R code for functional mixed model in scalar on function regression with repeated outcomes

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1. Main code

```
fmm_sofr <- function(data,
                     control = list(
                              pve = 0.95,
                              knots = 5,
                              p = 5,
                              m = 2,
                              center = TRUE,
                              lambda = NULL)){

  # input contains data and control
  # both data and control are lists

  Y <- data$Y   # response vector Yij
  Z <- data$Z   # numeric variable vector Zij
  Xt <- as.matrix(data$Xt) # functional covariate Xij(t) matrix
  ID <- data$ID # subject index

  subs <- unique(ID)
  nSubj <- length(subs)
  nRep <- sapply(subs, function(x) length(which(ID==x)))
  t <- 1:dim(Xt)[2]/dim(Xt)[2] # time grid
  D <- length(t) # time grid length

  library(refund)
  library(lme4)
  library(nlme)
  library(arm)
  library(RLRsim)
  library(MASS)

  ###############################################################################

  ### fpca on Xt ###
  results <- fpca.face(Xt,
                       center = control$center, argvals = t,
                       knots = control$knots, pve = control$pve,
                       p = control$p, lambda = control$lambda)
  npc <- results$npc
  score <- results$scores
  ascore <- score[, 1:npc]/sqrt(D)
  efunctions <- results$efunctions*sqrt(D)
```

```r
evalues <- results$evalues/D

##############################################################################

### data for bonferroni testing and FLM/FMM regression ###

designMatrix.reg <- data.frame(Y = Y,
                               Z = Z,
                               ID = as.factor(ID),
                               ascore = ascore)

##############################################################################

### equal variance testing ###
z.sim.uni = c()
ID.uni <- c()
index <- matrix(1:(nSubj*npc), nrow = npc, ncol = nSubj)
for (i in 1:length(nRep)){
  ID.uni = c(ID.uni, c(index[,i], rep(0, nRep[i] - npc)))
}
z.sim.uni = c()
# svd on random scores A_i for each subject i
for(k in 1:nSubj){
  if(k==1){
    svd <- svd(ascore[1:nRep[1], ] %*% t(ascore[1:nRep[1], ])) # SVD on A_i
  }else{
    svd <- svd(ascore[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k]), ] %*% t(ascore[(sum(nRep[1:(k-1)])+1):su
  }
  u.tra <- t(svd$v)
  u <- svd$u
  d <- (svd$d)[1:npc]
  if(k==1){
    Y[1:nRep[k]] <- u.tra %*% Y[1:nRep[k]]
    Z[1:nRep[k]] <- u.tra %*% Z[1:nRep[k]]
    ascore[1:nRep[k], ] <- rbind(u.tra[1:npc, ] %*% ascore[1:nRep[k], ],
                                 matrix(0, nrow = nRep[k] - npc,
                                        ncol = npc))
  }else{
    Y[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k])] <- u.tra %*% Y[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k])]
    Z[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k])] <- u.tra %*% Z[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k])]
    ascore[(sum(nRep[1:(k-1)])+1):sum(nRep[1:k]), ] <- rbind(u.tra[1:npc, ] %*% ascore[(sum(nRep[1:(k
                                                  matrix(0,
                                                         nrow = nRep[k] - npc,
                                                         ncol = npc))
  }
  # z.sim.uni is the coefficient for the random slope to be tested
  z.sim.uni <- c(z.sim.uni, sqrt(d), rep(0, nRep[k] - npc))
}

##############################################################################

### data for equal-variance testing ###
```

```
designMatrix <- data.frame(Y = Y,
                           Z = Z,
                           ID = as.factor(ID),
                           ID.uni = as.factor(ID.uni),
                           ascore = ascore,
                           z.sim.uni = z.sim.uni)

################################################################################

## equal-variance test ##
additive0.sim <- paste(1:npc, collapse = " + ascore.")
model.sim <- as.formula(paste("Y ~ 1 + Z + ascore.",
                              additive0.sim,
                              " + (0 + Z | ID) + (0 + z.sim.uni | ID.uni)",
                              sep = ""))
# fullReml is the model under alternative
fullReml <- lmer(model.sim, data = designMatrix)
# m.slope only contains the random effect to be tested
f.slope <- as.formula(paste("Y ~ 1 + Z + ascore.",
                            additive0.sim,
                            " + (0 + z.sim.uni | ID.uni)",
                            sep = ""))
m.slope <- lmer(f.slope, data = designMatrix)
# m0 is the model under the null
f0 <- as.formula(" . ~ . - (0 + z.sim.uni | ID.uni)")
m0 <- update(fullReml, f0)

EqualVar.test <- exactRLRT(m.slope, fullReml, m0)
EqualVar.pvalue <- EqualVar.test$p[1]

## bonferroni test ##
additive.heter <- paste0(" + (0 + ascore.", 1:npc, " | ID)", collapse = "")
bonf.test <- list()
for(i in 1:npc){
  ii <- paste("ascore.", i, sep = "")
  # f.slope only contains the random effect to be tested
  f.slope <- as.formula(paste("Y ~ 1 + Z + ascore.",
                              additive0.sim, " + (0 +", ii, " | ID)",
                              sep = ""))
  m.slope <- lmer(f.slope, data = designMatrix.reg)
