Clinical Trial A5055

01/22/2024

Installation of required packages and functions.

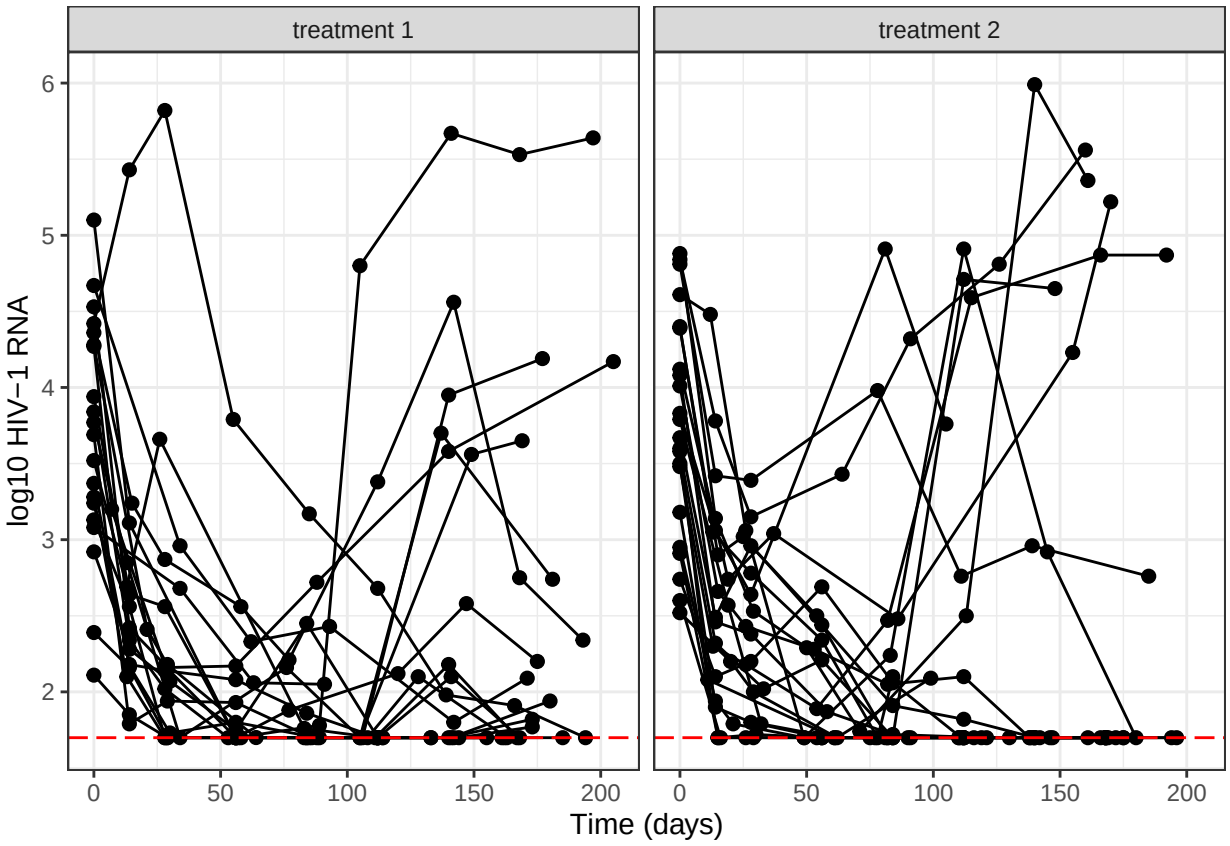
```
library(msm)
library(ggplot2)
library(tcltk)
library(numDeriv)
library(MASS)
library(base)
library(expm)
library(ARpLMEC)
```

Reading and setting the dataset

```
########################
# Dataset A5055        #
########################

data1 <- read.csv("dataA5055.csv")

attach(data1)
data1    <- subset(data1, !is.na(cd4))
subjects <- unique(data1$patid)
cluster  <- c(match(data1$patid,subjects))
m        <- length(subjects)
N        <- length(cluster)
y1       <- c(data1$logrna)
y2.1     <- c(data1$cd4)
x        <- c(data1$day)
tem      <- c(data1$day)
treat    <- data1$arm
nj       <- matrix(0,m,1)

for (j in 1:m){nj[j]=sum(cluster==j)}

cc                  <- (data1$rna<50)+0
y1[y1<=log10(50)]   <- log10(50)

###################################
# Excluding Subjects 4 and 8      #
###################################

for(i in c( 4,8))
{ y1[cluster==i]     = NA
```

```
y2.1[cluster==i]   = NA
x[cluster==i]      = NA
tem[cluster==i]    = NA
treat[cluster==i]  = NA
cc[cluster==i]     = NA
nj[i]              = NA
cluster[cluster==i]= NA }

y1      <- as.vector(na.omit(y1))
y2.1    <- as.vector(na.omit(y2.1))
x       <- as.vector(na.omit(x))
tem     <- as.vector(na.omit(tem))
treat   <- as.vector(na.omit(treat))
cc      <- as.vector(na.omit(cc))
nj      <- as.vector(na.omit(nj))
cluster <- as.vector(na.omit(cluster))

subjetos=unique(cluster)
for(i in 1:length(subjetos))
{
  cluster[cluster==subjetos[i]]=i
}

m <- length(nj)
N <- length(cluster)

##########################
# Design Matrix         #
##########################

xx1    <- cbind(rep(1,length(y1)),x,treat,y2.1^0.5,treat*x)
zz1    <- cbind(1,x)
cc1    <- cc
nj1    <- nj
y1     <- y1
tempo1 <- tem

#######################
# Profiles Plot       #
#######################

datas   <- cbind(cluster,treat,x,y1,cc,y2.1)
nam_row <- as.character((1:312))
nam_col <- c("cluster","arm","day","logrna","cens","cd4")
datas   <- matrix(datas,nrow=312,ncol=6,
                  dimnames=list(" "=nam_row," "=nam_col))
dados   <- as.data.frame(datas)
attach(dados, warn.conflicts = FALSE)
dados2  <- dados

dados2$arm[dados2$arm=="1"] <- "treatment 1"
dados2$arm[dados2$arm=="2"] <- "treatment 2"
```

```
grafico <- ggplot(dados2, aes(x=day,y=logrna,group = cluster))
grafico + geom_line() +   geom_point(size = 2) +
  labs(x = "Time (days)", y="log10 HIV-1 RNA") +
  facet_wrap(~ arm) +
  geom_hline(yintercept=log10(50),colour="red",linetype ="longdash")+
  theme_bw()
```



