HEMDAG Documentation

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Installation Getting Started

HEMDAG package:

- implements several Hierarchical Ensemble Methods (HEMs) for Directed Acyclic Graphs (DAGs);
- reconciles flat predictions with the topology of the ontology;
- can enhance the predictions of virtually any flat learning methods by taking into account the hierarchical relationships between ontology classes;
- guarantees biologically meaningful predictions that always obey the *true-path-rule*, the biological and logical rule that governs the internal coherence of biomedical ontologies;
- is specifically designed for exploiting the hierarchical relationships of DAG-structured taxonomies, such as the Human Phenotype Ontology (`HPO`) or the Gene Ontology (`GO`), but can be safely applied to tree-structured taxonomies as well (e.g. `FunCat`), since trees are DAGs;
- scales nicely both in terms of the complexity of the taxonomy and in the cardinality of the examples;
- provides several utility functions to process and analyze graphs;
- provides several performance metrics to evaluate HEMs algorithms.

CHAPTER 1

Quickstart

This short How-To guides you from downloading the HEMDAG, load it into your R environment and make a first computation.

1.1 Installation

Please goto the *Installation* section and use the *Installation via Conda* option to install HEMDAG.

1.2 Load HEMDAG library

Start R in your console using

```
$ R
```

then load the library by using

```
library("HEMDAG")
```

1.3 Your first classification

We will use the DESCENS algorithm to do some predictions on a DAG (Human Phenotype Ontology).

In contrast to the *vanilla* TPR-DAG version, DESCENS takes into account the contribution of all the descendants of each node instead of only that of its children. So DESCENS predictions are more influenced by the information embedded in the most specific terms of the taxonomy (e.g. leaf nodes), thus putting more emphasis on the terms that most characterize the gene under study.

```
# load a ontology DAG stored in g
data(graph);
# load scores for genes to HPO stored in S
data(scores);
# load labels in L (genes annotated to HPO terms)
data(labels);
# Set the root in your DAG
root <- root.node(g);
# Run DESCENS Threshold free
S.descensTF  <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold.free",
↪ topdown="HTD");
# Run DESCENS with threshold
S.descensT   <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold",␣
↪topdown="HTD", t=0.5);
# Run weighted DESCENS with threshold free
S.descensW   <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold.free", topdown="HTD", w=0.5);
# Run weighted DESCENS with threshold
S.descensWT  <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="HTD", t=0.5, w=05);
# Run DESCENS TAU
S.descensTAU <- TPR.DAG(S, g, root, positive="descendants", bottomup="tau", topdown=
↪"HTD", t=0.5);
```

CHAPTER 2

Installation

HEMDAG is available on CRAN as well as through Bioconda and also from source code. You can use one of the following ways for installing HEMDAG.

2.1 Installation via Conda

Note: This is the recommended way of installing for normal users.

This is the recommended way to install HEMDAG because it will enables you to switch software versions easily. And in addition R with all needed dependencies will be installed.

First, you have to install the Miniconda Python3 distribution. See here for installation instructions. Make sure to . . .

- Install the *Python 3* version of Miniconda.
- Answer yes to the question whether conda shall be put into your PATH.

Then, you can install HEMDAG with

```
$ conda install -c bioconda -c conda-forge r-hemdag
```

from the Bioconda channel.

2.2 Global Installation

You can directly install the library via R by issuing

```
$ R -e "install.packages('HEMDAG',repos = 'http://cran.us.r-project.org')"
```

in your terminal. But be sure to install R properly before that command.

Alternatively, you can install the `HEMDAG` library by typing in the `R` environment:

```
install.packages("HEMDAG");
```

Another possibility to install the development version of HEMDAG is by using the devtools package:

```
library(devtools);
install_github("marconotaro/HEMDAG");
```

Before running the above commands be sure to have correctly installed the devtools package (link)

2.3 Installing from Source

This section describes how to build HEMDAG from scratch.

2.3.1 Prequisites

For building HEMDAG, you will need the following dependencies

- R (2.10)
- **R-libraries:**
  - PerfMeas
  - rbgl (bioconductor)
  - graph (bioconductor)
  - precrec
  - preprocessCore (bioconductor)
  - plyr
  - foreach
  - doParallel

2.3.2 Package from CRAN

On a linux environment, download the package source from the CRAN repo and save it in the folder pippo. Then type:

```
R CMD INSTALL pippo/HEMDAG_2.6.0.tar.gz
```

2.3.3 Direct Git Checkout

Note: You only need to install from source if you want to develop HEMDAG yourself.

In this tutorial, we will download the HEMDAG sources and build them in ~/HEMDAG:

```
~ $ cd ~
~ $ git clone https://github.com/marconotaro/HEMDAG.git HEMDAG
```

2.3.4 Building

You can build HEMDAG by using:

```
R CMD build HEMDAG
```

This will generate the file `HEMDAG_2.5.9.tar.gz` and just install the package via:

```
R CMD INSTALL HEMDAG_2.5.9.tar.gz
```

CHAPTER 3

Usage of HEMDAG

For a detailed description of available functions in the HEMDAG package please goto the HEMDAG package on CRAN and have a look to the *Reference manual*.

CHAPTER 4

Tutorial

The hierarchical ensemble methods proposed in HEMDAG package can be run by using any ontology listed in OBO foundry (link). In this tutorial we perform experiments by using the Human Phenotype Ontology (HPO, link) and the Gene Ontology (GO, link).

Note: The experiments run on this tutorial were executed by using the HEMDAG version 2.6.0, the R version 3.6.1 and on a machine having Ubuntu 16.04 as operative system.

4.1 Hierarchical Prediction of HPO terms

Here we show a step-by-step application of HEMDAG to the hierarchical prediction of associations between human gene and abnormal phenotype. To this end we will use the small pre-built dataset available in the HEMDAG library. Nevertheless, you can perform the examples shown below by using the full dataset available at the following link.

Note: By using the full dataset the running time of the parametric ensemble variants is quite higher due to the tuning of the hyper-parameters...

Reminder. To load the HEMDAG library in the R environment, just type:

```
library(HEMDAG);
```

and to load an rda file in the R environment just type:

```
load("file_name.rda");
```

4.2 Loading the Flat Scores Matrix

In their more general form, the hierarchical ensemble methods adopt a two-step learning strategy: the first step consists in the flat learning of the ontology terms, while the second step *reconciles* the flat predictions by considering the topology of the ontology. Hence, the first *ingredient* that we need is the flat scores matrix. For the sake of simplicity, in the examples shown below we make use of the pre-built dataset available in the `HEMDAG` library. To load the flat scores matrix, open the `R` environment and type:

```
data(scores);
```

with the above command we loaded the flat scores matrix `S`, that is a named `100 X 23` matrix. Rows correspond to genes (`Entrez GeneID`) and columns to `HPO` terms/classes. The scores representing the likelihood that a given gene belongs to a given class: the higher the value, the higher the likelihood that a gene belongs to a given class. This flat scores matrix was obtained by running the `RANKS` package (link).

4.3 Loading the DAG

In order to know the hierarchical structure of the `HPO` terms, we must load the graph:

```
data(graph);
```

with the above command we loaded the graph `g`, an object of class `graphNEL`. The graph `g` has `23` nodes and `30` edges and represents the *ancestors view* of the `HPO` term `Camptodactyly of finger` (HP:0100490). Nodes of the graph `g` must correspond to classes of the flat scores matrix `S`.

4.3.1 Optional step: plotting the graph `g`

Note: To plot the graph you need to install before the *Rgraphviz* package. Yo can install this library for example by conda (`conda install -c bioconda bioconductor-rgraphviz`) or by Bioconductor (link).