  # mA is the model under alternative
  mA <- as.formula(paste("Y ~ 1 + Z + ascore.",
                         additive0.sim, " + (0 +", ii, " | ID)",
                         "+ (0 + Z | ID)",
                         sep = ""))
  fullReml <- lmer(mA, data = designMatrix.reg)
  #m0 is model under the null
  f0 <- as.formula(paste(" . ~ . - (0 + ", ii, "| ID)"))
  m0 <- update(fullReml, f0)
  bonf.test[[i]] <- exactRLRT(m.slope, fullReml, m0)
}
multiTest <- sapply(bonf.test, function(x) {
                    c(statistic = x$statistic[1],
```

```
                    "p-value" = x$p[1])})
# use bonferroni correctiong method to adjust p-value
bonf.pvalue <- p.adjust(multiTest[2,], "bonferroni")

##############################################################################

## estimation ##

# FLM: estimation without subject-specific random effect
noRandom.simpart <- paste(1:npc, collapse = " + ascore.")
noRandom.sim <- as.formula(paste("Y ~ 1 + Z + ascore.",
                                 noRandom.simpart,
                                 " + (0 + Z | ID)",
                                 sep = ""))
FLM <- lmer(noRandom.sim, data = designMatrix.reg)

# FMM: estimation with subject-specific random effect
Random.simpart <- paste0(" + (0 + ascore.", 1:npc,"|ID) ", collapse="")
Random.sim <- as.formula(paste("Y ~ 1 + Z + ascore.",
                               noRandom.simpart,
                               " + (0 + Z | ID) ",
                               Random.simpart,
                               sep = ""))
FMM <- lmer(Random.sim, data = designMatrix.reg)

##############################################################################

## get fixed effect beta(t) ##

# FLM
fixeff1 <- fixef(FLM)
beta1 <- efunctions %*% as.vector(fixeff1[match(paste0("ascore.",1:npc),names(fixeff1))]) # populatio
raneffect1 <- ranef(FLM)$ID
FLM.sum <- summary(FLM)
fixed.coeff1 <- FLM.sum$coefficients # fixed coefficient
fixed.vcov1  <- FLM.sum$vcov # coefficient covariance
# sigma is standard deviation for error term
sigma1 <- FLM.sum$sigma
# se is standard deviation for population effect beta(t)
se1 = apply(efunctions, 1, function(x) sqrt(x %*% as.matrix(fixed.vcov1[match(paste0("ascore.",1:npc)
yhat1 <- predict(FLM)

# FMM
fixeff2 <- fixef(FMM)
beta2 <- efunctions %*% as.vector(fixeff2[match(paste0("ascore.",1:npc),names(fixeff2))]) # populatio
raneffect2 <- ranef(FMM)$ID
betai_2 <- efunctions %*% t(as.matrix(raneffect2[,match(paste0("ascore.",1:npc),colnames(raneffect2))]
FMM.sum <- summary(FMM)
fixed.coeff2 <- FMM.sum$coefficients # fixed coefficient
fixed.vcov2  <- FMM.sum$vcov
sigma2 <- FMM.sum$sigma # error term se
# se is standard deviation for population effect
se2 = apply(efunctions, 1, function(x) sqrt(x %*% as.matrix(fixed.vcov2[match(paste0("ascore.",1:npc)
```

```
  yhat2 <- predict(FMM)

  ##############################################################################

  return(list(
        'fPCA_result' = list(
                              npc = npc,
                              ascore = ascore,
                              efunctions = efunctions,
                              evalues = evalues),
        'test_result' = list(
                             'equal-variance' = list(
                                                  EqualVar.test = EqualVar.test,
                                                  EqualVar.pvalue = EqualVar.pvalue),
                             'bonferroni' = list(
                                                  bonf.test = bonf.test,
                                                  bonf.pvalue = bonf.pvalue)),
        'estimation_result' = list(
                                   'FLM' = list(
                                                'fixed' = list(
                                                               'beta(t)' = beta1,
                                                               'coefficient' = fixed.coeff1,
                                                               'vcov' = fixed.vcov1,
                                                               'sigma' = sigma1,
                                                               'se_beta(t)' = se1),
                                                'random' = list('Zi' = raneffect1),
                                                'yhat' = yhat1,
                                                'FLM.fit' = FLM),
                                   'FMM' = list(
                                                'fixed' = list(
                                                               'beta(t)' = beta2,
                                                               'coefficient' = fixed.coeff2,
                                                               'vcov' = fixed.vcov2,
                                                               'sigma' = sigma2,
                                                               'se_beta(t)' = se2),
                                                'random' = list('Zi'=raneffect2[,1],
                                                                'beta_i(t)'=betai_2),
                                                'yhat' = yhat2,
                                                'FMM.fit' = FMM)
  )))
}
```

