HEMDAG Documentation

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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 *HowTo* guides you from downloading HEMDAG library, load it into your R environment and make first computations.

1.1 Installation

Please go to the *Installation* section and install HEMDAG by using one of the ways shown.

1.2 Load HEMDAG Library

Start R in your console using

```
$ R
```

then load the library by using

```
> library(HEMDAG)
```

1.3 First Classification – for the Impatient

HEMDAG encompasses in total 23 hierarchical ensemble methods. Below we show the *simple* call to all the hierarchical ensemble algorithms included in HEMDAG, bu using the pre-built datasets available in the HEMDAG for making predictions. For more details about datasets and methods have a look to section *Tutorial*.

A. Loading the pre-built dataset of HEMDAG

```
# load the DAG g
> data(graph);

# load the scores matrix S
> data(scores);

# load the annotation matrix L
> data(labels);

# compute the root node
> root <- root.node(g);
```

B. HTD-DAG: Hierarchical Top-Down for DAG

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

C. GPAV: Generalized Pool-Adjacent-Violators

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

D. TPR-DAG (True Path Rule for DAG) and all its 18 ensemble variants

```
> 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);

> 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.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);

> 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);
```

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```
> S.isodescensWT  <- tpr.dag(S, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="gpav", t=0.5, w=0.5);
> S.isodescensTAU <- tpr.dag(S, g, root, positive="descendants", bottomup="tau",␣
↪topdown="gpav", t=0.5);
```

E. Obozisnki heuristic methods

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

CHAPTER 2

Installation

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

2.1 Installation via Conda

This is the recommended way to install HEMDAG for normal users because it will enable you to switch software versions easily. 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 Python3 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 typing in your terminal:

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

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 (link):

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

2.3 Dependencies

To install or build HEMDAG the following dependencies are required:

- R (2.10)
- R dependencies
  - graph (bioconductor)
  - rbgl (bioconductor)
  - precrec
  - preprocessCore (bioconductor)
  - plyr
  - foreach
  - doParallel

Note: CRAN does not automatically install Bioconductor packages. To install them:

```
if(!requireNamespace("BiocManager", quietly=TRUE))
    install.packages("BiocManager")

BiocManager::install("graph")
BiocManager::install("rbgl")
BiocManager::install("preprocessCore")
```

2.4 Installing from Source

Here we describe how to build HEMDAG from scratch.

2.4.1 Package from CRAN

On a Linux environment, download the package source from the CRAN repo and save it (for instance) in the folder `pippo`. Then type:

```
R CMD INSTALL pippo/HEMDAG_<pkg-version-number>.tar.gz
```

Note: Replace `<pkg-version-number>` with the version number of the downloaded HEMDAG package.

2.4.2 Direct Git Checkout

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

Below, we will download the HEMDAG sources and build them in `~/hemdag`:

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

2.4.3 Building

You can build HEMDAG by using:

```
R CMD build hemdag
```

This will generate the file `HEMDAG_<package-version-number>.tar.gz` and just install the package via:

```
R CMD INSTALL HEMDAG_<package-version-number>.tar.gz
```

CHAPTER 3

Usage of HEMDAG

For a detailed description of the functions available in the HEMDAG library please go to the CRAN page and have a look to the reference manual.

CHAPTER 4

Tutorial

In this tutorial 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. However, all the hierarchical ensemble methods encompassed in HEMDAG library can be run by using:

- any ontology listed in OBO foundry (link);
- any flat score matrix, achieved by using any flat classifier ranging from linear, to probabilistic methods, to neural networks, to gradient boosting and many others;
- any annotation matrix.

Of course, the number of terms among the graph, the flat score matrix and the annotation matrix must match.

Note: To run the experiments shown in this page, make sure you have installed the following requirements:

- HEMDAG >= 2.7.4
- R >= 3.4.4
- Ubuntu >= 16.04

4.1 Load the HEMDAG Library

To load the HEMDAG library, open the R environment and type:

```
library(HEMDAG);
```

4.2 Load 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;
- the second step *reconciles* the flat predictions by considering the topology of the underlying ontology.

Consequently, the first *ingredient* that we need in a hierarchical ensemble classification is the flat score matrix. For the sake of simplicity, in the examples shown below we use the pre-built dataset available in the HEMDAG library. To load the flat score matrix, type in the the R environment:

```
data(scores);
```

With the above command we loaded the flat score matrix `S`, that is a named 100 X 23 matrix. Rows correspond to genes (Entrez GeneID) and columns to HPO terms/classes. The scores represent 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 score matrix was obtained by running the RANKS package (link).

4.2.1 Normalization

Since RANKS **returns a score and not a probability**, we must normalize the scores of the matrix `S` to make the flat scores comparable with the hierarchical ones. In case the flat classifier returns directly a probability there is no needed to normalize the flat score matrix, since the flat scores can be directly compared 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:

```
S.maxnorm <- scores.normalization(norm.type="maxnorm", S);
```

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

```
S.qnorm <- scores.normalization(norm.type="qnorm", 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)

Note: For the sake of simplicity, in all the examples shown in section *Hierarchical Ensemble Methods*, the input flat score matrix was normalized according to the `maxnorm` normalization:

```
S.norm <- scores.normalization(norm.type="maxnorm", S);
```

4.3 Load the Graph

In order to know how the hierarchical structure of the HPO terms, we need to load the graph:

```
data(graph);
```

