Dose-Time Response Modeling of Rat Brain AChE Activity: Aldicarb Gavage Dosing

June 29, 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. Aldicarb data have already been extracted and preprocessed to some extent, and the results saved in `data/wrkdata.RData`. These are loaded here:

```
> library(CarbamateData)

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

> data(wrkdata)
```

Set up lattice to use B and 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
```

The following code prints out documentation for the datasets in use:

```
> for (nm in names(wrkdata)) {
+     writeLines(c("", nm, ""))
+     printDataDoc(wrkdata[[nm]])
+ }

AggData

----------------------------------------
Data set: wrkdata[[nm]]

Dataset creation date: Wed May  4 12:22:35 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2005-05-04 12:21:45
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
----------------------------------------

humanData

----------------------------------------
Data set: wrkdata[[nm]]

Dataset creation date: Wed May  4 12:22:42 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2005-05-04 12:21:45
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
----------------------------------------

repeated_acute

----------------------------------------
Data set: wrkdata[[nm]]

Dataset creation date: Wed May  4 12:22:42 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2005-05-04 12:21:45
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
```

```
----------------------------------------

repeated_subchronic

----------------------------------------
Data set: wrkdata[[nm]]

Dataset creation date: Wed May  4 12:22:42 2005
Script name: /home/setzer/tasks/CarbamateCRA/EmpiricalDoseResponses/Data/getdata.R
Script last modified: 2005-05-04 12:21:45
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
----------------------------------------
```

This script is for modeling the dose-time response for rat brain. via gavage dosing. It includes acute, subchronic, and chronic studies.

All the data used for this DR model are in `wrkdata[["AggData"]]` The following MRIDs will be used:

```
> MRIDSforBrainDR <- as.character(c(43442302, 43442305, 43829601,
+     43829602, "MOSER-1", "MOSER-2", "MOSER-3"))
```

These are all the names used for the brain sections we want:

```
> BrainSections <- levels(AggData$sctn)[grep("(^BRAIN)|(^WHOLEBRAIN)|(LEFT HEMISPHERE)| (HALFBRAIN)",
+     levels(AggData$sctn))]
```

Now, set up the analysis dataset. Drop data when tmpstds >= 24 hours. Virtually no information about dose-response is there, and it really messes up the models

One study 43442305, used multiple chemicals: aldicarb, aldicarb sulfoxide, and aldicarb sulfone (and will probably thus be useful for the aldoxycarb modeling). Drop everything but the active ingredient:

```
> dta <- subset(wrkdata[["AggData"]], mrid %in% MRIDSforBrainDR &
+     sctn %in% BrainSections & dsmtd != "INUTERO/MILK" & !is.na(cheact) &
+     (n == 1 | !is.na(sd)) & (is.na(tmpstds) | (tmpstds < 24)) &
+     (is.na(ta) | ta %in% c("AI")))
```

Three records with n = 1 has sd == NA instead of 0. Fix that

```
> dta$sd[is.na(dta$sd) & dta$n == 1] <- 0
```

Fixup for tmpstds in mrid 43829602. It is NA in dta, but email from Elissa Reeves (March 17, 2005) indicates it should be 0.75 hr. (Actually, that value refers to the time post-dosing when the terminal bleed occurred).

```
> dta$tmpstds[dta$mrid == "43829602"] <- 0.75
```

Of these, only 43829602 is not an acute study; it has multiple values for tmonstdy. ID does not vary among times (though IA and tz might well do so; that was not tested). So, I need these new variables:

```
> dta$mridXsex <- factor(with(dta, paste(as.character(mrid), as.character(sex),
+     sep = ":")))
> dta$mridXtmonstdyXsex <- factor(with(dta, paste(as.character(mrid),
+     as.character(tmonstdy), as.character(sex), sep = ":")))
> dta$mridXtmonstdy <- factor(with(dta, paste(as.character(mrid),
+     as.character(tmonstdy), sep = ":")))
```

We can only estimate the time-course parameters (ldT and lTmax) in the acute studies. Try just estimating them using

```
> dta$sexXfdose <- factor(with(dta, paste(as.character(sex), as.character(dose),
+     sep = ":")))
```

Each of the doses in the subchronic study appears in multiple acute studies, so this might work

First do a cell mean model to get an idea of what the variance model needs to look like.

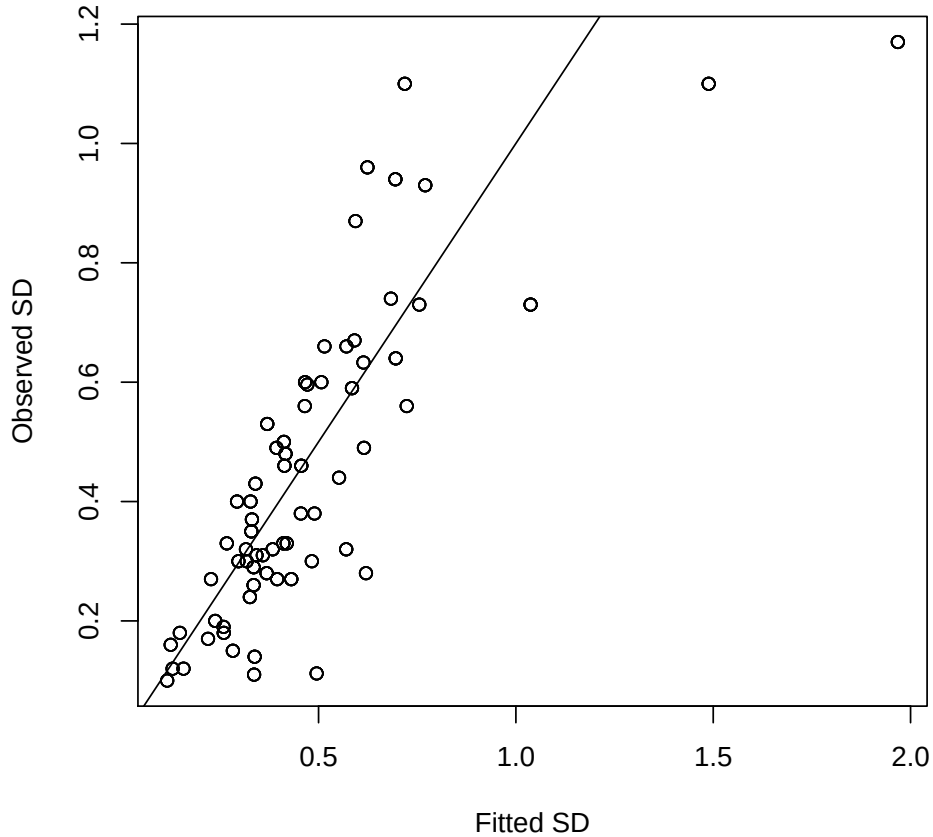
```
> dta$cellmeans <- factor(with(dta, paste(as.character(mrid), as.character(tmonstdy),
+     as.character(tmpstds), as.character(dose), as.character(sex),
+     sep = ":")))
```

Clean up the factors: drop the levels that don't appear

```
> for (nm in names(dta)) if (is.factor(dta[, nm])) dta[, nm] <- factor(dta[,
+     nm])
```

Use a cell mean model to look at the variance model.

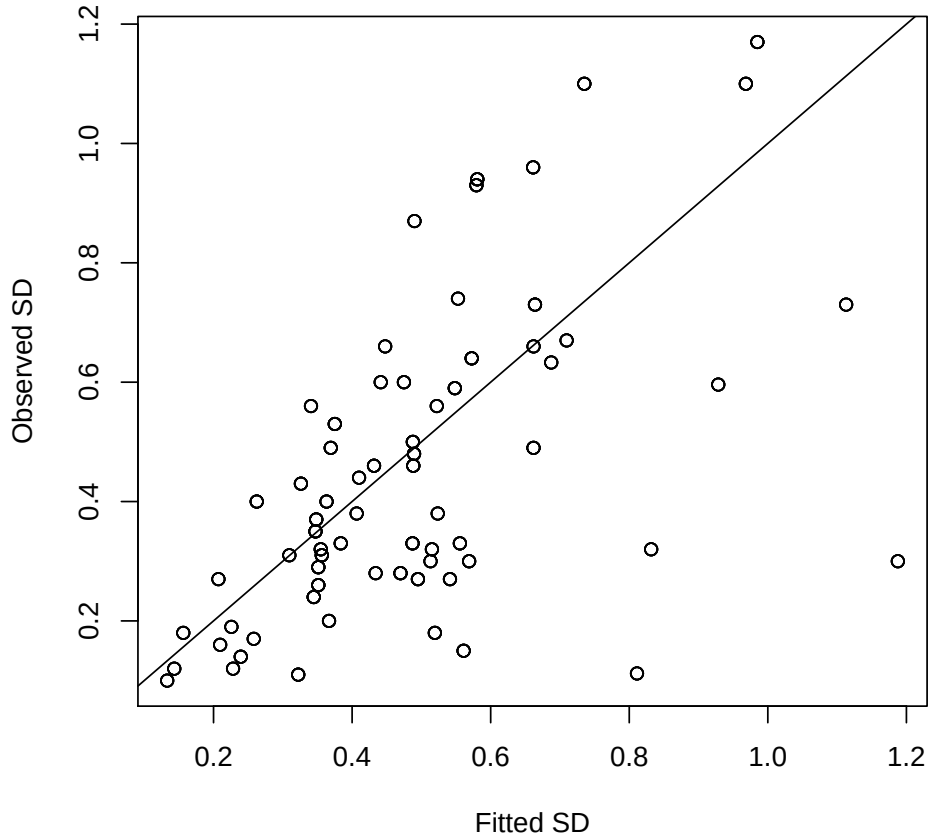
```
> ndta1 <- PhonyDF2(cbind(resp = cheact, sd = sd, n = n) ~ A, data = dta,
+     params = list(A ~ cellmeans), weights = varComb(varIdent(form = ~1 |
+         mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXtmonstdyXsex)))
> init.gls1 <- gls(cheact ~ cellmeans - 1, data = ndta1, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXtmonstdyXsex)))
> x <- init.gls1$sigma/varWeights(init.gls1[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
> abline(a = 0, b = 1)
```



Try collapsing the variance power to a single value:

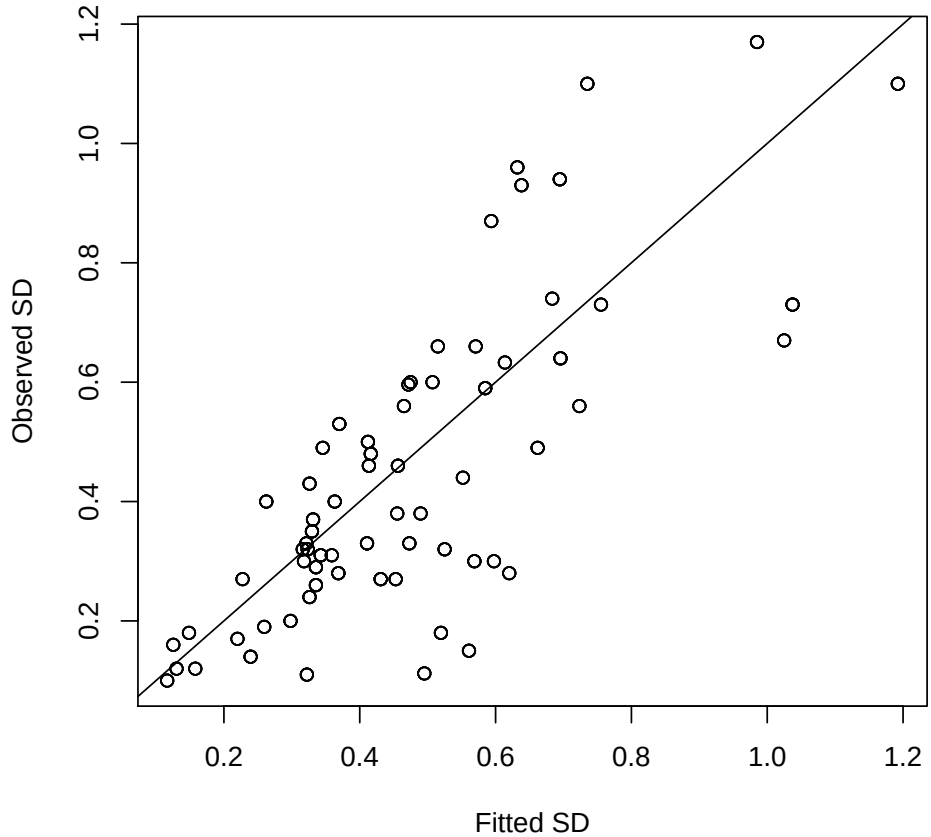
```
> init.gls2 <- gls(cheact ~ cellmeans - 1, data = ndta1, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdyXsex), varPower()))
> x <- init.gls2$sigma/varWeights(init.gls2[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
> abline(a = 0, b = 1)
> anova(init.gls1, init.gls2)
```

