpstds45138702:F:0.5  0.000              0.098
lA.mridXsexXtmpstds45138702:F:2    0.000              0.094
lA.mridXsexXtmpstds45138702:F:6    0.000              0.058
lD                                -0.001             -0.186
tz                                -0.001             -0.228
lTr                                0.000             -0.053
                                  lA.XX45138702:M:4 lA.XX45138702:M:8
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
```

```
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8    0.176
lA.mridXsexXtmpstds45138702:M:0.5  0.057             0.030
lA.mridXsexXtmpstds45138702:M:2    0.073             0.050
lA.mridXsexXtmpstds45138702:M:6    0.075             0.071
lA.mridXsexXtmpstds45138702:F:0   -0.001            -0.001
lA.mridXsexXtmpstds45138702:F:1    0.066             0.034
lA.mridXsexXtmpstds45138702:F:4    0.081             0.069
lA.mridXsexXtmpstds45138702:F:8    0.079             0.086
lA.mridXsexXtmpstds45138702:F:0.5  0.065             0.028
lA.mridXsexXtmpstds45138702:F:2    0.081             0.052
lA.mridXsexXtmpstds45138702:F:6    0.092             0.090
lD                                -0.139            -0.079
tz                                -0.134            -0.034
lTr                                0.114             0.194
                                  lA.XX45138702:M:0. lA.XX45138702:M:2
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2    0.191
lA.mridXsexXtmpstds45138702:M:6    0.144              0.184
lA.mridXsexXtmpstds45138702:F:0   -0.001             -0.002
lA.mridXsexXtmpstds45138702:F:1    0.080              0.080
lA.mridXsexXtmpstds45138702:F:4    0.055              0.071
lA.mridXsexXtmpstds45138702:F:8    0.025              0.051
lA.mridXsexXtmpstds45138702:F:0.5  0.089              0.085
lA.mridXsexXtmpstds45138702:F:2    0.083              0.088
lA.mridXsexXtmpstds45138702:F:6    0.044              0.069
lD                                -0.167             -0.152
tz                                -0.213             -0.203
lTr                               -0.076              0.004
