ACRM 2018 Longitudinal Data Analysis Workshop

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Practical Session 2: Curvilinear and Higher Order Mixed-Effects Models

This handout is designed to accompany the script you will be working with in the practical session. A copy of the script file, the data, set, and this handout can be found at: https://github.com/keithlohse/LMER Clinical Science.

The R code is interspersed with explanations below. All R code is highlighted in grey and color coded to show different functions, arguments, and comments in the code.

First, you will need to open the five packages we will be using for this session using the library function:

```
# Loading the essential libraries.
library("ggplot2"); library("lme4"); library("car"); library("dplyr");
library("lmerTest");
```

If you haven't already installed these packages, you will need to use the install.packages() function first. This can take some time and will require an internet connect.

```
# If these packages are not installed already, run the following code:
install.packages("ggplot2"); install.packages("lme4");
install.packages("car"); install.packages("dplyr");
install.packages("lmerTest");
```

2.1 Data Cleaning and Quality Assurance

One of the first steps is to set the working directory. This is a file-pathway that directs R to the folder in which the various data and script files are stored. Make sure the "data_session2.csv" file is saved in that folder and then use the read.csv() function to read the data into R.

```
##----- Data Cleaning and QA -----
## Setting the Directory ------
getwd()
# Note that R requires forward slashes, you will get errors with backslashes.
setwd("C:/ Users/Folder/SubFolder/SubSubFolder/")
# Make sure that the file data session2.csv is saved in your working
directory.
# Import the .csv file into R.
# We will save this file in the R environment as an object called "DATA".
DATA<-read.csv("./data session2.csv", header = TRUE, sep=",",
             na.strings=c("NA", "NaN", " ", ""))
# Use the head() function to check the structure of the data file.
head (DATA)
# Alternately you can also download the data file from the web here:
# DATA <-
read.csv("https://raw.githubusercontent.com/keithlohse/LMER Clinical Science/
master/data/data session2.csv")
# head(DATA)
```

At the end of the first module, you might have noticed that although the linear fit was statistically significant, there was a lot of room for improvement. Especially at the early time points (refer to the figures from Session 1) the linear fit was not very accurate, often over-estimating performance for the different participants. As a first step in fitting curvilinear models we want to plot the data for each participant or (at least) a subset of participants.

It is also important to separate curvilinear from truly nonlinear models. Different people might define these terms slight differently, however we will define curvilinear models as curved, but linear in their parameters. Nonlinear models, conversely, are not necessarily curved, nor are they linear in their parameters. For instance, a cubic model is curvilinear, taking the form:

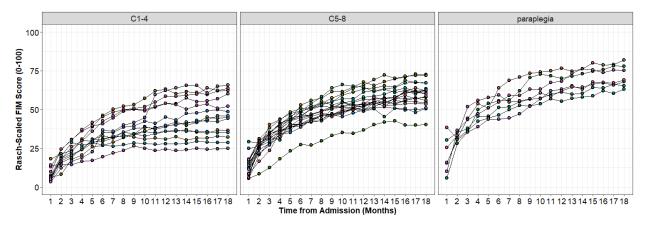
$$y_{ij} = \beta_0 + \beta_1 \left(Time_{ij} \right) + \beta_2 \left(Time_{ij}^2 \right) + \beta_3 \left(Time_{ij}^3 \right) + \epsilon_{ij}$$

Conversely, the negative exponential model has a similar curve, but does not emerge from a linear combination of the its parameters:

$$y_{ij} = \alpha_i - (\alpha_i - \pi_{0i})e^{-\pi_{1i}(Time_{ij})} + \varepsilon_{ij}$$

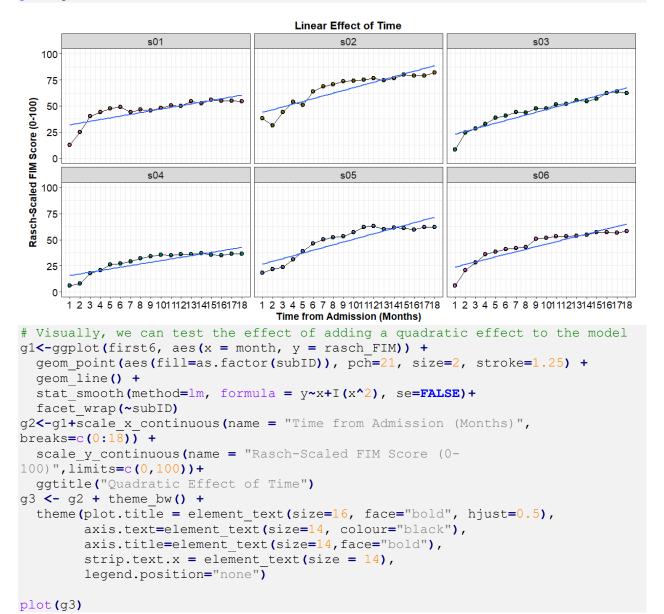
We will reserve truly nonlinear models for a later date as fitting these models is often much more complex. However, curvilinear models are very power and, when combined with curvilinear random-effects, can fit unique trajectories for very different individuals. Below, we will walk through visualizing the group-level data and individual linear, quadratic, and cubic models.

