Dose-Time Response Modeling of Rabbit RBC AChE Activity: Methiocarb Dermal Dosing

June 24, 2005

1 Preamble

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

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

```
> library(CarbamateData)

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

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

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

Use package `Hmisc` for some formatting support.

```
> library(Hmisc)

Hmisc library by Frank E Harrell Jr

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

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

Attaching package 'Hmisc':


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

         ecdf
```

The rat gavage data for this analysis are in `repeated_dermal`. The following code prints out documentation for the datasets in use:

```
> printDataDoc(repeated_dermal)
```

```
----------------------------------------
Data set: repeated_dermal

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

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

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

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

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

Set up the analysis dataset. Some of the time points are 16 hours past the end of the dosing period. Drop those, since we would expect substantial recovery to have happened by then, and there are not enough time points to actually estimate recovery.

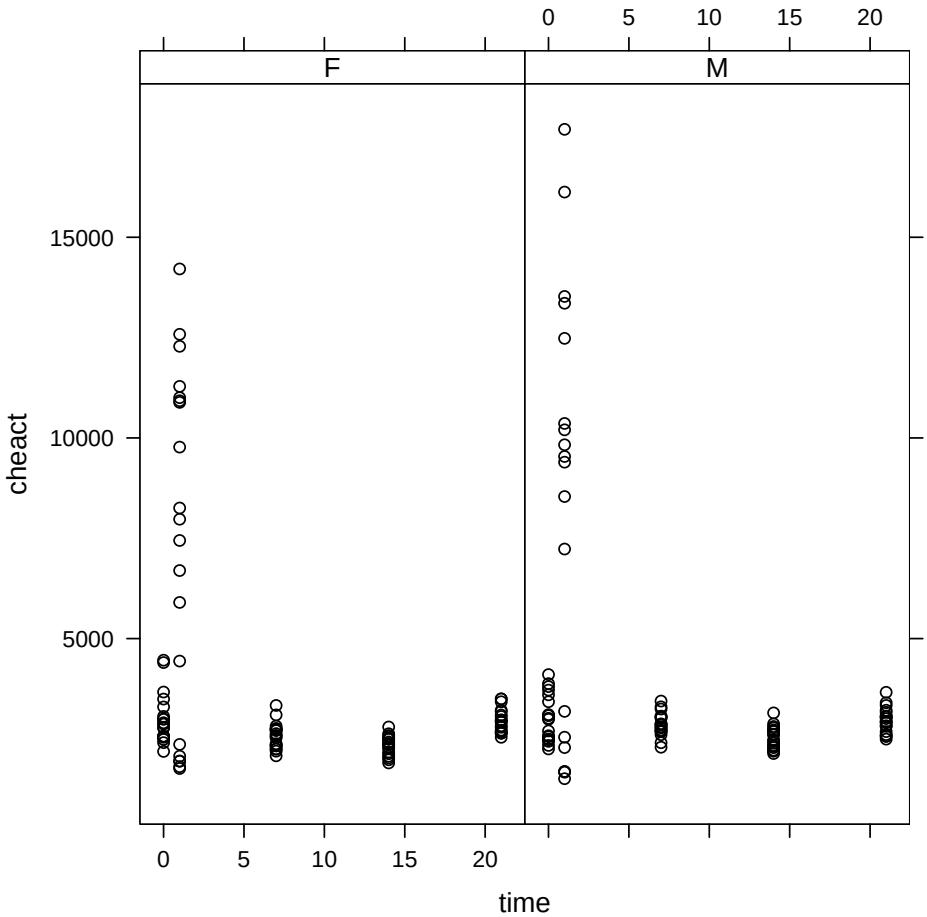
```
> dta <- CleanUp(subset(repeated_dermal, chemical %in% c("Methiocarb",
+     "methiocarb") & tmpstds < 16 & !is.na(cheact), select = c("dose",
+     "cheact", "time", "tmpstds", "id", "sex", "mrid", "time_unit")))
```