If you want to visualize the *ancestors view* of the term `HP:0100490`, just type:

```
library(Rgraphviz);
plot(g);
```

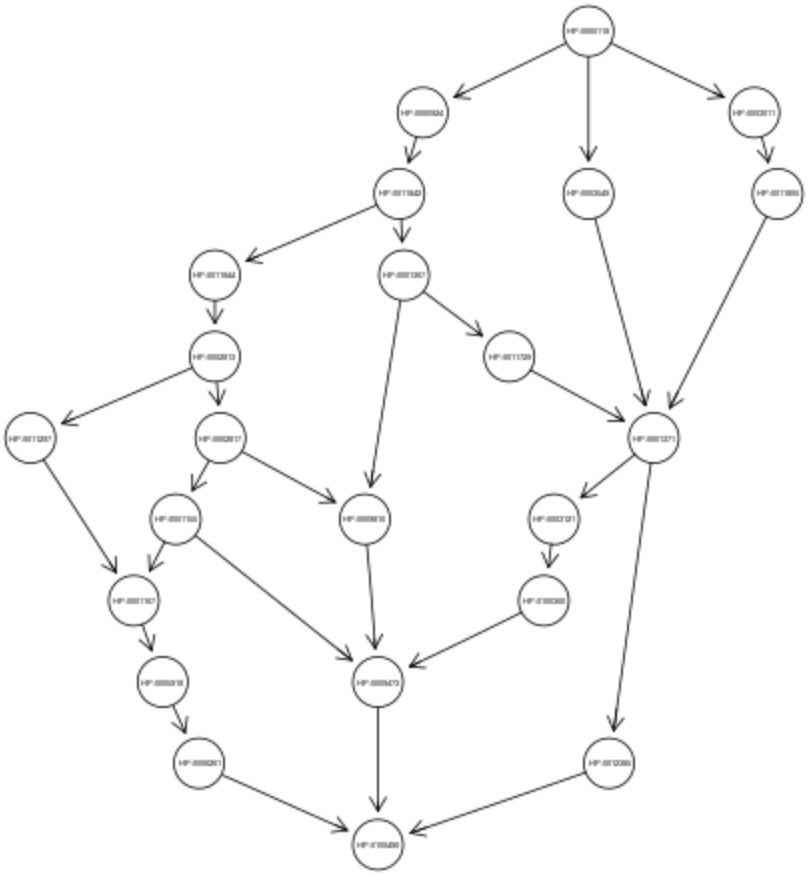
4.4 Scores Normalization

If the flat classifier used as base learner in `HEMDAG` library returns a score and not a probability, we must normalize the scores of the flat matrix to make the flat scores comparable with the hierarchical ones. `HEMDAG` allows to normalize the flat scores according to two different procedures:

1. **MaxNorm**: Normalization in the sense of the maximum: the score of each class is normalized by dividing the score values for the maximum score of that class:

```
maxnorm <- normalize.max(S);
```

2. **Qnorm**: Quantile normalization: quantile normalization of the `preprocessCore` package is used:



```
library(preprocessCore);
qnrom <- normalize.quantiles(S);
```

Be sure to install the `preprocessCore` package before running the above command. Yo can install it by conda (`conda install -c bioconda bioconductor-preprocesscore`) or by Bioconductor (link)

For the examples shown below, we normalize the flat scores matrix by applying the **MaxNorm**:

```
S <- normalize.max(S);
```

4.5 Running Hierarchical Ensemble Methods

First of all, we need to find the root node (i.e. node that is at the top-level of the hierarchy) of the `HPO` graph `g`. To do that just type:

```
root <- root.node(g);
```

in this way we store in the variable `root` the root node of the graph `g`.

Now, we are ready to run any ensemble algorithms implemented in the `HEMDAG` package. Depending on which ensemble variant you want to call, you must execute one of the command listed below:

4.5.1 HTD-DAG: Hierarchical Top Down for DAG

```
S.htd <- htd(S,g,root);
```

4.5.2 GPAV-DAG: Generalized Pool-Adjacent-Violators for DAG

```
S.gpav <- GPAV.over.examples(S, W=NULL, g);
```

4.5.3 TPR-DAG: True Path Rule for DAG

`TPR-DAG` is a family of algorithms according to the bottom-up approach adopted for the choice of the *positive* **children**. In the top-down step (that guarantees coherent predictions with the ontology ones) `TPR-DAG` strategy uses the `HTD-DAG` algorithm.

```
S.tprTF    <- TPR.DAG(S, g, root, positive="children", bottomup="threshold.free",␣
↪topdown="HTD");
S.tprT     <- TPR.DAG(S, g, root, positive="children", bottomup="threshold", topdown=
↪"HTD", t=0.5);
S.tprW     <- TPR.DAG(S, g, root, positive="children", bottomup="weighted.threshold.
↪free", topdown="HTD", w=0.5);
S.tprWT    <- TPR.DAG(S, g, root, positive="children", bottomup="weighted.threshold",␣
↪topdown="HTD", t=0.5, w=0.5);
```

4.5.4 ISO-TPR: Isotonic Regression for DAG

`TPR-DAG` is a family of algorithms according to the bottom-up approach adopted for the choice of the *positive* **children**. To make scores consistent with the ontology predictions `ISO-TPR` employs in the top-down step the `GPAV-DAG` algorithm.

```
S.ISOtprTF <- TPR.DAG(S, g, root, positive="children", bottomup="threshold.free",␣
↪topdown="GPAV");
S.ISOtprT  <- TPR.DAG(S, g, root, positive="children", bottomup="threshold", topdown=
↪"GPAV", t=0.5);
S.ISOtprW  <- TPR.DAG(S, g, root, positive="children", bottomup="weighted.threshold.
↪free", topdown="GPAV", w=0.5);
S.ISOtprWT <- TPR.DAG(S, g, root, positive="children", bottomup="weighted.threshold",␣
↪topdown="GPAV", t=0.5, w=0.5);
```

4.5.5 DESCENS: Descendants Ensemble Classifier

`DESCENS` is a family of algorithms according to the bottom-up approach adopted for the choice of the *positive* **descendants**. In the top-down step `DESCENS` uses the `HTD-DAG` algorithm.

```
S.descensTF      <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold.
↪free", topdown="HTD");
S.descensT       <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold",␣
↪topdown="HTD", t=0.5);
S.descensW       <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold.free", topdown="HTD", w=0.5);
S.descensWT      <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="HTD", t=0.5, w=05);
S.descensTAU     <- TPR.DAG(S, g, root, positive="descendants", bottomup="tau",␣
↪topdown="HTD", t=0.5);
S.ISOdescensTF   <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold.
↪free", topdown="GPAV");
S.ISOdescensT    <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold",␣
↪topdown="GPAV", t=0.5);
S.ISOdescensW    <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold.free", topdown="GPAV", w=0.5);
S.ISOdescensWT   <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="HTD", t=0.5, w=05);
S.ISOdescensTAU <- TPR.DAG(S, g, root, positive="descendants", bottomup="tau",␣
↪topdown="GPAV", t=0.5);
```

4.5.6 ISO-DESCENS: Isotonic Regression with Descendants Ensemble Classifier

`ISO-DESCENS` is a family of algorithms according to the bottom-up approach adopted for the choice of the *positive* **descendants**. For the top-down step `ISO-DESCENS` employs the `GPAV-DAG` algorithm.

```
S.ISOdescensTF  <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold.
↪free", topdown="GPAV");
S.ISOdescensT   <- TPR.DAG(S, g, root, positive="descendants", bottomup="threshold",␣
↪topdown="GPAV", t=0.5);
S.ISOdescensW   <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold.free", topdown="GPAV", w=0.5);
S.ISOdescensWT  <- TPR.DAG(S, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="HTD", t=0.5, w=05);
```

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```
S.ISOdescensTAU <- TPR.DAG(S, g, root, positive="descendants", bottomup="tau",␣
↪topdown="GPAV", t=0.5);
```

4.5.7 Obozinski Heuristic Methods

```
S.max <- heuristic.max(S,g,root);
S.and <- heuristic.and(S,g,root);
S.or  <- heuristic.or(S,g,root);
```

4.5.8 Hierarchical Constraints Check

The predictions returned by our ensemble methods always obey to the **True Path Rule**: positive instance for a class implies positive instance for all the ancestors of that class. To check this fact we can apply the function `check.hierarchy`:

```
check.hierarchy(S,g,root)$Status
[1] "NOTOK"

check.hierarchy(S.htd,g,root)$Status
[1] "OK"
```

Obviously, all the ensemble variants hold this property, for instance:

```
check.hierarchy(S.tprTF,g,root)$Status
[1] "OK"

check.hierarchy(S.descensW,g,root)$Status
[1] "OK"
```

4.5.9 Performance Evaluation

To know the ensemble methods behavior, the `HEMDAG` library, by using `precrec` package, provides several performance metrics:

- `AUROC`: area under the `ROC` curve;
- `AUPRC`: area under the precision-recall curve;
- `F-max`: maximum hierarchical `F-score` [Jiang2016];
- `PXR` : precision at different recall levels;

Note: `HEMDAG` allows to compute all the aforementioned performance metrics either **one-shot** or **averaged** across `k` fold. Depending on the size of your dataset, the metrics `F-max` and `PXR` could take a while to finish. Please refer to `HEMDAG` reference manual for further information about what these functions receive in input and return in output.

Loading the Annotation Matrix

To compare the hierarchical ensemble methods against the flat approach, we need of the annotation matrix:

```
data(labels);
```

with the above command we loaded the annotations table `L`, that is a named `100 X 23` matrix. Rows correspond to genes (`Entrez GeneID`) and columns to `HPO` terms/classes. `L[i, j] = 1` means that the gene `i` belong to class `j`, `L[i, j] = 0` means that the gene `i` does not belong to class `j`.

Flat vs Hierarchical

Before computing performance metrics we must remove the root node from the annotation matrix, the flat scores matrix and the hierarchical scores matrix. It does not make sense at all to take into account the predictions of the root node, since it is a *dummy* node added to the ontology for practical reasons (e.g. some graph-based software may require a single root node to work). In `R` this can be accomplished in one line of code.

