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

June 30, 2005

1 Preamble

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

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

```
> library(CarbamateData)

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

> 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 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
+ }
```

```
> 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
----------------------------------------
```

2 Creating Working Datasets

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

We'll create two datasets: one aggregated by dose, sex, tmonstdy, tmpstds, and mrid (dta), and the other individual (idta). The aggregated dataset is for guessing initial parameter values, and the individual dataset for model fitting. Because several of these studies are repeated measures studies, and because apparently the variance among animals is relatively large, we won't be able to identify a variance model without fitting the individual animal data.

We need two parallel datasets: one an individual dataset, and one aggregated by MRID X sex X time post dose X time on study X dose. We have some datasets in only the aggregated form, but we have all datasets that use a repeated measures design in both forms. Since there are several repeated measures study on this endpoint, all the analysis will be carried out using the individual datasets and linear or nonlinear mixed effects models. The aggregated datasets are used for plotting and getting initial values for the nonlinear fitting functions. The data used for this DR model are in wrkdata[["AggData"]], wrkdata[["repeated_acute"]] and wrkdata[["repeated_subchronic"]] The following MRIDs will be used: (drop 43829601: these seem to be data from pregnant/lactating females).

```
> MRIDSforRBCDR <- list(Agg = as.character(c(43442305)), acute = as.character(c(43442302,
+     45079705)), subchronic = as.character(c(43829602)))
```

The next bunch of code extracts the data we want, cleans it up a bit, changes variable names so they are consistent with each other, then creates the individual dataset from original aggregated, or an aggregated dataset from an original individual dataset, and stacks all the individual parts together to create two data sets: dta - the complete aggregated dataset, and idta, the complete individual dataset.

2.1 Processing the Aggregated Data

We only need to keep the variables:

```
> KeepVars <- c("mrid", "cheact", "n", "dose", "tmpstds", "tmonstdy",
+     "sex", "sd")
```

We need to select out the records for red blood cells of animals dosed via gavage. Drop records with missing values for cheact, and any The one aggregated study, 43442305, used multiple chemicals: aldicarb, aldicarb sulfoxide, and aldicarb sulfone. Drop everything but the active ingredient. However, the control group in that study used NA to code the control chemical, so we need to retain those records. Finally, make sure we have a value for sd for records with n greater than 1.

```
> dta <- CleanUp(subset(wrkdata[["AggData"]], mrid %in% MRIDSforRBCDR[["Agg"]] &
+     sctn %in% "RBC" & dsmtd == "GAVAGE" & !is.na(cheact) & (n ==
+     1 | !is.na(sd)) & (is.na(ta) | ta %in% c("AI")), select = KeepVars))
```

Create an "individual" dataset using PhonyDF. This works because all the fitting methods used here depend on the data only through group means and standard deviations, when there are no repeated measures.

```
> idta <- PhonyDF(dta$dose, dta$n, dta$cheact, dta$sd, "dose",
+     "cheact", dta[, c("mrid", "tmpstds", "tmonstdy", "sex")])
```

add an id variable

```
> idta$id <- factor(paste(as.character(idta$mrid), seq(along = idta$dose),
+     sep = ":"))
```

2.2 Repeated Acute Data

That finishes the processing of the aggregated data. Now the studies that use repeated measures designs for an acute time scale. These are time course studies. Here, time means tmpstds, and there is no timeonstdy.

```
> tmp <- subset(wrkdata[["repeated_acute"]], !is.na(rbc) & mrid %in%
+     MRIDSforRBCDR[["acute"]], select = c("mrid", "sex", "dose_mgkg",
+     "rbc", "time", "id"))
```

It may be easier if all ids are unique, so paste the mrid number on the id as a prefix.

```
> tmp$id <- factor(paste(as.character(tmp$mrid), as.character(tmp$id),
+     sep = ":"))
```

Rename some variables.

```
> nm <- names(tmp)
> nm[grep("dose", nm)] <- "dose"
> nm[grep("rbc", nm)] <- "cheact"
> nm[grep("time", nm)] <- "tmpstds"
> names(tmp) <- nm
> tmp$tmonstdy <- rep(1, nrow(tmp))
```

make an aggregated dataset

```
> atmp <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     mean)
```

aggregate() returns the aggregated variable names as "x". Rename "x" to "cheact".

```
> names(atmp)[grep("^x", names(atmp))] <- "cheact"
```

aggregate changes all its grouping variables to character; convert dose, tmpstds, and tmonstdy back to numeric.

```
> atmp$dose <- as.numeric(levels(atmp$dose))[atmp$dose]
> atmp$tmpstds <- as.numeric(levels(atmp$tmpstds))[atmp$tmpstds]
> atmp$tmonstdy <- as.numeric(levels(atmp$tmonstdy))[atmp$tmonstdy]
```

```
> atmp$sd <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     function(z) if (length(z) > 1) sd(z) else 0)$x
```

and sample sizes

```
> atmp$n <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     length)$x
```

Combine these new datasets with the old ones:

```
> dta <- rbind(dta, atmp[, names(dta)])
> idta <- rbind(idta, tmp[, names(idta)])
```

2.3 Repeated Subchronic Data

Finally, the study that uses repeated measures designs for a subchronic time scale.

```
> tmp <- subset(wrkdata[["repeated_subchronic"]], !is.na(rbc) &
+     mrid %in% MRIDSforRBCDR[["subchronic"]], select = c("mrid",
+     "sex", "dose_mgkg", "rbc", "time", "id"))
> tmp$id <- factor(paste(as.character(tmp$mrid), as.character(tmp$id),
+     sep = ":"))
```

Rename some variables for consistency with the other datasets:

```
> nm <- names(tmp)
> nm[grep("dose", nm)] <- "dose"
> nm[grep("rbc", nm)] <- "cheact"
> nm[grep("time", nm)] <- "tmonstdy"
> names(tmp) <- nm
```

In this study, all measurements were taken 0.75 hours after dosing (per email from Elissa Reaves):

```
> tmp$tmpstds <- rep(0.75, nrow(tmp))
```

Create the aggregated dataset as for the acute dataset, above:

```
> atmp <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     mean)
> names(atmp)[grep("^x", names(atmp))] <- "cheact"
> atmp$dose <- as.numeric(levels(atmp$dose))[atmp$dose]
> atmp$tmpstds <- as.numeric(levels(atmp$tmpstds))[atmp$tmpstds]
> atmp$tmonstdy <- as.numeric(levels(atmp$tmonstdy))[atmp$tmonstdy]
> atmp$sd <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     function(z) if (length(z) > 1) sd(z) else 0)$x
> atmp$n <- aggregate(tmp[, "cheact"], list(mrid = tmp$mrid, dose = tmp$dose,
+     sex = tmp$sex, tmpstds = tmp$tmpstds, tmonstdy = tmp$tmonstdy),
+     length)$x
```

Combine these new datasets

```
> dta <- CleanUp(rbind(dta, atmp[, names(dta)]))
> idta <- CleanUp(rbind(idta, tmp[, names(idta)]))
```

2.4 Creating New Classification Variables

We need several classification variables, or factors, to identify different groups. It would be natural to create these using the modeling terms, such as mrid : factor(tmonstdy) : sex, but the nonlinear modeling functions do not tolerate missing levels. Thus, we work with one dimentional factors

The analysis described below needs a classification variable to identify the unique groups. Call this cellmeans:

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

This next variable, modcellmeans is just cellmeans with all the "0" dose groups and negative time groups set to "Control".

```
> lvls <- sapply(strsplit(levels(idta$cellmeans), ":"), function(x) {
+     if (as.numeric(x[2]) < 0 || as.numeric(x[4]) == 0)
+         "Control"
+     else paste(x, collapse = ":")
+ })
> idta$modcellmeans <- idta$cellmeans
> levels(idta$modcellmeans) <- lvls
> idta$modcellmeans <- relevel(idta$modcellmeans, "Control")
```

Next, in the analysis in which modcellmeans gets used, "Control" never gets used; lump it with the next level down

```
> lvls <- levels(idta$modcellmeans)
> lvls[1] <- lvls[2]
> levels(idta$modcellmeans) <- lvls
```

Repeat all the above for dta:

```
> lvls <- sapply(strsplit(levels(dta$cellmeans), ":"), function(x) {
+     if (as.numeric(x[2]) < 0 || as.numeric(x[4]) == 0)
+         "Control"
+     else paste(x, collapse = ":")
+ })
> dta$modcellmeans <- dta$cellmeans
> levels(dta$modcellmeans) <- lvls
> dta$modcellmeans <- relevel(dta$modcellmeans, "Control")
> lvls <- levels(dta$modcellmeans)
> lvls[1] <- lvls[2]
> levels(dta$modcellmeans) <- lvls
```

A factor that makes a separate group for each sex within each mrid:

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

This sets up a separate group for every sex and time on study in each mrid

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

Summary of the relevant variables in this dataset:

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

idta$mrid: 43442305
      dose          cheact             mrid        tmpstds         tmonstdy
 Min.   :0.00   Min.   : 158.9   43442305:108   Min.   :1.000   Min.   :1
 1st Qu.:0.00   1st Qu.: 421.1   43442302:  0   1st Qu.:1.000   1st Qu.:1
 Median :0.25   Median : 731.0   45079705:  0   Median :4.000   Median :1
 Mean   :0.25   Mean   : 687.5   43829602:  0   Mean   :4.333   Mean   :1
 3rd Qu.:0.50   3rd Qu.: 888.9                  3rd Qu.:8.000   3rd Qu.:1
 Max.   :0.50   Max.   :1325.4                  Max.   :8.000   Max.   :1

 sex               id                    cellmeans               modcellmeans
 F:54   43442305:1  :  1   43442305:1:1:0.25:F: 6   43442302:1:0:0.1:F :36
 M:54   43442305:10 :  1   43442305:1:1:0.25:M: 6   43442305:1:1:0.25:F: 6
        43442305:100:  1   43442305:1:1:0.5:F : 6   43442305:1:1:0.25:M: 6
        43442305:101:  1   43442305:1:1:0.5:M : 6   43442305:1:1:0.5:F : 6
        43442305:102:  1   43442305:1:1:0:F   : 6   43442305:1:1:0.5:M : 6
        43442305:103:  1   43442305:1:1:0:M   : 6   43442305:1:4:0.25:F: 6
        (Other)     :102   (Other)            :72   (Other)            :42
      mridbysex     mridXtmonstdyXsex
 43442302:F: 0   43442305:1:F:54
 43442302:M: 0   43442305:1:M:54
 43442305:F:54   43442302:1:F: 0
 43442305:M:54   43442302:1:M: 0
 43829602:F: 0   43829602:0:F: 0
 43829602:M: 0   43829602:0:M: 0
 45079705:M: 0   (Other)     : 0
------------------------------------------------------------
idta$mrid: 43442302
      dose            cheact            mrid        tmpstds          tmonstdy
 Min.   :0.0000   Min.   : 63.0   43442305:  0   Min.   : 0.000   Min.   :1
 1st Qu.:0.0000   1st Qu.:233.2   43442302:148   1st Qu.: 0.500   1st Qu.:1
 Median :0.1000   Median :385.0   45079705:  0   Median : 2.000   Median :1
 Mean   :0.2574   Mean   :383.3   43829602:  0   Mean   : 5.588   Mean   :1
 3rd Qu.:0.4000   3rd Qu.:512.0                  3rd Qu.: 8.000   3rd Qu.:1
 Max.   :0.6000   Max.   :806.0                  Max.   :24.000   Max.   :1

 sex                id                    cellmeans               modcellmeans
 F:74   43442302:1005:  7   43442302:1:0:0.1:F:  3   43442302:1:0:0.1:F:42
 M:74   43442302:1006:  7   43442302:1:0:0.1:M:  3   43442302:1:0:0.1:M: 3
        43442302:1506:  7   43442302:1:0:0.4:F:  3   43442302:1:0:0.4:F: 3
        43442302:2004:  7   43442302:1:0:0.4:M:  3   43442302:1:0:0.4:M: 3
        43442302:2005:  7   43442302:1:0:0.6:F:  3   43442302:1:0:0.6:F: 3
        43442302:2006:  7   43442302:1:0:0.6:M:  3   43442302:1:0:0.6:M: 3
        (Other)      :106   (Other)           :130   (Other)           :91
      mridbysex     mridXtmonstdyXsex
 43442302:F:74   43442302:1:F:74
 43442302:M:74   43442302:1:M:74
```

```
 43442305:F: 0   43442305:1:F: 0
 43442305:M: 0   43442305:1:M: 0
 43829602:F: 0   43829602:0:F: 0
 43829602:M: 0   43829602:0:M: 0
 45079705:M: 0   (Other)     : 0
------------------------------------------------------------
idta$mrid: 45079705
      dose             cheact             mrid        tmpstds          tmonstdy
 Min.   :0.00000   Min.   : 356.0   43442305:  0   Min.   :0.0000   Min.   :1
 1st Qu.:0.00000   1st Qu.: 640.0   43442302:  0   1st Qu.:0.3333   1st Qu.:1
 Median :0.05000   Median : 783.0   45079705:228   Median :0.8333   Median :1
 Mean   :0.05395   Mean   : 748.6   43829602:  0   Mean   :1.6096   Mean   :1
 3rd Qu.:0.10000   3rd Qu.: 854.0                  3rd Qu.:2.0000   3rd Qu.:1
 Max.   :0.10000   Max.   :1032.0                  Max.   :6.0000   Max.   :1

 sex                id                                      cellmeans
 F:  0   45079705:884: 12   45079705:1:0:0.05:M                :  7
 M:228   45079705:885: 12   45079705:1:0:0.1:M                 :  7
         45079705:886: 12   45079705:1:0:0:M                   :  7
         45079705:887: 12   45079705:1:0.166666666666667:0.1:M :  7
         45079705:888: 12   45079705:1:0.333333333333333:0.05:M:  7
         45079705:892: 12   45079705:1:0.333333333333333:0.1:M :  7
         (Other)     :156   (Other)                            :186
                              modcellmeans      mridbysex
 43442302:1:0:0.1:F                 : 66   43442302:F:  0
 45079705:1:0:0.05:M                :  7   43442302:M:  0
 45079705:1:0:0.1:M                 :  7   43442305:F:  0
 45079705:1:0.166666666666667:0.1:M :  7   43442305:M:  0
 45079705:1:0.333333333333333:0.05:M:  7   43829602:F:  0
 45079705:1:0.333333333333333:0.1:M :  7   43829602:M:  0
 (Other)                            :127   45079705:M:228
    mridXtmonstdyXsex
 45079705:1:M:228
 43442302:1:F:  0
 43442302:1:M:  0
 43442305:1:F:  0
 43442305:1:M:  0
 43829602:0:F:  0
 (Other)     :  0
------------------------------------------------------------
idta$mrid: 43829602
      dose            cheact           mrid        tmpstds
 Min.   :0.0000   Min.   : 103   43442305:  0   Min.   :0.75
 1st Qu.:0.0500   1st Qu.: 390   43442302:  0   1st Qu.:0.75
 Median :0.2000   Median : 763   45079705:  0   Median :0.75
 Mean   :0.1615   Mean   : 821   43829602:595   Mean   :0.75
 3rd Qu.:0.2000   3rd Qu.:1160                  3rd Qu.:0.75
 Max.   :0.4000   Max.   :2422                  Max.   :0.75

    tmonstdy        sex                 id                        cellmeans
 Min.   :-91.0000   F:301   43829602:1526:  8   43829602:0:0.75:0.2:F : 20
 1st Qu.:-56.0000   M:294   43829602:1023:  7   43829602:0:0.75:0.2:M : 20
 Median :  0.0000           43829602:1024:  7   43829602:0:0.75:0:M   : 19
 Mean   : -0.1176           43829602:1026:  7   43829602:0:0.75:0.05:M: 18
```

```
 3rd Qu.: 56.0000           43829602:1027:  7   43829602:0:0.75:0.4:F : 18
 Max.   : 91.0000           43829602:1523:  7   43829602:0:0.75:0.05:F: 16
                            (Other)      :552   (Other)               :484
                 modcellmeans      mridbysex        mridXtmonstdyXsex
 43442302:1:0:0.1:F    :316   43442302:F:  0   43829602:0:M  : 72
 43829602:0:0.75:0.2:F : 20   43442302:M:  0   43829602:0:F  : 69
 43829602:0:0.75:0.2:M : 20   43442305:F:  0   43829602:-28:F: 40
 43829602:0:0.75:0.05:M: 18   43442305:M:  0   43829602:56:F : 40
 43829602:0:0.75:0.4:F : 18   43829602:F:301   43829602:-56:F: 39
 43829602:0:0.75:0.05:F: 16   43829602:M:294   43829602:56:M : 39
 (Other)               :187   45079705:M:  0   (Other)       :296
```

```
> by(idta, idta$mrid, function(x) with(x, table(tmonstdy, tmpstds)))

idta$mrid: 43442305
        tmpstds
tmonstdy 1  4  8
       1 36 36 36
------------------------------------------------------------
idta$mrid: 43442302
        tmpstds
tmonstdy 0  0.5 1  2  4  8  24
       1 24 22  22 17 20 22 21
------------------------------------------------------------
idta$mrid: 45079705
        tmpstds
tmonstdy 0  0.166666666666667 0.333333333333333 0.5 0.666666666666667
       1 21 19                20                20  19
        tmpstds
tmonstdy 0.833333333333333 1  1.5 2  3  4  6
       1 18                19 19  19 18 18 18
------------------------------------------------------------
idta$mrid: 43829602
        tmpstds
tmonstdy 0.75
     -91  76
     -56  75
     -28  77
     0   141
     28   73
     56   79
     91   74
```

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

idta$mrid: 43442305
      tmpstds
dose   1  4  8
  0    12 12 12
  0.25 12 12 12
  0.5  12 12 12
------------------------------------------------------------
idta$mrid: 43442302
     tmpstds
dose  0 0.5 1 2 4 8 24
```

```
  0   6 4   6 5 6 6 6
  0.1 6 6   5 6 5 6 5
  0.4 6 6   6 3 6 6 6
  0.6 6 6   5 3 3 4 4
-------------------------------------------------------------
idta$mrid: 45079705
      tmpstds
dose   0 0.166666666666667 0.333333333333333 0.5 0.666666666666667
  0    7 6                 6                 6   6
  0.05 7 6                 7                 7   6
  0.1  7 7                 7                 7   7
      tmpstds
dose   0.833333333333333 1 1.5 2 3 4 6
  0    5                 5 5   5 5 5 5
  0.05 6                 7 7   7 6 6 6
  0.1  7                 7 7   7 7 7 7
-------------------------------------------------------------
idta$mrid: 43829602
      tmpstds
dose   0.75
  0    146
  0.05 150
  0.2  155
  0.4  144
```

3 Identifying the Variance Model

The basic strategy is to fit something like a cell mean model to the data, and try different models for the variance. The problem is that different mrids have different scales, and that the real interindividual variance likely changes with response level, getting smaller at lower levels of AChE activity. The following model allows the interindividual variance to be scaled by the background.

```
> mm <- function(dose, tmonstdy, lA, lrho) {
+     res <- exp(ifelse(dose == 0 | tmonstdy < 0, lA, lA + lrho))
+     .grad <- matrix(0, nrow = length(res), ncol = 2)
+     colnames(.grad) <- c("lA", "lrho")
+     .grad[, "lA"] <- exp(ifelse(dose == 0 | tmonstdy < 0, lA,
+         lA + lrho))
+     .grad[, "lrho"] <- ifelse(dose == 0 | tmonstdy < 0, 0, exp(lA +
+         lrho))
+     attr(res, "gradient") <- .grad
+     res
+ }
```

That is,

$$E(cheact) = \begin{cases} e^{lA}, dose \equiv 0 or tmonstdy < 0 \\ e^{lA+lrho}, otherwise \end{cases} \tag{1}$$

This model is fit to the individual data, and will fit perfectly except for the control group at each time post dose in the acute studies, with the following fixed effects specification:

```
fixed=list( lA ~ mridXtmonstdyXsex - 1, lrho ~ modcellmeans - 1)
```

In the random effects specification, we let the background vary among subjects:

```
random = lA ~ 1|id
```

Ultimately, `mm()` is fit to `idta` using `nlme()`. This requires getting starting values for the parameters. The function `GetInitialValues()` (from the library `DRUtils`) can help here. `GetInitialValues()` is an interactive function that allows parameter values to be changed via sliders, and shows how the fitted values of the model changes, in real time as the parameter is changed. In the following code, crude starting values are arrived at using `lm()`, and are then refined using `GetInitialValues()`. The results are saved in the file pointed to by `initfile`. If that file exists, it is loaded when this file is re-run, and `GetInitialValues()` is not run.

```
> bckgrnd <- lm(cheact ~ mridXtmonstdyXsex - 1, data = subset(dta,
+     dose == 0))
> Start <- c(log(coef(bckgrnd)), rep(log(0.75), length(levels(dta$modcellmeans))))
> initfile <- paste("initvals-RBC-DR-1.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut <- GetInitialValues(cheact ~ mm(dose, tmonstdy,
+         lA, lrho), data = dta, params = list(lA ~ mridXtmonstdyXsex -
+         1, lrho ~ modcellmeans - 1), start = Start, weights = varIdent())
+     save(StartOut, file = initfile)
+ } else load(initfile)
```

Now, use `gnls()` to refine those estimates. As it turns out, the `gnls()` model will not converge from the estimates in `initvals-RBC-DR-1.RData`. So, perturb them a bit (that is what the call to `rnorm()` in the next code segment is doing). Keep trying until the model converges or we have tried more than 20 times.

```
> Start <- StartOut$start$beta
> icount <- 0
> repeat {
+     Start <- Start * (1 + rnorm(length(Start), sd = 0.05))
+     init1 <- try(gnls(cheact ~ mm(dose, tmonstdy, lA = lA, lrho = lrho),
+         data = idta, params = list(lA ~ mridXtmonstdyXsex - 1,
+             lrho ~ modcellmeans - 1), start = Start, control = gnlsControl(maxIter = 200)))
+     icount <- icount + 1
+     if (!inherits(init1, "try-error") || icount > 20)
+         break
+ }
```

Now use `nlme()` to fit three different variance models. In the first, the error variance is allowed to vary among mrids, but is constant within mrid:

```
> init2 <- nlme(cheact ~ mm(dose, tmonstdy, lA = lA, lrho = lrho),
+     data = idta, fixed = list(lA ~ mridXtmonstdyXsex - 1, lrho ~
+         modcellmeans - 1), random = list(id = lA ~ 1), weights = varIdent(form = ~1 |
+         mrid), start = coef(init1))
```

In the second, in addition to varying among mrids, variance is a power function of the mean within mrid:

```
> init3 <- update(init2, weights = varComb(varIdent(form = ~1 |
+     mrid), varPower()))
```

In the third, variance varies among mrid by sex, and is also a power function of the mean:

```
> init4 <- update(init3, weights = varComb(varIdent(form = ~1 |
+     mridbysex), varPower()))
```

Pinheiro and Bates (2000) recommend using likelihood based tests and comparisons for the random effects terms of these models. As long as the fixed effects specification is the same for all the models, this can be used on models fit by REML as well as ML:

```
> anova(init2, init3, init4)

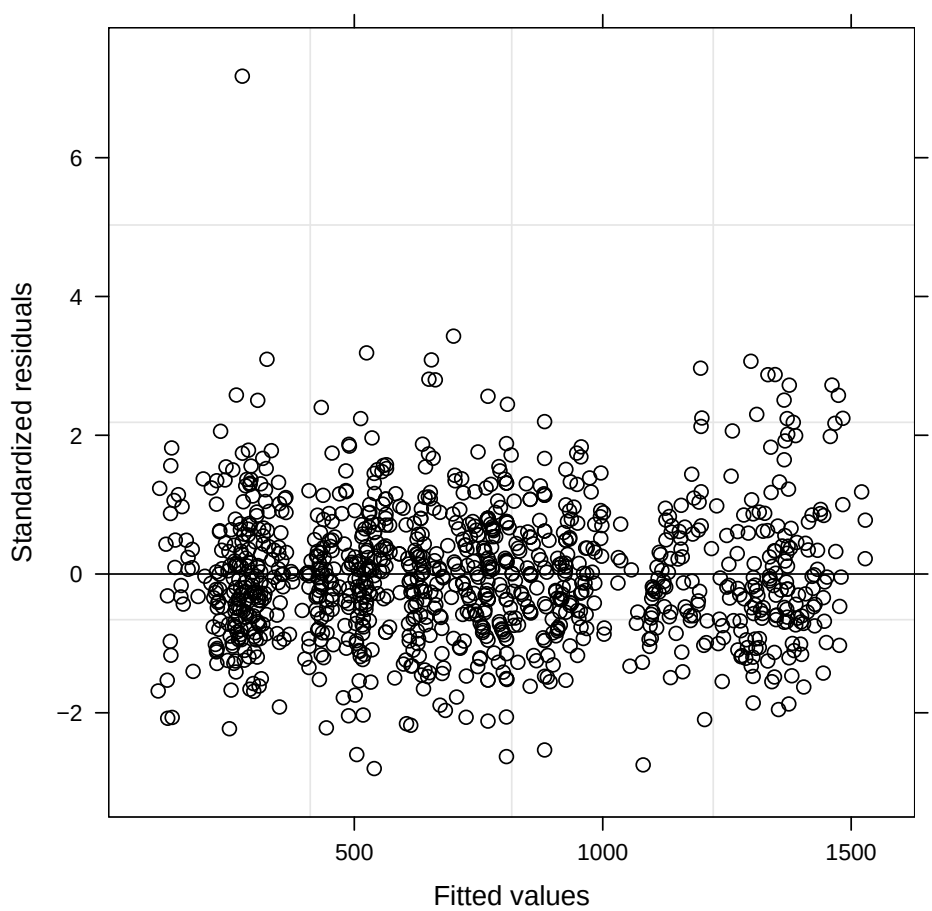
      Model  df      AIC      BIC    logLik   Test   L.Ratio p-value
init2     1 125 14118.01 14740.99 -6934.008
init3     2 126 13851.28 14479.24 -6799.642 1 vs 2 268.73044  <.0001
init4     3 129 13855.41 14498.31 -6798.702 2 vs 3   1.87987  0.5977
```

Since the scales for the response variable differ among the studies, there is no real point in testing whether the intercept term of the variance model should be constant across study. Clearly, the variance changes with mean response within studies: in the variance model

$$\sigma^2 = \gamma \times \mu^\rho$$

$\hat{\rho}$ is 1.56600237213587. Naively, one would expect a power of 2, so this result seems reasonable.

