NLME Class Exercise

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```r
# Clear environment
rm(list=ls())
# Clear all plots
if(!is.null(dev.list())) dev.off()
```

```
## null device
##          1
```

```r
# Load packages
library(nlme)
```

Question 2:

The form of the response suggests that a logistic model can be used to model the change in blood pressure as a function of the *logarithm* of the concentration of PBG.

```r
# load data
data("PBG")

# change dose to log(dose)
PBG$dose <- log(PBG$dose)
str(PBG)
```

```
## Classes 'nfnGroupedData', 'nfGroupedData', 'groupedData' and 'data.frame':   60 obs. of  5 variables
##  $ deltaBP  : num  0.5 4.5 10 26 37 32 1 1.25 4 12 ...
##  $ dose     : num  1.83 2.53 3.22 3.91 4.61 ...
##  $ Run      : Ord.factor w/ 10 levels "T5"<"T4"<"T3"<..: 10 10 10 10 10 10 8 8 8 8 ...
##  $ Treatment: Factor w/ 2 levels "MDL 72222","Placebo": 2 2 2 2 2 2 2 2 2 2 ...
##  $ Rabbit   : Ord.factor w/ 5 levels "5"<"3"<"2"<"4"<..: 5 5 5 5 5 5 5 3 3 3 3 ...
##  - attr(*, "formula")=Class 'formula'  language deltaBP ~ dose | Rabbit
##   .. ..- attr(*, ".Environment")=<environment: R_GlobalEnv>
##  - attr(*, "labels")=List of 2
##   ..$ x: chr "Dose of phenylbiguanide"
##   ..$ y: chr "Change in blood pressure"
##  - attr(*, "units")=List of 2
##   ..$ x: chr "(ug)"
##   ..$ y: chr "(mm Hg)"
##  - attr(*, "inner")=Class 'formula'  language ~Treatment
##   .. ..- attr(*, ".Environment")=<environment: R_GlobalEnv>
```

```r
head(PBG)
```

```
## Grouped Data: deltaBP ~ dose | Rabbit
##    deltaBP     dose Run Treatment Rabbit
```

```
## 1      0.5 1.832581  P1    Placebo        1
## 2      4.5 2.525729  P1    Placebo        1
## 3     10.0 3.218876  P1    Placebo        1
## 4     26.0 3.912023  P1    Placebo        1
## 5     37.0 4.605170  P1    Placebo        1
## 6     32.0 5.298317  P1    Placebo        1
```

Question 2(a):

Fit separate four-parameter logistic models to the data from each treatment within each rabbit. Note that the grouping formula should be ~Rabbit/Treatment, becasue each rabbit has observations for BOTH treatments, but the grouping display formula is ~Rabbit.

The model formulation for such a model is:

$$y_{ij} = B + \frac{A - B}{1 + \exp[(\phi_{xmid} - x_{dose})/\phi_{scal}]},$$

where A is the horizontal asymptote as dosages get very small, B is the horizontal asymptote as dosages get very large, ϕ_{xmid} is the inflection point and ϕ_{scal} is the scale parameter. y_{ij} is the change in blood pressure for rabbit i on treatment j.

```
# First update grouped data object to capture treatment within rabbit

pbg <- groupedData(deltaBP ~ dose | Rabbit/Treatment, data = PBG)
head(pbg)
```

```
## Grouped Data: deltaBP ~ dose | Rabbit/Treatment
##   deltaBP      dose Run Treatment Rabbit
## 1     0.5 1.832581  P1    Placebo        1
## 2     4.5 2.525729  P1    Placebo        1
## 3    10.0 3.218876  P1    Placebo        1
## 4    26.0 3.912023  P1    Placebo        1
## 5    37.0 4.605170  P1    Placebo        1
## 6    32.0 5.298317  P1    Placebo        1
```

```
# Now fit 4 parameter logistic model
mod1 <- nlsList(deltaBP ~ SSfpl(dose, A, B, xmid, scal), data = pbg)
```

```
## Warning: 2 times caught the same error in nls(y ~ cbind(1, 1/(1 + exp((xmid
## - x)/exp(lscal)))), data = xy, start = list(xmid = ir[1L], lscal =
## log(abs(ir[2L]))), algorithm = "plinear", ...): step factor 0.000488281 reduced
## below 'minFactor' of 0.000976562
```