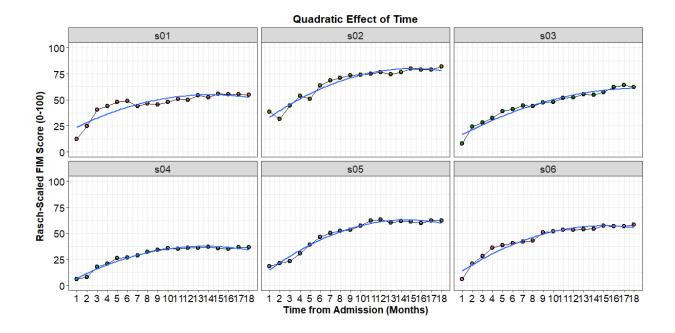
```
## ----- Visualizing the Effects of Time ------
# One of the major questions we address in this module is how to best model
the effects of time. That is, what is the most appropriate "shape" of the
time curve? Is it perfectly straight? Is curved? In this module we will build
from our linear model (that we used in Module 1) to a curvilinear model in
which we add quadratic and cubic components.
## FIM scores by group and time ----
g1 < -ggplot(DATA, aes(x = month, y = rasch FIM)) +
  geom point(aes(fill=as.factor(subID)), pch=21, size=2, stroke=1.25) +
  geom line(aes(group=subID)) +
  facet wrap(~AIS grade)
q2<-q1+scale x continuous(name = "Time from Admission (Months)",
breaks = c(0:18)) +
  scale y continuous(name = "Rasch-Scaled FIM Score (0-100)", limits=c(0,100))
g3 \leftarrow g2 + theme bw() +
  theme(axis.text=element text(size=14, colour="black"),
        axis.title=element text(size=14, face="bold")) +
  theme(strip.text.x = element text(size = 14))+
  theme(legend.position="none")
plot(q3)
```



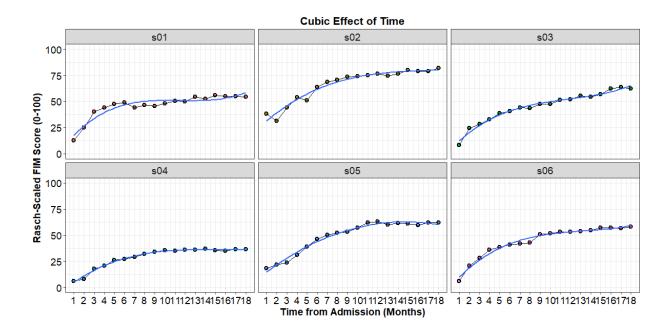
```
# We can see that these patterns are almost certainly not linear:
first6<-DATA[c(1:108),]
g1<-ggplot(first6, aes(x = month, y = rasch FIM)) +
  geom point(aes(fill=as.factor(subID)), pch=21, size=2, stroke=1.25) +
  geom line() +
  stat smooth (method=lm, se=FALSE) +
  facet wrap(~subID)
q2<-q1+scale x continuous(name = "Time from Admission (Months)",
breaks = c(0:18)) +
  scale_y_continuous(name = "Rasch-Scaled FIM Score (0-
100) ", limits=c(0,100))+
  ggtitle("Linear Effect of Time")
g3 \leftarrow g2 + theme bw() +
  theme(plot.title = element text(size=16, face="bold", hjust=0.5),
        axis.text=element text(size=14, colour="black"),
        axis.title=element_text(size=14, face="bold"),
        strip.text.x = element text(size = 14),
        legend.position="none")
```