```
          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
init.gls1     1 96 585.1827 927.7438 -196.5914
init.gls2     2 83 594.9021 891.0747 -214.4510 1 vs 2 35.71936   7e-04
```



Some of the powers are different!
Maybe it is sufficient to group power by mrid and sex

```
> ndta2 <- PhonyDF2(cbind(resp = cheact, sd = sd, n = n) ~ A, data = dta,
+     params = list(A ~ cellmeans), weights = varComb(varIdent(form = ~1 |
+         mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXsex)))
> init.gls3 <- gls(cheact ~ cellmeans - 1, data = ndta2, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXsex)))
> x <- init.gls3$sigma/varWeights(init.gls3[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
> abline(a = 0, b = 1)
> anova(init.gls1, init.gls3)

          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
init.gls1     1 96 585.1827 927.7438 -196.5914
init.gls3     2 92 588.9216 917.2093 -202.4608 1 vs 2 11.73885  0.0194
```



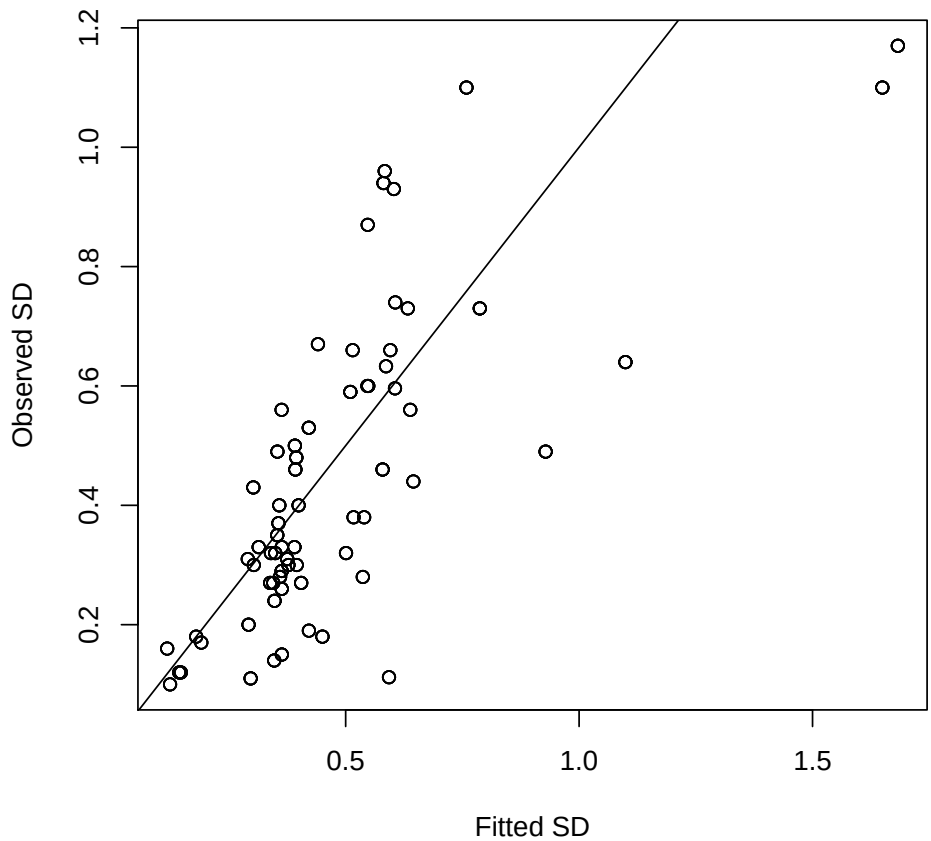
No. Maybe mridXtmonstdy

```
> ndta3 <- PhonyDF2(cbind(resp = cheact, sd = sd, n = n) ~ A, data = dta,
+     params = list(A ~ cellmeans), weights = varComb(varIdent(form = ~1 |
+         mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXtmonstdy)))
> init.gls4 <- gls(cheact ~ cellmeans - 1, data = ndta3, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdyXsex), varPower(form = ~fitted(.) | mridXtmonstdy)))
> x <- init.gls4$sigma/varWeights(init.gls4[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
> abline(a = 0, b = 1)
> anova(init.gls1, init.gls4)

          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
init.gls1     1 96 585.1827 927.7438 -196.5914
init.gls4     2 89 578.1285 895.7112 -200.0642 1 vs 2 6.945768  0.4345
```

Try simplifying the constant term:

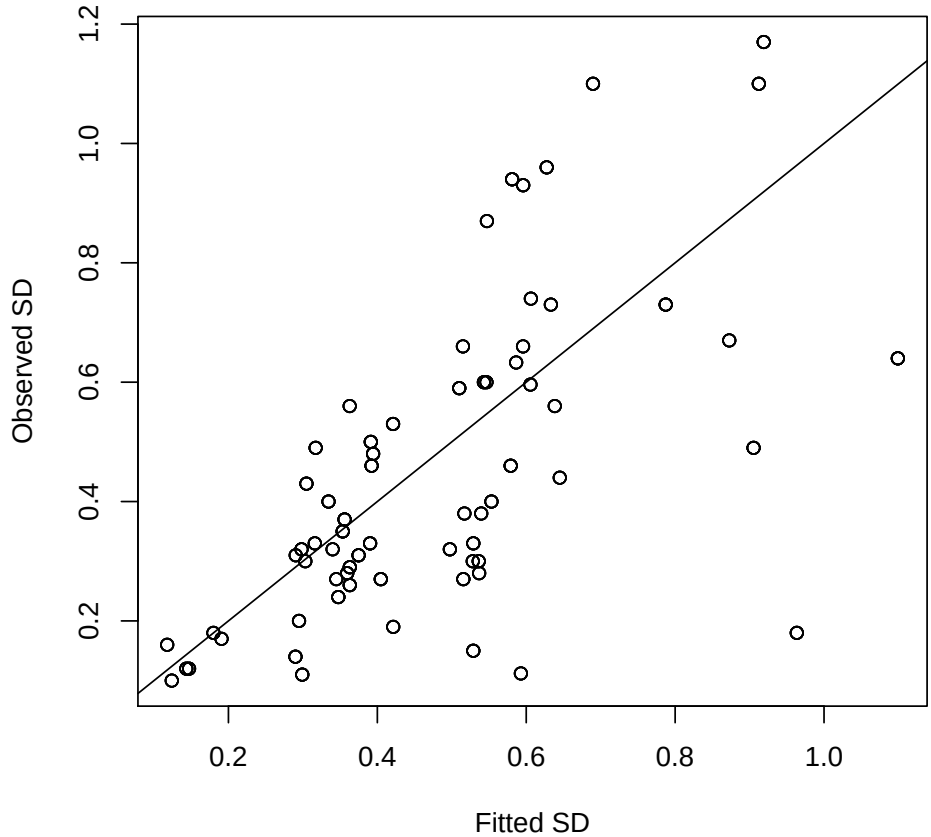
```
> init.gls5 <- gls(cheact ~ cellmeans - 1, data = ndta3, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
> x <- init.gls5$sigma/varWeights(init.gls5[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
```

```
> abline(a = 0, b = 1)
> anova(init.gls1, init.gls5)

          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
init.gls1     1 96 585.1827 927.7438 -196.5914
init.gls5     2 82 572.4925 865.0967 -204.2462 1 vs 2 15.30976  0.3573
```



Can I simplify the constant term further?

```
> ndta4 <- PhonyDF2(cbind(resp = cheact, sd = sd, n = n) ~ A, data = dta,
+     params = list(A ~ cellmeans), weights = varComb(varIdent(form = ~1 |
+         mrid), varPower(form = ~fitted(.) | mridXtmonstdy)))
> init.gls6 <- gls(cheact ~ cellmeans - 1, data = ndta4, weights = varComb(varIdent(form = ~1 |
+     mrid), varPower(form = ~fitted(.) | mridXtmonstdy)))
> x <- init.gls6$sigma/varWeights(init.gls6[[1]])
> y <- rep(dta$sd, dta$n)
> plot(y ~ x, xlab = "Fitted SD", ylab = "Observed SD")
> abline(a = 0, b = 1)
> anova(init.gls1, init.gls6)

          Model df      AIC      BIC    logLik   Test  L.Ratio p-value
init.gls1     1 96 585.1827 927.7438 -196.5914
init.gls6     2 80 581.1941 866.6616 -210.5970 1 vs 2 28.01134  0.0315
```



No. Use the model in init.gls5 as the variance model
Set contrasts for mridXtmonstdyXsex and sexXfdose to contr.sum

```
> dta$mridXtmonstdyXsex <- with(dta, C(mridXtmonstdyXsex, sum))
> dta$sexXfdose <- with(dta, C(sexXfdose, sum))
> dta$mridXsex <- with(dta, C(mridXsex, sum))
```

Set up start values. In the first pass, we need these parameters and models:

```
> params <- list(lA ~ mridXtmonstdyXsex - 1, lD ~ mridXsex - 1,
+     tz ~ mridXtmonstdyXsex - 1, lg ~ mridXtmonstdyXsex - 1, ldT ~
+         sexXfdose - 1, lTmax ~ sexXfdose - 1)
```

Get the values for lA. The other values will just replicate one common value for each level of their factor, but lA needs more finesse

```
> x1 <- coef(init.gls5)[grep("0:[FM]$", names(coef(init.gls5)))]
```

x1 now contains all the control values. Need to average over tmpstds

```
> nms <- levels(dta$mridXtmonstdyXsex)
> pattrns <- sub("(:[FM])$", ":.*\\1", nms)
> startlA <- sapply(pattrns, function(z) mean(x1[grep(z, names(x1))]))
> start <- with(dta, c(log(startlA), rep(log(0.2), nlevels(mridXsex)),
```

```
+     rep(log(0.1/(1 - 0.2)), nlevels(mridXtmonstdyXsex)), rep(log(2),
+         nlevels(mridXtmonstdyXsex)), rep(log(log(1.2)), nlevels(sexXfdose)),
+     rep(log(0.5), nlevels(sexXfdose))))
```

Use `GetInitialValues()` to get starting values and analyze the setup for parameter redundancy:

```
> initfile <- paste("initvals-brain-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     out <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn2(dose, tmpstds, tmpstds, lA = lA, tz = tz, lD = lD,
+             lg = lg, ldT = ldT, lTmax = lTmax), data = dta, params = params,
+         start = start, weights = varComb(varIdent(form = ~1 |
+             mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out, file = initfile)
+ } else load(initfile)
```

That model is too complex to be fit. Look at the first 7 condition indices (after dropping `ldT` and `lTmax` from consideration!):

```
> t(out$Redundancy[[1]][[1]])[1, 1:7, drop = FALSE]