```
## remove root node from annotation matrix
if(root %in% colnames(L))
    L <- L[,-which(colnames(L)==root)];

## remove root node from flat scores matrix
if(root %in% colnames(S))
    S <- S[,-which(colnames(S)==root)];

## remove root node from hierarchical scores matrix (eg S.htd)
if(root %in% colnames(S.htd))
    S.htd <- S.htd[,-which(colnames(S.htd)==root)];
```

Now we can compare the flat approach `RANKS` versus e.g. `HTD-DAG` by averaging the performance across `3` folds:

```
## FLAT
PRC.flat <- AUPRC.single.over.classes(L, S, folds=3, seed=1);
AUC.flat <- AUROC.single.over.classes(L, S, folds=3, seed=1);
PXR.flat <- precision.at.given.recall.levels.over.classes(L, S, recall.
↪levels=seq(from=0.1, to=1, by=0.1), folds=3, seed=1);
FMM.flat <- compute.Fmeasure.multilabel(L, S, n.round=3, f.criterion="F",␣
↪verbose=FALSE, b.per.example=TRUE, folds=3, seed=1);

## HIERARCHICAL
PRC.hier <- AUPRC.single.over.classes(L, S.htd, folds=3, seed=1);
AUC.hier <- AUROC.single.over.classes(L, S.htd, folds=3, seed=1);
PXR.hier <- precision.at.given.recall.levels.over.classes(L, S.htd, recall.
↪levels=seq(from=0.1, to=1, by=0.1), folds=3, seed=1);
FMM.hier <- compute.Fmeasure.multilabel(L, S.htd, n.round=3, f.criterion="F",␣
↪verbose=FALSE, b.per.example=TRUE, folds=3, seed=1);
```

By looking at the results we can see that `HTD-DAG` outperforms the flat classifier `RANKS`:

```
## AUC performance: flat vs hierarchical
 AUC.flat$average
 [1] 0.8263
 AUC.hier$average
 [1] 0.8312

 ## PRC performance: flat vs hierarchical
 PRC.flat$average
 [1] 0.4373
 PRC.hier$average
 [1] 0.4827
```

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```
## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.7071 0.6443 0.6853 0.6743 0.5768 0.7314 0.7020
FMM.hier$average
   P      R      S      F      avF    A      T
0.5087 0.9394 0.4430 0.6600 0.5922 0.6570 0.4457

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5872 0.5872 0.5872 0.5715 0.5715 0.4487 0.4361 0.4361 0.4361 0.4361
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6465 0.6465 0.6465 0.6227 0.6227 0.4996 0.4897 0.4897 0.4897 0.4897
```

Note: HTD-DAG is the simplest ensemble approach among those available. HTD-DAG strategy makes flat scores consistent with the hierarchy by propagating from to top to the bottom of the hierarchy the negative predictions. Hence, in the worst case might happen that the predictions at leaves nodes are all negatives. Other ensemble variants (such as GPAV-DAG and TPR-DAG and its variants) lead to better improvements.

4.6 Running Experiments with the Hierarchical Ensemble Methods

The HEMDAG library provides also high-level functions for batch experiments, where input and output data must be stored in compressed rda files. In this way we can run experiment with different ensemble variants by properly changing the arguments of high-level functions implemented in HEMDAG:

1. **Do.HTD**: high-level function to run experiments with HTD-DAG algorithm;
2. **Do.GPAV**: high-level function to run experiments with GPAV-DAG algorithm;
3. **Do.TPR.DAG**: high-level function to run experiments with all TPR-DAG variants;
4. **Do.HTD.holdout**: high-level function to run hold-out experiment with HTD-DAG algorithm;
5. **Do.GPAV.holdout**: high-level function to run hold-out experiment with GPAV-DAG algorithm;
6. **Do.TPR.DAG.holdout**: high-level function to run hold-out experiment with all TPR-DAG variants;

The normalization can be applied on-the-fly within the ensemble high-level function or can be pre-computed through the function Do.flat.scores.normalization. Please have a look to the reference manual for further details on this function.

4.6.1 Cross-Validated Experiments

Here we perform several experiments by using the high-level functions, which provide an user-friendly interface to facilitate the execution of hierarchical ensemble methods.

Data Preparation

For the following experiments we store the input data (i.e. the flat scores matrix `S`, the graph `g` and the annotation table `L`) in the directory `data` and the output data (i.e. the hierarchical scores matrix and the performances) in the folder `results`:

```
# load data
data(graph);
data(scores);
data(labels);

if(!dir.exists("data"))
    dir.create("data");

if(!dir.exists("results"))
    dir.create("results");

# store data
save(g,file="data/graph.rda");
save(L,file="data/labels.rda");
save(S,file="data/scores.rda");
```

HTD-DAG Experiments

Here we perform exactly the same experiment that we did above, but using this time the high-level `Do.HTD` to compute the `HTD-DAG` algorithm:

```
Do.HTD( norm=FALSE, norm.type="MaxNorm", folds=3, seed=1, n.round=3, f.criterion="F",
        recall.levels=seq(from=0.1, to=1, by=0.1), flat.file="scores", ann.file=
↪"labels",
        dag.file="graph", flat.dir="data/", ann.dir="data/", dag.dir="data/",
        hierScore.dir="results/", perf.dir="results/", compute.performance=TRUE);
```

Obviously the results returned by `Do.HTD` are identical to those obtained by the step-by-step experiment performed above:

```
load("results/PerfMeas.MaxNorm.scores.hierScores.HTD.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8263
AUC.hier$average
[1] 0.8312

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.4373
PRC.hier$average
[1] 0.4827

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.7071 0.6443 0.6853 0.6743 0.5768 0.7314 0.7020
FMM.hier$average
   P      R      S      F      avF    A      T
```

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```
0.5087 0.9394 0.4430 0.6600 0.5922 0.6570 0.4457

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5872 0.5872 0.5872 0.5715 0.5715 0.4487 0.4361 0.4361 0.4361 0.4361
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6465 0.6465 0.6465 0.6227 0.6227 0.4996 0.4897 0.4897 0.4897 0.4897
```

Note: All the high-level functions running ensemble-based algorithms automatically remove the root node from the annotation matrix, the flat and the hierarchical scores matrix before computing performance metrics.

GPAV-DAG Experiments

Burdakov et al. in [Burdakov06] proposed an approximate algorithm, named GPAV, to solve the *isotonic regression* (IR) or *monotonic regression* (MR) problem in its general case (i.e. partial order of the constraints). GPAV algorithm combines both low computational complexity (estimated to be $\mathcal{O}(|V|^2)$) and high accuracy.

To run experiments with GPAV-DAG we must type, for instance:

```
Do.GPAV( norm=FALSE, norm.type= "MaxNorm", W=NULL, parallel=TRUE, ncores=7,
         folds=3, seed=1, n.round=3, f.criterion ="F", flat.file="scores",
         recall.levels=seq(from=0.1, to=1, by=0.1), ann.file="labels",
         dag.file="graph", flat.dir="data/", ann.dir="data/", dag.dir="data/",
         hierScore.dir="results/", perf.dir="results/", compute.performance=TRUE);
```

By loading the GPAV-DAG performance results we can see that this ensemble variant outperforms the flat classifier RANKS:

```
load("results/PerfMeas.MaxNorm.scores.hierScores.GPAV.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8263
AUC.hier$average
[1] 0.8438

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.4373
PRC.hier$average
[1] 0.5201

## F-score performance: flat vs hierarchical
FMM.flat$average
     P      R      S      F    avF      A      T
0.7071 0.6443 0.6853 0.6743 0.5768 0.7314 0.7020
FMM.hier$average
     P      R      S      F    avF      A      T
0.5893 0.8581 0.5311 0.6988 0.6009 0.6983 0.5360

## Precision at different recall levels: flat vs hierarchical
```

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```
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9      1
0.5872 0.5872 0.5872 0.5715 0.5715 0.4487 0.4361 0.4361 0.4361 0.4361
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9      1
0.6976 0.6976 0.6976 0.6835 0.6835 0.5214 0.5005 0.5005 0.5005 0.5005
```

TPR-DAG and ISO-TPR experiments

TPR-DAG is a family of algorithms in according to the chosen bottom-up and top-down approach. There are both parametric and non-parametric variants. To change variant is sufficient to modify the argument of the following parameters of the Do.TPR.DAG high-level function:

- threshold;
- weight;
- positive;
- topdown;
- bottomup;

Please refer to the reference manual for further details about these parameters.

By replacing GPAV-DAG with HTD-DAG in the top-down step of TPR-DAG (variable topdown), we design the ISO-TPR algorithm. The most important feature of ISO-TPR is that it maintains the hierarchical constraints by construction and selects the closest solution (in the least square sense) to the bottom-up predictions that obey the *true path rule*, the logical and biological rule that govern the bio-ontology, such as HPO and GO.

Below we perform several experiments by playing with different TPR-DAG and ISO-TPR ensemble variants. In all the experiments, the performances were averaged across 3 folds.

Note: In Do.TPR-DAG high-level function the parameter kk refers to the number of folds of the cross validation on which tuning the parameters of the *parametric* variants of the hierarchical ensemble algorithms, whereas the parameter folds refers to number of folds of the cross validation on which computing the performance metrics averaged across folds. For the non-parametric variants (i.e. if bottomup = threshold.free), Do.TPR-DAG automatically set to zero the parameters kk and folds.

---

1. ISOtprT: flat scores matrix normalized by MaxNorm, *positive* **children** selection (normalizing the threshold on AUPRC (PRC) across 5 folds, parameter kk=5) and by applying GPAV-DAG strategy in the top-down step

```
Do.TPR.DAG( threshold=seq(0.1,0.9,0.1), weight=0, kk=5, folds=3, seed=1, norm=FALSE,
            norm.type="MaxNorm", positive="children", bottomup="threshold", topdown=
↪"GPAV",
            n.round=3, f.criterion="F", metric="PRC", recall.levels=seq(from=0.1,␣
↪to=1, by=0.1),
            flat.file="scores", ann.file="labels", dag.file="graph", flat.dir="data/",
            ann.dir="data/", dag.dir="data/", hierScore.dir="results/",
            perf.dir="results/", compute.performance=TRUE);
```

2. ISOdescensTF: flat scores matrix normalized by MaxNorm, *positive* **descendants** selection (without threshold) and by applying GPAV-DAG strategy in the top-down step

```
Do.TPR.DAG( threshold=0, weight=0, kk=NULL, folds=3, seed=73, norm=FALSE, norm.type=
↪"MaxNorm",
            positive="descendants", bottomup="threshold.free", topdown="GPAV", n.
↪round=3,
            f.criterion="F", metric=NULL, recall.levels=seq(from=0.1, to=1, by=0.1),
            flat.file="scores", ann.file="labels", dag.file="graph", flat.dir="data/",
            ann.dir="data/", dag.dir="data/", hierScore.dir="results/",
            perf.dir="results/", compute.performance=TRUE);
```

3. `ISOdescensTAU`: flat scores matrix normalized by `Qnorm`, *positive* **descendants** selection (maximizing the threshold on the `F-score` (`FMAX`) across `5` folds, parameter `kk=5`)and by applying `GPAV-DAG` strategy in the top-down step

```
Do.TPR.DAG( threshold=seq(0.1,0.9,0.1), weight=0, kk=5, folds=3, seed=1, norm=FALSE,
            norm.type="Qnorm", positive="descendants", bottomup="tau", topdown="GPAV",
            n.round=3, f.criterion="F", metric="FMAX", flat.file="scores",
            ann.file="labels", recall.levels=seq(from=0.1, to=1, by=0.1),
            dag.file="graph", flat.dir="data/", ann.dir="data/", dag.dir="data/",
            hierScore.dir="results/", perf.dir="results/", compute.performance=TRUE);
```

4. `tprT`: flat scores matrix normalized by `Qnorm`, *positive* **children** selection (maximizing the threshold on the `F-score` (`FMAX`) across `5` folds, parameter `kk=5`) and by applying `HTD-DAG` strategy in the top-down step

```
Do.TPR.DAG( threshold=seq(0.1,0.9,0.1), weight=0, kk=5, folds=3, seed=1, norm=FALSE,
            norm.type="Qnorm", positive="children", bottomup="threshold", topdown="HTD
↪",
            n.round=3, f.criterion="F", metric="FMAX", recall.levels=seq(from=0.1,␣
↪to=1, by=0.1),
            flat.file="scores", ann.file="labels", dag.file="graph", flat.dir="data/",
            ann.dir="data/", dag.dir="data/", hierScore.dir="results/",
            perf.dir="results/", compute.performance=TRUE);
```

5. `descensW`: flat scores matrix normalized by `MaxNorm`,*positive* **descendants** selection (maximizing the weight on the `F-score` (`FMAX`) across `5` folds, parameter `kk=5`) and by applying `HTD-DAG` strategy in the top-down step

```
Do.TPR.DAG( threshold=0, weight=seq(0.1,0.9,0.1), kk=5, folds=3, seed=1, norm=FALSE,
            norm.type="MaxNorm", positive="descendants", bottomup="weighted.threshold.
↪free",
            topdown="GPAV", n.round=3, f.criterion="F", metric="FMAX", flat.file=
↪"scores",
            recall.levels=seq(from=0.1, to=1, by=0.1), ann.file="labels", dag.file=
↪"graph",
            flat.dir="data/", ann.dir="data/", dag.dir="data/", hierScore.dir=
↪"results/",
            perf.dir="results/", compute.performance=TRUE);
```

6. `descensTF`: flat scores matrix normalized by `Qnorm`, *positive* **descendants** selection (without threshold) and by applying `HTD-DAG` strategy in the top-down step

```
Do.TPR.DAG( threshold=0, weight=0, kk=NULL, folds=3, seed=1, norm=FALSE,
            norm.type="Qnorm", positive="descendants", bottomup="threshold.free",
            topdown="HTD", n.round=3, f.criterion="F", metric=NULL, flat.file="scores
↪",
            recall.levels=seq(from=0.1, to=1, by=0.1), ann.file="labels", dag.file=
↪"graph",
            flat.dir="data/", ann.dir="data/", dag.dir="data/", hierScore.dir=
↪"results/",
```

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```
            perf.dir="results/", compute.performance=TRUE);
```

For instance, by loading the results of the `ISOtprT`, we can see that also this variant improves upon `RANKS` performances:

```
load("results/PerfMeas.MaxNorm.scores.hierScores.ISOtprT.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8263
AUC.hier$average
[1] 0.8446

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.4373
PRC.hier$average
[1] 0.5485

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.7071 0.6443 0.6853 0.6743 0.5768 0.7314 0.7020
FMM.hier$average
   P      R      S      F      avF    A      T
0.6007 0.8747 0.5261 0.7122 0.6224 0.7025 0.5827

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5872 0.5872 0.5872 0.5715 0.5715 0.4487 0.4361 0.4361 0.4361 0.4361
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.7043 0.7043 0.7043 0.6876 0.6876 0.5401 0.5219 0.5219 0.5219 0.5219
```

Obozinski Heuristic Methods experiments

`HEMDAG` implements also three heuristics ensemble methods (`AND`, `MAX`, `OR`) proposed in [Obozinski08]. Experiments with these variants can be performed exactly in the same way as done above. Please see the high-level function `Do.heuristic.methods` in the reference manual to further details about how to run experiments with the Obozinski's heuristic ensemble-variants.

4.6.2 Hold-out Experiments

`HEMDAG` library allows to do also classical hold-out experiments. Respect to the cross-validated experiments performed above, we only need to load the indices of the examples to be used in the test set:

```
data(test.index);
save(test.index, file="data/test.index.rda");
```

Now we can perform hold-out experiments. In all the experiments shown below, the performances were computed one-shot (`folds=NULL`). We store the results in the directory `results_ho`:

```
if(!dir.exists("results_ho"))
    dir.create("results_ho");
```

HTD-DAG Experiments: Hold-out Version

```
Do.HTD.holdout( norm=FALSE, norm.type="MaxNorm", n.round=3, f.criterion ="F",␣
↪folds=NULL,
                seed=NULL, recall.levels=seq(from=0.1, to=1, by=0.1), flat.file=
↪"scores",
                ann.file="labels", dag.file="graph", flat.dir="data/", ann.dir="data/
↪",
                dag.dir="data/", ind.test.set="test.index", ind.dir="data/",
                hierScore.dir="results_ho/", perf.dir="results_ho/",
                compute.performance=TRUE);
```

By looking at the performances we can see that HTD-DAG outperforms RANKS:

```
load("results_ho/PerfMeas.MaxNorm.scores.hierScores.HTD.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8621
AUC.hier$average
[1] 0.8997

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.2789
PRC.hier$average
[1] 0.4504

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.5952 0.8182 0.4190 0.6891 0.6404 0.7424 0.3770
FMM.hier$average
   P      R      S      F      avF    A      T
0.5589 0.9444 0.2824 0.7023 0.6506 0.6818 0.3590

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4424 0.4424 0.4424 0.4379 0.4379 0.3708 0.3621 0.3621 0.3621 0.3621
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6629 0.6629 0.6629 0.6174 0.6174 0.4698 0.4547 0.4547 0.4547 0.4547
```

GPAV-DAG Experiments: Hold-out Version

```
Do.GPAV.holdout( norm=FALSE, norm.type="MaxNorm", n.round=3, f.criterion ="F",␣
↪folds=NULL,
                 seed=NULL, recall.levels=seq(from=0.1, to=1, by=0.1), flat.file=
↪"scores",
                 ann.file="labels", dag.file="graph", flat.dir="data/", ann.dir="data/
↪",
```

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```
                dag.dir="data/", ind.test.set="test.index", ind.dir="data/",
                hierScore.dir="results_ho/", perf.dir="results_ho/",
                compute.performance=TRUE);
```

By looking at the performances we can see that GPAV-DAG outperforms the flat classifier RANKS:

```
load("results_ho/PerfMeas.MaxNorm.scores.hierScores.GPAV.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8621
AUC.hier$average
[1] 0.8925

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.2789
PRC.hier$average
[1] 0.3427

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.5952 0.8182 0.4190 0.6891 0.6404 0.7424 0.3770
FMM.hier$average
   P      R      S      F      avF    A      T
0.6952 0.8889 0.4606 0.7802 0.7239 0.8030 0.4370

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4424 0.4424 0.4424 0.4379 0.4379 0.3708 0.3621 0.3621 0.3621 0.3621
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5341 0.5341 0.5341 0.5250 0.5250 0.4333 0.4273 0.4273 0.4273 0.4273
```

TPR-DAG and ISO-TPR Experiments: Hold-out Version

Note: Similarly as done in the Do.TPR-DAG also in the hold-out version of the high-level function (Do.TPR-DAG.holdout), the parameter kk refers to the number of folds of the cross validation on which tuning the parameters of the *parametric* variants of the hierarchical ensemble algorithms, whereas the parameter folds refers to number of folds of the cross validation on which computing the performance metrics averaged across folds. For the non-parametric variants (i.e. if bottomup = threshold.free), Do.TPR-DAG.holdout automatically set to zero the parameters kk and folds.

1. descensT: flat scores matrix normalized by MaxNorm, *positive* **descendants** selection (maximizing the threshold on the AUPRC (PRC) across 5 folds, parameters kk=5) and by applying HTD-DAG strategy in the top-down step

```
Do.TPR.DAG.holdout( threshold=seq(0.1,0.9,0.1), weight=0, kk=5, folds=NULL, seed=1,␣
↪norm=FALSE,
                    norm.type="MaxNorm", positive="descendants", bottomup="threshold",
                    topdown="HTD", recall.levels=seq(from=0.1, to=1, by=0.1), n.
↪round=3,
```

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```
                    f.criterion="F", metric="PRC", flat.file="scores", ann.file=
↪"labels",
                    dag.file="graph", flat.dir="data/", ann.dir="data/", dag.dir=
↪"data/",
                    ind.test.set="test.index", ind.dir="data/", hierScore.dir=
↪"results_ho/",
                    perf.dir="results_ho/", compute.performance=TRUE);
```

2. `ISOdescensT`: flat scores matrix normalized by `MaxNorm`, *positive* **descendants** selection (maximizing the threshold on the `AUPRC` – `PRC` across `5` folds – `kk=5`) and by applying `GPAV-DAG` strategy in the top-down step

```
Do.TPR.DAG.holdout( threshold=seq(0.1,0.9,0.1), weight=0, kk=5, folds=NULL, seed=1,␣
↪norm=FALSE,
                    norm.type="MaxNorm", positive="descendants", topdown="GPAV",
                    bottomup="threshold", n.round=3, recall.levels=seq(from=0.1, to=1,
↪ by=0.1),
                    f.criterion="F", metric="FMAX", flat.file="scores", ann.file=
↪"labels",
                    dag.file="graph", flat.dir="data/", ann.dir="data/", dag.dir=
↪"data/",
                    ind.test.set="test.index", ind.dir="data/", hierScore.dir=
↪"results_ho/",
                    perf.dir="results_ho/", compute.performance=TRUE);
```

For instance, by loading the results of the `descensT` variant, we can see that this ensemble variant improves upon `RANKS` performances:

```
load("results_ho/PerfMeas.MaxNorm.scores.hierScores.descensT.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8621
AUC.hier$average
[1] 0.8789

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.2789
PRC.hier$average
[1] 0.5482

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.5952 0.8182 0.4190 0.6891 0.6404 0.7424 0.3770
FMM.hier$average
   P      R      S      F      avF    A      T
0.7481 0.8889 0.5532 0.8125 0.7809 0.8788 0.5510

