Accounting for correlated horizontal pleiotropy in two-sample Mendelian randomization using correlated instrumental variants

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2020-08-15

Introduction

This vignette provides an introduction to the `MR.Corr2` package. R package `MR.Corr2` implements MR-Corr^2, Accounting for correlated horizontal pleiotropy in two-sample Mendelian randomization using correlated instrumental variants :

```
library(devtools);
install_github("QingCheng0218/MR.Corr2");
```

Load the package using the following command:

```r
library(MR.Corr2);
```

Fit MR-Corr for the independent SNPs using simulated data

We first generate genotype data using function *genRawGeno*:

```r
library("MR.Corr2");
library("mvtnorm");
library("ggplot2");
set.seed(20200718)
rho = 0;L = 100; M = 1; p = M*L; m = p; Alrate = 0.1;
n1 = 20000; n2 = 20000; rho_ag = 0.2;
b0 = 0.1;h2y = 0.1;h2z = 0.1;
maf = runif(p, 0.05, 0.5);

G = genRawGeno(maf, L, M, rho, n1 + n2);
G1 = G[1:n1,];G2 = G[(n1+1):(n1+n2),]; G12 = G[1:(n1+n2),];
```

Generate the exposure data(y) and outcome data(z) with prespecified indirect(h_y^2) and direct(h_z^2) heritability based on

$$\mathbf{y} = \mathbf{G}_1\gamma + \mathbf{U}_x\eta_x + \mathbf{e}_1, \quad \mathbf{z} = \beta_0\mathbf{x} + \mathbf{G}_2\alpha + \mathbf{U}_y\eta_y + \mathbf{e}_2,$$

```r
# ------------------------------------------------------------------------

sigma2g = 1;
sigma2a = 1;

S_ag = matrix(c(sigma2a, rho_ag, rho_ag, sigma2g), nrow=2);
AG = rmvnorm(p, mean=rep(0, 2), sigma = S_ag,method="chol")
alpha = AG[,1]; gamma = AG[,2];
```

```
# ------------------------------------------------------------------------
q = 50
u = matrix(rnorm( (n1+n2) * q),ncol=q);
Su = matrix(c(1,0.8,0.8,1),nrow=2)
bu = rmvnorm(q,mean=rep(0,2), sigma = Su,method="chol")
by = bu[,1]; bz = bu[,2];
uby = u%*%by; ubz = u%*%bz;
uby = uby/sqrt(as.numeric(var(uby)/0.6));
ubz = ubz/sqrt(as.numeric(var(ubz)/0.2));

G12g = G12%*%gamma;

if(b0!=0){
  h2ga = (h2y *( 1 + b0^2))/(b0^2 * (1 - h2y));
  gamma0 = gamma/sqrt(as.numeric(var(G12g)/h2ga));
  G12g = G12%*%gamma0;
}


yall = G12g + uby + rnorm(n1+n2)*as.numeric(sqrt(1-var(uby)));
# The direct effects on Z
h2yb = var(b0*yall);
h2al = (h2z + h2z*h2yb)/(1 - h2z);
if(h2z==0){
  alpha = rep(0, p);
  G12a = G12%*%alpha;
}else{
  if(Alrate!=1){
    alno = floor(p*Alrate);
    # sparse setting for pleiotropy
    indxAL = sample(1:p,alno);
    alpha[-indxAL] = 0;
  }
  G12a = G12%*%alpha;
  alpha0 = alpha/sqrt(as.numeric(var(G12a)/(h2al)));
  G12a = G12%*%alpha0;
}

# ------------------------------------------------------------------------

resz = ubz + rnorm(n1+n2)*as.numeric(sqrt(1-var(ubz)));
zall = b0*yall  + G12a +  resz;
y = yall[1:n1];
z = zall[(n1+1):(n1+n2)];
# ------------------------------------
```

We then conduct single-variant analysis to obtain the summary statistics.

```
# create summary statistics
gammaSS = fastSigLm(y, G1);
GammaSS = fastSigLm(z, G2);
gammah = gammaSS$coef;
se1 = gammaSS$std;
Gammah = GammaSS$coef;
```