plot(g3)





```
# Further, we can see the effect of adding a cubic effect to the model
g1<-ggplot(first6, aes(x = month, y = rasch FIM)) +
  geom point(aes(fill=as.factor(subID)), pch=21, size=2, stroke=1.25) +
  geom line() +
  stat smooth (method=lm, formula = y \sim x + I(x^2) + I(x^3), se=FALSE)+
  facet wrap(~subID)
g2<-g1+scale x continuous(name = "Time from Admission (Months)",
breaks = c(0:18)) +
  scale y continuous(name = "Rasch-Scaled FIM Score (0-
100) ", limits=c(0,100))+
  ggtitle("Cubic Effect of Time")
g3 \leftarrow g2 + theme bw() +
  theme(plot.tit\overline{le} = element text(size=16, face="bold", hjust=0.5),
        axis.text=element_text(size=14, colour="black"),
        axis.title=element text(size=14, face="bold"),
        strip.text.x = element text(size = 14),
        legend.position="none")
plot(q3)
```



2.2 Comparing Different Effects of Time

In order to quantify what our visualizations show us qualitatively, we need to statistically compare models with linear, quadratic, and cubic effects of time.

```
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite
approximations to degrees of
 freedom [lmerMod]
Formula: rasch FIM ~ 1 + year.0 + (1 + year.0 | subID)
  Data: DATA
                 logLik deviance df.resid
    AIC
            BIC
 4794.8
          4822.3 -2391.4
                          4782.8
Scaled residuals:
   Min 1Q Median 3Q
                               Max
-4.7756 -0.4913 0.1596 0.6602 2.0907
Random effects:
               Variance Std.Dev. Corr
Groups Name
subID
        (Intercept) 47.83 6.916
         year.0 50.82
                            7.129 0.37
                   33.77 5.811
Residual
Number of obs: 720, groups: subID, 40
Fixed effects:
          Estimate Std. Error df t value Pr(>|t|)
(Intercept) 26.589 1.170 40.000 22.73 <2e-16 ***
year.0
                      1.233 40.000
                                     20.96
                                           <2e-16 ***
           25.857
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1
Correlation of Fixed Effects:
      (Intr)
year.0 0.189
```

```
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite
approximations to degrees of
  freedom [lmerMod]
Formula: rasch FIM \sim 1 + year.0 + year.0 sq + (1 + year.0 + year.0 sq |
subID)
  Data: DATA
            BIC logLik deviance df.resid
          4085.0 -2009.6
                           4019.3
Scaled residuals:
   Min
         1Q Median 3Q
-4.4894 -0.5194 0.0454 0.5442 3.0358
Random effects:
         Name
                   Variance Std.Dev. Corr
 Groups
         (Intercept) 46.224 6.799
subID
         year.0
                   242.048 15.558
                                      0.07
         year.0_sq 44.135 6.643 -0.08 -0.93
                      9.754 3.123
Residual
Number of obs: 720, groups: subID, 40
Fixed effects:
           Estimate Std. Error
                                  df t value Pr(>|t|)
(Intercept) 18.103 1.120 40.000 16.17 <2e-16 ***
                        2.666 40.000 24.03 <2e-16 ***
            64.044
year.0
                       1.262 40.000 -21.36 <2e-16 ***
           -26.956
year.0 sq
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1
Correlation of Fixed Effects:
         (Intr) year.0
year.0
         -0.030
year.0 sq 0.049 -0.921
# Cubic Effect of Time
time cube<-lmer(rasch FIM~
                   # Fixed-effects
                   1+year.0+year.0 sq+year.0 cu+
                   # Random-effects
                   (1+year.0+year.0 sq+year.0 cu|subID), data=DATA,
REML=FALSE)
summary(time cube)
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite
approximations to degrees of
 freedom [lmerMod]
Formula: rasch FIM ~ 1 + year.0 + year.0 sq + year.0 cu + (1 + year.0 +
   year.0 sq + year.0 cu | subID)
  Data: DATA
            BIC logLik deviance df.resid
          3810.1 -1855.7
                           3711.4
Scaled residuals:
  Min 1Q Median
                           3Q
                                  Max
```

```
-4.1697 -0.5265 -0.0002 0.5186 3.5018
Random effects:
Groups Name
                   Variance Std.Dev. Corr
         (Intercept) 42.779 6.541
subID
                    635.961 25.218
         year.0
                                     0.06
         year.0_sq 1179.872 34.349 -0.07 -0.88
         year.0 cu
                     213.006 14.595 0.10 0.77 -0.98
                       5.481 2.341
Residual
Number of obs: 720, groups: subID, 40
Fixed effects:
           Estimate Std. Error
                                  df t value Pr(>|t|)
                        1.073 40.000 13.954 < 2e-16 ***
(Intercept)
            14.977
                        4.378 39.990 21.706 < 2e-16 ***
year.0
             95.033
            -83.232
                       6.213 39.990 -13.397 2.22e-16 ***
year.0 sq
                       2.698 39.990 9.815 3.30e-12 ***
           26.483
year.0 cu
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Correlation of Fixed Effects:
         (Intr) year.0 yr.0_s
year.0
        -0.041
year.0 sq 0.027 -0.891
year.0 cu 0.001 0.797 -0.981
```