Look at residual plots, etc., to investigate the adequacy of the assumptions in this model. First, Pearson scaled residuals versus fitted value:



Notice the single extreme residual. Which record is that?

```
> idx <- which(residuals(init3, type = "p") > 6)
> idta[idx, c("cheact", "mrid", "dose", "sex", "id", "tmonstdy",
+     "tmpstds")]

    cheact     mrid dose sex            id tmonstdy tmpstds
507    958 43829602  0.2   M 43829602:3020       56    0.75
```

How does it compare with the other observations in its group?

```
> subset(idta, subset = mrid == "43829602" & dose == 0.2 & sex ==
+     "M" & tmonstdy == 56, select = c("id", "cheact"))

                id cheact
5011 43829602:3018    234
504  43829602:3019    191
507  43829602:3020    958
5101 43829602:3021    162
513  43829602:3022    179
516  43829602:3023    217
519  43829602:3024    245
522  43829602:3025    103
525  43829602:3026    141
528  43829602:3027    211
```

All the values in this group are between 103 and 245, except for the one extreme value of 958. Is this subject extreme in the other groups in which it appears (times 0 and -56)?

```
> subset(idta, subset = mrid == "43829602" & dose == 0.2 & sex ==
+     "M" & tmonstdy == 0, select = c("id", "cheact"))

                id cheact
469  43829602:3014    926
472  43829602:3015    900
475  43829602:3016   1164
478  43829602:3017   1136
4811 43829602:3023   1524
484  43829602:3024   1785
487  43829602:3025   1465
490  43829602:3026   1644
493  43829602:3027   2055
496  43829602:3028   1353
499  43829602:3018   1143
502  43829602:3019   1255
505  43829602:3020   1012
508  43829602:3021    986
5111 43829602:3022   2298
529  43829602:3001    906
532  43829602:3003    952
535  43829602:3005   1287
538  43829602:3007   1181
5411 43829602:3009   1211

> subset(idta, subset = mrid == "43829602" & dose == 0.2 & sex ==
+     "M" & tmonstdy == -56, select = c("id", "cheact"))

                id cheact
500  43829602:3018    452
503  43829602:3019    513
506  43829602:3020    313
509  43829602:3021    540
512  43829602:3022    327
515  43829602:3023    489
518  43829602:3024    438
```

```
5211 43829602:3025    486
524  43829602:3026    386
527  43829602:3027    304
```

No. Just how extreme is this point? Use a robust measure of scale and location to center and scale the points:

```
> yy <- subset(idta, subset = mrid == "43829602" & dose == 0.2 &
+     sex == "M" & tmonstdy == 56, select = c("id", "cheact"))$cheact
> (yy - median(yy))/mad(yy)

 [1]  0.6182832 -0.1873585 14.1830418 -0.7306983 -0.4121888  0.2997737
 [7]  0.8243776 -1.8361137 -1.1241513  0.1873585
```

That is, the point in question is over 14 standard deviations away from its group center. This is almost certainly a lab error (the appendix in the submitted report was checked, but it has the same value as the electronic dataset. Drop this value from the individual dataset:

```
> idta <- idta[-idx, ]
```

Now, rerun the three models, to make sure the decision about the variance model has not changed:

```
> init2 <- nlme(cheact ~ mm(dose, tmonstdy, lA = lA, lrho = lrho),
+     data = idta, fixed = list(lA ~ mridXtmonstdyXsex - 1, lrho ~
+         modcellmeans - 1), random = list(id = lA ~ 1), weights = varIdent(form = ~1 |
+         mrid), start = coef(init1))
> init3 <- update(init2, weights = varComb(varIdent(form = ~1 |
+     mrid), varPower()))
> init4 <- update(init3, weights = varComb(varIdent(form = ~1 |
+     mridbysex), varPower()))
> anova(init2, init3, init4)

      Model  df      AIC      BIC    logLik   Test  L.Ratio p-value
init2     1 125 14091.77 14714.62 -6920.883
init3     2 126 13766.65 14394.49 -6757.324 1 vs 2 327.1180  <.0001
init4     3 129 13772.58 14415.37 -6757.289 2 vs 3   0.0708  0.9951
```

So, the model has not changed. However, the relationship between variance and mean is closer to a constant coefficient of variation:

```
> init3

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheact ~ mm(dose, tmonstdy, lA = lA, lrho = lrho)
  Data: idta
  Log-likelihood: -6757.324
  Fixed: list(lA ~ mridXtmonstdyXsex - 1, lrho ~ modcellmeans - 1)
                    lA.mridXtmonstdyXsex43442302:1:F
                                         6.271212486
                    lA.mridXtmonstdyXsex43442302:1:M
                                         6.068152939
                    lA.mridXtmonstdyXsex43442305:1:F
                                         6.828019648
                    lA.mridXtmonstdyXsex43442305:1:M
                                         6.646153101
                    lA.mridXtmonstdyXsex43829602:0:F
                                         7.157613703
                    lA.mridXtmonstdyXsex43829602:0:M
```

```
                          7.084422847
   lA.mridXtmonstdyXsex43829602:-28:F
                          6.874856412
    lA.mridXtmonstdyXsex43829602:28:F
                          6.872923094
   lA.mridXtmonstdyXsex43829602:-28:M
                          6.261488758
    lA.mridXtmonstdyXsex43829602:28:M
                          6.263902262
   lA.mridXtmonstdyXsex43829602:-56:F
                          7.019396731
    lA.mridXtmonstdyXsex43829602:56:F
                          7.019276872
   lA.mridXtmonstdyXsex43829602:-56:M
                          6.069044660
    lA.mridXtmonstdyXsex43829602:56:M
                          6.424148812
   lA.mridXtmonstdyXsex43829602:-91:F
                          7.262493124
    lA.mridXtmonstdyXsex43829602:91:F
                          7.021570834
   lA.mridXtmonstdyXsex43829602:-91:M
                          6.453307299
    lA.mridXtmonstdyXsex43829602:91:M
                          6.231099271
     lA.mridXtmonstdyXsex45079705:1:M
                          6.721376324
  lrho.modcellmeans43442302:1:0:0.1:F
                         -0.218242495
  lrho.modcellmeans43442302:1:0:0.1:M
                          0.107909716
  lrho.modcellmeans43442302:1:0:0.4:F
                         -0.441180999
  lrho.modcellmeans43442302:1:0:0.4:M
                         -0.609085555
  lrho.modcellmeans43442302:1:0:0.6:F
                         -0.040693149
  lrho.modcellmeans43442302:1:0:0.6:M
                         -0.351925362
lrho.modcellmeans43442302:1:0.5:0.1:F
                         -0.415477304
lrho.modcellmeans43442302:1:0.5:0.1:M
                         -0.430121153
lrho.modcellmeans43442302:1:0.5:0.4:F
                         -1.107428148
lrho.modcellmeans43442302:1:0.5:0.4:M
                         -1.231392933
lrho.modcellmeans43442302:1:0.5:0.6:F
                         -1.327865421
lrho.modcellmeans43442302:1:0.5:0.6:M
                         -0.964239501
  lrho.modcellmeans43442302:1:1:0.1:F
                         -0.609560620
  lrho.modcellmeans43442302:1:1:0.1:M
```

```
                        -0.441020540
 lrho.modcellmeans43442302:1:1:0.4:F
                        -1.397052859
 lrho.modcellmeans43442302:1:1:0.4:M
                        -1.179230191
 lrho.modcellmeans43442302:1:1:0.6:F
                        -1.563084386
 lrho.modcellmeans43442302:1:1:0.6:M
                        -1.142505282
 lrho.modcellmeans43442302:1:2:0.1:F
                         0.027533636
 lrho.modcellmeans43442302:1:2:0.1:M
                        -0.259151238
 lrho.modcellmeans43442302:1:2:0.4:M
                        -1.027689990
 lrho.modcellmeans43442302:1:2:0.6:F
                        -1.089052804
 lrho.modcellmeans43442302:1:2:0.6:M
                        -0.703044566
lrho.modcellmeans43442302:1:24:0.1:F
                         0.144205424
lrho.modcellmeans43442302:1:24:0.1:M
                        -0.096845877
lrho.modcellmeans43442302:1:24:0.4:F
                        -0.170257388
lrho.modcellmeans43442302:1:24:0.4:M
                        -0.301796132
lrho.modcellmeans43442302:1:24:0.6:F
                         0.030258310
lrho.modcellmeans43442302:1:24:0.6:M
                        -0.133453633
 lrho.modcellmeans43442302:1:4:0.1:F
                         0.039671799
 lrho.modcellmeans43442302:1:4:0.1:M
                        -0.125001082
 lrho.modcellmeans43442302:1:4:0.4:F
                        -0.549549330
 lrho.modcellmeans43442302:1:4:0.4:M
                        -0.486272040
 lrho.modcellmeans43442302:1:4:0.6:F
                        -0.958088758
 lrho.modcellmeans43442302:1:4:0.6:M
                        -0.254654413
 lrho.modcellmeans43442302:1:8:0.1:F
                         0.112680934
 lrho.modcellmeans43442302:1:8:0.1:M
                         0.316194961
 lrho.modcellmeans43442302:1:8:0.4:F
                         0.178424930
 lrho.modcellmeans43442302:1:8:0.4:M
                         0.133549314
 lrho.modcellmeans43442302:1:8:0.6:F
                         0.120119589
 lrho.modcellmeans43442302:1:8:0.6:M
```

```
                            -0.202801051
    lrho.modcellmeans43442305:1:1:0.25:F
                            -1.180130453
    lrho.modcellmeans43442305:1:1:0.25:M
                            -1.040427712
     lrho.modcellmeans43442305:1:1:0.5:F
                            -1.240932629
     lrho.modcellmeans43442305:1:1:0.5:M
                            -1.127744894
    lrho.modcellmeans43442305:1:4:0.25:F
                            -0.113635891
    lrho.modcellmeans43442305:1:4:0.25:M
                            -0.059049807
     lrho.modcellmeans43442305:1:4:0.5:F
                            -0.386909815
     lrho.modcellmeans43442305:1:4:0.5:M
                            -0.448490300
    lrho.modcellmeans43442305:1:8:0.25:F
                            -0.015120495
    lrho.modcellmeans43442305:1:8:0.25:M
                             0.179027658
     lrho.modcellmeans43442305:1:8:0.5:F
                            -0.010351169
     lrho.modcellmeans43442305:1:8:0.5:M
                            -0.003859002
 lrho.modcellmeans43829602:0:0.75:0.05:F
                            -0.026238256
 lrho.modcellmeans43829602:0:0.75:0.05:M
                             0.112145914
  lrho.modcellmeans43829602:0:0.75:0.2:F
                             0.058828178
  lrho.modcellmeans43829602:0:0.75:0.2:M
                             0.093787093
  lrho.modcellmeans43829602:0:0.75:0.4:F
                             0.086028687
  lrho.modcellmeans43829602:0:0.75:0.4:M
                             0.109289054
lrho.modcellmeans43829602:28:0.75:0.05:F
                            -0.267827829
lrho.modcellmeans43829602:28:0.75:0.05:M
                            -0.393123501
 lrho.modcellmeans43829602:28:0.75:0.2:F
                            -1.224660569
 lrho.modcellmeans43829602:28:0.75:0.2:M
                            -0.675146163
 lrho.modcellmeans43829602:28:0.75:0.4:F
                            -1.181202753
 lrho.modcellmeans43829602:28:0.75:0.4:M
                            -0.636419571
lrho.modcellmeans43829602:56:0.75:0.05:F
                            -0.446543849
lrho.modcellmeans43829602:56:0.75:0.05:M
                            -0.713244550
 lrho.modcellmeans43829602:56:0.75:0.2:F
```

-1.465537097
lrho.modcellmeans43829602:56:0.75:0.2:M
-1.207988617
lrho.modcellmeans43829602:56:0.75:0.4:F
-1.272563895
lrho.modcellmeans43829602:56:0.75:0.4:M
-1.058285974
lrho.modcellmeans43829602:91:0.75:0.05:F
-0.509216376
lrho.modcellmeans43829602:91:0.75:0.05:M
-0.514480402
lrho.modcellmeans43829602:91:0.75:0.2:F
-1.168845850
lrho.modcellmeans43829602:91:0.75:0.2:M
-0.804376593
lrho.modcellmeans43829602:91:0.75:0.4:F
-1.258251104
lrho.modcellmeans43829602:91:0.75:0.4:M
-0.786796128
lrho.modcellmeans45079705:1:0:0.05:M
-0.021431183
lrho.modcellmeans45079705:1:0:0.1:M
0.021273883
lrho.modcellmeans45079705:1:0.166666666666667:0.05:M
-0.174997034
lrho.modcellmeans45079705:1:0.166666666666667:0.1:M
-0.424859205
lrho.modcellmeans45079705:1:0.333333333333333:0.05:M
-0.213631984
lrho.modcellmeans45079705:1:0.333333333333333:0.1:M
-0.479210204
lrho.modcellmeans45079705:1:0.5:0.05:M
-0.113985776
lrho.modcellmeans45079705:1:0.5:0.1:M
-0.436644572
lrho.modcellmeans45079705:1:0.666666666666667:0.05:M
-0.076945944
lrho.modcellmeans45079705:1:0.666666666666667:0.1:M
-0.325073579
lrho.modcellmeans45079705:1:0.833333333333333:0.05:M
-0.107926901
lrho.modcellmeans45079705:1:0.833333333333333:0.1:M
-0.291012611
lrho.modcellmeans45079705:1:1:0.05:M
-0.087416913
lrho.modcellmeans45079705:1:1:0.1:M
-0.578307682
lrho.modcellmeans45079705:1:1.5:0.05:M
-0.016509913
lrho.modcellmeans45079705:1:1.5:0.1:M
-0.277364930
lrho.modcellmeans45079705:1:2:0.05:M
-0.118470032
lrho.modcellmeans45079705:1:2:0.1:M

```
                                -0.195254942
lrho.modcellmeans45079705:1:3:0.05:M
                                 0.084980630
 lrho.modcellmeans45079705:1:3:0.1:M
                                 0.014536527
lrho.modcellmeans45079705:1:4:0.05:M
                                -0.039146011
 lrho.modcellmeans45079705:1:4:0.1:M
                                -0.006891412
lrho.modcellmeans45079705:1:6:0.05:M
                                -0.002650706
 lrho.modcellmeans45079705:1:6:0.1:M
                                -0.014912092

Random effects:
 Formula: lA ~ 1 | id
        lA.(Intercept)  Residual
StdDev:     0.07026357 0.4675838

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mrid
 Parameter estimates:
 43442305  43442302  45079705  43829602
1.0000000 0.7533071 0.3554718 1.1694757
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
   power
0.889542
Number of Observations: 1078
Number of Groups: 312
```

This model can also be used to look at the variation of background levels among studies and sexes. In the previous models, this variation was treated as the same for all studies and sexes. Thus, study 43442305, which uses a single observation for each animal in the study, benefitted from estimates of among animal variance based on the other studies. However, we need to omit that study if we want to ask whether among-animal variances in background level differ among studies. Also, since the variance model may be influenced by a misstaken random effects model, all three of the above models will be refit in the restricted dataset, first with the random effects model used above, second with `random = list(id = lA  mridbysex)`. Note that we cannot use `mrid + sex` because one of the studies has only males. We can, however, use `random = list(id = lA  mrid)` and `random = list(id = lA  sex)`. Use AIC to identify the best combination of random effects and variance model.

```
> ridta <- CleanUp(subset(idta, !mrid %in% "43442305"))
> ridta$cheacts <- ridta$cheact/400
> Start <- coef(init1)
> Start <- Start[-grep("43442305", names(Start))]
> Start[grep("^lA", names(Start))] <- Start[grep("^lA", names(Start))] -
+     log(400)
> rinit1 <- nlme(cheacts ~ mm(dose, tmonstdy, lA = lA, lrho = lrho),
+     data = ridta, fixed = list(lA ~ mridXtmonstdyXsex - 1, lrho ~
+         modcellmeans - 1), random = list(id = lA ~ 1), weights = varIdent(form = ~1 |
+         mrid), start = Start)
> rinit2 <- update(rinit1, weights = varComb(varIdent(form = ~1 |
```

```
+     mrid), varPower()))
> rinit3 <- update(rinit1, weights = varComb(varIdent(form = ~1 |
+     mridbysex), varPower()))
> rinit4 <- update(rinit1, random = list(id = lA ~ mridbysex))
> rinit5 <- update(rinit2, random = list(id = lA ~ mridbysex))
> rinit6 <- update(rinit3, random = list(id = lA ~ mridbysex))
> rinit7 <- update(rinit1, random = list(id = lA ~ mrid))
> rinit8 <- update(rinit2, random = list(id = lA ~ mrid))
> rinit9 <- update(rinit3, random = list(id = lA ~ mrid))
> rinit10 <- update(rinit1, random = list(id = lA ~ sex))
> rinit11 <- update(rinit2, random = list(id = lA ~ sex))
> rinit12 <- update(rinit3, random = list(id = lA ~ sex))
> rinit13 <- update(rinit1, weights = varPower(value = 0.84))
> rinit15 <- update(rinit8, weights = varPower(value = 0.84))
> rinit16 <- update(rinit10, weights = varPower(value = 0.84))
> Dimnames <- list(c("mridXsex+power", "mrid+power", "power", "mrid"),
+     c("~mridXsex", "~mrid", "~sex", "~1"))
> results <- list(rinit6, rinit5, NA, rinit4, rinit9, rinit8, rinit15,
+     rinit7, rinit12, rinit11, rinit16, rinit10, rinit3, rinit2,
+     rinit13, rinit1)
> lLtbl <- matrix(sapply(results, function(x) if (is.atomic(x)) NA else logLik(x)),
+     nrow = 4, ncol = 4, dimnames = Dimnames)
> AICtbl <- matrix(sapply(results, function(x) if (is.atomic(x)) NA else AIC(x)),
+     nrow = 4, ncol = 4, dimnames = Dimnames)
```

The model whose fit would be in `rinit14` always failed to converge; its value is replaced by `NA` in the following tables.

Table of log-Likelihoods:

```
> lLtbl
```

```
               ~mridXsex     ~mrid      ~sex        ~1
mridXsex+power -247.0593 -247.2611 -250.6028 -251.4403
mrid+power     -247.0703 -247.2903 -250.8252 -251.4709
power                 NA -379.9304 -390.8722 -391.1919
mrid           -393.9989 -396.2987 -410.0909 -410.1504
```

Table of AICs:

```
> AICtbl
```

```
               ~mridXsex     ~mrid      ~sex        ~1
mridXsex+power  748.1186  730.5222  731.2056  728.8806
mrid+power      744.1406  726.5807  727.6504  724.9418
power                 NA  987.8608 1003.7444 1000.3838
mrid           1035.9978 1022.5974 1044.1819 1040.3008
```

Columns correspond to models for the random effects for `lA`, and rows to variance models. Based on minimum AIC, the variance of `lA` is homogeneous across mrids and sexes, the error variance varies as a power of the fitted value, with an intercept term that varies among mrids, but not among sexes. So, the random effect will be:

```
lA ~ 1 | id
```

and the variance model will be:

```
varComb(varIdent(~1 | mrid), varPower(value = 0.84))
```

The `value = 0.84` argument to `varPower()` gives an initial value for estimating the power for the variance model.

4 Nonlinear Modeling

The strategy for fitting the nonlinear dose-time model to these data is to identify the "richest" parameterization the data will support, then use testing to identify a more parsimonius model. There is a mix of time-course studies and subchronic studies in this dataset:

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

dta$mrid: 43442305
, , sex = F

       dose
tmpstds 0 0.25 0.5
      1 1 1    1
      4 1 1    1
      8 1 1    1

, , sex = M

       dose
tmpstds 0 0.25 0.5
      1 1 1    1
      4 1 1    1
      8 1 1    1

------------------------------------------------------------
dta$mrid: 43442302
, , sex = F

       dose
tmpstds 0 0.1 0.4 0.6
    0   1 1   1   1
    0.5 1 1   1   1
    1   1 1   1   1
    2   1 1   0   1
    4   1 1   1   1
    8   1 1   1   1
    24  1 1   1   1

, , sex = M

       dose
tmpstds 0 0.1 0.4 0.6
    0   1 1   1   1
    0.5 1 1   1   1
    1   1 1   1   1
    2   1 1   1   1
    4   1 1   1   1
    8   1 1   1   1
    24  1 1   1   1

------------------------------------------------------------
dta$mrid: 45079705
, , sex = F
```

```
                   dose
tmpstds             0 0.05 0.1
  0                 0 0    0
  0.166666666666667 0 0    0
  0.333333333333333 0 0    0
  0.5               0 0    0
  0.666666666666667 0 0    0
  0.833333333333333 0 0    0
  1                 0 0    0
  1.5               0 0    0
  2                 0 0    0
  3                 0 0    0
  4                 0 0    0
  6                 0 0    0

, , sex = M

                   dose
tmpstds             0 0.05 0.1
  0                 1 1    1
  0.166666666666667 1 1    1
  0.333333333333333 1 1    1
  0.5               1 1    1
  0.666666666666667 1 1    1
  0.833333333333333 1 1    1
  1                 1 1    1
  1.5               1 1    1
  2                 1 1    1
  3                 1 1    1
  4                 1 1    1
  6                 1 1    1

------------------------------------------------------------
dta$mrid: 43829602
, , sex = F

       dose
tmpstds 0 0.05 0.2 0.4
   0.75 7 7    7   7

, , sex = M

       dose
tmpstds 0 0.05 0.2 0.4
   0.75 7 7    7   7
```

Mrids with time courses are 43442305, 43442302, 45079705, and there is a control group at each time point in those studies.

What are the doses in these mrids? Split it out by sex:

```
> with(subset(dta, mrid %in% c("43442305", "43442302", "45079705")),
+     table(dose, sex))

      sex
dose   F  M
```

```
  0    10 22
  0.05  0 12
  0.1   7 19
  0.25  3  3
  0.4   6  7
  0.5   3  3
  0.6   7  7
```

What are the doses in 43829602?

```
> with(subset(dta, mrid %in% c("43829602")), table(dose, sex))

      sex
dose   F M
  0    7 7
  0.05 7 7
  0.2  7 7
  0.4  7 7
```

How are subjects assigned to the times? We are only interested in the repeated measures acute studies, here:

```
> by(xx <- CleanUp(subset(idta, mrid %in% c("43442302", "45079705"))),
+     xx$mrid, function(x) with(CleanUp(x), table(tmpstds, id)))

xx$mrid: 43442302
       id
tmpstds 43442302:1004 43442302:1005 43442302:1006 43442302:1504 43442302:1505
    0   1             1             1             1             1
    0.5 1             1             1             0             0
    1   1             1             1             1             1
    2   0             1             1             1             1
    4   1             1             1             1             1
    8   1             1             1             1             1
    24  1             1             1             1             1
       id
tmpstds 43442302:1506 43442302:2004 43442302:2005 43442302:2006 43442302:2504
    0   1             1             1             1             1
    0.5 1             1             1             1             1
    1   1             1             1             1             0
    2   1             1             1             1             1
    4   1             1             1             1             0
    8   1             1             1             1             1
    24  1             1             1             1             0
       id
tmpstds 43442302:2505 43442302:2506 43442302:3004 43442302:3005 43442302:3006
    0   1             1             1             1             1
    0.5 1             1             1             1             1
    1   1             1             1             1             1
    2   1             1             1             1             1
    4   1             1             1             1             1
    8   1             1             1             1             1
    24  1             1             1             1             1
       id
tmpstds 43442302:3504 43442302:3505 43442302:3506 43442302:4004 43442302:4005
    0   1             1             1             1             1
    0.5 1             1             1             1             1
```

```
    1   1             1             1             1             0
    2   0             0             0             0             0
    4   1             1             1             0             0
    8   1             1             1             0             0
    24  1             1             1             0             0
       id
tmpstds 43442302:4006 43442302:4504 43442302:4505 43442302:4506
    0   1             1             1             1
    0.5 1             1             1             1
    1   1             1             1             1
    2   1             0             1             1
    4   1             0             1             1
    8   1             1             1             1
    24  1             1             1             1
-------------------------------------------------------------
xx$mrid: 45079705
                   id
tmpstds             45079705:884 45079705:885 45079705:886 45079705:887
  0                 1            1            1            1
  0.166666666666667 1            1            1            1
  0.333333333333333 1            1            1            1
  0.5               1            1            1            1
  0.666666666666667 1            1            1            1
  0.833333333333333 1            1            1            1
  1                 1            1            1            1
  1.5               1            1            1            1
  2                 1            1            1            1
  3                 1            1            1            1
  4                 1            1            1            1
  6                 1            1            1            1
                   id
tmpstds             45079705:888 45079705:889 45079705:892 45079705:893
  0                 1            1            1            1
  0.166666666666667 1            0            1            1
  0.333333333333333 1            0            1            1
  0.5               1            0            1            1
  0.666666666666667 1            0            1            1
  0.833333333333333 1            0            1            1
  1                 1            0            1            1
  1.5               1            0            1            1
  2                 1            0            1            1
  3                 1            0            1            1
  4                 1            0            1            1
  6                 1            0            1            1
                   id
tmpstds             45079705:894 45079705:895 45079705:896 45079705:898
  0                 1            1            1            1
  0.166666666666667 1            1            1            0
  0.333333333333333 1            1            1            1
  0.5               1            1            1            1
  0.666666666666667 1            1            1            0
  0.833333333333333 1            1            1            0
  1                 1            1            1            1
  1.5               1            1            1            1
```

```
  2                 1            1            1            1
  3                 1            1            1            0
  4                 1            1            1            0
  6                 1            1            1            0
                   id
tmpstds             45079705:899 45079705:900 45079705:901 45079705:902
  0                 1            1            1            1
  0.166666666666667 1            1            1            1
  0.333333333333333 1            1            1            1
  0.5               1            1            1            1
  0.666666666666667 1            1            1            1
  0.833333333333333 1            1            0            1
  1                 1            1            0            1
  1.5               1            1            0            1
  2                 1            1            0            1
  3                 1            1            0            1
  4                 1            1            0            1
  6                 1            1            0            1
                   id
tmpstds             45079705:903 45079705:904 45079705:905 45079705:906
  0                 1            1            1            1
  0.166666666666667 1            1            1            1
  0.333333333333333 1            1            1            1
  0.5               1            1            1            1
  0.666666666666667 1            1            1            1
  0.833333333333333 1            1            1            1
  1                 1            1            1            1
  1.5               1            1            1            1
  2                 1            1            1            1
  3                 1            1            1            1
  4                 1            1            1            1
  6                 1            1            1            1
                   id
tmpstds             45079705:907
  0                 1
  0.166666666666667 1
  0.333333333333333 1
  0.5               1
  0.666666666666667 1
  0.833333333333333 1
  1                 1
  1.5               1
  2                 1
  3                 1
  4                 1
  6                 1
```

So, in these two studies, most subjects are sampled at each time point. Thus, for these two studies, each subject can be used as its own control, and any variation among time points, due to assay differences, can be accounted for. This line of thinking is elaborated below in the

These summaries will be useful when thinking about how many levels of ldT to estimate.

4.1 MRID 43829602, Non-Acute Study

MRID 43829602 is the only non-acute study in this group. Its design involved sampling at day 0, before dosing started, then, on the sampling days, taking a sample pre-dosing (has a negative value for tmonstdy) and post-dosing (positive value for tmonstdy). Several questions need to be answered about this study before the full parameterization of the model for all the studies can be settled. These will be answered using analyses of the data from this mrid only.