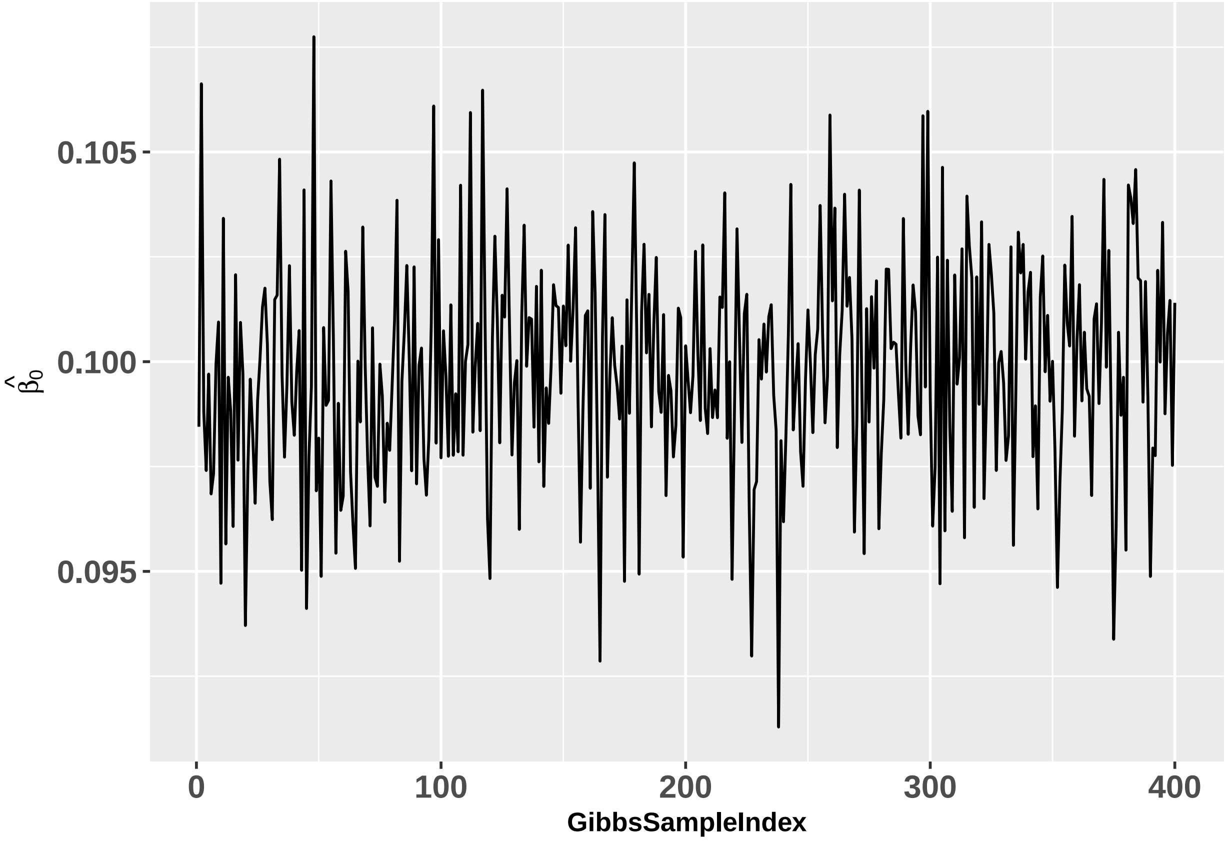
```
se2 = GammaSS$std;
```

`opt` list the prior parameters used in MRcorr. $agm = 0.001, bgm = 0.001$ are for σ_γ^2 and $aal = 0.001, bal = 0.001$ are for σ_α^2. a and b are the prior parameters for ω. `burnin` is the number of iterations we throw away at the beginning of Gibbs sampling. `maxIter` is the number of iteration for Gibbs after burnin, the value of interval for recording Gibbs results denoted by `thin`.

```
opt = list(agm = 0.001, bgm = 0.001, aal = 0.001, bal = 0.001,
           a = 1, b = p, maxIter = 4000, thin = 10, burnin = 1000);

SimResIndep = MRcorr(gammah, Gammah, se1,  se2, opt);
```

