Clinical Trial A5055

Installation of required packages and functions.

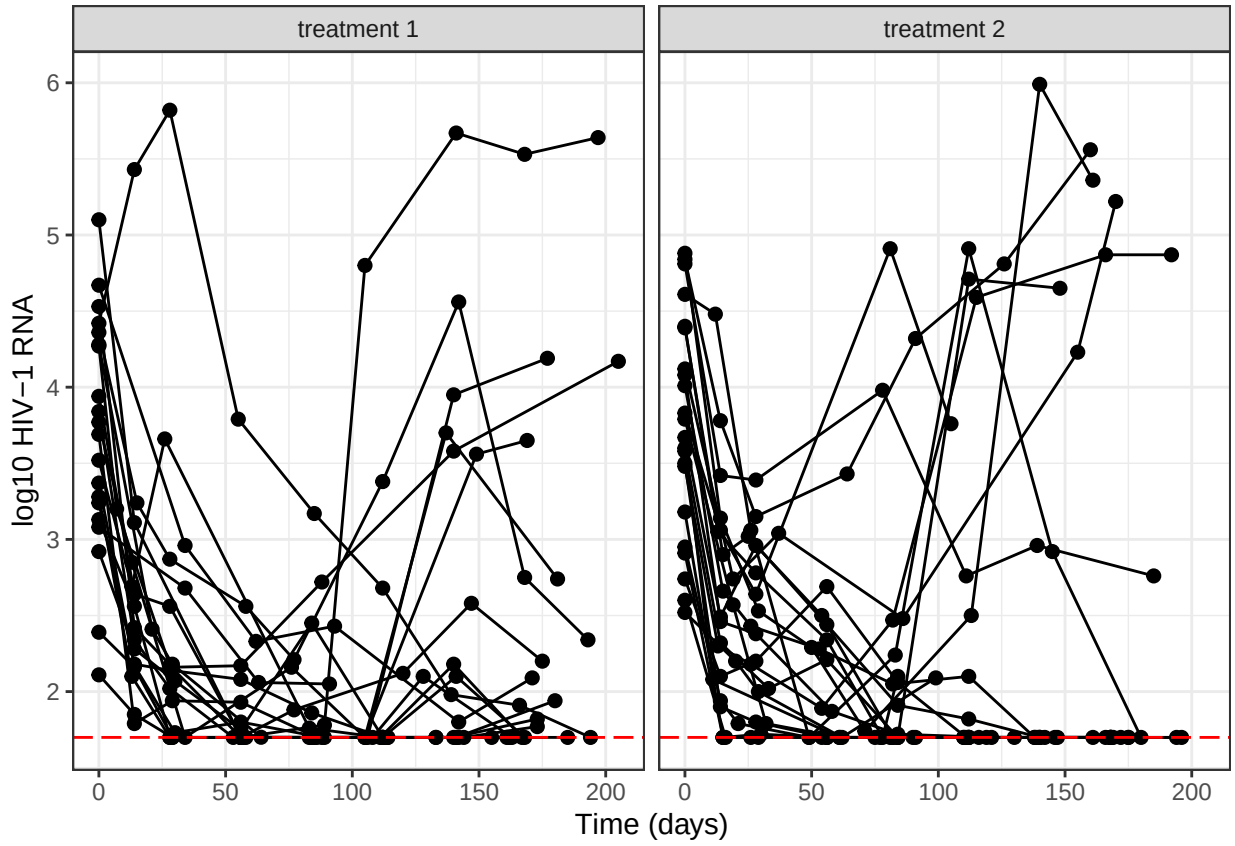
```
source("tmecArpRCO.R")
source("utils_tmecArpRCO.R")

library(mvtnorm)
library(mnormt)
library(lmec)
library(tmvtnorm)
library(msm)
library(ggplot2)
library(tcltk)
library(numDeriv)
library(MASS)
library(base)
library(expm)
library(ARpLMEC)
library(Rcpp)
library(MomTrunc)
library(TTmoment)
```

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)
```

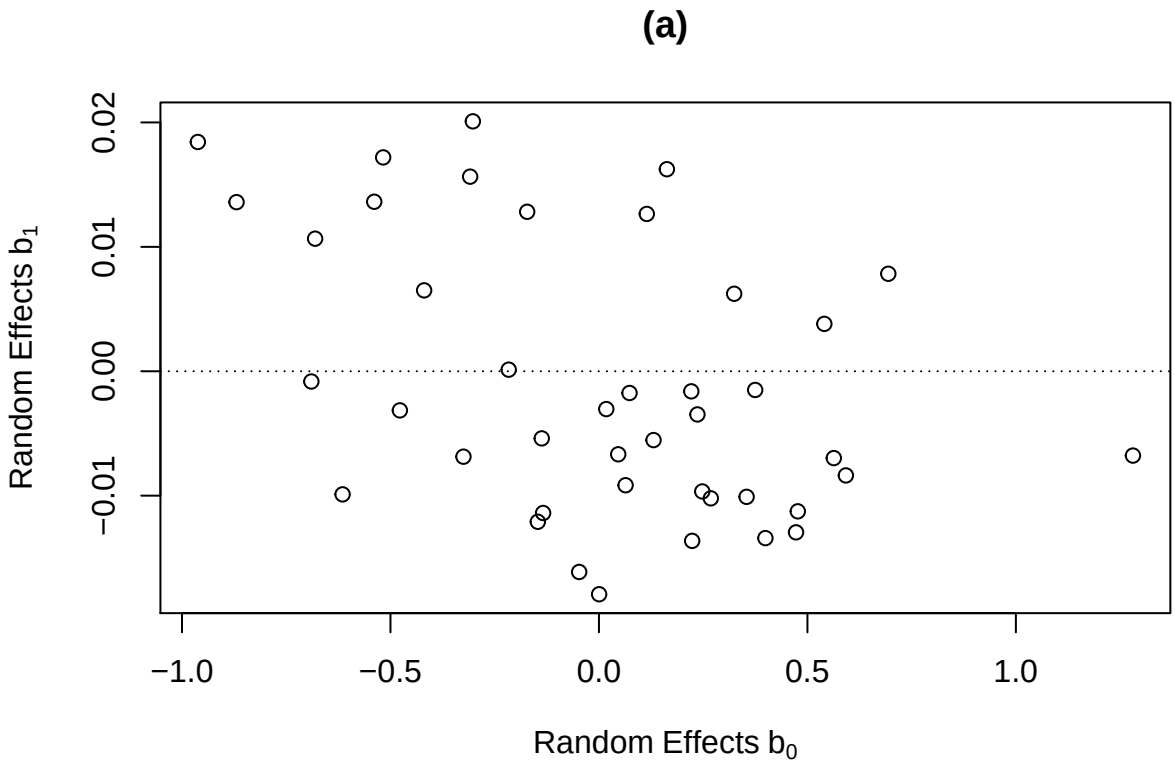
```
##
## ----------------------------------------------------
## DEC censored mixed-effects models
```