Getting initial values from the UNC-N-LMEC model

```
lm1.un1 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                       nj = nj1, struc = "UNC", typeModel = "Normal",
                       error = 0.00001, MaxIter = 10)
```

```
##
## ----------------------------------------------------
## DEC censored mixed-effects models
## ----------------------------------------------------
##
## Case = UNC
## Distribution = Normal
##
## Subjects = 42 ; Observations = 312
##
## -----------
## Estimates
```

```
## -----------
##
## - Fixed effects
##
##           Est    SE         IConf(95%)
## beta 1  4.165 0.540  < 3.107 , 5.223 >
## beta 2 -0.003 0.010 < -0.023 , 0.017 >
## beta 3  0.269 0.270  < -0.26 , 0.798 >
## beta 4 -0.097 0.032 < -0.16 , -0.034 >
## beta 5 -0.001 0.005 < -0.011 , 0.009 >
##
##
## - Sigma^2
##
##           Est    SE       IConf(95%)
## Sigma^2 0.741 0.077 < 0.59 , 0.892 >
##
##
## - Random effects
##
##             Est    SE         IConf(95%)
## Alpha 11  0.304 0.185      < 0 , 0.667 >
## Alpha 12 -0.003 0.005 < -0.013 , 0.007 >
## Alpha 22  0.000 0.000          < 0 , 0 >
##
##
## ------------------------
## Model selection criteria
## ------------------------
##
##        Loglik    AIC     BIC
## Value -365.92 749.84 783.527
##
## -------
## Details
## -------
##
## Convergence reached? = FALSE
## Iterations = 10 / 10
## Processing time = 11.27578 secs
```

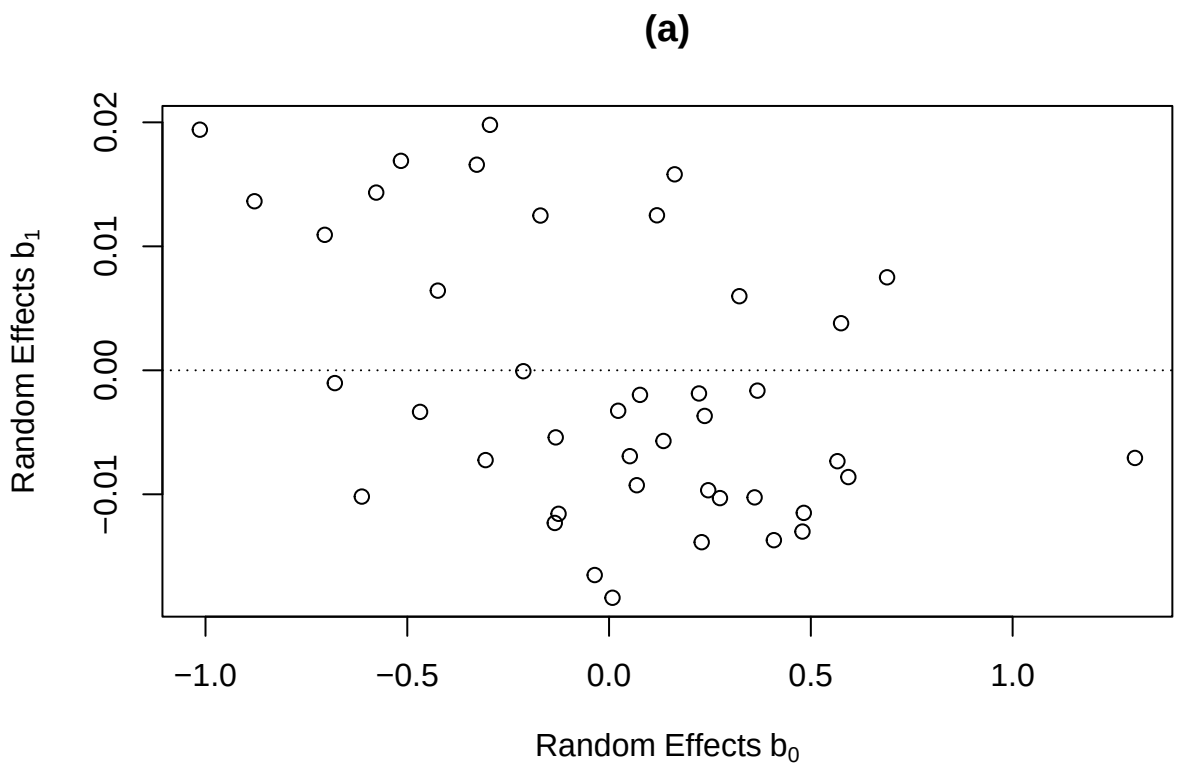
```
betasI  <- as.vector(lm1.un1$FixEffec$Est)
sigma2I <- lm1.un1$Sigma2$Est
alphasI <- diag(2)
LL1     <- rep(-Inf,length(y1))
LU1     <- as.vector(y1)

initial1 <- list(betas=betasI,sigma2=sigma2I,alphas=alphasI)
```