2. Simulate a sample dataset (20 subjects, 50 visits for each subject as a training dataset; generate 10 more new visits for each of 20 subjects as a test dataset), and test function fmm_sofr.r

2.1 Simulate a training dataset

```
  library(refund)
  library(lme4)
```

```r
library(nlme)
library(arm)
library(RLRsim)
library(MASS)

################################################################################

### generate a training dataset ###

nSubj <- 20
nRep <- 50
smooth = 0 # if 0, Xt is with measurement error and thus unsmoothed; if smooth=1, no measurement erro
heter = 1 # if 1, random scores are heterogeneous; if 0, random scores are homogeneous
r.sim = 0.08
set.seed(12345)

D <- 80 # time grid number
totalN <- nSubj * nRep
thetaK.true <- 2
timeGrid <- (1:D)/D

npc.true <- 3
SNR <- 3 # 5, signal noise ratio

sd.epsilon <- 1 # or 0.5
delta.true <- 0.5
a.mean <- 0

gamma.true <- 2
gammaVar.true <- 1
# generate random slope of dummy variable
gammaI.true.i <- mapply(rnorm, nSubj, gamma.true, rep(sqrt(gammaVar.true), 1))
gammaI.true <- gammaI.true.i[rep(1:nrow(gammaI.true.i), each = nRep), ]

dummyX <- rbinom(n = totalN, size = 1, prob = 0.5) # dummyX: Z

# lambda is variance of each random score
lambda.sim <- function(degree) {
  return(0.5^(degree - 1))
}
# eigen functions
psi.fourier <- function(t, degree) {
  result <- NA
  if(degree == 1){
    result <- sqrt(2) * sinpi(2*t)
  }else if(degree == 2){
    result <- sqrt(2) * cospi(4*t)
  }else if(degree == 3){
    result <- sqrt(2) * sinpi(4*t)
  }
  return(result)
}
```

```
lambdaVec.true <- mapply(lambda.sim, 1: npc.true)

# true eigen-functions
psi.true <- matrix(data = mapply(psi.fourier, rep(timeGrid, npc.true), rep(1:npc.true, each=D)),
                   nrow = npc.true,
                   ncol = D,
                   byrow = TRUE)

# generate functional covariates
ascore.true <- mvrnorm(totalN, rep(a.mean, npc.true), diag(lambdaVec.true))
Mt.true <-  ascore.true %*% psi.true
error <- rnorm(totalN, mean = 0, sd = sd.epsilon)

if(heter==0){
  thetaIK.true1 <- mvrnorm(nSubj, rep(thetaK.true, npc.true), diag(rep(r.sim, npc.true)))
}
if(heter==1){
  thetaIK.true1 <- mvrnorm(nSubj, rep(0, npc.true), diag(c(r.sim, r.sim/2, r.sim/4)))
}

thetaIK.true <- thetaIK.true1[rep(1:nrow(thetaIK.true1), each = nRep), ]
betaM.true <- (thetaK.true+thetaIK.true) * ascore.true
betaM.true <- rowSums(betaM.true)

Y <- delta.true + dummyX * gammaI.true + betaM.true + error
ID <- rep(1:nSubj, each = nRep)

if(smooth == 0){
  Merror.Var <- sum(lambdaVec.true) / SNR  #SNR = sum(lambdaVec.true)/Merror.Var
  Mt.hat <- Mt.true + matrix(rnorm(totalN*D, mean = 0, sd = sqrt(Merror.Var)), totalN, D)
}
if(smooth == 1){
  Merror.Var <- 0  #SNR = sum(lambdaVec.true)/Merror.Var
  Mt.hat <- Mt.true
}

M <- Mt.hat
traindata <- list(Y=Y, Z=dummyX, Xt=M, ID=ID)
```