```
> ndta <- CleanUp(subset(dta, mrid == "43829602"))
> indta <- CleanUp(subset(idta, mrid == "43829602"))
> ndta$dose2 <- with(ndta, ifelse(tmpstds == 0, 0, dose))
> indta$dose2 <- with(indta, ifelse(tmpstds == 0, 0, dose))
```

4.1.1 Modeling Background Parameters and Dose-Response Parameters

It makes sense to ask whether there is heterogeneity among the pre-dosing values, whether they differ from the day 0 values, and whether the background values differ from the post-dosing background values. The answers will determine how many levels to assign to the background parameters for this mrid.

In 43829602, the records from day 0 are pre-dosing, so the dose is 0 for them. The records from negative tmonstdy are pre-dose for that day; If there is no long term effect, then there should be no dose-response among those observations, but we need to check whether that is true. So, the strategy for these parameters is to first fit a separate set of dose-response parameters for both positive and negative tmonsdty,and test whether there is a significant dose-response among the negative values for tmonstdy. We can then answer the questions about background parameters from the fitted background in this model. Use linear models to keep all this simpler.

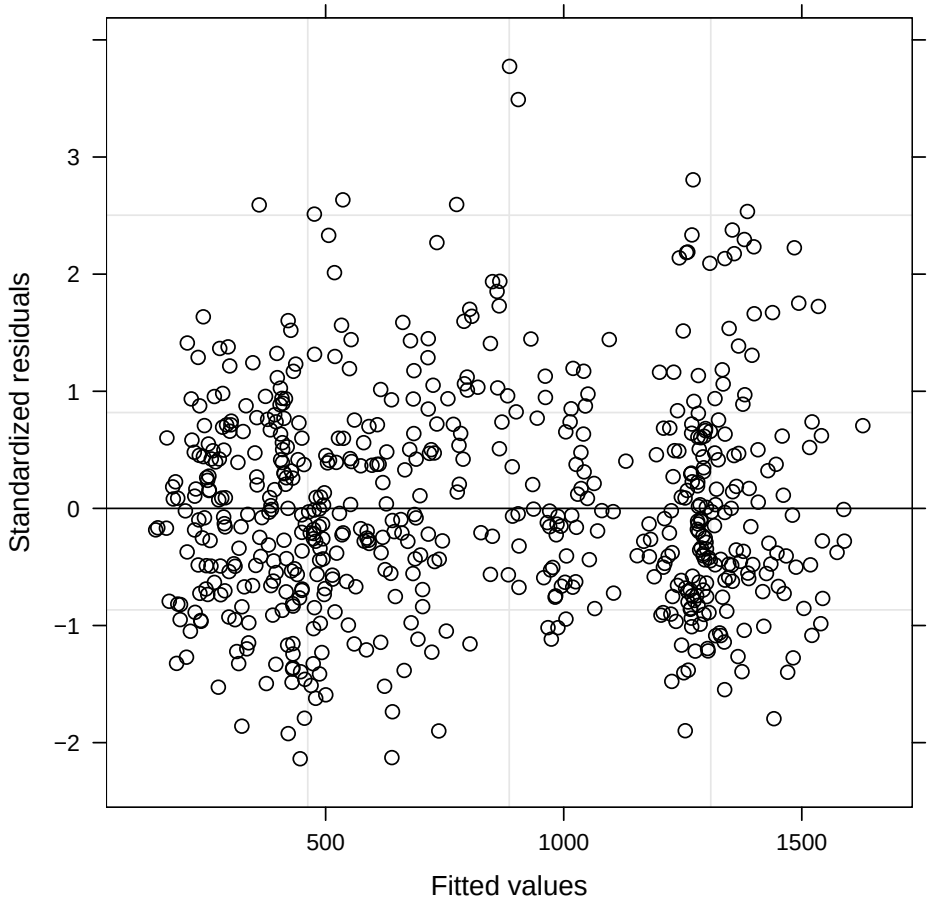
```
> lmout <- lme(fixed = cheact ~ mridXtmonstdyXsex + mridXtmonstdyXsex:dose,
+     data = indta, random = ~1 | id, weights = varPower())
> lmout

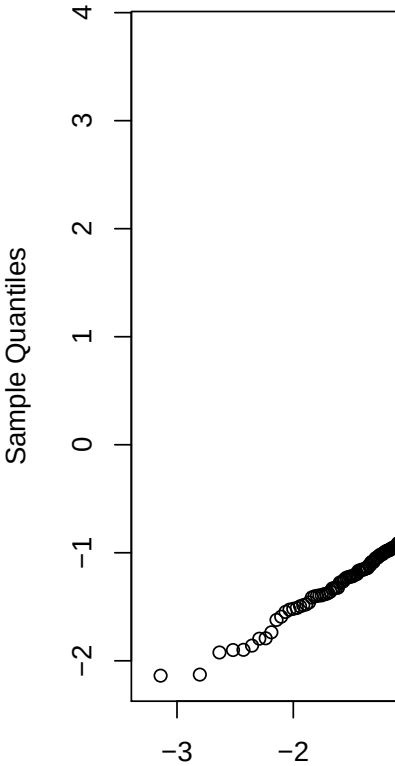
Linear mixed-effects model fit by REML
  Data: indta
  Log-restricted-likelihood: -3898.617
  Fixed: cheact ~ mridXtmonstdyXsex + mridXtmonstdyXsex:dose
                        (Intercept)        mridXtmonstdyXsex43829602:0:M
                         1275.72574                            -18.15018
     mridXtmonstdyXsex43829602:-28:F       mridXtmonstdyXsex43829602:28:F
                         -289.00055                           -527.91520
     mridXtmonstdyXsex43829602:-28:M       mridXtmonstdyXsex43829602:28:M
                         -776.83948                           -860.68684
     mridXtmonstdyXsex43829602:-56:F       mridXtmonstdyXsex43829602:56:F
                          -72.05605                           -492.77543
     mridXtmonstdyXsex43829602:-56:M       mridXtmonstdyXsex43829602:56:M
                         -823.79707                           -878.97300
     mridXtmonstdyXsex43829602:-91:F       mridXtmonstdyXsex43829602:91:F
                          235.26554                           -488.32473
     mridXtmonstdyXsex43829602:-91:M       mridXtmonstdyXsex43829602:91:M
                         -611.99524                           -895.58888
  mridXtmonstdyXsex43829602:0:F:dose   mridXtmonstdyXsex43829602:0:M:dose
                          343.15044                            247.13268
mridXtmonstdyXsex43829602:-28:F:dose  mridXtmonstdyXsex43829602:28:F:dose
                          -95.66171                          -1275.08762
mridXtmonstdyXsex43829602:-28:M:dose  mridXtmonstdyXsex43829602:28:M:dose
                          137.08129                           -447.93054
mridXtmonstdyXsex43829602:-56:F:dose  mridXtmonstdyXsex43829602:56:F:dose
                         -510.05164                          -1383.37270
```

```
mridXtmonstdyXsex43829602:-56:M:dose  mridXtmonstdyXsex43829602:56:M:dose
                           -102.74074                           -627.44101
mridXtmonstdyXsex43829602:-91:F:dose  mridXtmonstdyXsex43829602:91:F:dose
                           -485.26456                          -1308.80705
mridXtmonstdyXsex43829602:-91:M:dose  mridXtmonstdyXsex43829602:91:M:dose
                           -158.58371                           -451.93480

Random effects:
 Formula: ~1 | id
        (Intercept)  Residual
StdDev:    77.32155 0.5332085

Variance function:
 Structure: Power of variance covariate
 Formula: ~fitted(.)
 Parameter estimates:
    power
0.9136703
Number of Observations: 594
Number of Groups: 159
```





Standardized residuals from this fit look reasonably normal via qq plot as do the random effects.
Use contrasts in anova.lme to test hypotheses, per Pinheiro & Bates (2000). The columns in the contrast

matrix correspond to elements in the parameter vector (or rows in the following table):

```
> cbind(summary(lmout)$tTable, "Parameter Number" = 1:28)
```

	Value	Std.Error	DF	t-value	p-value	Parameter Number
(Intercept)	1275.72574	69.31808	408	18.4039384	1.655815e-55	1
mridXtmonstdyXsex43829602:0:M	-18.15018	93.82623	408	-0.1934446	8.467070e-01	2
mridXtmonstdyXsex43829602:-28:F	-289.00055	96.27050	408	-3.0019636	2.847329e-03	3
mridXtmonstdyXsex43829602:28:F	-527.91520	85.44648	408	-6.1783145	1.569799e-09	4
mridXtmonstdyXsex43829602:-28:M	-776.83948	80.14844	408	-9.6925093	3.950202e-20	5
mridXtmonstdyXsex43829602:28:M	-860.68684	77.32856	408	-11.1302582	2.615596e-25	6
mridXtmonstdyXsex43829602:-56:F	-72.05605	104.99383	408	-0.6862884	4.929211e-01	7
mridXtmonstdyXsex43829602:56:F	-492.77543	83.88096	408	-5.8746992	8.801051e-09	8
mridXtmonstdyXsex43829602:-56:M	-823.79707	79.64648	408	-10.3431700	2.008511e-22	9
mridXtmonstdyXsex43829602:56:M	-878.97300	76.05492	408	-11.5570831	6.410695e-27	10
mridXtmonstdyXsex43829602:-91:F	235.26554	120.86365	408	1.9465368	5.227630e-02	11
mridXtmonstdyXsex43829602:91:F	-488.32473	85.81586	408	-5.6903789	2.423400e-08	12
mridXtmonstdyXsex43829602:-91:M	-611.99524	84.96687	408	-7.2027510	2.867246e-12	13
mridXtmonstdyXsex43829602:91:M	-895.58888	76.15129	408	-11.7606530	1.067012e-27	14
mridXtmonstdyXsex43829602:0:F:dose	343.15044	313.54771	408	1.0944122	2.744199e-01	15
mridXtmonstdyXsex43829602:0:M:dose	247.13268	307.79030	408	0.8029255	4.224853e-01	16
mridXtmonstdyXsex43829602:-28:F:dose	-95.66171	302.32743	408	-0.3164176	7.518474e-01	17
mridXtmonstdyXsex43829602:28:F:dose	-1275.08762	168.87509	408	-7.5504776	2.865787e-13	18
mridXtmonstdyXsex43829602:-28:M:dose	137.08129	199.21739	408	0.6880990	4.917814e-01	19
mridXtmonstdyXsex43829602:28:M:dose	-447.93054	134.49564	408	-3.3304466	9.459869e-04	20
mridXtmonstdyXsex43829602:-56:F:dose	-510.05164	335.79982	408	-1.5189158	1.295582e-01	21
mridXtmonstdyXsex43829602:56:F:dose	-1383.37270	164.84257	408	-8.3920840		
mridXtmonstdyXsex43829602:-56:M:dose	-102.74074	173.07649	408	-0.5936146		
mridXtmonstdyXsex43829602:56:M:dose	-627.44101	118.31255	408	-5.3032496		
mridXtmonstdyXsex43829602:-91:F:dose	-485.26456	419.88401	408	-1.1557110		
mridXtmonstdyXsex43829602:91:F:dose	-1308.80705	175.16688	408	-7.4717723		
mridXtmonstdyXsex43829602:-91:M:dose	-158.58371	223.04285	408	-0.7110011		
mridXtmonstdyXsex43829602:91:M:dose	-451.93480	125.50297	408	-3.6009889		

```
mridXtmonstdyXsex43829602:56:F:dose  7.919685e-16              22
mridXtmonstdyXsex43829602:-56:M:dose 5.530988e-01              23
mridXtmonstdyXsex43829602:56:M:dose  1.868729e-07              24
mridXtmonstdyXsex43829602:-91:F:dose 2.484757e-01              25
mridXtmonstdyXsex43829602:91:F:dose  4.860095e-13              26
mridXtmonstdyXsex43829602:-91:M:dose 4.774898e-01              27
mridXtmonstdyXsex43829602:91:M:dose  3.560604e-04              28
```

Is there a dose-response on day 0? Test Jointly whether the corresponding coefficients for dose (...0:F:dose, ...0:M.dose) are zero. 2 df test:

Contrast matrix:

```
> L <- matrix(0, nrow = 2, ncol = 28)
> L[cbind(1:2, c(15, 16))] <- 1
> anova(lmout, L = L)

F-test for linear combination(s)
  mridXtmonstdyXsex43829602:0:F:dose mridXtmonstdyXsex43829602:0:M:dose
1                                  1                                  0
2                                  0                                  1
  numDF denDF   F-value p-value
1     2   408 0.9212137  0.3989
```

No (so the experiment is sane, so far).

Is there a dose-response among the pre-dosing samples? Test the null hypothesis that pre-dosing slopes at 28, 56, and 91 days, both males and females, are 0. 6 df test.

Contrast matrix:

```
> L <- matrix(0, nrow = 6, ncol = 28)
> L[cbind(1:6, seq(17, 27, by = 2))] <- 1
> anova(lmout, L = L)

F-test for linear combination(s)
  mridXtmonstdyXsex43829602:-28:F:dose mridXtmonstdyXsex43829602:-28:M:dose
1                                    1                                    0
2                                    0                                    1
3                                    0                                    0
4                                    0                                    0
5                                    0                                    0
6                                    0                                    0
  mridXtmonstdyXsex43829602:-56:F:dose mridXtmonstdyXsex43829602:-56:M:dose
1                                    0                                    0
2                                    0                                    0
3                                    1                                    0
4                                    0                                    1
5                                    0                                    0
6                                    0                                    0
  mridXtmonstdyXsex43829602:-91:F:dose mridXtmonstdyXsex43829602:-91:M:dose
1                                    0                                    0
2                                    0                                    0
3                                    0                                    0
4                                    0                                    0
5                                    1                                    0
6                                    0                                    1
  numDF denDF   F-value p-value
1     6   408 0.8402314  0.5393
```

So, the effects of the previous day's treatment have disappeared by the time of the next treatment.

Do the background levels change between pre- and post-treatment times? Contrast matrix:

```
> L <- matrix(0, nrow = 6, ncol = 28)
> L[cbind(1:6, c(3, 5, 7, 9, 11, 13))] <- 1
> L[cbind(1:6, c(4, 6, 8, 10, 12, 14))] <- -1
> anova(lmout, L = L)

F-test for linear combination(s)
  mridXtmonstdyXsex43829602:-28:F mridXtmonstdyXsex43829602:28:F
1                               1                              -1
2                               0                               0
3                               0                               0
4                               0                               0
5                               0                               0
6                               0                               0
  mridXtmonstdyXsex43829602:-28:M mridXtmonstdyXsex43829602:28:M
1                               0                               0
2                               1                              -1
3                               0                               0
4                               0                               0
5                               0                               0
6                               0                               0
  mridXtmonstdyXsex43829602:-56:F mridXtmonstdyXsex43829602:56:F
1                               0                               0
2                               0                               0
3                               1                              -1
4                               0                               0
5                               0                               0
6                               0                               0
  mridXtmonstdyXsex43829602:-56:M mridXtmonstdyXsex43829602:56:M
1                               0                               0
2                               0                               0
3                               0                               0
4                               1                              -1
5                               0                               0
6                               0                               0
  mridXtmonstdyXsex43829602:-91:F mridXtmonstdyXsex43829602:91:F
1                               0                               0
2                               0                               0
3                               0                               0
4                               0                               0
5                               1                              -1
6                               0                               0
  mridXtmonstdyXsex43829602:-91:M mridXtmonstdyXsex43829602:91:M
1                               0                               0
2                               0                               0
3                               0                               0
4                               0                               0
5                               0                               0
6                               1                              -1
  numDF denDF  F-value p-value
1     6   408 17.20292  <.0001
```

This is surprising. Look at the individual contrasts:

```
> tTable <- cbind(Contrast = num <- c(L %*% fixed.effects(lmout)),
+     SE = den <- c(sqrt(diag(L %*% lmout$varFix %*% t(L)))), "t-value" = num/den,
+     "P-value" = pt(num/den, df = 409, lower.tail = FALSE))
> rownames(tTable) <- c("28:F", "28:M", "56:F", "56:M", "91:F",
+     "91:M")
> tTable
```

```
      Contrast        SE  t-value      P-value
28:F 238.91465  83.67838 2.855154 2.260308e-03
28:M  83.84736  47.63303 1.760278 3.955408e-02
56:F 420.71938  92.48080 4.549262 3.552742e-06
56:M  55.17593  44.49688 1.239996 1.078440e-01
91:F 723.59027 111.46784 6.491471 1.232502e-10
91:M 283.59364  53.64676 5.286315 1.017820e-07
```

They are all positive; that is, the background level pre-dosing is always less than the background level post-dosing (on average). Is this about circadian rhythms or problems with the biochemistry? Or, an artifact due to model miss-specification? To check this, refit the same model, using only the controls:

```
> lmout2 <- lme(fixed = cheact ~ mridXtmonstdyXsex, data = CleanUp(subset(indta,
+     dose == 0)), random = ~1 | id, weights = varPower())
> tTab <- summary(lmout2)$tTable
> rownames(tTab) <- gsub("mridXtmonstdyXsex43829602:", "", rownames(tTab))
> cbind(tTab, "Parameter Number" = 1:nrow(tTab))
```

```
                 Value Std.Error DF    t-value      p-value Parameter Number
(Intercept) 1292.33920  97.18864 93 13.2972250 3.131309e-23                1
0:M         -109.65214 124.93010 93 -0.8777079 3.823641e-01                2
-28:F       -332.24192 126.22828 93 -2.6320721 9.936221e-03                3
28:F        -330.24179 133.53489 93 -2.4730750 1.521153e-02                4
-28:M       -804.11534 106.95720 93 -7.5181039 3.398076e-11                5
28:M        -775.44558 108.69483 93 -7.1341534 2.086371e-10                6
-56:F        -96.12658 143.37670 93 -0.6704477 5.042340e-01                7
56:F        -179.24896 137.09159 93 -1.3075124 1.942619e-01                8
-56:M       -837.89858 107.91674 93 -7.7643057 1.049981e-11                9
56:M        -698.10039 110.73644 93 -6.3041616 9.611444e-09               10
-91:F        250.61779 171.43226 93  1.4619057 1.471380e-01               11
91:F        -193.42790 143.32766 93 -1.3495504 1.804363e-01               12
-91:M       -671.08259 111.44529 93 -6.0216329 3.410959e-08               13
91:M        -767.57581 108.83270 93 -7.0528052 3.055381e-10               14
```

Now, test whether the pre- and post-treatment background values differ:

```
> L <- matrix(0, nrow = 6, ncol = 14)
> L[cbind(1:6, seq(3, 13, by = 2))] <- 1
> L[cbind(1:6, seq(4, 14, by = 2))] <- -1
> anova(lmout2, L = L)
```

```
F-test for linear combination(s)
  mridXtmonstdyXsex43829602:-28:F mridXtmonstdyXsex43829602:28:F
1                               1                              -1
2                               0                               0
3                               0                               0
4                               0                               0
5                               0                               0
6                               0                               0
```

```
  mridXtmonstdyXsex43829602:-28:M mridXtmonstdyXsex43829602:28:M
1                               0                              0
2                               1                             -1
3                               0                              0
4                               0                              0
5                               0                              0
6                               0                              0
  mridXtmonstdyXsex43829602:-56:F mridXtmonstdyXsex43829602:56:F
1                               0                              0
2                               0                              0
3                               1                             -1
4                               0                              0
5                               0                              0
6                               0                              0
  mridXtmonstdyXsex43829602:-56:M mridXtmonstdyXsex43829602:56:M
1                               0                              0
2                               0                              0
3                               0                              0
4                               1                             -1
5                               0                              0
6                               0                              0
  mridXtmonstdyXsex43829602:-91:F mridXtmonstdyXsex43829602:91:F
1                               0                              0
2                               0                              0
3                               0                              0
4                               0                              0
5                               1                             -1
6                               0                              0
  mridXtmonstdyXsex43829602:-91:M mridXtmonstdyXsex43829602:91:M
1                               0                              0
2                               0                              0
3                               0                              0
4                               0                              0
5                               0                              0
6                               1                             -1
  numDF denDF  F-value p-value
1     6    93 2.523948  0.0262
```

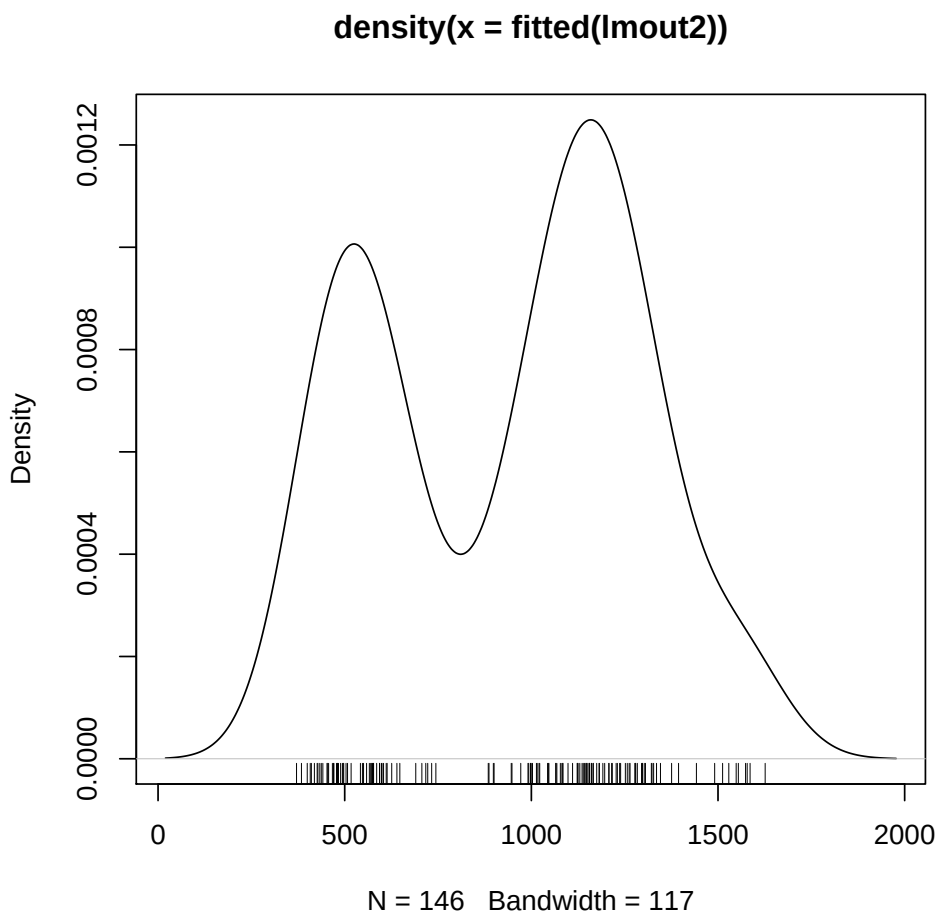
Yes, still. Look at individual contrasts:

```
> tTable2 <- cbind(Contrast = num <- c(L %*% fixed.effects(lmout2)),
+     SE = den <- c(sqrt(diag(L %*% lmout2$varFix %*% t(L)))),
+     "t-value" = num/den, "P-value" = pt(num/den, df = 93, lower.tail = FALSE))
> rownames(tTable2) <- c("28:F", "28:M", "56:F", "56:M", "91:F",
+     "91:M")
> tTable2
```

```
        Contrast        SE     t-value     P-value
28:F   -2.000134 122.79342 -0.01628860 0.506480479
28:M  -28.669759  51.09990 -0.56105317 0.711944673
56:F   83.122383 143.59868  0.57885200 0.282044191
56:M -139.798197  58.80188 -2.37744454 0.990259760
91:F  444.045690 176.74590  2.51233934 0.006858064
91:M   96.493213  60.50328  1.59484275 0.057070172
```

So, still an overall significant difference, but smaller in magnitude, probably driven by the 91:F group. Interestingly, the fitted values seem to be bimodal:

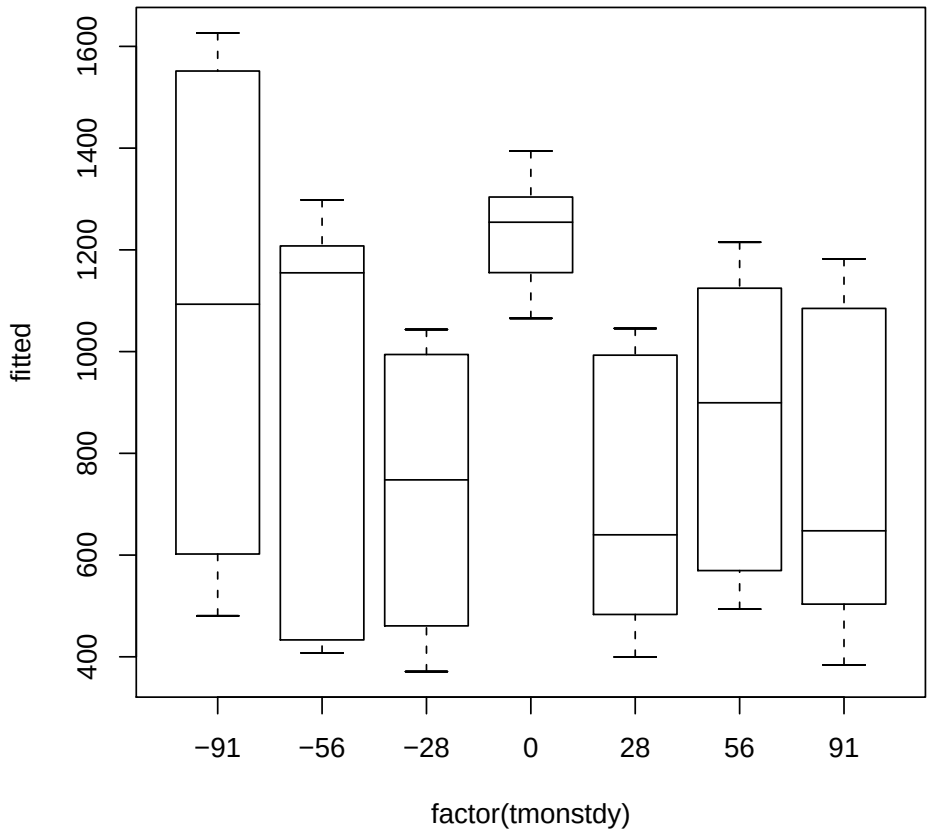
```
> plot(density(fitted(lmout2)))
> rug(fitted(lmout2))
```



The larger mode is about twice the smaller: could this be a dilution error?

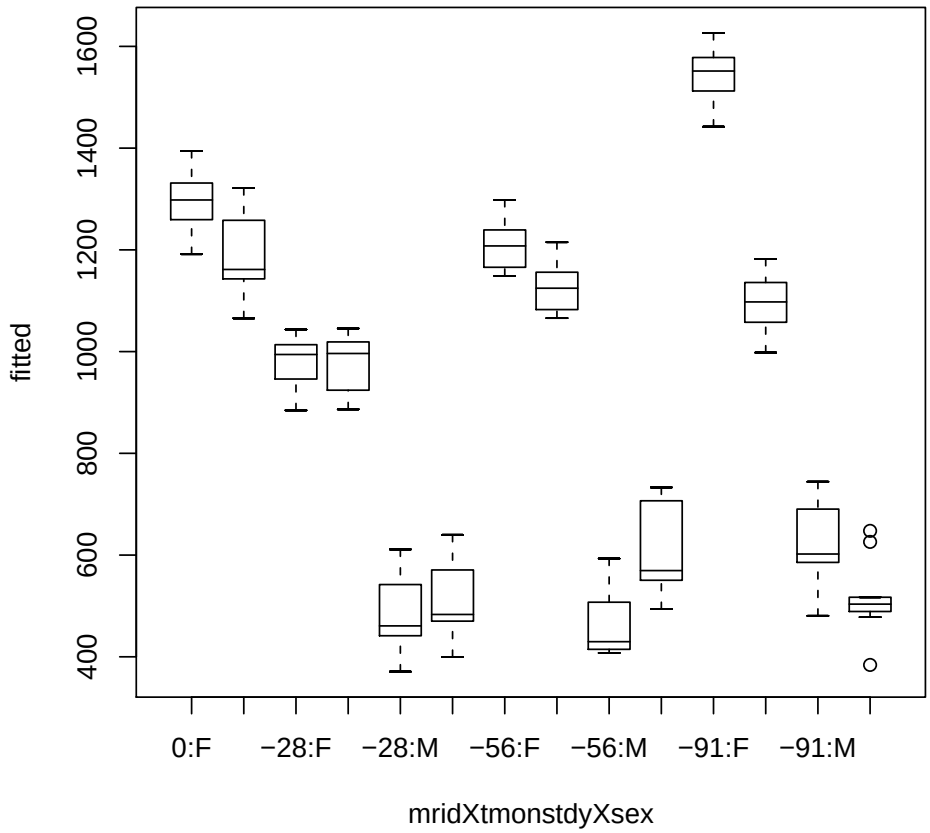
Also, the time 0 values are quite large:

```
> tmp <- subset(indta, dose == 0)
> tmp$fitted <- fitted(lmout2)
> plot(fitted ~ factor(tmonstdy), data = tmp)
```



even better:

```
> levels(tmp$mridXtmonstdyXsex) <- sub("43829602\\:", "", levels(tmp$mridXtmonstdyXsex))
> plot(fitted ~ mridXtmonstdyXsex, data = tmp)
```



Looking at fitted values in this case smooths out the error variance. The negative-positive pairs are pretty similar except for the day 91 females.

Based on this, fit the same background for negative and positive tmpstds except for 91 days in females.

Finally, do the slopes wrt dose differ with time Do this for each sex, and compare the first two slopes to the mean of the slopes

```
> L <- matrix(0, nrow = 4, ncol = 28)
> L[1, 18] <- 2
> L[1, 22] <- -1
> L[1, 26] <- -1
> L[2, 18] <- -1
> L[2, 22] <- 2
> L[2, 26] <- -1
> L[3, 20] <- 2
> L[3, 24] <- -1
> L[3, 28] <- -1
> L[4, 20] <- -1
> L[4, 24] <- 2
> L[4, 28] <- -1
> anova(lmout, L = L)
```

```
F-test for linear combination(s)
  mridXtmonstdyXsex43829602:28:F:dose mridXtmonstdyXsex43829602:28:M:dose
```

```
1                                  2                                   0
2                                 -1                                   0
3                                  0                                   2
4                                  0                                  -1
  mridXtmonstdyXsex43829602:56:F:dose mridXtmonstdyXsex43829602:56:M:dose
1                                 -1                                   0
2                                  2                                   0
3                                  0                                  -1
4                                  0                                   2
  mridXtmonstdyXsex43829602:91:F:dose mridXtmonstdyXsex43829602:91:M:dose
1                                 -1                                   0
2                                 -1                                   0
3                                  0                                  -1
4                                  0                                  -1
  numDF denDF   F-value p-value
1     4   408 0.4994036  0.7362
```

So, the relationship with dose seems to be not changing over time, since the P-value is quite a bit larger than 0.05.

4.2 Modeling the Time-Course Parameters

The time-course parameters, *ldT* and *lTmax* apply to all the datasets, but can only be estimated from the data in the time course datasets.

Fortunately, the doses in the acute studies and those in the subchronic study overlap, so make a factor by cutting dose in even intervals, so that each interval includes doses both from acute and from sub-chronic studies. We also want to include the control (dose = 0) in one of the intervals with positive doses. Since the time course parameters have no effect in the control group, we would otherwise have a level of each parameter that could not be estimated, and the optimization algorithm would fail. Use the following groupings of dose: [0,0.1], (0.1,0.3],(0.3,0.4],(0.4,0.5],(0.5,Inf).