Preliminary analysis

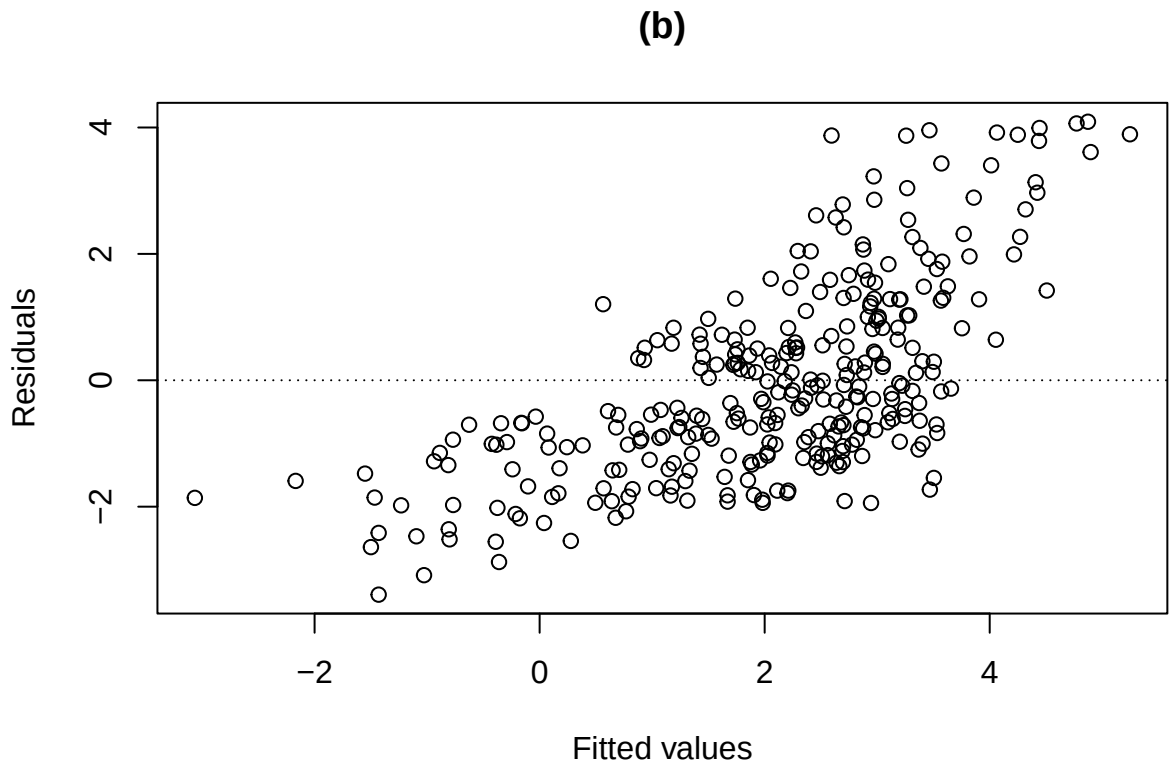
```
############################################################
# Fit of the N-LMEC model without correlation structures  #
```

```
#############################################################
fitN     <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "UNC",initial = initial1,
                        typeModel = "Normal",LI=LL1,LS=LU1, error = 1e-4,
                        MaxIter = 500)
```

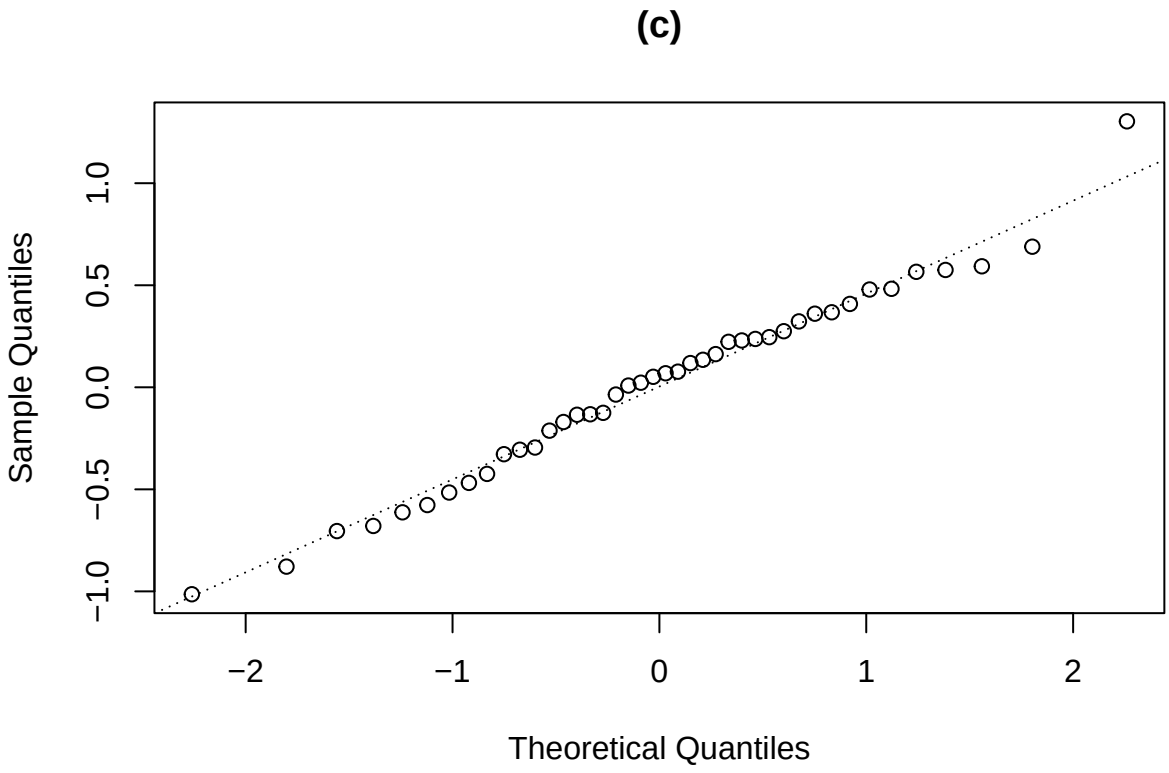
```
#####################################################################
# Residuals of the N-LMEC model without correlation structures  #
#####################################################################
res    <- fitY<-rep(0,length(y1))
efectob<- matrix(0,length(nj),2)
for (i in 1:length(nj)){
  efectob[i,] = fitN$others$ubi[(((i-1)*2)+1) : (i*2),i]
  resi        = fitN$others$yog[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))]-
  xx1[(sum(nj[1:i-1])+1) : (sum(nj[1:i])),]%*%fitN$FixEffect$Est
  res[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))] = ((fitN$Sigma2$Est)^(-0.5))*resi
  fitY[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))]= xx1[(sum(nj[1:i-1])+1):(sum(nj[1:i]))
                                                ,]%*%fitN$FixEffect$Est+
                                  zz1[(sum(nj[1:i-1])+1):(sum(nj[1:i])),]%*%efectob[i,]
}

plot(efectob[,1],efectob[,2],xlab=expression(Random~Effects~b[0]),
     ylab=expression(Random~Effects~b[1]) ,main = "(a)")
abline(h=0, lty=3)
```