Check the convergence of Gibbs sampler using trace plot.

```
traceplot(SimResIndep$Beta0res);
```



One can increase the number of `burnin` or `maxIter` if the trace plot did not coverage.

```
beta_hat = mean(SimResIndep$Beta0res);
beta_se = sd(SimResIndep$Beta0res);
beta_pvalue = 2*(1 - pnorm(abs(beta_hat/beta_se)));
Eta1index = which(SimResIndep$Eta==1);
```

```
cat("The estimated effect of the exposure on outcome: ", beta_hat);
```

```
## The estimated effect of the exposure on outcome:  0.09978347
```

```
cat("Standard error of beta_hat: ", beta_se);
```

```
## Standard error of beta_hat:  0.002567654
```

```
cat("P-value for beta_hat: ", beta_pvalue);
```

```
## P-value for beta_hat:  0
```

```
cat("The index of nonzero orthogonal projected pleiotropic effect:", "\n",Eta1index);
```

```
## The index of nonzero orthogonal projected pleiotropic effect:
##  6 7 8 17 19 51 58 59 76 91
```

Fit MR-Corr^2 for the correlated SNPs using simulated data

We first generate genotype data using function *genRawGeno*:

```
rm(list = ls());
library(MR.Corr2);
library("mvtnorm");
library(ggplot2);
set.seed(20200718)
rho = 0.4;L = 100; M = 10; p = M*L; m = p; Alrate = 0.1;
n1 = 20000; n2 = 20000; n3 = 500; lambda = 0.055;
rho_ag = 0.2; b0 = 0.1; h2y = 0.1;h2z = 0.1;
maf = runif(p, 0.05, 0.5);

G = genRawGeno(maf, L, M, rho, n1 + n2 + n3);
G1 = G[1:n1,];
G2 = G[(n1+1):(n1+n2),];
G12 = G[1:(n1+n2),];
G3 = G[(n1+n2+1):(n1+n2+n3),];

nblocks = L;
block_inf <- cbind(seq(1, p, M), seq(M, p, M));
block_inf1 <- block_inf - 1;
R = Cal_block_SimR(block_inf1, G3, lambda)
```

Generate the exposure data(y) and outcome data(z) with prespecified indirect(h_y^2) and direct(h_z^2) heritability based on

$$\mathbf{y} = \mathbf{G}_1\gamma + \mathbf{U}_x\eta_x + \mathbf{e}_1, \quad \mathbf{z} = \beta_0\mathbf{x} + \mathbf{G}_2\alpha + \mathbf{U}_y\eta_y + \mathbf{e}_2,$$

```
# ------------------------------------------------------------------------
sigma2g = 1;
sigma2a = 1;

S_ag = matrix(c(sigma2a, rho_ag, rho_ag, sigma2g), nrow=2);
AG = rmvnorm(p, mean=rep(0, 2), sigma = S_ag,method="chol")
alpha = AG[,1]; gamma = AG[,2];

# ------------------------------------------------------------------------
q = 50
u = matrix(rnorm( (n1+n2) * q),ncol=q);
Su = matrix(c(1,0.8,0.8,1),nrow=2)
bu = rmvnorm(q,mean=rep(0,2), sigma = Su,method="chol")
by = bu[,1]; bz = bu[,2];
```

```
uby = u%*%by; ubz = u%*%bz;
uby = uby/sqrt(as.numeric(var(uby)/0.6));
ubz = ubz/sqrt(as.numeric(var(ubz)/0.2));

G12g = G12%*%gamma;

if(b0!=0){
  h2ga = (h2y *( 1 + b0^2))/(b0^2 * (1 - h2y));
  gamma0 = gamma/sqrt(as.numeric(var(G12g)/h2ga));
  G12g = G12%*%gamma0;
}


yall = G12g + uby + rnorm(n1+n2)*as.numeric(sqrt(1-var(uby)));
# ------------------------------------------------------------------------
# The direct effects on Z
h2yb = var(b0*yall);
h2al = (h2z + h2z*h2yb)/(1 - h2z);

if(h2z==0){
  alpha = rep(0, p);
  G12a = G12%*%alpha;
}else{
  if(Alrate!=1){
    alno = floor(L*Alrate);
    ind = sample(1:L,alno);
    if(length(ind)==1){
      indxAL = block_inf[ind, 1]:block_inf[ind, 2]
      alpha[-indxAL] = 0;
    }else{
      indxAL = NULL;
      for(i in 1:length(ind)){
        tmp = block_inf[ind[i], 1]:block_inf[ind[i], 2]
        indxAL = append(indxAL, tmp);
      }
      alpha[-indxAL] = 0;
      G12a = G12%*%alpha;
      alpha0 = alpha/sqrt(as.numeric(var(G12a)/(h2al)));
      G12a = G12%*%alpha0;
    }
  }
}

# ------------------------------------------------------------------------
resz = ubz + rnorm(n1+n2)*as.numeric(sqrt(1-var(ubz)));
zall = b0*yall  + G12a +  resz;

y = yall[1:n1];
z = zall[(n1+1):(n1+n2)];

G1 = G12[1:n1, ];
G2 = G12[(n1+1):(n1+n2), ]
```