Now that we have all of these models constructed, we can make a statistical comparison between models using the anova() and the AIC as our index of model fit.

```
anova(time linear, time square, time cube)
```

```
Data: DATA
Models:
object: rasch FIM ~ 1 + year.0 + (1 + year.0 | subID)
..1: rasch FIM \sim 1 + year.0 + year.0 sq + (1 + year.0 + year.0 sq |
        subID)
...2: rasch FIM ~ 1 + year.0 + year.0 sq + year.0 cu + (1 + year.0 +
       year.0 sq + year.0 cu | subID)
..2:
         AIC
                 BIC logLik deviance Chisq Chi Df Pr(>Chisq)
object 6 4794.8 4822.3 -2391.4 4782.8
..1
     10 4039.3 4085.0 -2009.6 4019.3 763.58 4 < 2.2e-16 ***
      15 3741.4 3810.1 -1855.7 3711.4 307.87
..2
                                                 5 < 2.2e-16 ***
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '' 1
```

The cubic model provides far and away the best fit, however, note the large degrees of freedom in this model (5 more than the quadratic and 9 more than the linear model!). Having 15 degrees of freedom may not seem like a problem right now, but as we add fixed-effect to our model, we might want to have more "room" in the model to add interactions between fixed effects. As such, it might be interesting to compare our model that has cubic fixed- and random-effects to a model that has only a fixed-effect.

```
Data: DATA

Models:
object: rasch_FIM ~ 1 + year.0 + year.0_sq + year.0_cu + (1 + year.0 + object: year.0_sq | subID)
..1: rasch_FIM ~ 1 + year.0 + year.0_sq + year.0_cu + (1 + year.0 + ..1: year.0_sq + year.0_cu | subID)

Df AIC BIC logLik deviance Chisq Chi Df Pr(>Chisq)
object 11 3795.6 3845.9 -1886.8 3773.6
..1 15 3741.4 3810.1 -1855.7 3711.4 62.181 4 1.009e-12 ***
---
Signif. codes: 0 \***' 0.001 \**' 0.01 \*' 0.05 \'.' 0.1 \' 1
```

Based on the AIC, it looks like those 4-extra degrees of freedom are worth it and statistically improve our model fit. However, it is worth remembering that you can add fixed- and random-effects for your time variable separately. Occasionally, you might find that a linear random-effect is necessary, but quadratic and cubic random-effects are not, which would imply little variation between individuals in these components. As you build these models, remember that they do not need to be any more complex then necessary and exploring these random-effects of time is an essential first step before moving on to more complicated fixed-effect models.

2.3 Conditional Curvilinear Models

As with our linear models, we are interested in how a person's AIS grade affects not only where they begin, but how they progress through therapy. We will start with our best fitting random-effects model: the cubic model of time:

$$y_{ij} = B_0 + \beta_1 (Time_{ij}) + \beta_2 (Time_{ij}^2) + \beta_3 (Time_{ij}^3) + U_0 + U_{1j} (Time_{ij}) + U_{2j} (Time_{ij}^2) + U_{3j} (Time_{ij}^3) + \epsilon_{ij}$$

In the equation, we have highlighted the fixed-effects in blue, the random-effects in red, and random-errors in green. It is important to remember that our AIS grade variable has three levels ("C1-4", "C5-8", and "paraplegia"). To test the effects of this variable, therefore, we need two separate contrasts. By default, R will create these contrasts using "treatment coding" (also referred to as "dummy coding") in which one group serves as a reference against which the other groups are compared. R assigns these levels alphanumerically, so "C1-4" will serve as the reference group. To begin, we will add a main-effect of AIS grade, and the linear interaction of AIS and Time:

$$y_{ij} = B_0 + \beta_1 (Time_{ij}) + \beta_2 (Time_{ij}^2) + \beta_3 (Time_{ij}^3) +$$

$$\beta_4 (C5to8_j) + \beta_5 (Paraplegia_j) + \beta_6 (Time_{ij} \times C5to8_j) + \beta_7 (Time_{ij} \times Paraplegia_j) +$$

$$U_0 + U_{1j} (Time_{ij}) + U_{2j} (Time_{ij}^2) + U_{3j} (Time_{ij}^3) + \epsilon_{ij}$$

We have color-coded the main-effect of AIS grade in orange and the linear interactions of AIS and Time in black. Note that AIS grade is only coded by the sub-script "j", because this variable only changes between participants, it does not vary over time.

