Statistical Approach for Pleiotropy Informed and Functional Annotation Tree Guided Prioritization of GWAS Results with '*multiGPATree*' Package

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1 Overview

This vignette provides an introduction to the ***multiGPATree*** package. R package ***multiGPATree*** implements the ***multiGPATree*** method, a novel statistical approach to prioritizing risk-associated SNPs and the combinations of functional annotations related to one or more trait risk-associated SNPs. The ***multiGPATree*** approach employs a hierarchical model to integrate GWAS summary statistics for multiple traits and functional annotation information within a unified framework by combining an iterative procedure (EM algorithm (Dempster, Laird, and Rubin 1977)) and a multivariate decision tree algorithm (MVPART (De'Ath 2002)).

The package can be loaded with the command:

```
> # install.packages("devtools")
> # library(devtools)
> # devtools::install_github("cran/mvpart")
> # library(mvpart)
> # devtools::install_github("asthakhatiwada/multiGPATree")
> library(multiGPATree)
```

This vignette is organized as follows. Section 2 discusses the data structure required to implement the ***multiGPATree*** method and section 3 describes the workflow to implement the ***multiGPATree*** method. Section 3.1 discusses how to fit a ***multiGPATree*** model, section 3.2 describes how to prune a large ***multiGPATree*** model, section 3.3 describes the ***multiGPATree*** model plot and functional annotation tree, and finally, section 3.4 explain command lines for association mapping and identification of combination of functional annotations for one or more traits using ***multiGPATree***.

Please feel free to contact Dongjun Chung at `chung.911@osc.edu` or Aastha Khatiwada at `khatiwadaa@njhealth.org` for any questions or suggestions regarding the ***multiGPATree*** package.

2 Data structure

In this vignette, we use the simulated data (*simdata*) provided in the package to fit the ***multiGPATree*** model for post-GWAS analysis. The simulated data includes information for two traits/phenotypes (P1 and P2). In the simulated data, the number of SNPs and the number of functional annotations are set to $M = 1000$ and $K = 10$, respectively. The GWAS association p-values for the SNPs are stored in *simdata$gwasPval* and the binary functional annotation information for the SNPs are stored in *simdata$annMat*, respectively. The number of rows in *simdata$gwasPval* is assumed to be the same as the number of rows in *simdata$annMat* where the i-th ($i = 1, ..., M$) row of *gwasPval* and *annMat* correspond to the same SNPs.

```
> data("simdata")
> class(simdata)
[1] "list"
> names(simdata)
[1] "annMat"   "gwasPval"
> dim(simdata$gwasPval)
[1] 1000    2
> dim(simdata$annMat)
[1] 1000   10
> head(simdata$gwasPval)
              P1         P2
SNP_1 0.98281150 0.42126064
SNP_2 0.52555968 0.59463902
SNP_3 0.07748063 0.91700262
SNP_4 0.63208756 0.15856348
SNP_5 0.28658882 0.11983350
SNP_6 0.96132083 0.06235469
> head(simdata$annMat)
      A1 A2 A3 A4 A5 A6 A7 A8 A9 A10
SNP_1  1  0  0  0  0  0  0  0  0   1
SNP_2  1  0  0  0  0  0  0  0  1   0
SNP_3  1  0  0  0  0  0  0  0  0   0
SNP_4  1  0  0  0  0  0  0  0  1   1
SNP_5  1  0  0  0  0  0  0  0  0   0
SNP_6  1  0  0  0  0  0  0  0  0   0
```