              [,1]     [,2]     [,3]     [,4]     [,5]     [,6]     [,7]
CondIndex 86919394 59479413 32.86463 24.67450 23.76555 19.00409 12.47650
```

The first two indices are huge, indicating strong non-identifiability among several variables:

```
> t(round(out$Redundancy[[1]][[1]][1:7, ], digits = 2))

                                      [,1]     [,2]  [,3]  [,4]  [,5]  [,6]
CondIndex                         86919394 59479413 32.86 24.67 23.77 19.00
mu                                       0        0  0.05  0.07  0.07  0.09
lA.mridXtmonstdyXsex43442305:1:F         0        0  0.00  0.00  0.00  0.00
lA.mridXtmonstdyXsex43442305:1:M         0        0  0.00  0.00  0.00  0.00
lA.mridXtmonstdyXsex43829602:28:F        0        0  0.00  0.31  0.00  0.00
lA.mridXtmonstdyXsex43829602:28:M        0        0  0.33  0.00  0.00  0.00
lA.mridXtmonstdyXsex43829602:56:F        0        0  0.00  0.22  0.00  0.00
lA.mridXtmonstdyXsex43829602:56:M        0        0  0.13  0.00  0.00  0.00
lA.mridXtmonstdyXsex43829602:91:F        0        0  0.00  0.22  0.00  0.00
lA.mridXtmonstdyXsex43829602:91:M        0        0  0.24  0.00  0.00  0.00
lA.mridXtmonstdyXsexMOSER-1:NA:F         0        0  0.00  0.00  0.00  0.00
lA.mridXtmonstdyXsexMOSER-1:NA:M         0        0  0.00  0.00  0.00  0.00
lA.mridXtmonstdyXsexMOSER-2:NA:F         0        0  0.00  0.00  0.35  0.00
lA.mridXtmonstdyXsexMOSER-2:NA:M         0        0  0.00  0.00  0.00  0.24
lA.mridXtmonstdyXsexMOSER-3:NA:F         0        0  0.00  0.00  0.00  0.00
lA.mridXtmonstdyXsexMOSER-3:NA:M         0        0  0.00  0.00  0.00  0.00
lD.mridXsex43442305:F                    1        0  0.00  0.00  0.00  0.00
lD.mridXsex43442305:M                    0        1  0.00  0.00  0.00  0.00
lD.mridXsex43829602:F                    0        0  0.00  0.99  0.00  0.00
lD.mridXsex43829602:M                    0        0  0.96  0.00  0.00  0.00
lD.mridXsexMOSER-1:F                     0        0  0.00  0.00  0.00  0.00
lD.mridXsexMOSER-1:M                     0        0  0.00  0.00  0.00  0.00
lD.mridXsexMOSER-2:F                     0        0  0.00  0.00  0.97  0.00
lD.mridXsexMOSER-2:M                     0        0  0.00  0.00  0.00  0.92
lD.mridXsexMOSER-3:F                     0        0  0.00  0.00  0.00  0.00
lD.mridXsexMOSER-3:M                     0        0  0.00  0.00  0.00  0.00
tz.mridXtmonstdyXsex43442305:1:F         1        0  0.00  0.00  0.00  0.00
```

tz.mridXtmonstdyXsex43442305:1:M	0	1	0.00	0.00	0.00	0.00
tz.mridXtmonstdyXsex43829602:28:F	0	0	0.00	0.62	0.00	0.00
tz.mridXtmonstdyXsex43829602:28:M	0	0	0.78	0.00	0.00	0.00
tz.mridXtmonstdyXsex43829602:56:F	0	0	0.00	0.35	0.00	0.00
tz.mridXtmonstdyXsex43829602:56:M	0	0	0.01	0.00	0.00	0.00
tz.mridXtmonstdyXsex43829602:91:F	0	0	0.00	0.52	0.00	0.00
tz.mridXtmonstdyXsex43829602:91:M	0	0	0.79	0.00	0.00	0.00
tz.mridXtmonstdyXsexMOSER-1:NA:F	0	0	0.00	0.00	0.00	0.00
tz.mridXtmonstdyXsexMOSER-1:NA:M	0	0	0.00	0.00	0.00	0.00
tz.mridXtmonstdyXsexMOSER-2:NA:F	0	0	0.00	0.00	0.85	0.00
tz.mridXtmonstdyXsexMOSER-2:NA:M	0	0	0.00	0.00	0.00	0.79
tz.mridXtmonstdyXsexMOSER-3:NA:F	0	0	0.00	0.00	0.00	0.00
tz.mridXtmonstdyXsexMOSER-3:NA:M	0	0	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsex43442305:1:F	1	0	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsex43442305:1:M	0	1	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsex43829602:28:F	0	0	0.00	0.94	0.00	0.00
lg.mridXtmonstdyXsex43829602:28:M	0	0	0.93	0.00	0.00	0.00
lg.mridXtmonstdyXsex43829602:56:F	0	0	0.00	0.97	0.00	0.00
lg.mridXtmonstdyXsex43829602:56:M	0	0	0.93	0.00	0.00	0.00
lg.mridXtmonstdyXsex43829602:91:F	0	0	0.00	0.97	0.00	0.00
lg.mridXtmonstdyXsex43829602:91:M	0	0	0.94	0.00	0.00	0.00
lg.mridXtmonstdyXsexMOSER-1:NA:F	0	0	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsexMOSER-1:NA:M	0	0	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsexMOSER-2:NA:F	0	0	0.00	0.00	1.00	0.00
lg.mridXtmonstdyXsexMOSER-2:NA:M	0	0	0.00	0.00	0.00	0.99
lg.mridXtmonstdyXsexMOSER-3:NA:F	0	0	0.00	0.00	0.00	0.00
lg.mridXtmonstdyXsexMOSER-3:NA:M	0	0	0.00	0.00	0.00	0.00

	[,7]
CondIndex	12.48
mu	0.14
lA.mridXtmonstdyXsex43442305:1:F	0.00
lA.mridXtmonstdyXsex43442305:1:M	0.00
lA.mridXtmonstdyXsex43829602:28:F	0.00
lA.mridXtmonstdyXsex43829602:28:M	0.00
lA.mridXtmonstdyXsex43829602:56:F	0.00
lA.mridXtmonstdyXsex43829602:56:M	0.00
lA.mridXtmonstdyXsex43829602:91:F	0.00
lA.mridXtmonstdyXsex43829602:91:M	0.00
lA.mridXtmonstdyXsexMOSER-1:NA:F	0.27
lA.mridXtmonstdyXsexMOSER-1:NA:M	0.00
lA.mridXtmonstdyXsexMOSER-2:NA:F	0.00
lA.mridXtmonstdyXsexMOSER-2:NA:M	0.00
lA.mridXtmonstdyXsexMOSER-3:NA:F	0.00
lA.mridXtmonstdyXsexMOSER-3:NA:M	0.00
lD.mridXsex43442305:F	0.00
lD.mridXsex43442305:M	0.00
lD.mridXsex43829602:F	0.00
lD.mridXsex43829602:M	0.00
lD.mridXsexMOSER-1:F	0.98
lD.mridXsexMOSER-1:M	0.00
lD.mridXsexMOSER-2:F	0.00
lD.mridXsexMOSER-2:M	0.00
lD.mridXsexMOSER-3:F	0.00
lD.mridXsexMOSER-3:M	0.00

```
tz.mridXtmonstdyXsex43442305:1:F   0.00
tz.mridXtmonstdyXsex43442305:1:M   0.00
tz.mridXtmonstdyXsex43829602:28:F  0.00
tz.mridXtmonstdyXsex43829602:28:M  0.00
tz.mridXtmonstdyXsex43829602:56:F  0.00
tz.mridXtmonstdyXsex43829602:56:M  0.00
tz.mridXtmonstdyXsex43829602:91:F  0.00
tz.mridXtmonstdyXsex43829602:91:M  0.00
tz.mridXtmonstdyXsexMOSER-1:NA:F   0.27
tz.mridXtmonstdyXsexMOSER-1:NA:M   0.00
tz.mridXtmonstdyXsexMOSER-2:NA:F   0.00
tz.mridXtmonstdyXsexMOSER-2:NA:M   0.00
tz.mridXtmonstdyXsexMOSER-3:NA:F   0.00
tz.mridXtmonstdyXsexMOSER-3:NA:M   0.00
lg.mridXtmonstdyXsex43442305:1:F   0.00
lg.mridXtmonstdyXsex43442305:1:M   0.00
lg.mridXtmonstdyXsex43829602:28:F  0.00
lg.mridXtmonstdyXsex43829602:28:M  0.00
lg.mridXtmonstdyXsex43829602:56:F  0.00
lg.mridXtmonstdyXsex43829602:56:M  0.00
lg.mridXtmonstdyXsex43829602:91:F  0.00
lg.mridXtmonstdyXsex43829602:91:M  0.00
lg.mridXtmonstdyXsexMOSER-1:NA:F   0.98
lg.mridXtmonstdyXsexMOSER-1:NA:M   0.00
lg.mridXtmonstdyXsexMOSER-2:NA:F   0.00
lg.mridXtmonstdyXsexMOSER-2:NA:M   0.00
lg.mridXtmonstdyXsexMOSER-3:NA:F   0.00
lg.mridXtmonstdyXsexMOSER-3:NA:M   0.00
```

The directions associated with the largest condition indices include an estimate of `lD`, `tz`, and `lg` Simplify it: Leave lA, and lD, alone, for now. Fit `lg+tz` $\sim$ `sex`. Define a new variable `Cdose`, which is 1 if dose $<$ 0.125, 2 if dose is between 0.125 and 0.375, and 3 otherwise, and make it a factor (use cut). Define `ldT` on that set of intervals. Estimate a single value of `lTmax`.

```
> dta$Cdose <- cut(dta$dose, breaks = c(0, 0.125, 0.375, Inf),
+     include.lowest = TRUE)
> params <- list(lA ~ mridXtmonstdyXsex - 1, lD ~ mridXsex - 1,
+     tz ~ sex, lg ~ sex, ldT ~ Cdose:sex - 1, lTmax ~ 1)
> start <- with(dta, c(log(startlA), rep(log(0.2), nlevels(mridXsex)),
+     rep(log(0.1/(1 - 0.2)), nlevels(sex)), rep(log(1), nlevels(sex)),
+     rep(log(log(1.2)), nlevels(Cdose:sex)), rep(log(0.5), 1)))
> initfile <- paste("initvals-brain-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+     out <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn2(dose, tmpstds, tmpstds, lA = lA, tz = tz, lD = lD,
+             lg = lg, ldT = ldT, lTmax = lTmax), data = dta, params = params,
+         start = start, weights = varComb(varIdent(form = ~1 |
+             mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out, file = initfile)
+ } else load(initfile)
```

This model is still singular as it stands, but the estimates of tz you get from "eyeballing" the data with `GetInitialValues()` are all small (less than -10), indicating little data to support a non-zero horizontal asymptote. Also, the levels of `ldT` for the larger doses are similar to each other, but optimization will force the values at the lowest dose levels to decrease until an arithmetic error occurs. Notwithstanding that, increasing the value

of ldT for the lowest dose levels does not decrease the overall fit by much. Perhaps, at the lowest dose, only a single time point is affected, and by the next time point, AChE levels have fully recovered. Then there would be insufficient information to estimate the shape of the recovery time course, only enough to say that the recovery half life must small enough that the observed effect would have disappeared before the next time point.

So, set tz to -10, and make a new version of Cdose based on a cut in dose at 0.375.