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4424 0.4424 0.4424 0.4379 0.4379 0.3708 0.3621 0.3621 0.3621 0.3621
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.7538 0.7538 0.7538 0.6932 0.6932 0.4851 0.4796 0.4796 0.4796 0.4796
```

Obozinski Heuristic Methods experiments: Hold-out Version

Hold-out experiments with the three Obozinski heuristic variants can be performed exactly in the same way as done above. Please see the high-level function `Do.heuristic.methods.holdout` in the reference manual to further details about how to run experiments with the Obozinski's heuristic ensemble-variants.

4.7 Hierarchical Prediction of GO terms

Let us show now a step-by-step application of `HEMDAG` to the hierarchical prediction of protein function by using the model organism `DROME` (*D. melanogaster*).

Note: For the sake of space here we show experiments with the ensemble-based hierarchical learning algorithms `GPAV` and `ISO-TPR`. However, any other ensemble-based variants executed for the `HPO`-term prediction and more in general listed in the `HEMDAG` library can be also applied for the `GO`-term prediction.

4.8 Data Description

The data used in the experiments shown below can be downloaded at the following link.

1. `7227_DROME_GO_MF_DAG_STRING_v10.5_20DEC17.rda`: object of class `graphNEL` that represents the hierarchy of terms of the `GO` subontology *Molecular Function* (`MF`). This `DAG` has `1736` nodes (`GO` terms) and `2295` edges (between-term relationships). From the `GO` obo file (December 2017 release) we extracted both the `is_a` and the `part_of` relationships, since it is safe grouping annotations by using both these `GO` relationships.

2. `7227_DROME_GO_MF_ANN_STRING_v10.5_20DEC17.rda`: annotation matrix in which the transitive closure of annotation was performed. Rows correspond to `STRING-ID` and columns to `GO` terms. If `T` represents the annotation table, `i` a protein and `j` a `GO` term, `T[i,j]=1` means that the protein `i` is annotated with the term `j`, `T[i,j]=0` means that protein `i` is not annotated with the term `j`. We downloaded the `GO` labels from the Gene Ontology Annotation (GOA) website (December 2017 release). We extracted just the experimentally supported annotations, i.e. the annotations that are directly supported by experimental evidences. The Experimental Evidence codes used to annotate the proteins are the following: (*i*) Inferred from Experiment (`EXP`); (*ii*) Inferred from Direct Assay (`IDA`); (*iii*) Inferred from Physical Interaction (`IPI`); (*iv*) Inferred from Mutant Phenotype (`IMP`); (*v*) Inferred from Genetic Interaction (`IGI`); (*vi*) Inferred from Expression Pattern (`IEP`). Annotation matrix size: `13702 X 1736`.

3. `Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.5fcv.rda`: flat scores matrix representing the probability (or a score) that a gene product `i` belong to a given functional class `j`. The higher the value, the higher the probability that a protein belongs to a given `GO` terms. This flat scores matrix was obtained by running the caret (Classification And REgression Training) *R* package (link). As flat classifier we used the `LogitBoost` setting the number of boosting iterations to `10` (i.e., we used the default parameter setting). The protein-protein interaction network used to create this flat scores matrix was downloaded from the STRING website (version 10.5). We evaluated the generalization performance of the `LogitBoost` classifier, cross-validating the model on the fourth-fifths of the data (training set) and evaluating the performance on the remaining one-fifths (test data). More precisely we created stratified-folds, that is folds containing the same amount of positives and negatives examples (i.e., proteins). In addition, to reduce the empirical temporal complexity, during the training phase, we selected from the `STRING` network the first `100` top-ranked features by using the classical Pearson's correlation coefficient. The supervised feature selection method was cross-validated in an unbiased way, since we chose the

top-ranked features during the training phase and then we used the selected features in the test phase. However this entails to repeat the feature selection 'on the fly' in each training fold of the cross-validation, with a consequent selection of diverse top-ranked features in every training set. Finally, in order to avoid the prediction of GO terms having too few annotations for a reliable assessment, we considered only those classes having 10 or more annotations, obtaining so a flat scores matrix having 13702 rows (STRING-ID) and 327 columns (GO terms). It is worth noting that by adopting a stratified 5-fold cross-validation and taking into account only those GO terms having more than 10 annotations, we guaranteed to have at least 2 positive instances in each training fold of the cross-validation.

4.9 Running Experiments with the Hierarchical Ensemble Methods

Let us start to play with the ensemble-based hierarchical learning algorithms GPAV and ISO-TPR to predict the protein function of the model organism DROME.

4.10 Loading the Data

We load the input data (i.e. the flat scores matrix S, the graph g and the annotation table ann) and we store them in the directory data. The output data (i.e. the hierarchical scores matrix and the performances) will be store in the folder results:

```
# load input data
load(url("https://raw.githubusercontent.com/marconotaro/HEMDAG/master/docs/data/7227_
↪DROME_GO_MF_DAG_STRING_v10.5_20DEC17.rda"));
load(url("https://raw.githubusercontent.com/marconotaro/HEMDAG/master/docs/data/7227_
↪DROME_GO_MF_ANN_STRING_v10.5_20DEC17.rda"));
load(url("https://raw.githubusercontent.com/marconotaro/HEMDAG/master/docs/data/
↪Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.5fcv.rda"));

if(!dir.exists("data"))
    dir.create("data");

if(!dir.exists("results"))
    dir.create("results");

# store data
save(g,file="data/7227_DROME_GO_MF_DAG_STRING_v10.5_20DEC17.rda");
save(ann,file="data/7227_DROME_GO_MF_ANN_STRING_v10.5_20DEC17.rda");
save(S,file="data/Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.5fcv.rda");
```

4.11 Cross-Validated Experiments

In the same way we carried-out the experiments shown in section *Cross-Validated Experiments* for the prediction of human gene-abnormal phenotype associations, below we perform the experiments for the prediction of functions of DROME proteins by using the Gene Ontology annotations as protein labels. In all the experiments shown below the flat scores matrix was normalized in the sense of the maximum, i.e. the score of each GO term was normalized by dividing the score values for the maximum score of that class (variable `norm.type = MaxNorm`).

Note: All the high-level functions in the HEMDAG library check if the number of classes between the flat scores matrix and the annotation matrix mismatched. If that happen, the number of terms of the annotation matrix is shrunk to the

number of terms of the flat scores matrix and the corresponding subgraph is computed as well. It is assumed that all the nodes of the subgraph are accessible from the root.

First of all, we need to load the `HEMDAG` library and set the path of input files and the directories where to store the results:

```
# loading library
library(HEMDAG);

# setting variables
dag.dir <- flat.dir <- ann.dir <- "data/";
hierScore.dir <- perf.dir <- "results/";
dag.file <- "7227_DROME_GO_MF_DAG_STRING_v10.5_20DEC17";
ann.file <- "7227_DROME_GO_MF_ANN_STRING_v10.5_20DEC17";
flat.file <- "Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.5fcv";
```

4.11.1 GPAV Experiments

Now we can run the `GPAV` high-level function:

```
Do.GPAV( norm=FALSE, norm.type= "MaxNorm", W=NULL, parallel=TRUE, ncores=7,␣
↪folds=NULL,
         seed=NULL, n.round=3, f.criterion ="F", recall.levels=seq(from=0.1, to=1,␣
↪by=0.1),
         flat.file=flat.file, ann.file=ann.file, dag.file=dag.file, flat.dir=flat.dir,
         ann.dir=ann.dir, dag.dir=dag.dir, hierScore.dir=hierScore.dir,
         perf.dir=perf.dir, compute.performance=TRUE);
```

By looking at the results it easy to see that the learning algorithm `GPAV` outperforms the flat classifier `LogitBoost`:

```
load("results/PerfMeas.MaxNorm.Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.
↪5fcv.hierScores.GPAV.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8211
AUC.hier$average
[1] 0.8552

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.1995
PRC.hier$average
[1] 0.2352

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.4255 0.5515 0.9781 0.4803 0.4055 0.9684 0.1190
FMM.hier$average
   P      R      S      F      avF    A      T
0.4837 0.5582 0.9830 0.5183 0.4398 0.9735 0.1080

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
```

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```
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4053 0.3349 0.2795 0.2304 0.1839 0.1349 0.0911 0.0597 0.0314 0.0105
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4687 0.3896 0.3356 0.2924 0.2352 0.1778 0.1223 0.0797 0.0401 0.0119
```

4.11.2 ISO-TPR Experiments

Here we run some `ISO-TPR` variants:

1. `ISOtprTF`: *positive* **children** selection (without threshold)

```
Do.TPR.DAG( threshold=0, weight=0, kk=NULL, folds=NULL, seed=NULL, norm=FALSE,
            norm.type="MaxNorm", positive="children", bottomup="threshold.free",␣
↪topdown="GPAV",
            W=NULL, parallel=TRUE, ncores=7, n.round=3, f.criterion="F", metric=NULL,
            recall.levels=seq(from=0.1, to=1, by=0.1), flat.file=flat.file, ann.
↪file=ann.file,
            dag.file=dag.file, flat.dir=flat.dir, ann.dir=ann.dir, dag.dir=dag.dir,
            hierScore.dir=hierScore.dir, perf.dir=perf.dir, compute.performance=TRUE);
```

By looking at the results we can see that our ensemble-based algorithm `ISOtprTF` outperforms the flat classifier `LogitBoost`:

```
load("results/PerfMeas.MaxNorm.Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.
↪5fcv.hierScores.ISOtprTF.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8211
(AUC.hier$average
[1] 0.8544

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.1995
PRC.hier$average
[1] 0.2397

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.4255 0.5515 0.9781 0.4803 0.4055 0.9684 0.1190
FMM.hier$average
   P      R      S      F      avF    A      T
0.4820 0.5652 0.9822 0.5203 0.4413 0.9729 0.1200

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4053 0.3349 0.2795 0.2304 0.1839 0.1349 0.0911 0.0597 0.0314 0.0105
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4764 0.4025 0.3444 0.2938 0.2383 0.1773 0.1226 0.0794 0.0402 0.0119
```

