Lab

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```
setwd('/Users/ivanxu/Desktop/PhD/Robust MR-SPI CI')
library(devtools)
## Loading required package: usethis
devtools::install_github("MinhaoYaooo/MR-SPI", force = TRUE)
## Downloading GitHub repo MinhaoYaooo/MR-SPI@HEAD
##
## -- R CMD build -----
##
        checking for file '/private/var/folders/cf/cl9mxhwx3m75m11pmlyf49zc0000gn/T/RtmpU4gdhZ/remotes4
##
     - preparing 'MR.SPI':
##
       checking DESCRIPTION meta-information ... v checking DESCRIPTION meta-information
##
     - checking for LF line-endings in source and make files and shell scripts
     - checking for empty or unneeded directories
##
     Omitted 'LazyData' from DESCRIPTION
##
##
     - building 'MR.SPI_0.1.0.tar.gz'
##
##
library(CVXR)
## Warning in .recacheSubclasses(def@className, def, env): undefined subclass
## "pcorMatrix" of class "ConstVal"; definition not updated
## Warning in .recacheSubclasses(def@className, def, env): undefined subclass
## "pcorMatrix" of class "ConstValListORExpr"; definition not updated
## Warning in .recacheSubclasses(def@className, def, env): undefined subclass
## "pcorMatrix" of class "ConstValORExpr"; definition not updated
## Warning in .recacheSubclasses(def@className, def, env): undefined subclass
## "pcorMatrix" of class "ConstValORNULL"; definition not updated
## Attaching package: 'CVXR'
## The following object is masked from 'package:stats':
##
##
      power
library(MR.SPI)
library(bigstatsr)
library(igraph)
##
## Attaching package: 'igraph'
```

```
## The following objects are masked from 'package:stats':
##
##
       decompose, spectrum
## The following object is masked from 'package:base':
##
##
       union
library(intervals)
##
## Attaching package: 'intervals'
## The following objects are masked from 'package:igraph':
##
##
       clusters, contract
## The following object is masked from 'package:CVXR':
##
##
       size
library(matrixStats)
library(svMisc)
##
## Attaching package: 'svMisc'
## The following object is masked from 'package:utils':
##
##
options(warn=0)
```

Step1: Find the smallest lower bound and largest upper bound by only using half the selected IV.

Short-term: iterate selected IV value Long-term: optimization algorithm

```
robust_ci_temp <- function(gamma, Gamma, se_gamma, se_Gamma, alpha=0.05,n1=10000,n2=20000) {
  pz = length(Gamma)
  V_gamma <- matrix(nrow = pz, ncol = pz)</pre>
  V_Gamma <- matrix(nrow = pz, ncol = pz)</pre>
  for (i in 1:pz) {
    for (j in i:pz) {
      if(i==j){
        V_gamma[i,i] <- se_gamma[i]^2</pre>
        V_Gamma[i,i] <- se_Gamma[i]^2</pre>
        V_gamma[i,j] <- V_gamma[j,i] <- gamma[i]*gamma[j] / n1</pre>
        V_Gamma[i,j] <- V_Gamma[j,i] <- Gamma[i]*Gamma[j] / n2</pre>
    }
  } # Construct V_gamma_hat and V_Gamma_hat
  L1 <- 100
  U1 <- -100
  L2 <- 100
  U2 <- -100
  comb \leftarrow combn(c(1:pz),pz%/%2+1)
```

```
for (i in 1:dim(comb)[2]){
  excl.index <- combn(c(1:pz),pz\%/\%2+1)[,i]
  betaVarHat.i <- var_TSHT(gamma[-excl.index], Gamma[-excl.index], V_gamma[-excl.index, -excl.index], V_G
  betaHat.i <- sum(gamma[-excl.index] * Gamma[-excl.index]) / sum(gamma[-excl.index]^2)
  if (betaHat.i - stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i) < L1){</pre>
    L1 <- betaHat.i - stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i)
  if (betaHat.i + stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i) > U1){
    U1 <- betaHat.i + stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i)
  loose_ci=c(L1,U1)
  excl.index \leftarrow combn(c(1:pz),pz%/%2)[,i]
  betaVarHat.i <- var_TSHT(gamma[-excl.index],Gamma[-excl.index],V_gamma[-excl.index,-excl.index],V_G
  betaHat.i <- sum(gamma[-excl.index] * Gamma[-excl.index]) / sum(gamma[-excl.index]^2)
  if (betaHat.i - stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i) < L2){</pre>
    L2 <- betaHat.i - stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i)
  if (betaHat.i + stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i) > U2){
    U2 <- betaHat.i + stats::qnorm(1-alpha/2) * sqrt(betaVarHat.i)
  }
  strict_ci=c(L2,U2)
return(list(loose_ci=loose_ci, strict_ci=strict_ci))
```

Step2: Combine the bound found in step1 with the Robust CI found using MR.SPI.