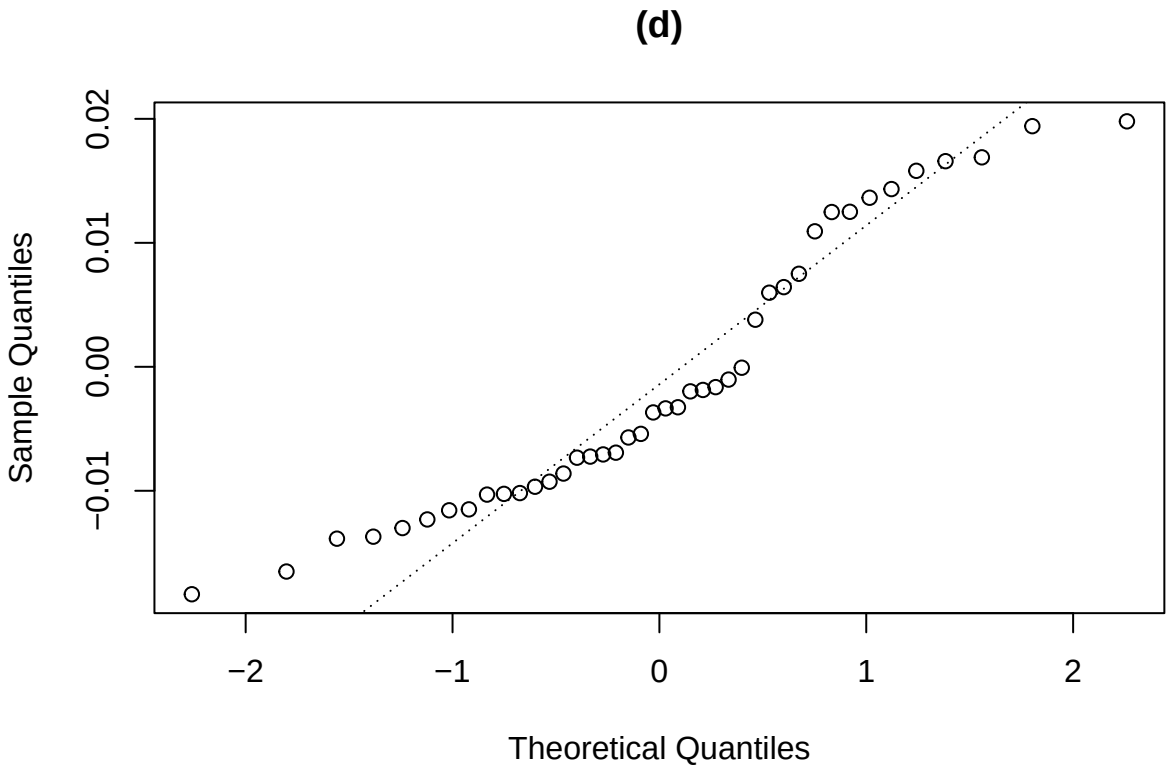
```r
plot(fitY,res,xlab= "Fitted values", ylab= "Residuals", main="(b)")
abline(h=0, lty=3, col=9)
```



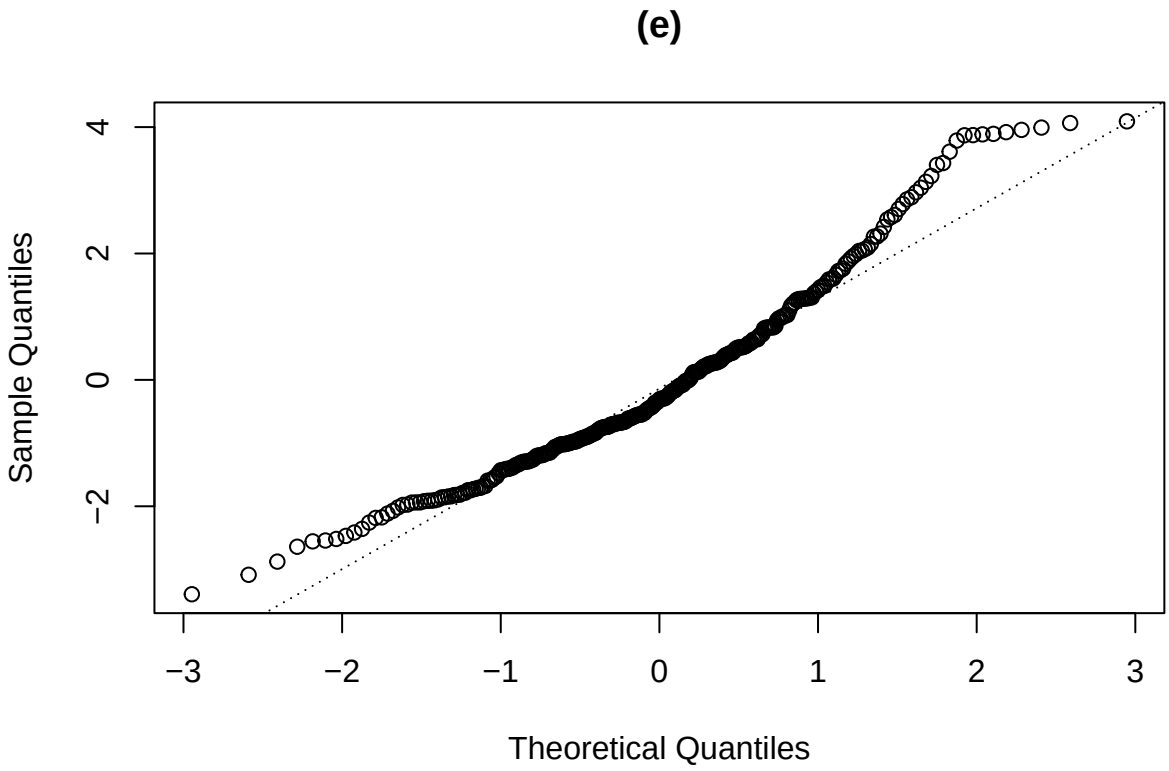

```r
qqnorm(efectob[,1], main = "(c)")
qqline(efectob[,1], lty=3)
```




```
qqnorm(efectob[,2], main = "(d)")
qqline(efectob[,2], lty=3)
```




```
qqnorm(res ,main = "(e)")
qqline(res , lty=3)
```