We then conduct single-variant analysis to obtain the summary statistics.

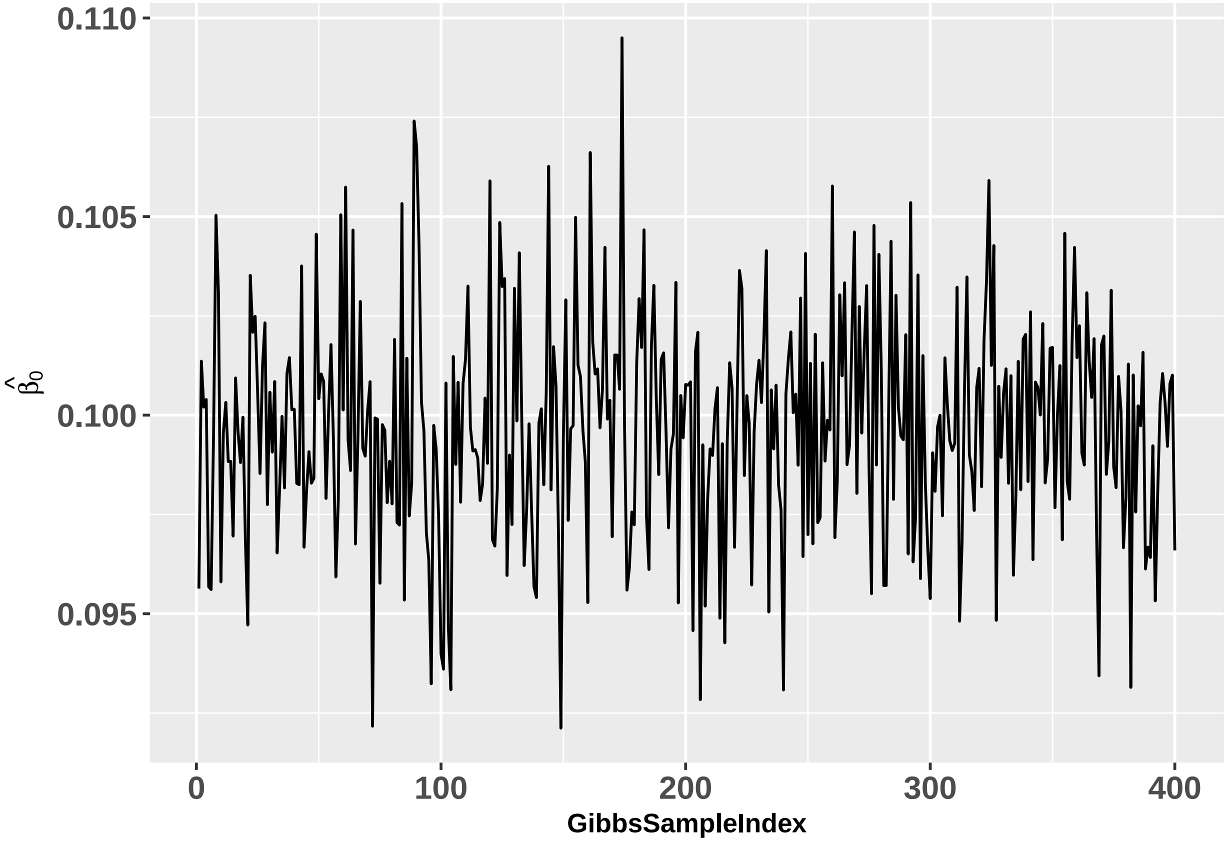
```
gammaSS = fastSigLm(y, G1);
GammaSS = fastSigLm(z, G2);
gammah = gammaSS$coef;
se1 = gammaSS$std;
Gammah = GammaSS$coef;
se2 = GammaSS$std;
```