                                  lA.XX45138702:M:6 lA.mXX45138702:F:0
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
```

```
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2
lA.mridXsexXtmpstds45138702:M:6
lA.mridXsexXtmpstds45138702:F:0   -0.001
lA.mridXsexXtmpstds45138702:F:1    0.048             0.181
lA.mridXsexXtmpstds45138702:F:4    0.076             0.191
lA.mridXsexXtmpstds45138702:F:8    0.087             0.161
lA.mridXsexXtmpstds45138702:F:0.5  0.043             0.162
lA.mridXsexXtmpstds45138702:F:2    0.066             0.184
lA.mridXsexXtmpstds45138702:F:6    0.095             0.183
lD                                -0.100             0.001
tz                                -0.077             0.007
lTr                                0.171             0.000
                                  lA.XX45138702:F:1 lA.XX45138702:F:4
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2
lA.mridXsexXtmpstds45138702:M:6
lA.mridXsexXtmpstds45138702:F:0
lA.mridXsexXtmpstds45138702:F:1
lA.mridXsexXtmpstds45138702:F:4    0.284
lA.mridXsexXtmpstds45138702:F:8    0.215             0.275
lA.mridXsexXtmpstds45138702:F:0.5  0.149             0.113
lA.mridXsexXtmpstds45138702:F:2    0.149             0.138
lA.mridXsexXtmpstds45138702:F:6    0.106             0.152
lD                                -0.213            -0.163
tz                                -0.285            -0.174
lTr                               -0.060             0.148
                                  lA.XX45138702:F:8 lA.XX45138702:F:0.
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
```

```
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2
lA.mridXsexXtmpstds45138702:M:6
lA.mridXsexXtmpstds45138702:F:0
lA.mridXsexXtmpstds45138702:F:1
lA.mridXsexXtmpstds45138702:F:4
lA.mridXsexXtmpstds45138702:F:8
lA.mridXsexXtmpstds45138702:F:0.5  0.064
lA.mridXsexXtmpstds45138702:F:2    0.105             0.324
lA.mridXsexXtmpstds45138702:F:6    0.163             0.261
lD                                -0.102            -0.252
tz                                -0.046            -0.316