Fit of the t-LMEC model under differents correlation structures

```
####################
# Initial values   #
####################

initial1 <- list(betas=betasI,sigma2=sigma2I,alphas=alphasI,nu=3)

#########################
# Fitted t-LMEC models  #
#########################


model1T1 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "UNC",initial = initial1 ,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
model1T2 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "DEC", initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
model1T3 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "DEC(AR)",initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
```

```
model1T4 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "SYM",initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
model1T5 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 1,initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
model1T6 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 2,initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
model1T7 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 3,initial = initial1,
                        nu.fixed = FALSE, typeModel = "Student", error = 1e-4,
                        MaxIter = 500)
```

```
#########################
# Parameters estimates  #
#########################
Table1Betas  <- cbind(model1T1$FixEffect$Est,model1T2$FixEffect$Est,
                      model1T3$FixEffect$Est,model1T4$FixEffect$Est,
                      model1T5$FixEffect$Est,model1T6$FixEffect$Est,
                      model1T7$FixEffect$Est)
Table1sigmae <- cbind(model1T1$Sigma2$Est,model1T2$Sigma2$Est,
                      model1T3$Sigma2$Est,model1T4$Sigma2$Est,
                      model1T5$Sigma2$Est,model1T6$Sigma2$Est,
                      model1T7$Sigma2$Est)
Table1D      <- cbind(model1T1$RandEffect$Est,model1T2$RandEffect$Est,
                      model1T3$RandEffect$Est,model1T4$RandEffect$Est,
                      model1T5$RandEffect$Est,model1T6$RandEffect$Est,
                      model1T7$RandEffect$Est)
Table1Phi1   <- cbind(0,model1T2$Phi$Est[1],model1T3$Phi$Est,model1T4$Phi$Est,
                      model1T5$Phi$Est,model1T6$Phi$Est[1],model1T7$Phi$Est[1])
Table1Phi2   <- cbind(0,model1T2$Phi$Est[2],1,0,
                      0,model1T6$Phi$Est[2],model1T7$Phi$Est[2])
Table1Phi3   <- cbind(0,0,0,0,0,0,model1T7$Phi$Est[3])
Table1Nu     <- cbind(model1T1$nu,model1T2$nu,model1T3$nu,model1T4$nu,
                      model1T5$nu,model1T6$nu,model1T7$nu)

tableTlmec<-round(rbind(Table1Betas,Table1sigmae,Table1D,Table1Phi1,
                        Table1Phi2,Table1Phi3,Table1Nu),3)

colnames(tableTlmec)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(tableTlmec) <- c("beta0","beta1","beta2","beta3","beta4","sigma2",
                           "alpha11","alpha12","alpha22","phi1","phi2","phi3","nu")

print(tableTlmec)
```

```
##            UNC    DEC DEC(AR)    SYM  AR(1)  AR(2)  AR(3)
## beta0    3.976  3.975   4.063  3.977  3.977  3.972  4.077
## beta1   -0.005 -0.005  -0.004 -0.005 -0.005 -0.005 -0.004
## beta2    0.356  0.355   0.381  0.351  0.356  0.358  0.353
## beta3   -0.085 -0.085  -0.093 -0.085 -0.085 -0.085 -0.093
```

```
## beta4   -0.004 -0.004  -0.004 -0.004 -0.004 -0.004 -0.004
## sigma2   0.469  0.466   0.519  0.492  0.286  0.279  0.176
## alpha11  0.215  0.212   0.217  0.182  0.214  0.210  0.221
## alpha12 -0.001 -0.001  -0.002 -0.002 -0.001 -0.001 -0.002
## alpha22  0.000  0.000   0.000  0.000  0.000  0.000  0.000
## phi1     0.000  0.106   0.899  0.065  0.628  0.731  0.279
## phi2     0.000  0.998   1.000  0.000  0.000 -0.420  0.106
## phi3     0.000  0.000   0.000  0.000  0.000  0.000 -0.786
## nu       2.974  2.774   3.704  2.969  2.908  2.889  4.512
```

```
####################
# Standard errors  #
####################

SET <- round(cbind(model1T1$FixEffect$SE,model1T2$FixEffect$SE,
                   model1T3$FixEffect$SE,model1T4$FixEffect$SE,
                   model1T5$FixEffect$SE,model1T6$FixEffect$SE,
                   model1T7$FixEffect$SE),3)

colnames(SET)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(SET) <- c("beta0","beta1","beta2","beta3","beta4")

print(SET)
```

```
##         UNC   DEC DEC(AR)   SYM AR(1) AR(2) AR(3)
## beta0 0.618 0.508   0.540 0.500 0.623 0.606 0.644
## beta1 0.008 0.007   0.008 0.007 0.008 0.008 0.008
## beta2 0.314 0.249   0.269 0.246 0.317 0.308 0.324
## beta3 0.020 0.020   0.021 0.019 0.021 0.020 0.021
## beta4 0.006 0.005   0.005 0.005 0.006 0.005 0.006
```

```
#########################
# Information criterias  #
#########################

Table1AIC    <- cbind(model1T1$AIC,model1T2$AIC,model1T3$AIC,
                      model1T4$AIC,model1T5$AIC,model1T6$AIC,
                      model1T7$AIC)
Table1BIC    <- cbind(model1T1$BIC,model1T2$BIC,model1T3$BIC,
                      model1T4$BIC,model1T5$BIC,model1T6$BIC,
                      model1T7$BIC)
Table1loglik <- cbind(model1T1$loglik,model1T2$loglik,model1T3$loglik,
                      model1T4$loglik,model1T5$loglik,model1T6$loglik,
                      model1T7$loglik)

CriteriasT            <- rbind(Table1loglik,Table1AIC,Table1BIC)
colnames(CriteriasT)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(CriteriasT) <- c("loglik","AIC","BIC")

print(CriteriasT)
```

```
##              UNC       DEC   DEC(AR)       SYM     AR(1)     AR(2)     AR(3)
## loglik -353.6822 -353.6362 -349.6190 -353.3074 -353.4796 -353.2864 -351.9953
## AIC     729.3644  731.2724  721.2381  728.6149  728.9591  730.5729  729.9906
## BIC     770.5375  776.1884  762.4111  769.7879  770.1321  775.4889  778.6497
```