```
summary(mod1)
```

```
## Call:
##   Model: deltaBP ~ SSfpl(dose, A, B, xmid, scal) | Rabbit/Treatment
##    Data: pbg
##
## Coefficients:
##    A
##             Estimate Std. Error   t value    Pr(>|t|)
## 5/MDL 72222       NA         NA        NA          NA
## 5/Placebo   1.414461  1.1628011 1.2164252 0.22992363
## 3/MDL 72222       NA         NA        NA          NA
## 3/Placebo   1.599543  1.1479042 1.3934463 0.21840624
```

```
## 2/MDL 72222 1.367542  0.8993165 1.5206461 0.02291775
## 2/Placebo    1.484219  1.0385680 1.4291009 0.17548112
## 4/MDL 72222 1.906251  0.9405797 2.0266766 0.04762826
## 4/Placebo    1.407493  1.2068066 1.1662952 0.32449553
## 1/MDL 72222 1.129670  1.1370699 0.9934924 0.25306024
## 1/Placebo    1.809386  1.3132471 1.3777956 0.59806458
##    B
##             Estimate Std. Error   t value     Pr(>|t|)
## 5/MDL 72222       NA        NA        NA           NA
## 5/Placebo   19.02344   1.156925 16.443108 0.0018726635
## 3/MDL 72222       NA        NA        NA           NA
## 3/Placebo   23.75878   1.447282 16.416140 0.0022868001
## 2/MDL 72222 28.61228   2.568972 11.137640 0.0004420652
## 2/Placebo   29.68330   1.792043 16.563943 0.0017482593
## 4/MDL 72222 24.14892   5.430718  4.446728 0.0104809898
## 4/Placebo   34.19865   1.544994 22.135136 0.0016498505
## 1/MDL 72222 41.81663   4.259712  9.816773 0.0040332824
## 1/Placebo   34.78786   1.309839 26.558877 0.0069113533
##    xmid
##             Estimate Std. Error  t value     Pr(>|t|)
## 5/MDL 72222       NA         NA       NA           NA
## 5/Placebo   3.537364 0.12078711 29.28594 5.914868e-04
## 3/MDL 72222       NA         NA       NA           NA
## 3/Placebo   3.858121 0.08894182 43.37803 3.284796e-04
## 2/MDL 72222 4.604876 0.05540421 83.11419 7.943378e-06
## 2/Placebo   4.038171 0.08197878 49.25873 1.981426e-04
## 4/MDL 72222 4.703260 0.20037096 23.47276 3.819230e-04
## 4/Placebo   3.842638 0.06877666 55.87125 2.595010e-04
## 1/MDL 72222 4.468772 0.12038891 37.11946 2.836884e-04
## 1/Placebo   3.561040 0.07350986 48.44302 2.092550e-03
##    scal
##              Estimate Std. Error  t value  Pr(>|t|)
## 5/MDL 72222        NA         NA       NA        NA
## 5/Placebo   0.2289159 0.07435370 3.078742 0.04961478
## 3/MDL 72222        NA         NA       NA        NA
## 3/Placebo   0.2693228 0.10348756 2.602466 0.08044135
## 2/MDL 72222 0.1838222 0.14725085 1.248361 0.03345424
## 2/Placebo   0.2778989 0.08069461 3.443835 0.03823903
## 4/MDL 72222 0.2662095 0.19344279 1.376166 0.09551404
## 4/Placebo   0.3050609 0.07174099 4.252254 0.04201320
## 1/MDL 72222 0.4104945 0.09277862 4.424452 0.01939680
## 1/Placebo   0.3092112 0.05772591 5.356541 0.13721631
##
## Residual standard error: 1.532128 on 16 degrees of freedom
```

The error means that nlsList was unable to fit models for rabbit 5 with treatment MDL 72222 and rabbit 3 with treatment MDL 72222 , however it was able to fit models for all the other rabbit*treatment combinations.

Question 2(b):

Plot the confidence intervals of the coefficients for Model 1.