2.2 Perform two testing procedures and etimation using FLM and FMM on the training dataset

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

result <- fmm_sofr(traindata)

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

2.3 Generate a test dataset

```
### generate a test dataset ###

### for each subject, generate newvisitN more new visits
gene_newdata <- function(newvisitN){
  #generate new Z
  dummyX <- rbinom(n = nSubj*newvisitN, size = 1, prob = 0.5) # new dummyX: Z
  #generate new x_ij(t) for new visit
  ascore.true <- mvrnorm(nSubj*newvisitN, rep(a.mean, npc.true), diag(lambdaVec.true))
  #sum new x_ij(t)(beta_t + betai_t)
  Mt.true <- ascore.true %*% psi.true
  #generate new error
  error <- rnorm(nSubj*newvisitN, mean = 0, sd = sd.epsilon)
  #generate new random scores
  thetaIK.true <- thetaIK.true1[rep(1:nrow(thetaIK.true1), each = newvisitN), ]
  betaM.true <- (thetaIK.true+thetaK.true) * ascore.true
  betaM.true <- rowSums(betaM.true)

  gammaI.true <- gammaI.true.i[rep(1:nrow(gammaI.true.i), each = newvisitN), ]

  # generate new Y
  Y <- delta.true + dummyX * gammaI.true + betaM.true + error

  totalN <- nSubj*newvisitN
  ID <- rep(1:nSubj, each = newvisitN)

  if(smooth == 0){
    Merror.Var <- sum(lambdaVec.true) / SNR  #SNR = sum(lambdaVec.true)/Merror.Var
    Mt.hat <- Mt.true + matrix(rnorm(totalN*D, mean=0, sd = sqrt(Merror.Var)), totalN, D)
  }
  if(smooth == 1){
    Merror.Var <- 0
    Mt.hat <- Mt.true
  }

  M <- Mt.hat
  # projection to get new xi_{ijk}
  efunctions <- result$fPCA_result$efunctions
  xi <- (M-as.vector(rep(1, dim(M)[1])) %*% t(colMeans(M))) %*% efunctions/D

  designMatrix <- data.frame(Y = Y,
                             Z = dummyX,
                             ID = as.factor(ID),
                             ascore = xi)
  return(list(newY=Y,
              newdata=designMatrix,
              Xt = M))
}

# generate new testdata
newvisit <- 10
testdata <- gene_newdata(newvisit)
```

