Distributional data analysis via quantile functions and its application to modelling digital biomarkers of gait in Alzheimer's Disease

Rahul Ghosal

09/15/2021

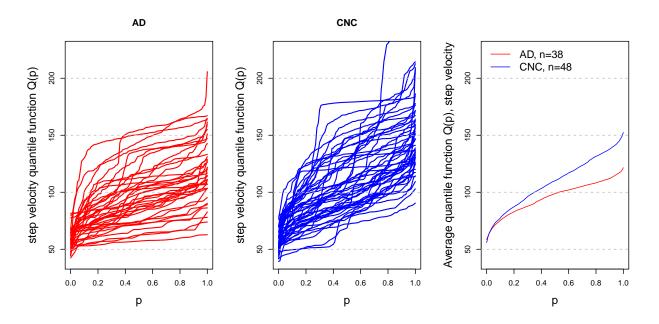
Introduction

This document presents an illustration of the SOQFR and SOQFR-L method proposed in Ghosal et al. (2021) using the gait features collected on AD and CNC participants from KU-ADC. In particular, we illustrate the methods using the gait feature step velocity and the response cognitive status (mild AD or CNC). First, we plot the individual (left two panel) and average (right panel) quantile functions of step velocity for AD and CNC (Figure 1 in the paper).

```
####Load the data##########
load("spearman correlations-20180913.RData")
#preprocessing
gait<-gait[,-c(14,15,71,72,73,74)]
gait$sex<-as.numeric(gait$sex)-1
gait$adstatus<-as.numeric(gait$adstatus)-1
#names(gait)
#select id,age,sex,adstatus and gait feature step velocity
gait<-gait[,c(1,2,3,9,61)]
head(gait)</pre>
```

```
id age sex adstatus Step_Velocity__cm_sec_
##
## 1 2 67
            1
                     1
                                     119.3454
## 2 2 67
                                     137.5917
## 3 2 67
           1
                     1
                                     138.2585
## 4 2 67
                     1
                                     139.4403
## 5 2 67
                     1
                                     139.4684
            1
## 6 2 67
                                     140.0375
```

```
ady<-which(agg1$adstatus==1)</pre>
svely<-agg2$Step_Velocity__cm_sec_[ady,]</pre>
sveln<-agg2$Step_Velocity__cm_sec_[-ady,]</pre>
for(i in 1:ncol(svely)){
 svely[is.na(svely[,i]), i] <- mean(svely[,i], na.rm = TRUE)</pre>
}
for(i in 1:ncol(sveln)){
 sveln[is.na(sveln[,i]), i] <- mean(sveln[,i], na.rm = TRUE)</pre>
###########Plotting subject-specific and average QF##########
par(mfrow=c(1,3))
par(mar = c(5.1, 4.5, 4.1, 2.1))
matplot(p, t(svely), type="l", lty=rep(1,38),
       ylab="step velocity quantile function Q(p)", xlab="p",
       cex.lab=1.5, lwd=1.5,
       col="red",main="AD",ylim=c(40,225))
abline(h=c(50,100,150,200),col="grey",lty=2)
matplot(p, t(sveln), type="l", lty=rep(1,48),
       ylab="step velocity quantile function Q(p)", xlab="p",
       cex.lab=1.5, lwd=1.5,
       col="blue",main="CNC",ylim=c(40,225))
abline(h=c(50,100,150,200),col="grey",lty=2)
plot(p,colMeans(svely),ylab="Average quantile function Q(p), step velocity",xlab="p",col="red",ylim=c(4
lines(p,colMeans(sveln),ylab=" Average quantile function Q(p), step velocity",xlab="p",col="blue")
abline(h=c(50,100,150,200),col="grey",lty=2)
legend('topleft',c("AD, n=38","CNC, n=48") ,
      lty=c(1,1), col=c("red", "blue"), bty='n', cex=1.4)
```