3 Workflow

3.1 Fitting the multiGPATree Model

We are now ready to fit a ***multiGPATree*** model using the GWAS p-value and functional annotatio data described above. We can fit the ***multiGPATree*** model with the command:

```
> fit.mGPATree <- multiGPATree(gwasPval = simdata$gwasPval,
+                              annMat = simdata$annMat,
+                              initAlpha = 0.1,
+                              cpTry = 0.005)
> fit.mGPATree
Summary: multiGPATree model results (class: multiGPATree)
```

```
--------------------------------------------------
Data summary:
    Number of GWAS data: 2
    Number of Annotations: 10
    Number of SNPs: 1000
    Alpha estimates: 0.3691, 0.434
Functional annotation tree description:
       local FDR P1 local FDR P2 A1 A5 A4 A3 A6 A2
LEAF 1       0.9568      0.95756  0  0  0  -  -  -
LEAF 2       0.9889      0.25543  0  0  1  1  -  -
LEAF 3       0.9627      0.78918  0  0  1  0  -  -
LEAF 4       0.8816      0.68446  0  1  -  -  0  -
LEAF 5       0.1454      0.07836  0  1  -  -  1  -
LEAF 6       0.0690      0.95888  1  -  -  -  -  1
LEAF 7       0.7743      0.87926  1  -  -  -  -  0
--------------------------------------------------
```

3.2 Prunning the multiGPATree model

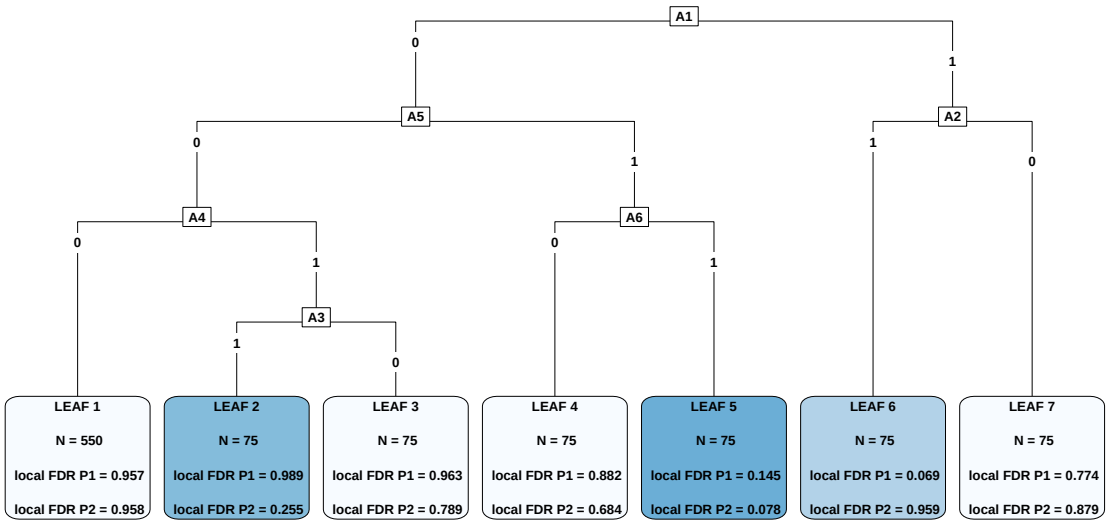
The `prune()` function will prune the *multiGPATree* model using any cp value between 0 and 1 as shown below.

```
> fit.mGPATree.pruned <- prune(fit.mGPATree, cp = 0.20)
> fit.mGPATree.pruned
Summary: multiGPATree model results (class: multiGPATree)
--------------------------------------------------
Data summary:
    Number of GWAS data: 2
    Number of Annotations: 10
    Number of SNPs: 1000
    Alpha estimates: 0.3691, 0.434
Functional annotation tree description:
       local FDR P1 local FDR P2 A1 A5
LEAF 1       0.9608       0.8643  0  0
LEAF 2       0.5135       0.3814  0  1
LEAF 3       0.4216       0.9191  1  -
--------------------------------------------------
```

3.3 Functional annotation tree

The `plot()` and `leaf()` functions will plot the *multiGPATree* functional annotation tree and provide information about the leaves (terminal nodes) in the tree as shown below.

```
> plot(fit.mGPATree)
```




```
> leaf(fit.mGPATree)
       local FDR P1 local FDR P2 A1 A5 A4 A3 A6 A2
LEAF 1       0.9568       0.95756  0  0  0  -  -  -
LEAF 2       0.9889       0.25543  0  0  1  1  -  -
LEAF 3       0.9627       0.78918  0  0  1  0  -  -
LEAF 4       0.8816       0.68446  0  1  -  -  0  -
LEAF 5       0.1454       0.07836  0  1  -  -  1  -
LEAF 6       0.0690       0.95888  1  -  -  -  -  1
LEAF 7       0.7743       0.87926  1  -  -  -  -  0
```