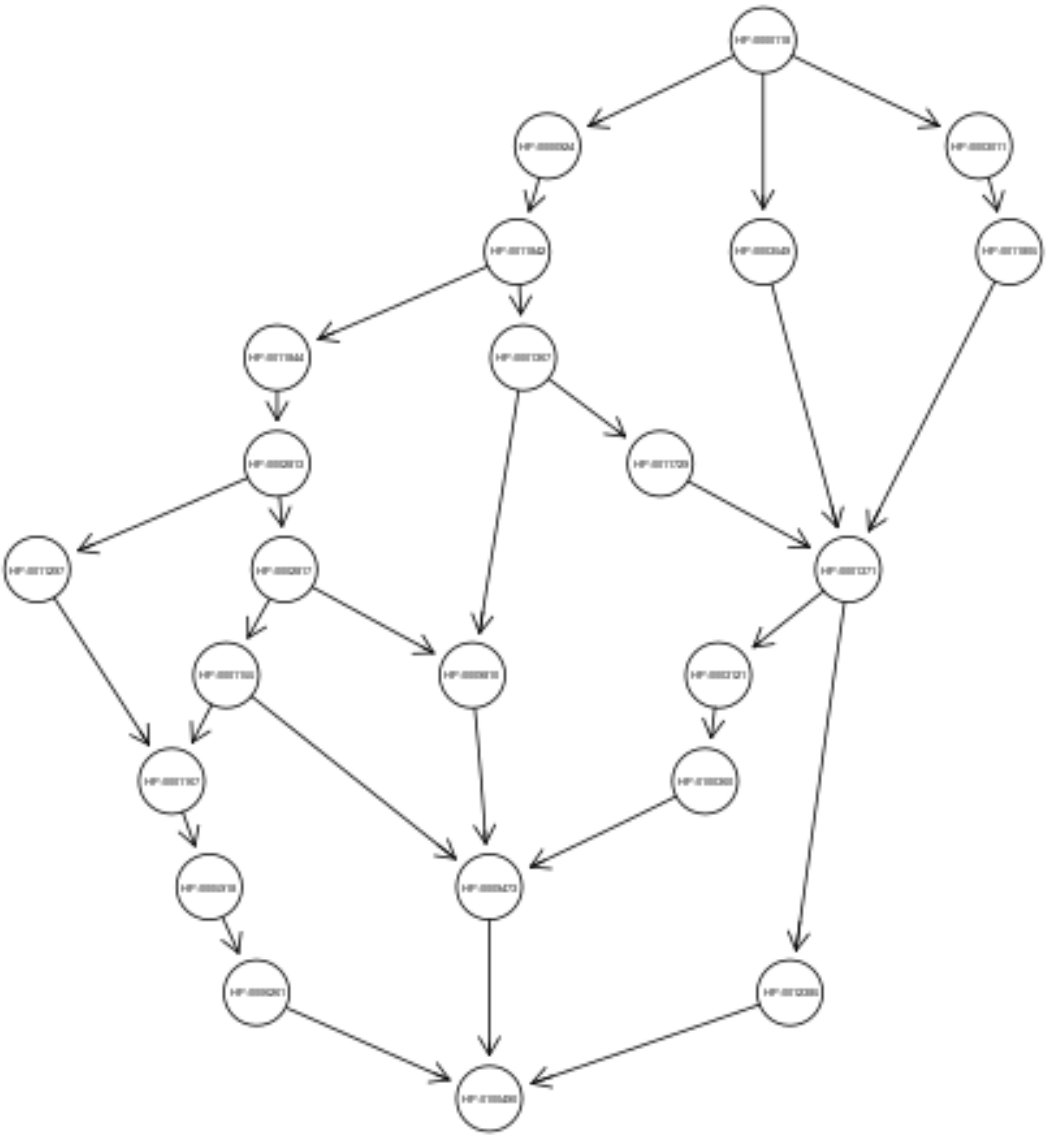
With the above command we loaded the graph `g`, an object of class `graphNEL`. The graph `g` has 23 nodes and 30 edges and represents the *ancestors view* of the HPO term `Camptodactyly of finger` (HP:0100490). Nodes of the graph `g` correspond to terms of the flat score matrix `S`.

4.3.1 Plot the Graph (optional)

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);
```



4.3.2 Utility Functions for Graphs (optional)

HEMDAG includes 33 utility functions (listed below) to process and analyze graphs as well as I/O functions to import a graph as object of class `graphNEL` or to export a graph as object of class `graphNEL` in a plain text file (in the classical tupla format). For more details on these functions, refer to the reference manual.

```
build.ancestors                          build.parents                          ␣
↪constraints.matrix
build.ancestors.bottom.up                build.parents.bottom.up                ␣
↪distances.from.leaves
build.ancestors.per.level                build.parents.top.down                 ␣
↪find.leaves
build.children                           build.parents.topological.sorting      ␣
↪graph.levels
build.children.bottom.up                 build.scores.matrix.from.list          ␣
↪lexicographical.topological.sort
build.children.top.down                  build.scores.matrix.from.tupla         ␣
↪read.graph
build.consistent.graph                   build.subgraph                         ␣
↪read.undirected.graph
build.descendants                        check.dag.integrity                    ␣
↪root.node
build.descendants.bottom.up              check.hierarchy                        ␣
↪tupla.matrix
build.descendants.per.level              check.hierarchy.single.sample          ␣
↪weighted.adjacency.matrix
build.edges.from.hpo.obo                 compute.flipped.graph                  ␣
↪write.graph
```

4.4 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.

4.4.1 HTD-DAG: Hierarchical Top Down for DAG

The HTD-DAG algorithm modifies the flat scores according to the hierarchy of a DAG G through a unique run across the nodes of the graph. For a given example x, the flat predictions $f(x) = \hat{y}$ are hierarchically corrected to $\bar{y}$, by per-level visiting the nodes of the DAG from top to bottom according to the following simple rule:

$$\bar{y}_i := \begin{cases} \hat{y}_i & \text{if} \quad i \in root(G) \\ \min_{j \in par(i)} \bar{y}_j & \text{if} \quad \min_{j \in par(i)} \bar{y}_j < \hat{y}_i \\ \hat{y}_i & \text{otherwise} \end{cases}$$

The node levels correspond to their maximum path length from the root. To call the HTD-DAG algorithm just type:

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

Alternatively, we can call the `htd.vanilla` function (instead of `htd`), which it allows to normalize the flat score matrix `S` (according to **maxnorm** or **qnorm** normalization) *on the fly*:

run a normalization method (between **maxnorm** and **qnrom**) *on the fly*:

```
S.htd <- htd.vanilla(S, g, norm=TRUE, norm.type="maxnorm");
```

Note: In `htd.vanilla`, if `norm=FALSE` and `norm.type=NULL` the flat score matrix `S` is not normalized.

4.4.2 GPAV: Generalized Pool-Adjacent-Violators

Burdakov et al. in [1] 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 $\mathcal{O}(|V|^2)$, where V is the number of nodes of the graph) and high accuracy. Formally, given a vector of observed values $\hat{y} \in R^n$, a strictly positive vector of weights $w \in R^n$ and a dag $G(V, E)$, GPAV finds the vector of fitted values $\bar{y} \in \mathbb{R}^n$ that solves the following convex quadratic program:

$$\begin{array}{ll} \min\limits_{\bar{y}} & \sum\limits_{i \in V} w_i(\bar{y}_i - \hat{y}_i)^2 \\ s.t. & \bar{y}_j \geq \bar{y}_i \quad \forall (i,j) \in E \end{array} \tag{4.1}$$

To call the GPAV algorithm just type:

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

It is worth noting that there is also a parallel version of the GPAV algorithm:

```
S.gpav <- gpav.parallel(S.norm, g, W=NULL, ncores=8);
```

Similarly to HTD-DAG also for GPAV, we can use the function `gpav.vanilla` (instead of `gpav.over.examples` or `gpav.parallel`) to normalize the flat score matrix `S` (according to **maxnorm** or **qnorm** normalization) *on the fly*:

```
S.gpav <- gpav.vanilla(S, g, W=NULL, parallel=TRUE, ncores=8, norm=TRUE, norm.type=
↪"maxnorm");
```

4.4.3 TPR-DAG: True Path Rule for DAG

TPR-DAG is a family of algorithms on the basis of the choice of the **bottom-up** step adopted for the selection of *positive* children. Indeed, in their more general form, the TPR-DAG algorithms adopt a two step learning strategy:

1. in the first step they compute a *per-level bottom-up* visit from leaves to root to propagate *positive* predictions across the hierarchy;
2. in the second step they compute a *per-level top-down* visit from root to leaves in order to assure the consistency of the predictions. In other word, the *HTD-DAG: Hierarchical Top Down for DAG* algorithm is applied.

Note: Levels (both in the first and second step) are defined in terms of the maximum path length from the root node. Please refer to [3] for further details.

The *vanilla* TPR-DAG adopts a per-level bottom-up traversal of the DAG to modify the flat predictions $\hat{y}_i$ according to the following formula:

$$\bar{y}_i := \frac{1}{1+|\phi_i|}(\hat{y}_i + \sum_{j \in \phi_i} \bar{y}_j)$$

where ϕ_i are the positive children of i (parameter `positive="children"`).

Different strategies to select the positive children ϕ_i can be applied:

1. **threshold-free** strategy (parameter `bottom="threshold.free"`): the positive nodes are those children that can increment the score of the node i, that is those nodes that achieve a score higher than that of their parents:

$$\phi_i := \{j \in child(i) | \bar{y}_j > \hat{y}_i\}$$

2. **threshold** strategy (parameter `bottom="threshold"`): the positive children are selected on the basis of a threshold that can be selected in two different ways:

   a) a unique threshold $\bar{t}$ is a priori selected for all nodes to determine the set of positives

$$\phi_i := \{j \in child(i) | \bar{y}_j > \bar{t}\}, \forall i \in V$$

   For instance if the predictions represent probabilities it could be meaningful set $\bar{t} = 0.5$.

   b) a threshold is selected to maximize some imbalance-aware performance metric $\mathcal{M}$ estimated on the training data, as for instance the Fmax or the AUPRC. In other words, the threshold is selected to maximize the measure $\mathcal{M}(j,t)$ on the training data for the term j with respect to the threshold t. The corresponding set of positives for each $i \in V$ is:

$$\phi_i := \{j \in child(i) | \bar{y}_j > t_j^*, t_j^* = \arg\max_t \mathcal{M}(j,t)\}$$

   Internal cross-validation is used to select t_j^* within a set of possible thresholds $t \in (0,1)$;

The weighted TPR-DAG version (parameter `bottom="weighted.threshold.free"`) can be designed by adding a weight $w \in [0,1]$ to balance the contribution of the parent node i and its positive children ϕ:

$$\bar{y}_i := w\hat{y}_i + \frac{(1-w)}{|\phi_i|} \sum_{j \in \phi_i} \bar{y}_j$$

If $w = 1$ no weight is attributed to the children and the TPR-DAG reduces to the HTD-DAG algorithm. If $w = 0$ only the predictors associated to the children nodes vote to predict node i. In the intermediate cases we attribute more importance to the predictor for the node i or to its children depending on the values of w.

By combining the weighted and the threshold variant, we design the *weighted-threshold* variant (parameter `bottom="weighted.threshold"`).

All the *vanilla* TPR-DAG variants use the HTD-DAG algorithm in the top-down step (parameter `topdown="htd"`) to provide ontology-based predictions (i.e. predictions that are coherent with the ontology structure):

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

4.4.4 DESCENS: Descendants Ensemble Classifier

As shown in [5] for tree-based hierarchies, the contribution of the descendants of a given node decays exponentially with their distance from the node itself and it is straightforward to see that this property also holds for DAG structured taxonomies. To overcame this limitation and in order to enhance the contribution of the most specific nodes to the overall decision of the ensemble we design the ensemble variant DESCENS. The novelty of DESCENS consists in strongly considering the contribution of all the descendants of each node instead of only that of its children (`positive="descendants"`). Therefore DESCENS predictions are more influenced by the information embedded in the leaves nodes, that are the classes containing the most informative and meaningful information from a biological and medical standpoint. DESCENS variants can be designed on the choice of the *positive* descendants Δ_i. The same strategies adopted for the choice of ϕ_i can be also adopted for the choice of Δ_i, simply by replacing ϕ_i with Δ_i and $child(i)$ with $desc(i)$ in the various formulas shown in *TPR-DAG: True Path Rule for DAG*. Furthermore, we designed a variant specific only for DESCENS, that we named DESCENS-τ (parameter `bottomup="tau"`). The DESCENS-τ variant balances the contribution between the *positives* children of a node i and that of its *positives* descendants excluding its children by adding a weight $\tau \in [0, 1]$:

$$\bar{y}_i := \frac{\tau}{1+|\phi_i|}(\hat{y}_i + \sum_{j \in \phi_i} \bar{y}_j) + \frac{1-\tau}{1+|\delta_i|}(\hat{y}_i + \sum_{j \in \delta_i} \bar{y}_j)$$

where ϕ_i are the *positive* children of i and $\delta_i = \Delta_i \setminus \phi_i$ the descendants of i without its children.

If $\tau = 1$ we consider only the contribution of the *positive* children of i; if $\tau = 0$ only the descendants that are not children contribute to the score, while for intermediate values of τ we can balance the contribution of ϕ_i and δ_i positive nodes.

All the DESCENS variants adopt in the second step the HTD-DAG algorithm to assure the consistency of the predictions:

```
S.descensTF  <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="threshold.
↪free", topdown="htd");
S.descensT   <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="threshold",
↪ topdown="htd", t=0.5);
S.descensW   <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="weighted.
↪threshold.free", topdown="htd", w=0.5);
S.descensWT  <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="weighted.
↪threshold", topdown="htd", t=0.5, w=05);
S.descensTAU <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="tau",␣
↪topdown="htd", t=0.5);
```

4.4.5 ISO-TPR: Isotonic Regression for DAG

The ISO-TPR algorithms (parameter `positive="children"` and `topdown="gpav"`) considering the **positive children** in the bottom-up step and adopt GPAV (*GPAV: Generalized Pool-Adjacent-Violators*) instead of HTD-DAG (*HTD-DAG: Hierarchical Top Down for DAG*) in the consistency step. The most important feature of the ISO-TPR

algorithms is that they maintain the hierarchical constraints by construction by selecting the closest solution (in the least square sense) to the bottom-up predictions that obey the *True Path Rule*:

```
S.isotprTF <- tpr.dag(S.norm, g, root, positive="children", bottomup="threshold.free",
↪ topdown="gpav");
S.isotprT  <- tpr.dag(S.norm, g, root, positive="children", bottomup="threshold",␣
↪topdown="gpav", t=0.5);
S.isotprW  <- tpr.dag(S.norm, g, root, positive="children", bottomup="weighted.
↪threshold.free", topdown="gpav", w=0.5);
S.isotprWT <- tpr.dag(S.norm, g, root, positive="children", bottomup="weighted.
↪threshold", topdown="gpav", t=0.5, w=0.5);
```

4.4.6 ISO-DESCENS: Isotonic Regression with Descendants Ensemble Classifier

The ISO-DESCENS variants (parameter `positive="descendants"` and `topdown="gpav"`) considering the **positive descendants** instead of **positive children** in the bottom-up step and adopt GPAV (instead of the HTD-DAG algorithm) to guarantee the consistency of the predictions:

```
S.isodescensTF  <- tpr.dag(S.norm, g, root, positive="descendants", bottomup=
↪"threshold.free", topdown="gpav");
S.isodescensT   <- tpr.dag(S.norm, g, root, positive="descendants", bottomup=
↪"threshold", topdown="gpav", t=0.5);
S.isodescensW   <- tpr.dag(S.norm, g, root, positive="descendants", bottomup=
↪"weighted.threshold.free", topdown="gpav", w=0.5);
S.isodescensWT  <- tpr.dag(S.norm, g, root, positive="descendants", bottomup=
↪"weighted.threshold", topdown="gpav", t=0.5, w=0.5);
S.isodescensTAU <- tpr.dag(S.norm, g, root, positive="descendants", bottomup="tau",␣
↪topdown="gpav", t=0.5);
```

4.4.7 Obozinski Heuristic Methods

HEMDAG includes also the three heuristics ensemble methods (And, Max, Or) proposed in [4]:

1. **Max**: reports the largest logistic regression (LR) value of self and all descendants: $p_i = max_{j \in descendants(i)} \hat{p_j}$;
2. **And**: reports the product of LR values of all ancestors and self. This is equivalent to computing the probability that all ancestral terms are "on" assuming that, conditional on the data, all predictions are independent: $p_i = \prod_{j \in ancestors(i)} \hat{p_j}$;
3. **Or**: computes the probability that at least one of the descendant terms is "on" assuming again that, conditional on the data, all predictions are independent: $1 - p_i = \prod_{j \in descendants(i)} (1 - \hat{p_j})$;

To call Obozinski's heuristic methods, just type:

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

Alternatively, the Obozinski's methods can be also called by properly setting the parameter `heuristic` of the function `obozinski.methods`:

```
S.max <- obozinski.methods(S, g, heuristic="max", norm=TRUE, norm.type="maxnorm");
S.and <- obozinski.methods(S, g, heuristic="and", norm=TRUE, norm.type="maxnorm");
S.or  <- obozinski.methods(S, g, heuristic="or",  norm=TRUE, norm.type="maxnorm");
```

4.5 Check Hierarchical Constraints

Predictions returned by a flat classifier **do not respect** the *True Path Rule* (since they neglect the structural information between different ontology terms), whereas the predictions returned by a hierarchical ensemble methods **always obey** the *True Path Rule*. According to this rule a *positive* instance for a class implies *positive* instance for all the ancestors of that class. We can easily check this fact by using the function `check.hierarchy`. Below (as an example) we check the consistency of the scores corrected according to the HTD-DAG strategy. Of course, all the scores matrices corrected with any hierarchical ensemble variants included in HEMDAG, respect the **True Path Rule**. We leave to the user the freedom to check the consistency of the scores matrix of the remaining 22 hierarchical ensemble variants encompassed in HEMDAG.