Fit of the N-LMEC model under differents correlation structures

```
####################
# Initial values   #
####################

initial1 <- list(betas=betasI,sigma2=sigma2I,alphas=alphasI)

#########################
# Fitted N-LMEC models  #
#########################

model1N1 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "UNC", initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N2 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "DEC",  initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N3 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "DEC(AR)", initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N4 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "SYM", initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N5 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 1, initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N6 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 2,  initial = initial1,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
model1N7 <- ARpMMEC.est(y = y1, x = xx1, z = zz1, tt = tempo1, cc = cc1,
                        nj = nj1, struc = "ARp", order = 3,
                        typeModel = "Normal", error = 1e-4, MaxIter = 500)
```

```
#########################
# Parameters estimates  #
#########################

Table1Betas  <- cbind(model1N1$FixEffect$Est,model1N2$FixEffect$Est,
                      model1N3$FixEffect$Est,model1N4$FixEffect$Est,
                      model1N5$FixEffect$Est,model1N6$FixEffect$Est,
                      model1N7$FixEffect$Est)
Table1sigmae <- cbind(model1N1$Sigma2$Est,model1N2$Sigma2$Est,
                      model1N3$Sigma2$Est,model1N4$Sigma2$Est,
                      model1N5$Sigma2$Est,model1N6$Sigma2$Est,
                      model1N7$Sigma2$Est)
Table1D      <- cbind(model1N1$RandEffect$Est,model1N2$RandEffect$Est,
                      model1N3$RandEffect$Est,model1N4$RandEffect$Est,
                      model1N5$RandEffect$Est,model1N6$RandEffect$Est,
                      model1N7$RandEffect$Est)
Table1Phi1   <- cbind(0,model1N2$Phi$Est[1],model1N3$Phi$Est,model1N4$Phi$Est,
                      model1N5$Phi$Est,model1N6$Phi$Est[1],model1N7$Phi$Est[1])
Table1Phi2   <- cbind(0,model1N2$Phi$Est[2],1,0,
                      0,model1N6$Phi$Est[2],model1N7$Phi$Est[2])
```

```
Table1Phi3   <- cbind(0,0,0,0,0,0,model1N7$Phi$Est[3])

tableNlmec    <- round(rbind(Table1Betas,Table1sigmae,Table1D,Table1Phi1,
                             Table1Phi2,Table1Phi3),4)

colnames(tableNlmec)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(tableNlmec) <- c("beta0","beta1","beta2","beta3","beta4","sigma2",
                           "alpha11","alpha12","alpha22","phi1","phi2","phi3")

print(tableNlmec)
```

```
##            UNC    DEC DEC(AR)    SYM  AR(1)  AR(2)  AR(3)
## beta0    4.381  4.381   4.379  4.388  4.383  4.384  4.284
## beta1   -0.004 -0.004  -0.004 -0.004 -0.004 -0.004 -0.003
## beta2    0.304  0.305   0.304  0.304  0.307  0.307  0.359
## beta3   -0.111 -0.111  -0.111 -0.112 -0.111 -0.111 -0.113
## beta4   -0.003 -0.003  -0.003 -0.003 -0.003 -0.003 -0.003
## sigma2   0.732  0.732   0.732  0.765  0.427  0.418  0.195
## alpha11  0.382  0.382   0.382  0.353  0.382  0.384  0.293
## alpha12 -0.004 -0.004  -0.004 -0.004 -0.004 -0.004 -0.003
## alpha22  0.000  0.000   0.000  0.000  0.000  0.000  0.000
## phi1     0.000  0.998   0.106  0.043  0.652  0.759  0.275
## phi2     0.000  0.106   1.000  0.000  0.000 -0.481  0.100
## phi3     0.000  0.000   0.000  0.000  0.000  0.000 -0.817
```

```
####################
# Standard errors  #
####################

SEN <- round(cbind(model1N1$FixEffect$SE,model1N2$FixEffect$SE,
                   model1N3$FixEffect$SE,model1N4$FixEffect$SE,
                   model1N5$FixEffect$SE,model1N6$FixEffect$SE,
                   model1N7$FixEffect$SE),4)

colnames(SEN)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(SEN) <- c("beta0","beta1","beta2","beta3","beta4")

print(SEN)
```

```
##         UNC   DEC DEC(AR)   SYM AR(1) AR(2) AR(3)
## beta0 0.533 0.003   0.002 0.010 0.539 0.553 0.586
## beta1 0.009 0.008   0.008 0.008 0.009 0.009 0.009
## beta2 0.308 0.058   0.058 0.014 0.309 0.309 0.315
## beta3 0.031 0.010   0.010 0.008 0.031 0.032 0.034
## beta4 0.005 0.004   0.004 0.004 0.005 0.005 0.006
```