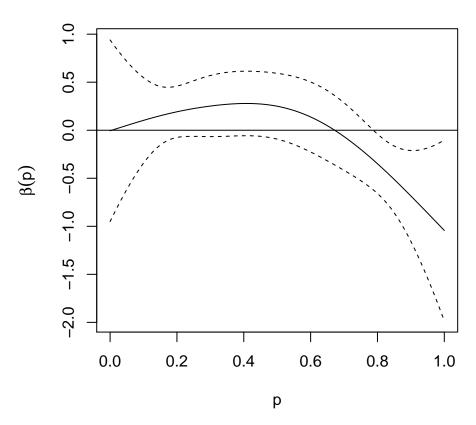


SOQFR for discrimination of AD

We illustrate the SOQFR method with logit-link to model mild-AD vs CNC using subject-specific quantile functions of step velocity and and adjusting for age, sex. We display the estimated coefficient function $\beta(p)$.

```
####fitting SOQFR###########
agg < -cbind(agg1[,c(3,4,5)])
svel<-agg2[,6]</pre>
####Replace NA############
for(i in 1:ncol(svel)){
svel[is.na(svel[,i]), i] <- mean(svel[,i], na.rm = TRUE)</pre>
agg$step_vel<-svel
library(refund)
fit.lf <- pfr(adstatus ~ age+sex+lf(step_vel,argvals = p, k=20, bs="ps",m=2), data=agg,family="binomial
deviance<-1-(fit.lf$deviance/fit.lf$null.deviance)</pre>
summary(fit.lf)
##
## Family: binomial
## Link function: logit
##
## Formula:
## adstatus ~ age + sex + s(x = step_vel.tmat, by = L.step_vel,
##
      k = 20, bs = "ps", m = 2)
##
## Parametric coefficients:
               Estimate Std. Error z value Pr(>|z|)
## (Intercept) 16.87647
                          5.65643
                                     2.984 0.00285 **
## age
              -0.14831
                           0.05599 -2.649 0.00808 **
               3.70658
                           0.90441
                                    4.098 4.16e-05 ***
## sex
## ---
## Signif. codes: 0 '***' 0.001 '**' 0.05 '.' 0.1 ' ' 1
##
## Approximate significance of smooth terms:
##
                                 edf Ref.df Chi.sq p-value
## s(step_vel.tmat):L.step_vel 3.041 3.387 16.37 0.00184 **
## ---
## Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' 1
##
## R-sq.(adj) = 0.508
                        Deviance explained = 49.8%
## -REML = 34.587 Scale est. = 1
bhat.lf <- coef(fit.lf, n=101)</pre>
bhat.lf$upper <- bhat.lf$value + 1.96*bhat.lf$se
bhat.lf$lower <- bhat.lf$value - 1.96*bhat.lf$se
matplot(p, bhat.lf[,c("value", "upper", "lower")],
          type="l", lty=c(1,2,2), col=1,
          ylab=expression(paste(beta(p))), xlab="p",main="Distributional effect of Q(p)")
abline(h=0)
```

Distributional effect of Q(p)



We report the average cross-validated area under the curve (AUC) of the receiver operating characteristic as an estimate for the out-of-sample prediction performance of the considered models. In particular, we perform a repeated 10-fold cross-validation (B=100 times) and report the average cross-validated AUC (cvAUC).

```
###calculating mean of the measures for comparison
svelmean<-agg1[,6]</pre>
svelmean[is.na(svelmean)] <-mean(svelmean,na.rm = TRUE)</pre>
agg$mean<-svelmean
n<-nrow(agg)</pre>
meancv3<-matrix(0,100,2) #matrix for storing cvAUC for SOQFR and model on mean
for (it in 1:100)
{library(caret)
set.seed(it)
find<-createFolds(y=as.factor(agg$adstatus), k = 10,
                   list = FALSE, returnTrain = FALSE)
cvauc3<-matrix(0,10,2)</pre>
    for (k in 1:10)
    {
      tempind=which(find==k)
      tr<-agg[-tempind,]</pre>
      te<-agg[tempind,]</pre>
      fit.lf <- pfr(adstatus ~ age+sex+lf(step_vel), data=tr,family="binomial")</pre>
```

```
fit.lf2 <- pfr(adstatus ~ age+sex+mean, data=tr,family="binomial")
    ###getting prediction
    pte<-as.numeric(predict(fit.lf,newdata=te,type="response"))
    pte2<-as.numeric(predict(fit.lf2,newdata=te,type="response"))
    cte<-as.numeric(te$adstatus)
    library(cvAUC)
    cvauc3[k,1]<-AUC(pte,cte)
    cvauc3[k,2]<-AUC(pte2,cte)
}
meancv3[it,]<-colMeans(cvauc3)
}
mean(meancv3[,1]) #cvAUC from SOQFR</pre>
```

```
## [1] 0.8937417
```

```
mean(meancv3[,2]) #cvAUC from GLM on mean of step-velocity
```

```
## [1] 0.8022625
```