```
## ------------------------------------------------
##
## Case = UNC
## Distribution = Normal
## Subjects = 42 ; Observations = 312
##
## -----------
## Estimates
## -----------
##
## - Fixed effects
##
##           Est    SE          IConf(95%)
## beta 1  4.205 0.067   < 4.074 , 4.336 >
## beta 2 -0.003 0.009  < -0.021 , 0.015 >
## beta 3  0.270 0.248  < -0.216 , 0.756 >
## beta 4 -0.099 0.027 < -0.152 , -0.046 >
## beta 5 -0.001 0.005  < -0.011 , 0.009 >
##
##
## - Sigma^2
##
##           Est    SE       IConf(95%)
## Sigma^2 0.733 0.075 < 0.586 , 0.88 >
##
##
## - Autoregressives parameters
##
## NULL
##
##
## - Random effects
##
##             Est    SE         IConf(95%)
## Alpha 11  0.337 0.202      < 0 , 0.733 >
## Alpha 12 -0.004 0.005 < -0.014 , 0.006 >
## Alpha 22  0.000 0.000          < 0 , 0 >
##
##
## ------------------------
## Model selection criteria
## ------------------------
##
##         Loglik     AIC     BIC
## Value -366.292 750.585 784.272
##
## -------
## Details
## -------
##
## Convergence reached? = FALSE
## Iterations = 10 / 10
## Processing time = 20.71864 secs
```

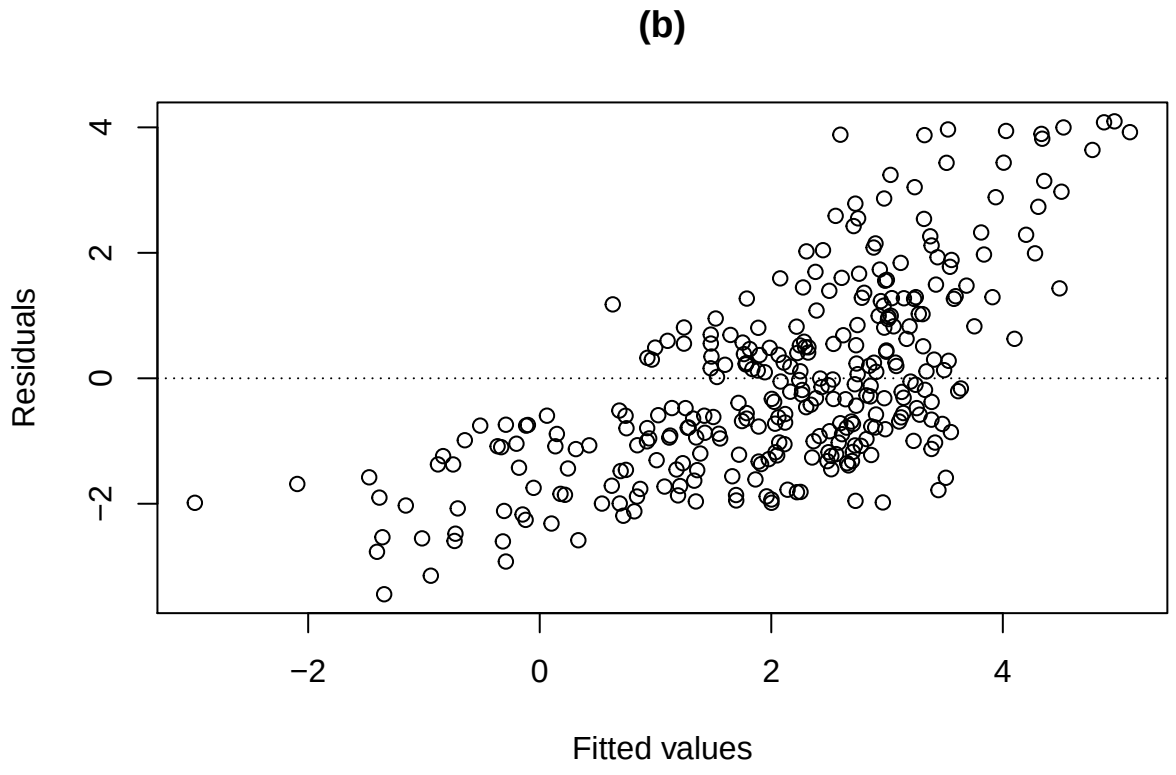
```
betasI  <- as.vector(lm1.un1$FixEffec$Est)
sigma2I <- lm1.un1$Sigma2$Est
alphasI <- diag(2)
phi1I   <- 0.1
phi2I   <- 1
LL1     <- rep(-Inf,length(y1))
LU1     <- as.vector(y1)