lTr                                0.294            -0.112
                                  lA.XX45138702:F:2 lA.XX45138702:F:6 lD
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2
lA.mridXsexXtmpstds45138702:M:6
lA.mridXsexXtmpstds45138702:F:0
lA.mridXsexXtmpstds45138702:F:1
lA.mridXsexXtmpstds45138702:F:4
lA.mridXsexXtmpstds45138702:F:8
lA.mridXsexXtmpstds45138702:F:0.5
lA.mridXsexXtmpstds45138702:F:2
lA.mridXsexXtmpstds45138702:F:6    0.320
lD                                -0.243            -0.154
tz                                -0.278            -0.114             0.235
lTr                                0.008             0.264             0.116
                                  tz
lA.mridXsexXtmpstds45138703:M:1
lA.mridXsexXtmpstds45138703:M:4
lA.mridXsexXtmpstds45138703:M:24
lA.mridXsexXtmpstds45138703:M:8
lA.mridXsexXtmpstds45138703:M:2
lA.mridXsexXtmpstds45138703:F:0
lA.mridXsexXtmpstds45138703:F:1
lA.mridXsexXtmpstds45138703:F:4
```

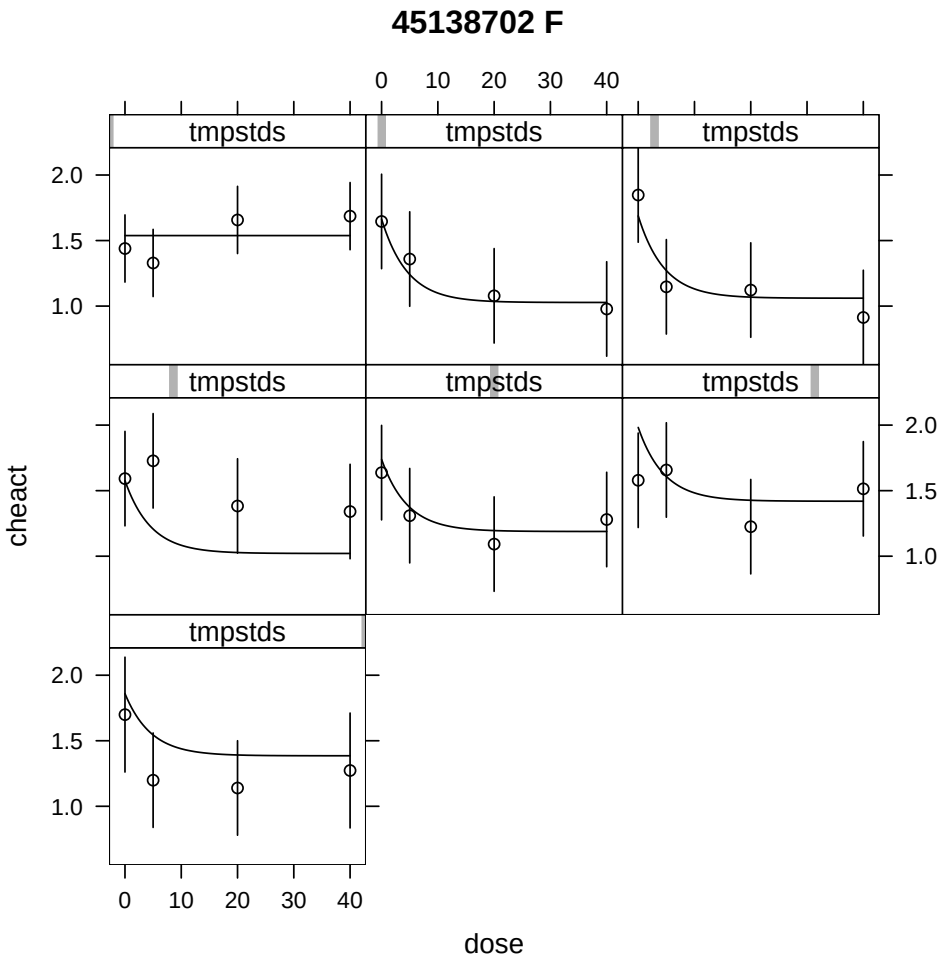
```
lA.mridXsexXtmpstds45138703:F:24
lA.mridXsexXtmpstds45138702:M:0
lA.mridXsexXtmpstds45138702:M:1
lA.mridXsexXtmpstds45138702:M:4
lA.mridXsexXtmpstds45138702:M:8
lA.mridXsexXtmpstds45138702:M:0.5
lA.mridXsexXtmpstds45138702:M:2
lA.mridXsexXtmpstds45138702:M:6
lA.mridXsexXtmpstds45138702:F:0
lA.mridXsexXtmpstds45138702:F:1
lA.mridXsexXtmpstds45138702:F:4
lA.mridXsexXtmpstds45138702:F:8
lA.mridXsexXtmpstds45138702:F:0.5
lA.mridXsexXtmpstds45138702:F:2
lA.mridXsexXtmpstds45138702:F:6
lD
tz
lTr                                 0.390

Standardized Within-Group Residuals:
       Min         Q1        Med         Q3        Max
-2.6485913 -0.6412745 -0.1110211  0.4927486  4.5013246

Number of Observations: 501
Number of Groups: 148
```

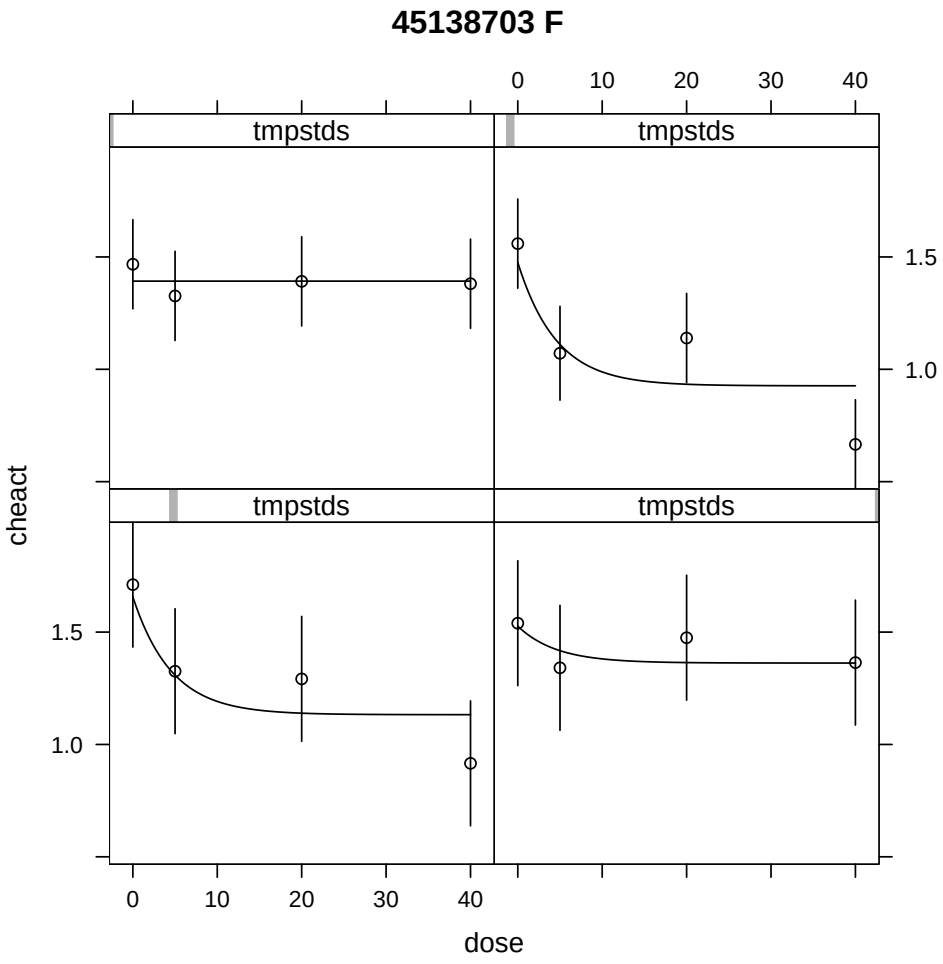
Diagnostic plots for this model:

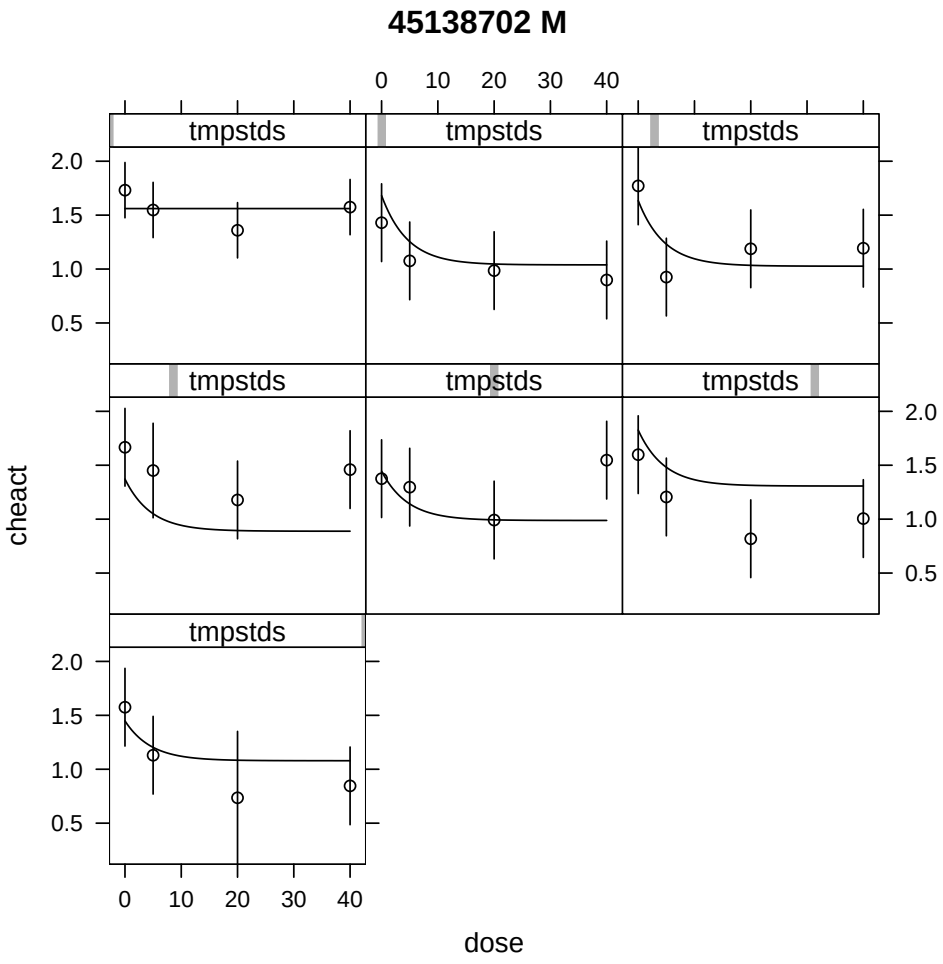
First, dose-response. Each figure is for one mrid × sex combination, plotting activity versus dose at each value of `tmpstds`. The following code sets up the predicted values for the range of doses at each mrid × sex × time.