From this initial model, we will add quadratic and cubic interactions to see which model provides the best explanation of the data.

```
Data: DATA
Models:
object: rasch FIM ~ 1 + year.0 * AIS grade + year.0 sq + year.0 cu +
object: (1 + year.0 + year.0 sq + year.0 cu | subID)
..1: rasch FIM ~ 1 + year.0 * AIS grade + year.0 sq * AIS grade +
       year.0 cu + (1 + year.0 + year.0 sq + year.0 cu | subID)
..2: rasch FIM ~ 1 + year.0 * AIS grade + year.0 sq * AIS grade +
        year.0 cu * AIS grade + (1 + year.0 + year.0 sq + year.0 cu |
..2:
        subID)
           AIC
      Df
                  BIC logLik deviance Chisq Chi Df Pr(>Chisq)
object 19 3711.5 3798.5 -1836.7 3673.5
..1
                                 3672.6 0.8533
      21 3714.6 3810.8 -1836.3
                                                    2
                                                         0.6527
..2
      23 3716.5 3821.8 -1835.3 3670.5 2.1146
                                                    2
                                                          0.3474
```

Note the large degrees of freedom in these models. Including cubic random-effects and several interactions in the fixed-effects add up quickly! Ultimately, it looks like our first model provides the best explanation of the data based on the AIC:

```
summary(cond 01)
```

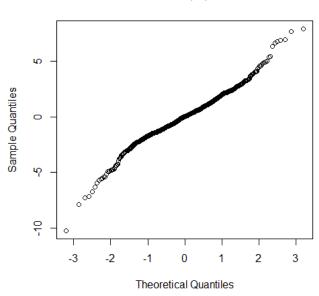
```
Linear mixed model fit by maximum likelihood t-tests use Satterthwaite
approximations to degrees of
 freedom [lmerMod]
Formula: rasch FIM \sim 1 + year.0 * AIS grade + year.0 sq + year.0 cu +
    (1 + year.0 + year.0 sq + year.0 cu | subID)
  Data: DATA
                  logLik deviance df.resid
             BIC
  3711.5
          3798.5 -1836.7 3673.5
Scaled residuals:
                          3Q
          1Q Median
-4.3757 -0.5280 0.0089 0.5130 3.3788
Random effects:
                    Variance Std.Dev. Corr
Groups Name
         (Intercept) 21.488 4.636
subID
                    594.874 24.390 -0.33
         vear.0
         year.0 sq 1179.874 34.349 0.21 -0.88
         year.0 cu 213.006 14.595 -0.15 0.77 -0.98
                       5.481 2.341
Number of obs: 720, groups: subID, 40
Fixed effects:
```

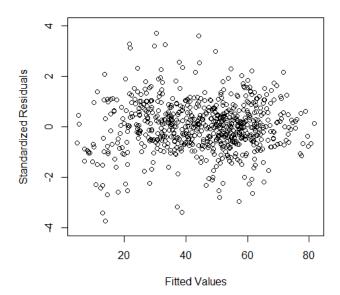
```
Estimate Std. Error
                                             df t value Pr(>|t|)
                            9.083
                                             43.160
                                                      7.209 6.28e-09 ***
(Intercept)
                                       1.260
                            91.906
                                       4.426 45.790 20.765 < 2e-16 ***
year.0
AIS gradeC5-8
                            7.022
                                       1.608 40.000 4.367 8.66e-05 ***
                           14.619
                                       2.113 40.000
                                                     6.918 2.44e-08 ***
AIS gradeparaplegia
year.0 sq
                          -83.232
                                       6.213 40.030 -13.397 2.22e-16 ***
year.0 cu
                           26.483
                                       2.698 40.020
                                                     9.815 3.28e-12 ***
year.0:AIS_gradeC5-8
                            4.048
                                       1.968 40.000
                                                     2.057
                                                            0.0462 *
                            6.879
                                       2.586 40.000
                                                     2.660
                                                            0.0112 *
year.0:AIS_gradeparaplegia
Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
Correlation of Fixed Effects:
           (Intr) year.0 AIS C5 AIS gr yr.0 s yr.0 c y.0:AIS C
year.0
           -0.281
AIS grdC5-8 -0.735 0.047
AIS grdprpl -0.559 0.035 0.438
year.0 sq
           0.181 -0.859 0.000 0.000
year.0 cu -0.144 0.768 0.000 0.000 -0.981
y.0:AI\overline{S} C5- 0.134 -0.256 -0.182 -0.080 0.000 0.000
yr.0:AIS gr 0.102 -0.195 -0.080 -0.182 0.000 0.000 0.438
```