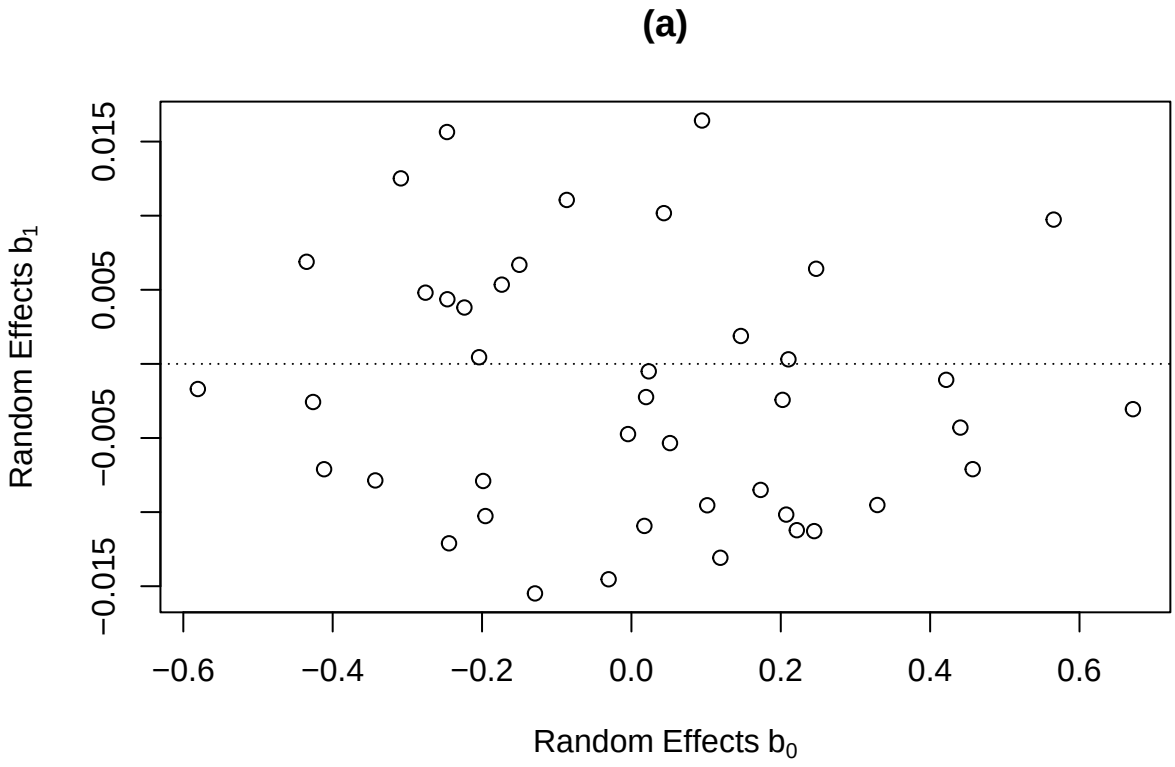
```
#########################
# Information criterias  #
#########################

Table1AIC1    <- cbind(model1N1$AIC,model1N2$AIC,model1N3$AIC,
                       model1N4$AIC,model1N5$AIC,model1N6$AIC,model1N7$AIC)
Table1BIC1    <- cbind(model1N1$BIC,model1N2$BIC,model1N3$BIC,
                       model1N4$BIC,model1N5$BIC,model1N6$BIC,model1N7$BIC)
Table1loglik1 <- cbind(model1N1$loglik,model1N2$loglik,model1N3$loglik,
```

```
                      model1N4$loglik,model1N5$loglik,model1N6$loglik,
                      model1N7$loglik)

CriteriasN           <- rbind(Table1loglik1,Table1AIC1,Table1BIC1)
colnames(CriteriasN)  <- c("UNC","DEC","DEC(AR)","SYM","AR(1)","AR(2)","AR(3)")
row.names(CriteriasN) <- c("loglik","AIC","BIC")

print(CriteriasN)
```

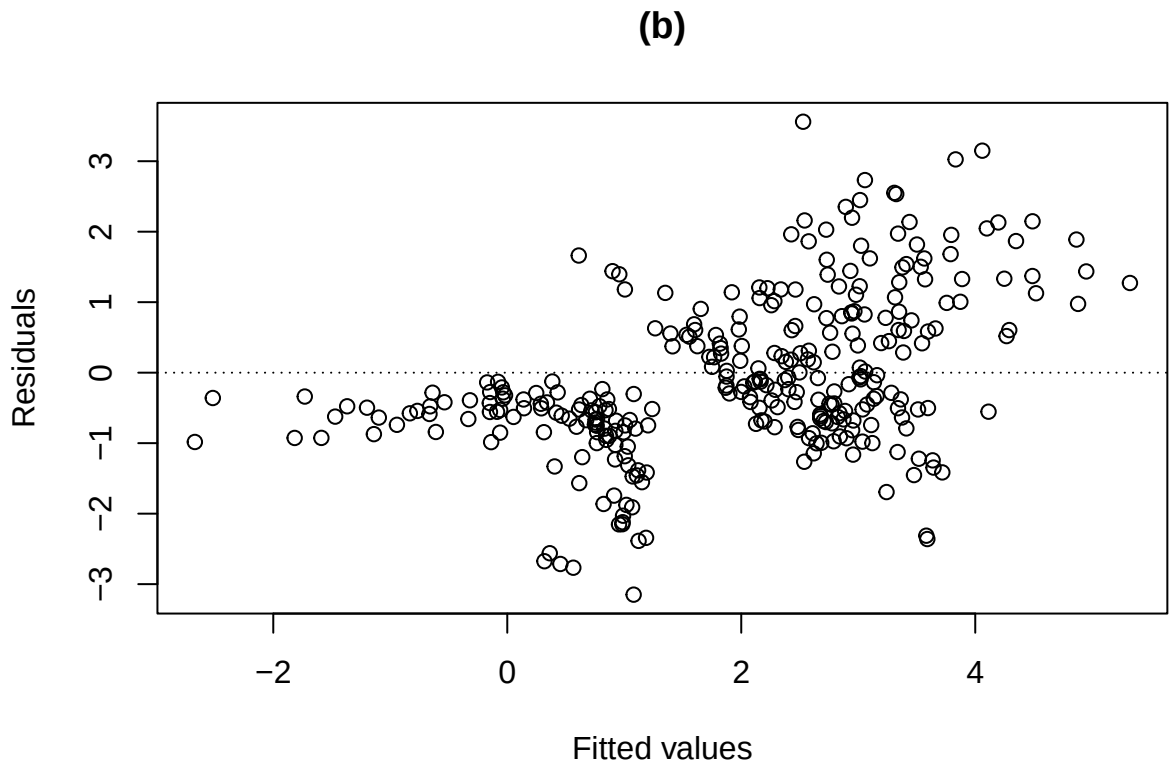
```
##              UNC       DEC   DEC(AR)       SYM     AR(1)     AR(2)     AR(3)
## loglik -362.6051 -362.6255 -362.6460 -362.5751 -362.3400 -362.3978 -355.4445
## AIC     743.2102  747.2511  745.2919  745.1501  744.6799  746.7957  734.8889
## BIC     776.8973  788.4241  782.7220  782.5802  782.1100  787.9687  779.8050
```