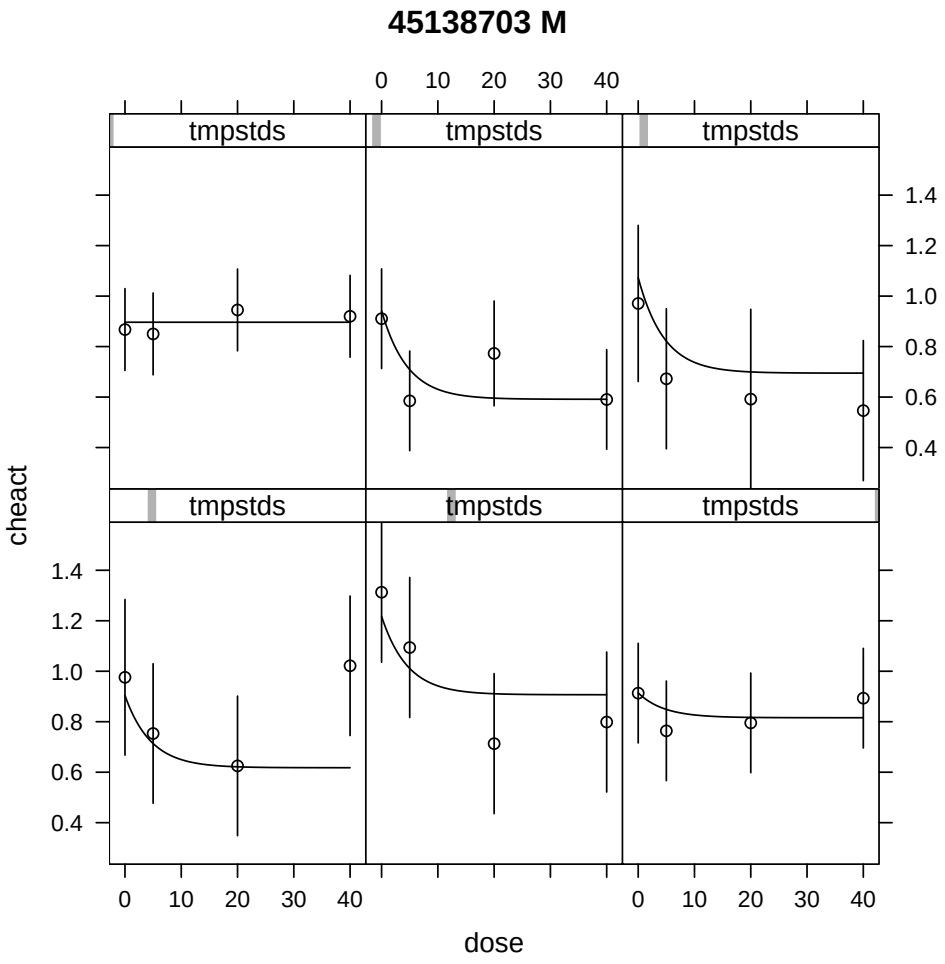
```
> ndta <- local({
+     tmp <- drmod5
+     tmp$contrasts <- NULL
+     ndta <- do.call("rbind", by(dta, with(dta, interaction(sex,
+         mrid, drop = TRUE, sep = ":")), function(x) {
+         expand.grid(sex = levels(factor(x$sex)), mrid = levels(factor(x$mrid)),
+             dose2 = seq(0, max(x$dose), length = 101), tmpstds = sort(unique(x$tmpstds)))
+     }))
+     ndta$mridXsexXtmpstds <- with(ndta, interaction(mrid, sex,
+         tmpstds, drop = TRUE, sep = ":"))
+     ndta$pred <- predict(tmp, newdata = ndta, level = 0)
+     ndta
+ })
> mnsd <- local({
+     dta$mridXsexXtmpstdsXdose <- with(dta, interaction(mrid,
+         sex, tmpstds, dose, drop = TRUE, sep = ":"))