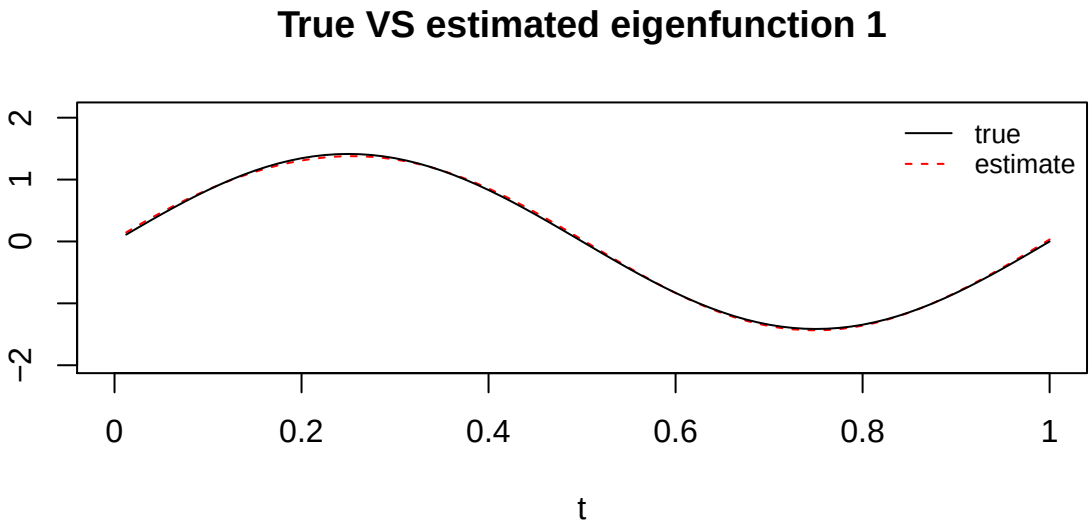


Figure 1: output

2.4 Etimation using FLM and FMM on the testing dataset

```
# yhat: predict for the new testdata
test_FLM.yhat <- predict(result$estimation_result$FLM$FLM.fit, testdata$newdata)
test_FMM.yhat <- predict(result$estimation_result$FMM$FMM.fit, testdata$newdata)
```

3. Visualize results

3.1 Visualize estimated eigenfunctions vs true eigenfunctions

```
### FPCA ###
efunctions <- result$fPCA_result$efunctions
npc <- result$fPCA_result$npc
# correct for sign of eigen-functions
sign_correct <- diag(sign(colSums(efunctions*t(psi.true))))
efunctions.correct <- efunctions %*% sign_correct
myat <- seq(0, 1, by=0.2)
for (i in 1:npc){
  plot(timeGrid, efunctions.correct[,i],type="l",
     xlab="t",
     ylab="",
     xaxt="n",
     xlim=c(0.0,1.0),
     main=paste0("True VS estimated eigenfunction ",i), lwd=1, col="red", lty=2, ylim=c(min(efunctions
  axis(1, at = myat, labels = round(myat,digits=1))
  lines(timeGrid, psi.true[i,], col="black")
  legend("topright", c("true","estimate"), col = c("black","red"), lty = c(1,2), bty = "n", cex = 0.8)
}
```