Summary of this dataset:

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

dta$mrid: 40922301
      dose           cheact           time         tmpstds        id
 Min.   :  0.0   Min.   : 1509   Min.   : 0.0   Min.   :6   1011   :  5
 1st Qu.: 15.0   1st Qu.: 2486   1st Qu.: 1.0   1st Qu.:6   1021   :  5
 Median :150.0   Median : 2773   Median : 7.0   Median :6   1031   :  5
 Mean   :148.8   Mean   : 3759   Mean   : 8.5   Mean   :6   1042   :  5
 3rd Qu.:375.0   3rd Qu.: 3206   3rd Qu.:14.0   3rd Qu.:6   1052   :  5
 Max.   :375.0   Max.   :17690   Max.   :21.0   Max.   :6   1511   :  5
                                                            (Other):164
 sex          mrid        time_unit
 F:97   40922301:194   day     :145
 M:97   41771701:  0   pre-dose: 49
```

```
------------------------------------------------------------
dta$mrid: 41771701
      dose           cheact          time           tmpstds            id
 Min.   :  0.0   Min.   :1921   Min.   : 0.000   Min.   :0.000   1021   : 5
 1st Qu.:  0.0   1st Qu.:3120   1st Qu.: 1.000   1st Qu.:6.000   1031   : 5
 Median :500.0   Median :3488   Median : 7.000   Median :6.000   1041   : 5
 Mean   :252.5   Mean   :3762   Mean   : 8.616   Mean   :4.788   1051   : 5
 3rd Qu.:500.0   3rd Qu.:3924   3rd Qu.:14.000   3rd Qu.:6.000   1511   : 5
 Max.   :500.0   Max.   :9197   Max.   :21.000   Max.   :6.000   1521   : 5
                                                                 (Other):69
 sex          mrid       time_unit
 F:50   40922301: 0   day     :99
 M:49   41771701:99   pre-dose: 0

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

dta$mrid: 40922301
       time
tmpstds 0  1  7  14 21
      6 39 39 40 38 38
------------------------------------------------------------
dta$mrid: 41771701
       time
tmpstds 0  1  7  14 21
      0 20  0  0  0  0
      6  0 20 19 20 20

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

dta$mrid: 40922301
     time
dose  0  1  7  14 21
  0    9 10 10 10 10
  60  10 10 10  8  8
  150 10  9 10 10 10
  375 10 10 10 10 10
------------------------------------------------------------
dta$mrid: 41771701
     time
dose  0  1  7  14 21
  0   10 10  9 10 10
  500 10 10 10 10 10
```

Although there are two mrids here, one of them uses only a single high dose; inappropropriate for dose-response modeling. So, drop 41771701 from the analysis. In mrid 40922301, something is wrong with the 1 day sample:



The variance is very large compared to the other times. This originally showed up after fitting the model in the next section. Drop the 1 day time point, and model the others:

```
> dta <- CleanUp(subset(dta, mrid == "40922301" & time != 1))
```

2 Dose-Response Modeling

First, some preliminary modeling to help plot the dose-response in a way that allows the repeated-measures design to be accommodated. Use a linear model to model log(cheact), which corresponds to a multiplicative model on the original scale. First, set up the data so that we can estimate the log of the fraction of activity at different doses.

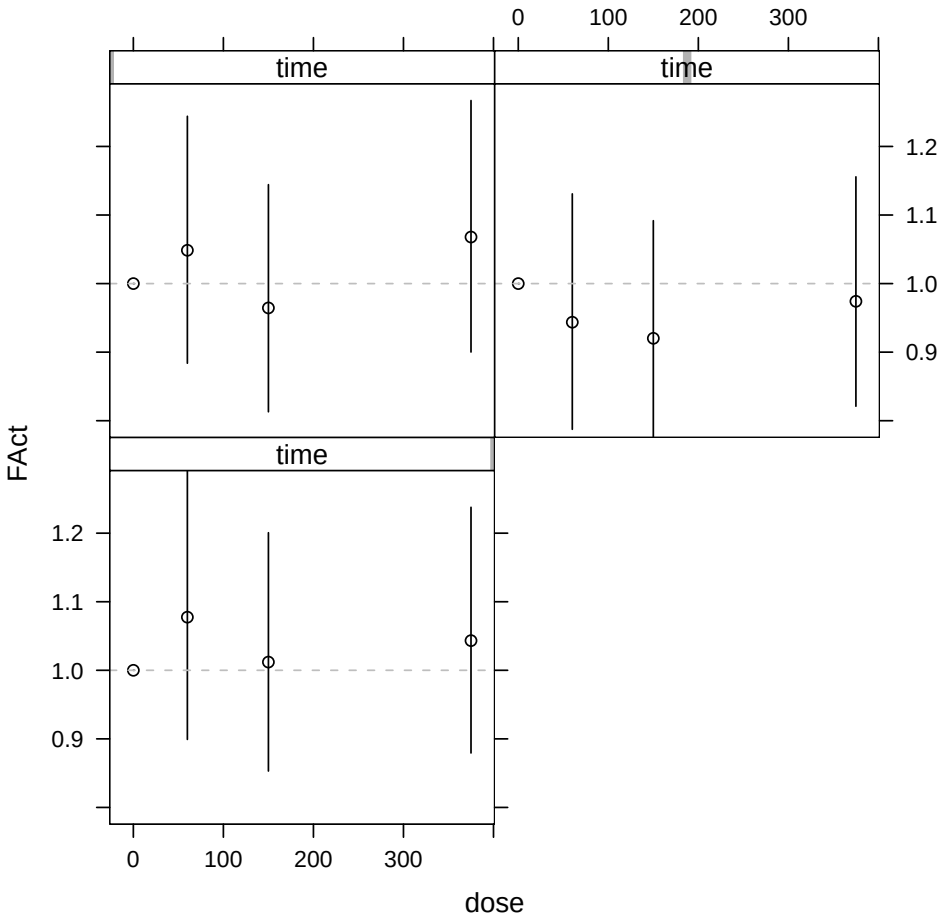
```
> dta$lncheact <- log(dta$cheact)
> dta$dose2 <- with(dta, ifelse(time > 0, dose, 0))
> dta$mridXsexXtime <- with(dta, interaction(mrid, sex, time, drop = TRUE,
+     sep = ":"))
> dta$mridXsexXtimeXdose <- with(dta, interaction(mrid, sex, time,
+     dose2, drop = TRUE, sep = ":"))
> lvls <- levels(dta$mridXsexXtimeXdose)
> lvls[grep(":0$", lvls)] <- "Control"
> levels(dta$mridXsexXtimeXdose) <- lvls
```

The model itself:

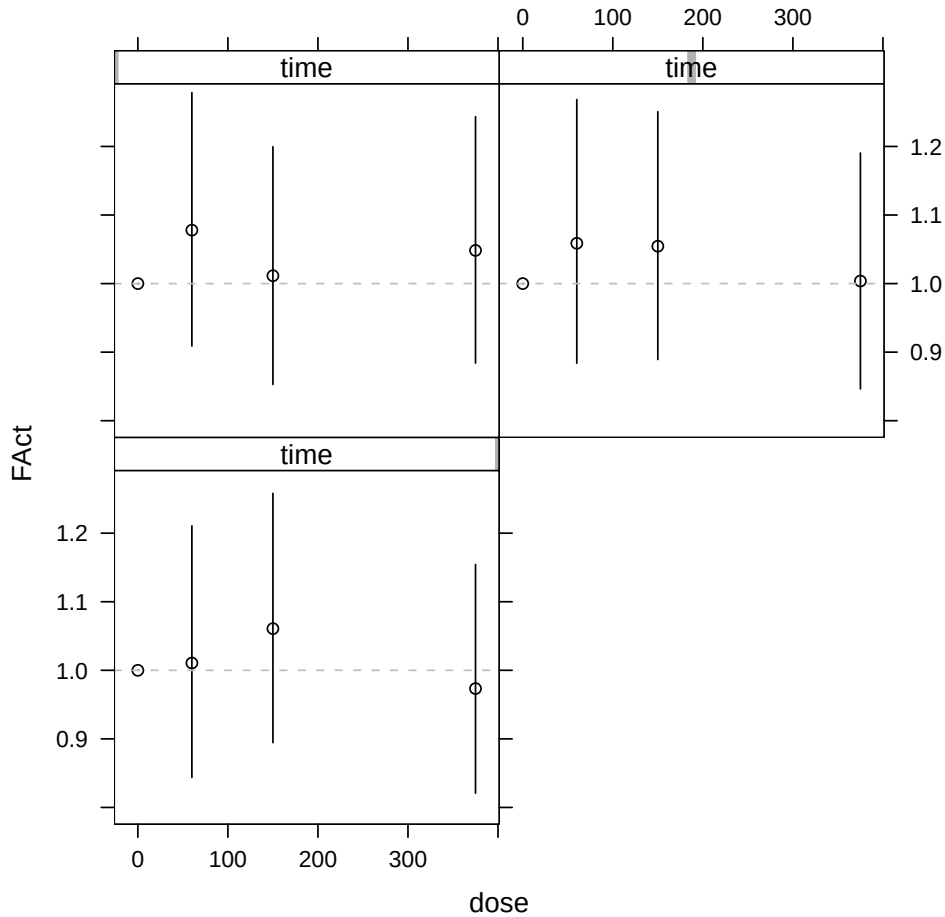
```
> drmod0 <- lme(lncheact ~ mridXsexXtime + mridXsexXtimeXdose -
+     1, data = dta, random = ~1 | id)
```

Now, plot fraction of background AChE activity as a function of dose for each time and sex. First, extract the useful information from the model:

```
> Ints <- intervals(drmod0, which = "fixed")$fixed
> nms <- rownames(Ints)
> indx <- grep("dose", nms)
> Ints <- Ints[indx, ]
> nms <- gsub("mridXsexXtimeXdose", "", nms[indx])
> pdta <- data.frame(lower = exp(Ints[, "lower"]), upper = exp(Ints[,
+     "upper"]), FAct = exp(Ints[, "est."]), sex = factor(sapply(strsplit(nms,
+     ":"), function(x) x[2])), time = as.numeric(sapply(strsplit(nms,
+     ":"), function(x) x[3])), dose = as.numeric(sapply(strsplit(nms,
+     ":"), function(x) x[4])))
> ftms <- sort(unique(pdta$time[pdta$sex == "F"]))
> mtms <- sort(unique(pdta$time[pdta$sex == "M"]))
> nftms <- length(ftms)
> nmtms <- length(mtms)
> npdta <- data.frame(lower = rep(1, nftms + nmtms), upper = rep(1,
+     nftms + nmtms), FAct = rep(1, nftms + nmtms), sex = factor(rep(c("F",
+     "M"), c(nftms, nmtms))), dose = rep(0, nftms + nmtms), time = c(ftms,
+     mtms))
> pdta <- rbind(pdta, npdta)
```



Females: Males:



There is no evidence of a dose-response in these data, and they will not be modeled further.

3 Summary

There is no evidence for a dose-response in these data, so no BMD is calculated.

species RABBIT

mrid `[1] "40922301"`

Save everything:

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

Save the results for incorporating into a database:

```
> methiocarb.dermal.rbc <- list(mrid = levels(dta$mrid), species = levels(dta$species))
> save(methiocarb.dermal.rbc, file = file.path("..", "..", "01Summaries",
+     "methiocarb.dermal.rbc.RData"))
```