```
> dta$fdose <- cut(dta$dose, breaks = c(-Inf, 0.1, 0.3, 0.4, 0.5,
+     Inf))
> idta$fdose <- cut(idta$dose, breaks = c(-Inf, 0.1, 0.3, 0.4,
+     0.5, Inf))
> dta$sexXfdose <- factor(with(dta, paste(as.character(sex), as.character(fdose),
+     sep = ":")))
> idta$sexXfdose <- factor(with(idta, paste(as.character(sex),
+     as.character(fdose), sep = ":")))
```

When tmonstdy is negative in the subchronic study, dose is really 0:

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

4.3 Model Parameterization

4.3.1 Background: `lA`

The background parameter, `lA`, likely varies among subjects, and so will be treated as a random effect in the modeling: `random = lA  1| id`. It may be that the variance among subjects differs among studies and sexes. If it varies among studies, including both repeated measures studies and non-repeated measures studies in the same analysis will be difficult. To test this, run What factors do we need? We need to split out `lA` so that every reasonable background level is covered, so that we can control for variation in background among time points for each sex separatel. The repeated measures studies are set up so that each individual can serve as its own control: there are observations on each individual preceeding exposure. The mrids fall into three categories: 43442305,

a non-repeated measures acute study; 43442302 and 45079705, repeated measures acute studies with similar designs; and 43829602, a repeated measures subchronic study.

The parameterization for background is: `lA` $\sim$ `mridXtimeXsex - 1`. The following paragraphs describe the values these variables must take to make all this work.

Category 1: 43442305 There are no data for `tmpstds` $==$ 0, and this is not a repeated measures study. The levels of `mridXtimeXsex` are made by concatenating the mrid level with tmpstds.The result will be, that background levels for all observations in this mrid will be:

$$lA_{is} = \tau_{is}, i = 1, \ldots, n; s = F, M$$

where i indexes the times the animals were observed post dosing and s indexes sex.

Category 2: 43442302 and 45079705 These are two acute studies using repeated measures. Each individual was observed at time 0, so can serve as their own control, but there is also a control group observed at each time point, so potential variation among times due to methodological variation can be adjusted for. The background model is the same as in Category 1 Create `mridXtimeXsex` as for the previous category (there are no females in mrid 45079705).

Category 3: 43829602 This is a subchronic repeated measures study. Subjects were observed prior to the initiation of dosing at the beginning of the study, and before and after the daily gavage dose at each of several time points. There is a control group. Set `mridXtimeXsex` by concatenating `mrid` and `abs(tmonstdy)` except for the 91-day time point, where the before and after time points need to be distinguished. Set the dose to 0 at the negative and 0 values of tmonstdy.

```
> dta$mridXtimeXsex <- with(dta, interaction(mrid, ifelse(mrid %in%
+     "43829602", tmonstdy, tmpstds), sex, drop = TRUE, sep = ":"))
> idta$mridXtimeXsex <- with(idta, interaction(mrid, ifelse(mrid %in%
+     "43829602", tmonstdy, tmpstds), sex, drop = TRUE, sep = ":"))
> lvls <- levels(dta$mridXtimeXsex)
> levels(dta$mridXtimeXsex) <- gsub("(43829602\\:)-([25])", "\\1\\2",
+     lvls)
> lvls <- levels(idta$mridXtimeXsex)
> levels(idta$mridXtimeXsex) <- gsub("(43829602\\:)-([25])", "\\1\\2",
+     lvls)
```

4.3.2 Benchmark Dose: `lD`

Ultimately, different values of `lD` will be estimated for males and females, and variation among studies will be treated as random. For now, set `lD` $\sim$ `mrid + sex` to get initial estimates.

4.3.3 High Dose Shape: `tz`

If the dose-response has no horizontal asymptote greater than 0, or if all the responses are substantially lower than the horizontal asymptote, this parameter is not estimable. This is one of the parameters whose estimation benefits from combining datasets. Try initially estimating a single value. If that is feasible, split it between sexes, and times on study to see if the shape varies. Most likely, it will end up fixed at -10.

4.3.4 Low Dose Shape: `lg`

This seems to be usually estimable. Again, this parameter benefits from estimation on multiple datasets. Try fitting different values for the sexes, first.

4.4 Model Fitting

```
> params <- list(lA ~ mridXtimeXsex - 1, lD ~ mridbysex - 1, tz ~
+     1, lg ~ sex, ldT ~ sexXfdose - 1, lTmax ~ sexXfdose - 1)
> lAstart.lm <- lm(cheact ~ mridXtimeXsex - 1, data = subset(dta,
+     dose == 0 | tmonstdy < 0))
> Start <- with(dta, c(log(coef(lAstart.lm)), rep(log(0.1), nlevels(mridbysex)),
+     -3, c(0, 0), rep(0, nlevels(sexXfdose)), rep(log(0.5), nlevels(sexXfdose))))
> initfile <- paste("initvals-RBC-DR-2.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut2 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn2(dose2, 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 |
+             mrid), varPower()))
+     save(StartOut2, file = initfile)
+ } else load(initfile)
```

The time of peak effect, `lTmax`, is strongly intertwined with `ldT`. Try estimating a single value:

```
> par <- StartOut2$start$beta
> Start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par["tz"], par[grep("^lg", names(par))], par[grep("^ldT",
+         names(par))], mean(par[grep("^lTmax", names(par))]))
> initfile <- paste("initvals-RBC-DR-3.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut3 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn2(dose2, tmpstds, tmpstds, lA = lA, tz = tz,
+         lD = lD, lg = lg, ldT = ldT, lTmax = lTmax), data = dta,
+         params = list(lA ~ mridXtimeXsex - 1, lD ~ mridbysex -
+             1, tz ~ 1, lg ~ sex, ldT ~ sexXfdose - 1, lTmax ~
+             1), start = Start, weights = varComb(varIdent(form = ~1 |
+             mrid), varPower()))
+     save(StartOut3, file = initfile)
+ } else load(initfile)
```

This has a disturbing result. Optimization within `GetInitialValues()` results in out of range values for some parameters. It is not clear whether the problem is NaN's that result from bad coding, or from identifiability problems. Try again, using `tcmfn4()`, the model with the simplified time course. This model has been written so that it does not generate NaN's.

```
> par <- StartOut2$start$beta
> Start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par["tz"], par[grep("^lg", names(par))], rep(lTrest(mean(par[grep("^ldT",
+         names(par))]), mean(par[grep("^lTmax", names(par))])),
+         nlevels(dta$sexXfdose)))
> formals(tcmfn4)$delta <- with(dta, min(tmpstds[tmpstds > 0]))
> initfile <- paste("initvals-RBC-DR-4.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut4 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD,
+         lg = lg, lTr = lTr), data = dta, params = list(lA ~ mridXtimeXsex -
+         1, lD ~ mridbysex - 1, tz ~ 1, lg ~ sex, lTr ~ sexXfdose -
+         1), start = Start, weights = varComb(varIdent(form = ~1 |
+         mrid), varPower()))
```

```
+     save(StartOut4, file = initfile)
+ } else load(initfile)
```

The estimate of `lD.mirdbysex43442305:M` is -29 after optimizing the above, and the inverse covariance matrix has inifinite or missing values in it. If we try a redundancy analysis fixing that parameter, the largest condition index is 1600520.2, and has strong loadings (1) with `lg.sexM`, `lg.(Intercept)`, `lD.43442302:F`, `lD.43442305:F`, `lD.43829602:F`. Fixing `lg.sexM` drops the largest condition index to 19.9. So, try a model with a single level for `lg`.

```
> par <- StartOut4$start$beta
> Start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par["tz"], par[grep("^lg\\.\\(In", names(par))], par[grep("^lTr",
+         names(par))])
> formals(tcmfn4)$delta <- with(dta, min(tmpstds[tmpstds > 0]))
> initfile <- paste("initvals-RBC-DR-5.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut5 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD,
+         lg = lg, lTr = lTr), data = dta, params = list(lA ~ mridXtimeXsex -
+         1, lD ~ mridbysex - 1, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -
+         1), start = Start, weights = varComb(varIdent(form = ~1 |
+         mrid), varPower()))
+     save(StartOut5, file = initfile)
+ } else load(initfile)
```

This fixes the redundancy among `lg` and other levels of the `lD` variable, but not the problem with `lD.43442305:M`. Perhaps `lD` is overparameterized. Try `lD ~ mrid + sex - 1`, which should give an estimate for each mrid, and an offset for males.

```
> par <- StartOut5$start$beta
> lDvals <- par[grep("^lD", names(par))]
> lDvals.mrid <- tapply(lDvals, factor(sapply(strsplit(names(lDvals),
+     ":"), function(x) x[1])), mean)
> lDvals.mrid[lDvals.mrid < -70] <- -3.4
> Start <- c(par[grep("^lA", names(par))], c(lDvals.mrid, 0), par["tz"],
+     par["lg"], par[grep("^lTr", names(par))])
> formals(tcmfn4)$delta <- with(dta, min(tmpstds[tmpstds > 0]))
> initfile <- paste("initvals-RBC-DR-6.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut6 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD,
+         lg = lg, lTr = lTr), data = dta, params = list(lA ~ mridXtimeXsex -
+         1, lD ~ mrid + sex - 1, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -
+         1), start = Start, weights = varComb(varIdent(form = ~1 |
+         mrid), varPower()))
+     save(StartOut6, file = initfile)
+ } else load(initfile)
```

That seems to help (and makes it easier to get starting values for nlme). There is still pretty strong redundancy between some of the `lD` parameters and some of the `lTr` parameters. In particular, `lD.43442305` still wants to go very large negative. Try cutting fdose over a larger swath of values:

```
> dta$fdose <- cut(dta$dose, breaks = c(-Inf, 0.1, 0.3, 0.5, Inf))
> idta$fdose <- cut(idta$dose, breaks = c(-Inf, 0.1, 0.3, 0.5,
+     Inf))
> dta$sexXfdose <- factor(with(dta, paste(as.character(sex), as.character(fdose),
```

```
+     sep = ":")))
> idta$sexXfdose <- factor(with(idta, paste(as.character(sex),
+     as.character(fdose), sep = ":")))
> par <- StartOut6$start$beta
> lTrvals <- par[grep("^lTr", names(par))]
> Start <- c(par[grep("^lA", names(par))], par[grep("^lD", names(par))],
+     par["tz"], par["lg"], lTrvals[-c(2, 7)])
> formals(tcmfn4)$delta <- with(dta, min(tmpstds[tmpstds > 0]))
> initfile <- paste("initvals-RBC-DR-7.RData", sep = "")
> if (!file.exists(initfile)) {
+     StartOut7 <- GetInitialValues(cbind(resp = cheact, sd = sd,
+         n = n) ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD,
+         lg = lg, lTr = lTr), data = dta, params = list(lA ~ mridXtimeXsex -
+         1, lD ~ mrid + sex - 1, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -
+         1), start = StartOut7$start$beta, weights = varComb(varIdent(form = ~1 |
+         mrid), varPower()))
+     save(StartOut7, file = initfile)
+ } else load(initfile)
```

The problem is that data set 43442305 does not contain adequate dose-response information. The lowest dose results in an almost maximal response, so the estimate of `lD` for this group is only bounded above: decreasing `lD` decreases the residual sum of squares (and increases the likelihood). It may be that `nlme()` will be able to handle this; that the estimate of `lD` for 43442305 will be shrunk back to the values for the other studies.

```
> par <- StartOut7$start$beta
> lDvals <- par[grep("^lD", names(par))]
> lDM <- lDvals[grep("M$", names(lDvals))]
> lDInt <- mean(lDvals[grep("mrid", names(lDvals))][-1])
> Start <- c(par[grep("^lA", names(par))], c(lDInt, lDM), par["tz"],
+     par["lg"], par[grep("^lTr", names(par))])
> drmod1 <- nlme(cheact ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
+     lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+     mridXtimeXsex - 1, lD ~ sex, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -
+     1), random = list(mrid = lD ~ 1, id = lA ~ 1), start = Start,
+     weights = varComb(varIdent(form = ~1 | mrid), varPower(value = 0.84)))
```

This fails with:

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

The problem seems to be that we just cannot estimate `lg` with the other dose-response parameters. Fix it to 2. Also, rescaling the response variable seems to help. Dividing by 400 gives a standard deviation of around 1.0. Start with a constance variance model, then a model with `varPower()`, but a fixed power (0.5). Walk up the fixed powers,

```
> par <- StartOut7$start$beta
> lDvals <- par[grep("^lD", names(par))]
> lDM <- lDvals[grep("M$", names(lDvals))]
> lDInt <- mean(lDvals[grep("mrid", names(lDvals))][-1])
> Start <- c(par[grep("^lA", names(par))], c(lDInt, lDM), par["tz"],
+     par[grep("^lTr", names(par))])
> formals(tcmfn4)$lg <- log(2)
> idta$cheacts <- idta$cheact/400
> Start[grep("^lA", names(Start))] <- Start[grep("^lA", names(Start))] -
+     log(400)
> drmod1d <- nlme(cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
```

```
+     lD = lD, lTr = lTr), data = idta, fixed = list(lA ~ mridXtimeXsex -
+     1, lD ~ sex, tz ~ 1, lTr ~ sexXfdose - 1), random = list(mrid = lD ~
+     1, id = lA ~ 1), start = Start)
> drmod1 <- nlme(cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
+     lD = lD, lTr = lTr), data = idta, fixed = list(lA ~ mridXtimeXsex -
+     1, lD ~ sex, tz ~ 1, lTr ~ sexXfdose - 1), random = list(mrid = lD ~
+     1, id = lA ~ 1), start = list(fixed = fixed.effects(drmod1d),
+     random = lapply(random.effects(drmod1d), data.matrix)), weights = varComb(varIdent(form = ~1 |
+     mrid), varPower(fixed = 0.5)))
> drmod1b <- nlme(cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
+     lD = lD, lTr = lTr), data = idta, fixed = list(lA ~ mridXtimeXsex -
+     1, lD ~ sex, tz ~ 1, lTr ~ sexXfdose - 1), random = list(mrid = lD ~
+     1, id = lA ~ 1), start = list(fixed = fixed.effects(drmod1),
+     random = lapply(random.effects(drmod1), data.matrix)), weights = varComb(varIdent(form = ~1 |
+     mrid), varPower(fixed = 0.7)))
> summary(drmod1b)$tTable

                                                     Value  Std.Error  DF
lA.mridXtimeXsex43442305:1:M                    0.43394618 0.07420874 303
lA.mridXtimeXsex43442305:4:M                    0.55627293 0.06278779 303
lA.mridXtimeXsex43442305:8:M                    0.78354640 0.05444905 303
lA.mridXtimeXsex43442305:1:F                    0.74211394 0.06926089 303
lA.mridXtimeXsex43442305:4:F                    0.96501375 0.06867723 303
lA.mridXtimeXsex43442305:8:F                    0.91352699 0.06056083 303
lA.mridXtimeXsex43442302:0:M                   -0.12247938 0.06790951 720
lA.mridXtimeXsex43442302:0.5:M                  0.06846970 0.09300810 720
lA.mridXtimeXsex43442302:1:M                   -0.06574240 0.09178516 720
lA.mridXtimeXsex43442302:4:M                   -0.02833964 0.07798885 720
lA.mridXtimeXsex43442302:8:M                    0.27926724 0.06756687 720
lA.mridXtimeXsex43442302:24:M                  -0.06224768 0.07296255 720
lA.mridXtimeXsex43442302:2:M                   -0.11733301 0.09295622 720
lA.mridXtimeXsex43442302:0:F                    0.02285134 0.06536797 720
lA.mridXtimeXsex43442302:1:F                    0.09019526 0.08353371 720
lA.mridXtimeXsex43442302:2:F                    0.32314359 0.08182126 720
lA.mridXtimeXsex43442302:4:F                    0.26106998 0.07779981 720
lA.mridXtimeXsex43442302:8:F                    0.54153571 0.06628413 720
lA.mridXtimeXsex43442302:24:F                   0.29207355 0.06418629 720
lA.mridXtimeXsex43442302:0.5:F                  0.49127546 0.11545042 720
lA.mridXtimeXsex45079705:0:M                    0.72837855 0.02554595 720
lA.mridXtimeXsex45079705:0.166666666666667:M    0.76373630 0.03200211 720
lA.mridXtimeXsex45079705:0.333333333333333:M    0.65950990 0.03148909 720
lA.mridXtimeXsex45079705:0.5:M                  0.74530244 0.03093836 720
lA.mridXtimeXsex45079705:0.666666666666667:M    0.78073013 0.03118459 720
lA.mridXtimeXsex45079705:0.833333333333333:M    0.75458319 0.03201326 720
lA.mridXtimeXsex45079705:1:M                    0.68542110 0.03190743 720
lA.mridXtimeXsex45079705:1.5:M                  0.77443195 0.03189503 720
lA.mridXtimeXsex45079705:2:M                    0.70540179 0.03229791 720
lA.mridXtimeXsex45079705:3:M                    0.86375551 0.03170594 720
lA.mridXtimeXsex45079705:4:M                    0.78732616 0.03095144 720
lA.mridXtimeXsex45079705:6:M                    0.72781932 0.02908331 720
lA.mridXtimeXsex43829602:0:M                    1.17191247 0.02956158 720
lA.mridXtimeXsex43829602:28:M                   0.33087864 0.04249763 720
lA.mridXtimeXsex43829602:56:M                   0.17613903 0.04395257 720
lA.mridXtimeXsex43829602:-91:M                  0.46271578 0.04993812 720
```

```
lA.mridXtimeXsex43829602:91:M                 0.27237652 0.06988312 720
lA.mridXtimeXsex43829602:28:F                 0.90100558 0.03599407 720
lA.mridXtimeXsex43829602:0:F                  1.20059487 0.02994217 720
lA.mridXtimeXsex43829602:56:F                 1.00201004 0.03490741 720
lA.mridXtimeXsex43829602:-91:F                1.27009079 0.03884758 720
lA.mridXtimeXsex43829602:91:F                 0.99944029 0.05874275 720
lD.(Intercept)                               -4.09396122 1.02145931 720
lD.sexM                                       0.69618286 1.00845793 720
tz                                           -1.28688213 0.15961090 720
lTr.sexXfdoseF:(0.1,0.3]                      1.00314174 0.20463794 720
lTr.sexXfdoseF:(0.3,0.5]                      1.16581931 0.18814568 720
lTr.sexXfdoseF:(0.5,Inf]                      1.69424352 0.26172671 720
lTr.sexXfdoseF:(-Inf,0.1]                    -0.73926973 0.36633166 720
lTr.sexXfdoseM:(0.1,0.3]                      0.15422541 0.17477356 720
lTr.sexXfdoseM:(0.3,0.5]                      0.50655081 0.17158270 720
lTr.sexXfdoseM:(0.5,Inf]                      0.33445571 0.34009601 720
lTr.sexXfdoseM:(-Inf,0.1]                     0.67109480 0.19879299 720
                                                t-value       p-value
lA.mridXtimeXsex43442305:1:M                  5.8476422  1.289995e-08
lA.mridXtimeXsex43442305:4:M                  8.8595715  6.956169e-17
lA.mridXtimeXsex43442305:8:M                 14.3904508  3.848132e-36
lA.mridXtimeXsex43442305:1:F                 10.7147616  6.288711e-23
lA.mridXtimeXsex43442305:4:F                 14.0514359  7.030910e-35
lA.mridXtimeXsex43442305:8:F                 15.0844524  9.693664e-39
lA.mridXtimeXsex43442302:0:M                 -1.8035674  7.171705e-02
lA.mridXtimeXsex43442302:0.5:M                0.7361692  4.618675e-01
lA.mridXtimeXsex43442302:1:M                 -0.7162640  4.740606e-01
lA.mridXtimeXsex43442302:4:M                 -0.3633806  7.164272e-01
lA.mridXtimeXsex43442302:8:M                  4.1331977  3.998484e-05
lA.mridXtimeXsex43442302:24:M                -0.8531456  3.938623e-01
lA.mridXtimeXsex43442302:2:M                 -1.2622394  2.072714e-01
lA.mridXtimeXsex43442302:0:F                  0.3495800  7.267561e-01
lA.mridXtimeXsex43442302:1:F                  1.0797468  2.806165e-01
lA.mridXtimeXsex43442302:2:F                  3.9493840  8.605458e-05
lA.mridXtimeXsex43442302:4:F                  3.3556633  8.332879e-04
lA.mridXtimeXsex43442302:8:F                  8.1699146  1.385237e-15
lA.mridXtimeXsex43442302:24:F                 4.5504042  6.283347e-06
lA.mridXtimeXsex43442302:0.5:F                4.2552939  2.363727e-05
lA.mridXtimeXsex45079705:0:M                 28.5124864 2.875629e-120
lA.mridXtimeXsex45079705:0.166666666666667:M 23.8651841  3.405131e-93
lA.mridXtimeXsex45079705:0.333333333333333:M 20.9440749  1.992339e-76
lA.mridXtimeXsex45079705:0.5:M               24.0899111  1.693257e-94
lA.mridXtimeXsex45079705:0.666666666666667:M 25.0357688 5.373994e-100
lA.mridXtimeXsex45079705:0.833333333333333:M 23.5709574  1.723938e-91
lA.mridXtimeXsex45079705:1:M                 21.4815487  1.760309e-79
lA.mridXtimeXsex45079705:1.5:M               24.2806478  1.322688e-95
lA.mridXtimeXsex45079705:2:M                 21.8404780  1.573853e-81
lA.mridXtimeXsex45079705:3:M                 27.2427006 7.258015e-113
lA.mridXtimeXsex45079705:4:M                 25.4374678 2.457553e-102
lA.mridXtimeXsex45079705:6:M                 25.0253293 6.181218e-100
lA.mridXtimeXsex43829602:0:M                 39.6430990 3.516889e-183
lA.mridXtimeXsex43829602:28:M                 7.7858139  2.414362e-14
lA.mridXtimeXsex43829602:56:M                 4.0074800  6.775976e-05
lA.mridXtimeXsex43829602:-91:M                9.2657822  2.196496e-19
```

```
lA.mridXtimeXsex43829602:91:M                 3.8976007  1.062183e-04
lA.mridXtimeXsex43829602:28:F                25.0320588 5.648019e-100
lA.mridXtimeXsex43829602:0:F                 40.0971203 1.241304e-185
lA.mridXtimeXsex43829602:56:F                28.7047943 2.183522e-121
lA.mridXtimeXsex43829602:-91:F               32.6942082 1.960085e-144
lA.mridXtimeXsex43829602:91:F                17.0138500  8.105566e-55
lD.(Intercept)                               -4.0079533  6.762713e-05
lD.sexM                                       0.6903440  4.902004e-01
tz                                           -8.0626204  3.112546e-15
lTr.sexXfdoseF:(0.1,0.3]                      4.9020321  1.172845e-06
lTr.sexXfdoseF:(0.3,0.5]                      6.1963650  9.719640e-10
lTr.sexXfdoseF:(0.5,Inf]                      6.4733305  1.773238e-10
lTr.sexXfdoseF:(-Inf,0.1]                    -2.0180340  4.395814e-02
lTr.sexXfdoseM:(0.1,0.3]                      0.8824299  3.778389e-01
lTr.sexXfdoseM:(0.3,0.5]                      2.9522255  3.257541e-03
lTr.sexXfdoseM:(0.5,Inf]                      0.9834156  3.257333e-01
lTr.sexXfdoseM:(-Inf,0.1]                     3.3758473  7.753822e-04
```

Increasing the power any further results in an error:

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

This is pretty close to the power found in earlier models, so the variance is probably modeled sufficiently well to trust the P-value for the difference in `lD` between the sexes (see above table).

Refit, changing the model for `lD`, and again trying to estimate a power in the variance model:

```
> fe1b <- fixed.effects(drmod1b)
> re1 <- lapply(random.effects(drmod1b), data.matrix)
> fe1 <- c(fe1b[grep("^lA", names(fe1b))], fe1b["lD.(Intercept)"],
+     fe1b["tz"], fe1b[grep("^lTr", names(fe1b))])
> drmod1c <- nlme(cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
+     lD = lD, lTr = lTr), data = idta, fixed = list(lA ~ mridXtimeXsex -
+     1, lD ~ 1, tz ~ 1, lTr ~ sexXfdose - 1), random = list(mrid = lD ~
+     1, id = lA ~ 1), start = list(fixed = fe1, random = re1),
+     weights = varComb(varIdent(form = ~1 | mrid), varPower(value = 0.8)))
```

Now, perhaps we can estimate `lg`, too:

```
> fe1b <- fixed.effects(drmod1c)
> re1 <- lapply(random.effects(drmod1c), data.matrix)
> fe1 <- c(fe1b[grep("^lA", names(fe1b))], fe1b["lD"], fe1b["tz"],
+     log(1), fe1b[grep("^lTr", names(fe1b))])
> drmod1e <- nlme(cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz,
+     lD = lD, lg = lg, lTr = lTr), data = idta, fixed = list(lA ~
+     mridXtimeXsex - 1, lD ~ 1, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -
+     1), random = list(mrid = lD ~ 1, id = lA ~ 1), start = list(fixed = fe1,
+     random = re1), weights = varComb(varIdent(form = ~1 | mrid),
+     varPower(value = 0.8)))
```

Now, go back to `tcmfn2()`, and see if we can fit the corresponding model (and, incidentally, compare estimates from the two models). Assuming that `Tmax` is 0.15 hours (about what we saw in the human RBC data), we can convert the estimates of `lTr` from the previous model into starting values for the estimates of `ldT`:

$$
\begin{aligned}
Y &= \frac{\ln(2)T_{max}}{T_r} \\
ldT &= \ln\left(\ln\left(-\frac{\text{LambertW}\left(-\frac{Y}{\exp(Y)}\right)}{Y}\right)\right)
\end{aligned}
$$

We need to use branch -1 of `lambertw()`

```
> fe2b <- fixed.effects(drmod1e)
> Tr <- exp(fe2b[grep("^lTr", names(fe2b))])
> Y <- log(2) * 0.15/Tr
> alpha <- Re(-lambertw(-Y/exp(Y), -1)/Y)
> ldT <- log(log(alpha))
> re2 <- lapply(random.effects(drmod1e), data.matrix)
> fe2 <- c(fe2b[grep("^lA", names(fe2b))], fe2b["lD"], fe2b["tz"],
+     fe2b["lg"], ldT)
> formals(tcmfn2)$lTmax <- log(0.15)
> drmod2 <- nlme(cheacts ~ tcmfn2(dose2, tmpstds, tmpstds, lA = lA,
+     tz = tz, lD = lD, lg = lg, ldT = ldT), data = idta, fixed = list(lA ~
+     mridXtimeXsex - 1, lD ~ 1, tz ~ 1, lg ~ 1, ldT ~ sexXfdose -
+     1), random = list(mrid = lD ~ 1, id = lA ~ 1), start = list(fixed = fe2,
+     random = re2), weights = varComb(varIdent(form = ~1 | mrid),
+     varPower(value = 0.8)))
```

Success! I wonder which model gives the better fit? Refit both drmod1e and drmod2 using maximum likelihood so we can compare AIC:

```
> drmod1eML <- update(drmod1e, method = "ML")
> drmod2ML <- update(drmod2, method = "ML")
> anova(drmod1eML, drmod2ML)

          Model df      AIC      BIC    logLik
drmod1eML     1 60 884.2940 1183.266 -382.1470
drmod2ML      2 60 884.8937 1183.866 -382.4469
```

The two models achieve virtually identical log likelihoods and AICs. Since it gives direct estimates of recovery half-life, base the rest of the analysis on model `drmod1e`, the simple exponential recovery model.

