

GTEx data analysis

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Here is a brief introduction of analyzing the results of our proposed approach on GTEx. In this analysis, we considered to model the variance contributed by gender, brain regions, and genes.

Preparations

```
suppressPackageStartupMessages({
  require(ggplot2)
  require(formatR)
  require(knitr)
  require(cluster)
  require(factoextra)
  require(dplyr)
  require(RColorBrewer)
  require(clusterProfiler)
  require(org.Hs.eg.db)
  require(enrichplot)
  require(stringr)
  require(forcats)
  require(DOSE)
  require(extrafont)
})
```

```
## Warning: package 'S4Vectors' was built under R version 3.6.3
```

```
truncated_var <- function(x){
  remove_idx <- c(which.max(x), which.min(x))
  var(x[-remove_idx])
}
wrap_labal <- function(x, width = 60){
  str_wrap(x, width=60)
}
```

```
loadfonts(quiet = T)
setwd("~/data/Results/gtex")
load("GTEx_l1l2_penalty_13.RData")
str(fitted_obj)
```

```
## List of 6
## $ iter      : int 30960
## $ trainset   : num [1:988, 1:49999] 0.0229 0 0.0216 0.0204 0.0149 ...
## ..- attr(*, "dimnames")=List of 2
## .. ..$ : chr [1:988] "GTEx-WZT0-0011-R4A-SM-3NMC7" "GTEx-1HFI6-0011-R4b-SM-A96RT" "GTEx-12WSA-0011-R4b-SM-A96RT" ...
## .. ..$ : chr [1:49999] "DDX11L1" "WASH7P" "MIR6859-1" "MIR1302-2HG" ...
## $ tissue_factor: num [1:13, 1:13] 2.279 0.367 2.619 0.909 1.413 ...
```

```
## $ gender_factor: num [1:2, 1:13] 4.62 4.16 -3.38 3.84 7.41 ...
## $ column_factor: num [1:13, 1:49999] 0.00 0.00 1.39e-04 1.33e-05 0.00 ...
## $ optimal_rmse : num 0.415

attach(fitted_obj) # greatest positive difference

donor_info <- read.csv("meta.csv", stringsAsFactors = F)

load("included_gene_mapping.RData")
ensg_id <- gsub(included_gene_mapping[[1]], pattern="\.[0-9]+$", replacement="")
meta <- data.frame(ensg_id, included_gene_mapping, stringsAsFactors = F)

cat("Overall age distribution:\n")

## Overall age distribution:
print(table(donor_info[,c(3,4)]))
```

```
##      AGE
## SEX 20-29 30-39 40-49 50-59 60-69 70-79
##   1    15     3    41   149   248    38
##   2    16    17    62   121   256    22
```

Investigate the difference in BPs between both genders across different brain regions