```
pSNP <- runif(10, 0.05, 0.95) # generate allele frequency
     Z1 <- sapply(pSNP, rbinom, n = n1, size = 2) # generate raw genotype of sample 1
     Z1 \leftarrow scale(Z1)
     Z2 <- sapply(pSNP, rbinom, n = n2, size = 2) # generate raw genotype of sample 2
     Z2 \leftarrow scale(Z2)
     D1 <- Z1 %*% gamma + rnorm(n1, 0, 1) # generate the exposure of sample 1
     epsilonSigma = matrix(c(1,0.8,0.8,1),2,2)
     epsilon = MASS::mvrnorm(n2,rep(0,2),epsilonSigma)
     D2 <- Z2 %*% gamma + epsilon[,1] # generate the exposure of sample 2
     Y2 <- D2*beta + Z2 %*% pi + epsilon[,2] # generate the outcome of sample 2
     GWAS2 <- big_univLinReg(X = as_FBM(Z2), y.train = Y2) # calculate summary statistics of Y~Z
     GammaHat = as.numeric(GWAS2$estim); gammaHat = as.numeric(GWAS1$estim)
     se_Gamma <- as.numeric(GWAS2$std.err); se_gamma <- as.numeric(GWAS1$std.err);</pre>
     return(list(GammaHat=GammaHat,gammaHat=gammaHat,se_Gamma=se_Gamma,se_gamma=se_gamma,n1=n1,n2=n2))
}
sim.result4 <- data.frame()</pre>
pi_list \leftarrow list(c(rep(0,6),rep(1,4)),c(rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),1,1,0.25,0.25),c(rep(0,4),rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),rep(0,6),rep(0,4),rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),rep(0,6),rep(0,4),rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),rep(0,6),rep(0,6),rep(0,4),rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),rep(0,6),rep(0,4),rep(0,4),rep(1,3),rep(-1,3)),c(rep(0,6),rep(0,6),rep(0,4),rep(0,4),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep(0,6),rep
for (pi in pi_list){
    print(pi)
    1 = robust_1 = robust_strict_10 = robust_loose_10 = robust_11=0
```

```
u = robust_u = robust_strict_u0 = robust_loose_u0 = robust_u1=0
pi = 0.25*pi
cnt = robust_cnt = robust_cnt0_loose = robust_cnt0_strict = robust_cnt1=0
time.default = time.robust = time.robust0 = 0
max_iter <- 1000
pb <- txtProgressBar(min = 0, max = max_iter, style = 3)</pre>
for (i in 1:max_iter){
  setTxtProgressBar(pb, i)
  result <- generate_example(beta=0.5, pi=pi)
  t1 <- Sys.time()
  mr.spi.default <- MR.SPI(result$gammaHat, result$GammaHat, result$se_gamma, result$se_Gamma, result
  # print(c(mr.spi.robust$ci[[1]][1],mr.spi.robust$ci[[2]]))
  t2 <- Sys.time()
  suppressWarnings(mr.spi.robust <-MR.SPI(result$gammaHat, result$GammaHat, result$se_gamma, result$s
  t3 <- Sys.time()
  robust_ci_0 <- robust_ci_temp(gamma = result$gammaHat[mr.spi.default$VHat[[1]]],</pre>
                                  Gamma = result$GammaHat[mr.spi.default$VHat[[1]]],
                                  se_gamma = result$se_gamma,
                                  se_Gamma = result$se_Gamma
  t4<-Sys.time()
  if (mr.spi.default$ci[[1]][1]>0.5 | mr.spi.default$ci[[1]][2]<0.5){
    cnt <- cnt + 1
  if (mr.spi.robust$ci[[1]][1]>0.5 | mr.spi.robust$ci[[2]]<0.5){</pre>
    robust_cnt <- robust_cnt + 1</pre>
  }
  if (robust_ci_0$loose_ci[1]>0.5 | robust_ci_0$loose_ci[2]<0.5){</pre>
    robust_cnt0_loose <- robust_cnt0_loose + 1</pre>
  if (robust_ci_0$strict_ci[1]>0.5 | robust_ci_0$strict_ci[2]<0.5){</pre>
    robust_cnt0_strict <- robust_cnt0_strict + 1</pre>
  robust_l1_t <- max(mr.spi.robust$ci[[1]][1],robust_ci_0$strict_ci[1])</pre>
  robust_u1_t <- min(mr.spi.robust$ci[[2]],robust_ci_0$strict_ci[2])</pre>
  if (robust_l1_t>0.5 | robust_u1_t<0.5){</pre>
    robust_cnt1 <- robust_cnt1 + 1</pre>
  time.default <- time.default + (t2 - t1)
  time.robust <- time.robust + (t3 - t2)
  time.robust0 <- time.robust0 + (t4 - t3)</pre>
  1 <- l+mr.spi.default$ci[[1]][1]</pre>
  u <- u+mr.spi.default$ci[[1]][2]
  robust_l <- robust_l+mr.spi.robust$ci[[1]][1]</pre>
  robust_u <- robust_u+mr.spi.robust$ci[[2]]</pre>
  robust_loose_10 <- robust_loose_10+robust_ci_0$loose_ci[1]</pre>
  robust_loose_u0 <- robust_loose_u0+robust_ci_0$loose_ci[2]</pre>
  robust_strict_10 <- robust_strict_10+robust_ci_0$strict_ci[1]</pre>
  robust_strict_u0 <- robust_strict_u0+robust_ci_0$strict_ci[2]</pre>
```