```
check.hierarchy(S, g, root)$status
"NOTOK"

check.hierarchy(S.htd, g, root)$status
"OK"
```

4.6 Performance Evaluation

To know the behavior of the hierarchical ensemble methods, the HEMDAG library provides both *term-centric* and *protein-centric* performance metrics:

- `AUPRC`: area under the precision-recall curve;
- `AUROC`: area under the ROC curve;
- `Fmax` : maximum hierarchical F-score [2];
- `PXR` : precision at different recall levels;

Note:

1. HEMDAG allows to compute all the aforementioned performance metrics either **one-shot** or **averaged** across k fold. Depending on the dataset size, the metrics `Fmax` and `PXR` could take a while to finish. Please refer to HEMDAG reference manual for further information about the input arguments of these functions.
2. For computing the *term-centric* metrics (`AUROC`, `AUPRC` and `PXR`), HEMDAG makes use of the R package *precrec* (link).

4.6.1 Load the Annotation Matrix

To compare the hierarchical ensemble methods against the flat approach, we need to load 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`.

4.6.2 Flat vs Hierarchical

Before computing performance metrics we should remove the root node from the annotation matrix, the flat score matrix and the hierarchical scores matrix. Indeed, it does not make sense to take into account the predictions of the root node, since it is a *fake* 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 the normalized flat score matrix
if(root %in% colnames(S.norm))
    S.norm <- S.norm[,-which(colnames(S.norm)==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 the HTD-DAG strategy, by averaging (for instance) the performance across 3 folds:

```
## RANKS
prc.flat  <- auprc.single.over.classes(L, S.norm, folds=3, seed=23);
auc.flat  <- auroc.single.over.classes(L, S.norm, folds=3, seed=23);
pxr.flat  <- precision.at.given.recall.levels.over.classes(L, S.norm, recall.
↪levels=seq(from=0.1, to=1, by=0.1), folds=3, seed=23);
fmax.flat <- compute.fmax(L, S.norm, n.round=3, verbose=FALSE, b.per.example=TRUE,␣
↪folds=3, seed=23);

## HTD-DAG
prc.htd  <- auprc.single.over.classes(L, S.htd, folds=3, seed=23);
auc.htd  <- auroc.single.over.classes(L, S.htd, folds=3, seed=23);
pxr.htd  <- precision.at.given.recall.levels.over.classes(L, S.htd, recall.
↪levels=seq(from=0.1, to=1, by=0.1), folds=3, seed=23);
fmax.htd <- compute.fmax(L, S.htd, n.round=3, verbose=FALSE, b.per.example=TRUE,␣
↪folds=3, seed=23);
```

By looking at the results, it easy to see that the HTD-DAG outperforms the flat classifier RANKS:

```
## AUC performance: RANKS VS HTD-DAG
auc.flat$average
0.8297
auc.htd$average
0.8336

## PRC performance: RANKS VS HTD-DAG
prc.flat$average
0.4333
prc.htd$average
0.4627

## Fmax performance: RANKS VS HTD-DAG
fmax.flat$average
    P      R      S      F     avF      A      T
0.5042 0.8639 0.4485 0.6368 0.5269 0.6612 0.5720
fmax.htd$average
```

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```
    P      R      S      F    avF      A      T
0.5576 0.7745 0.6519 0.6484 0.5617 0.7521 0.6487

## PXR: RANKS VS HTD-DAG
pxr.flat$average
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5821 0.5821 0.5821 0.5531 0.5531 0.4483 0.4388 0.4388 0.4388 0.4388
pxr.htd$average
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6218 0.6218 0.6218 0.5941 0.5941 0.4798 0.4668 0.4668 0.4668 0.4668
```

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

4.7 Tuning of Hyper-Parameter(s)

14 out of 18 of the TPR-DAG hierarchical algorithms are parametric. Instead of use a fixed threshold (as done in *TPR-DAG: True Path Rule for DAG*), we can tune the hyper-parameter(s) of the parametric variants through the function `tpr.dag.cv`. The hyper-parameter(s) can be maximize on the basis of `AUPRC` (parameter `metric="prc"`) or `Fmax` (parameter `metric="fmax"`). Below, as an example, we maximize the threshold of the parametric variant `isotprT` on the basis of `AUPRC` metric.

```
threshold <- seq(0.1, 0.9, 0.1);

S.isotprT <- tpr.dag.cv(S, g, ann=L, norm=TRUE, norm.type="maxnorm", positive=
↪"children",
                        bottomup="threshold", topdown="gpav", W=NULL, parallel=FALSE,
                        ncores=1, threshold=threshold, weight=0, kk=3, seed=23,
                        metric="auprc", n.round=NULL);

## stdout
maxnorm normalization: done
training fold:  1   top auprc avg found:    0.4743567   best threshold: 0.1
training fold:  1   top auprc avg found:    0.4883769   best threshold: 0.5
training fold:  2   top auprc avg found:    0.2249245   best threshold: 0.1
training fold:  2   top auprc avg found:    0.2274687   best threshold: 0.3
training fold:  2   top auprc avg found:    0.2469059   best threshold: 0.4
training fold:  3   top auprc avg found:    0.8167777   best threshold: 0.1
training fold:  3   top auprc avg found:    0.8264204   best threshold: 0.3
training fold:  3   top auprc avg found:    0.8329289   best threshold: 0.7
tpr-dag correction done
```