We considered all metagenes in this analysis. The figure below shows the up-regulated BPs of genes with the greatest positive difference between male and female.

```
metagene_var <- apply(gender_factor, 2, function(x) abs(x[1] - x[2]))
ord <- order(metagene_var, decreasing = T)

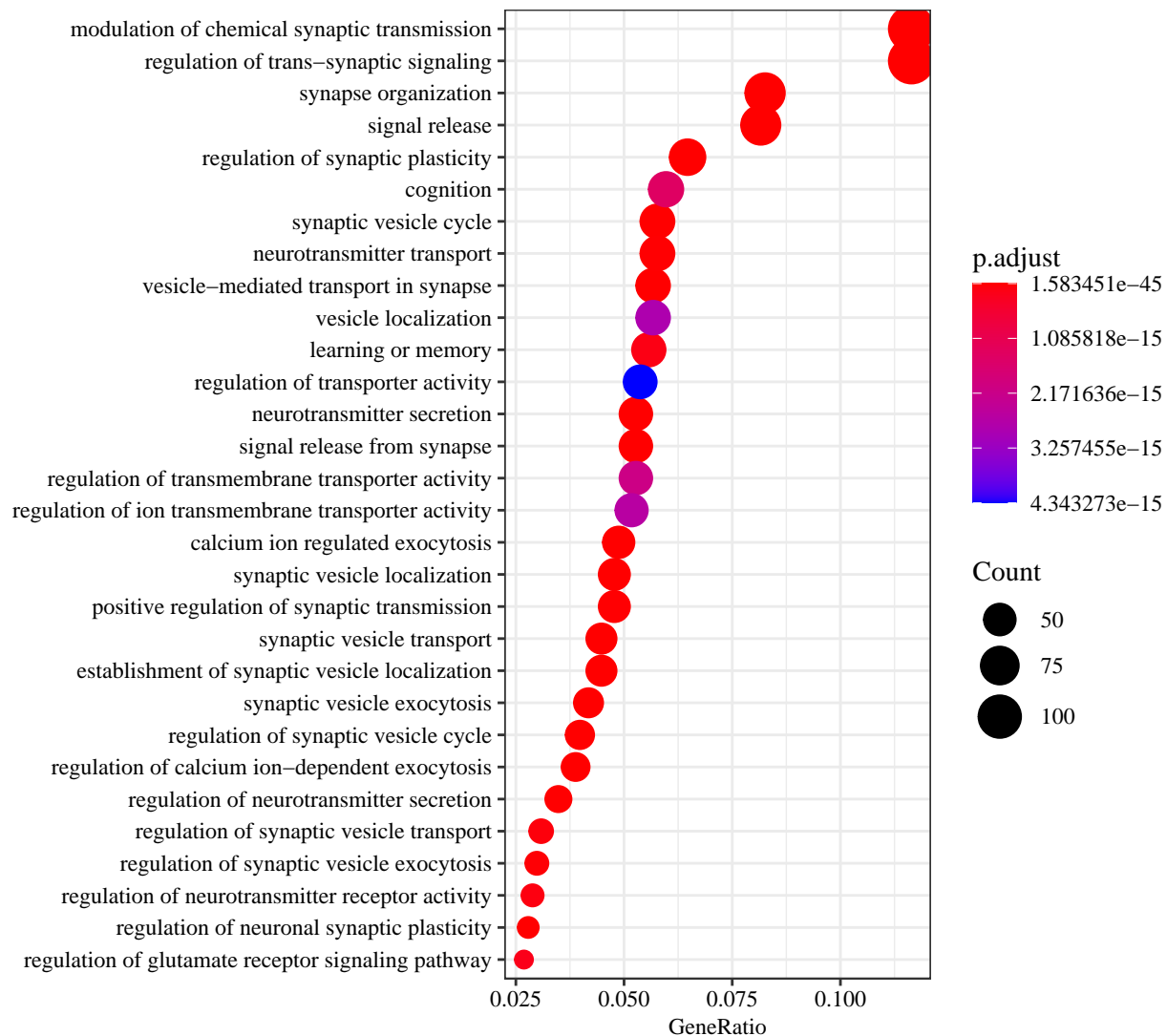
k <- 13
gender_expr_profiles <- gender_factor[, ord[1:k]] %*% column_factor[ord[1:k],]
colnames(gender_expr_profiles) <- colnames(trainset)

# The first row stands for the male and the second for the female.
diff <- gender_expr_profiles[1, ] - gender_expr_profiles[2, ]

cutoffs <- quantile(diff, probs = seq(0, 1, 0.025))
# selected <- (diff <= cutoffs[2]) # greatest negative difference
selected <- (diff >= cutoffs[length(cutoffs)-1])

upreg <- enrichGO(gene      = unique(meta[selected,1]),
                  OrgDb     = 'org.Hs.eg.db',
                  keyType   = 'ENSEMBL',
                  ont        = "BP",
                  readable  = TRUE)

# summary(upreg)
dotplot(upreg, font.size = 9, showCategory=30) +
  scale_y_discrete(labels = function(x) wrap_labal(x)) +
  theme(text=element_text(family="Times New Roman"))
```