initial1 <- list(betas=betasI,sigma2=sigma2I,alphas=alphasI,
                 phi1=phi1I,phi2=phi2I,nu=150)
```

Preliminary analysis

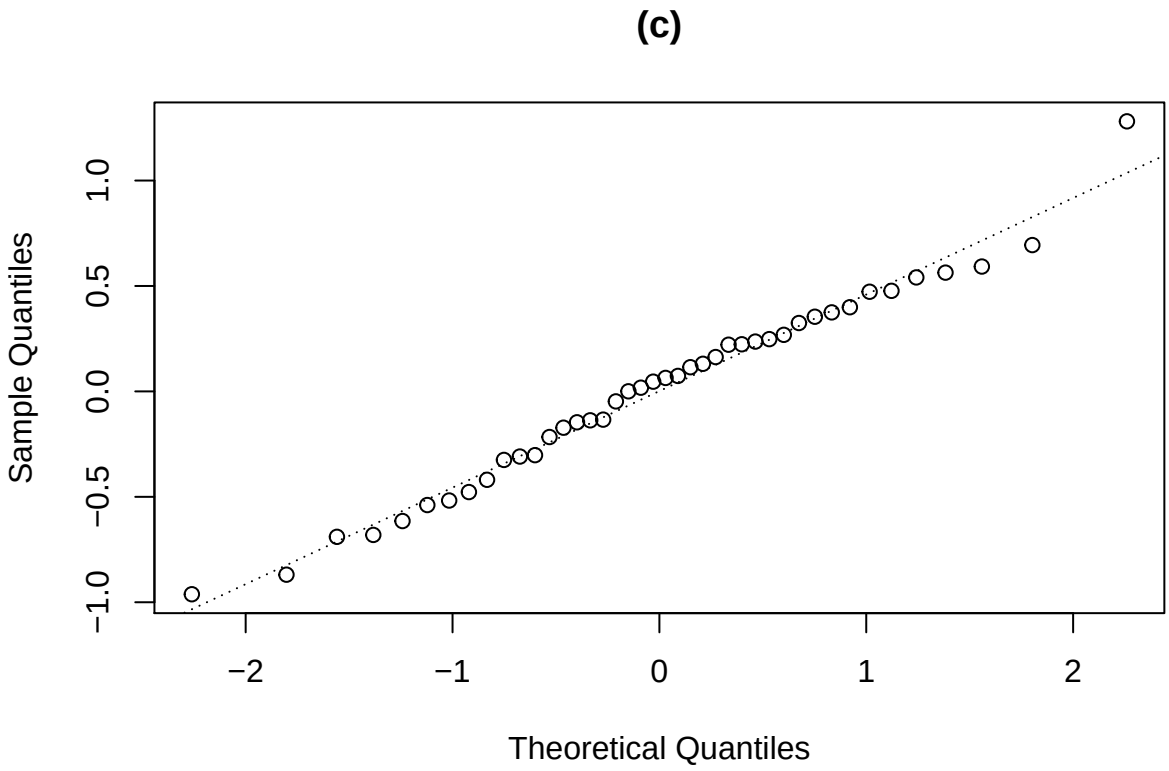
```
#############################################################
# Fit of the N-LMEC model without correlation structures  #
#############################################################

fitN     <- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,struc="unc",
                     nu.fixed=TRUE,iter.max=500,precision=1e-4)


#####################################################################
# 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$ubi[(((i-1)*2)+1) : (i*2),i]
  resi        = fitN$yog[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))]-
                xx1[(sum(nj[1:i-1])+1) : (sum(nj[1:i])),]%*%fitN$beta1

