An integrative multi-context Mendelian randomization method for identifying risk genes across human tissues

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Introduction

This vignette provides an introduction to the `mintMR` package. The R package `mintMR` implements the mintMR method for integrative multi-context Mendelian randomization analysis.

To install the development version of the `mintMR` package, please load the `devtools` package first. Note that `mintMR` requires the `CCA`, `Rcpp`, and `RcppArmadillo` packages.

To install this package, run the following command in R

```
library(devtools)
install_github("ylustat/mintMR")
```

Load the package using the following command:

```r
library("mintMR")
```

This vignette depends on R packages `MendelianRandomization`, `ggplot2` and `tidyverse`, you can load these packages using the following command:

```r
suppressMessages(library("tidyverse"))
library("ggplot2")
library("MendelianRandomization")
```

Fit mintMR for correlated SNPs using simulated data

In this section, we fit mintMR using simulated data (provided in the package) as an example to illustrate the basic usage of mintMR. `gamma_hat` and `se_g` are the estimated IV-to-exposure effect and its standard error, and `Gammah_hat` and `se_G` are the estimated IV-to-outcome effect and its standard error. `LD` is the estimated linkage disequilibrium matrix among IVs. `latent status` is the true underlying effect status, where `1` indicates the presence of non-zero effect and `0` indicates the absence of effect.

```r
data(example_data)
names(example_data)
```

```
## [1] "gamma_hat"     "Gamma_hat"     "se_g"          "se_G"
## [5] "LD"            "latent_status"
```

The example data includes 50 simulated genes, each with effects from 5 different contexts/tissues.

```r
L <- length(example_data$gamma_hat)
K1 <- K2 <- 5
L
```

```
## [1] 50
```

In the input IV-to-exposure statistics, each exposure have effects from multiple contexts/tissues. The `group` variable is used to represent the indices of contexts/tissues in the input statistics that belong to each exposure. The `group` variable is a list, and each element of it is a vector of column indices for the `gamma_hat` and `se_g`.

```
group <- list(exposure1 = 1:K1, exposure2 = 1:K2+K1)
# column 1 to 5 in gamma_hat and se_g are from exposure 1
# column 6 to 10 in gamma_hat and se_g are from exposure 2
group
```

```
## $exposure1
## [1] 1 2 3 4 5
##
## $exposure2
## [1]  6  7  8  9 10
```

In addition, mintMR takes IV-to-exposure effect (a list of $I_g \times \sum K_l$ matrices with length L) and standard errors, IV-to-outcome effect and standard errors. The LD matrices (`corr_mat`) and sample overlap (`Lambda`) are optional.

The default prior parameters used in the algorithm is

```
opts <- get_opts(L)
names(opts)
```

```
##  [1] "a_gamma" "b_gamma" "a_alpha" "b_alpha" "a_beta"  "b_beta"  "a"
##  [8] "b"       "maxIter" "thin"    "burnin"
```

It can be changed by specifying the parameters you would like to use. For example:

```
opts <- get_opts(L, maxIter = 1000)
```

MintMR can be run without specifying LD or sample overlap using the following command.

```
set.seed(1)
res_no_LD <- mintMR(gammah = example_data$gamma_hat,
                    Gammah = example_data$Gamma_hat,
                    se1 = example_data$se_g,
                    se2 = example_data$se_G,
                    group = group)
```

When LD information is available and is formatted as a list of matrices, it can be accounted for:

```
set.seed(1)
res <- mintMR(gammah = example_data$gamma_hat,
              Gammah = example_data$Gamma_hat,
              se1 = example_data$se_g,
              se2 = example_data$se_G,
              corr_mat = example_data$LD,
              group = group)
```