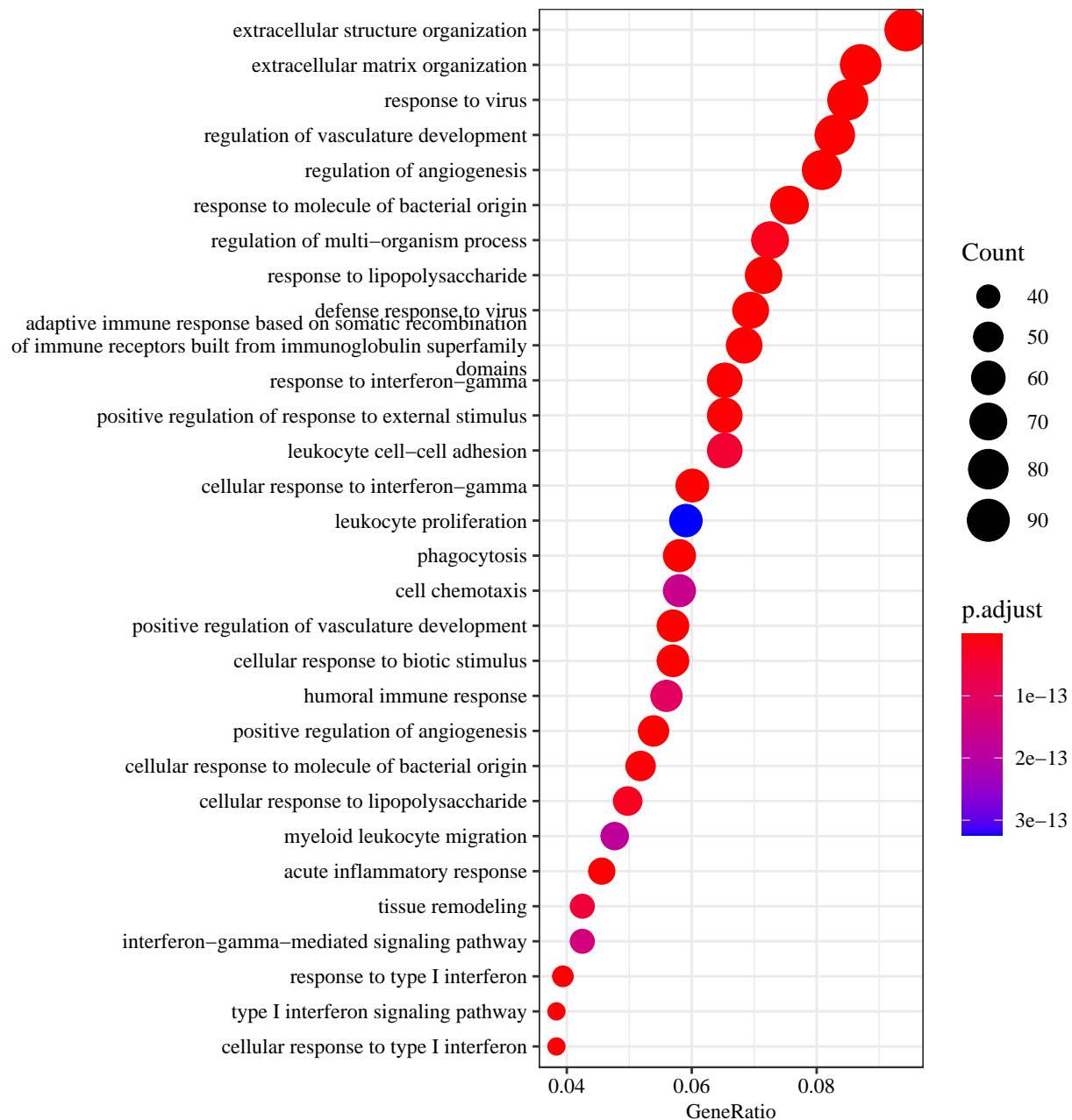
The figure below shows the down-regulated BPs of genes with the greatest negative difference between male and female.

```
k <- 13
gender_expr_profiles <- gender_factor[, ord[1:k]] %*% column_factor[ord[1:k],]
diff <- gender_expr_profiles[1, ] - gender_expr_profiles[2, ]

cutoffs <- quantile(diff, probs = seq(0, 1, 0.025))
selected <- (diff <= cutoffs[2]) # greatest negative difference

downreg <- enrichGO(gene          = unique(meta[selected,1]),
                    OrgDb         = 'org.Hs.eg.db',
                    keyType       = 'ENSEMBL',
                    ont           = "BP",
                    readable      = TRUE)

dotplot(downreg, font.size = 9, showCategory=30) +
  scale_y_discrete(labels = function(x) wrap_label(x)) +
  theme(text=element_text(family="Times New Roman"))
```