```
> dta$Cdose <- cut(dta$dose, breaks = c(0, 0.375, Inf), include.lowest = TRUE)
> params <- list(lA ~ mridXtmonstdyXsex - 1, lD ~ mridXsex - 1,
+     lg ~ sex, ldT ~ Cdose:sex - 1, lTmax ~ 1)
> par <- out$start$beta
> start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par[grep("^lg", names(par))], par[grep("^ldT", names(par))][c(2,
+         3, 5, 6)], par["lTmax"])
> formals(tcmfn2)$tz <- -10
> initfile <- paste("initvals-brain-DR-3.RData", sep = "")
> if (!file.exists(initfile)) {
+     out <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn2(dose, tmpstds, tmpstds, lA = lA, lD = lD, lg = lg,
+             ldT = ldT, lTmax = lTmax), data = dta, params = params,
+         start = start, weights = varComb(varIdent(form = ~1 |
+             mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out, file = initfile)
+ } else load(initfile)
```

The model repesented above might work. The largest condition index may still be too large, with heavy loadings of all the time course parameters, the low-dose shape (lg), and one of the benchmark doses:

```
> t(round(out$Redundancy[[1]][[1]][1:5, ], digits = 1))
```

	[,1]	[,2]	[,3]	[,4]	[,5]
CondIndex	21.8	14.9	10.0	3.0	2.8
mu	0.1	0.1	0.2	0.6	0.6
lA.mridXtmonstdyXsex43442305:1:F	0.1	0.0	0.0	0.1	0.0
lA.mridXtmonstdyXsex43442305:1:M	0.1	0.0	0.0	0.8	0.0
lA.mridXtmonstdyXsex43829602:28:F	0.0	0.1	0.0	0.0	0.0
lA.mridXtmonstdyXsex43829602:28:M	0.0	0.0	0.1	0.0	0.0
lA.mridXtmonstdyXsex43829602:56:F	0.0	0.1	0.0	0.0	0.0
lA.mridXtmonstdyXsex43829602:56:M	0.0	0.0	0.1	0.0	0.0
lA.mridXtmonstdyXsex43829602:91:F	0.0	0.1	0.0	0.0	0.0
lA.mridXtmonstdyXsex43829602:91:M	0.0	0.0	0.1	0.0	0.0
lA.mridXtmonstdyXsexMOSER-1:NA:F	0.0	0.0	0.0	0.0	0.0
lA.mridXtmonstdyXsexMOSER-1:NA:M	0.0	0.0	0.1	0.0	0.0
lA.mridXtmonstdyXsexMOSER-2:NA:F	0.0	0.0	0.0	0.0	0.0
lA.mridXtmonstdyXsexMOSER-2:NA:M	0.0	0.0	0.1	0.0	0.2
lA.mridXtmonstdyXsexMOSER-3:NA:F	0.0	0.0	0.0	0.0	0.0
lA.mridXtmonstdyXsexMOSER-3:NA:M	0.0	0.0	0.1	0.0	0.6
lD.mridXsex43442305:F	0.3	0.3	0.1	0.0	0.0
lD.mridXsex43442305:M	0.0	0.1	0.4	0.1	0.0
lD.mridXsex43829602:F	0.3	0.6	0.1	0.0	0.0
lD.mridXsex43829602:M	0.6	0.0	0.4	0.0	0.0
lD.mridXsexMOSER-1:F	0.3	0.4	0.1	0.0	0.0
lD.mridXsexMOSER-1:M	0.0	0.1	0.7	0.0	0.0
lD.mridXsexMOSER-2:F	0.3	0.4	0.1	0.0	0.0
lD.mridXsexMOSER-2:M	0.0	0.1	0.7	0.0	0.1
lD.mridXsexMOSER-3:F	0.2	0.3	0.1	0.0	0.0

```
lD.mridXsexMOSER-3:M                0.0  0.1  0.5  0.0  0.3
lg.(Intercept)                      0.3  0.5  0.1  0.0  0.0
lg.sexM                             0.2  0.7  0.2  0.0  0.0
ldT.Cdose[0,0.375]:sexF             0.8  0.1  0.0  0.0  0.0
ldT.Cdose(0.375,Inf]:sexF           0.9  0.0  0.0  0.0  0.0
ldT.Cdose[0,0.375]:sexM             0.7  0.0  0.0  0.1  0.0
ldT.Cdose(0.375,Inf]:sexM           0.9  0.1  0.0  0.0  0.0
lTmax                               0.9  0.1  0.0  0.0  0.0
```

Try the following nlme model.

```
> par <- out$start$beta
> lDM <- mean(par[grep("^lD.*M$", names(par))])
> lDF <- mean(par[grep("^lD.*F$", names(par))])
> start <- list(fixed = c(par[grep("^lA", names(par))], c(lDF,
+     lDM), par[grep("^lg", names(par))], par[grep("^ldT", names(par))],
+     par["lTmax"]))
> idta <- out$data
> idta$mrid <- factor(sapply(strsplit(as.character(idta$mridXsex),
+     ":"), function(x) x[1]))
```

```
> out2 <- nlme(cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA,
+     lD = lD, lg = lg, ldT = ldT, lTmax = lTmax), data = idta,
+     fixed = list(lA ~ mridXtmonstdyXsex - 1, lD ~ sex - 1, lg ~
+         sex, ldT ~ Cdose:sex - 1, lTmax ~ 1), random = list(mrid = lD ~
+         1), weights = varComb(varIdent(form = ~1 | mridXtmonstdy),
+         varPower(form = ~fitted(.) | mridXtmonstdy)), start = start)
```

That gives the error:

> Error in nlme.formula(cheact tcmfn2(dose, tmpstds, tmpstds, lA = lA, : Step halving factor reduced below minimum in PNLS step

Try combining the F and M versions of ldT, so it only depends on dose, not sex. Also, try a single value for lg. Run it through `GetInitialValues()` to check for redundancy, etc.

```
> par <- out$start$beta
> ldT.lower <- mean(par[grep("\\[0", names(par))])
> ldT.upper <- mean(par[grep("Inf\\]", names(par))])
> ldT.all <- mean(par[grep("^ldT", names(par))])
> start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par[grep("^lg\\.\\(In", names(par))], ldT = as.vector(ldT.all),
+     par["lTmax"])
> initfile <- paste("initvals-brain-DR-4.RData", sep = "")
> if (!file.exists(initfile)) {
+     out4 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn2(dose, tmpstds, tmpstds, lA = lA, lD = lD, lg = lg,
+             ldT = ldT, lTmax = lTmax), data = dta, params = list(lA ~
+         mridXtmonstdyXsex - 1, lD ~ mridXsex - 1, lg ~ 1, ldT ~
+         1, lTmax ~ 1), start = start, weights = varComb(varIdent(form = ~1 |
+         mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out4, file = initfile)
+ } else load(initfile)
```

It looks impossible to jointly estimate lTmax and ldT. Fix lTmax to be log(0.5), and try to estimate everything else. Again, use `GetInitialValues()`. In the previous setup, the estimated standard error for ldT was enormous, when it was estimated jointly with lTmax. This would probably cause nlme to fail. What happens if we don't fit lTmax?

```
> formals(tcmfn2)$lTmax <- log(0.5)
> par <- out4$start$beta
> start <- par[-grep("lTmax", names(par))]
> initfile <- paste("initvals-brain-DR-5.RData", sep = "")
> if (!file.exists(initfile)) {
+     out5 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn2(dose, tmpstds, tmpstds, lA = lA, lD = lD, lg = lg,
+             ldT = ldT), data = dta, params = list(lA ~ mridXtmonstdyXsex -
+         1, lD ~ mridXsex - 1, lg ~ 1, ldT ~ 1), start = start,
+         weights = varComb(varIdent(form = ~1 | mridXtmonstdy),
+             varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out5, file = initfile)
+ } else load(initfile)
```

That gives reasonable condition indices and standard errors for all the parameters. Can we fit an `nlme()` model?

```
> par <- out5$start$beta
> start <- list(fixed = c(par[grep("^lA", names(par))], c(mean(par[grep("^lD.*F$",
+     names(par))]), mean(par[grep("^lD.*M$", names(par))])), par["lg"],
+     par["ldT"]))
> lD.par <- data.frame(lD = par[grep("^lD", names(par))])
> lvls <- gsub("lD\\.mridXsex", "", names(par)[grep("^lD", names(par))])
> lD.par$mrid <- factor(sapply(strsplit(lvls, ":"), function(x) x[1]))
> lD.par$sex <- factor(sapply(strsplit(lvls, ":"), function(x) x[2]))
> rndm <- coef(lm(lD ~ mrid - 1, data = lD.par))
> rndm <- rndm - mean(rndm)
> start$random = list(matrix(rndm, ncol = 1))
> rownames(start$random[[1]]) <- gsub("mrid", "", names(rndm))
> idta <- out5$data
> idta$mrid <- with(idta, factor(sapply(strsplit(as.character(mridXsex),
+     ":"), function(x) x[1])))
> idta$sex <- with(idta, factor(sapply(strsplit(as.character(mridXsex),
+     ":"), function(x) x[2])))
> out6 <- nlme(cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA,
+     lD = lD, lg = lg, ldT = ldT), data = idta, fixed = list(lA ~
+     mridXtmonstdyXsex - 1, lD ~ sex - 1, lg ~ 1, ldT ~ 1), random = lD ~
+     1 | mrid, start = start)
> summary(out6)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA, lD = lD, lg = lg,      ldT = ldT)
 Data: idta
       AIC      BIC    logLik
  593.3999 669.3817 -276.6999

Random effects:
 Formula: lD ~ 1 | mrid
        lD.(Intercept)  Residual
StdDev:      0.3380206 0.5426231

Fixed effects: list(lA ~ mridXtmonstdyXsex - 1, lD ~ sex - 1, lg ~ 1, ldT ~      1)
                                      Value  Std.Error  DF   t-value p-value
lA.mridXtmonstdyXsex43442305:1:F   1.8539293 0.01579628 308 117.36493       0
lA.mridXtmonstdyXsex43442305:1:M   1.7988649 0.01591324 308 113.04202       0
lA.mridXtmonstdyXsex43829602:28:F  1.8753806 0.02642602 308  70.96721       0
```

```
lA.mridXtmonstdyXsex43829602:28:M  1.9009105 0.02522914 308  75.34584       0
lA.mridXtmonstdyXsex43829602:56:F  1.7180464 0.03035167 308  56.60468       0
lA.mridXtmonstdyXsex43829602:56:M  1.7241592 0.02944654 308  58.55218       0
lA.mridXtmonstdyXsex43829602:91:F  1.6810645 0.03137840 308  53.57394       0
lA.mridXtmonstdyXsex43829602:91:M  1.6790110 0.03110981 308  53.97047       0
lA.mridXtmonstdyXsexMOSER-1:NA:F   1.8972629 0.03640149 308  52.12047       0
lA.mridXtmonstdyXsexMOSER-1:NA:M   1.8353906 0.03717893 308  49.36641       0
lA.mridXtmonstdyXsexMOSER-2:NA:F   1.9910292 0.03117880 308  63.85843       0
lA.mridXtmonstdyXsexMOSER-2:NA:M   1.9660788 0.03070374 308  64.03385       0
lA.mridXtmonstdyXsexMOSER-3:NA:F   1.5499293 0.04011059 308  38.64140       0
lA.mridXtmonstdyXsexMOSER-3:NA:M   1.5464155 0.03876409 308  39.89299       0
lD.sexF                           -2.7823929 0.18024269 308 -15.43692       0
lD.sexM                           -2.6521757 0.17874061 308 -14.83813       0
lg                                 0.3327795 0.05575339 308   5.96878       0
ldT                                0.9081831 0.09320142 308   9.74431       0
 Correlation:
                                  lA.XX43442305:1:F lA.XX43442305:1:M
lA.mridXtmonstdyXsex43442305:1:M   0.251
lA.mridXtmonstdyXsex43829602:28:F  0.043             0.003
lA.mridXtmonstdyXsex43829602:28:M  0.007             0.051
lA.mridXtmonstdyXsex43829602:56:F  0.038             0.002
lA.mridXtmonstdyXsex43829602:56:M  0.006             0.044
lA.mridXtmonstdyXsex43829602:91:F  0.036             0.002
lA.mridXtmonstdyXsex43829602:91:M  0.007             0.038
lA.mridXtmonstdyXsexMOSER-1:NA:F   0.020            -0.018
lA.mridXtmonstdyXsexMOSER-1:NA:M  -0.019             0.026
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.033            -0.011
lA.mridXtmonstdyXsexMOSER-2:NA:M  -0.009             0.040
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.030             0.000
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.002             0.035
lD.sexF                           -0.048            -0.022
lD.sexM                           -0.020            -0.056
lg                                -0.141            -0.135
ldT                                0.457             0.398
                                  lA.XX43829602:28:F lA.XX43829602:28:M
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M  0.080
lA.mridXtmonstdyXsex43829602:56:F  0.119              0.069
lA.mridXtmonstdyXsex43829602:56:M  0.068              0.125
lA.mridXtmonstdyXsex43829602:91:F  0.115              0.067
lA.mridXtmonstdyXsex43829602:91:M  0.059              0.106
lA.mridXtmonstdyXsexMOSER-1:NA:F   0.055             -0.003
lA.mridXtmonstdyXsexMOSER-1:NA:M  -0.003              0.059
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.070              0.005
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.006              0.075
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.057              0.012
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.013              0.060
lD.sexF                           -0.127             -0.083
lD.sexM                           -0.081             -0.127
lg                                -0.212             -0.208
ldT                                0.036              0.041
                                  lA.XX43829602:56:F lA.XX43829602:56:M
lA.mridXtmonstdyXsex43442305:1:M
```