  res[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))] = ((fitN$sigmae)^(-0.5))*resi
  fitY[(sum(nj[1:i-1])+1) : (sum(nj[1:i]))]= xx1[(sum(nj[1:i-1])+1):(sum(nj[1:i]))
                                                 ,]%*%fitN$beta1+ 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)
```



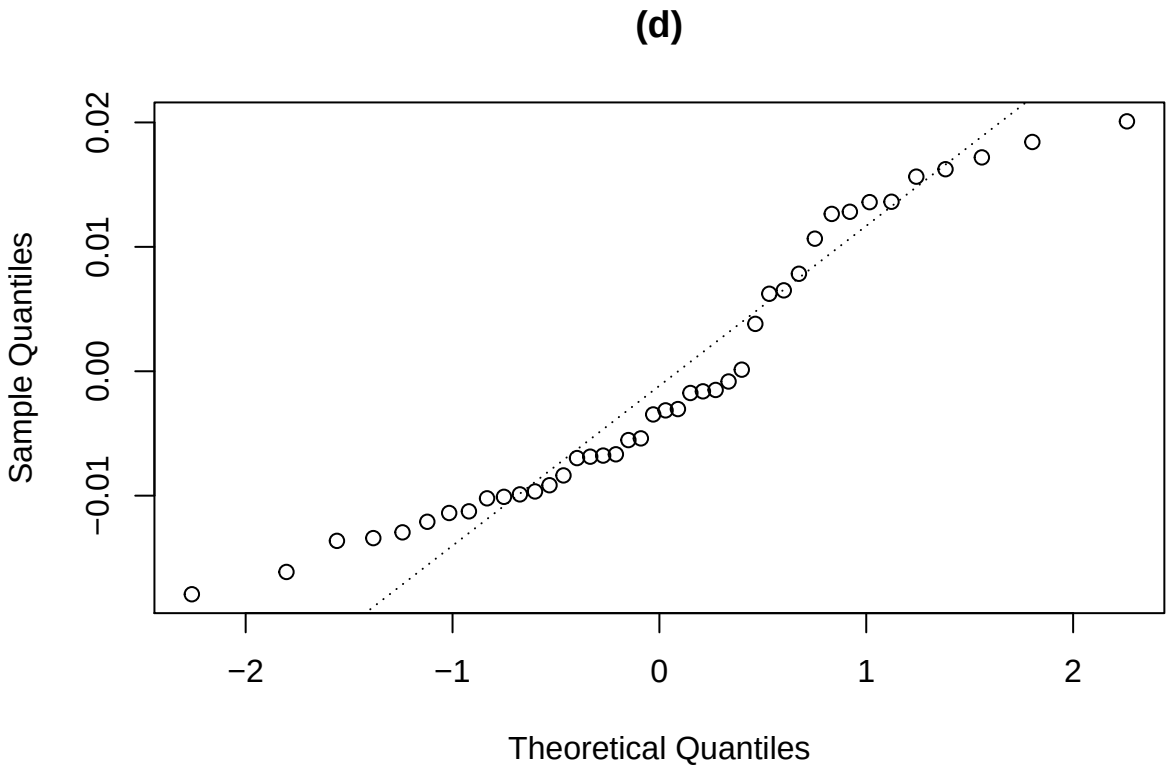

```
plot(fitY,res,xlab= "Fitted values", ylab= "Residuals", main="(b)")
abline(h=0, lty=3, col=9)
```



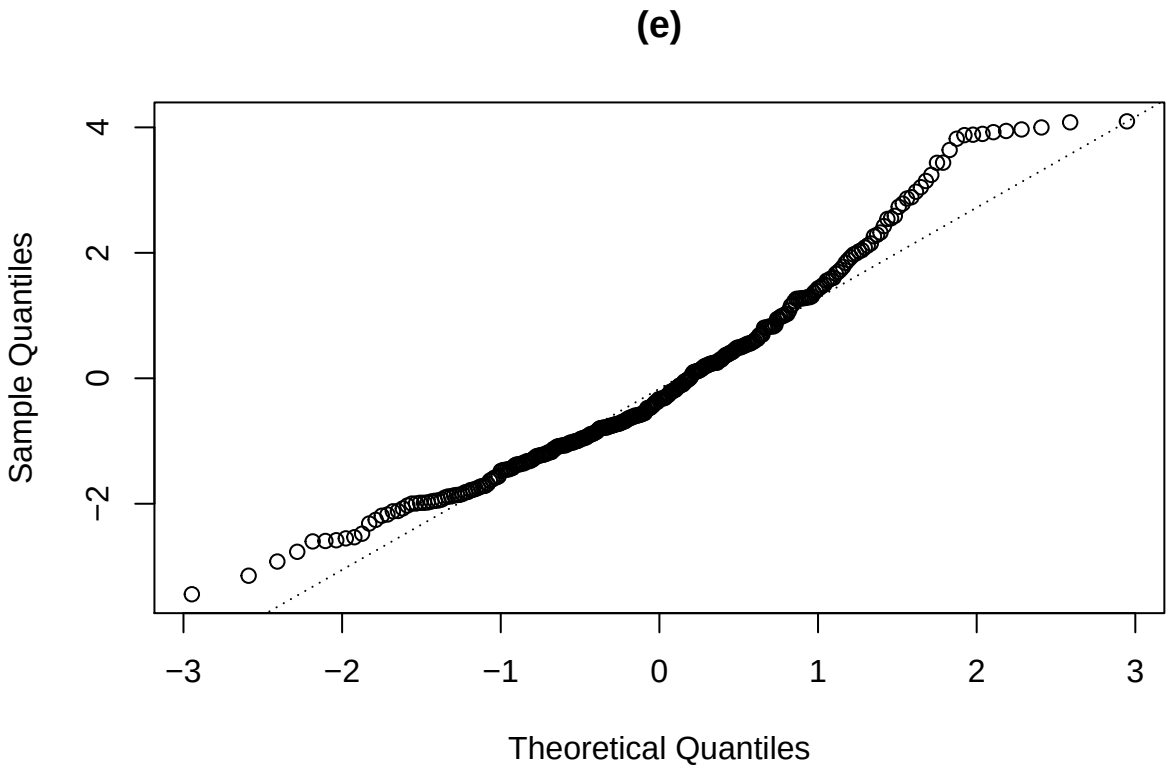

```
qqnorm(efectob[,1], main = "(c)")
qqline(efectob[,1], lty=3)
```




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




```
qqnorm(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,phi1=phi1I,
                 phi2=phi2I,nu=3)

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

model1T1 <- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj1,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,struc="unc",
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
model1T2 <- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,struc="dec",
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
model1T3 <- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,struc="ar",
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
model1T4 <- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,struc="sym",
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
```

```
model1T5 <- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,Arp=1,
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
model1T6 <- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,Arp=2,
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)
model1T7 <- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                     LL=LL1,LU=LU1,initial=initial1,Arp=3,
                     nu.fixed=FALSE,iter.max=500,precision=1e-4)