Investigate BPs involving in the interaction between genders and different brain regions

In the analysis, we explored the BPs of genes showing the difference in the brain region in which there is the greatest difference in correlation between both gender.

```
rownames(tissue_factor) <- unique(donor_info[[7]])
rownames(gender_factor) <- c("male", "female")
gender_tissue <- cor(t(gender_factor), t(tissue_factor))

# idx <- which(rownames(tissue_factor) == "Brain - Nucleus accumbens (basal ganglia)")
# idx <- 2
idx <- order(apply(gender_tissue, 2, function(x) abs(x[1] - x[2])), decreasing = T)[1]
```

```

cat("Overall age distribution:", rownames(tissue_factor)[idx], "\n")

## Overall age distribution: Brain - Putamen (basal ganglia)
print(table(donor_info[donor_info$SMTSD == rownames(tissue_factor)[idx],c(3,4)]))

##      AGE
## SEX 20-29 40-49 50-59 60-69 70-79
##   1      1      2      17      16      2
##   2      1      3      13      19      2

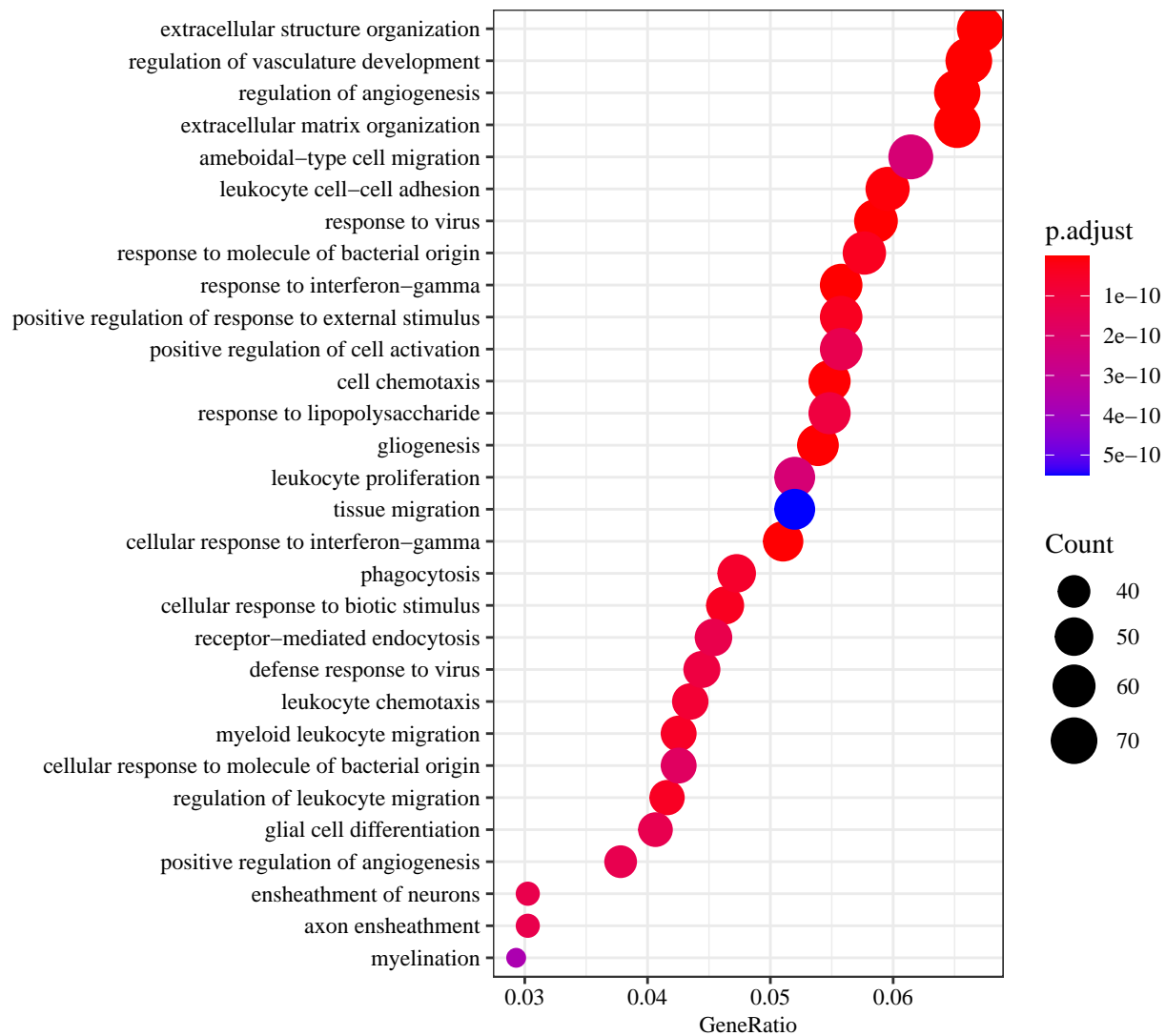
interaction <- t(apply(gender_factor, 1, function(x) x * tissue_factor[idx,]))
interaction_var <- apply(interaction, 2, var)
ord <- order(interaction_var, decreasing = T)

k <- 8 # 4