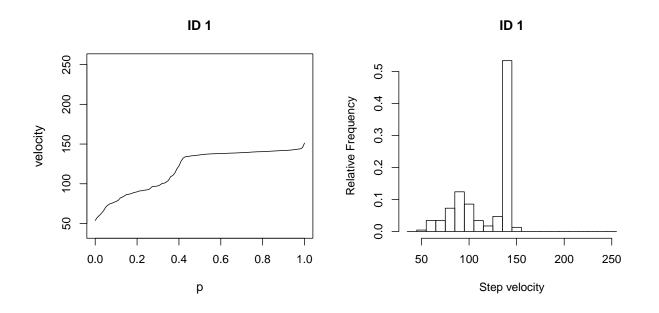
cvAUC of the proposed SOQFR method is calculated to be 0.89 for step-velocity, higher compared to the corresponding generalized linear model on mean of step-velocity (0.80).

Comparison of SOQFR with histogram based modelling

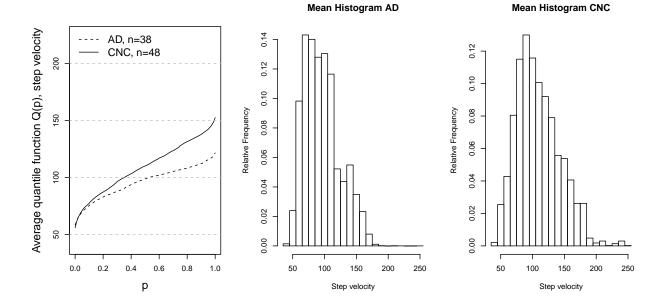
We compare the proposed SOQFR method with the histogram-based approach by Augustin and others (2017). In particular, we focus on step velocity and obtain subject-specific histograms (relative frequency) in 22 bins of equal width (10) between step velocity values of 35 and 255 (cm/second). The following plots show both the quantile function and histogram of step velocity for a random subject from our study. The group average of quantile functions and the group average of histogram (relative frequency) for AD and CNC groups are also shown.

```
rng<-range(gait$Step_Velocity__cm_sec_,na.rm = TRUE)</pre>
breaks < -seq(35, 255, by=10)
m=length(breaks)-1
uid<-unique(gait$id)</pre>
n<-length(uid)</pre>
Z<-matrix(0,n,m)</pre>
P<-matrix(0,n,m)
for(i in 1:n)
{gaittemp<-gait[gait$id==uid[i],]
gaittempsvel<-gaittemp$Step_Velocity__cm_sec_</pre>
h<-hist(gaittempsvel,breaks = breaks,plot=FALSE)
Z[i,]<-h$counts / sum(h$counts)</pre>
P[i,]<-h$mids
}
##Replace NA
for(i in 1:ncol(Z)){
 Z[is.na(Z[,i]), i] \leftarrow mean(Z[,i], na.rm = TRUE)
```

```
par(mfrow=c(1,2))
plot(p,svel[1,],ylab="Quantile function Q(p), step
velocity",xlab="p",col="black",ylim=c(40,255),type="l",cex.lab=1.1,main="ID 1")
gaittemp<-gait[gait$id==uid[1],]
gaittempsvel<-gaittemp$Step_Velocity__cm_sec_
h<-hist(gaittempsvel,breaks = breaks,plot = FALSE)
h$counts <- h$counts / sum(h$counts)
plot(h, freq=TRUE, ylab="Relative Frequency",xlab="Step velocity",main="ID 1")</pre>
```



```
par(mfrow=c(1,3))
plot(p,colMeans(svely),ylab="Average quantile function Q(p), step velocity",xlab="p",col="black",lty=2,
lines(p,colMeans(sveln),ylab=" Average quantile function Q(p), step velocity",xlab="p",col="black",lty=
abline(h=c(50,100,150,200),col="grey",lty=2)
legend('topleft',c("AD, n=38","CNC, n=48") ,
       lty=c(2,1), col=c("black", "black"), bty='n', cex=1.4)
svelhistY<-Z[ady,]</pre>
svelhistN<-Z[-ady,]</pre>
gaittemp<-gait[gait$id==uid[1],]</pre>
gaittempsvel<-gaittemp$Step_Velocity__cm_sec_</pre>
h<-hist(gaittempsvel,breaks = breaks,plot = FALSE )
h$counts<-colMeans(svelhistY)</pre>
plot(h, freq=TRUE, ylab="Relative Frequency",xlab="Step velocity",main="Mean Histogram AD")
######
gaittemp<-gait[gait$id==uid[1],]</pre>
gaittempsvel<-gaittemp$Step_Velocity__cm_sec_</pre>
h<-hist(gaittempsvel,breaks = breaks,plot = FALSE)
h$counts<-colMeans(svelhistN)
plot(h, freq=TRUE, ylab="Relative Frequency",xlab="Step velocity",main="Mean Histogram CNC")
```