Evaluating `isotprT` by computing *term*- and *protein*- centric performance (always averaging the performance across 3 folds), it easy to see how this ensemble variant outperform both the flat classifier RANKS and the hierarchical algorithm HTD-DAG:

```
## remove root node before computing performance
if(root %in% colnames(S.isotprT))
    S.isotprT <- S.isotprT[,-which(colnames(S.isotprT)==root)];
```

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```
prc.isotprT  <- auprc.single.over.classes(L, S.isotprT, folds=3, seed=23);
auc.isotprT  <- auroc.single.over.classes(L, S.isotprT, folds=3, seed=23);
pxr.isotprT  <- precision.at.given.recall.levels.over.classes(L, S.isotprT, recall.
↪levels=seq(from=0.1, to=1, by=0.1), folds=3, seed=23);
fmax.isotprT <- compute.fmax(L, S.isotprT, n.round=3, verbose=FALSE, b.per.
↪example=TRUE, folds=3, seed=23);

## AUC performance: RANKS VS HTD-DAG vs isotprT
auc.flat$average
0.8297
auc.htd$average
0.8336
auc.isotprT$average
0.8446

## PRC performance: RANKS VS HTD-DAG vs isotprT
prc.flat$average
0.4333
prc.htd$average
0.4627
prc.isotprT$average
0.5346

## Fmax performance: RANKS VS HTD-DAG vs isotprT
fmax.flat$average
    P      R      S      F    avF      A      T
0.5042 0.8639 0.4485 0.6368 0.5269 0.6612 0.5720
fmax.htd$average
    P      R      S      F    avF      A      T
0.5576 0.7745 0.6519 0.6484 0.5617 0.7521 0.6487
fmax.isotprT$average
    P      R      S      F    avF      A      T
0.5896 0.8306 0.5283 0.6896 0.6106 0.7066 0.6340

## PXR: RANKS VS HTD-DAG vs isotprT
pxr.flat$average
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.5821 0.5821 0.5821 0.5531 0.5531 0.4483 0.4388 0.4388 0.4388 0.4388
pxr.htd$average
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6218 0.6218 0.6218 0.5941 0.5941 0.4798 0.4668 0.4668 0.4668 0.4668
pxr.isotprT$average
   0.1    0.2    0.3    0.4    0.5    0.6    0.7    0.8    0.9    1
0.6848 0.6848 0.6848 0.6697 0.6697 0.5417 0.5027 0.5027 0.5027 0.5027
```

By properly setting the parameters `positive`, `bottomup` and `topdown` of the function `tpr.dag.cv`, it is easy to make experiments with all the 18 TPR-DAG ensemble variants. For further details on the other input arguments of the function `tpr.dag.cv`, please refer to the reference manual.

Note: Note that tuning the hyper-parameter(s) of the ensemble variants on the basis of `Fmax` might involve high running time (due to the nature itself of the `Fmax` metric).

4.8 Hold-out Functions

For all the hierarchical ensemble algorithms encompassed in the HEMDAG library there is also a corresponding hold-out version. The hold-out functions respect to the *vanilla* ones, require in input a vector of integer numbers corresponding to the indexes of the elements (rows) of the scores matrix `S` to be used in the test set (parameter `testIndex`). The hold-out ensemble functions included in HEMDAG are:

- `htd.holdout`;
- `gpav.holdout`;
- `tpr.dag.holdout`;
- `obozinski.holdout`;

For the sake of space we do not show here experiments by using the hold-out version of the hierarchical functions. Please refer to the reference manual, for further details on these functions.

References

CHAPTER 5

HEMDAG programmatic call and evaluation

Here we explain how to apply the ensemble algorithms of the HEMDAG family in both cross-validated and hold-out experiments.

HEMDAG can in principle boost the predictions of any flat learning method by reconciling the flat predictions with the topology of the underlying ontology. Hence, to run HEMDAG we need the following *ingredients*:

1) the label matrix `M` representing the protein annotations to functional terms;
2) the graph `g` representing the hierarchy of the functional terms;
3) the flat score matrix `S` representing a score or a probability that a gene/protein belongs to a given functional term;

To build the graph, the label matrix and the protein-protein interaction network you can use this pipeline. Instead, to obtain the flat score matrix you can use the shogun library or the caret package or any other software returning a score or a probability that a protein belongs to a functional term.

Note: HEMDAG is built upon flat predictions. HEMDAG corrects all the violations of the hierarchical relationships between ontology terms.

Note: To run the experiments shown below, make sure you have installed the following requirements:

- HEMDAG >= 2.7.4
- R >= 4.0.4
- Ubuntu >= 16.04

5.1 HEMDAG Call Script

To call any hierarchical ensemble algorithm of the HEMDAG family on either a time-lapse hold-out or a cross-validated dataset you can execute the following script:

```
#!/usr/bin/Rscript

## load library
library(HEMDAG);
suppressPackageStartupMessages(library(graph)); ## silence biocgenerics mask messages...
library(optparse);