#########################
# Parameters estimates  #
#########################

Table1Betas  <- cbind(model1T1$beta1,model1T2$beta1,model1T3$beta1,
                      model1T4$beta1,model1T5$beta1,model1T6$beta1,
                      model1T7$beta1)
Table1sigmae <- cbind(model1T1$sigmae,model1T2$sigmae,model1T3$sigmae,
                      model1T4$sigmae,model1T5$sigmae,model1T6$sigmae,
                      model1T7$sigmae)
Table1D      <- cbind(model1T1$dd,model1T2$dd,model1T3$dd,model1T4$dd,
                      model1T5$dd,model1T6$dd,model1T7$dd)
Table1Phi1   <- cbind(0,model1T2$phi1,model1T3$phi1,model1T4$phi1,
                      model1T5$phi,model1T6$phi[1],model1T7$phi[1])
Table1Phi2   <- cbind(0,model1T2$phi2,model1T3$phi2,model1T4$phi2,
                      0,model1T6$phi[2],model1T7$phi[2])
Table1Phi3   <- cbind(0,0,0,0,0,0,model1T7$phi[3])
Table1Nu     <- cbind(model1T1$nu,model1T2$nu,model1T3$nu,model1T4$nu,
                      model1T5$nu,model1T6$nu,model1T7$nu)

tableTlmec<-round(rbind(Table1Betas,Table1sigmae,Table1D,Table1Phi1,
                        Table1Phi2,Table1Phi3,Table1Nu),4)

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    4.0445  4.0443  4.1077  4.0560  4.0471  4.0444  4.1446
## beta1   -0.0046 -0.0046 -0.0041 -0.0045 -0.0046 -0.0047 -0.0042
## beta2    0.3438  0.3441  0.3783  0.3382  0.3451  0.3454  0.3471
## beta3   -0.0888 -0.0887 -0.0955 -0.0897 -0.0890 -0.0889 -0.0981
## beta4   -0.0037 -0.0036 -0.0041 -0.0035 -0.0039 -0.0039 -0.0037
## sigma2   0.4958  0.4919  0.5406  0.5365  0.2909  0.2890  0.1802
## alpha11  0.2383  0.2374  0.2284  0.2152  0.2386  0.2379  0.2416
## alpha12 -0.0018 -0.0018 -0.0020 -0.0019 -0.0018 -0.0018 -0.0020
## alpha22  0.0001  0.0001  0.0001  0.0001  0.0001  0.0001  0.0001
## phi1     0.0000  0.1061  0.8993  0.0620  0.6449  0.7401  0.2865
## phi2     0.0000  0.9980  1.0000  0.0000  0.0000 -0.4325  0.0959
## phi3     0.0000  0.0000  0.0000  0.0000  0.0000  0.0000 -0.7872
## nu       4.5110  4.2730  5.4342  4.3559  4.5567  4.2991  7.3481
```

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

SET <- round(cbind(sqrt(diag(solve(model1T1$Infbetas))),
                   sqrt(diag(solve(model1T2$Infbetas))),
                   sqrt(diag(solve(model1T3$Infbetas))),
                   sqrt(diag(solve(model1T4$Infbetas))),
                   sqrt(diag(solve(model1T5$Infbetas))),
                   sqrt(diag(solve(model1T6$Infbetas))),
                   sqrt(diag(solve(model1T7$Infbetas)))),4)

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 0.4997 0.5013  0.5187 0.5088 0.5030 0.5007 0.5392
## beta1 0.0072 0.0072  0.0073 0.0072 0.0072 0.0072 0.0076
## beta2 0.2484 0.2491  0.2607 0.2527 0.2501 0.2490 0.2714
## beta3 0.0193 0.0193  0.0198 0.0195 0.0194 0.0193 0.0201
## beta4 0.0048 0.0048  0.0049 0.0048 0.0048 0.0048 0.0050
```

```
#########################
# 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 -355.8039 -355.8885 -350.7299 -356.0035 -355.5502 -355.5399 -353.1112
## AIC     731.6078  735.7771  723.4598  734.0071  733.1004  735.0798  732.2224
## BIC     769.0378  780.6931  764.6328  775.1801  774.2734  779.9959  780.8815
```

Fit of the N-LMEC model under differents correlation structures

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

```
####################

initial1 <- list(betas=betasI,sigma2=sigma2I,alphas=alphasI,phi1=phi1I
                 ,phi2=phi2I,nu=150)

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

model1N1<- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,struc="unc",
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N2<- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,struc="dec",
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N3<- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,struc="ar",
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N4<- tmec.DEC(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,struc="sym",
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N5<- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,Arp=1,
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N6<- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,Arp=2,
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)
model1N7<- tmec.Arp(y=y1,cc=cc1,x=xx1,z=zz1,nj=nj,ttc=tempo1,
                    LL=LL1,LU=LU1,initial=initial1,Arp=3,
                    nu.fixed=TRUE,iter.max=500,precision=1e-4)

#########################
# Parameters estimates  #
#########################

Table1Betas    <- cbind(model1N1$beta1,model1N2$beta1,model1N3$beta1,
                        model1N4$beta1,model1N5$beta1,model1N6$beta1,
                        model1N7$beta1)
Table1sigmae   <- cbind(model1N1$sigmae,model1N2$sigmae,model1N3$sigmae,
                        model1N4$sigmae,model1N5$sigmae,model1N6$sigmae,
                        model1N7$sigmae)
Table1D        <- cbind(model1N1$dd,model1N2$dd,model1N3$dd,model1N4$dd,
                        model1N5$dd,model1N6$dd,model1N7$dd)
Table1Phi1     <- cbind(0,model1N2$phi1,model1N3$phi1,model1N4$phi1,
                        model1N5$phi,model1N6$phi[1],model1N7$phi[1])
Table1Phi2     <- cbind(0,model1N2$phi2,model1N3$phi2,model1N4$phi2,0,
                        model1N6$phi[2],model1N7$phi[2])
Table1Phi3     <- cbind(0,0,0,0,0,0,model1N7$phi[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)")
```

```r
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    4.3668  4.3667  4.3430  4.3711  4.3657  4.3637  4.2908
## beta1   -0.0040 -0.0040 -0.0033 -0.0040 -0.0040 -0.0039 -0.0033
## beta2    0.3064  0.3064  0.3530  0.3056  0.3094  0.3085  0.3601
## beta3   -0.1097 -0.1097 -0.1127 -0.1102 -0.1100 -0.1099 -0.1123
## beta4   -0.0029 -0.0029 -0.0032 -0.0030 -0.0030 -0.0029 -0.0035
## sigma2   0.7134  0.7136  0.7246  0.7450  0.4132  0.4074  0.1926
## alpha11  0.3756  0.3756  0.3254  0.3459  0.3744  0.3763  0.2992
## alpha12 -0.0039 -0.0039 -0.0037 -0.0039 -0.0039 -0.0039 -0.0031
## alpha22  0.0002  0.0002  0.0002  0.0002  0.0002  0.0002  0.0002
## phi1     0.0000  0.1064  0.8993  0.0426  0.6551  0.7603  0.2785
## phi2     0.0000  0.9979  1.0000  0.0000  0.0000 -0.4809  0.0963
## phi3     0.0000  0.0000  0.0000  0.0000  0.0000  0.0000 -0.8128
```