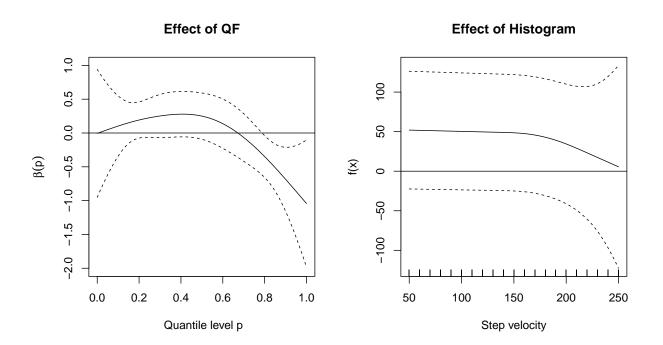
Following Augustin and others (2017), we fit a GLM model for the binary outcome of cognitive status (mild-AD vs CNC) with subject-specific histograms $H_i(x_j)$ of step velocity as functional predictors and adjust the model for age and sex. We compare the estimates and the performance of this model to the SOQFR model for step velocity.

```
library(refund)
fit.lf <- pfr(adstatus ~ age+sex+lf(step_vel,argvals = p, k=20, bs="ps",m=2), data=agg,family="binomial
summary(fit.lf)

##
## Family: binomial
## Link function: logit</pre>
```

```
## Link function: logit
##
## Formula:
## adstatus ~ age + sex + s(x = step_vel.tmat, by = L.step_vel,
##
      k = 20, bs = "ps", m = 2)
##
## Parametric coefficients:
##
               Estimate Std. Error z value Pr(>|z|)
  (Intercept) 16.87647
                           5.65643
                                     2.984
                                           0.00285 **
##
               -0.14831
                           0.05599
                                    -2.649
                                           0.00808 **
##
                3.70658
                                     4.098 4.16e-05 ***
##
  sex
                           0.90441
##
## Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' 1
##
## Approximate significance of smooth terms:
##
                                 edf Ref.df Chi.sq p-value
## s(step_vel.tmat):L.step_vel 3.041 3.387 16.37 0.00184 **
                  0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' 1
## Signif. codes:
## R-sq.(adj) = 0.508
                         Deviance explained = 49.8%
## -REML = 34.587 Scale est. = 1
```

```
pfrprob<-predict(fit.lf,type="response")</pre>
bhat.lf <- coef(fit.lf, n=101)</pre>
bhat.lf$upper <- bhat.lf$value + 1.96*bhat.lf$se
bhat.lf$lower <- bhat.lf$value - 1.96*bhat.lf$se
par(mfrow=c(1,2))
matplot(p, bhat.lf[,c("value", "upper", "lower")],
        type="1", lty=c(1,2,2), col=1,
        ylab=expression(paste(beta(p))), xlab="Quantile level p", main="Effect of QF", ylim=c(-2,1))
abline(h=0)
library(mgcv)
agg<-cbind(agg1[,c(3,4,5)])
agg$Z<-Z
agg$P<-P
kPA<-10
out<-gam(adstatus ~ age+sex+s(P[,-1],k=kPA,by=Z[,-1],bs="ad"),data=agg,family="binomial",method="REML")
plot(out,xlab="Step velocity",ylab="f(x)",main="Effect of Histogram")
#not significant
abline(h=0)
```



The 95% credible intervals from GAM for $f_x(x)$ include zero at all values of step velocity and hence subject specific representation of step-velocity in terms of histogram (relative frequency) is not statistically significant. On the contrary, the functional regression coefficient $\beta(p)$ for SOQFR is statistically significant for quantile levels of p > 0.8. This illustrates that a higher maximal level of step velocity is associated with a reduced odds of AD.