## command line arguments
## for a detailed description, please see the manual: https://cran.r-project.org/web/packages/HEMDAG/HEMDAG.pdf
optionList <- list(
    make_option(c("-o", "--organism"), type="character", default="7227_drome",
        help="organism name in the form <taxon>_<name> (def. 7227_drome)"),
    make_option(c("-d", "--domain"), type="character", default="mf",
        help="go domain. It can be: bp, mf or cc (def. mf)"),
    make_option(c("-e", "--exptype"), type="character", default="ho",
        help="type of dataset on which run HEMDAG. It can be: ho (hold-out) or cv (cross-validated) -- def. ho"),
    make_option(c("-f", "--flat"), type="character", default="svmlinear",
        help="flat classifier"),
    make_option(c("-p", "--positive"), type="character", default="descendants",
        help="positive nodes selection. It can be: children or descendants.
                Skip this parameter if only topdown strategy is applied (def. descendants)"),
    make_option(c("-b", "--bottomup"), type="character", default="tau",
        help="bottomup strategy. It can be: none, threshold.free, threshold, weighted.threshold.free, weighted.threshold or tau.
                If none only topdown strategy is applied (def. tau)"),
    make_option(c("-t", "--topdown"), type="character", default="gpav",
        help="topdown strategy. It can be: htd or gpav (def. gpav)"),
    make_option(c("-c", "--threshold"), type="character", default="seq(from=0.1, to=0.9, by=0.1)",
        help="threshold for the choice of positive nodes.
                It can be a fixed value or an array of values (def. seq(from=0.1, to=0.9, by=0.1))"),
    make_option(c("-w", "--weight"), type="character", default="0",
        help="weight for the choice of positive nodes. It can be a fixed value or an array of values (def. 0)"),
    make_option(c("-m", "--metric"), type="character", default="auprc",
        help="performance metric on which maximize the parametric ensemble algorithms. It can be: auprc or fmax (def. auprc)"),
    make_option(c("-r", "--round"), type="integer", default="3",
        help="number of rounding digits to be applied for choosing the best Fmax. To be used only if metric is set to fmax (def. 3)"),
    make_option(c("-s", "--seed"), type="integer", default="23",
        help="seed for the random generator to create folds (def. 23)"),
    make_option(c("-k", "--fold"), type="integer", default="5",
        help="number of folds for the cross validation (def. 5)"),
    make_option(c("-l", "--parallel"), type="logical", default=FALSE, action="store_true",
        help="should the sequential or parallel version of gpav be run?
                If flag -p is 'on' the gpav parallel version is run. NB: only gpav can be run in parallel (def. FALSE)"),
    make_option(c("-n", "--cores"), type="integer", default="1",
        help="number of cores to use for the parallel execution of gpav (def. 1)"),
    make_option(c("-z", "--norm"), type="logical", default=FALSE, action="store_true",
```

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```
        help="should the flat score matrix be normalized? If flag -p is 'on' the input flat scores is normalized (def. FALSE)"),
    make_option(c("-y", "--normtype"), type="character", default="none",
        help="type of normalization. It can be maxnorm or qnorm (def. none)")
);

optParser <- OptionParser(option_list=optionList);
opt <- parse_args(optParser);

prefix    <- opt$organism;
organism  <- strsplit(prefix,"_")[[1]][2];
exptype   <- opt$exptype;
flat      <- opt$flat;
positive  <- opt$positive;
bottomup  <- opt$bottomup;
topdown   <- opt$topdown;
domain    <- opt$domain;
threshold <- eval(parse(text=opt$threshold));
weight    <- eval(parse(text=opt$weight));
metric    <- opt$metric;
round     <- opt$round;
seed      <- opt$seed;
kk        <- opt$fold;
parallel  <- opt$parallel;
cores     <- opt$cores;
norm      <- opt$norm;
normtype  <- opt$normtype;
if(normtype == "none")
    normtype <- NULL;

## hemdag algorithm to be displayed in output file name -> 18 iso/tpr-dag ensemble combinations + gpav + htd (tot 20 hemdag family)
if(positive=="children" && bottomup=="threshold.free" && topdown=="htd")
    hemdag.name <- "tprTF";
if(positive=="children" && bottomup=="threshold" && topdown=="htd")
    hemdag.name <- "tprT";
if(positive=="children" && bottomup=="weighted.threshold.free" && topdown=="htd")
    hemdag.name <- "tprW";
if(positive=="children" && bottomup=="weighted.threshold" && topdown=="htd")
    hemdag.name <- "tprwt";
if(positive=="descendants" && bottomup=="threshold.free" && topdown=="htd")
    hemdag.name <- "descensTF";
if(positive=="descendants" && bottomup=="threshold" && topdown=="htd")
    hemdag.name <- "descensT";
if(positive=="descendants" && bottomup=="weighted.threshold.free" && topdown=="htd")
    hemdag.name <- "descensW";
if(positive=="descendants" && bottomup=="weighted.threshold" && topdown=="htd")
    hemdag.name <- "descensWT";
if(positive=="descendants" && bottomup=="tau" && topdown=="htd")
    hemdag.name <- "descensTAU";
if(positive=="children" && bottomup=="threshold.free" && topdown=="gpav")
    hemdag.name <- "isotprTF";
if(positive=="children" && bottomup=="threshold" && topdown=="gpav")
    hemdag.name <- "isotprT";
if(positive=="children" && bottomup=="weighted.threshold.free" && topdown=="gpav")
    hemdag.name <- "isotprW";
if(positive=="children" && bottomup=="weighted.threshold" && topdown=="gpav")
```

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```
    hemdag.name <- "isotprWT";
if(positive=="descendants" && bottomup=="threshold.free" && topdown=="gpav")
    hemdag.name <- "isodescensTF";
if(positive=="descendants" && bottomup=="threshold" && topdown=="gpav")
    hemdag.name <- "isodescensT";
if(positive=="descendants" && bottomup=="weighted.threshold.free" && topdown=="gpav")
    hemdag.name <- "isodescensW";
if(positive=="descendants" && bottomup=="weighted.threshold" && topdown=="gpav")
    hemdag.name <- "isodescensWT";
if(positive=="descendants" && bottomup=="tau" && topdown=="gpav")
    hemdag.name <- "isodescensTAU";
if(bottomup=="none" && topdown=="gpav")
    hemdag.name <- "gpav";
if(bottomup=="none" && topdown=="htd")
    hemdag.name <- "htd";

## I/O directories
data.dir <- paste0("../data/", exptype, "/");
res.dir  <- paste0("../res/",  exptype, "/");
if(!dir.exists(res.dir)){dir.create(res.dir, recursive=TRUE);}

## flat/ann/dag/testIndex files
files <- list.files(data.dir);
flat.file <- files[grep(paste0(organism, ".*", domain, ".scores.*", flat), files)];
ann.file  <- files[grep(paste0(domain,".ann"), files)];
dag.file  <- files[grep(paste0(domain,".dag"), files)];
if(exptype == "ho"){
    idx.file  <- files[grep(paste0(domain,".testindex"), files)];
    if(length(idx.file)==0)
        stop("no index file found\n");
}