```
> summary(drmod1e)

Nonlinear mixed-effects model fit by maximum likelihood
  Model: cheacts ~ tcmfn4(dose2, tmpstds, lA = lA, tz = tz, lD = lD, lg = lg,      lTr = lTr)
 Data: idta
      AIC      BIC   logLik
  884.294 1183.266 -382.147

Random effects:
 Formula: lD ~ 1 | mrid
               lD
StdDev: 0.3614691

 Formula: lA ~ 1 | id %in% mrid
        lA.(Intercept)  Residual
StdDev:     0.07579309 0.2526541

Combination of variance functions:
 Structure: Different standard deviations per stratum
 Formula: ~1 | mrid
 Parameter estimates:
 43442305  43442302  45079705  43829602
1.0000000 0.8567890 0.3849914 1.2109545
 Structure: Power of variance covariate
```

```
 Formula: ~fitted(.)
 Parameter estimates:
   power
0.821288
Fixed effects: list(lA ~ mridXtimeXsex - 1, lD ~ 1, tz ~ 1, lg ~ 1, lTr ~ sexXfdose -      1)
                                              Value Std.Error  DF   t-value
lA.mridXtimeXsex43442305:1:M                 0.417686 0.0715511 303   5.83760
lA.mridXtimeXsex43442305:4:M                 0.552954 0.0629144 303   8.78900
lA.mridXtimeXsex43442305:8:M                 0.781878 0.0566243 303  13.80815
lA.mridXtimeXsex43442305:1:F                 0.739026 0.0682258 303  10.83206
lA.mridXtimeXsex43442305:4:F                 0.978655 0.0715830 303  13.67162
lA.mridXtimeXsex43442305:8:F                 0.924048 0.0639423 303  14.45127
lA.mridXtimeXsex43442302:0:M                -0.127792 0.0692881 720  -1.84436
lA.mridXtimeXsex43442302:0.5:M               0.095064 0.0893688 720   1.06373
lA.mridXtimeXsex43442302:1:M                -0.065660 0.0885514 720  -0.74149
lA.mridXtimeXsex43442302:4:M                -0.028237 0.0791231 720  -0.35687
lA.mridXtimeXsex43442302:8:M                 0.280408 0.0716410 720   3.91407
lA.mridXtimeXsex43442302:24:M               -0.062105 0.0749229 720  -0.82892
lA.mridXtimeXsex43442302:2:M                -0.118812 0.0910940 720  -1.30428
lA.mridXtimeXsex43442302:0:F                 0.021425 0.0676641 720   0.31663
lA.mridXtimeXsex43442302:1:F                 0.089541 0.0849594 720   1.05393
lA.mridXtimeXsex43442302:2:F                 0.362511 0.0899901 720   4.02834
lA.mridXtimeXsex43442302:4:F                 0.270488 0.0821666 720   3.29195
lA.mridXtimeXsex43442302:8:F                 0.558649 0.0715364 720   7.80929
lA.mridXtimeXsex43442302:24:F                0.295213 0.0684904 720   4.31028
lA.mridXtimeXsex43442302:0.5:F               0.424565 0.0984595 720   4.31207
lA.mridXtimeXsex45079705:0:M                 0.728281 0.0255519 720  28.50210
lA.mridXtimeXsex45079705:0.166666666666667:M 0.768198 0.0359403 720  21.37431
lA.mridXtimeXsex45079705:0.333333333333333:M 0.664545 0.0350371 720  18.96692
lA.mridXtimeXsex45079705:0.5:M               0.746421 0.0342210 720  21.81177
lA.mridXtimeXsex45079705:0.666666666666667:M 0.783566 0.0339689 720  23.06713
lA.mridXtimeXsex45079705:0.833333333333333:M 0.757664 0.0344682 720  21.98152
lA.mridXtimeXsex45079705:1:M                 0.682152 0.0341177 720  19.99409
lA.mridXtimeXsex45079705:1.5:M               0.774039 0.0335704 720  23.05720
lA.mridXtimeXsex45079705:2:M                 0.705943 0.0333851 720  21.14546
lA.mridXtimeXsex45079705:3:M                 0.863042 0.0324684 720  26.58099
lA.mridXtimeXsex45079705:4:M                 0.786859 0.0312978 720  25.14106
lA.mridXtimeXsex45079705:6:M                 0.727207 0.0291129 720  24.97887
lA.mridXtimeXsex43829602:0:M                 1.171254 0.0313477 720  37.36335
lA.mridXtimeXsex43829602:28:M                0.336486 0.0403599 720   8.33714
lA.mridXtimeXsex43829602:56:M                0.177624 0.0411788 720   4.31349
lA.mridXtimeXsex43829602:-91:M               0.462674 0.0490167 720   9.43912
lA.mridXtimeXsex43829602:91:M                0.273812 0.0637968 720   4.29193
lA.mridXtimeXsex43829602:28:F                0.898199 0.0363923 720  24.68098
lA.mridXtimeXsex43829602:0:F                 1.200332 0.0318540 720  37.68234
lA.mridXtimeXsex43829602:56:F                0.992798 0.0356599 720  27.84072
lA.mridXtimeXsex43829602:-91:F               1.270510 0.0417130 720  30.45838
lA.mridXtimeXsex43829602:91:F                0.992451 0.0575362 720  17.24917
lD                                          -3.475706 0.2820115 720 -12.32470
tz                                          -1.233868 0.1461561 720  -8.44212
lg                                           0.646737 0.1802450 720   3.58810
lTr.sexXfdoseF:(0.1,0.3]                     1.069453 0.2071855 720   5.16181
lTr.sexXfdoseF:(0.3,0.5]                     1.222479 0.1918155 720   6.37320
lTr.sexXfdoseF:(0.5,Inf]                     1.775772 0.2705205 720   6.56428
```

```
lTr.sexXfdoseF:(-Inf,0.1]                    0.092615 0.4087774 720   0.22657
lTr.sexXfdoseM:(0.1,0.3]                     0.180354 0.1639428 720   1.10010
lTr.sexXfdoseM:(0.3,0.5]                     0.483078 0.1617810 720   2.98600
lTr.sexXfdoseM:(0.5,Inf]                     0.406459 0.3296719 720   1.23292
lTr.sexXfdoseM:(-Inf,0.1]                    0.647582 0.1983588 720   3.26470
                                            p-value
lA.mridXtimeXsex43442305:1:M                 0.0000
lA.mridXtimeXsex43442305:4:M                 0.0000
lA.mridXtimeXsex43442305:8:M                 0.0000
lA.mridXtimeXsex43442305:1:F                 0.0000
lA.mridXtimeXsex43442305:4:F                 0.0000
lA.mridXtimeXsex43442305:8:F                 0.0000
lA.mridXtimeXsex43442302:0:M                 0.0655
lA.mridXtimeXsex43442302:0.5:M               0.2878
lA.mridXtimeXsex43442302:1:M                 0.4586
lA.mridXtimeXsex43442302:4:M                 0.7213
lA.mridXtimeXsex43442302:8:M                 0.0001
lA.mridXtimeXsex43442302:24:M                0.4074
lA.mridXtimeXsex43442302:2:M                 0.1926
lA.mridXtimeXsex43442302:0:F                 0.7516
lA.mridXtimeXsex43442302:1:F                 0.2923
lA.mridXtimeXsex43442302:2:F                 0.0001
lA.mridXtimeXsex43442302:4:F                 0.0010
lA.mridXtimeXsex43442302:8:F                 0.0000
lA.mridXtimeXsex43442302:24:F                0.0000
lA.mridXtimeXsex43442302:0.5:F               0.0000
lA.mridXtimeXsex45079705:0:M                 0.0000
lA.mridXtimeXsex45079705:0.166666666666667:M 0.0000
lA.mridXtimeXsex45079705:0.333333333333333:M 0.0000
lA.mridXtimeXsex45079705:0.5:M               0.0000
lA.mridXtimeXsex45079705:0.666666666666667:M 0.0000
lA.mridXtimeXsex45079705:0.833333333333333:M 0.0000
lA.mridXtimeXsex45079705:1:M                 0.0000
lA.mridXtimeXsex45079705:1.5:M               0.0000
lA.mridXtimeXsex45079705:2:M                 0.0000
lA.mridXtimeXsex45079705:3:M                 0.0000
lA.mridXtimeXsex45079705:4:M                 0.0000
lA.mridXtimeXsex45079705:6:M                 0.0000
lA.mridXtimeXsex43829602:0:M                 0.0000
lA.mridXtimeXsex43829602:28:M                0.0000
lA.mridXtimeXsex43829602:56:M                0.0000
lA.mridXtimeXsex43829602:-91:M               0.0000
lA.mridXtimeXsex43829602:91:M                0.0000
lA.mridXtimeXsex43829602:28:F                0.0000
lA.mridXtimeXsex43829602:0:F                 0.0000
lA.mridXtimeXsex43829602:56:F                0.0000
lA.mridXtimeXsex43829602:-91:F               0.0000
lA.mridXtimeXsex43829602:91:F                0.0000
lD                                           0.0000
tz                                           0.0000
lg                                           0.0004
lTr.sexXfdoseF:(0.1,0.3]                     0.0000
lTr.sexXfdoseF:(0.3,0.5]                     0.0000
lTr.sexXfdoseF:(0.5,Inf]                     0.0000
```

```
lTr.sexXfdoseF:(-Inf,0.1]                      0.8208
lTr.sexXfdoseM:(0.1,0.3]                       0.2717
lTr.sexXfdoseM:(0.3,0.5]                       0.0029
lTr.sexXfdoseM:(0.5,Inf]                       0.2180
lTr.sexXfdoseM:(-Inf,0.1]                      0.0011
 Correlation:
                                              lA.XX43442305:1:M
lA.mridXtimeXsex43442305:4:M                   0.134
lA.mridXtimeXsex43442305:8:M                   0.040
lA.mridXtimeXsex43442305:1:F                  -0.002
lA.mridXtimeXsex43442305:4:F                   0.017
lA.mridXtimeXsex43442305:8:F                   0.015
lA.mridXtimeXsex43442302:0:M                   0.000
lA.mridXtimeXsex43442302:0.5:M                 0.060
lA.mridXtimeXsex43442302:1:M                   0.086
lA.mridXtimeXsex43442302:4:M                   0.066
lA.mridXtimeXsex43442302:8:M                   0.024
lA.mridXtimeXsex43442302:24:M                  0.000
lA.mridXtimeXsex43442302:2:M                   0.092
lA.mridXtimeXsex43442302:0:F                   0.000
lA.mridXtimeXsex43442302:1:F                  -0.013
lA.mridXtimeXsex43442302:2:F                  -0.018
lA.mridXtimeXsex43442302:4:F                   0.000
lA.mridXtimeXsex43442302:8:F                   0.006
lA.mridXtimeXsex43442302:24:F                  0.002
lA.mridXtimeXsex43442302:0.5:F                -0.009
lA.mridXtimeXsex45079705:0:M                   0.000
lA.mridXtimeXsex45079705:0.166666666666667:M -0.001
lA.mridXtimeXsex45079705:0.333333333333333:M  0.001
lA.mridXtimeXsex45079705:0.5:M                 0.003
lA.mridXtimeXsex45079705:0.666666666666667:M  0.004
lA.mridXtimeXsex45079705:0.833333333333333:M  0.005
lA.mridXtimeXsex45079705:1:M                   0.006
lA.mridXtimeXsex45079705:1.5:M                 0.008
lA.mridXtimeXsex45079705:2:M                   0.009
lA.mridXtimeXsex45079705:3:M                   0.010
lA.mridXtimeXsex45079705:4:M                   0.009
lA.mridXtimeXsex45079705:6:M                   0.007
lA.mridXtimeXsex43829602:0:M                   0.000
lA.mridXtimeXsex43829602:28:M                  0.122
lA.mridXtimeXsex43829602:56:M                  0.114
lA.mridXtimeXsex43829602:-91:M                 0.001
lA.mridXtimeXsex43829602:91:M                  0.161
lA.mridXtimeXsex43829602:28:F                 -0.006
lA.mridXtimeXsex43829602:0:F                   0.000
lA.mridXtimeXsex43829602:56:F                 -0.007
lA.mridXtimeXsex43829602:-91:F                 0.000
lA.mridXtimeXsex43829602:91:F                 -0.010
lD                                            -0.020
tz                                             0.044
lg                                             0.007
lTr.sexXfdoseF:(0.1,0.3]                       0.029
lTr.sexXfdoseF:(0.3,0.5]                       0.030
lTr.sexXfdoseF:(0.5,Inf]                       0.012
```

```
lTr.sexXfdoseF:(-Inf,0.1]                    -0.063
lTr.sexXfdoseM:(0.1,0.3]                      0.336
lTr.sexXfdoseM:(0.3,0.5]                      0.298
lTr.sexXfdoseM:(0.5,Inf]                      0.065
lTr.sexXfdoseM:(-Inf,0.1]                     0.020
                                             lA.XX43442305:4:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M                  0.037
lA.mridXtimeXsex43442305:1:F                 -0.012
lA.mridXtimeXsex43442305:4:F                  0.069
lA.mridXtimeXsex43442305:8:F                  0.061
lA.mridXtimeXsex43442302:0:M                  0.000
lA.mridXtimeXsex43442302:0.5:M                0.011
lA.mridXtimeXsex43442302:1:M                  0.058
lA.mridXtimeXsex43442302:4:M                  0.062
lA.mridXtimeXsex43442302:8:M                  0.023
lA.mridXtimeXsex43442302:24:M                 0.000
lA.mridXtimeXsex43442302:2:M                  0.079
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                 -0.040
lA.mridXtimeXsex43442302:2:F                 -0.023
lA.mridXtimeXsex43442302:4:F                  0.024
lA.mridXtimeXsex43442302:8:F                  0.034
lA.mridXtimeXsex43442302:24:F                 0.011
lA.mridXtimeXsex43442302:0.5:F               -0.072
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.002
lA.mridXtimeXsex45079705:0.333333333333333:M  0.004
lA.mridXtimeXsex45079705:0.5:M                0.006
lA.mridXtimeXsex45079705:0.666666666666667:M  0.007
lA.mridXtimeXsex45079705:0.833333333333333:M  0.009
lA.mridXtimeXsex45079705:1:M                  0.010
lA.mridXtimeXsex45079705:1.5:M                0.012
lA.mridXtimeXsex45079705:2:M                  0.013
lA.mridXtimeXsex45079705:3:M                  0.013
lA.mridXtimeXsex45079705:4:M                  0.012
lA.mridXtimeXsex45079705:6:M                  0.009
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.074
lA.mridXtimeXsex43829602:56:M                 0.070
lA.mridXtimeXsex43829602:-91:M                0.001
lA.mridXtimeXsex43829602:91:M                 0.098
lA.mridXtimeXsex43829602:28:F                -0.029
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.030
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.044
lD                                           -0.007
tz                                            0.177
lg                                            0.006
lTr.sexXfdoseF:(0.1,0.3]                      0.117
lTr.sexXfdoseF:(0.3,0.5]                      0.121
lTr.sexXfdoseF:(0.5,Inf]                      0.060
lTr.sexXfdoseF:(-Inf,0.1]                    -0.054
```

```
lTr.sexXfdoseM:(0.1,0.3]                      0.270
lTr.sexXfdoseM:(0.3,0.5]                      0.304
lTr.sexXfdoseM:(0.5,Inf]                      0.083
lTr.sexXfdoseM:(-Inf,0.1]                     0.025
                                             lA.XX43442305:8:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F                 -0.004
lA.mridXtimeXsex43442305:4:F                  0.023
lA.mridXtimeXsex43442305:8:F                  0.021
lA.mridXtimeXsex43442302:0:M                  0.000
lA.mridXtimeXsex43442302:0.5:M                0.003
lA.mridXtimeXsex43442302:1:M                  0.020
lA.mridXtimeXsex43442302:4:M                  0.021
lA.mridXtimeXsex43442302:8:M                  0.008
lA.mridXtimeXsex43442302:24:M                 0.000
lA.mridXtimeXsex43442302:2:M                  0.027
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                 -0.013
lA.mridXtimeXsex43442302:2:F                 -0.007
lA.mridXtimeXsex43442302:4:F                  0.008
lA.mridXtimeXsex43442302:8:F                  0.012
lA.mridXtimeXsex43442302:24:F                 0.004
lA.mridXtimeXsex43442302:0.5:F               -0.024
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.001
lA.mridXtimeXsex45079705:0.333333333333333:M  0.001
lA.mridXtimeXsex45079705:0.5:M                0.002
lA.mridXtimeXsex45079705:0.666666666666667:M  0.002
lA.mridXtimeXsex45079705:0.833333333333333:M  0.003
lA.mridXtimeXsex45079705:1:M                  0.003
lA.mridXtimeXsex45079705:1.5:M                0.004
lA.mridXtimeXsex45079705:2:M                  0.004
lA.mridXtimeXsex45079705:3:M                  0.004
lA.mridXtimeXsex45079705:4:M                  0.004
lA.mridXtimeXsex45079705:6:M                  0.003
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.021
lA.mridXtimeXsex43829602:56:M                 0.020
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.028
lA.mridXtimeXsex43829602:28:F                -0.010
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.010
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.015
lD                                           -0.002
tz                                            0.060
lg                                            0.002
lTr.sexXfdoseF:(0.1,0.3]                      0.040
lTr.sexXfdoseF:(0.3,0.5]                      0.041
lTr.sexXfdoseF:(0.5,Inf]                      0.021
lTr.sexXfdoseF:(-Inf,0.1]                    -0.017
lTr.sexXfdoseM:(0.1,0.3]                      0.074
```

```
lTr.sexXfdoseM:(0.3,0.5]                        0.104
lTr.sexXfdoseM:(0.5,Inf]                        0.028
lTr.sexXfdoseM:(-Inf,0.1]                       0.008
                                               lA.XX43442305:1:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F                    0.145
lA.mridXtimeXsex43442305:8:F                    0.104
lA.mridXtimeXsex43442302:0:M                    0.000
lA.mridXtimeXsex43442302:0.5:M                  0.017
lA.mridXtimeXsex43442302:1:M                    0.003
lA.mridXtimeXsex43442302:4:M                   -0.006
lA.mridXtimeXsex43442302:8:M                   -0.003
lA.mridXtimeXsex43442302:24:M                   0.000
lA.mridXtimeXsex43442302:2:M                   -0.004
lA.mridXtimeXsex43442302:0:F                    0.000
lA.mridXtimeXsex43442302:1:F                    0.073
lA.mridXtimeXsex43442302:2:F                    0.044
lA.mridXtimeXsex43442302:4:F                    0.068
lA.mridXtimeXsex43442302:8:F                    0.045
lA.mridXtimeXsex43442302:24:F                   0.007
lA.mridXtimeXsex43442302:0.5:F                  0.064
lA.mridXtimeXsex45079705:0:M                    0.000
lA.mridXtimeXsex45079705:0.166666666666667:M -0.005
lA.mridXtimeXsex45079705:0.333333333333333:M -0.006
lA.mridXtimeXsex45079705:0.5:M                 -0.006
lA.mridXtimeXsex45079705:0.666666666666667:M -0.006
lA.mridXtimeXsex45079705:0.833333333333333:M -0.006
lA.mridXtimeXsex45079705:1:M                   -0.006
lA.mridXtimeXsex45079705:1.5:M                 -0.006
lA.mridXtimeXsex45079705:2:M                   -0.005
lA.mridXtimeXsex45079705:3:M                   -0.005
lA.mridXtimeXsex45079705:4:M                   -0.004
lA.mridXtimeXsex45079705:6:M                   -0.003
lA.mridXtimeXsex43829602:0:M                    0.000
lA.mridXtimeXsex43829602:28:M                   0.004
lA.mridXtimeXsex43829602:56:M                   0.004
lA.mridXtimeXsex43829602:-91:M                  0.000
lA.mridXtimeXsex43829602:91:M                   0.005
lA.mridXtimeXsex43829602:28:F                   0.090
lA.mridXtimeXsex43829602:0:F                   -0.001
lA.mridXtimeXsex43829602:56:F                   0.097
lA.mridXtimeXsex43829602:-91:F                  0.000
lA.mridXtimeXsex43829602:91:F                   0.141
lD                                             -0.006
tz                                             -0.068
lg                                              0.010
lTr.sexXfdoseF:(0.1,0.3]                        0.188
lTr.sexXfdoseF:(0.3,0.5]                        0.159
lTr.sexXfdoseF:(0.5,Inf]                        0.019
lTr.sexXfdoseF:(-Inf,0.1]                       0.061
lTr.sexXfdoseM:(0.1,0.3]                       -0.032
lTr.sexXfdoseM:(0.3,0.5]                       -0.037
```

```
lTr.sexXfdoseM:(0.5,Inf]                      -0.016
lTr.sexXfdoseM:(-Inf,0.1]                     -0.006
                                              lA.XX43442305:4:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F                   0.295
lA.mridXtimeXsex43442302:0:M                   0.000
lA.mridXtimeXsex43442302:0.5:M                -0.095
lA.mridXtimeXsex43442302:1:M                  -0.019
lA.mridXtimeXsex43442302:4:M                   0.033
lA.mridXtimeXsex43442302:8:M                   0.014
lA.mridXtimeXsex43442302:24:M                 -0.001
lA.mridXtimeXsex43442302:2:M                   0.024
lA.mridXtimeXsex43442302:0:F                   0.000
lA.mridXtimeXsex43442302:1:F                  -0.009
lA.mridXtimeXsex43442302:2:F                   0.020
lA.mridXtimeXsex43442302:4:F                   0.164
lA.mridXtimeXsex43442302:8:F                   0.157
lA.mridXtimeXsex43442302:24:F                  0.039
lA.mridXtimeXsex43442302:0.5:F                -0.135
lA.mridXtimeXsex45079705:0:M                   0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.001
lA.mridXtimeXsex45079705:0.333333333333333:M  0.003
lA.mridXtimeXsex45079705:0.5:M                 0.005
lA.mridXtimeXsex45079705:0.666666666666667:M  0.007
lA.mridXtimeXsex45079705:0.833333333333333:M  0.008
lA.mridXtimeXsex45079705:1:M                   0.009
lA.mridXtimeXsex45079705:1.5:M                 0.012
lA.mridXtimeXsex45079705:2:M                   0.013
lA.mridXtimeXsex45079705:3:M                   0.013
lA.mridXtimeXsex45079705:4:M                   0.012
lA.mridXtimeXsex45079705:6:M                   0.009
lA.mridXtimeXsex43829602:0:M                   0.000
lA.mridXtimeXsex43829602:28:M                 -0.018
lA.mridXtimeXsex43829602:56:M                 -0.018
lA.mridXtimeXsex43829602:-91:M                 0.000
lA.mridXtimeXsex43829602:91:M                 -0.024
lA.mridXtimeXsex43829602:28:F                  0.036
lA.mridXtimeXsex43829602:0:F                  -0.001
lA.mridXtimeXsex43829602:56:F                  0.039
lA.mridXtimeXsex43829602:-91:F                 0.000
lA.mridXtimeXsex43829602:91:F                  0.057
lD                                             0.017
tz                                             0.391
lg                                             0.014
lTr.sexXfdoseF:(0.1,0.3]                       0.546
lTr.sexXfdoseF:(0.3,0.5]                       0.534
lTr.sexXfdoseF:(0.5,Inf]                       0.194
lTr.sexXfdoseF:(-Inf,0.1]                      0.043
lTr.sexXfdoseM:(0.1,0.3]                       0.180
lTr.sexXfdoseM:(0.3,0.5]                       0.210
lTr.sexXfdoseM:(0.5,Inf]                       0.091
```

```
lTr.sexXfdoseM:(-Inf,0.1]                      0.025
                                              lA.XX43442305:8:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M                   0.000
lA.mridXtimeXsex43442302:0.5:M                -0.084
lA.mridXtimeXsex43442302:1:M                  -0.016
lA.mridXtimeXsex43442302:4:M                   0.029
lA.mridXtimeXsex43442302:8:M                   0.012
lA.mridXtimeXsex43442302:24:M                 -0.001
lA.mridXtimeXsex43442302:2:M                   0.021
lA.mridXtimeXsex43442302:0:F                   0.000
lA.mridXtimeXsex43442302:1:F                  -0.016
lA.mridXtimeXsex43442302:2:F                   0.012
lA.mridXtimeXsex43442302:4:F                   0.133
lA.mridXtimeXsex43442302:8:F                   0.130
lA.mridXtimeXsex43442302:24:F                  0.032
lA.mridXtimeXsex43442302:0.5:F                -0.123
lA.mridXtimeXsex45079705:0:M                   0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.002
lA.mridXtimeXsex45079705:0.333333333333333:M  0.004
lA.mridXtimeXsex45079705:0.5:M                 0.005
lA.mridXtimeXsex45079705:0.666666666666667:M  0.007
lA.mridXtimeXsex45079705:0.833333333333333:M  0.008
lA.mridXtimeXsex45079705:1:M                   0.009
lA.mridXtimeXsex45079705:1.5:M                 0.011
lA.mridXtimeXsex45079705:2:M                   0.012
lA.mridXtimeXsex45079705:3:M                   0.012
lA.mridXtimeXsex45079705:4:M                   0.011
lA.mridXtimeXsex45079705:6:M                   0.008
lA.mridXtimeXsex43829602:0:M                   0.000
lA.mridXtimeXsex43829602:28:M                 -0.016
lA.mridXtimeXsex43829602:56:M                 -0.016
lA.mridXtimeXsex43829602:-91:M                 0.000
lA.mridXtimeXsex43829602:91:M                 -0.022
lA.mridXtimeXsex43829602:28:F                  0.018
lA.mridXtimeXsex43829602:0:F                   0.000
lA.mridXtimeXsex43829602:56:F                  0.020
lA.mridXtimeXsex43829602:-91:F                 0.000
lA.mridXtimeXsex43829602:91:F                  0.029
lD                                             0.015
tz                                             0.343
lg                                             0.011
lTr.sexXfdoseF:(0.1,0.3]                       0.435
lTr.sexXfdoseF:(0.3,0.5]                       0.441
lTr.sexXfdoseF:(0.5,Inf]                       0.164
lTr.sexXfdoseF:(-Inf,0.1]                      0.029
lTr.sexXfdoseM:(0.1,0.3]                       0.158
lTr.sexXfdoseM:(0.3,0.5]                       0.184
lTr.sexXfdoseM:(0.5,Inf]                       0.080
lTr.sexXfdoseM:(-Inf,0.1]                      0.022
```

	lA.XX43442302:0:M
lA.mridXtimeXsex43442305:4:M	
lA.mridXtimeXsex43442305:8:M	
lA.mridXtimeXsex43442305:1:F	
lA.mridXtimeXsex43442305:4:F	
lA.mridXtimeXsex43442305:8:F	
lA.mridXtimeXsex43442302:0:M	
lA.mridXtimeXsex43442302:0.5:M	0.081
lA.mridXtimeXsex43442302:1:M	0.082
lA.mridXtimeXsex43442302:4:M	0.092
lA.mridXtimeXsex43442302:8:M	0.102
lA.mridXtimeXsex43442302:24:M	0.097
lA.mridXtimeXsex43442302:2:M	0.080
lA.mridXtimeXsex43442302:0:F	0.000
lA.mridXtimeXsex43442302:1:F	0.000
lA.mridXtimeXsex43442302:2:F	0.000
lA.mridXtimeXsex43442302:4:F	0.000
lA.mridXtimeXsex43442302:8:F	0.000
lA.mridXtimeXsex43442302:24:F	0.000
lA.mridXtimeXsex43442302:0.5:F	0.000
lA.mridXtimeXsex45079705:0:M	0.000
lA.mridXtimeXsex45079705:0.166666666666667:M	0.000
lA.mridXtimeXsex45079705:0.333333333333333:M	0.000
lA.mridXtimeXsex45079705:0.5:M	0.000
lA.mridXtimeXsex45079705:0.666666666666667:M	0.000
lA.mridXtimeXsex45079705:0.833333333333333:M	0.000
lA.mridXtimeXsex45079705:1:M	0.000
lA.mridXtimeXsex45079705:1.5:M	0.000
lA.mridXtimeXsex45079705:2:M	0.000
lA.mridXtimeXsex45079705:3:M	0.000
lA.mridXtimeXsex45079705:4:M	0.000
lA.mridXtimeXsex45079705:6:M	0.000
lA.mridXtimeXsex43829602:0:M	0.000
lA.mridXtimeXsex43829602:28:M	0.000
lA.mridXtimeXsex43829602:56:M	0.000
lA.mridXtimeXsex43829602:-91:M	0.000
lA.mridXtimeXsex43829602:91:M	0.000
lA.mridXtimeXsex43829602:28:F	0.000
lA.mridXtimeXsex43829602:0:F	0.000
lA.mridXtimeXsex43829602:56:F	0.000
lA.mridXtimeXsex43829602:-91:F	0.000
lA.mridXtimeXsex43829602:91:F	0.000
lD	0.000
tz	0.000
lg	0.000
lTr.sexXfdoseF:(0.1,0.3]	0.000
lTr.sexXfdoseF:(0.3,0.5]	0.000
lTr.sexXfdoseF:(0.5,Inf]	0.000
lTr.sexXfdoseF:(-Inf,0.1]	0.000
lTr.sexXfdoseM:(0.1,0.3]	0.000
lTr.sexXfdoseM:(0.3,0.5]	0.001
lTr.sexXfdoseM:(0.5,Inf]	0.000
lTr.sexXfdoseM:(-Inf,0.1]	0.000
	lA.XX43442302:0.5:M