Further, we compare the predictive performance of the two approaches in terms of cross-validated area under the curve (AUC) of the receiver operating characteristic. Specifically, we perform a repeated 10-fold cross-validation (B=100 times) and report the average cross-validated AUC (cvAUC).

```
#####we already did it for SOQFR as shown earlier, it was calculated to be 0.89
###performing cv for histogram-based modelling
###doing repeated train test and cross validation
###takes time to run
meancv3<-c()
for (it in 1:100)
{library(caret)
  set.seed(it)
  #trind<- createDataPartition(y= trainnew$adstatus, p=0.7, list = FALSE)
  find<-createFolds(y=as.factor(agg$adstatus), k = 10, list = FALSE, returnTrain = FALSE)
  cvauc3<-c()
  for (k in 1:10)
    tempind=which(find==k)
    tr<-agg[-tempind,]</pre>
    te<-agg[tempind,]</pre>
  out<-gam(adstatus ~ age+sex+s(P[,-1],k=kPA,by=Z[,-1],bs="ad"),
           data=tr,family="binomial",method="REML")
   ###getting prediction
    pte<-as.numeric(predict(out,newdata=te,type="response"))</pre>
    cte<-as.numeric(te$adstatus)</pre>
    library(cvAUC)
    cvauc3[k]<-AUC(pte,cte)
 meancv3[it] <-mean(cvauc3)</pre>
mean(meancv3) ### cvAUC from histogram (relative-frequency) based model
```

[1] 0.7871792

cvAUC of the proposed SOQFR method is calculated to be 0.89, which is much higher than cvAUC of 0.79 for the histogram-based approach. This illustrates a higher predictive (discriminatory) power of the quantile function distributional respesentation of step-velocity in our application.

SOQFR-L for discrimination of AD

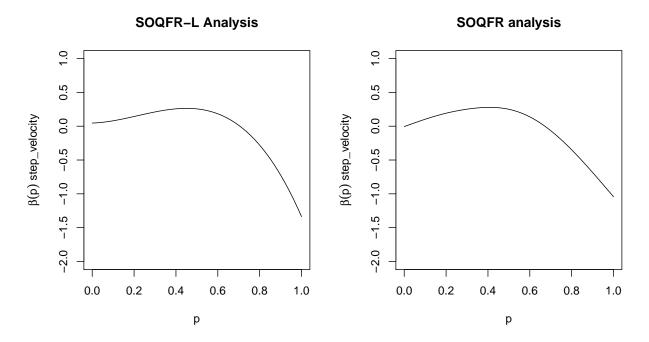
Next, We illustrate the SOQFR-L method with logit-link to model mild-AD vs CNC using subject-specific L-moments of step velocity and adjusting for age, sex. Finally We display the estimated coefficient function $\beta(p)$ from SOQFR-L.

```
age sex adstatus step_vel L_ 1 step_vel L_ 2 step_vel L_ 3 step_vel L_ 4
##
                                                  -4.20857914
                                                                 -0.2473097
## 1 67
          1
                   1
                         118.66671
                                       14.283733
                                                                  2.1709742
## 2 77
          1
                   1
                         108.29013
                                       6.390106
                                                  -2.69455205
## 3 79
          0
                   1
                          62.70655
                                        4.315913
                                                   0.85176849
                                                                  0.9894494
## 4
     83
          1
                   1
                          71.76222
                                       4.380337
                                                  -0.72913200
                                                                  0.7133580
## 5 68
                          96.29518
          1
                   1
                                       10.659547
                                                  -0.83558694
                                                                  0.5474216
                          76.20300
## 6 76
                                       5.993737
                                                   0.04845354
                                                                  0.8160179
SOQFR_L<-glm(adstatus~.,data=aggsvel,family = "binomial")</pre>
summary(SOQFR_L)
##
## Call:
## glm(formula = adstatus ~ ., family = "binomial", data = aggsvel)
##
## Deviance Residuals:
                                         Max
##
      Min
                1Q
                     Median
                                  3Q
## -2.2867 -0.4442 -0.0585
                              0.4475
                                       1.8164
##
## Coefficients:
##
                  Estimate Std. Error z value Pr(>|z|)
## (Intercept)
                  18.20321
                              6.06171
                                      3.003 0.00267 **
                              0.05746 -2.637 0.00836 **
## age
                  -0.15152
## sex
                   3.70622
                              0.91500
                                      4.051 5.11e-05 ***
## 'step_vel L_ 1' -0.04440
                              0.03193 -1.390 0.16441
## 'step_vel L_ 2' -0.48015
                              0.14901 -3.222 0.00127 **
## 'step_vel L_ 3' -0.60122
                              0.28703
                                      -2.095 0.03620 *
## 'step_vel L_ 4' -0.21182
                              0.41532 -0.510 0.61004
## ---
## Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' 1
##
## (Dispersion parameter for binomial family taken to be 1)
##
      Null deviance: 118.056 on 85 degrees of freedom
##
## Residual deviance: 60.495 on 79 degrees of freedom
## AIC: 74.495
## Number of Fisher Scoring iterations: 6
devianceL<-1-(SOQFR_L$deviance/SOQFR_L$null.deviance)</pre>
devianceL
```