3.4 Association mapping

For the fitted *multiGPATree* model, we can make inferences about SNPs using the `assoc()` function by: (1) prioritizing risk-associated SNPs for one or more traits, and (2) identifying the leaves of the *multiGPATree* model in which one or more trait risk-associated SNPs are located. In this case, the `assoc()` function returns four columns. The first column contains binary values where 1 indicates that the SNP is marginally associated with the first trait (P1) and 0 indicates otherwise. Similarly, the second column contains binary values where 1 indicates that the SNP is marginally associated with the second trait (P2) and 0 indicates otherwise. The third column contains binary values where 1 indicates that the SNP is jointly associated with both traits (P1 and P2) and 0 indicates otherwise.Finally, the fourth column provides information regarding the leaf in which a SNP is located in the *multiGPATree* plot. The `assoc()` function allows both local (`fdrControl="local"`) and global FDR controls (`fdrControl="global"`) and users can set the threshold to be between 0 and 1 using the 'FDR' argument.

For the simulated data, *multiGPATree* model identified 4 SNPs to be jointly associated with traits P1 and P2 at the nominal global FDR level of 0.01, all of which are located in leaf 5 which can be interpreted as the 4 risk SNPs being simultaneously annotated for both annotations $A5$ and $A6$. Similarly, *multiGPATree* model identified 38 SNPs to be marginally associated with trait P1 at the nominal global FDR level of 0.01. Of the 38 SNPs, 27 SNPs are located in leaf 6 and are simultaneously annotated for annotations $A1$ and $A2$ and 11 SNPs are located in leaf 5 and are simultaneously annotated for $A5$ and $A6$.The following lines of code can be used to investigate association mapping and functional annotation tree for *multiGPATree* models.

```
> assoc.mGPATree <- assoc(fit.mGPATree,
+                         FDR = 0.01,
```

```
+                         fdrControl="global")
> head(assoc.mGPATree)
      P1 P2 P1_P2   leaf
SNP_1  0  0     0 LEAF 7
SNP_2  0  0     0 LEAF 7
SNP_3  0  0     0 LEAF 7
SNP_4  0  0     0 LEAF 7
SNP_5  0  0     0 LEAF 7
SNP_6  0  0     0 LEAF 7
> table(assoc.mGPATree$P1_P2)

  0   1
996   4
> table(assoc.mGPATree$P1_P2, assoc.mGPATree$leaf)

    LEAF 1 LEAF 2 LEAF 3 LEAF 4 LEAF 5 LEAF 6 LEAF 7
  0    550     75     75     75     71     75     75
  1      0      0      0      0      4      0      0
> table(assoc.mGPATree$P1)

  0   1
962  38
> table(assoc.mGPATree$P1, assoc.mGPATree$leaf)

    LEAF 1 LEAF 2 LEAF 3 LEAF 4 LEAF 5 LEAF 6 LEAF 7
  0    550     75     75     75     64     48     75
  1      0      0      0      0     11     27      0
> table(assoc.mGPATree$P2)

  0   1
977  23
> table(assoc.mGPATree$P2, assoc.mGPATree$leaf)

    LEAF 1 LEAF 2 LEAF 3 LEAF 4 LEAF 5 LEAF 6 LEAF 7
  0    550     70     75     75     57     75     75
  1      0      5      0      0     18      0      0
>
> table(assoc.mGPATree$P1, assoc.mGPATree$P2)

     0   1
  0 944  18
  1  33   5
> table(assoc.mGPATree$P1, assoc.mGPATree$P2, assoc.mGPATree$P1_P2)
, ,  = 0


     0   1
  0 944  18
  1  33   1

, ,  = 1
```

```
    0   1
0   0   0
1   0   4
```

References

De'Ath, Glenn. 2002. "Multivariate Regression Trees: A New Technique for Modeling Species–Environment Relationships." *Ecology* 83 (4): 1105–17.

Dempster, Arthur P, Nan M Laird, and Donald B Rubin. 1977. "Maximum Likelihood from Incomplete Data via the EM Algorithm." *Journal of the Royal Statistical Society: Series B (Methodological)* 39 (1): 1–22.