```
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M  0.060
lA.mridXtmonstdyXsex43829602:91:F  0.100              0.058
lA.mridXtmonstdyXsex43829602:91:M  0.052              0.091
lA.mridXtmonstdyXsexMOSER-1:NA:F   0.048             -0.003
lA.mridXtmonstdyXsexMOSER-1:NA:M  -0.003              0.051
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.061              0.004
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.005              0.064
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.050              0.011
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.011              0.051
lD.sexF                           -0.111             -0.072
lD.sexM                           -0.071             -0.109
lg                                -0.184             -0.178
ldT                                0.031              0.035
                                  lA.XX43829602:91:F lA.XX43829602:91:M
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M  0.050
lA.mridXtmonstdyXsexMOSER-1:NA:F   0.046              0.000
lA.mridXtmonstdyXsexMOSER-1:NA:M  -0.003              0.044
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.059              0.006
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.005              0.056
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.048              0.011
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.011              0.045
lD.sexF                           -0.107             -0.065
lD.sexM                           -0.069             -0.096
lg                                -0.178             -0.161
ldT                                0.030              0.032
                                  lA.XXMOSER-1:NA:F lA.XXMOSER-1:NA:M
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M   0.199
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.056            -0.008
lA.mridXtmonstdyXsexMOSER-2:NA:M  -0.008             0.060
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.045             0.000
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.001             0.047
lD.sexF                           -0.114            -0.070
lD.sexM                           -0.071            -0.113
lg                                -0.129            -0.121
ldT                               -0.008            -0.011
                                  lA.XXMOSER-2:NA:F lA.XXMOSER-2:NA:M
lA.mridXtmonstdyXsex43442305:1:M
```

```
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.225
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.057             0.007
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.007             0.059
lD.sexF                           -0.140            -0.091
lD.sexM                           -0.090            -0.139
lg                                -0.184            -0.179
ldT                                0.009             0.010
                                  lA.XXMOSER-3:NA:F lA.XXMOSER-3:NA:M lD.sxF
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F
lA.mridXtmonstdyXsexMOSER-2:NA:M
lA.mridXtmonstdyXsexMOSER-3:NA:F
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.234
lD.sexF                           -0.138            -0.103
lD.sexM                           -0.104            -0.135             0.968
lg                                -0.169            -0.163             0.457
ldT                                0.019             0.020             0.004
                                  lD.sxM lg
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F
lA.mridXtmonstdyXsexMOSER-2:NA:M
lA.mridXtmonstdyXsexMOSER-3:NA:F
lA.mridXtmonstdyXsexMOSER-3:NA:M
lD.sexF
lD.sexM
lg                                 0.438
ldT                                0.003 -0.221

Standardized Within-Group Residuals:
```

```
        Min          Q1         Med          Q3         Max
-2.54526582 -0.59764975 -0.04038248  0.49946329  4.10360335

Number of Observations: 330
Number of Groups: 5
```

That converges. Redo it, adding a weights term. After a day trying to get it to converge, it has proven impossible to fit the full weight function identified above. No weight function that includes `varPower()` seems to be able to converge. Fit a model that includes a separate standard deviation for each mrid X tmonstdy, and live with some additional variance heterogeneity. Change the parmeterization of `lD` to `lD` $\sim$ `sex`, to be able to read off the contrast between the sexes in the output. Also, change the parameterization of `ldT` to `ldT` $\sim$ `sex`, to make sure the timecourse is similar between the sexes.

```
> par <- fixed.effects(out6)
> start <- list(fixed = c(par[grep("^lD", names(par))][1], 0, par[grep("^lA",
+     names(par))], par["lg"], c(par["ldT"], 0)))
> idta$Cdose <- with(idta, factor(cut(dose, c(0, 0.375, Inf), include.lowest = TRUE)))
> out7 <- nlme(cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA,
+     lD = lD, lg = lg, ldT = ldT), data = idta, fixed = list(lD ~
+     sex, lA ~ mridXtmonstdyXsex - 1, lg ~ 1, ldT ~ sex), random = lD ~
+     1 | mrid, start = start, weights = varIdent(form = ~1 | mridXtmonstdy))
> summary(out7)$tTable
```

```
                                      Value  Std.Error  DF    t-value
lD.(Intercept)                    -3.0563231 0.18912037 307 -16.160730
lD.sexM                            0.1983882 0.05569039 307   3.562341
lA.mridXtmonstdyXsex43442305:1:F   1.8476044 0.01432227 307 129.002182
lA.mridXtmonstdyXsex43442305:1:M   1.8094277 0.01579220 307 114.577332
lA.mridXtmonstdyXsex43829602:28:F  1.9048354 0.03657006 307  52.087294
lA.mridXtmonstdyXsex43829602:28:M  1.9218253 0.03485002 307  55.145598
lA.mridXtmonstdyXsex43829602:56:F  1.7495266 0.03008301 307  58.156637
lA.mridXtmonstdyXsex43829602:56:M  1.7464284 0.02923146 307  59.744821
lA.mridXtmonstdyXsex43829602:91:F  1.7133225 0.02408140 307  71.147118
lA.mridXtmonstdyXsex43829602:91:M  1.7000342 0.02373352 307  71.630101
lA.mridXtmonstdyXsexMOSER-1:NA:F   1.9024821 0.04719707 307  40.309330
lA.mridXtmonstdyXsexMOSER-1:NA:M   1.8402314 0.04852158 307  37.926044
lA.mridXtmonstdyXsexMOSER-2:NA:F   2.0001751 0.03920522 307  51.018086
lA.mridXtmonstdyXsexMOSER-2:NA:M   1.9756267 0.03868704 307  51.066883
lA.mridXtmonstdyXsexMOSER-3:NA:F   1.5722623 0.02174734 307  72.296757
lA.mridXtmonstdyXsexMOSER-3:NA:M   1.5665815 0.02102514 307  74.509908
lg                                 0.1905402 0.05189759 307   3.671466
ldT.(Intercept)                    0.7876583 0.13357279 307   5.896847
ldT.sexM                           0.2336712 0.16156628 307   1.446287
                                       p-value
lD.(Intercept)                    6.145769e-43
lD.sexM                           4.259381e-04
lA.mridXtmonstdyXsex43442305:1:F  1.844181e-269
lA.mridXtmonstdyXsex43442305:1:M  5.681136e-254
lA.mridXtmonstdyXsex43829602:28:F 1.878924e-154
lA.mridXtmonstdyXsex43829602:28:M 2.507251e-161
lA.mridXtmonstdyXsex43829602:56:F 8.482146e-168
lA.mridXtmonstdyXsex43829602:56:M 4.236577e-171
lA.mridXtmonstdyXsex43829602:91:F 8.107893e-193
lA.mridXtmonstdyXsex43829602:91:M 1.142750e-193
lA.mridXtmonstdyXsexMOSER-1:NA:F  1.186940e-124
```

```
lA.mridXtmonstdyXsexMOSER-1:NA:M  7.001143e-118
lA.mridXtmonstdyXsexMOSER-2:NA:F  5.672550e-152
lA.mridXtmonstdyXsexMOSER-2:NA:M  4.362222e-152
lA.mridXtmonstdyXsexMOSER-3:NA:F  7.793162e-195
lA.mridXtmonstdyXsexMOSER-3:NA:M  1.223415e-198
lg                                 2.843564e-04
ldT.(Intercept)                    9.764920e-09
ldT.sexM                           1.491168e-01
```

Following Pinheiro and Bates, base inferences about model parameters on the t-tests. Those authors specifically say that we should not use likelihood ratio tests for fixed effects in either lme or nlme models; they are strongly anti-conservative. `lD` differs significantly between sexes (females are slightly but significantly more sensitive), but `ldT` does not. Refit the model accordingly, fitting a separate value of lD for females and males (rather than a contrast).

```
> par <- fixed.effects(out7)
> start <- list(fixed = c(c(par[grep("^lD.*ept\\)$", names(par))],
+     par[grep("^lD.*ept\\)$", names(par))] + par[grep("^lD.*sexM$",
+         names(par))]), par[grep("^lA", names(par))], par["lg"],
+     par[grep("^ldT.*ept\\)", names(par))]))
> out8 <- nlme(cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA,
+     lD = lD, lg = lg, ldT = ldT), data = idta, fixed = list(lD ~
+     sex - 1, lA ~ mridXtmonstdyXsex - 1, lg ~ 1, ldT ~ 1), random = lD ~
+     1 | mrid, start = start, weights = varIdent(form = ~1 | mridXtmonstdy))
> summary(out8)
```

```
Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ tcmfn2(dose, tmpstds, tmpstds, lA = lA, lD = lD, lg = lg,      ldT = ldT)
 Data: idta
       AIC      BIC    logLik
  557.4521 656.2285 -252.7260

Random effects:
 Formula: lD ~ 1 | mrid
        lD.(Intercept)  Residual
StdDev:      0.3470292 0.4741799

Variance function:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mridXtmonstdy
 Parameter estimates:
 43442305:1 43829602:28 43829602:56 43829602:91  MOSER-1:NA  MOSER-2:NA
  1.0000000   1.6315582   1.1324776   0.8330959   1.5191499   1.4505628
 MOSER-3:NA
  0.5720979
Fixed effects: list(lD ~ sex - 1, lA ~ mridXtmonstdyXsex - 1, lg ~ 1, ldT ~      1)
                                     Value  Std.Error  DF   t-value p-value
lD.sexF                         -3.0398759 0.18752370 308 -16.21062   0e+00
lD.sexM                         -2.8852383 0.18551375 308 -15.55269   0e+00
lA.mridXtmonstdyXsex43442305:1:F   1.8557584 0.01392604 308 133.25815   0e+00
lA.mridXtmonstdyXsex43442305:1:M   1.8001955 0.01399148 308 128.66365   0e+00
lA.mridXtmonstdyXsex43829602:28:F  1.9030961 0.03645013 308  52.21096   0e+00
lA.mridXtmonstdyXsex43829602:28:M  1.9250204 0.03472290 308  55.43950   0e+00
lA.mridXtmonstdyXsex43829602:56:F  1.7475220 0.03013827 308  57.98349   0e+00
lA.mridXtmonstdyXsex43829602:56:M  1.7496906 0.02925684 308  59.80451   0e+00
```