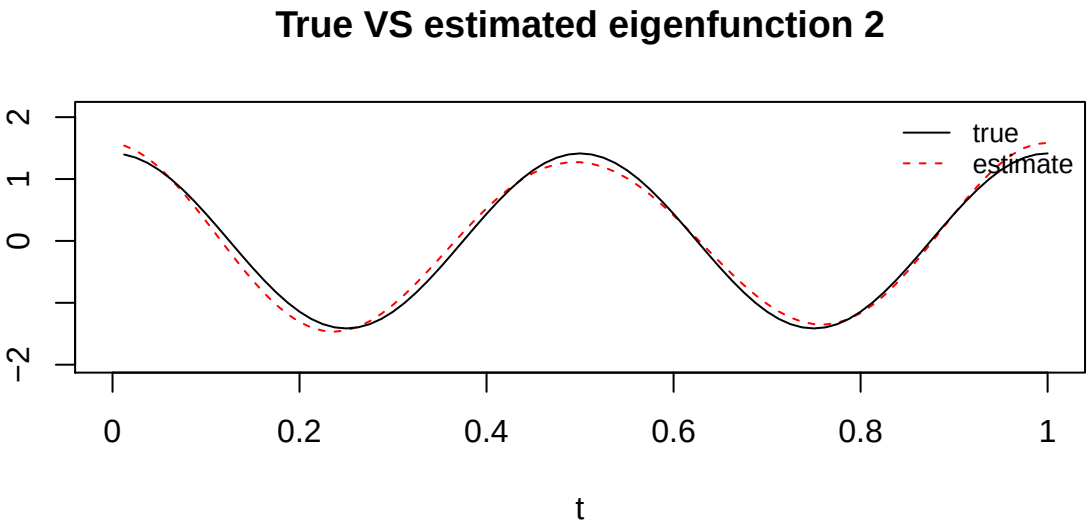


Figure 2: output

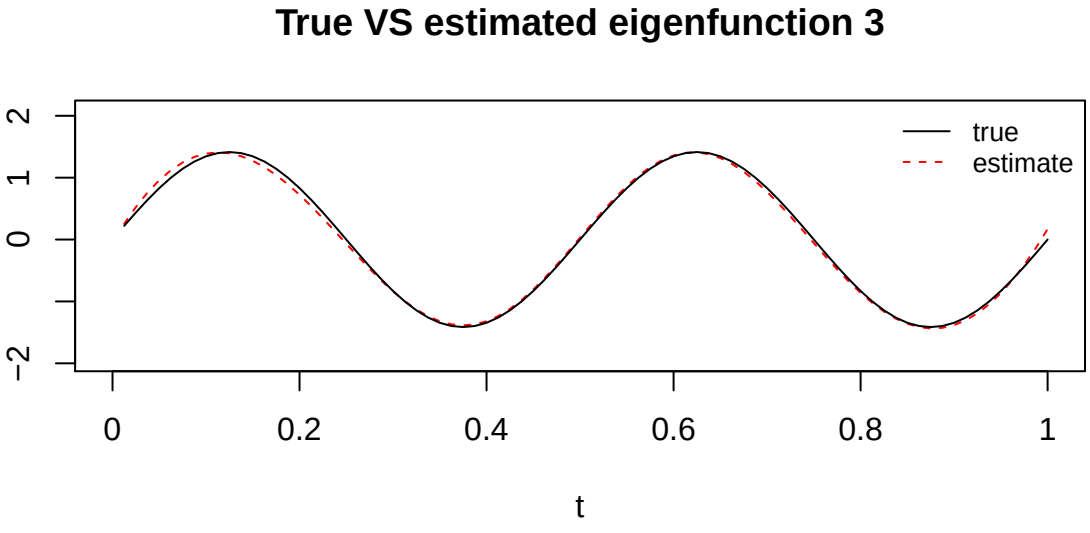


Figure 3: output

3.2 Two testing results

```
  # equal-variance test result
  result$test_result$`equal-variance`
```

```
# $EqualVar.test
#
#   simulated finite sample distribution of RLRT.
#
#   (p-value based on 10000 simulated values)
#
# data:
# RLRT = 84.549, p-value < 2.2e-16
#
#
# $EqualVar.pvalue
# [1] 0
```

```
  # bonferroni test result
  result$test_result$bonferroni
```

```
# $bonf.test
# $bonf.test[[1]]
#
#   simulated finite sample distribution of RLRT.
#
#   (p-value based on 10000 simulated values)
#
# data:
# RLRT = 85.749, p-value < 2.2e-16
#
#
# $bonf.test[[2]]
#
#   simulated finite sample distribution of RLRT.
#
#   (p-value based on 10000 simulated values)
#
# data:
# RLRT = 2.8686, p-value = 0.0385
#
#
# $bonf.test[[3]]
#
#   simulated finite sample distribution of RLRT.
#
#   (p-value based on 10000 simulated values)
#
# data:
# RLRT = 2.0248, p-value = 0.0643
#
#
#
# $bonf.pvalue
# [1] 0.0000 0.1155 0.1929
```