2.4 Checking the Assumptions of our Best Fitting Model

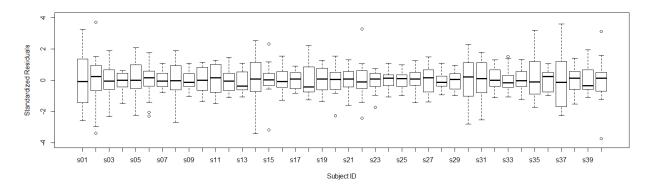
```
## Level 1 Assumptions ----
# Normality
qqnorm(resid(cond 01))
```

Normal Q-Q Plot



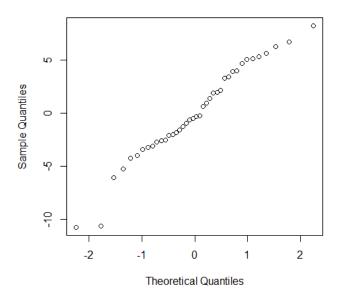


```
# Influential Participants
plot(DATA$subID, resid(cond_01)/sd(resid(cond_01)),
    ylab="Standardized Residuals", xlab="Subject ID",
    ylim=c(-4,4))
```



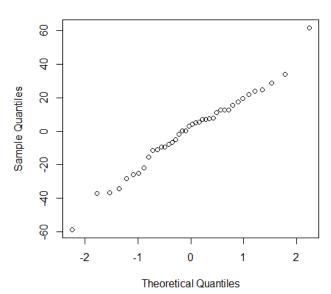
```
## Level 2 Assumptions ----
LVL2<-summarize(group by(DATA, subID),
                AIS grade = AIS grade[1])
head (LVL2)
ranef(cond 01)
LVL2$RE int<-ranef(cond 01)$subID$`(Intercept)`
LVL2$STD int<-LVL2$RE int/sd(LVL2$RE int)
LVL2$RE year<-ranef(cond 01)$subID$year.0
LVL2$STD year<-LVL2$RE year/sd(LVL2$RE year)
LVL2$RE year sq<-ranef(cond 01)$subID$year.0 sq
LVL2$STD year sq<-LVL2$RE year sq/sd(LVL2$RE year sq)
LVL2$RE year cu<-ranef(cond 01)$subID$year.0 cu
LVL2$STD year cu<-LVL2$RE year cu/sd(LVL2$RE year cu)
head (LVL2)
# Normality of Random-Effects
qqnorm(LVL2$RE int)
```

Normal Q-Q Plot

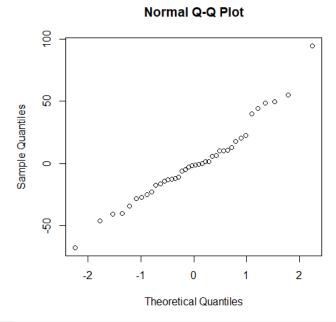


qqnorm(LVL2\$RE_year)

Normal Q-Q Plot

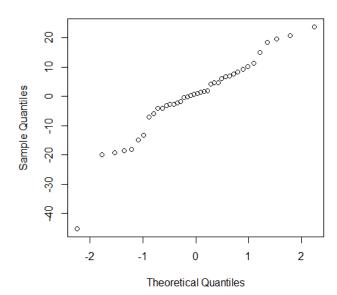


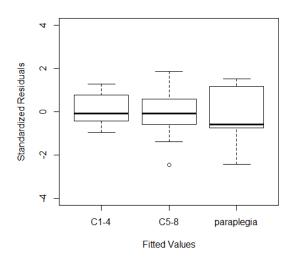
qqnorm(LVL2\$RE year sq)



qqnorm(LVL2\$RE_year_cu)

Normal Q-Q Plot





```
plot(x=LVL2$AIS_grade, y=LVL2$STD_year,
    xlab = "Fitted Values", ylab="Standardized Residuals",
    ylim=c(-4,4))
```