```
plot(intervals(mod1))
```
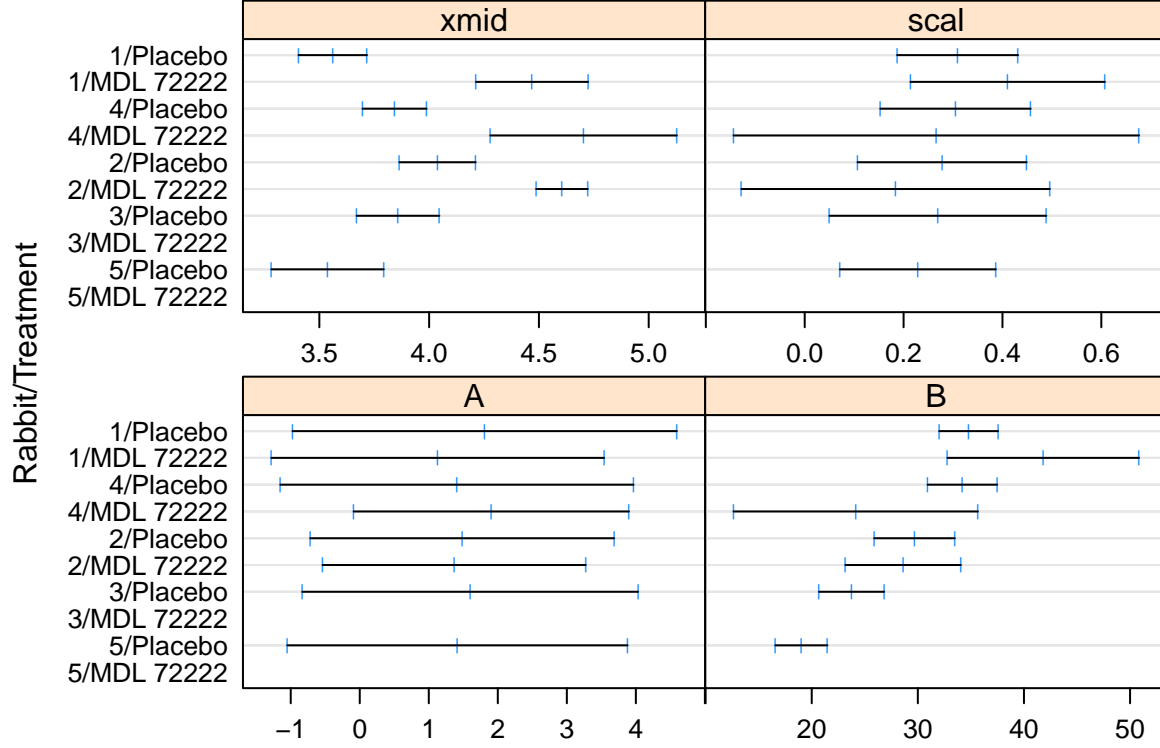
A, the horizontal asymptote on the left, as well as to some extent the scale parameter ϕ_{scal} both seem to be constant across all Rabbit/Treatment combinations, suggesting that these parameters may not need random effects. The horizontal asymptote on the right B definitely seems to vary across all Rabbit/Treatment combinations, suggesting that random effects at the rabbit-level and treatment-level may be needed on this parameter.

The inflection point parameter ϕ_{xmid} seems to vary in a *systematic* way with treatment, with the placebo intervals always located on the left and MDL 72222 treatment intervals always on the right, suggesting that ϕ_{xmid} may need a treatment *fixed* effect. ϕ_{xmid} intervals also vary randomly from one rabbit to the next, suggesting that a rabbit-level random effect may also be needed on this parameter.

Question 2(c):

Now we will fit a model with a fixed effect for treatment on the ϕ_{xmid} parameter, denoted X_{treat} and random effects for rabbit on the B parameter, denoted b_{0i}, and for treatment within rabbit on the B, denoted $b_{0i,j}$, and ϕ_{xmid}, denoted $b_{1i,j}$.

$$y_{ij} = (B + b_{0i} + b_{0i,j}) + \frac{A - (B + b_{0i} + b_{0i,j})}{1 + \exp[(\phi_{xmid} + X_{treat} + b_{1i,j} - x_{dose})/\phi_{scal}]},$$

We begin with just a simple diagonal ψ_2 matrix