3.3 Visualize population effect estimation using FLM VS FMM

```
  # true beta(t): population effect
  beta_t <- t(psi.true)%*%as.vector(rep(thetaK.true, npc.true))
  beta_t.FMM <- result$estimation_result$FMM$fixed$`beta(t)`
  beta_t.FLM <- result$estimation_result$FLM$fixed$`beta(t)`

  sprintf("MISE of estimated beta(t) using FMM is: %.3f", mean((beta_t.FMM-beta_t)^2))
```

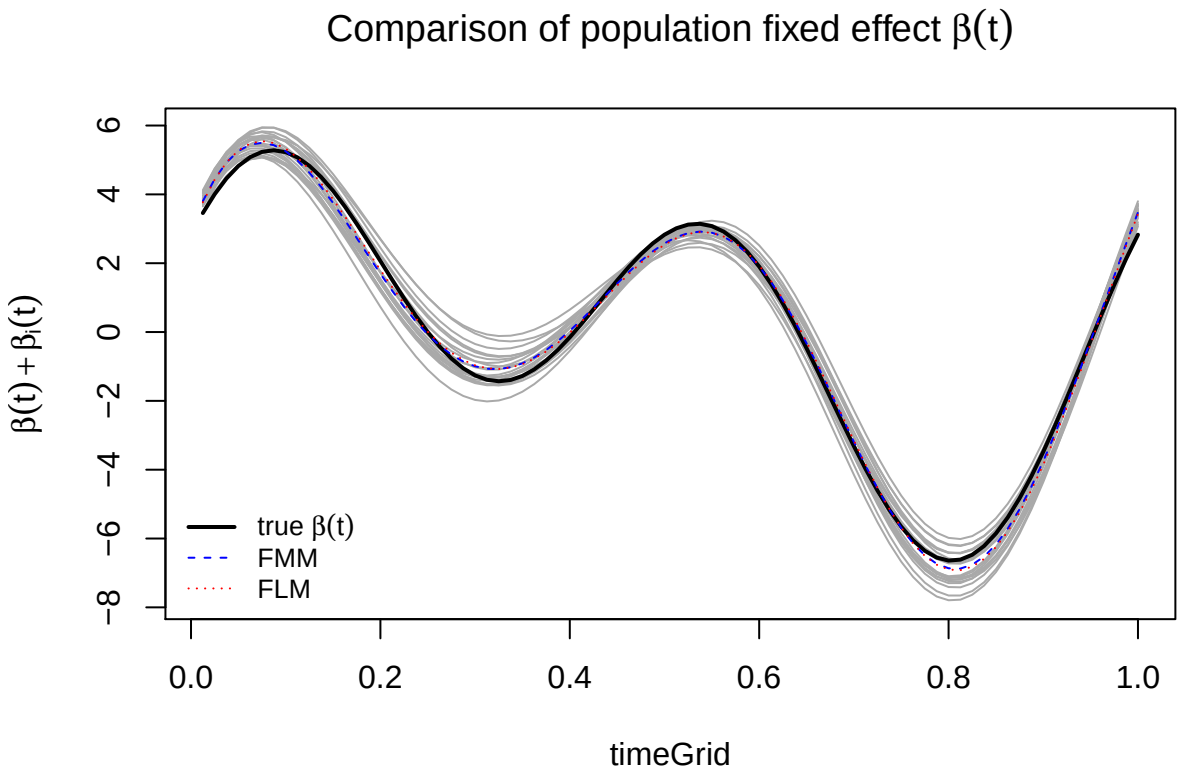
```
# [1] "MISE of estimated beta(t) using FMM is: 0.065"
```

```
  sprintf("MISE of estimated beta(t) using FLM is: %.3f", mean((beta_t.FLM-beta_t)^2))
```

```
# [1] "MISE of estimated beta(t) using FLM is: 0.066"
```

```
  betait.FMM <- result$estimation_result$FMM$random$`beta_i(t)`
  beta.comp <- cbind(apply(betait.FMM, 2, function(x) x+beta_t.FMM), beta_t, beta_t.FMM, beta_t.FLM)
  colnames(beta.comp) <- c(paste0("Subject", 1:nSubj), "true_Fixed_effect", "Fixed_effect.FMM", "Fixed_

  # visualization
  matplot(timeGrid,beta.comp[,1:nSubj], col="darkgrey",type="l", lty=1,
          main = expression(paste("Comparison of population fixed effect ",beta(t))),
          ylab=expression(beta(t)+beta[i](t)))
  lines(timeGrid, beta.comp[,nSubj+1], col="black",lty=1, lwd = 2)
  lines(timeGrid, beta.comp[,nSubj+2], col="blue",lty=2)
  lines(timeGrid, beta.comp[,nSubj+3], col="red",lty=3)
  #lines(timeGrid, beta.comp[,53] + 1.96*result$estimation_result$FMM$fixed$`se_beta(t)`, col="blue",lty
  #lines(timeGrid, beta.comp[,53] - 1.96*result$estimation_result$FMM$fixed$`se_beta(t)`, col="blue",lty
  legend("bottomleft", c(expression(paste("true ", beta(t))),
                         "FMM", "FLM"),
         col=c("black","blue","red"), lty = c(1,2,3), lwd = c(2,1,1), bty = "n", cex = 0.8)
```