When sample overlap information $\widehat{C}$ is available as a $(1 + \sum_l K_l) \times (1 + \sum_l K_l)$ matrix, it can be used in the function as

```
set.seed(1)
# Example correlation matrix for sample overlap. In real data, it can be pre-estimated.
C <- 0.9 * diag(1,(1+K1+K2)) +
  0.1 * matrix(1,nrow=1+K1+K2,ncol=1+K1+K2)

Lambda <- solve(C)

res_LD_sample_overlap <- mintMR(gammah = example_data$gamma_hat,
                                Gammah = example_data$Gamma_hat,
                                se1 = example_data$se_g,
                                se2 = example_data$se_G,
                                corr_mat = example_data$LD,
                                Lambda = Lambda,
                                group = group)
```

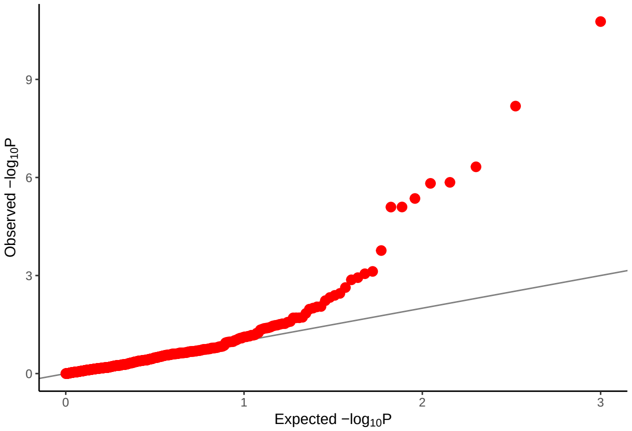
The output includes the effect estimates and p-values for each exposure in each context/tissue.

```
names(res)
```

```
## [1] "Estimate" "Pvalue"
```

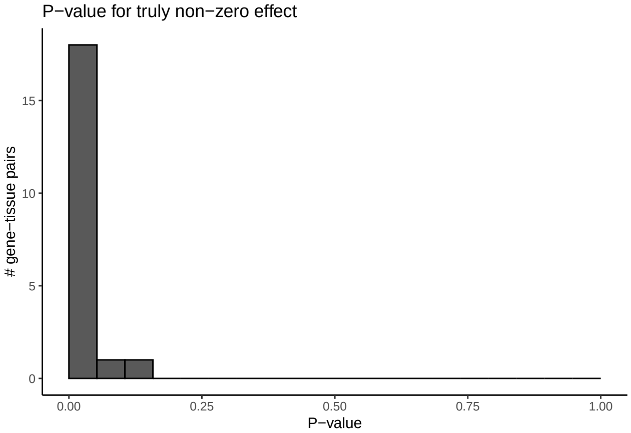
The p-value distribution for all gene-tissue pairs analyzed can be visualized as below.

```
p <- data.frame(mintMR = as.vector(res$Pvalue))
p %>%
  arrange(mintMR) %>%
  mutate(unif = ppoints(n())) %>%
  mutate(value = -log10(mintMR), unif = -log10(unif)) %>%
  ggplot(aes(y = value, x = unif))+
  geom_abline(intercept = 0, slope = 1, alpha = 0.5)+
  geom_point(size = 3, col = "red", alpha=1)+
  theme_classic()+
  labs(y = expression(paste("Observed -log"[10], plain(P))),
       x = expression(paste("Expected -log"[10], plain(P))))
```



The p-value distribution for truly non-zero effects:

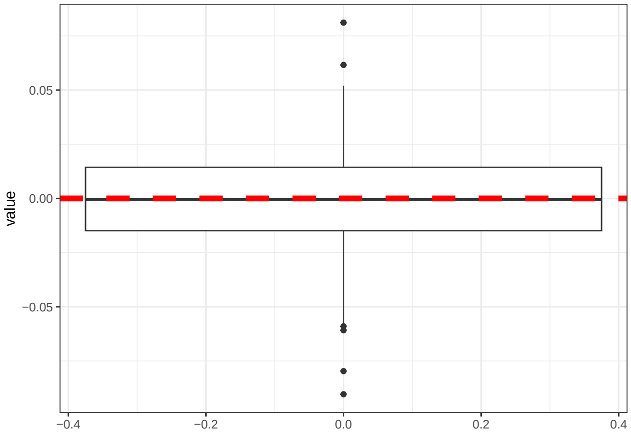
```
p <- data.frame(mintMR = res$Pvalue[example_data$latent_status == 1])
p %>%
  ggplot(aes(x = mintMR))+
  geom_histogram(col="black", boundary = 0, bins=20)+
  theme_classic()+
  scale_x_continuous(limits = c(NA,1))+
  labs(x = "P-value", y = "# gene-tissue pairs",
       title = "P-value for truly non-zero effect")
```