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

SEN <- round(cbind(sqrt(diag(solve(model1N1$Infbetas))),
                   sqrt(diag(solve(model1N2$Infbetas))),
                   sqrt(diag(solve(model1N3$Infbetas))),
                   sqrt(diag(solve(model1N4$Infbetas))),
                   sqrt(diag(solve(model1N5$Infbetas))),
                   sqrt(diag(solve(model1N6$Infbetas))),
                   sqrt(diag(solve(model1N7$Infbetas)))),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 0.4966 0.4961  0.5007 0.4972 0.4982 0.4981 0.5182
## beta1 0.0073 0.0073  0.0073 0.0073 0.0073 0.0073 0.0075
## beta2 0.2564 0.2561  0.2613 0.2568 0.2571 0.2571 0.2671
## beta3 0.0187 0.0187  0.0186 0.0187 0.0188 0.0188 0.0191
## beta4 0.0047 0.0047  0.0047 0.0047 0.0047 0.0047 0.0048
```

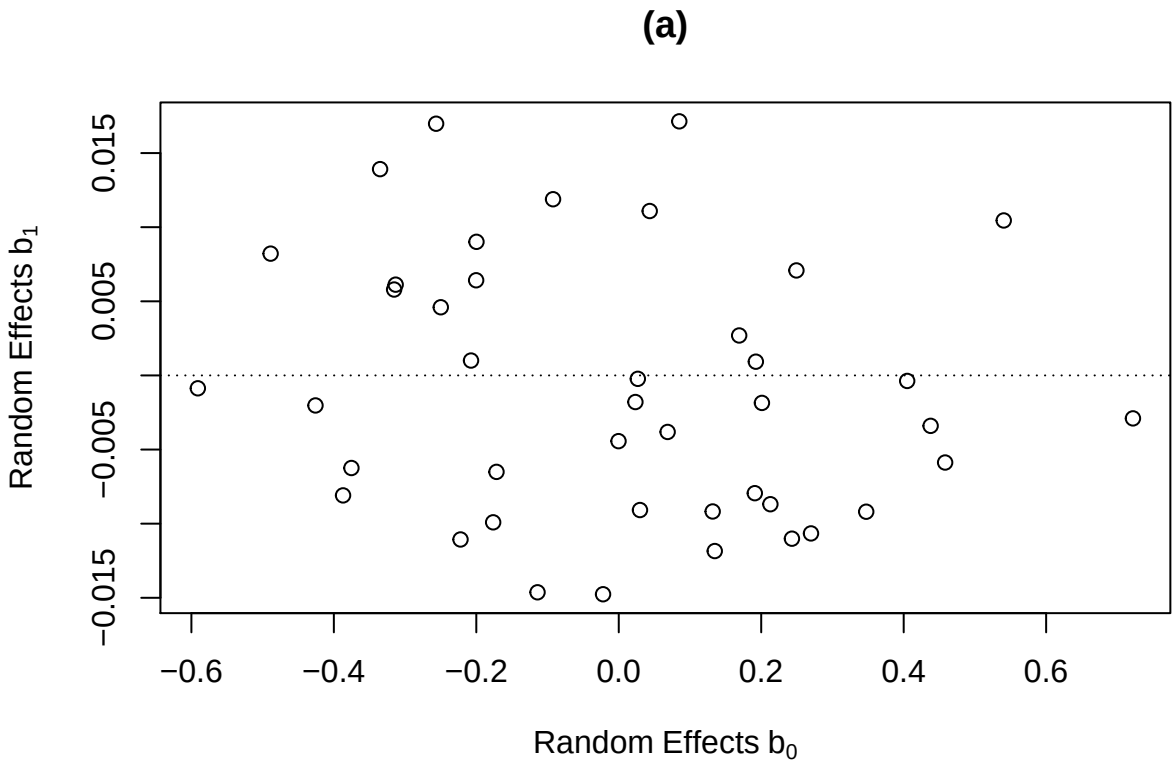
```r
##########################
# Information criterias  #
##########################

