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. R package `mintMR` implements the mintMR method for integrative multi-context Mendelian randomization.

Install the development version of `mintMR` by use of the `devtools` package. Note that `mintMR` depends on the `CCA`, `Rcpp`, and `RcppArmadillo` package.

To install this package, run the following command in R

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

Load the package using the following command:

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

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

```
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 basic usage of mintMR. `gamma_hat` is the IV-to-Exposure effect and standard error, `Gammah_hat` is the IV-to-Outcome effect and standard error. `LD` is the estimated genetic correlations among IVs. `latent status` is the true underlying effect status, where `1` indicates true non-zero effect and `0` indicates true zero effect.

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

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

The example data include 50 simulated genes, each of them with 5 contexts.

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

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

The mintMR requires the information for which context is included for each exposure (the `group` variable). The `group` variable is a list, where each element 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), IV-to-outcome effect and corresponding standard errors. The LD matrices (`corr_mat`) and sample overlap (`Lambda`) are optional.

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 want to use. For example:

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

MintMR can be run without specifying LD or sample overlap using 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 the LD information is available and 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)
```

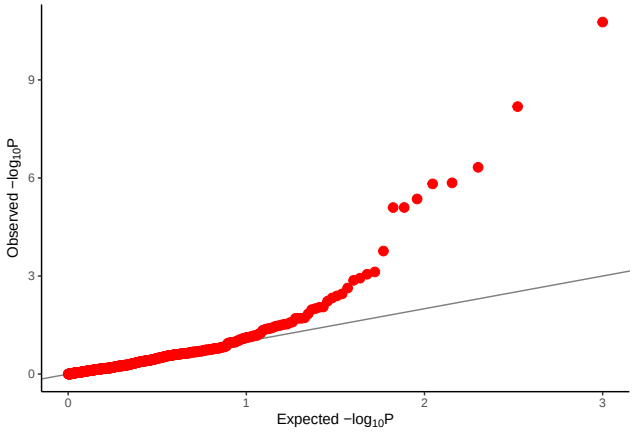
The output includes the effect estimates and p-values.

```
names(res)
```

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

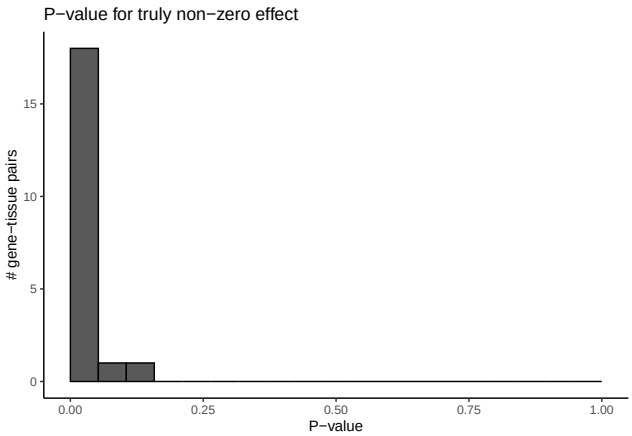
The p-value distribution for all gene-tissue pairs analyzed can be visualized as below.

```
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:

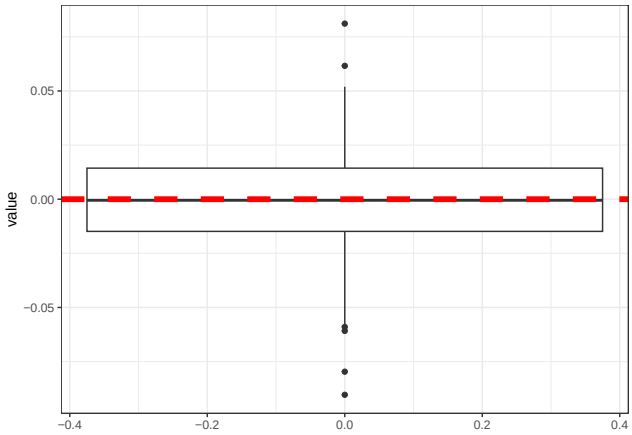
```
p <- data.frame(mintMR = res$Pvalue[example_data$latent_status == 1])
p %>%
  ggplot(aes(x = mintMR))+
  geom_histogram(col="black", boundary = 0, bins=20)+
  theme_classic()+
  scale_x_continuous(limits = c(NA,1))+
  labs(x = "P-value", y = "# gene-tissue pairs",
       title = "P-value for truly 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, the parameter `b_beta` is recommended to be estimated first using other MR methods. For example,

```
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 new 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))))
```