Residual analysis of the DEC(AR)-t-LMEC model

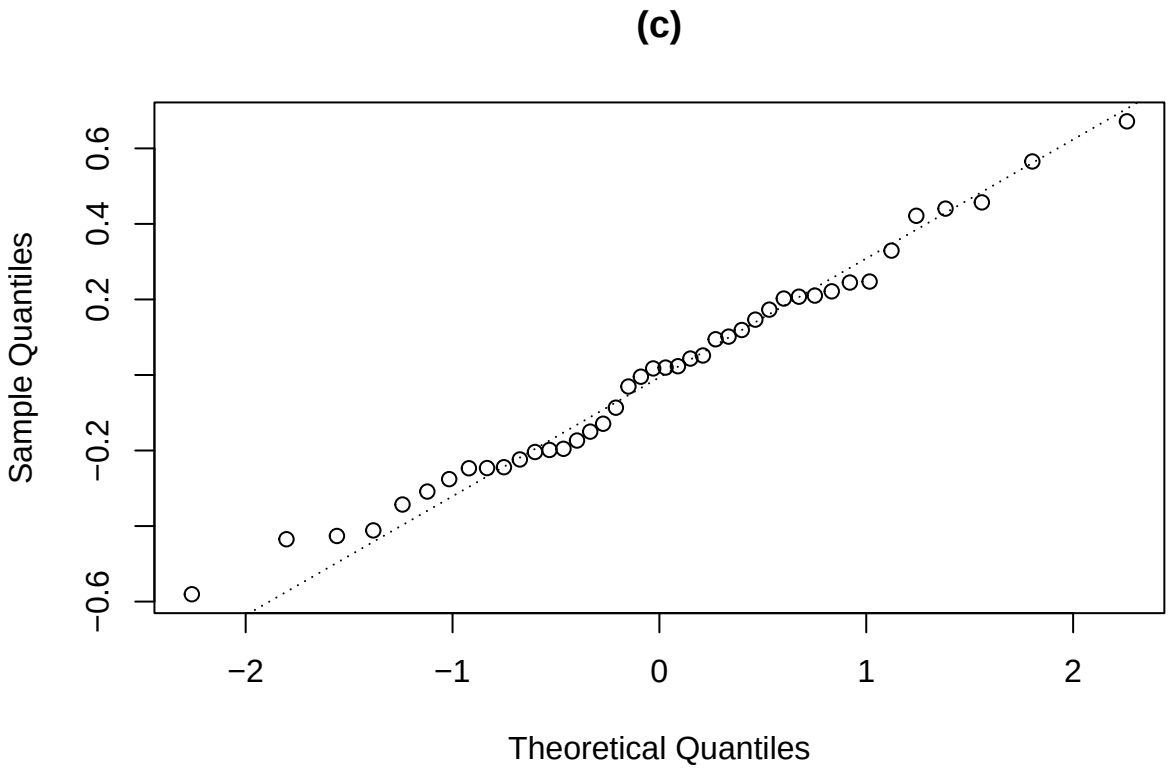
```
obj     <- model1T3
efectob <- matrix(0,length(nj),2)
for (k in 1:length(nj)){
  efectob[k,] <- obj$others$ubi[(((k-1)*dim(zz1)[2])+1) : (k*dim(zz1)[2]), k]
}
plot(efectob[,1],efectob[,2],xlab=expression(Random~Effects~b[0]),
     ylab=expression(Random~Effects~b[1]) ,main = "(a)")
abline(h=0, lty=3)
```



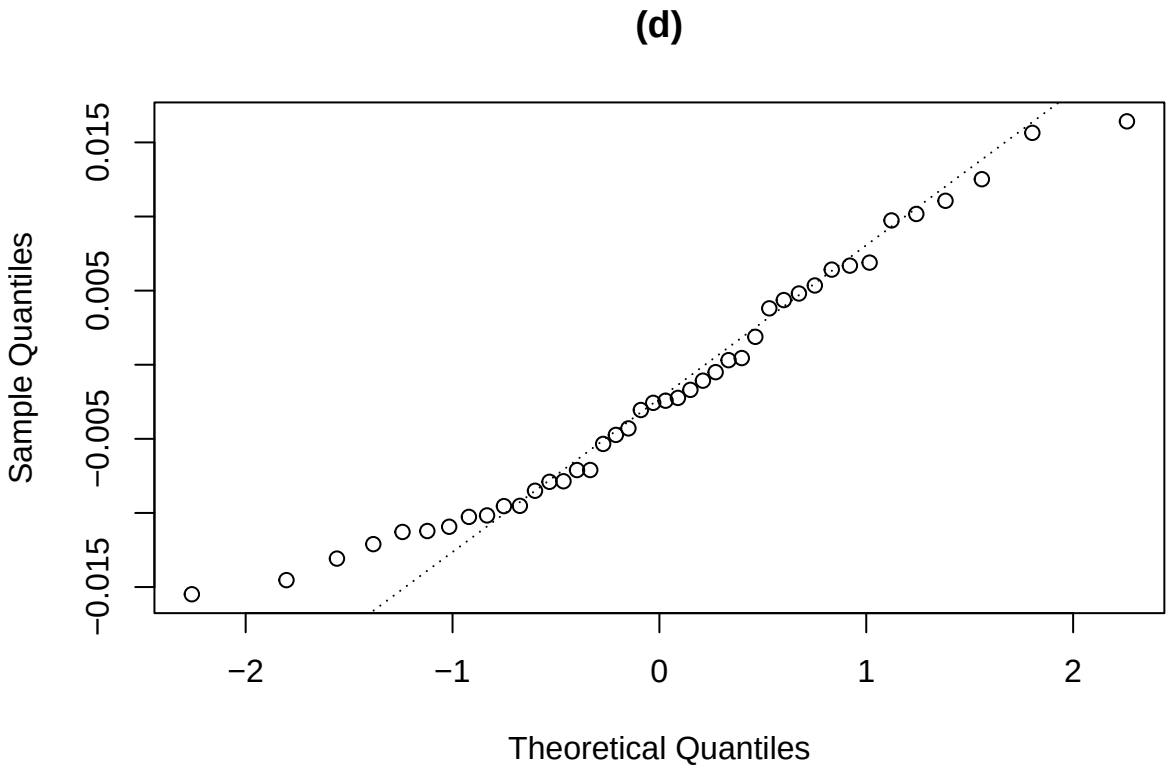
```
plot(obj$Yfit,obj$Residual,xlab= "Fitted values", ylab= "Residuals",main = "(b)")
abline(h=0, lty=3, col=9)
```




```
qqnorm(efectob[,1], main = "(c)")
qqline(efectob[,1], lty=3)
```




```
qqnorm(efectob[,2],main = "(d)")
qqline(efectob[,2], lty=3)
```




```
qqnorm(obj$Residual,main = "(e)")
qqline(obj$Residual, lty=3)
```

(e)