```
lA.mridXtmonstdyXsex43829602:91:F  1.7112948 0.02388968 308  71.63322   0e+00
lA.mridXtmonstdyXsex43829602:91:M  1.7032074 0.02352055 308  72.41358   0e+00
lA.mridXtmonstdyXsexMOSER-1:NA:F   1.9035129 0.04787717 308  39.75826   0e+00
lA.mridXtmonstdyXsexMOSER-1:NA:M   1.8359397 0.04896389 308  37.49579   0e+00
lA.mridXtmonstdyXsexMOSER-2:NA:F   2.0017733 0.03926501 308  50.98109   0e+00
lA.mridXtmonstdyXsexMOSER-2:NA:M   1.9743155 0.03856519 308  51.19424   0e+00
lA.mridXtmonstdyXsexMOSER-3:NA:F   1.5733632 0.02171926 308  72.44092   0e+00
lA.mridXtmonstdyXsexMOSER-3:NA:M   1.5660841 0.02093639 308  74.80202   0e+00
lg                                 0.1862172 0.05177998 308   3.59632   4e-04
ldT                                0.9067369 0.08283888 308  10.94579   0e+00
 Correlation:
                                  lD.sxF lD.sxM lA.XX43442305:1:F
lD.sexM                            0.968
lA.mridXtmonstdyXsex43442305:1:F  -0.038 -0.009
lA.mridXtmonstdyXsex43442305:1:M  -0.012 -0.047  0.259
lA.mridXtmonstdyXsex43829602:28:F -0.097 -0.065  0.027
lA.mridXtmonstdyXsex43829602:28:M -0.065 -0.097  0.000
lA.mridXtmonstdyXsex43829602:56:F -0.118 -0.078  0.033
lA.mridXtmonstdyXsex43829602:56:M -0.077 -0.115  0.000
lA.mridXtmonstdyXsex43829602:91:F -0.149 -0.099  0.042
lA.mridXtmonstdyXsex43829602:91:M -0.094 -0.135  0.003
lA.mridXtmonstdyXsexMOSER-1:NA:F  -0.100 -0.069  0.014
lA.mridXtmonstdyXsexMOSER-1:NA:M  -0.068 -0.100 -0.015
lA.mridXtmonstdyXsexMOSER-2:NA:F  -0.120 -0.083  0.022
lA.mridXtmonstdyXsexMOSER-2:NA:M  -0.083 -0.120 -0.011
lA.mridXtmonstdyXsexMOSER-3:NA:F  -0.198 -0.133  0.045
lA.mridXtmonstdyXsexMOSER-3:NA:M  -0.134 -0.192 -0.009
lg                                 0.477  0.454 -0.115
ldT                                0.021  0.019  0.469
                                  lA.XX43442305:1:M lA.XX43829602:28:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F -0.002
lA.mridXtmonstdyXsex43829602:28:M  0.035             0.046
lA.mridXtmonstdyXsex43829602:56:F -0.002             0.092
lA.mridXtmonstdyXsex43829602:56:M  0.041             0.055
lA.mridXtmonstdyXsex43829602:91:F -0.003             0.116
lA.mridXtmonstdyXsex43829602:91:M  0.047             0.064
lA.mridXtmonstdyXsexMOSER-1:NA:F  -0.014             0.027
lA.mridXtmonstdyXsexMOSER-1:NA:M   0.019            -0.003
lA.mridXtmonstdyXsexMOSER-2:NA:F  -0.013             0.036
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.028             0.001
lA.mridXtmonstdyXsexMOSER-3:NA:F  -0.012             0.075
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.055             0.016
lg                                -0.110            -0.158
ldT                                0.406             0.019
                                  lA.XX43829602:28:M lA.XX43829602:56:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F  0.056
```

```
lA.mridXtmonstdyXsex43829602:56:M  0.097              0.067
lA.mridXtmonstdyXsex43829602:91:F  0.071              0.140
lA.mridXtmonstdyXsex43829602:91:M  0.109              0.077
lA.mridXtmonstdyXsexMOSER-1:NA:F  -0.003              0.033
lA.mridXtmonstdyXsexMOSER-1:NA:M   0.031             -0.003
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.000              0.043
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.040              0.002
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.014              0.090
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.079              0.020
lg                                -0.152             -0.192
ldT                                0.023              0.023
                                  lA.XX43829602:56:M lA.XX43829602:91:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F  0.084
lA.mridXtmonstdyXsex43829602:91:M  0.129              0.097
lA.mridXtmonstdyXsexMOSER-1:NA:F  -0.004              0.041
lA.mridXtmonstdyXsexMOSER-1:NA:M   0.036             -0.004
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.000              0.055
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.048              0.002
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.016              0.114
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.093              0.025
lg                                -0.180             -0.242
ldT                                0.027              0.029
                                  lA.XX43829602:91:M lA.XXMOSER-1:NA:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F  -0.003
lA.mridXtmonstdyXsexMOSER-1:NA:M   0.041              0.212
lA.mridXtmonstdyXsexMOSER-2:NA:F   0.002              0.029
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.054             -0.006
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.024              0.053
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.108             -0.004
lg                                -0.218             -0.081
ldT                                0.033             -0.006
                                  lA.XXMOSER-1:NA:M lA.XXMOSER-2:NA:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
```

```
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F  -0.006
lA.mridXtmonstdyXsexMOSER-2:NA:M   0.033             0.242
lA.mridXtmonstdyXsexMOSER-3:NA:F  -0.006             0.070
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.057             0.002
lg                                -0.076            -0.121
ldT                               -0.008             0.002
                                  lA.XXMOSER-2:NA:M lA.XXMOSER-3:NA:F
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F
lA.mridXtmonstdyXsexMOSER-2:NA:M
lA.mridXtmonstdyXsexMOSER-3:NA:F   0.001
lA.mridXtmonstdyXsexMOSER-3:NA:M   0.075             0.259
lg                                -0.118            -0.299
ldT                                0.002             0.017
                                  lA.XXMOSER-3:NA:M lg
lD.sexM
lA.mridXtmonstdyXsex43442305:1:F
lA.mridXtmonstdyXsex43442305:1:M
lA.mridXtmonstdyXsex43829602:28:F
lA.mridXtmonstdyXsex43829602:28:M
lA.mridXtmonstdyXsex43829602:56:F
lA.mridXtmonstdyXsex43829602:56:M
lA.mridXtmonstdyXsex43829602:91:F
lA.mridXtmonstdyXsex43829602:91:M
lA.mridXtmonstdyXsexMOSER-1:NA:F
lA.mridXtmonstdyXsexMOSER-1:NA:M
lA.mridXtmonstdyXsexMOSER-2:NA:F
lA.mridXtmonstdyXsexMOSER-2:NA:M
lA.mridXtmonstdyXsexMOSER-3:NA:F
lA.mridXtmonstdyXsexMOSER-3:NA:M
lg                                -0.285
ldT                                0.019            -0.172

Standardized Within-Group Residuals:
        Min          Q1         Med          Q3         Max
-2.69628667 -0.59999061 -0.05519918  0.53354565  3.69501023

Number of Observations: 330
Number of Groups: 5
```

```
> RatBrainFit <- out8
> save.image(file = "RatBrainDR.RData")
```

It seemed reasonable to try to use the simplified model for these data, to try to use the more elaborate variance model. The following text show the steps to do this, but, since the simplified model does not help, they are not shown with output, here.

```
> dta$Cdose <- cut(dta$dose, breaks = c(0, 0.125, 0.375, Inf),
+     include.lowest = TRUE)
> start <- with(dta, c(log(startlA), -4, rep(log(0.05), nlevels(mridXsex)),
+     0, rep(log(1), nlevels(Cdose:sex))))
> initfile <- paste("initvals-brain-DR-6.RData", sep = "")
> if (!file.exists(initfile)) {
+     formals(tcmfn4)$delta <- with(dta, min(tmpstds[!is.na(tmpstds) &
+         tmpstds > 0]))
+     out9 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg,
+             lTr = lTr), data = dta, params = list(lA ~ mridXtmonstdyXsex -
+         1, tz ~ 1, lD ~ mridXsex - 1, lg ~ 1, lTr ~ Cdose:sex -
+         1), start = start, weights = varComb(varIdent(form = ~1 |
+         mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out9, file = initfile)
+ } else load(initfile)
```

As with `tcmfn2()`, there is inadequate data to estimate `tz`; just set it to -10, as before.

```
> initfile <- paste("initvals-brain-DR-7.RData", sep = "")
> if (!file.exists(initfile)) {
+     formals(tcmfn4)$delta <- with(dta, min(tmpstds[!is.na(tmpstds) &
+         tmpstds > 0]))
+     formals(tcmfn4)$tz <- -10
+     start <- with(dta, c(log(startlA), rep(log(0.05), nlevels(mridXsex)),
+         0, rep(log(1), nlevels(Cdose:sex))))
+     out10 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmfn4(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr),
+         data = dta, params = list(lA ~ mridXtmonstdyXsex - 1,
+             lD ~ mridXsex - 1, lg ~ 1, lTr ~ Cdose:sex - 1),
+         start = start, weights = varComb(varIdent(form = ~1 |
+             mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out10, file = initfile)
+ } else load(initfile)
```

Just as with the more complex model, we cannot really estimate the recovery half-lives in the lowest dose category. Build a wrapper for tcmfn4 that sets lTr to -5 if dose < 0.125, and zeros out the corresponding part of the gradient matrix.