```
robust_l1 <- robust_l1+robust_l1_t</pre>
    robust_u1 <- robust_u1+robust_u1_t</pre>
  close(pb)
  sim.result4 <- rbind(sim.result4, data.frame(</pre>
    #beta = beta,
    # tau = tau,
    #gamma = gamma,
    coverage = 1-cnt/max_iter,
    ci_length = u/max_iter-l/max_iter,
    robust_ci_length = robust_u/max_iter-robust_l/max_iter,
    robust_loose_ci0_length = robust_loose_u0/max_iter-robust_loose_l0/max_iter,
    robust_strict_ci0_length = robust_strict_u0/max_iter-robust_strict_l0/max_iter,
    robust_ci1_length = robust_u1/max_iter-robust_l1/max_iter,
    robust_coverage = 1-robust_cnt/max_iter,
    robust_coverage0_loose = 1-robust_cnt0_loose/max_iter,
    robust_coverage0_strict = 1-robust_cnt0_strict/max_iter,
    robust_coverage1 = 1-robust_cnt1/max_iter,
    time.default <- time.default/max_iter,</pre>
    time.robust <- time.robust/max iter,
    time.robust0 <- time.robust0/max_iter</pre>
 ))
   [1] 0 0 0 0 0 0 1 1 1 1
##
##
```

The new robust CI garantees the CI length is smaller then the robust CI found using MR-SPI and simulation results show it has over 95% coverage.

```
## default_ci_length robust_ci_length
## (0,0,0,0,0,1,1,1,1) 0.09826303 0.2025967
## (0,0,0,0,1,1,1,-1,-1,-1) 0.12885330 1.5808239
```

##	(0,0,0,0,0,0,1,1,0.25,0.25)	0.09733507	0.2000011
##	(0,0,0,0,1,1,0.25,-1,-1,-0.25)	0.12477270	0.2544223
##		new_robust_ci_length	default_coverage
##	(0,0,0,0,0,0,1,1,1,1)	0.1920005	0.950
##	(0, 0,0,0,1,1,1,-1,-1,-1)	0.2263439	0.939
##	(0,0,0,0,0,0,1,1,0.25,0.25)	0.1892054	0.924
##	(0,0,0,0,1,1,0.25,-1,-1,-0.25)	0.2204170	0.748
##	robust_coverage new_robust_coverage		
##	(0,0,0,0,0,0,1,1,1,1)	0.999	0.999
##	(0, 0,0,0,1,1,1,-1,-1,-1)	0.992	0.979
##	(0,0,0,0,0,0,1,1,0.25,0.25)	1.000	1.000
##	(0,0,0,0,1,1,0.25,-1,-1,-0.25)	0.997	0.970