2. `ISOdescensTF`: *positive* **descendants** selection (without threshold)

```
Do.TPR.DAG( threshold=0, weight=0, kk=NULL, folds=NULL, seed=NULL, norm=FALSE,
            norm.type="MaxNorm", positive="descendants", bottomup="threshold.free",
            topdown="GPAV", W=NULL, parallel=TRUE, ncores=7, n.round=3, f.criterion="F
↪",
            metric=NULL, recall.levels=seq(from=0.1, to=1, by=0.1), flat.file=flat.
↪file,
            ann.file=ann.file, dag.file=dag.file, flat.dir=flat.dir, ann.dir=ann.dir,
            dag.dir=dag.dir, hierScore.dir=hierScore.dir,
            perf.dir=perf.dir, compute.performance=TRUE);
```

By looking at the results we can see that our ensemble-based algorithm `ISOdescensTF` outperforms the flat classifier `LogitBoost`:

```
load("results/PerfMeas.MaxNorm.Scores.7227.DROME.GO.MF.pearson.100.feature.LogitBoost.
↪5fcv.hierScores.ISOdescensTF.rda");

## AUC performance: flat vs hierarchical
AUC.flat$average
[1] 0.8211
AUC.hier$average
[1] 0.8549

## PRC performance: flat vs hierarchical
PRC.flat$average
[1] 0.1995
PRC.hier$average
[1] 0.2449

## F-score performance: flat vs hierarchical
FMM.flat$average
   P      R      S      F      avF    A      T
0.4255 0.5515 0.9781 0.4803 0.4055 0.9684 0.1190
FMM.hier$average
   P      R      S      F      avF    A      T
0.4798 0.5683 0.9817 0.5203 0.4406 0.9725 0.1200

## Precision at different recall levels: flat vs hierarchical
PXR.flat$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.4053 0.3349 0.2795 0.2304 0.1839 0.1349 0.0911 0.0597 0.0314 0.0105
PXR.hier$avgPXR
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5023 0.4109 0.3528 0.3027 0.2427 0.1785 0.1226 0.0781 0.0400 0.0118
```

4.12 Hold-out Experiments

For the sake of the space we do not show the hold-out experiments for the `GO` term prediction for the model organism `DROME`, since they can be executed exactly in the same way of the hold-out experiments performed in section *Hold-out Experiments* for the prediction of human gene-`HPO` term associations. All that you need to do is properly set the input files name.

CHAPTER 5

Frequently Asked Questions

5.1 Where are the questions?

Right now, there are no frequently asked questions. Please contact the authors if you have questions.

CHAPTER 6

Cite HEMDAG

If you use this software package please cite our BMC Bioinformatics article:

```
M. Notaro, M. Schubach, P. N. Robinson, and G Valentini.
Prediction of Human Phenotype Ontology terms by means of hierarchical ensemble␣
↪methods.
BMC Bioinformatics, 18(1):449, 2017.
```

CHAPTER 7

Contributing

Contributions are welcome, and they are greatly appreciated! Every little bit helps, and credit will always be given.

You can contribute in many ways:

7.1 Types of Contributions

7.1.1 Report Bugs

Report bugs at https://github.com/marconotaro/HEMDAG/issues

If you are reporting a bug, please include:

- Your operating system name and version.
- Any details about your local setup that might be helpful in troubleshooting.
- Detailed steps to reproduce the bug.

7.1.2 Fix Bugs

Look through the Github issues for bugs. If you want to start working on a bug then please write short message on the issue tracker to prevent duplicate work.

7.1.3 Implement Features

Look through the Github issues for features. If you want to start working on an issue then please write short message on the issue tracker to prevent duplicate work.

7.1.4 Write Documentation

HEMDAG could always use more documentation, whether as part of the official HEMDAG docs, in docstrings, or even on the web in blog posts, articles, and such.

HEMDAG uses Sphinx for the user manual (that you are currently reading). See *doc_guidelines* on how the documentation reStructuredText is used. See *doc_setup* on creating a local setup for building the documentation.

7.1.5 Submit Feedback

The best way to send feedback is to file an issue at https://github.com/marconotaro/HEMDAG/issues

If you are proposing a feature:

- Explain in detail how it would work.
- Keep the scope as narrow as possible, to make it easier to implement.
- Remember that this is a volunteer-driven project, and that contributions are welcome :)

7.2 Documentation Guidelines

For the documentation, please adhere to the following guidelines:

- Put each sentence on its own line, this makes tracking changes through Git SCM easier.
- Provide hyperlink targets, at least for the first two section levels.
- Use the section structure from below.

```
.. heading_1:

=========
Heading 1
=========


.. heading_2:

---------
Heading 2
---------


.. heading_3:

Heading 3
=========


.. heading_4:

Heading 4
---------


.. heading_5:
```

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```
Heading 5
~~~~~~~~~


.. heading_6:

Heading 6
:::::::::
```

7.3 Documentation Setup

For building the documentation, you have to install the Python program Sphinx. We use conda for that, see *Installation via Conda*

Use the following steps for installing Sphinx and the dependencies for building the HEMDAG documentation:

```
$ cd HEMDAG/docs
$ conda create --name sphinx --file environment.yml
$ source activate sphinx
```

Use the following for building the documentation. If you are not in the sphinx environment (e.g. you uses `source deactivate sphinx`) please activate the virtual environment using `source activate sphinx` Afterwards, you can always use `make html` for building.

```
(sphinx) $ cd HEMDAG/docs
(sphinx) $ make html  # rebuild for changed files only
(sphinx) $ make clean && make html  # force rebuild
```

7.4 Get Started!

Ready to contribute?

1. Fork the *HEMDAG* repo on GitHub.
2. Clone your fork locally:

   ```
   $ git clone git@github.com:your_name_here/HEMDAG.git
   ```

3. Create a branch for local development:

   ```
   $ git checkout -b name-of-your-bugfix-or-feature
   ```

   Now you can make your changes locally.

4. When you're done making your changes, make sure that the build runs through.

   ```
   $ cd docs && make clean && make html
   ```

5. Commit your changes and push your branch to GitHub:

```
$ git add .
$ git commit -m "Your detailed description of your changes."
$ git push origin name-of-your-bugfix-or-feature
```

7. Submit a pull request through the GitHub website.

7.5 Pull Request Guidelines

Before you submit a pull request, check that it meets these guidelines:

1. The pull request should include tests.
2. If the pull request adds functionality, the docs should be updated.
3. Describe your changes in the `CHANGELOG` file.

CHAPTER 8

Authors

in alphabetical order

- Marco Notaro
- Max Schubach
- Giorgio Valentini

CHAPTER 9

History

```
#### HEMDAG 2.6.0

###### CHANGES
- fixed NAMESPACE notes in CRAN checks;
- added link to the GitHub repository ``obogaf::parser``;
- adjusted link to read the docs;

#### HEMDAG 2.5.9

###### NEW FEATURES
- added ``build.consistent.graph``;

###### CHANGES
- added some warning checks in functions that compute performance metrics;
- improved some graph utility functions;
- improved manual;
- improved tutorial on read the docs -- [link](https://hemdag.readthedocs.io);
- namespace made clearer;
- fixed minor bugs;
- removed defunct functions;

#### HEMDAG 2.4.8

###### CHANGES
- fixed a minor bug in ``Do.GPAV.holdout``;
- improved package description;

#### HEMDAG 2.4.7

###### NEW FEATURES
- fixed degenerate case in ``precision.at.all.recall.levels.single.class`` (labels␣
↪are all negatives/positives);
- fixed degenerate case in ``precision.at.given.recall.levels.over.classes`` (labels␣
↪in a fold are all negatives/positives);
```

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```
- fixed degenerate case in ``do.stratified.cv.data.single.class`` (sampling of the␣
↪labels with just one positive/negative);
- added input variable ``compute.performance`` to the following high level functions:
    - ``Do.TPR.DAG`` and ``Do.TPR.DAG.holdout``;
    - ``Do.HTD`` and ``Do.HTD.holdout``;
    - ``Do.GPAV`` and ``Do.GPAV.holdout``;
    - ``Do.heuristic.methods`` and ``Do.heuristic.methods.holdout``;

###### CHANGES
- improved manual;

#### HEMDAG 2.3.6

###### NEW FEATURES
- added ``lexicographical.topological.sort``;

###### CHANGES
- fixed minor bugs;
- improved manual;

#### HEMDAG 2.2.5

###### NEW FEATURES
- precision-recall performance computed through ``precrec`` package:
    - added ``precision.at.all.recall.levels.single.class``;
    - ``PXR.at.multiple.recall.levels.over.classes`` substituted with ``precision.at.
↪given.recall.levels.over.classes``;
- improved IO functions: the extension of the input or output file can be or plain␣
↪text (``.txt``) or compressed (``.gz``);