`opt` list the prior parameters used in MR-Corr^2. `coreNum` is the number of cores in your CPU. `block_inf1` is the block information for the correlation matrix.

```
coreNum = 20;
opt = list(agm = 0.001, bgm = 0.001, aal = 0.001, bal = 0.001,
           a = 1, b = L, maxIter = 4000, thin = 10, burnin = 1000);

SimRes = MRCorr2Sim(gammah, Gammah, se1, se2, R,  block_inf1, coreNum, opt);
```

Check the convergence of Gibbs sampler using trace plot.

```
traceplot(SimRes$Beta0res);
```



One can increase the number of `burnin` or `maxIter` if the trace plot did not coverage.

```
beta_hat = mean(SimRes$Beta0res);
beta_se = sd(SimRes$Beta0res);
beta_pvalue = 2*(1 - pnorm(abs(beta_hat/beta_se)));
Eta1index = which(SimRes$Eta==1);
```

```
cat("The estimated effect of the exposure on outcome: ", beta_hat);
```

```
## The estimated effect of the exposure on outcome:  0.09969995
```

```
cat("Standard error of beta_hat: ", beta_se);
```

```
## Standard error of beta_hat:  0.002786722
```

```
cat("P-value for beta_hat: ", beta_pvalue);
```

```
## P-value for beta_hat:  0
```

```
cat("The index of nonzero orthogonal projected pleiotropic effect:", "\n",Eta1index);
```

```
## The index of nonzero orthogonal projected pleiotropic effect:
##  11 17 19 30 31 68 79 88 96 99
```

We are able to use the following code to compare the true signal of orthogonal projected pleiotropic effect (ind) and estimated signal index.

```
ind%in%Eta1index;
```

```
##  [1] TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE TRUE
```

Fit MR-Corr^2 using BMI-T2D study.

Furthermore, we give an example to illustrate the implements of MR-Corr^2 for real data analysis. The following datasets(`BBJ.BMImatch1KG.txt`, `BMIcauseSummaryStat.txt`, `T2DcauseSummaryStat.txt`, `all_chr_1000G.bed`, `all_chr_1000G.fam`, `all_chr_1000G.bim`, `fourier_ls-all.bed`) should be prepared. Download here(https://zenodo.org/record/3986509#.Xze3yxMzaL8).

```
filescreen= "BBJ.BMImatch1KG.txt";
fileexposure = "BMIcauseSummaryStat.txt";
fileoutcome = "T2DcauseSummaryStat.txt";
stringname3 = "all_chr_1000G";
block_file = "fourier_ls-all.bed"
```

`filescreen`, `fileexposure`, `fileoutcome` are the datasets names for screen, exposure and outcome, respectively. These three datasets must have the following format(note that it must be tab delimited):

SNP	chr	BP	A1	A2	beta	se	pvalue
rs1000000	12	126890980	A	G	0.013210	0.005182	0.01081
rs10000010	4	21618674	C	T	-0.003465	0.004022	0.38900
rs1000002	3	183635768	T	C	0.002628	0.003550	0.45910
rs10000023	4	95733906	T	G	-0.005581	0.003614	0.12250
rs1000003	3	98342907	G	A	-0.004571	0.004665	0.32720