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)
```

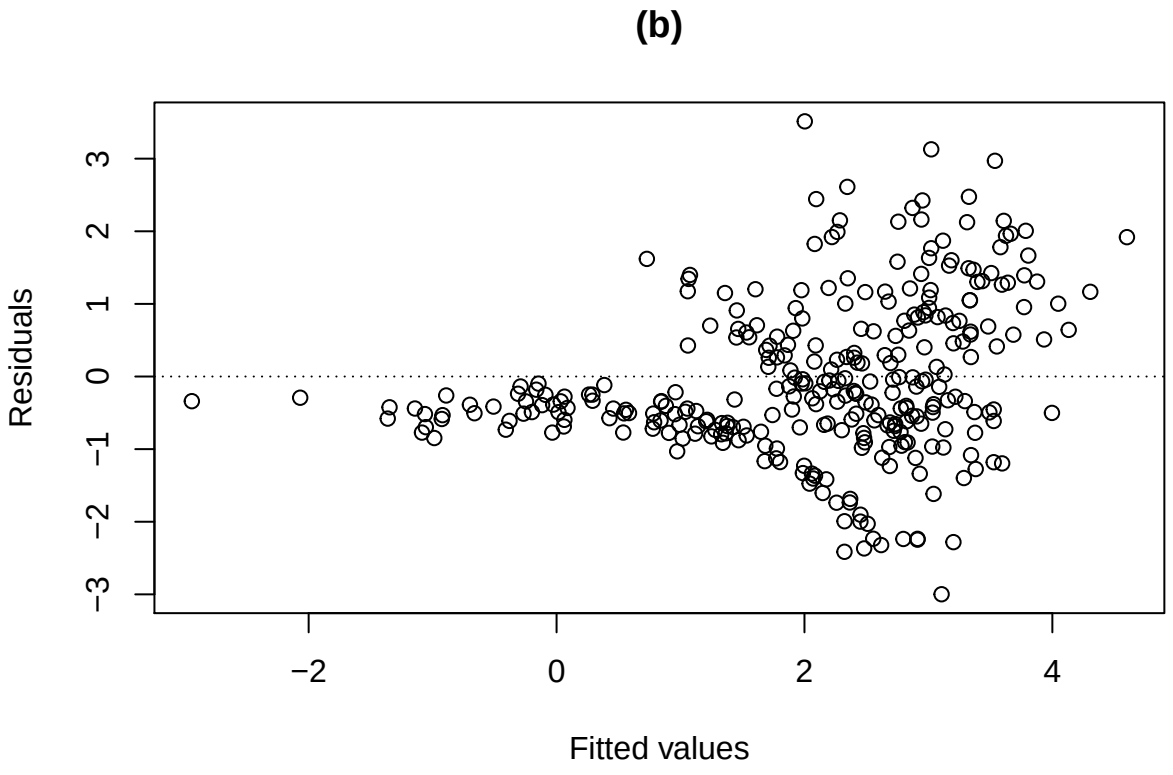
```
##              UNC       DEC   DEC(AR)       SYM     AR(1)     AR(2)     AR(3)
## loglik -362.0229 -362.0222 -354.9770 -361.9947 -361.7953 -361.8760 -355.1145
## AIC     744.0458  748.0443  731.9539  745.9893  745.5905  747.7519  736.2290
## BIC     781.4758  792.9604  773.1270  787.1623  786.7636  792.6679  784.8880
```

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

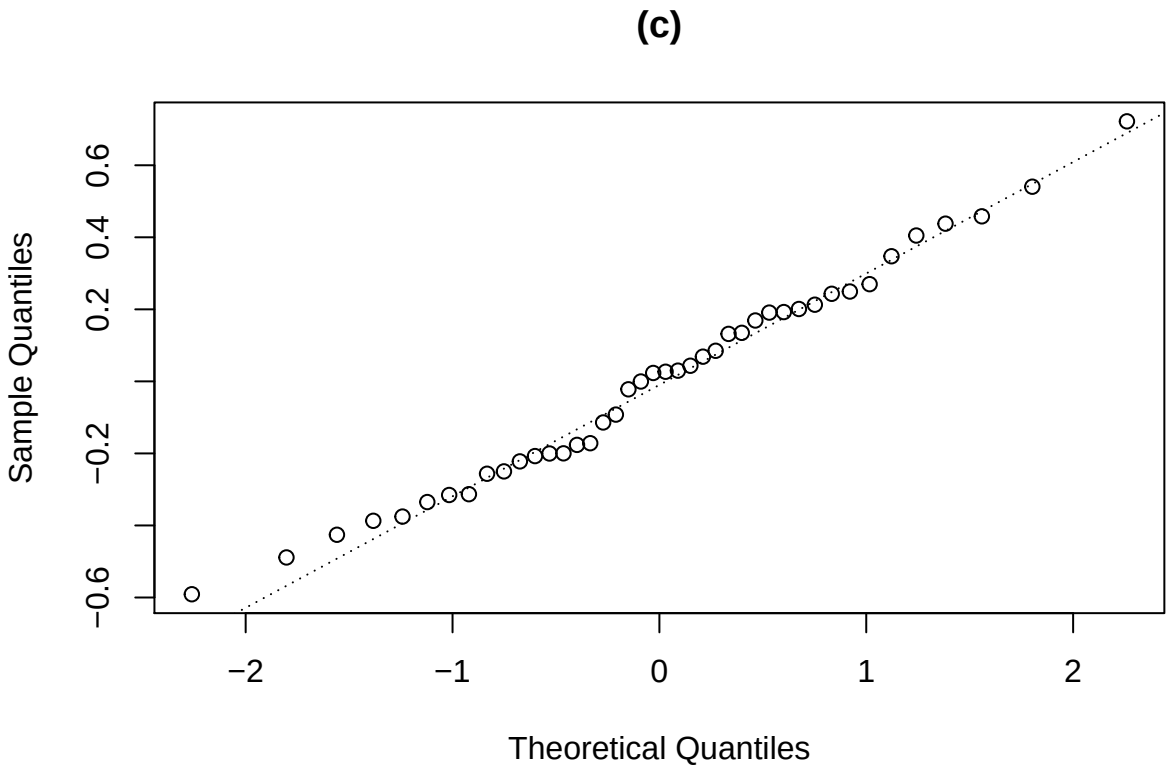
```
obj     <- model1T3
Di      <- matrix(0,dim(zz1)[2],dim(zz1)[2])
bet     <- obj$beta1
Di[upper.tri(Di, diag = T)] <- obj$dd
Di[lower.tri(Di, diag = T)] <- obj$dd
Di      <- round(Di,6)
sig     <- obj$sigmae
rese    <- Yi<- Ye<- vector(mode = "numeric", length = length(y1))
efectob <- matrix(0,length(nj),2)
for (k in 1:length(nj)){
  tc          <- tem[(sum(nj[1:k-1])+1) : (sum(nj[1:k]))]
  bi          <- obj$ubi[(((k-1)*dim(zz1)[2])+1) : (k*dim(zz1)[2]), k]
  efectob[k,] <- bi
  Mq          <- MatDec(tc,obj$phi1,obj$phi2,"ar")
  Sii         <- zz1[(sum(nj[1:k-1])+1) : (sum(nj[1:k])),]%*%Di%*%t(zz1[(sum(nj[1
                 :k-1])+1) : (sum(nj[1:k])),])+sig*Mq
  Sii         <- round(Sii,6)
  Mui         <- xx1[(sum(nj[1:k-1])+1) : (sum(nj[1:k])),]%*%bet
  Yi          <- obj$yog[(sum(nj[1:k-1])+1) : (sum(nj[1:k]))]