+     out <- lme(cheact ~ mridXsexXtmpstdsXdose - 1, data = dta,
+         random = ~1 | id)
+     out <- intervals(out, which = "fixed")$fixed
+     nms <- gsub("mridXsexXtmpstdsXdose", "", rownames(out))
+     data.frame(mrid = factor(sapply(strsplit(nms, ":"), function(x) x[1])),
+         sex = factor(sapply(strsplit(nms, ":"), function(x) x[2])),
+         tmpstds = as.numeric(sapply(strsplit(nms, ":"), function(x) x[3])),
+         dose = as.numeric(sapply(strsplit(nms, ":"), function(x) x[4])),
```

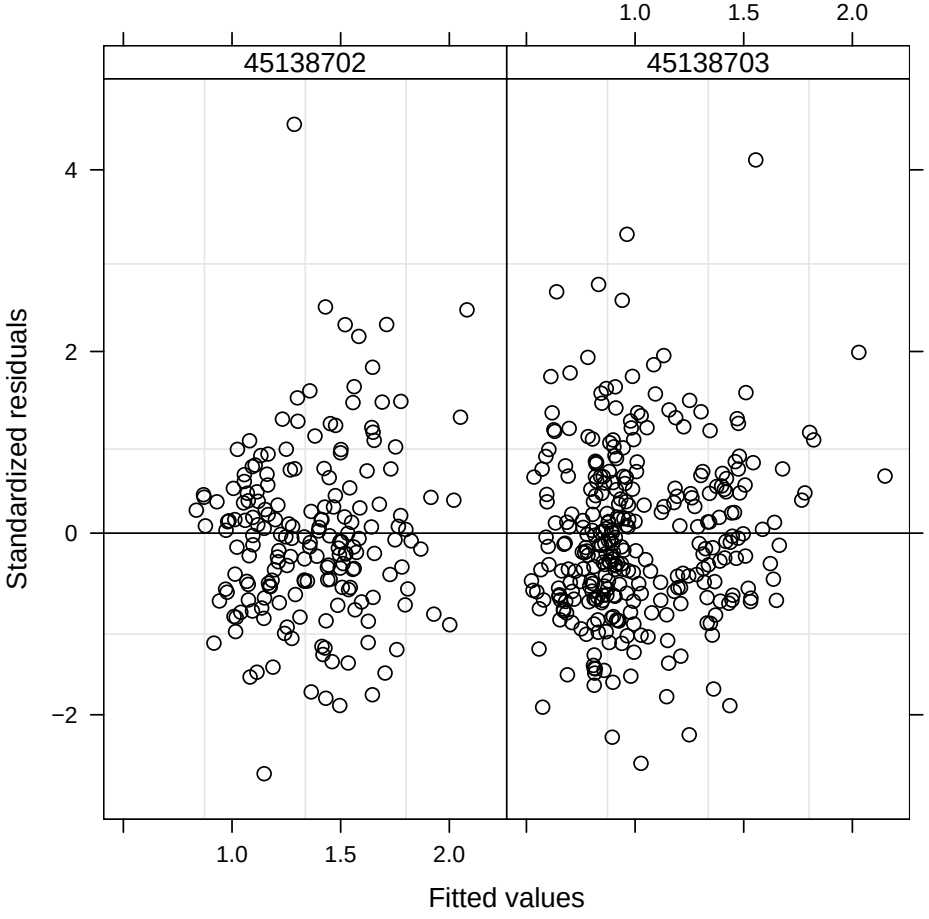
```
+          cheact = out[, "est."], llim = out[, "lower"], ulim = out[,
+              "upper"])
+ })
```

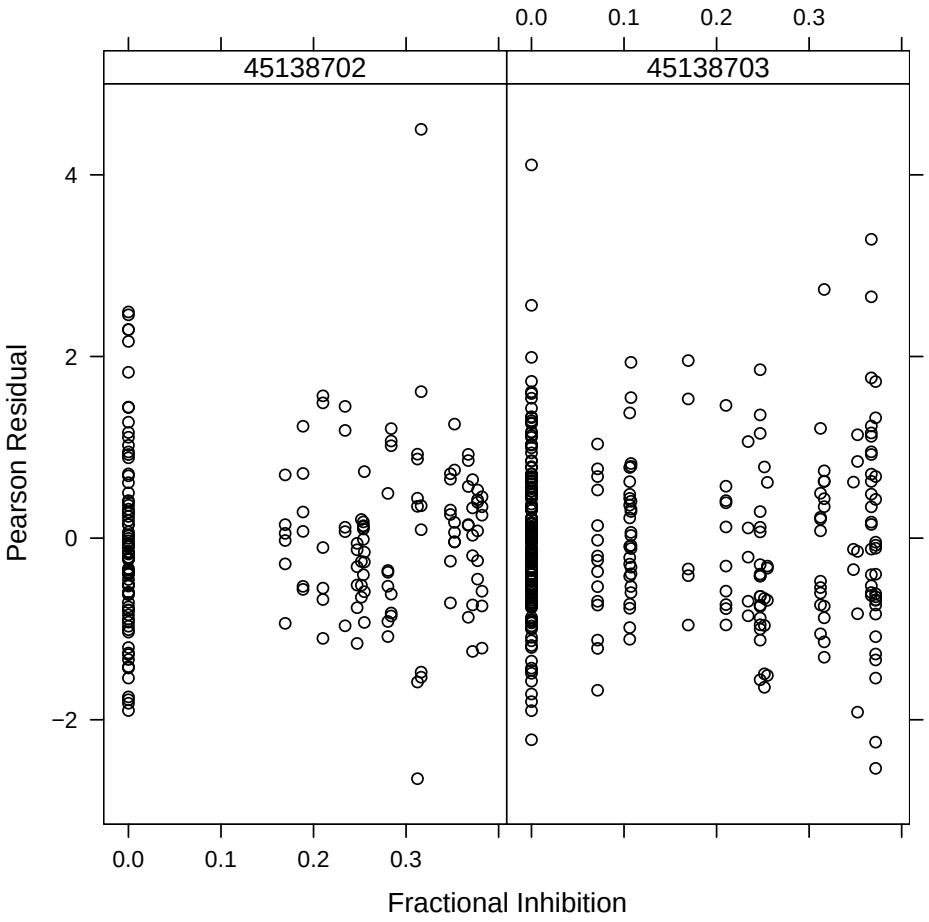


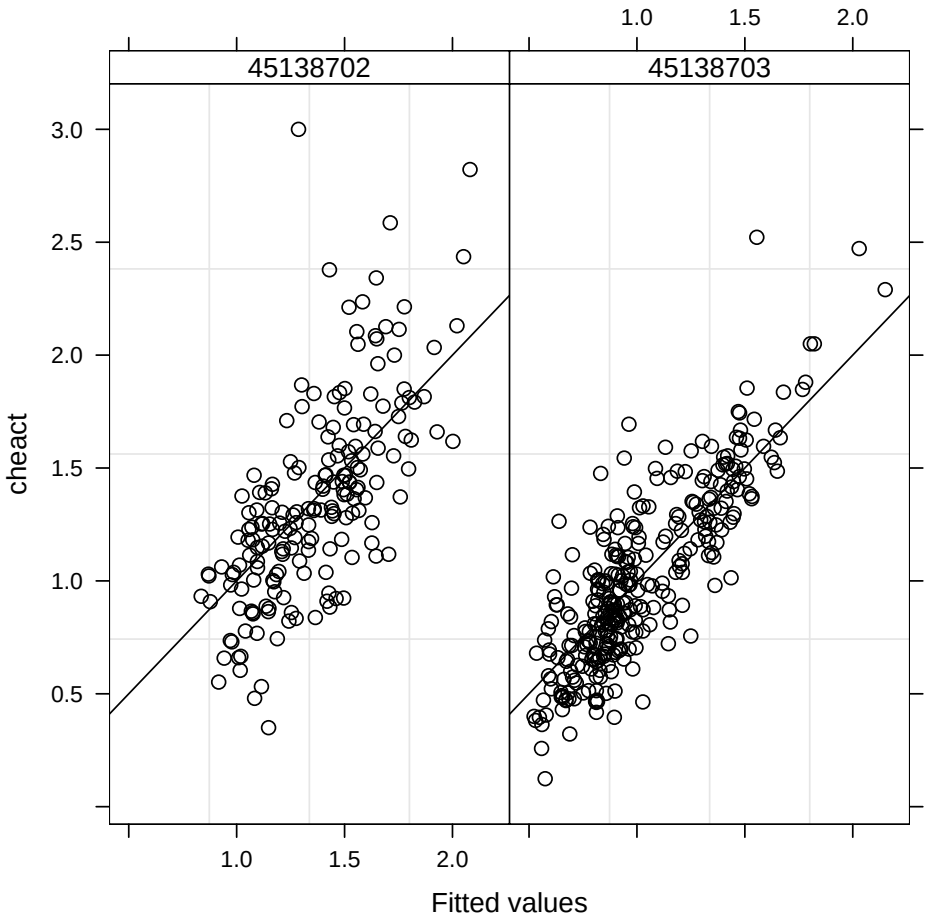