###### CHANGES
- fixed minor bugs;
- improved manual;

#### HEMDAG 2.2.4

###### CHANGES
- fixed ``CRAN`` Package Check Results: removed unneeded header and define from␣
↪``GPAV C++`` source code

#### HEMDAG 2.2.3

###### NEW FEATURES
- Added ``GPAV`` algorithm (Burdakov et al., *Journal of Computational Mathematics*,␣
↪2006 -- [link](https://doi.org/10.1007/0-387-30065-1_3));
- Embedded ``GPAV`` algorithm in the top-down step of the functions ``TPR.DAG``, ``Do.
↪TPR.DAG`` and ``Do.TPR.DAG.holdout``;
- Some functions have been defunct. To know the defunct functions just typing in the␣
↪R environment: ``help("HEMDAG-defunct")``;

###### CHANGES
- improved manual;

###### AUTHOR
- Added **Alessandro Petrini** as author for his contribution in writing the ``C++``␣
↪code of ``GPAV`` algorithm;
```

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```
#### HEMDAG 2.1.3

###### CHANGES
- various fixes from 2.1.2

#### HEMDAG 2.1.2

###### NEW FEATURES
- Improved performance metrics:
    - added ``compute.Fmeasure.multilabel``;
    - added ``PXR.at.multiple.recall.levels.over.classes``;
    - all the performance metrics (``AUPRC``, ``AUROC``, ``FMM``, ``PXR``) can be␣
↪computed either **one-shot** or averaged **across folds**;

- Improved the high-level hierarchical ensemble functions:
    - embedded the new performance metric functions;
    - added the parameter ``metric``: maximization by ``FMAX`` or ``PRC`` (see manual␣
↪for further details);
    - added some checkers (warning/stop messages) to make the library more user-
↪friendly;

###### CHANGES
- improved manual;

#### HEMDAG 2.0.1

###### CHANGES
- fixed bug in ``do.stratified.cv.data.single.class``;

#### HEMDAG 2.0.0

###### NEW FEATURES
- Added ``TPR-DAG``: function gathering several hierarchical ensemble variants;
- Added ``Do.TPR.DAG``: high-level function to run ``TPR-DAG`` **cross-validated**␣
↪experiments;
- Added ``Do.TPR.DAG.holdout``: high-level functions to run ``TPR-DAG`` **holdout**␣
↪experiments;

- The following ``TPR-DAG`` and ``DESCENS`` high-level functions were removed:
    - Do.tpr.threshold.free;
    - Do.tpr.threshold.cv;
    - Do.tpr.weighted.threshold.free.cv;
    - Do.tpr.weighted.threshold.cv;
    - Do.descens.threshold.free;
    - Do.descens.threshold.cv;
    - Do.descens.weighted.threshold.free.cv;
    - Do.descens.tau.cv;
    - Do.descens.weighted.threshold.cv;
    - Do.tpr.threshold.free.holdout;
    - Do.tpr.threshold.holdout;
    - Do.tpr.weighted.threshold.free.holdout;
    - Do.tpr.weighted.threshold.holdout;
    - Do.descens.threshold.free.holdout;
    - Do.descens.threshold.holdout;
    - Do.descens.weighted.threshold.free.holdout;
    - Do.descens.tau.holdout;
    - Do.descens.weighted.threshold.holdout;
```

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```
> NOTE: all the removed functions can be run opportunely setting the input parameters␣
↪of the new high-level function ``Do.TPR.DAG`` (for **cross-validated** experiments)␣
↪and ``Do.TPR.DAG.holdout`` (for **hold-out** experiments);

###### CHANGES
- improved manual;

#### HEMDAG 1.1.1

###### NEW FEATURES
- Added ``DESCENS`` algorithm;
- Added Heuristic Methods ``MAX``, ``AND``, ``OR`` (Obozinski et al., Genome Biology,␣
↪2008 -- [link](https://genomebiology.biomedcentral.com/articles/10.1186/gb-2008-9-
↪s1-s6));
- Added ``tupla.matrix`` function;

###### CHANGES
- improved manual;
- Added link to the GitHub repository ``HPOparser`` (note: from version ``2.6.0``␣
↪``HPOparser`` was changed in ``obogaf::parser``);
- Added ``CITATION`` file;

#### HEMDAG 1.0.0

###### PACKAGE GENESIS
```

CHAPTER 10

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```
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                       Version 3, 29 June 2007

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  A compilation of a covered work with other separate and independent
works, which are not by their nature extensions of the covered work,
and which are not combined with it such as to form a larger program,
in or on a volume of a storage or distribution medium, is called an
"aggregate" if the compilation and its resulting copyright are not
used to limit the access or legal rights of the compilation's users
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in an aggregate does not cause this License to apply to the other
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  6. Conveying Non-Source Forms.

  You may convey a covered work in object code form under the terms
of sections 4 and 5, provided that you also convey the
machine-readable Corresponding Source under the terms of this License,
in one of these ways:

    a) Convey the object code in, or embodied in, a physical product
    (including a physical distribution medium), accompanied by the
    Corresponding Source fixed on a durable physical medium
    customarily used for software interchange.

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    (including a physical distribution medium), accompanied by a
    written offer, valid for at least three years and valid for as
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    model, to give anyone who possesses the object code either (1) a
    copy of the Corresponding Source for all the software in the
    product that is covered by this License, on a durable physical
    medium customarily used for software interchange, for a price no
    more than your reasonable cost of physically performing this
    conveying of source, or (2) access to copy the
    Corresponding Source from a network server at no charge.

    c) Convey individual copies of the object code with a copy of the
    written offer to provide the Corresponding Source.  This
    alternative is allowed only occasionally and noncommercially, and
    only if you received the object code with such an offer, in accord
    with subsection 6b.

    d) Convey the object code by offering access from a designated
    place (gratis or for a charge), and offer equivalent access to the
    Corresponding Source in the same way through the same place at no
    further charge.  You need not require recipients to copy the
    Corresponding Source along with the object code.  If the place to
    copy the object code is a network server, the Corresponding Source
    may be on a different server (operated by you or a third party)
    that supports equivalent copying facilities, provided you maintain
    clear directions next to the object code saying where to find the
    Corresponding Source.  Regardless of what server hosts the
    Corresponding Source, you remain obligated to ensure that it is
    available for as long as needed to satisfy these requirements.

    e) Convey the object code using peer-to-peer transmission, provided
    you inform other peers where the object code and Corresponding
    Source of the work are being offered to the general public at no
    charge under subsection 6d.

  A separable portion of the object code, whose source code is excluded
from the Corresponding Source as a System Library, need not be
included in conveying the object code work.

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tangible personal property which is normally used for personal, family,
or household purposes, or (2) anything designed or sold for incorporation
into a dwelling.  In determining whether a product is a consumer product,
doubtful cases shall be resolved in favor of coverage.  For a particular
product received by a particular user, "normally used" refers to a
typical or common use of that class of product, regardless of the status
of the particular user or of the way in which the particular user
actually uses, or expects or is expected to use, the product.  A product
is a consumer product regardless of whether the product has substantial
commercial, industrial or non-consumer uses, unless such uses represent
the only significant mode of use of the product.

  "Installation Information" for a User Product means any methods,
procedures, authorization keys, or other information required to install
and execute modified versions of a covered work in that User Product from
a modified version of its Corresponding Source.  The information must
suffice to ensure that the continued functioning of the modified object
code is in no case prevented or interfered with solely because
modification has been made.
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  If you convey an object code work under this section in, or with, or
specifically for use in, a User Product, and the conveying occurs as
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User Product is transferred to the recipient in perpetuity or for a
fixed term (regardless of how the transaction is characterized), the
Corresponding Source conveyed under this section must be accompanied
by the Installation Information.  But this requirement does not apply
if neither you nor any third party retains the ability to install
modified object code on the User Product (for example, the work has
been installed in ROM).

  The requirement to provide Installation Information does not include a
requirement to continue to provide support service, warranty, or updates
for a work that has been modified or installed by the recipient, or for
the User Product in which it has been modified or installed.  Access to a
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adversely affects the operation of the network or violates the rules and
protocols for communication across the network.

  Corresponding Source conveyed, and Installation Information provided,
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