  Ye[(sum(nj[1:k-1])+1) : (sum(nj[1:k]))]   <- xx1[(sum(nj[1:k-1])+1) : (sum(nj[1:k])),
                                               ]%*%bet+zz1[(sum(nj[1:k-1])+1) : (sum
                                               (nj[1:k])),]%*%bi
  rese[(sum(nj[1:k-1])+1) : (sum(nj[1:k]))] <- (sqrtm(solve(Sii))%*%(Yi-Mui))
}

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



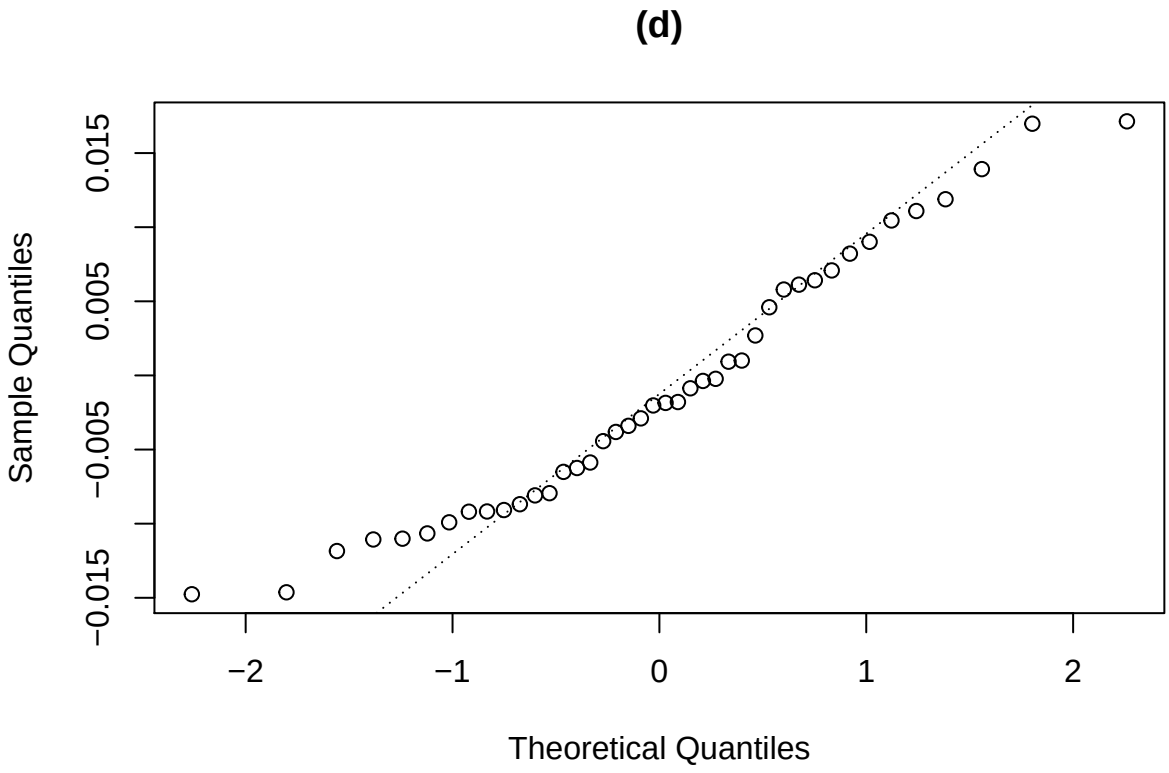

```
plot(Ye,rese,xlab= "Fitted values", ylab= "Residuals",main = "(b)")
abline(h=0, lty=3, col=9)
```




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




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




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

(e)