The effect estimates for truly zero effects:

```
estimate <- res$Estimate
estimate[example_data$latent_status == 1] <- NA

estimate %>%
  reshape2::melt() %>%
  tidyr::drop_na() %>%
  ggplot(aes(y = value))+
  theme_bw()+
  geom_boxplot()+
  geom_hline(yintercept = 0,col="red",linetype="dashed",linewidth=2)
```



In real data analysis, we recommend to first estimate the parameter `b_beta` for the prior distribution of causal effects using other MR methods. For example, we may fit MVMR-IVW and calculated the estimate as follows

```
ivw <- mapply(function(bx,by,bxse,byse,ld) {
  res <- mr_mvivw(mr_mvinput(bx = bx, by = as.numeric(by),
                             bxse = bxse, byse = as.numeric(byse),
                             correlation = ld))
  return(list(p = res$Pvalue, b = res$Estimate))
},example_data$gamma_hat,example_data$Gamma_hat,
example_data$se_g,example_data$se_G,
example_data$LD,SIMPLIFY = F)

b_ivw <- lapply(ivw, function(x) x$b) %>% do.call(rbind,.)
```

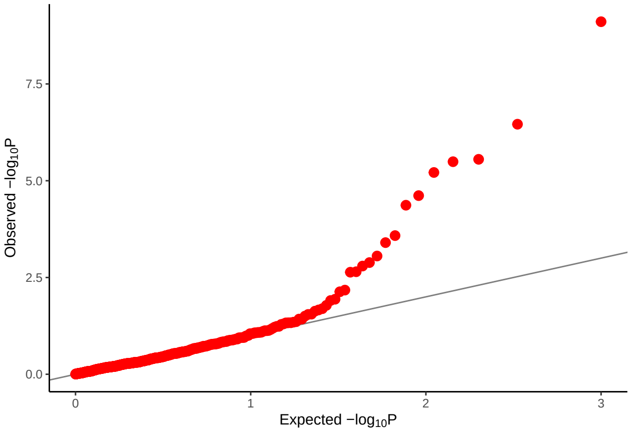
```
p_ivw <- lapply(ivw, function(x) x$p) %>% do.call(rbind,.)

b_beta <- var(b_ivw[p_ivw > 0.05]) * (K1+K2) / 2
opts <- get_opts(L, b_beta = rep(b_beta,L))
```

The estimated parameter can be used in the mintMR by setting the `opts` option.

```
set.seed(1)
res <- mintMR(gammah = example_data$gamma_hat,
              Gammah = example_data$Gamma_hat,
              se1 = example_data$se_g,
              se2 = example_data$se_G,
              corr_mat = example_data$LD,
              group = group,
              opts = opts)

p <- data.frame(mintMR = as.vector(res$Pvalue))
p %>%
  arrange(mintMR) %>%
  mutate(unif = ppoints(n())) %>%
  mutate(value = -log10(mintMR), unif = -log10(unif)) %>%
  ggplot(aes(y = value, x = unif))+
  geom_abline(intercept = 0, slope = 1, alpha = 0.5)+
  geom_point(size = 3, col = "red", alpha=1)+
  theme_classic()+
  labs(y = expression(paste("Observed -log"[10], plain(P))),
       x = expression(paste("Expected -log"[10], plain(P))))
```


Observed $-\log_{10}$P
Expected $-\log_{10}$P