[1] 0.4875766

We display the coefficient function $\beta(p)$ from SOQFR-L below, along with the estimated $\beta(p)$ from SOQFR.

```
####Calculate the beta(p) from SOQFR-L,number of L-momets=4####
beta<-as.numeric(coef(SOQFR_L)[-c(1:3)])
p0<-function(x){1}
p1<-function(x){-1 + 2*x }
p2<-function(x){</pre>
```



Higher maximal performance for step velocity is found to be associated with lower odds of AD.

SOQFR-L for modelling cognitive score of VM

Next, We illustrate an eample of the SOQFR-L method with identity-link to model VM score (one of the cognitive scores) using subject-specific L-moments of step velocity and and adjusting for age, sex and education. The second order L-moment is found to be associated with VM.

```
out < -lm(VM~.,data = dfsvel[,-c(1,5,7)])
summary(out)
##
## Call:
## lm(formula = VM \sim ., data = dfsvel[, -c(1, 5, 7)])
## Residuals:
##
      Min
                1Q Median
                               3Q
                                      Max
## -3.3497 -0.8845 0.0171 1.0027
                                   3.0869
##
## Coefficients:
##
                    Estimate Std. Error t value Pr(>|t|)
                   -3.283e+00 2.311e+00 -1.420
## (Intercept)
                                                  0.1595
## sex
                  -1.591e+00 3.269e-01 -4.865 5.83e-06 ***
## age
                   9.013e-03 2.393e-02
                                          0.377
                                                  0.7074
## Edu
                   1.191e-01 5.199e-02
                                          2.291
                                                  0.0246 *
## 'step_vel L_ 1'
                   7.410e-06 1.500e-02
                                          0.000
                                                  0.9996
## 'step_vel L_ 2' 1.313e-01 5.210e-02
                                          2.520
                                                  0.0138 *
## 'step_vel L_ 3' 9.408e-02 1.001e-01
                                          0.940
                                                  0.3502
## 'step_vel L_ 4' 1.188e-01 1.889e-01
                                          0.629
                                                  0.5313
## ---
## Signif. codes: 0 '*** 0.001 '** 0.01 '* 0.05 '.' 0.1 ' 1
## Residual standard error: 1.452 on 78 degrees of freedom
## Multiple R-squared: 0.4091, Adjusted R-squared: 0.356
## F-statistic: 7.713 on 7 and 78 DF, p-value: 4.602e-07
```

JIVE with L-moments.