```
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M                  0.315
lA.mridXtimeXsex43442302:4:M                  0.161
lA.mridXtimeXsex43442302:8:M                  0.109
lA.mridXtimeXsex43442302:24:M                 0.083
lA.mridXtimeXsex43442302:2:M                  0.225
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                  0.089
lA.mridXtimeXsex43442302:2:F                  0.019
lA.mridXtimeXsex43442302:4:F                 -0.043
lA.mridXtimeXsex43442302:8:F                 -0.050
lA.mridXtimeXsex43442302:24:F                -0.012
lA.mridXtimeXsex43442302:0.5:F                0.225
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.002
lA.mridXtimeXsex45079705:0.333333333333333:M  0.000
lA.mridXtimeXsex45079705:0.5:M               -0.002
lA.mridXtimeXsex45079705:0.666666666666667:M -0.004
lA.mridXtimeXsex45079705:0.833333333333333:M -0.005
lA.mridXtimeXsex45079705:1:M                 -0.006
lA.mridXtimeXsex45079705:1.5:M               -0.008
lA.mridXtimeXsex45079705:2:M                 -0.010
lA.mridXtimeXsex45079705:3:M                 -0.010
lA.mridXtimeXsex45079705:4:M                 -0.010
lA.mridXtimeXsex45079705:6:M                 -0.008
lA.mridXtimeXsex43829602:0:M                  0.001
lA.mridXtimeXsex43829602:28:M                 0.068
lA.mridXtimeXsex43829602:56:M                 0.068
lA.mridXtimeXsex43829602:-91:M                0.001
lA.mridXtimeXsex43829602:91:M                 0.094
lA.mridXtimeXsex43829602:28:F                 0.027
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.028
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.040
lD                                           -0.086
tz                                           -0.241
lg                                           -0.007
lTr.sexXfdoseF:(0.1,0.3]                     -0.165
lTr.sexXfdoseF:(0.3,0.5]                     -0.163
lTr.sexXfdoseF:(0.5,Inf]                     -0.080
lTr.sexXfdoseF:(-Inf,0.1]                    -0.112
lTr.sexXfdoseM:(0.1,0.3]                     -0.060
lTr.sexXfdoseM:(0.3,0.5]                      0.045
lTr.sexXfdoseM:(0.5,Inf]                      0.286
lTr.sexXfdoseM:(-Inf,0.1]                    -0.021
                                             lA.XX43442302:1:M
lA.mridXtimeXsex43442305:4:M
```

```
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M                  0.196
lA.mridXtimeXsex43442302:8:M                  0.129
lA.mridXtimeXsex43442302:24:M                 0.089
lA.mridXtimeXsex43442302:2:M                  0.254
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                  0.042
lA.mridXtimeXsex43442302:2:F                  0.005
lA.mridXtimeXsex43442302:4:F                 -0.010
lA.mridXtimeXsex43442302:8:F                 -0.009
lA.mridXtimeXsex43442302:24:F                 0.000
lA.mridXtimeXsex43442302:0.5:F                0.118
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.005
lA.mridXtimeXsex45079705:0.333333333333333:M  0.010
lA.mridXtimeXsex45079705:0.5:M                0.014
lA.mridXtimeXsex45079705:0.666666666666667:M  0.018
lA.mridXtimeXsex45079705:0.833333333333333:M  0.021
lA.mridXtimeXsex45079705:1:M                  0.023
lA.mridXtimeXsex45079705:1.5:M                0.028
lA.mridXtimeXsex45079705:2:M                  0.030
lA.mridXtimeXsex45079705:3:M                  0.031
lA.mridXtimeXsex45079705:4:M                  0.029
lA.mridXtimeXsex45079705:6:M                  0.021
lA.mridXtimeXsex43829602:0:M                  0.001
lA.mridXtimeXsex43829602:28:M                 0.068
lA.mridXtimeXsex43829602:56:M                 0.067
lA.mridXtimeXsex43829602:-91:M                0.001
lA.mridXtimeXsex43829602:91:M                 0.093
lA.mridXtimeXsex43829602:28:F                -0.003
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.004
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.006
lD                                           -0.067
tz                                           -0.046
lg                                           -0.004
lTr.sexXfdoseF:(0.1,0.3]                     -0.035
lTr.sexXfdoseF:(0.3,0.5]                     -0.030
lTr.sexXfdoseF:(0.5,Inf]                     -0.011
lTr.sexXfdoseF:(-Inf,0.1]                    -0.101
lTr.sexXfdoseM:(0.1,0.3]                      0.041
lTr.sexXfdoseM:(0.3,0.5]                      0.196
lTr.sexXfdoseM:(0.5,Inf]                      0.347
lTr.sexXfdoseM:(-Inf,0.1]                     0.058
                                             lA.XX43442302:4:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
```

```
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M                  0.137
lA.mridXtimeXsex43442302:24:M                 0.102
lA.mridXtimeXsex43442302:2:M                  0.195
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                 -0.006
lA.mridXtimeXsex43442302:2:F                 -0.002
lA.mridXtimeXsex43442302:4:F                  0.014
lA.mridXtimeXsex43442302:8:F                  0.018
lA.mridXtimeXsex43442302:24:F                 0.006
lA.mridXtimeXsex43442302:0.5:F               -0.007
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.008
lA.mridXtimeXsex45079705:0.333333333333333:M  0.020
lA.mridXtimeXsex45079705:0.5:M                0.030
lA.mridXtimeXsex45079705:0.666666666666667:M  0.038
lA.mridXtimeXsex45079705:0.833333333333333:M  0.046
lA.mridXtimeXsex45079705:1:M                  0.052
lA.mridXtimeXsex45079705:1.5:M                0.064
lA.mridXtimeXsex45079705:2:M                  0.070
lA.mridXtimeXsex45079705:3:M                  0.072
lA.mridXtimeXsex45079705:4:M                  0.067
lA.mridXtimeXsex45079705:6:M                  0.050
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.039
lA.mridXtimeXsex43829602:56:M                 0.039
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.053
lA.mridXtimeXsex43829602:28:F                -0.018
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.019
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.028
lD                                           -0.018
tz                                            0.084
lg                                           -0.004
lTr.sexXfdoseF:(0.1,0.3]                      0.054
lTr.sexXfdoseF:(0.3,0.5]                      0.059
lTr.sexXfdoseF:(0.5,Inf]                      0.033
lTr.sexXfdoseF:(-Inf,0.1]                    -0.027
lTr.sexXfdoseM:(0.1,0.3]                      0.081
lTr.sexXfdoseM:(0.3,0.5]                      0.204
lTr.sexXfdoseM:(0.5,Inf]                      0.197
lTr.sexXfdoseM:(-Inf,0.1]                     0.137
                                             lA.XX43442302:8:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
```

```
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M                 0.110
lA.mridXtimeXsex43442302:2:M                  0.133
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                 -0.004
lA.mridXtimeXsex43442302:2:F                  0.000
lA.mridXtimeXsex43442302:4:F                  0.007
lA.mridXtimeXsex43442302:8:F                  0.008
lA.mridXtimeXsex43442302:24:F                 0.003
lA.mridXtimeXsex43442302:0.5:F               -0.009
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.004
lA.mridXtimeXsex45079705:0.333333333333333:M  0.010
lA.mridXtimeXsex45079705:0.5:M                0.015
lA.mridXtimeXsex45079705:0.666666666666667:M  0.019
lA.mridXtimeXsex45079705:0.833333333333333:M  0.023
lA.mridXtimeXsex45079705:1:M                  0.026
lA.mridXtimeXsex45079705:1.5:M                0.032
lA.mridXtimeXsex45079705:2:M                  0.035
lA.mridXtimeXsex45079705:3:M                  0.036
lA.mridXtimeXsex45079705:4:M                  0.034
lA.mridXtimeXsex45079705:6:M                  0.025
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.013
lA.mridXtimeXsex43829602:56:M                 0.013
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.018
lA.mridXtimeXsex43829602:28:F                -0.007
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.008
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.011
lD                                           -0.003
tz                                            0.036
lg                                           -0.002
lTr.sexXfdoseF:(0.1,0.3]                      0.024
lTr.sexXfdoseF:(0.3,0.5]                      0.025
lTr.sexXfdoseF:(0.5,Inf]                      0.014
lTr.sexXfdoseF:(-Inf,0.1]                    -0.002
lTr.sexXfdoseM:(0.1,0.3]                      0.031
lTr.sexXfdoseM:(0.3,0.5]                      0.076
lTr.sexXfdoseM:(0.5,Inf]                      0.083
lTr.sexXfdoseM:(-Inf,0.1]                     0.069
                                             lA.XX43442302:24:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
```

```
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M                  0.090
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                  0.000
lA.mridXtimeXsex43442302:2:F                  0.000
lA.mridXtimeXsex43442302:4:F                  0.000
lA.mridXtimeXsex43442302:8:F                  0.000
lA.mridXtimeXsex43442302:24:F                 0.000
lA.mridXtimeXsex43442302:0.5:F                0.000
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.000
lA.mridXtimeXsex45079705:0.333333333333333:M  0.000
lA.mridXtimeXsex45079705:0.5:M                0.000
lA.mridXtimeXsex45079705:0.666666666666667:M  0.000
lA.mridXtimeXsex45079705:0.833333333333333:M  0.000
lA.mridXtimeXsex45079705:1:M                  0.000
lA.mridXtimeXsex45079705:1.5:M                0.000
lA.mridXtimeXsex45079705:2:M                  0.000
lA.mridXtimeXsex45079705:3:M                  0.001
lA.mridXtimeXsex45079705:4:M                  0.000
lA.mridXtimeXsex45079705:6:M                  0.000
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.000
lA.mridXtimeXsex43829602:56:M                 0.000
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.000
lA.mridXtimeXsex43829602:28:F                 0.000
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.000
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.001
lD                                            0.000
tz                                           -0.002
lg                                            0.000
lTr.sexXfdoseF:(0.1,0.3]                     -0.001
lTr.sexXfdoseF:(0.3,0.5]                     -0.001
lTr.sexXfdoseF:(0.5,Inf]                     -0.001
lTr.sexXfdoseF:(-Inf,0.1]                     0.001
lTr.sexXfdoseM:(0.1,0.3]                     -0.001
lTr.sexXfdoseM:(0.3,0.5]                      0.000
lTr.sexXfdoseM:(0.5,Inf]                      0.023
lTr.sexXfdoseM:(-Inf,0.1]                     0.001
                                             lA.XX43442302:2:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
```

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lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F                  0.000
lA.mridXtimeXsex43442302:1:F                  0.009
lA.mridXtimeXsex43442302:2:F                 -0.001
lA.mridXtimeXsex43442302:4:F                  0.009
lA.mridXtimeXsex43442302:8:F                  0.014
lA.mridXtimeXsex43442302:24:F                 0.006
lA.mridXtimeXsex43442302:0.5:F                0.037
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.009
lA.mridXtimeXsex45079705:0.333333333333333:M  0.020
lA.mridXtimeXsex45079705:0.5:M                0.030
lA.mridXtimeXsex45079705:0.666666666666667:M  0.037
lA.mridXtimeXsex45079705:0.833333333333333:M  0.045
lA.mridXtimeXsex45079705:1:M                  0.051
lA.mridXtimeXsex45079705:1.5:M                0.062
lA.mridXtimeXsex45079705:2:M                  0.068
lA.mridXtimeXsex45079705:3:M                  0.070
lA.mridXtimeXsex45079705:4:M                  0.065
lA.mridXtimeXsex45079705:6:M                  0.048
lA.mridXtimeXsex43829602:0:M                  0.001
lA.mridXtimeXsex43829602:28:M                 0.061
lA.mridXtimeXsex43829602:56:M                 0.060
lA.mridXtimeXsex43829602:-91:M                0.001
lA.mridXtimeXsex43829602:91:M                 0.083
lA.mridXtimeXsex43829602:28:F                -0.018
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.020
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.029
lD                                           -0.042
tz                                            0.064
lg                                           -0.004
lTr.sexXfdoseF:(0.1,0.3]                      0.039
lTr.sexXfdoseF:(0.3,0.5]                      0.045
lTr.sexXfdoseF:(0.5,Inf]                      0.027
lTr.sexXfdoseF:(-Inf,0.1]                    -0.066
lTr.sexXfdoseM:(0.1,0.3]                      0.091
lTr.sexXfdoseM:(0.3,0.5]                      0.262
lTr.sexXfdoseM:(0.5,Inf]                      0.271
lTr.sexXfdoseM:(-Inf,0.1]                     0.132
                                             lA.XX43442302:0:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
```

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lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F                  0.088
lA.mridXtimeXsex43442302:2:F                  0.083
lA.mridXtimeXsex43442302:4:F                  0.091
lA.mridXtimeXsex43442302:8:F                  0.104
lA.mridXtimeXsex43442302:24:F                 0.109
lA.mridXtimeXsex43442302:0.5:F                0.076
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.000
lA.mridXtimeXsex45079705:0.333333333333333:M  0.000
lA.mridXtimeXsex45079705:0.5:M                0.000
lA.mridXtimeXsex45079705:0.666666666666667:M  0.000
lA.mridXtimeXsex45079705:0.833333333333333:M  0.000
lA.mridXtimeXsex45079705:1:M                  0.000
lA.mridXtimeXsex45079705:1.5:M                0.000
lA.mridXtimeXsex45079705:2:M                  0.000
lA.mridXtimeXsex45079705:3:M                  0.000
lA.mridXtimeXsex45079705:4:M                  0.000
lA.mridXtimeXsex45079705:6:M                  0.000
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.000
lA.mridXtimeXsex43829602:56:M                 0.000
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.000
lA.mridXtimeXsex43829602:28:F                 0.000
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.000
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.000
lD                                            0.000
tz                                            0.000
lg                                            0.000
lTr.sexXfdoseF:(0.1,0.3]                      0.000
lTr.sexXfdoseF:(0.3,0.5]                      0.000
lTr.sexXfdoseF:(0.5,Inf]                     -0.001
lTr.sexXfdoseF:(-Inf,0.1]                     0.000
lTr.sexXfdoseM:(0.1,0.3]                      0.000
lTr.sexXfdoseM:(0.3,0.5]                      0.000
lTr.sexXfdoseM:(0.5,Inf]                      0.000
lTr.sexXfdoseM:(-Inf,0.1]                     0.000
                                             lA.XX43442302:1:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
```

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lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F                  0.215
lA.mridXtimeXsex43442302:4:F                  0.170
lA.mridXtimeXsex43442302:8:F                  0.153
lA.mridXtimeXsex43442302:24:F                 0.115
lA.mridXtimeXsex43442302:0.5:F                0.251
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.000
lA.mridXtimeXsex45079705:0.333333333333333:M  0.001
lA.mridXtimeXsex45079705:0.5:M                0.001
lA.mridXtimeXsex45079705:0.666666666666667:M  0.001
lA.mridXtimeXsex45079705:0.833333333333333:M  0.001
lA.mridXtimeXsex45079705:1:M                  0.001
lA.mridXtimeXsex45079705:1.5:M                0.001
lA.mridXtimeXsex45079705:2:M                  0.001
lA.mridXtimeXsex45079705:3:M                  0.002
lA.mridXtimeXsex45079705:4:M                  0.001
lA.mridXtimeXsex45079705:6:M                  0.001
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                -0.009
lA.mridXtimeXsex43829602:56:M                -0.011
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                -0.017
lA.mridXtimeXsex43829602:28:F                 0.090
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.096
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.140
lD                                           -0.013
tz                                           -0.216
lg                                           -0.009
lTr.sexXfdoseF:(0.1,0.3]                     -0.090
lTr.sexXfdoseF:(0.3,0.5]                     -0.006
lTr.sexXfdoseF:(0.5,Inf]                      0.137
lTr.sexXfdoseF:(-Inf,0.1]                     0.208
lTr.sexXfdoseM:(0.1,0.3]                     -0.111
lTr.sexXfdoseM:(0.3,0.5]                     -0.114
lTr.sexXfdoseM:(0.5,Inf]                     -0.030
lTr.sexXfdoseM:(-Inf,0.1]                     0.003
                                             lA.XX43442302:2:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
```

```
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F                  0.196
lA.mridXtimeXsex43442302:8:F                  0.187
lA.mridXtimeXsex43442302:24:F                 0.117
lA.mridXtimeXsex43442302:0.5:F                0.176
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.002
lA.mridXtimeXsex45079705:0.333333333333333:M  0.007
lA.mridXtimeXsex45079705:0.5:M                0.010
lA.mridXtimeXsex45079705:0.666666666666667:M  0.013
lA.mridXtimeXsex45079705:0.833333333333333:M  0.016
lA.mridXtimeXsex45079705:1:M                  0.019
lA.mridXtimeXsex45079705:1.5:M                0.023
lA.mridXtimeXsex45079705:2:M                  0.026
lA.mridXtimeXsex45079705:3:M                  0.027
lA.mridXtimeXsex45079705:4:M                  0.025
lA.mridXtimeXsex45079705:6:M                  0.019
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                -0.037
lA.mridXtimeXsex43829602:56:M                -0.040
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                -0.058
lA.mridXtimeXsex43829602:28:F                 0.072
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.078
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.114
lD                                            0.017
tz                                           -0.077
lg                                           -0.006
lTr.sexXfdoseF:(0.1,0.3]                     -0.007
lTr.sexXfdoseF:(0.3,0.5]                      0.034
lTr.sexXfdoseF:(0.5,Inf]                      0.230
lTr.sexXfdoseF:(-Inf,0.1]                     0.335
lTr.sexXfdoseM:(0.1,0.3]                     -0.061
lTr.sexXfdoseM:(0.3,0.5]                     -0.059
lTr.sexXfdoseM:(0.5,Inf]                     -0.017
lTr.sexXfdoseM:(-Inf,0.1]                     0.051
                                             lA.XX43442302:4:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
```

```
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F                  0.276
lA.mridXtimeXsex43442302:24:F                 0.154
lA.mridXtimeXsex43442302:0.5:F                0.058
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.001
lA.mridXtimeXsex45079705:0.333333333333333:M  0.005
lA.mridXtimeXsex45079705:0.5:M                0.007
lA.mridXtimeXsex45079705:0.666666666666667:M  0.010
lA.mridXtimeXsex45079705:0.833333333333333:M  0.012
lA.mridXtimeXsex45079705:1:M                  0.013
lA.mridXtimeXsex45079705:1.5:M                0.017
lA.mridXtimeXsex45079705:2:M                  0.019
lA.mridXtimeXsex45079705:3:M                  0.019
lA.mridXtimeXsex45079705:4:M                  0.018
lA.mridXtimeXsex45079705:6:M                  0.013
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                -0.026
lA.mridXtimeXsex43829602:56:M                -0.027
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                -0.039
lA.mridXtimeXsex43829602:28:F                 0.037
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.039
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.057
lD                                            0.018
tz                                            0.159
lg                                            0.004
lTr.sexXfdoseF:(0.1,0.3]                      0.174
lTr.sexXfdoseF:(0.3,0.5]                      0.306
lTr.sexXfdoseF:(0.5,Inf]                      0.353
lTr.sexXfdoseF:(-Inf,0.1]                     0.162
lTr.sexXfdoseM:(0.1,0.3]                      0.061
lTr.sexXfdoseM:(0.3,0.5]                      0.076
lTr.sexXfdoseM:(0.5,Inf]                      0.035
lTr.sexXfdoseM:(-Inf,0.1]                     0.037
                                             lA.XX43442302:8:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
```

```
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F                 0.172
lA.mridXtimeXsex43442302:0.5:F                0.039
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.001
lA.mridXtimeXsex45079705:0.333333333333333:M  0.003
lA.mridXtimeXsex45079705:0.5:M                0.005
lA.mridXtimeXsex45079705:0.666666666666667:M  0.007
lA.mridXtimeXsex45079705:0.833333333333333:M  0.008
lA.mridXtimeXsex45079705:1:M                  0.009
lA.mridXtimeXsex45079705:1.5:M                0.011
lA.mridXtimeXsex45079705:2:M                  0.012
lA.mridXtimeXsex45079705:3:M                  0.013
lA.mridXtimeXsex45079705:4:M                  0.012
lA.mridXtimeXsex45079705:6:M                  0.009
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                -0.018
lA.mridXtimeXsex43829602:56:M                -0.018
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                -0.026
lA.mridXtimeXsex43829602:28:F                 0.009
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.010
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.014
lD                                            0.013
tz                                            0.206
lg                                            0.007
lTr.sexXfdoseF:(0.1,0.3]                      0.186
lTr.sexXfdoseF:(0.3,0.5]                      0.292
lTr.sexXfdoseF:(0.5,Inf]                      0.431
lTr.sexXfdoseF:(-Inf,0.1]                     0.075
lTr.sexXfdoseM:(0.1,0.3]                      0.089
lTr.sexXfdoseM:(0.3,0.5]                      0.107
lTr.sexXfdoseM:(0.5,Inf]                      0.048
lTr.sexXfdoseM:(-Inf,0.1]                     0.025
                                             lA.XX43442302:24:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
```

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lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F                0.066
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M  0.000
lA.mridXtimeXsex45079705:0.333333333333333:M  0.001
lA.mridXtimeXsex45079705:0.5:M                0.001
lA.mridXtimeXsex45079705:0.666666666666667:M  0.002
lA.mridXtimeXsex45079705:0.833333333333333:M  0.002
lA.mridXtimeXsex45079705:1:M                  0.003
lA.mridXtimeXsex45079705:1.5:M                0.003
lA.mridXtimeXsex45079705:2:M                  0.003
lA.mridXtimeXsex45079705:3:M                  0.004
lA.mridXtimeXsex45079705:4:M                  0.003
lA.mridXtimeXsex45079705:6:M                  0.003
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                -0.006
lA.mridXtimeXsex43829602:56:M                -0.006
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                -0.008
lA.mridXtimeXsex43829602:28:F                -0.001
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.001
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.002
lD                                            0.003
tz                                            0.063
lg                                            0.002
lTr.sexXfdoseF:(0.1,0.3]                      0.051
lTr.sexXfdoseF:(0.3,0.5]                      0.070
lTr.sexXfdoseF:(0.5,Inf]                      0.154
lTr.sexXfdoseF:(-Inf,0.1]                     0.022
lTr.sexXfdoseM:(0.1,0.3]                      0.027
lTr.sexXfdoseM:(0.3,0.5]                      0.033
lTr.sexXfdoseM:(0.5,Inf]                      0.016
lTr.sexXfdoseM:(-Inf,0.1]                     0.007
                                             lA.XX43442302:0.5:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
```

```
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M                  0.000
lA.mridXtimeXsex45079705:0.166666666666667:M -0.002
lA.mridXtimeXsex45079705:0.333333333333333:M -0.007
lA.mridXtimeXsex45079705:0.5:M               -0.011
lA.mridXtimeXsex45079705:0.666666666666667:M -0.015
lA.mridXtimeXsex45079705:0.833333333333333:M -0.019
lA.mridXtimeXsex45079705:1:M                 -0.021
lA.mridXtimeXsex45079705:1.5:M               -0.027
lA.mridXtimeXsex45079705:2:M                 -0.030
lA.mridXtimeXsex45079705:3:M                 -0.031
lA.mridXtimeXsex45079705:4:M                 -0.029
lA.mridXtimeXsex45079705:6:M                 -0.022
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.021
lA.mridXtimeXsex43829602:56:M                 0.019
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.026
lA.mridXtimeXsex43829602:28:F                 0.103
lA.mridXtimeXsex43829602:0:F                 -0.001
lA.mridXtimeXsex43829602:56:F                 0.109
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.160
lD                                           -0.062
tz                                           -0.453
lg                                           -0.014
lTr.sexXfdoseF:(0.1,0.3]                     -0.271
lTr.sexXfdoseF:(0.3,0.5]                     -0.230
lTr.sexXfdoseF:(0.5,Inf]                     -0.049
lTr.sexXfdoseF:(-Inf,0.1]                     0.110
lTr.sexXfdoseM:(0.1,0.3]                     -0.206
lTr.sexXfdoseM:(0.3,0.5]                     -0.212
lTr.sexXfdoseM:(0.5,Inf]                     -0.043
lTr.sexXfdoseM:(-Inf,0.1]                    -0.060
                                             lA.XX45079705:0: lA.XX45079705:0.1
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
```

lA.mridXtimeXsex43442302:1:F		
lA.mridXtimeXsex43442302:2:F		
lA.mridXtimeXsex43442302:4:F		
lA.mridXtimeXsex43442302:8:F		
lA.mridXtimeXsex43442302:24:F		
lA.mridXtimeXsex43442302:0.5:F		
lA.mridXtimeXsex45079705:0:M		
lA.mridXtimeXsex45079705:0.166666666666667:M	0.313	
lA.mridXtimeXsex45079705:0.333333333333333:M	0.321	0.655
lA.mridXtimeXsex45079705:0.5:M	0.329	0.642
lA.mridXtimeXsex45079705:0.666666666666667:M	0.331	0.619
lA.mridXtimeXsex45079705:0.833333333333333:M	0.326	0.592
lA.mridXtimeXsex45079705:1:M	0.329	0.575
lA.mridXtimeXsex45079705:1.5:M	0.335	0.523
lA.mridXtimeXsex45079705:2:M	0.337	0.476
lA.mridXtimeXsex45079705:3:M	0.346	0.419
lA.mridXtimeXsex45079705:4:M	0.359	0.382
lA.mridXtimeXsex45079705:6:M	0.386	0.344
lA.mridXtimeXsex43829602:0:M	0.000	0.000
lA.mridXtimeXsex43829602:28:M	0.000	0.003
lA.mridXtimeXsex43829602:56:M	0.000	0.003
lA.mridXtimeXsex43829602:-91:M	0.000	0.000
lA.mridXtimeXsex43829602:91:M	0.000	0.004
lA.mridXtimeXsex43829602:28:F	0.000	0.000
lA.mridXtimeXsex43829602:0:F	0.000	0.000
lA.mridXtimeXsex43829602:56:F	0.000	0.000
lA.mridXtimeXsex43829602:-91:F	0.000	0.000
lA.mridXtimeXsex43829602:91:F	0.000	0.000
lD	0.000	-0.297
tz	0.000	0.003
lg	0.000	-0.446
lTr.sexXfdoseF:(0.1,0.3]	0.000	0.006
lTr.sexXfdoseF:(0.3,0.5]	0.000	0.002
lTr.sexXfdoseF:(0.5,Inf]	0.000	0.002
lTr.sexXfdoseF:(-Inf,0.1]	0.000	0.008
lTr.sexXfdoseM:(0.1,0.3]	0.000	0.006
lTr.sexXfdoseM:(0.3,0.5]	0.000	0.005
lTr.sexXfdoseM:(0.5,Inf]	0.000	0.004
lTr.sexXfdoseM:(-Inf,0.1]	-0.001	0.052
	lA.XX45079705:0.3	
lA.mridXtimeXsex43442305:4:M		
lA.mridXtimeXsex43442305:8:M		
lA.mridXtimeXsex43442305:1:F		
lA.mridXtimeXsex43442305:4:F		
lA.mridXtimeXsex43442305:8:F		
lA.mridXtimeXsex43442302:0:M		
lA.mridXtimeXsex43442302:0.5:M		
lA.mridXtimeXsex43442302:1:M		
lA.mridXtimeXsex43442302:4:M		
lA.mridXtimeXsex43442302:8:M		
lA.mridXtimeXsex43442302:24:M		
lA.mridXtimeXsex43442302:2:M		
lA.mridXtimeXsex43442302:0:F		
lA.mridXtimeXsex43442302:1:F		

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lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M                0.650
lA.mridXtimeXsex45079705:0.666666666666667:M  0.631
lA.mridXtimeXsex45079705:0.833333333333333:M  0.610
lA.mridXtimeXsex45079705:1:M                  0.600
lA.mridXtimeXsex45079705:1.5:M                0.559
lA.mridXtimeXsex45079705:2:M                  0.518
lA.mridXtimeXsex45079705:3:M                  0.463
lA.mridXtimeXsex45079705:4:M                  0.426
lA.mridXtimeXsex45079705:6:M                  0.379
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.004
lA.mridXtimeXsex43829602:56:M                 0.004
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.006
lA.mridXtimeXsex43829602:28:F                -0.001
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.002
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.002
lD                                           -0.288
tz                                            0.009
lg                                           -0.445
lTr.sexXfdoseF:(0.1,0.3]                      0.010
lTr.sexXfdoseF:(0.3,0.5]                      0.006
lTr.sexXfdoseF:(0.5,Inf]                      0.005
lTr.sexXfdoseF:(-Inf,0.1]                     0.027
lTr.sexXfdoseM:(0.1,0.3]                      0.009
lTr.sexXfdoseM:(0.3,0.5]                      0.012
lTr.sexXfdoseM:(0.5,Inf]                      0.009
lTr.sexXfdoseM:(-Inf,0.1]                     0.139
                                             lA.XX45079705:0.5
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
```