45138703 F
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0
10
20
30
40
1.0
1.5

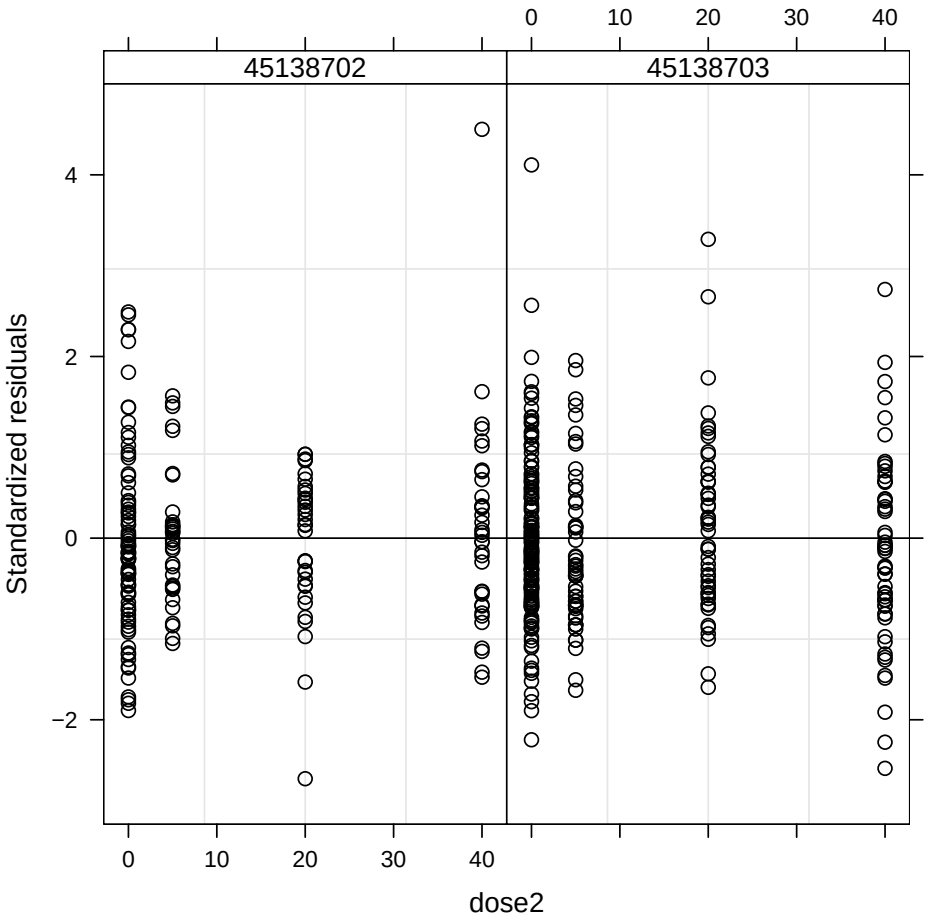

45138702 M
tmpstds
cheact
dose
0
10
20
30
40
0.5
1.0
1.5
2.0

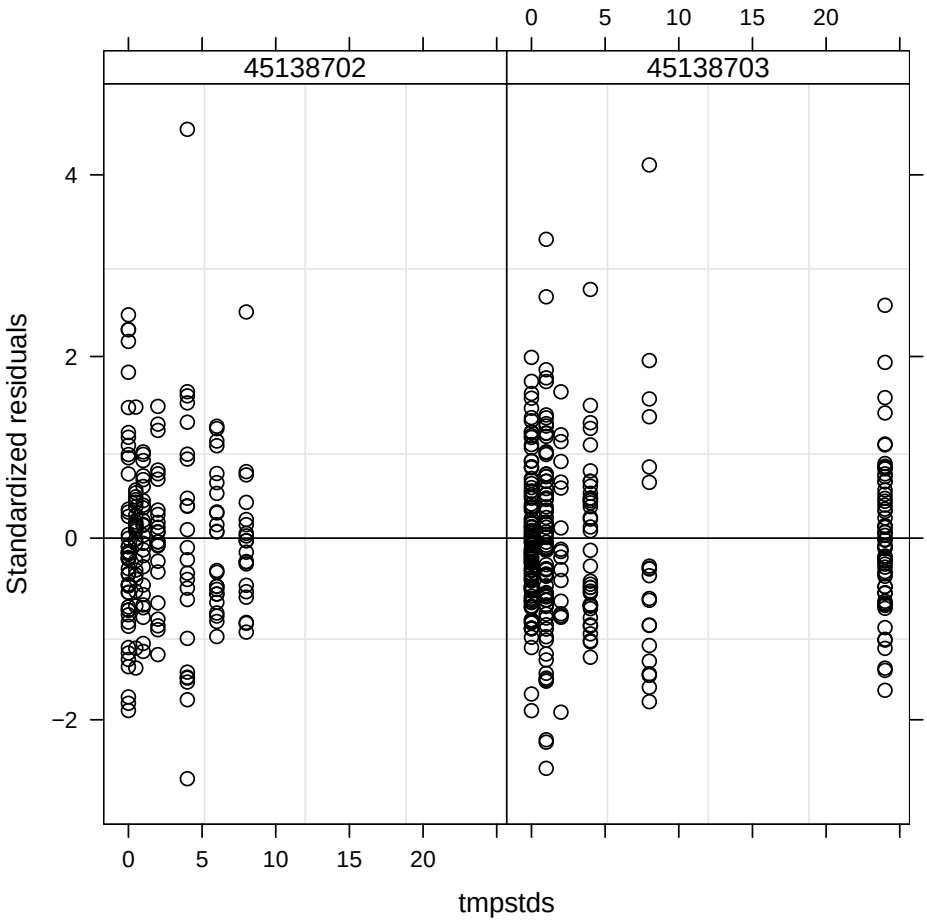

45138703 M
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
tmpstds
cheact
dose
0
10
20
30
40
0.4
0.6
0.8
1.0
1.2
1.4


45138702
45138703
Standardized residuals
Fitted values
4
2
0
−2
1.0
1.5
2.0


45138702
45138703
Pearson Residual
Fractional Inhibition
4
2
0
−2
0.0
0.1
0.2
0.3

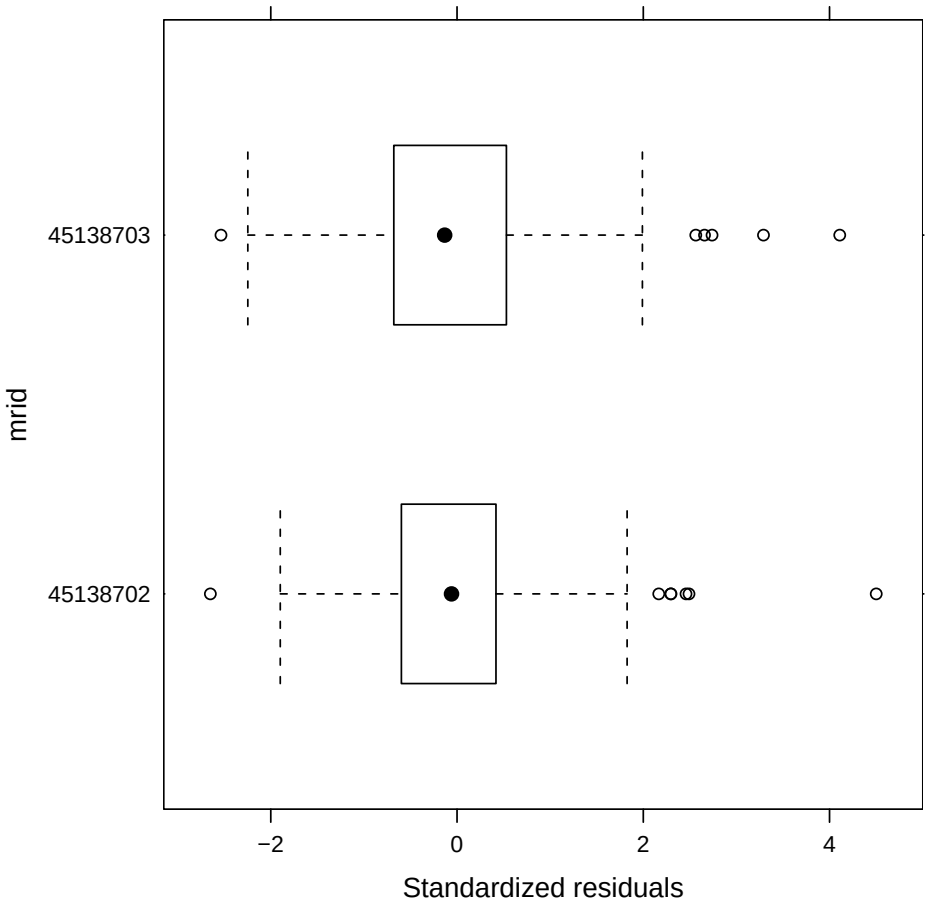

45138702
45138703
cheact
Fitted values
3.0
2.5
2.0
1.5
1.0
0.5
1.0
1.5
2.0

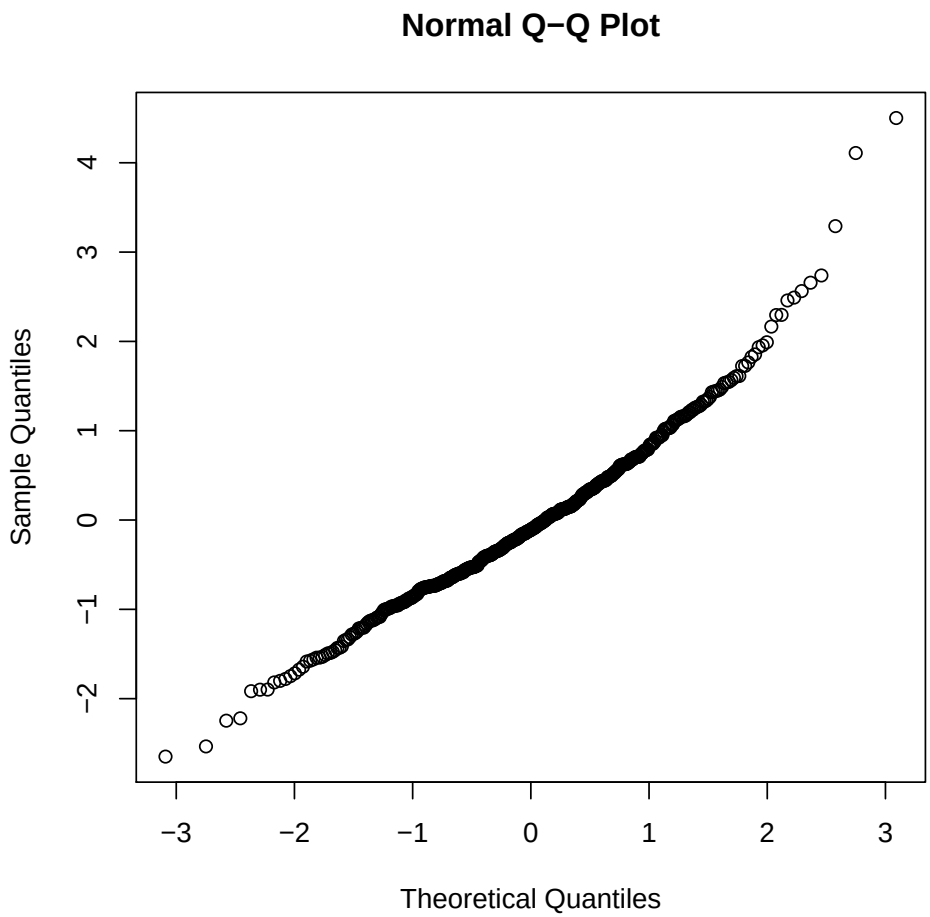

45138702
45138703
Standardized residuals