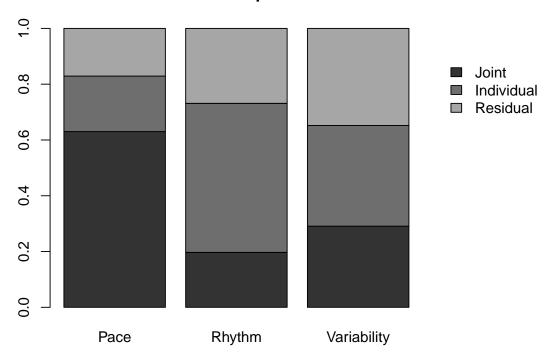
We illustrate the JIVE approach with L-moments developed in Section 3.2 of the paper. We focus on the domains Pace (3 features), Rhythm (13 features) and Variability (19 features).

```
rm(list = ls())
load("spearman correlations-20180913.RData")
#preprocessing
gait < -gait[, -c(14, 15, 71, 72, 73, 74)]
gait$sex<-as.numeric(gait$sex)-1</pre>
gait$adstatus<-as.numeric(gait$adstatus)-1</pre>
#names(qait)
gait<-gait[,14:68] ##all the gait features</pre>
namegait<-names(gait)</pre>
#REMOVE fraap framl frav #####these are repeated features###
gait < -gait[, -c(9, 10, 11)]
namegaitnew<-names(gait)</pre>
###load previously extracted pre-normalized and standardized L-moments data for all features #########
load("prenormlmomallfeat.RData")
domain<-c("Amplitude", "Pace", "Rhythm", "Symmetry", "Variability")</pre>
facdom<-as.numeric(as.factor(domain))</pre>
```

```
3,5,3,5,2,5,2,2,5,3,5,1,5,5)
lmomlist < -lmom1subj[-c(9,10,11)]
group \leftarrow group \left[-c(9,10,11)\right]
datablock<-list()</pre>
for(j in 1:5)
{indj<-which(group==j)</pre>
tempdata<-lmomlist[indj]
data<-Reduce(cbind, tempdata)</pre>
datablock[[i]]<-t(data)</pre>
}
#######We focus on 3 domains of Pace, Rhythm and Variability" #######
datablock<-datablock[c(2,3,5)]</pre>
names(datablock) < -domain[c(2,3,5)]
library(r.jive)
Results = jive(datablock)
## Estimating joint and individual ranks via permutation...
## Running JIVE algorithm for ranks:
## joint rank: 2 , individual ranks: 3 6 6
## JIVE algorithm converged after 42 iterations.
## Re-estimating joint and individual ranks via permutation...
## Running JIVE algorithm for ranks:
## joint rank: 2 , individual ranks: 2 7 9
## JIVE algorithm converged after 39 iterations.
## Re-estimating joint and individual ranks via permutation...
## Final joint rank: 2 , final individual ranks: 2 7 9
summary(Results)
## $Method
## [1] "perm"
##
## $Ranks
##
                    Rank
       Source
                     "2"
## [1,] "Joint"
                     "2"
## [2,] "Pace"
                     "7"
## [3,] "Rhythm"
## [4,] "Variability" "9"
##
## $Variance
##
              Pace Rhythm Variability
## Joint
             0.630 0.197
                               0.291
## Individual 0.199 0.534
                               0.361
## Residual 0.171 0.269
                               0.348
```

The amount of variation explained by joint and individual components in each of the three domains are displayed below.

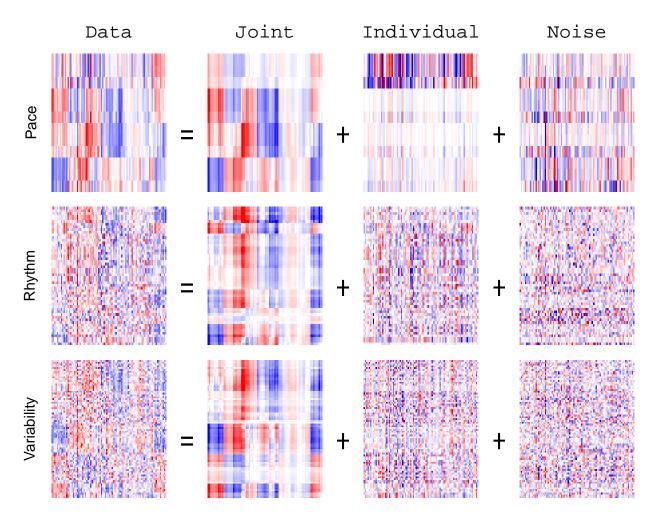
Variation Explained



 ${\it JIVE}$ estimates of the joint and individual structures are displayed below.

showHeatmaps(Results)

29	2	17	6	21	1	25	13
30	3	18	7	22	10	26	14
31	4	19	8	23	11	27	15
32	5	20	9	24	12	28	16



The joint structure explains quite a large variation in the pace domain, where as the individual structures explain the majority of the variation in the Rhythm and Variability domain.