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lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M  0.639
lA.mridXtimeXsex45079705:0.833333333333333:M  0.622
lA.mridXtimeXsex45079705:1:M                  0.617
lA.mridXtimeXsex45079705:1.5:M                0.586
lA.mridXtimeXsex45079705:2:M                  0.551
lA.mridXtimeXsex45079705:3:M                  0.500
lA.mridXtimeXsex45079705:4:M                  0.463
lA.mridXtimeXsex45079705:6:M                  0.410
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.005
lA.mridXtimeXsex43829602:56:M                 0.005
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.007
lA.mridXtimeXsex43829602:28:F                -0.003
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.003
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.004
lD                                           -0.271
tz                                            0.013
lg                                           -0.427
lTr.sexXfdoseF:(0.1,0.3]                      0.013
lTr.sexXfdoseF:(0.3,0.5]                      0.009
lTr.sexXfdoseF:(0.5,Inf]                      0.008
lTr.sexXfdoseF:(-Inf,0.1]                     0.043
lTr.sexXfdoseM:(0.1,0.3]                      0.013
lTr.sexXfdoseM:(0.3,0.5]                      0.017
lTr.sexXfdoseM:(0.5,Inf]                      0.013
lTr.sexXfdoseM:(-Inf,0.1]                     0.212
                                             lA.XX45079705:0.6
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
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lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M  0.623
lA.mridXtimeXsex45079705:1:M                  0.619
lA.mridXtimeXsex45079705:1.5:M                0.597
lA.mridXtimeXsex45079705:2:M                  0.568
lA.mridXtimeXsex45079705:3:M                  0.527
lA.mridXtimeXsex45079705:4:M                  0.490
lA.mridXtimeXsex45079705:6:M                  0.434
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.006
lA.mridXtimeXsex43829602:56:M                 0.006
lA.mridXtimeXsex43829602:-91:M                0.000
lA.mridXtimeXsex43829602:91:M                 0.008
lA.mridXtimeXsex43829602:28:F                -0.004
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                -0.004
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                -0.006
lD                                           -0.244
tz                                            0.017
lg                                           -0.393
lTr.sexXfdoseF:(0.1,0.3]                      0.015
lTr.sexXfdoseF:(0.3,0.5]                      0.012
lTr.sexXfdoseF:(0.5,Inf]                      0.011
lTr.sexXfdoseF:(-Inf,0.1]                     0.056
lTr.sexXfdoseM:(0.1,0.3]                      0.015
lTr.sexXfdoseM:(0.3,0.5]                      0.022
lTr.sexXfdoseM:(0.5,Inf]                      0.016
lTr.sexXfdoseM:(-Inf,0.1]                     0.272
                                             lA.XX45079705:0.8 lA.XX45079705:1:
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
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lA.mridXtimeXsex43442302:24:F		
lA.mridXtimeXsex43442302:0.5:F		
lA.mridXtimeXsex45079705:0:M		
lA.mridXtimeXsex45079705:0.166666666666667:M		
lA.mridXtimeXsex45079705:0.333333333333333:M		
lA.mridXtimeXsex45079705:0.5:M		
lA.mridXtimeXsex45079705:0.666666666666667:M		
lA.mridXtimeXsex45079705:0.833333333333333:M		
lA.mridXtimeXsex45079705:1:M	0.620	
lA.mridXtimeXsex45079705:1.5:M	0.607	0.619
lA.mridXtimeXsex45079705:2:M	0.584	0.600
lA.mridXtimeXsex45079705:3:M	0.548	0.564
lA.mridXtimeXsex45079705:4:M	0.512	0.529
lA.mridXtimeXsex45079705:6:M	0.452	0.466
lA.mridXtimeXsex43829602:0:M	0.000	0.000
lA.mridXtimeXsex43829602:28:M	0.006	0.007
lA.mridXtimeXsex43829602:56:M	0.006	0.007
lA.mridXtimeXsex43829602:-91:M	0.000	0.000
lA.mridXtimeXsex43829602:91:M	0.009	0.010
lA.mridXtimeXsex43829602:28:F	-0.004	-0.005
lA.mridXtimeXsex43829602:0:F	0.000	0.000
lA.mridXtimeXsex43829602:56:F	-0.005	-0.005
lA.mridXtimeXsex43829602:-91:F	0.000	0.000
lA.mridXtimeXsex43829602:91:F	-0.007	-0.008
lD	-0.225	-0.214
tz	0.021	0.023
lg	-0.371	-0.360
lTr.sexXfdoseF:(0.1,0.3]	0.017	0.019
lTr.sexXfdoseF:(0.3,0.5]	0.015	0.017
lTr.sexXfdoseF:(0.5,Inf]	0.013	0.015
lTr.sexXfdoseF:(-Inf,0.1]	0.069	0.079
lTr.sexXfdoseM:(0.1,0.3]	0.017	0.019
lTr.sexXfdoseM:(0.3,0.5]	0.026	0.030
lTr.sexXfdoseM:(0.5,Inf]	0.019	0.021
lTr.sexXfdoseM:(-Inf,0.1]	0.330	0.373
	lA.XX45079705:1.	lA.XX45079705:2
lA.mridXtimeXsex43442305:4:M		
lA.mridXtimeXsex43442305:8:M		
lA.mridXtimeXsex43442305:1:F		
lA.mridXtimeXsex43442305:4:F		
lA.mridXtimeXsex43442305:8:F		
lA.mridXtimeXsex43442302:0:M		
lA.mridXtimeXsex43442302:0.5:M		
lA.mridXtimeXsex43442302:1:M		
lA.mridXtimeXsex43442302:4:M		
lA.mridXtimeXsex43442302:8:M		
lA.mridXtimeXsex43442302:24:M		
lA.mridXtimeXsex43442302:2:M		
lA.mridXtimeXsex43442302:0:F		
lA.mridXtimeXsex43442302:1:F		
lA.mridXtimeXsex43442302:2:F		
lA.mridXtimeXsex43442302:4:F		
lA.mridXtimeXsex43442302:8:F		
lA.mridXtimeXsex43442302:24:F		

lA.mridXtimeXsex43442302:0.5:F		
lA.mridXtimeXsex45079705:0:M		
lA.mridXtimeXsex45079705:0.166666666666667:M		
lA.mridXtimeXsex45079705:0.333333333333333:M		
lA.mridXtimeXsex45079705:0.5:M		
lA.mridXtimeXsex45079705:0.666666666666667:M		
lA.mridXtimeXsex45079705:0.833333333333333:M		
lA.mridXtimeXsex45079705:1:M		
lA.mridXtimeXsex45079705:1.5:M		
lA.mridXtimeXsex45079705:2:M	0.621	
lA.mridXtimeXsex45079705:3:M	0.597	0.605
lA.mridXtimeXsex45079705:4:M	0.565	0.576
lA.mridXtimeXsex45079705:6:M	0.498	0.510
lA.mridXtimeXsex43829602:0:M	0.000	0.000
lA.mridXtimeXsex43829602:28:M	0.008	0.008
lA.mridXtimeXsex43829602:56:M	0.008	0.009
lA.mridXtimeXsex43829602:-91:M	0.000	0.000
lA.mridXtimeXsex43829602:91:M	0.012	0.012
lA.mridXtimeXsex43829602:28:F	-0.007	-0.007
lA.mridXtimeXsex43829602:0:F	0.000	0.000
lA.mridXtimeXsex43829602:56:F	-0.007	-0.008
lA.mridXtimeXsex43829602:-91:F	0.000	0.000
lA.mridXtimeXsex43829602:91:F	-0.010	-0.011
lD	-0.168	-0.132
tz	0.029	0.032
lg	-0.302	-0.252
lTr.sexXfdoseF:(0.1,0.3]	0.022	0.023
lTr.sexXfdoseF:(0.3,0.5]	0.021	0.023
lTr.sexXfdoseF:(0.5,Inf]	0.018	0.020
lTr.sexXfdoseF:(-Inf,0.1]	0.099	0.108
lTr.sexXfdoseM:(0.1,0.3]	0.023	0.024
lTr.sexXfdoseM:(0.3,0.5]	0.037	0.040
lTr.sexXfdoseM:(0.5,Inf]	0.026	0.028
lTr.sexXfdoseM:(-Inf,0.1]	0.463	0.505
	lA.XX45079705:3	lA.XX45079705:4
lA.mridXtimeXsex43442305:4:M		
lA.mridXtimeXsex43442305:8:M		
lA.mridXtimeXsex43442305:1:F		
lA.mridXtimeXsex43442305:4:F		
lA.mridXtimeXsex43442305:8:F		
lA.mridXtimeXsex43442302:0:M		
lA.mridXtimeXsex43442302:0.5:M		
lA.mridXtimeXsex43442302:1:M		
lA.mridXtimeXsex43442302:4:M		
lA.mridXtimeXsex43442302:8:M		
lA.mridXtimeXsex43442302:24:M		
lA.mridXtimeXsex43442302:2:M		
lA.mridXtimeXsex43442302:0:F		
lA.mridXtimeXsex43442302:1:F		
lA.mridXtimeXsex43442302:2:F		
lA.mridXtimeXsex43442302:4:F		
lA.mridXtimeXsex43442302:8:F		
lA.mridXtimeXsex43442302:24:F		
lA.mridXtimeXsex43442302:0.5:F		

lA.mridXtimeXsex45079705:0:M		
lA.mridXtimeXsex45079705:0.166666666666667:M		
lA.mridXtimeXsex45079705:0.333333333333333:M		
lA.mridXtimeXsex45079705:0.5:M		
lA.mridXtimeXsex45079705:0.666666666666667:M		
lA.mridXtimeXsex45079705:0.833333333333333:M		
lA.mridXtimeXsex45079705:1:M		
lA.mridXtimeXsex45079705:1.5:M		
lA.mridXtimeXsex45079705:2:M		
lA.mridXtimeXsex45079705:3:M		
lA.mridXtimeXsex45079705:4:M	0.582	
lA.mridXtimeXsex45079705:6:M	0.523	0.517
lA.mridXtimeXsex43829602:0:M	0.000	0.000
lA.mridXtimeXsex43829602:28:M	0.008	0.008
lA.mridXtimeXsex43829602:56:M	0.009	0.008
lA.mridXtimeXsex43829602:-91:M	0.000	0.000
lA.mridXtimeXsex43829602:91:M	0.012	0.011
lA.mridXtimeXsex43829602:28:F	-0.008	-0.007
lA.mridXtimeXsex43829602:0:F	0.000	0.000
lA.mridXtimeXsex43829602:56:F	-0.008	-0.008
lA.mridXtimeXsex43829602:-91:F	0.000	0.000
lA.mridXtimeXsex43829602:91:F	-0.012	-0.011
lD	-0.084	-0.055
tz	0.033	0.031
lg	-0.184	-0.137
lTr.sexXfdoseF:(0.1,0.3]	0.024	0.022
lTr.sexXfdoseF:(0.3,0.5]	0.024	0.022
lTr.sexXfdoseF:(0.5,Inf]	0.021	0.019
lTr.sexXfdoseF:(-Inf,0.1]	0.113	0.105
lTr.sexXfdoseM:(0.1,0.3]	0.025	0.023
lTr.sexXfdoseM:(0.3,0.5]	0.041	0.038
lTr.sexXfdoseM:(0.5,Inf]	0.028	0.026
lTr.sexXfdoseM:(-Inf,0.1]	0.524	0.487
	lA.XX45079705:6	lA.XX43829602:0:M
lA.mridXtimeXsex43442305:4:M		
lA.mridXtimeXsex43442305:8:M		
lA.mridXtimeXsex43442305:1:F		
lA.mridXtimeXsex43442305:4:F		
lA.mridXtimeXsex43442305:8:F		
lA.mridXtimeXsex43442302:0:M		
lA.mridXtimeXsex43442302:0.5:M		
lA.mridXtimeXsex43442302:1:M		
lA.mridXtimeXsex43442302:4:M		
lA.mridXtimeXsex43442302:8:M		
lA.mridXtimeXsex43442302:24:M		
lA.mridXtimeXsex43442302:2:M		
lA.mridXtimeXsex43442302:0:F		
lA.mridXtimeXsex43442302:1:F		
lA.mridXtimeXsex43442302:2:F		
lA.mridXtimeXsex43442302:4:F		
lA.mridXtimeXsex43442302:8:F		
lA.mridXtimeXsex43442302:24:F		
lA.mridXtimeXsex43442302:0.5:F		
lA.mridXtimeXsex45079705:0:M		

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lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M                  0.000
lA.mridXtimeXsex43829602:28:M                 0.006           0.061
lA.mridXtimeXsex43829602:56:M                 0.006           0.062
lA.mridXtimeXsex43829602:-91:M                0.000           0.049
lA.mridXtimeXsex43829602:91:M                 0.008           0.039
lA.mridXtimeXsex43829602:28:F                -0.005           0.000
lA.mridXtimeXsex43829602:0:F                  0.000           0.000
lA.mridXtimeXsex43829602:56:F                -0.006           0.000
lA.mridXtimeXsex43829602:-91:F                0.000           0.000
lA.mridXtimeXsex43829602:91:F                -0.008           0.000
lD                                           -0.024           0.000
tz                                            0.023           0.000
lg                                           -0.077           0.000
lTr.sexXfdoseF:(0.1,0.3]                      0.016           0.000
lTr.sexXfdoseF:(0.3,0.5]                      0.017           0.000
lTr.sexXfdoseF:(0.5,Inf]                      0.014           0.000
lTr.sexXfdoseF:(-Inf,0.1]                     0.079           0.000
lTr.sexXfdoseM:(0.1,0.3]                      0.017          -0.002
lTr.sexXfdoseM:(0.3,0.5]                      0.028           0.002
lTr.sexXfdoseM:(0.5,Inf]                      0.020           0.000
lTr.sexXfdoseM:(-Inf,0.1]                     0.363           0.000
                                             lA.XX43829602:28:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
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lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M                 0.158
lA.mridXtimeXsex43829602:-91:M                0.036
lA.mridXtimeXsex43829602:91:M                 0.190
lA.mridXtimeXsex43829602:28:F                 0.014
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.015
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.022
lD                                           -0.038
tz                                           -0.047
lg                                           -0.003
lTr.sexXfdoseF:(0.1,0.3]                     -0.029
lTr.sexXfdoseF:(0.3,0.5]                     -0.034
lTr.sexXfdoseF:(0.5,Inf]                     -0.030
lTr.sexXfdoseF:(-Inf,0.1]                    -0.132
lTr.sexXfdoseM:(0.1,0.3]                      0.192
lTr.sexXfdoseM:(0.3,0.5]                      0.148
lTr.sexXfdoseM:(0.5,Inf]                      0.030
lTr.sexXfdoseM:(-Inf,0.1]                     0.015
                                             lA.XX43829602:56:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
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lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M                0.037
lA.mridXtimeXsex43829602:91:M                 0.188
lA.mridXtimeXsex43829602:28:F                 0.014
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.015
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.022
lD                                           -0.039
tz                                           -0.045
lg                                           -0.003
lTr.sexXfdoseF:(0.1,0.3]                     -0.028
lTr.sexXfdoseF:(0.3,0.5]                     -0.033
lTr.sexXfdoseF:(0.5,Inf]                     -0.031
lTr.sexXfdoseF:(-Inf,0.1]                    -0.139
lTr.sexXfdoseM:(0.1,0.3]                      0.175
lTr.sexXfdoseM:(0.3,0.5]                      0.144
lTr.sexXfdoseM:(0.5,Inf]                      0.030
lTr.sexXfdoseM:(-Inf,0.1]                     0.015
                                             lA.XX43829602:-91:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
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lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M                 0.047
lA.mridXtimeXsex43829602:28:F                 0.000
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.000
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.000
lD                                            0.000
tz                                           -0.001
lg                                            0.000
lTr.sexXfdoseF:(0.1,0.3]                      0.000
lTr.sexXfdoseF:(0.3,0.5]                      0.000
lTr.sexXfdoseF:(0.5,Inf]                      0.000
lTr.sexXfdoseF:(-Inf,0.1]                     0.000
lTr.sexXfdoseM:(0.1,0.3]                      0.001
lTr.sexXfdoseM:(0.3,0.5]                      0.002
lTr.sexXfdoseM:(0.5,Inf]                      0.000
lTr.sexXfdoseM:(-Inf,0.1]                     0.000
                                             lA.XX43829602:91:M
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
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lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F                 0.020
lA.mridXtimeXsex43829602:0:F                  0.000
lA.mridXtimeXsex43829602:56:F                 0.021
lA.mridXtimeXsex43829602:-91:F                0.000
lA.mridXtimeXsex43829602:91:F                 0.031
lD                                           -0.056
tz                                           -0.062
lg                                           -0.004
lTr.sexXfdoseF:(0.1,0.3]                     -0.039
lTr.sexXfdoseF:(0.3,0.5]                     -0.046
lTr.sexXfdoseF:(0.5,Inf]                     -0.043
lTr.sexXfdoseF:(-Inf,0.1]                    -0.201
lTr.sexXfdoseM:(0.1,0.3]                      0.255
lTr.sexXfdoseM:(0.3,0.5]                      0.196
lTr.sexXfdoseM:(0.5,Inf]                      0.042
lTr.sexXfdoseM:(-Inf,0.1]                     0.022
                                             lA.XX43829602:28:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
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lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F                  0.062
lA.mridXtimeXsex43829602:56:F                 0.163
lA.mridXtimeXsex43829602:-91:F                0.047
lA.mridXtimeXsex43829602:91:F                 0.196
lD                                           -0.005
tz                                           -0.164
lg                                           -0.007
lTr.sexXfdoseF:(0.1,0.3]                      0.023
lTr.sexXfdoseF:(0.3,0.5]                      0.012
lTr.sexXfdoseF:(0.5,Inf]                     -0.020
lTr.sexXfdoseF:(-Inf,0.1]                     0.158
lTr.sexXfdoseM:(0.1,0.3]                     -0.072
lTr.sexXfdoseM:(0.3,0.5]                     -0.089
lTr.sexXfdoseM:(0.5,Inf]                     -0.046
lTr.sexXfdoseM:(-Inf,0.1]                    -0.015
                                             lA.XX43829602:0:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
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lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F                 0.072
lA.mridXtimeXsex43829602:-91:F                0.057
lA.mridXtimeXsex43829602:91:F                 0.040
lD                                            0.000
tz                                            0.001
lg                                            0.000
lTr.sexXfdoseF:(0.1,0.3]                     -0.002
lTr.sexXfdoseF:(0.3,0.5]                      0.000
lTr.sexXfdoseF:(0.5,Inf]                      0.000
lTr.sexXfdoseF:(-Inf,0.1]                     0.000
lTr.sexXfdoseM:(0.1,0.3]                      0.001
lTr.sexXfdoseM:(0.3,0.5]                      0.001
lTr.sexXfdoseM:(0.5,Inf]                      0.000
lTr.sexXfdoseM:(-Inf,0.1]                     0.000
                                             lA.XX43829602:56:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
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lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F                0.051
lA.mridXtimeXsex43829602:91:F                 0.212
lD                                           -0.005
tz                                           -0.173
lg                                           -0.008
lTr.sexXfdoseF:(0.1,0.3]                      0.030
lTr.sexXfdoseF:(0.3,0.5]                      0.011
lTr.sexXfdoseF:(0.5,Inf]                     -0.021
lTr.sexXfdoseF:(-Inf,0.1]                     0.172
lTr.sexXfdoseM:(0.1,0.3]                     -0.076
lTr.sexXfdoseM:(0.3,0.5]                     -0.094
lTr.sexXfdoseM:(0.5,Inf]                     -0.048
lTr.sexXfdoseM:(-Inf,0.1]                    -0.016
                                             lA.XX43829602:-91:F
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
```

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lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F
lA.mridXtimeXsex43829602:91:F                 0.057
lD                                            0.000
tz                                            0.000
lg                                            0.000
lTr.sexXfdoseF:(0.1,0.3]                      0.000
lTr.sexXfdoseF:(0.3,0.5]                      0.000
lTr.sexXfdoseF:(0.5,Inf]                      0.000
lTr.sexXfdoseF:(-Inf,0.1]                     0.001
lTr.sexXfdoseM:(0.1,0.3]                      0.000
lTr.sexXfdoseM:(0.3,0.5]                      0.000
lTr.sexXfdoseM:(0.5,Inf]                      0.000
lTr.sexXfdoseM:(-Inf,0.1]                     0.000
                                             lA.XX43829602:91:F lD     tz
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
```

```
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F
lA.mridXtimeXsex43829602:91:F
lD                                          -0.007
tz                                          -0.253              0.042
lg                                          -0.012              0.611  0.036
lTr.sexXfdoseF:(0.1,0.3]                     0.043              0.031  0.662
lTr.sexXfdoseF:(0.3,0.5]                     0.017              0.029  0.684
lTr.sexXfdoseF:(0.5,Inf]                    -0.030              0.020  0.354
lTr.sexXfdoseF:(-Inf,0.1]                    0.252              0.111 -0.078
lTr.sexXfdoseM:(0.1,0.3]                    -0.111             -0.005  0.460
lTr.sexXfdoseM:(0.3,0.5]                    -0.138             -0.015  0.539
lTr.sexXfdoseM:(0.5,Inf]                    -0.071             -0.032  0.235
lTr.sexXfdoseM:(-Inf,0.1]                   -0.024              0.035  0.063
                                            lg     lT.XF:(0.1 lT.XF:(0.3
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
```

```
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F
lA.mridXtimeXsex43829602:91:F
lD
tz
lg
lTr.sexXfdoseF:(0.1,0.3]                      0.013
lTr.sexXfdoseF:(0.3,0.5]                      0.025  0.618
lTr.sexXfdoseF:(0.5,Inf]                      0.012  0.273      0.349
lTr.sexXfdoseF:(-Inf,0.1]                    -0.018  0.033      0.054
lTr.sexXfdoseM:(0.1,0.3]                      0.010  0.306      0.314
lTr.sexXfdoseM:(0.3,0.5]                      0.018  0.356      0.368
lTr.sexXfdoseM:(0.5,Inf]                      0.007  0.152      0.162
lTr.sexXfdoseM:(-Inf,0.1]                    -0.056  0.042      0.046
                                             lT.XF:(0.5 lT.XF:(- lT.XM:(0.1
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
```