interaction_profiles <- interaction[, ord[1:k]] %*% column_factor[ord[1:k],]
diff <- interaction_profiles[1, ] - interaction_profiles[2, ]

cutoffs <- quantile(diff, probs = seq(0, 1, 0.025))
selected <- (diff <= cutoffs[2]) # greatest negative difference

downreg <- enrichGO(gene      = unique(meta[selected,1]),
                    OrgDb      = 'org.Hs.eg.db',
                    keyType     = 'ENSEMBL',
                    ont         = "BP",
                    readable    = TRUE)
dotplot(downreg, font.size = 9, showCategory=30) +
  scale_y_discrete(labels = function(x) wrap_labal(x)) +
  theme(text=element_text(family="Times New Roman"))

```



```
k <- 8 # 6
interaction_profiles <- interaction[, ord[1:k]] %*% column_factor[ord[1:k],]
diff <- interaction_profiles[1, ] - interaction_profiles[2, ]
selected <- (diff >= cutoffs[length(cutoffs)-1])

upreg <- enrichGO(gene      = unique(meta[selected,1]),
                  OrgDb      = 'org.Hs.eg.db',
                  keyType     = 'ENSEMBL',
                  ont         = "BP",
                  readable    = TRUE)

dotplot(upreg, font.size = 9, showCategory=30) +
  scale_y_discrete(labels = function(x) wrap_label(x)) +
  theme(text=element_text(family="Times New Roman"))
```