```
> tcmalt <- function(x, Tpd, lA, lD, lg, lTr) {
+     lTr <- ifelse(x < 0.125, -30, lTr)
+     out <- tcmfn4(x, Tpd, lA, tz = -10, lD, lg, lTr)
+     grad <- attr(out, "gradient")
+     grad[, "lTr"] <- ifelse(x < 0.125, 0, grad[, "lTr"])
+     attr(out, "gradient") <- grad
+     out
+ }
> dta$Cdose <- cut(dta$dose, breaks = c(0, 0.375, Inf), include.lowest = TRUE)
> initfile <- paste("initvals-brain-DR-8.RData", sep = "")
```

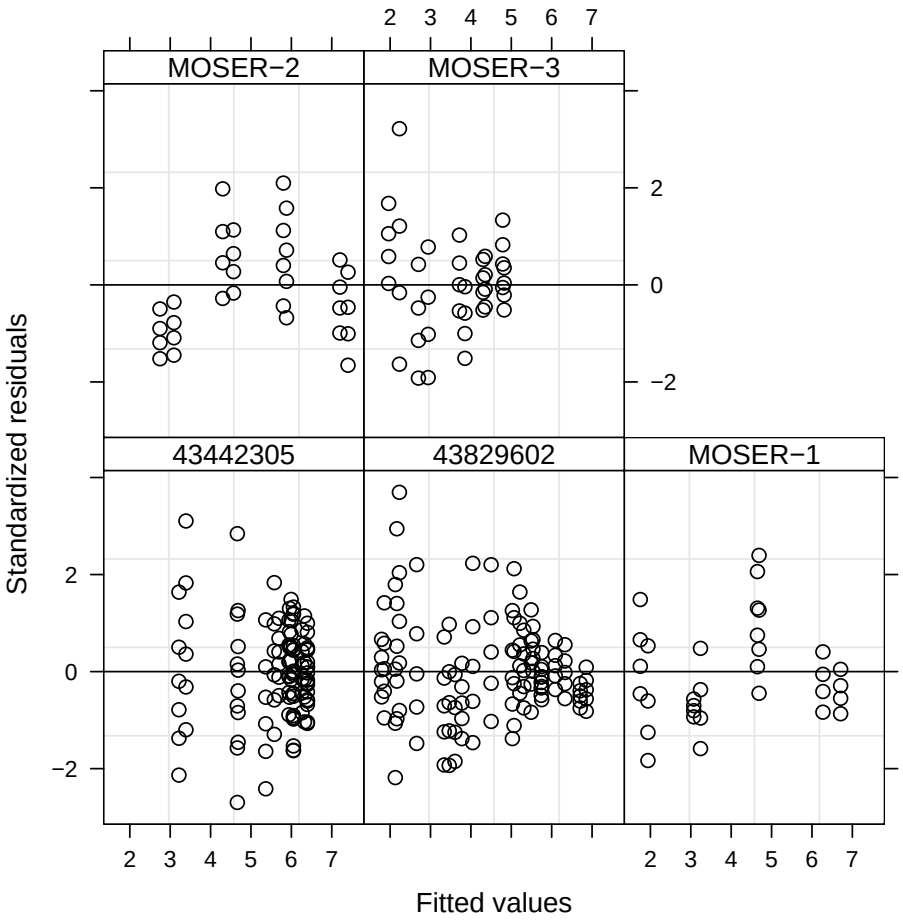
```
> if (!file.exists(initfile)) {
+     start <- with(dta, c(log(startlA), rep(log(0.05), nlevels(mridXsex)),
+         0, rep(log(1), nlevels(Cdose:sex))))
+     out11 <- GetInitialValues(cbind(resp = cheact, sd = sd, n = n) ~
+         tcmalt(dose, tmpstds, lA = lA, lD = lD, lg = lg, lTr = lTr),
+         data = dta, params = list(lA ~ mridXtmonstdyXsex - 1,
+             lD ~ mridXsex - 1, lg ~ 1, lTr ~ Cdose:sex - 1),
+         start = start, weights = varComb(varIdent(form = ~1 |
+             mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
+     save(out11, file = initfile)
+ } else load(initfile)
> idta <- out11$data
> idta$mrid <- factor(with(idta, sapply(strsplit(as.character(mridXsex),
+     ":"), function(x) x[1])))
> par <- out11$start$beta
> start <- list(fixed = c(par[grep("^lA", names(par))], c(mean(par[grep("^lD",
+     names(par))]), 0), par["lg"], par[grep("^lTr", names(par))]))
> out12 <- nlme(cheact ~ tcmalt(dose, tmpstds, lA = lA, lD = lD,
+     lg = lg, lTr = lTr), data = idta, fixed = list(lA ~ mridXtmonstdyXsex -
+     1, lD ~ sex, lg ~ 1, lTr ~ Cdose:sex - 1), random = lD ~
+     1 | mrid, start = start, weights = varComb(varIdent(form = ~1 |
+     mridXtmonstdy), varPower(form = ~fitted(.) | mridXtmonstdy)))
> out12
```

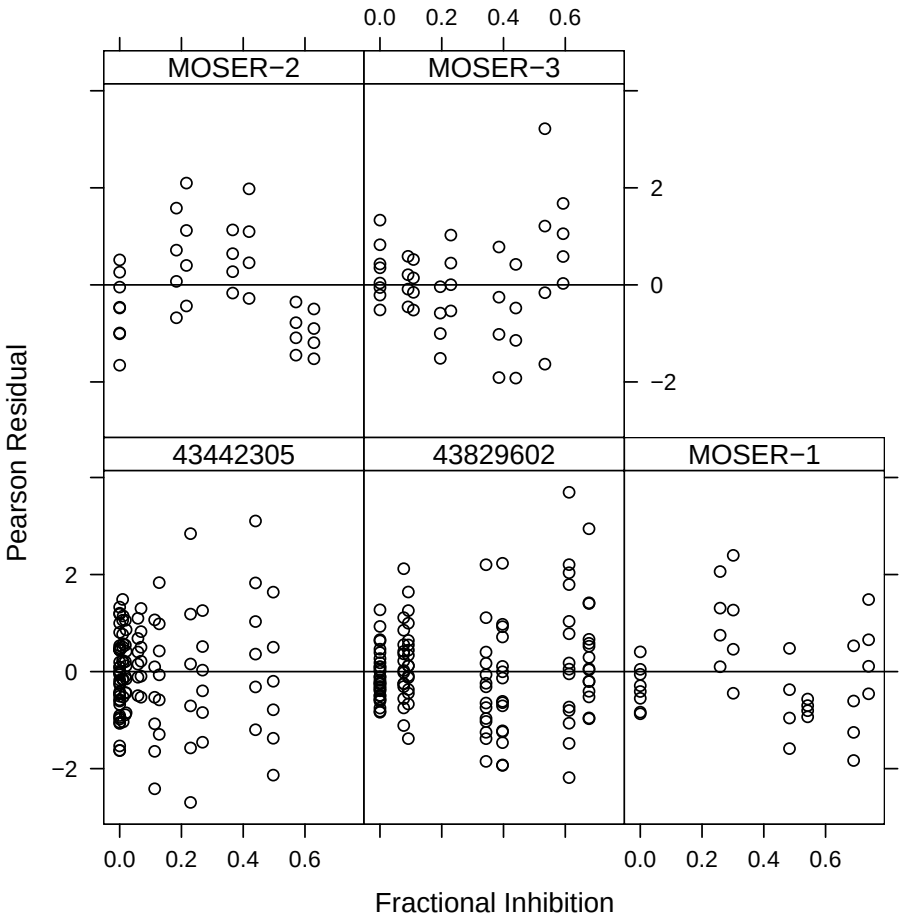
This fails with the same error in the PNLS step:

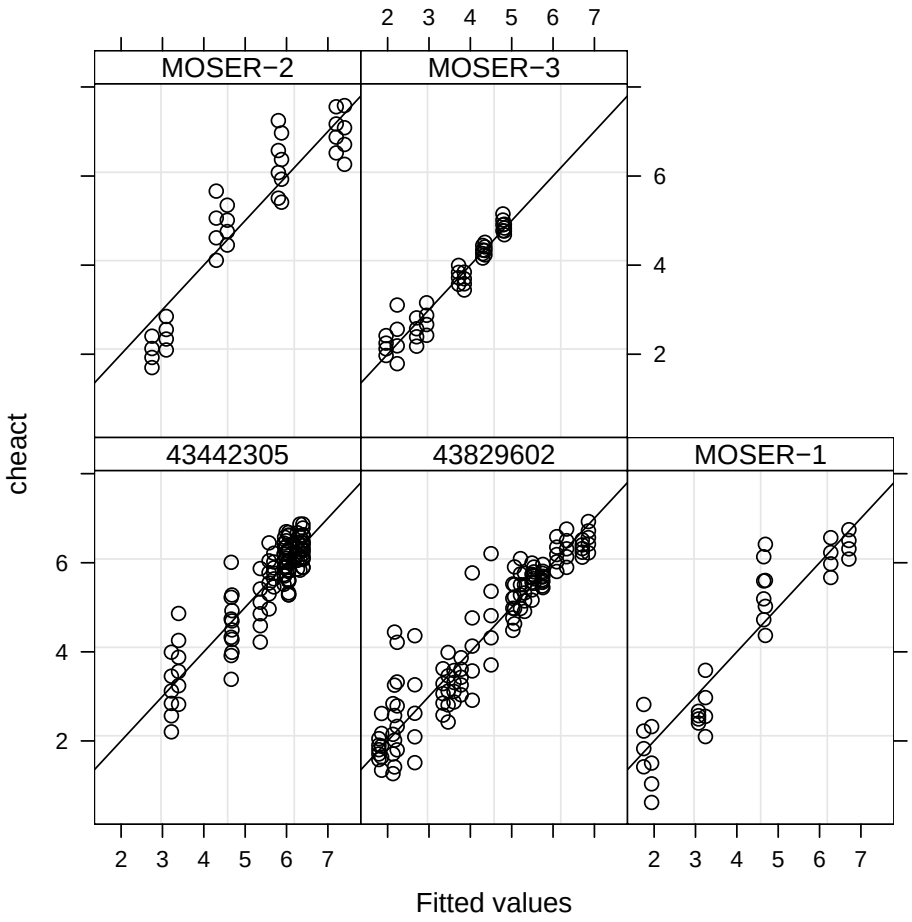
```
Error in nlme.formula(cheact ~ tcmalt(dose, tmpstds, lA = lA, lD = lD,  :
      Step halving factor reduced below minimum in PNLS step
```

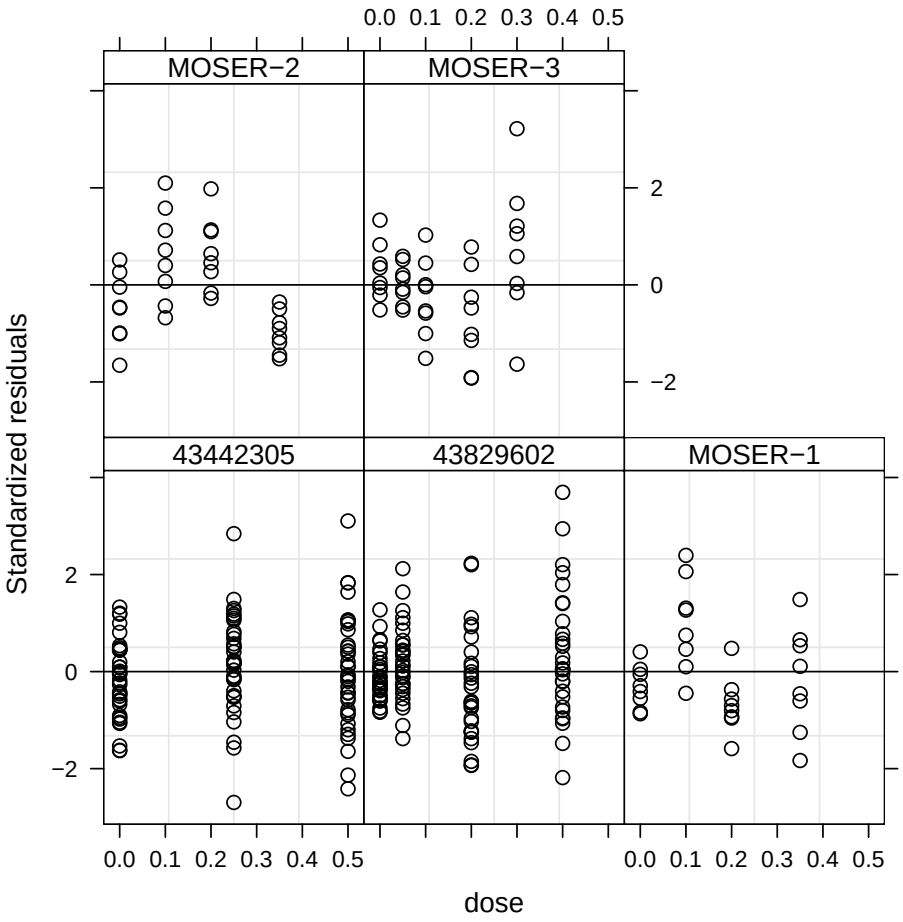
So, use the answer from out8.

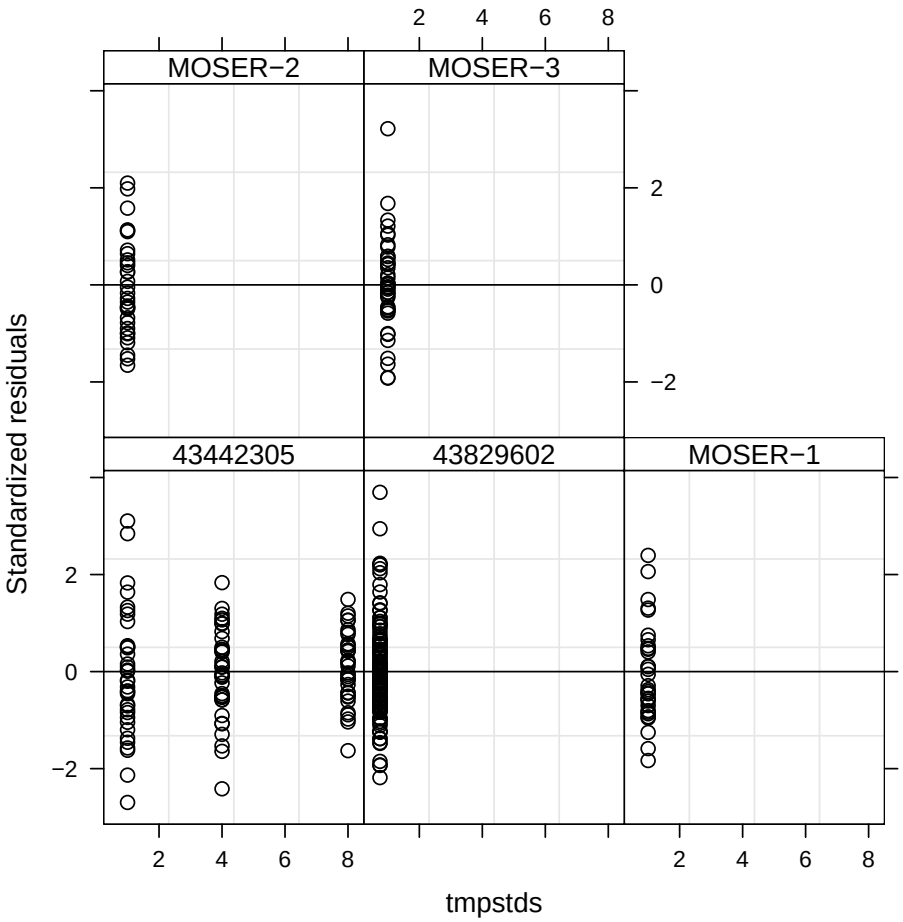
Diagnostic graphics for the model in out8:

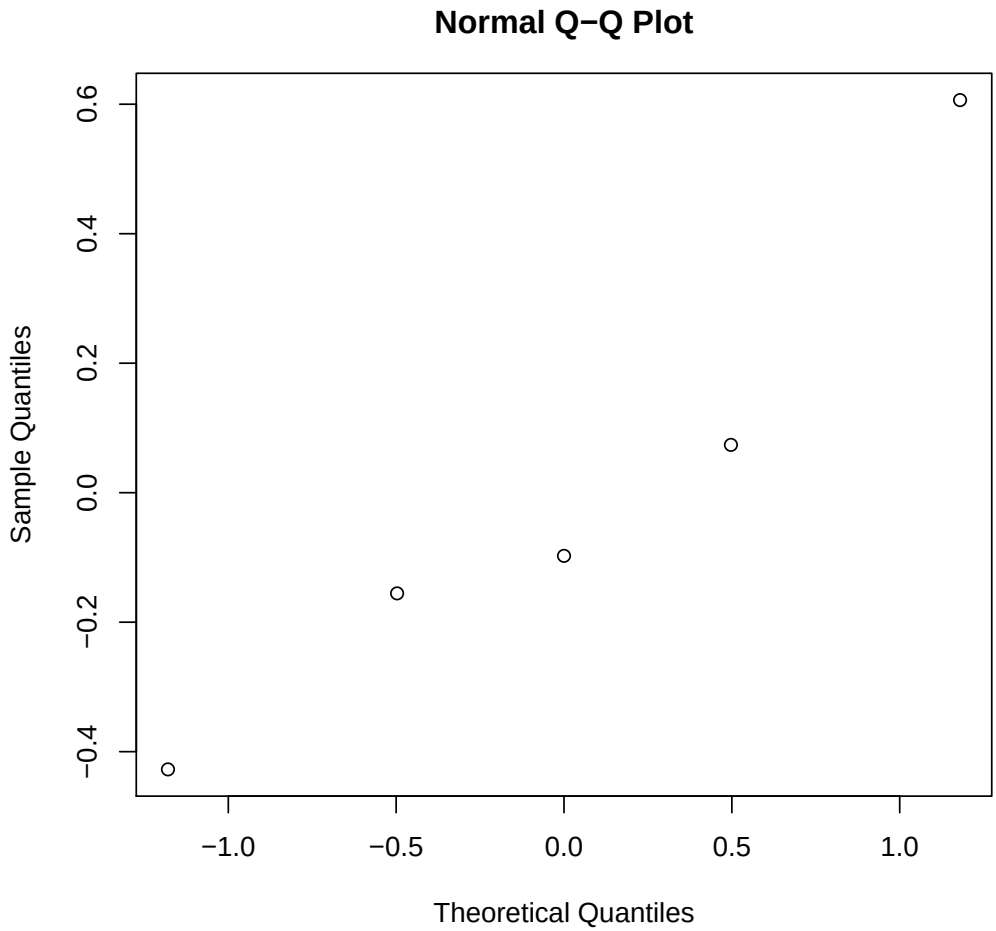

MOSER−2
MOSER−3
43442305
43829602
MOSER−1
Standardized residuals
Fitted values
2
3
4
5
6
7
0
−2


MOSER−2
MOSER−3
43442305
43829602
MOSER−1
Pearson Residual
Fractional Inhibition
0.0
0.2
0.4
0.6
2
0
−2


MOSER−2
MOSER−3
43442305
43829602
MOSER−1
cheact
Fitted values
2
3
4
5
6
7


MOSER−2
MOSER−3
43442305
43829602
MOSER−1
Standardized residuals
dose
0.0 0.1 0.2 0.3 0.4 0.5
2
0
−2


MOSER−2
MOSER−3
43442305
43829602
MOSER−1
Standardized residuals
tmpstds
2
4
6
8
0
−2



These give the following estimates for benchmark dose and recovery half life. These are conditional on the assumption that the time to peak effect is a half hour. Estimates of *lD* and *lTr*, with standard errors, their covariance matrix, 95% confidence intervals for BMD, recovery half-life at the lower dose, and time to peak effect. Time units are hours, and dose units are mg/kg. Since we estimated a separate BMD for males and females, we do calculations for each sex separately, females first:

```
> par <- fixed.effects(out8)[c("lD.sexF", "lD.sexM", "ldT")]
> Var <- out8$varFix[c("lD.sexF", "lD.sexM", "ldT"), c("lD.sexF",
+     "lD.sexM", "ldT")]
> par <- c(par, lTmax = log(0.5))
> Var <- rbind(cbind(Var, lTmax = c(0, 0, 0)), lTmax = c(0, 0,
+     0, 0))
> tmpF <- lTrest.se(par[1], par[3], par[4], Var[c("lD.sexF", "ldT",
+     "lTmax"), c("lD.sexF", "ldT", "lTmax")])
> tTableF <- cbind(Est = tmpF$Est, SE = sqrt(diag(tmpF$Cov)))
> rownames(tTableF) <- c("lD", "lTr", "lTmax")
> tTableF
```

```
             Est        SE
lD    -3.0398759 0.1823377
lTr    0.4220281 0.1372121
lTmax -0.6931472 0.0000000
```

```
> dimnames(tmpF$Cov) <- list(c("lD", "ldT", "lTmax"), c("lD", "ldT",
+     "lTmax"))
> tmpF$Cov

                lD          ldT lTmax
lD    0.0332470407 0.0005129964     0
ldT   0.0005129964 0.0188271502     0
lTmax 0.0000000000 0.0000000000     0

> cov2cor(tmpF$Cov)

              lD        ldT lTmax
lD    1.00000000 0.02050433   NaN
ldT   0.02050433 1.00000000   NaN
lTmax        NaN        NaN     1

> FCIs <- matrix(0, nrow = 3, ncol = 3, dimnames = list(c("BMD",
+     "Tr", "Tmax"), c("0.025%", "Estimate", "97.5%")))
> FCIs[, 2] <- exp(tmpF$Est)
> FCIs[, 1] <- exp(tmpF$Est + qnorm(0.025) * sqrt(diag(tmpF$Cov)))
> FCIs[, 3] <- exp(tmpF$Est + qnorm(0.975) * sqrt(diag(tmpF$Cov)))
> FBMDL <- exp(tmpF$Est[1] + qnorm(0.05) * sqrt(diag(tmpF$Cov)[1]))
> FCIs

         0.025%   Estimate      97.5%
BMD  0.03346513 0.04784083 0.06839192
Tr   1.16543854 1.52505145 1.99562813
Tmax 0.50000000 0.50000000 0.50000000
```

Now, males:

```
> tmpM <- lTrest.se(par[2], par[3], par[4], Var[c("lD.sexF", "ldT",
+     "lTmax"), c("lD.sexF", "ldT", "lTmax")])
> tTableM <- cbind(Est = tmpM$Est, SE = sqrt(diag(tmpM$Cov)))
> rownames(tTableM) <- c("lD", "lTr", "lTmax")
> tTableM

             Est        SE
lD    -2.8852383 0.1823377
lTr    0.4220281 0.1372121
lTmax -0.6931472 0.0000000

> dimnames(tmpM$Cov) <- list(c("lD", "ldT", "lTmax"), c("lD", "ldT",
+     "lTmax"))
> tmpM$Cov

                lD          ldT lTmax
lD    0.0332470407 0.0005129964     0
ldT   0.0005129964 0.0188271502     0
lTmax 0.0000000000 0.0000000000     0

> cov2cor(tmpM$Cov)

              lD        ldT lTmax
lD    1.00000000 0.02050433   NaN
ldT   0.02050433 1.00000000   NaN
lTmax        NaN        NaN     1
```

```
> MCIs <- matrix(0, nrow = 3, ncol = 3, dimnames = list(c("BMD",
+     "Tr", "Tmax"), c("0.025%", "Estimate", "97.5%")))
> MCIs[, 2] <- exp(tmpM$Est)
> MCIs[, 1] <- exp(tmpM$Est + qnorm(0.025) * sqrt(diag(tmpM$Cov)))
> MCIs[, 3] <- exp(tmpM$Est + qnorm(0.975) * sqrt(diag(tmpM$Cov)))
> MBMDL <- exp(tmpF$Est[1] + qnorm(0.05) * sqrt(diag(tmpF$Cov)[1]))
> MCIs
```

```
         0.025%   Estimate      97.5%
BMD  0.03906167 0.05584148 0.07982944
Tr   1.16543854 1.52505145 1.99562813
Tmax 0.50000000 0.50000000 0.50000000
```

2 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] "43442305" "43829602" "MOSER-1"  "MOSER-2"  "MOSER-3"`

Female `lD` -3.0398759085281

standard error of Female `lD` 0.182337710516545

Male `lD` -2.88523830349363

standard error of Male `lD` 0.182337710516545

Female BMD (95% CI) 0.0478408257643567 (0.0334651307903611,0.0683919218530218)

Female BMDL, the one-sided lower 95% CL 0.0354442317972809

Male BMD (95% CI) 0.0558414807308328 (0.0390616680696393,0.0798294369982537)

Male BMDL, the one-sided lower 95% CL 0.0354442317972809

`lTr` 0.422028149223185

standard error of `lTr` 0.137212063043129

Recovery Half-life (95% CI) 1.52505145309280 (1.16543854238180, 1.99562812623931)

Time to Peak Effect (95% CI) Assumed to be 0.5.

Save everything:

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

Save the results for incorporating into a database:

```
> aldicarb.oral.brain <- list(mrid = levels(dta$mrid), species = "RAT",
+     BMDs = list(female = list(lD = tTableF[1, 1], lD.se = tTableF[1,
+         2], BMD = FCIs[1, 2], BMD.CI = FCIs[1, c(1, 3)], BMDL = FBMDL),
+         male = list(lD = tTableM[1, 1], lD.se = tTableM[1, 2],
+             BMD = MCIs[1, 2], BMD.CI = MCIs[1, c(1, 3)], BMDL = MBMDL)),
+     HalfLives = list(lTr = tTableF[2, 1], lTr.se = tTableF[2,
```

```
+         2], Tr = FCIs[2, 2], Tr.CI = FCIs[2, c(1, 3)]), Tmax.assumed = FCIs[3,
+         2])
> save(aldicarb.oral.brain, file = file.path("..", "..", "01Summaries",
+     "aldicarb.oral.brain.RData"))
```