`stringname3` is the name of reference panel data. Here we use samples from `1000 Genome Project Phase 1` which is in plink binary format. `block_file` is used to partition the whole genome into blocks.

matchscreen function is used to match the three datasets with a cutoff for `filescreen` named `pva_cutoff`.

```
library(MR.Corr2);
pva_cutoff = 1e-4;
scrres = matchscreen(filescreen, fileexposure, fileoutcome, stringname3, pva_cutoff);
bh1 = as.numeric(scrres$bh1);
bh2 = as.numeric(scrres$bh2);
s12 = as.numeric(scrres$s12);
s22 = as.numeric(scrres$s22);
chr = as.numeric(scrres$chr);
```

```
bp = scrres$bp;
rsname = scrres$rsname
avbIndex = scrres$idxin;
idx4panel = scrres$idx4panel;
```

`bh1` and `s12` are the SNP effects and corresponding standard errors on the exposure variable, `bh2` and `s22` are the SNP effects and corresponding standard errors on the outcome variable. After matching the three datasets, we obtain `chr` (chromosome number) , `bp` (base position),`rsname`(rs number).`avbIndex`(location) and `idx4panel` (Indicators to be adjusted in reference panel data).

One can using the following function *summaryQC* to remove the MHC region(QCindex $= 1$), or skip the procedure(QCindex $= 0$).

```
QCindex = 1;
if(QCindex){
  QCresult = summaryQC(mhcstart, mhcend, bh1, bh2, s12, s22, bp,
                       chr, rsname, avbIndex, idx4panel, Inf, Inf)
  bh1new = QCresult$bh1new;
  bh2new = QCresult$bh2new;
  s12new = QCresult$s12new;
  s22new = QCresult$s22new;
  bpnew = QCresult$bpnew;
  chrnew = QCresult$chrnew;
  avbIndexnew = QCresult$avbIndexnew;
  idx4panelnew = QCresult$idx4panel
  rsnamenew = QCresult$rsnamenew;
}else{
  bh1new = bh1;
  bh2new = bh2;
  s12new = s12;
  s22new = s22;
  bpnew = bp;
  chrnew = chr;
  rsnamenew = rsname;
  idx4panelnew = idx4panel;
  avbIndexnew = avbIndex;
}

p = length(avbIndexnew);
```

We use the following function to calculate the number of blocks for correlation matrix.

```
# block information
infres = Cal_blockinf(bpnew, chrnew, block_file);
nblocks = infres$nblocks;
```