3.4 Visualize MSE for each subject

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

### violin plot of MSE for each subject in the new testdata ###

# MSE for each subject
ID <- testdata$newdata$ID
subs <- unique(ID)
nSubj <- length(subs)
calculateMSE_i <- function(Y, EST){
  out <- (Y - EST)^2
  mse <- rep(0, length(unique(ID)))
  for(i in c(1:nSubj)){
    mse[i] <- mean(out[which(ID == i)])
  }
  return(mse)
}

# MSE for each subject
MSE_FMM <- calculateMSE_i(testdata$newY, test_FMM.yhat)
MSE_FLM <- calculateMSE_i(testdata$newY, test_FLM.yhat)
sprintf("MSE of FMM is: %.3f", mean(MSE_FMM))
```

```
# [1] "MSE of FMM is: 1.214"
```

```
sprintf("MSE of FLM is: %.3f", mean(MSE_FLM))
```

```
# [1] "MSE of FLM is: 1.487"
```

```r
#library(MuMIn)
rsquare_FMM <- MuMIn::r.squaredGLMM(result$estimation_result$FMM$FMM.fit)
rsquare_FLM <- MuMIn::r.squaredGLMM(result$estimation_result$FLM$FLM.fit)
sprintf("R-square of FMM is: %.3f", rsquare_FMM[,2])
```

```
# [1] "R-square of FMM is: 0.888"
```

```r
sprintf("R-square of FLM is: %.3f", rsquare_FLM[,2])
```

```
# [1] "R-square of FLM is: 0.871"
```

```r
violin <- data.frame(cbind(c(MSE_FLM, MSE_FMM),
                           rep(1:2, each = nSubj)))
colnames(violin) <- c("MSE","Model")
violin$Model <- as.factor(violin$Model)

library(ggplot2)
ggplot(violin, aes(x = Model, y = MSE)) +
  geom_violin(trim = FALSE) + geom_boxplot(width = 0.1, outlier.alpha = 0.1) +
  geom_jitter(width = 0.2, alpha = 0.6) +
  geom_hline(aes(yintercept = median(MSE_FMM)), color = "red", linetype = "dashed", size = 0.8) +
  scale_x_discrete(breaks = c("1", "2"),
                   labels = c("FLM", "FMM")) +
  labs(title = "MSE comparison of FLM and FMM (out-of-sample)") +
  theme_classic() +
  theme(plot.title = element_text(hjust = 0.5, size = rel(0.9), face="bold")) +
  theme(axis.title.y = element_text(size = rel(0.8))) +
  theme(axis.title.x = element_text(size = rel(0.8)))
```