dose2
0
10
20
30
40
4
2
0
−2

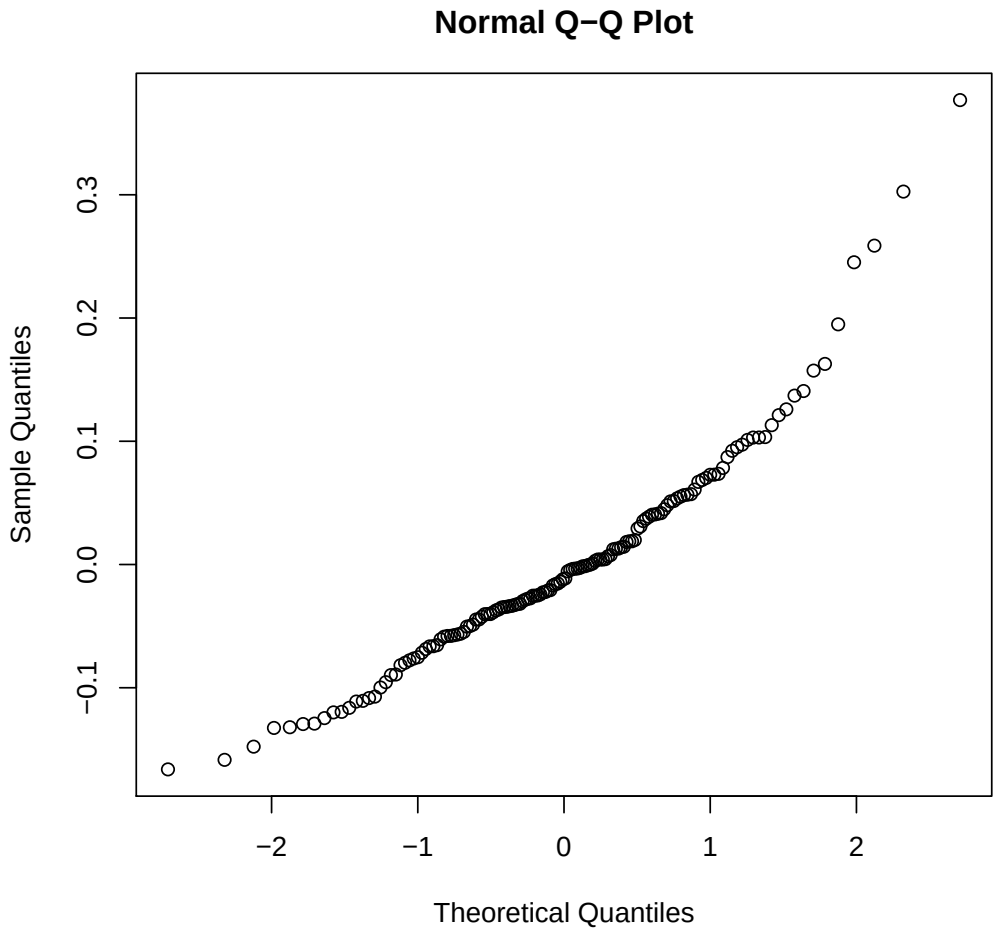


Some more graphs:

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


45138703
45138702
mrid
−2
0
2
4
Standardized residuals


Normal Q−Q Plot
Sample Quantiles
Theoretical Quantiles
−2
−1
0
1
2
3
4
−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, 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] "45138702" "45138703"`

`lD` **(se)** 0.329119764126751 (0.271975321888833)

BMD (95% CI) 1.38974428713210 (0.825880332686492, 2.33858236741603)

BMDL, the one-sided lower 95% CL 0.898296983153935

`lTr (standard error)` 2.55293961339391 (0.404526356528822)

Recovery Half-life (95% CI) 12.8448071059262 (5.92320607453996, 27.8546900972489)

Save the results:

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

Save the results for incorporating into a database:

```
> thiodicarb.oral.rbc <- list(mrid = levels(dta$mrid), species = levels(dta$species),
+     BMDs = list(combined = list(lD = tTab["lD", "Value"], lD.se = tTab["lD",
+         "Std.Error"], BMD = exp(Ints["lD", 2]), BMD.CI = exp(Ints["lD",
+         c(1, 3)]), BMDL = exp(Ints90["lD", 1]))), HalfLives = list(combined = list(lTr = tTab["lTr",
+         "Value"], lTr.se = tTab["lTr", "Std.Error"], Tr = exp(Ints["lTr",
+         "est."]), Tr.CI = exp(Ints["lTr", c("lower", "upper")]))))
> save(thiodicarb.oral.rbc, file = file.path("..", "..", "01Summaries",
+     "thiodicarb.oral.rbc.RData"))
```