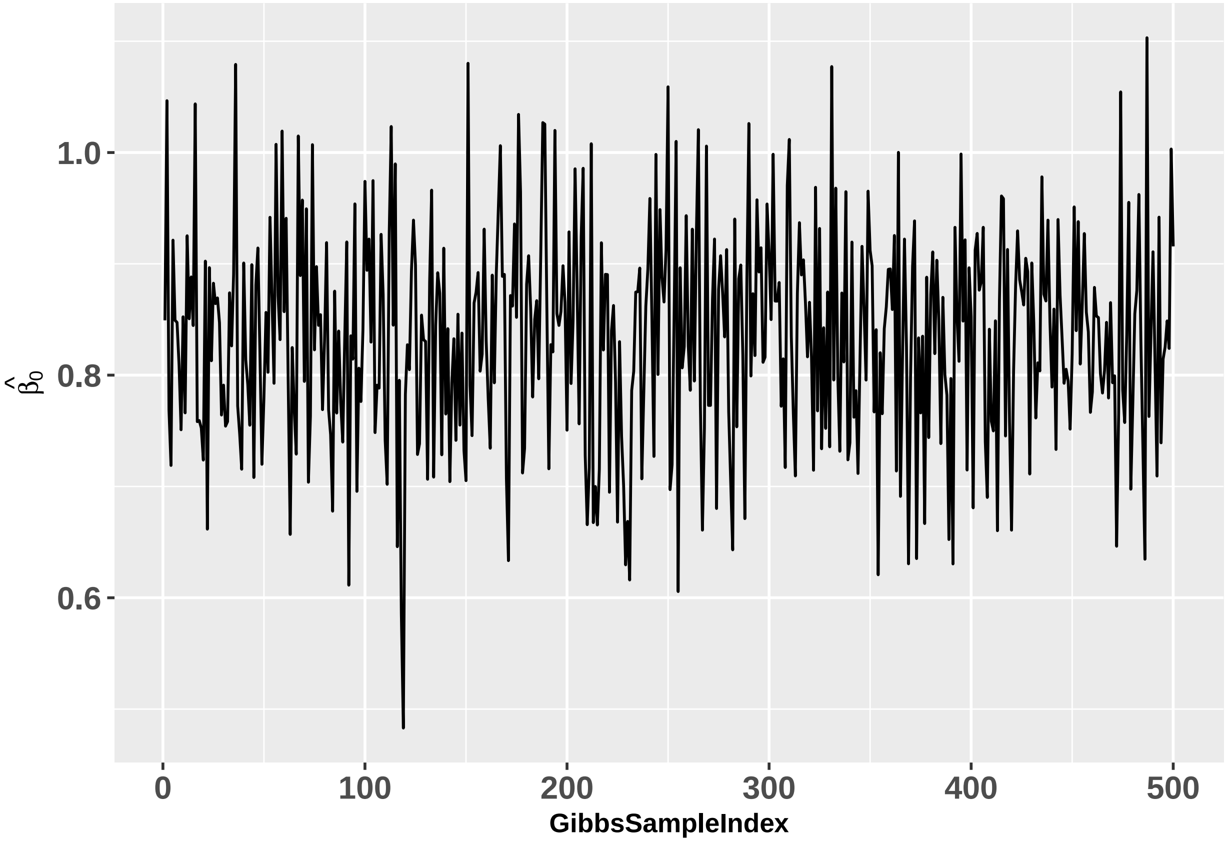
In real data analysis, we adopted an alternative computational cost saving methodology to obtain the correlation matrix, here, we fixed the shrinkage factor `lambda1 = 0.9`. `ld_r2_thresh` is the threshold for pruning LD. Since MR-Corr^2 make full use of correlated instrumental variants, hence don't need to prune LD. In other words, the value of `ld_r2_thresh` has no impact on the result of MR-Corr^2 .

```
lambda1 = 0.9; ld_r2_thresh = 1; coreNum = 24;

opt = list(agm = 0.001, bgm = 0.001, aal = 0.001, bal = 0.001,
           a = 1, b = nblocks, maxIter = 5000, thin = 10, burnin = 5000);
```

```r
RealRes = MRCorr2Real(bpnew, chrnew, avbIndexnew-1,
                      idx4panelnew, block_file, stringname3,
                      ld_r2_thresh, bh1new, bh2new, s12new,
                      s22new, lambda1, coreNum, opt)

bhat = RealRes$Beta0res
```

Check the convergence of Gibbs sampler using trace plot.

```r
library(ggplot2)
traceplot(bhat)
```



One can increase the number of `burnin` or `maxIter` if the trace plot did not coverage.

```r
beta_hat = mean(bhat);
beta_se = sd(bhat);
beta_pvalue = 2*(1 - pnorm(abs(beta_hat/beta_se)));
Eta1index = which(RealRes$Eta==1);
Indpid = RealRes$Indpid + 1;
```

Report the results of MR-Corr^2. `Indpid` is index of the near-independent SNPs , if we set a appropriate threshold value.

```r
cat("The estimated effect of the exposure on outcome: ", beta_hat);
```

```
## The estimated effect of the exposure on outcome:  0.8337523
```

```r
cat("Standard error of beta_hat: ", beta_se);
```

```
## Standard error of beta_hat:  0.09577545
```

```
cat("P-value for beta_hat: ", beta_pvalue);
```

```
## P-value for beta_hat:  0
```