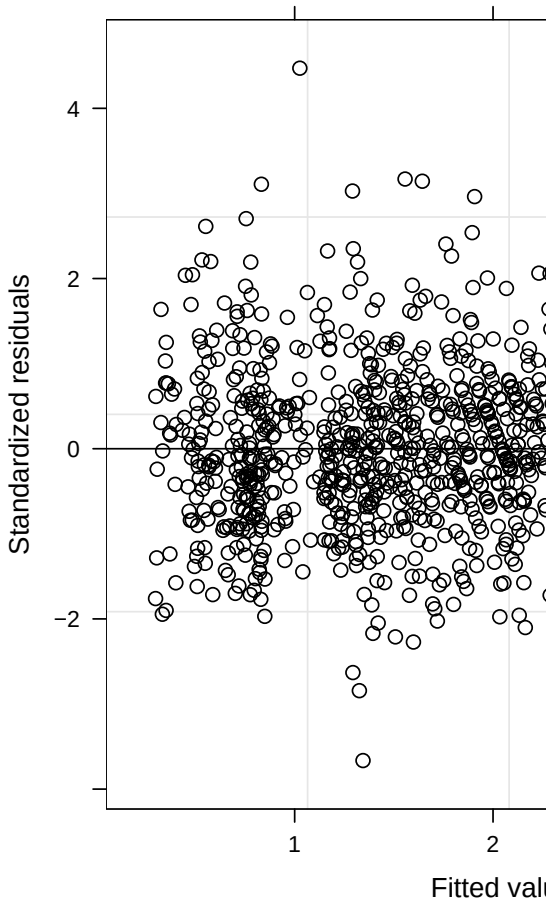
```
lA.mridXtimeXsex43829602:0:M
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F
lA.mridXtimeXsex43829602:91:F
lD
tz
lg
lTr.sexXfdoseF:(0.1,0.3]
lTr.sexXfdoseF:(0.3,0.5]
lTr.sexXfdoseF:(0.5,Inf]
lTr.sexXfdoseF:(-Inf,0.1]                    0.098
lTr.sexXfdoseM:(0.1,0.3]                     0.155     -0.125
lTr.sexXfdoseM:(0.3,0.5]                     0.187     -0.136    0.424
lTr.sexXfdoseM:(0.5,Inf]                     0.086     -0.086    0.146
lTr.sexXfdoseM:(-Inf,0.1]                    0.040      0.218    0.045
                                            lT.XM:(0.3 lT.XM:(0.5
lA.mridXtimeXsex43442305:4:M
lA.mridXtimeXsex43442305:8:M
lA.mridXtimeXsex43442305:1:F
lA.mridXtimeXsex43442305:4:F
lA.mridXtimeXsex43442305:8:F
lA.mridXtimeXsex43442302:0:M
lA.mridXtimeXsex43442302:0.5:M
lA.mridXtimeXsex43442302:1:M
lA.mridXtimeXsex43442302:4:M
lA.mridXtimeXsex43442302:8:M
lA.mridXtimeXsex43442302:24:M
lA.mridXtimeXsex43442302:2:M
lA.mridXtimeXsex43442302:0:F
lA.mridXtimeXsex43442302:1:F
lA.mridXtimeXsex43442302:2:F
lA.mridXtimeXsex43442302:4:F
lA.mridXtimeXsex43442302:8:F
lA.mridXtimeXsex43442302:24:F
lA.mridXtimeXsex43442302:0.5:F
lA.mridXtimeXsex45079705:0:M
lA.mridXtimeXsex45079705:0.166666666666667:M
lA.mridXtimeXsex45079705:0.333333333333333:M
lA.mridXtimeXsex45079705:0.5:M
lA.mridXtimeXsex45079705:0.666666666666667:M
lA.mridXtimeXsex45079705:0.833333333333333:M
lA.mridXtimeXsex45079705:1:M
lA.mridXtimeXsex45079705:1.5:M
lA.mridXtimeXsex45079705:2:M
lA.mridXtimeXsex45079705:3:M
lA.mridXtimeXsex45079705:4:M
lA.mridXtimeXsex45079705:6:M
lA.mridXtimeXsex43829602:0:M
```

```
lA.mridXtimeXsex43829602:28:M
lA.mridXtimeXsex43829602:56:M
lA.mridXtimeXsex43829602:-91:M
lA.mridXtimeXsex43829602:91:M
lA.mridXtimeXsex43829602:28:F
lA.mridXtimeXsex43829602:0:F
lA.mridXtimeXsex43829602:56:F
lA.mridXtimeXsex43829602:-91:F
lA.mridXtimeXsex43829602:91:F
lD
tz
lg
lTr.sexXfdoseF:(0.1,0.3]
lTr.sexXfdoseF:(0.3,0.5]
lTr.sexXfdoseF:(0.5,Inf]
lTr.sexXfdoseF:(-Inf,0.1]
lTr.sexXfdoseM:(0.1,0.3]
lTr.sexXfdoseM:(0.3,0.5]
lTr.sexXfdoseM:(0.5,Inf]                        0.263
lTr.sexXfdoseM:(-Inf,0.1]                       0.078      0.054

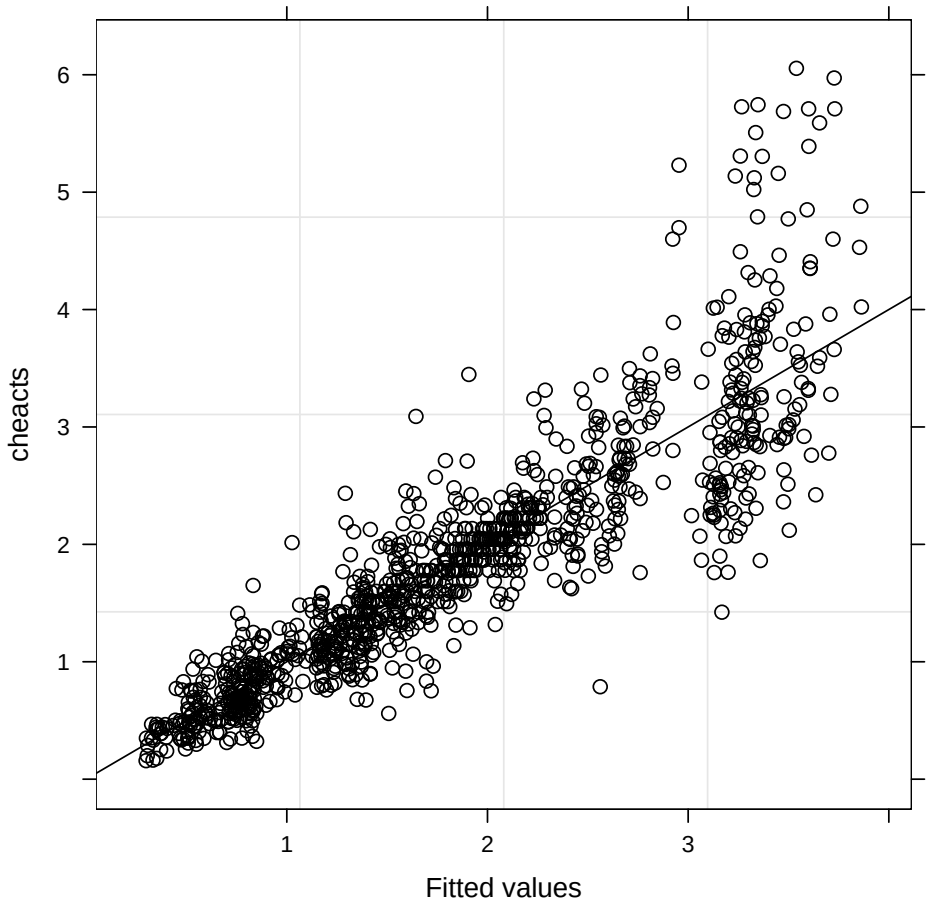
Standardized Within-Group Residuals:
        Min          Q1         Med           Q3         Max
-3.66434563 -0.62686991 -0.07443746  0.57262805  4.47217928

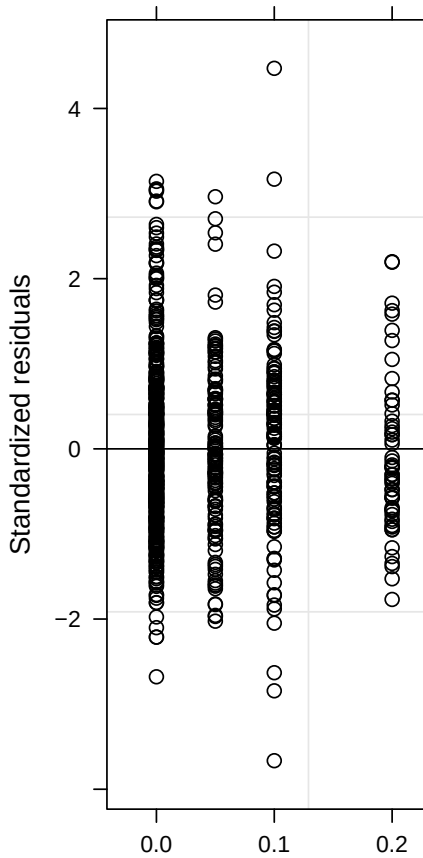
Number of Observations: 1078
Number of Groups:
        mrid id %in% mrid
           4          312
```

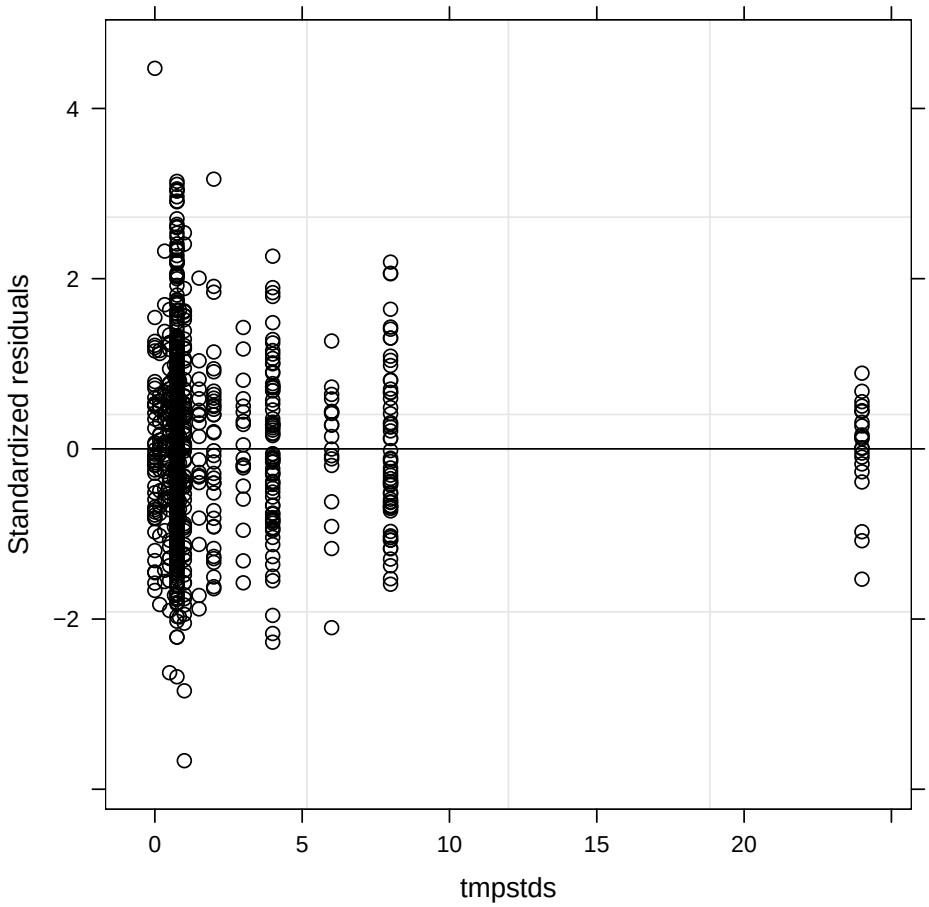
Graphs of the fit: Pearson residuals versus fitted value, (scaled) observed value versus fitted value (with identity



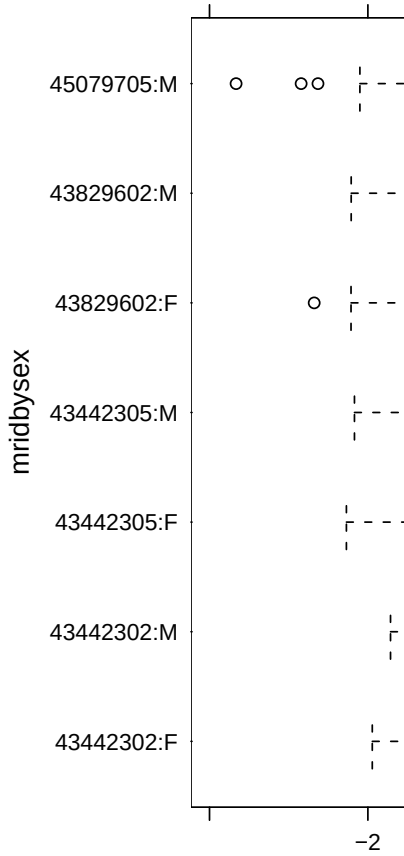
line), Pearson residuals versus dose, and Pearson residuals versus time post dose.


cheacts
Fitted values
1
2
3
4
5
6
1
2
3

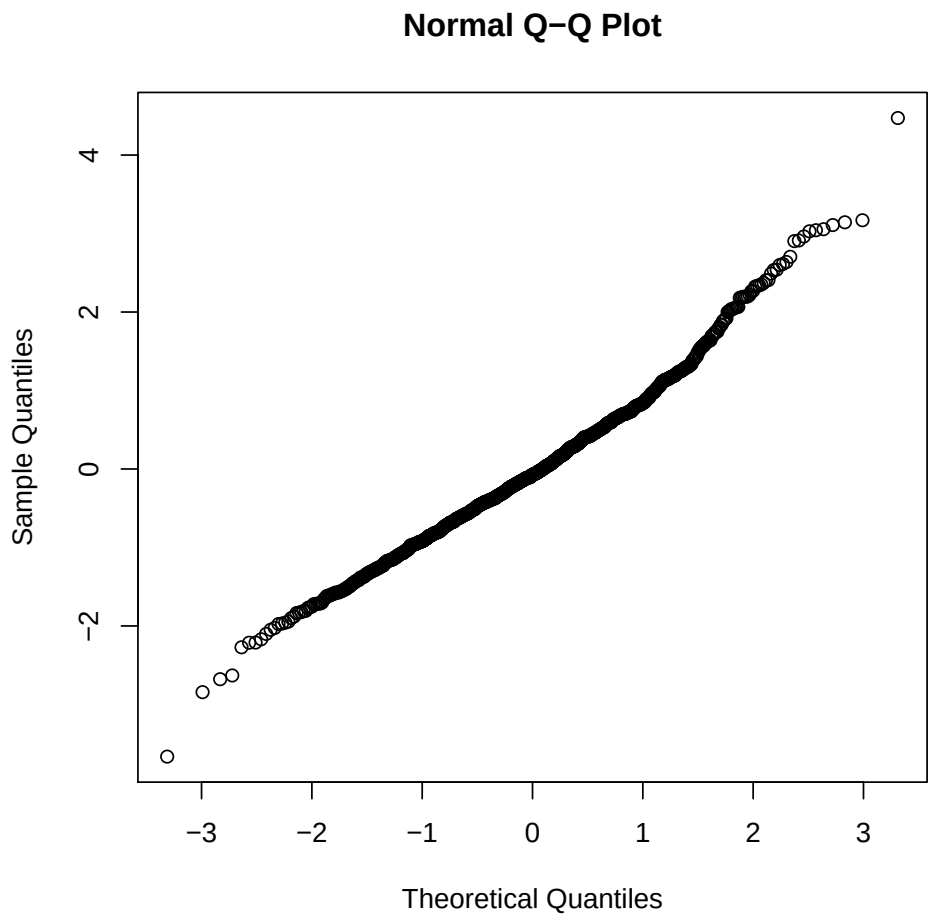

Standardized residuals
4
2
0
−2
0.0
0.1
0.2

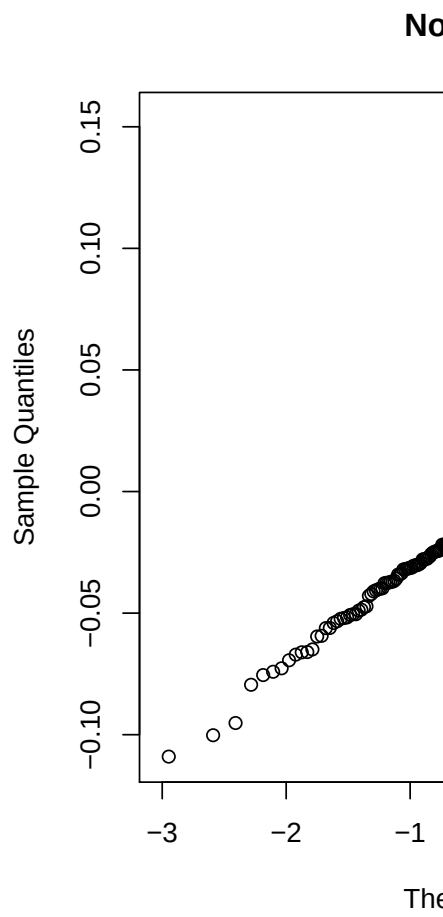


Some more graphs: Pear-



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





The model seems to fit pretty well: residual and random effects distributions look reasonably normal, and the residuals are generally distributed about 0, with no trend in dose, time, or fitted value.

To simplify the model, determine if there are gender differences in the recovery half-lives, then whether the apparent differences between doses are real.

A table to help with construction the contrast matrices:

```
> cbind(fixed.effects(drmod1e), 1:length(fixed.effects(drmod1e)))

                                                [,1] [,2]
lA.mridXtimeXsex43442305:1:M                 0.41768644    1
lA.mridXtimeXsex43442305:4:M                 0.55295438    2
lA.mridXtimeXsex43442305:8:M                 0.78187773    3
lA.mridXtimeXsex43442305:1:F                 0.73902582    4
lA.mridXtimeXsex43442305:4:F                 0.97865514    5
lA.mridXtimeXsex43442305:8:F                 0.92404791    6
lA.mridXtimeXsex43442302:0:M                -0.12779238    7
lA.mridXtimeXsex43442302:0.5:M               0.09506392    8
lA.mridXtimeXsex43442302:1:M                -0.06565964    9
lA.mridXtimeXsex43442302:4:M                -0.02823704   10
lA.mridXtimeXsex43442302:8:M                 0.28040763   11
lA.mridXtimeXsex43442302:24:M               -0.06210488   12
lA.mridXtimeXsex43442302:2:M                -0.11881246   13
lA.mridXtimeXsex43442302:0:F                 0.02142463   14
```

```
lA.mridXtimeXsex43442302:1:F                  0.08954117   15
lA.mridXtimeXsex43442302:2:F                  0.36251109   16
lA.mridXtimeXsex43442302:4:F                  0.27048835   17
lA.mridXtimeXsex43442302:8:F                  0.55864888   18
lA.mridXtimeXsex43442302:24:F                 0.29521302   19
lA.mridXtimeXsex43442302:0.5:F                0.42456463   20
lA.mridXtimeXsex45079705:0:M                  0.72828143   21
lA.mridXtimeXsex45079705:0.166666666666667:M  0.76819825   22
lA.mridXtimeXsex45079705:0.333333333333333:M  0.66454542   23
lA.mridXtimeXsex45079705:0.5:M                0.74642107   24
lA.mridXtimeXsex45079705:0.666666666666667:M  0.78356572   25
lA.mridXtimeXsex45079705:0.833333333333333:M  0.75766412   26
lA.mridXtimeXsex45079705:1:M                  0.68215161   27
lA.mridXtimeXsex45079705:1.5:M                0.77403902   28
lA.mridXtimeXsex45079705:2:M                  0.70594286   29
lA.mridXtimeXsex45079705:3:M                  0.86304207   30
lA.mridXtimeXsex45079705:4:M                  0.78685862   31
lA.mridXtimeXsex45079705:6:M                  0.72720716   32
lA.mridXtimeXsex43829602:0:M                  1.17125430   33
lA.mridXtimeXsex43829602:28:M                 0.33648603   34
lA.mridXtimeXsex43829602:56:M                 0.17762438   35
lA.mridXtimeXsex43829602:-91:M                0.46267415   36
lA.mridXtimeXsex43829602:91:M                 0.27381164   37
lA.mridXtimeXsex43829602:28:F                 0.89819882   38
lA.mridXtimeXsex43829602:0:F                  1.20033224   39
lA.mridXtimeXsex43829602:56:F                 0.99279783   40
lA.mridXtimeXsex43829602:-91:F                1.27050995   41
lA.mridXtimeXsex43829602:91:F                 0.99245077   42
lD                                           -3.47570611   43
tz                                           -1.23386835   44
lg                                            0.64673734   45
lTr.sexXfdoseF:(0.1,0.3]                      1.06945316   46
lTr.sexXfdoseF:(0.3,0.5]                      1.22247913   47
lTr.sexXfdoseF:(0.5,Inf]                      1.77577222   48
lTr.sexXfdoseF:(-Inf,0.1]                     0.09261498   49
lTr.sexXfdoseM:(0.1,0.3]                      0.18035418   50
lTr.sexXfdoseM:(0.3,0.5]                      0.48307753   51
lTr.sexXfdoseM:(0.5,Inf]                      0.40645949   52
lTr.sexXfdoseM:(-Inf,0.1]                     0.64758157   53
```

Test whether there is a gender diffence in recovery half-lives:

```
> L <- matrix(0, nrow = 4, ncol = 53)
> L[1, 49] <- L[2, 46] <- L[3, 47] <- L[4, 48] <- 1
> L[1, 53] <- L[2, 50] <- L[3, 51] <- L[4, 52] <- -1
> anova(drmod1e, L = L)

F-test for linear combination(s)
  lTr.sexXfdoseF:(0.1,0.3] lTr.sexXfdoseF:(0.3,0.5] lTr.sexXfdoseF:(0.5,Inf]
1                        0                        0                       0
2                        1                        0                       0
3                        0                        1                       0
4                        0                        0                       1
  lTr.sexXfdoseF:(-Inf,0.1] lTr.sexXfdoseM:(0.1,0.3] lTr.sexXfdoseM:(0.3,0.5]
1                         1                        0                        0
```

```
2                          0                        -1                          0
3                          0                         0                         -1
4                          0                         0                          0
  lTr.sexXfdoseM:(0.5,Inf] lTr.sexXfdoseM:(-Inf,0.1]
1                        0                        -1
2                        0                         0
3                        0                         0
4                       -1                         0
  numDF denDF  F-value p-value
1     4   720 9.144115  <.0001
```

Yes. Could this be due to the study 45079705? It only has males, and all its doses are in the (-Inf, 0.1] dose category. It would seem, therefore, that the effect of that study would be restricted to the estimates of male-female differences in the lowest category. Here is a table of differences (actually, ratios: Female half-life / Male half-life) in the different dose-categories:

```
> tbl <- exp(L %*% fixed.effects(drmod1e))
> rownames(tbl) <- levels(idta$fdose)
> tbl
```

```
               [,1]
(-Inf,0.1] 0.5740914
(0.1,0.3]  2.4329365
(0.3,0.5]  2.0946817
(0.5,Inf]  3.9326470
```

Except in the lowest dose category, in which the female half-life is half that of the males, half-life in females range from two- to four-fold that of males. It may be useful to look at the distribution of data in the four dose categories across study and sex:

```
> with(idta, table(fdose, mridbysex))
```

```
            mridbysex
fdose        43442302:F 43442302:M 43442305:F 43442305:M 43829602:F 43829602:M
  (-Inf,0.1]  37         41         18         18        145        151
  (0.1,0.3]    0          0         18         18         78         76
  (0.3,0.5]   18         21         18         18         78         66
  (0.5,Inf]   19         12          0          0          0          0
            mridbysex
fdose        45079705:M
  (-Inf,0.1] 228
  (0.1,0.3]    0
  (0.3,0.5]    0
  (0.5,Inf]    0
```

Although clearly not perfectly balanced, it does not appear likely that the female-male differences found here are solely due to interactions due to differences in different studies.

4.5 Comparison of Among-Subject Variance to Error Variance

It is of interest to know how the variance partitions to among subject components and error components. The parameterization of background makes it easier to answer this in terms of coefficients of variation, since the variation among subjects is modeled as a log-normal distribution (log of background is normally distributed). The CV for background is a relatively simple function of the among subject variance of the log-backgrounds:

```
> sigma2 <- as.numeric(VarCorr(drmod1e)[4, 1])
> CV <- sqrt(exp(sigma2) - 1)
```

Table 1: % Coefficient of Variation among Controls

Control Group Error Coefficients of Variation	F	M
43442305	22.56204	21.577110
43442302	20.90365	21.371209
45079705		8.563017
43829602	25.05553	28.562333

This gives a coefficient of variation for the among-subject random effect of 7.6%.

The error standard deviation is more complicated, because it is different for each observation. For our purposes, focus on the control groups (dose equal to zero, or time less than or equal to zero). We take advantage of the fact that the standard deviation is returned as an attribute of the "residuals" component of `drmod1e`. Average *variance* within `mridbysex` levels, and return as standard deviation the square root of the average. Use corresponding means of background levels as the denominator for CV:

```
> idta$sd <- attr(drmod1e[["residuals"]], "std")
> idta$var <- idta$sd^2
> tmp <- subset(idta, dose2 == 0 | tmpstds <= 0)
> var.lm <- lm(var ~ mridbysex - 1, data = tmp)
> rbc.lm <- lm(cheacts ~ mridbysex - 1, data = tmp)
> CV2 <- sqrt(coef(var.lm))/coef(rbc.lm)
> errorCV <- CV2 * 100
> tbl <- matrix(as.numeric(NA), nrow = nlevels(idta$mrid), ncol = 2,
+     dimnames = list(levels(idta$mrid), c("F", "M")))
> indx <- cbind(match(sapply(strsplit(names(errorCV), ":"), function(x) x[1]),
+     paste("mridbysex", levels(idta$mrid), sep = "")), match(sapply(strsplit(names(errorCV),
+     ":"), function(x) x[2]), levels(idta$sex)))
> tbl[indx] <- errorCV
> latex(tbl, title = "Control Group Error Coefficients of Variation",
+     file = "", caption = "\\% Coefficient of Variation among Controls")
```

The among-subject coeffient of variation is about a third the error coefficient of variation.

4.6 Estimates of BMD, Half-Life, and Confidence Intervals

In this endpoint, there was no evidence that BMD differed between the sexes. The overall mean `BMD` is 0.0309 mg/kg, with 95% confidence limits (0.0180324, 0.0530869).

Half-lives differ between sexes and dose-levels, generally increasing with dose:

```
> hl <- intervals(drmod1e, which = "fixed")[["fixed"]]
> hl <- hl[grep("^lTr", rownames(hl)), ]
> hl <- hl[c(4, 1, 2, 3, 8, 5, 6, 7), ]
> tbl <- signif(exp(hl), digits = 3)
> tbl <- cbind(tbl[1:4, ], tbl[5:8, ])
> rownames(tbl) <- levels(idta$fdose)
> latex(tbl, title = "Half Lives", file = "", caption = "Recovery Half-Lives and 95\\% CI (in hours)",
+     cgroup = c("F", "M"), n.cgroup = c(3, 3))
```

5 Summary

The critical estimates from this analysis are listed below. In this analysis, the model with exponential time course was used. This model assumes purely exponential recovery from the first observation, so there is no estimate of

Table 2: Recovery Half-Lives and 95% CI (in hours)

Half Lives	**F**			**M**		
	lower	est.	upper	lower	est.	upper
(-Inf,0.1]	0.502	1.10	2.40	1.310	1.91	2.79
(0.1,0.3]	1.960	2.91	4.33	0.875	1.20	1.64
(0.3,0.5]	2.350	3.40	4.90	1.190	1.62	2.21
(0.5,Inf]	3.520	5.90	9.91	0.799	1.50	2.82

Table 3: Recovery Half-Lives and standard errors
`lTr` **by dose and sex, and standard errors**

Ln Half Lives	**F**		**M**	
	Value	Std.Error	Value	Std.Error
(-Inf,0.1]	0.09261498	0.4087774	0.6475816	0.1983588
(0.1,0.3]	1.06945316	0.2071855	0.1803542	0.1639428
(0.3,0.5]	1.22247913	0.1918155	0.4830775	0.1617810
(0.5,Inf]	1.77577222	0.2705205	0.4064595	0.3296719

Half-lives and 95% CI

Table 4: Recovery Half-Lives and 95% CI (in hours)

Half Lives	**F**			**M**		
	lower	est.	upper	lower	est.	upper
(-Inf,0.1]	0.5016031	1.097039	2.399297	1.3071442	1.910914	2.793565
(0.1,0.3]	1.9597531	2.913786	4.332253	0.8750302	1.197641	1.639195
(0.3,0.5]	2.3520064	3.395595	4.902227	1.1893001	1.621056	2.209553
(0.5,Inf]	3.5179885	5.904839	9.911097	0.7987858	1.501492	2.822383

the time of peak effect. Estimates 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 does not differ between sexes, but values for recovery half-life were estimated for four different dose levels, and for both sexes.

BMD has units mg/kg, and times are in hours.

species RAT

mrid `[1] "43442305" "43442302" "45079705" "43829602"`

`lD` -3.47570610660854

standard error of `lD` 0.282011527565909

BMD (95% CI) 0.0309399791844621 (0.0180323616167019, 0.0530869074324851)

BMDL, the one-sided lower 95% CL 0.0196710010931722

Save the results of this analysis:

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

save the results for incorporating into a database:

```
> aldicarb.oral.rbc <- list(mrid = levels(idta$mrid), species = "RAT",
+     BMDs = list(combined = c(lD = fixed.effects(drmod1e)["lD"],
```

```
+         lD.se = summary(drmod1e)[["tTable"]]["lD", 2], BMD = exp(fixed.effects(drmod1e)["lD"]),
+         BMD.CI = exp(intervals(drmod1e, which = "fixed")[["fixed"]]["lD",
+             c("lower", "upper")]), BMDL = exp(intervals(drmod1e,
+             which = "fixed", level = 0.9)[["fixed"]]["lD", "lower"]))),
+     HalfLives = list(females = list("[0,0.1]" = list(lTr = tbl[1,
+         1], lTr.se = tbl[1, 2], Tr = tbl2[1, 2], Tr.CI = tbl2[1,
+         c(1, 3)]), "(0.1,0.3]" = list(lTr = tbl[2, 1], lTr.se = tbl[2,
+         2], Tr = tbl2[2, 2], Tr.CI = tbl2[2, c(1, 3)]), "(0.3,0.5]" = list(lTr = tbl[3,
+         1], lTr.se = tbl[3, 2], Tr = tbl2[3, 2], Tr.CI = tbl2[3,
+         c(1, 3)]), "(0.5,0.6]" = list(lTr = tbl[4, 1], lTr.se = tbl[4,
+         2], Tr = tbl2[4, 2], Tr.CI = tbl2[4, c(1, 3)])), males = list("[0,0.1]" = list(lTr = tbl[1,
+         3], lTr.se = tbl[1, 4], Tr = tbl2[1, 5], Tr.CI = tbl2[1,
+         c(4, 6)]), "(0.1,0.3]" = list(lTr = tbl[2, 3], lTr.se = tbl[2,
+         4], Tr = tbl2[2, 5], Tr.CI = tbl2[2, c(4, 6)]), "(0.3,0.5]" = list(lTr = tbl[3,
+         3], lTr.se = tbl[3, 4], Tr = tbl2[3, 5], Tr.CI = tbl2[3,
+         c(4, 6)]), "(0.5,0.6]" = list(lTr = tbl[4, 3], lTr.se = tbl[4,
+         4], Tr = tbl2[4, 5], Tr.CI = tbl2[4, c(3, 6)]))))
> save(aldicarb.oral.rbc, file = file.path("..", "..", "01Summaries",
+     "aldicarb.oral.rbc.RData"))
```