## check if flat|ann|dag exists
if(length(flat.file)==0 || length(ann.file)==0 || length(dag.file)==0)
    stop("no flat|ann|dag file found\n");

## load data
S <- get(load(paste0(data.dir, flat.file)));
g <- get(load(paste0(data.dir, dag.file)));
ann <- get(load(paste0(data.dir, ann.file)));
if(exptype == "ho")
    testIndex <- get(load(paste0(data.dir, idx.file)));

## shrink graph g to terms of matrix S -- if number of nodes between g and S mismatch
root <- root.node(g);
nd <- colnames(S);
class.check <- ncol(S) != graph::numNodes(g);
if(class.check){
    root.check <- root %in% colnames(S);
    if(!root.check)
        nd <- c(root, nd);
    g <- build.subgraph(nd, g, edgemode="directed");
    ann <- ann[, colnames(S)];
}

## address case when (iso)descensW is called with a fixed value of w to enter in the␣
↪right branch
```

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```
if(bottomup=="weighted.threshold.free" && length(weight)==1)
    threshold <- 0;

## elapsed time
start.elapsed <- proc.time();

## HEMDAG calling
if(exptype == "ho"){
    if(bottomup=="none"){
        if(topdown=="gpav"){
            S.hier <- gpav.holdout(S=S, g=g, testIndex=testIndex, W=NULL, parallel=parallel,
                ncores=cores, norm=norm, norm.type=normtype);
        }else{
            S.hier <- htd.holdout(S=S, g=g, testIndex=testIndex, norm=norm, norm.type=normtype);
        }
    }else{ ## branch to call HEMDAG by tuning the parameters
        if(length(threshold)>1 || length(weight)>1){
            S.hier <- tpr.dag.holdout(S, g, ann=ann, testIndex=testIndex, norm=norm, norm.type=normtype,
                positive=positive, bottomup=bottomup, topdown=topdown, W=NULL, parallel=parallel, ncores=cores,
                threshold=threshold, weight=weight, kk=kk, seed=seed, metric=metric, n.round=round);
        }else{ ## branch to call HEMDAG with fixed the parameters
            ## add root node if it does not exist
            if(!(root %in% colnames(S))){
                max.score <- max(S);
                z <- rep(max.score,nrow(S));
                S <- cbind(z,S);
                colnames(S)[1] <- root;
            }
            ## normalization
            if(norm){
                S <- scores.normalization(norm.type=normtype, S);
                cat(normtype, "normalization done\n");
            }
            ## shrink S to test indexes
            S.test <- S[testIndex,];
            ## degenerate case when test set has just one row/example
            if(!is.matrix(S.test)){
                test.sample <- rownames(S)[testIndex];
                S.test <- matrix(S.test, ncol=length(S.test), dimnames=list(test.sample, names(S.test)));
            }
            ## tpr-dag correction
            S.hier <- tpr.dag(S.test, g, root=root, positive=positive, bottomup=bottomup, topdown=topdown,
                t=threshold, w=weight, W=NULL, parallel=parallel, ncores=cores);
            ## print chosen parameters
            if(bottomup=="weighted.threshold.free"){
                cat("fixed weight:", weight, "\n");
            }else if(bottomup=="weighted.threshold"){
                cat("fixed weight:", weight, "fixed threshold:", threshold, "\n");
            }else{
                cat("fixed threshold:", threshold, "\n");
```

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```
            }
            cat("tpr-dag correction done\n");
        }
    }
}else{
    if(bottomup=="none"){
        if(topdown=="gpav"){
            S.hier <- gpav.vanilla(S=S, g=g, W=NULL, parallel=parallel, ncores=cores, norm=norm, norm.type=normtype);
        }else{
            S.hier <- htd.vanilla(S=S, g=g, norm=norm, norm.type=normtype);
        }
    }else{  ## branch to call HEMDAG by tuning the parameters
        if(length(threshold)>1 || length(weight)>1){
            S.hier <- tpr.dag.cv(S, g, ann=ann, norm=norm, norm.type=normtype, positive=positive, bottomup=bottomup,
                topdown=topdown, W=NULL, parallel=parallel, ncores=cores, threshold=threshold, weight=weight,
                kk=kk, seed=seed, metric=metric, n.round=round);
        }else{  ## branch to call HEMDAG with fixed parameters
            ## add root node if it does not exist
            if(!(root %in% colnames(S))){
                max.score <- max(S);
                z <- rep(max.score,nrow(S));
                S <- cbind(z,S);
                colnames(S)[1] <- root;
            }
            ## normalization
            if(norm){
                S <- scores.normalization(norm.type=normtype, S);
                cat(normtype, "normalization done\n");
            }
            S.hier <- tpr.dag(S, g, root=root, positive=positive, bottomup=bottomup, topdown=topdown,
                t=threshold, w=weight, W=NULL, parallel=parallel, ncores=cores);
            ## print chosen parameters
            if(bottomup=="weighted.threshold.free"){
                cat("weight: ", weight, "\n");
            }else if(bottomup=="weighted.threshold"){
                cat("weight: ", weight, "threshold: ", threshold, "\n");
            }else{
                cat("threshold: ", threshold, "\n");
            }
            cat("tpr-dag correction done\n");
        }
    }
}

stop.elapsed <- proc.time() - start.elapsed;
timing.s <- stop.elapsed["elapsed"];
timing.m <- round(timing.s/(60),4);
timing.h <- round(timing.m/(60),4);
cat(hemdag.name, "running time:", timing.s["elapsed"], "(seconds)", "|", timing.m["elapsed"], "(minutes)", "|" , timing.h["elapsed"], "(hours)", "\n\n");

## store results
## outname
```

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```
fname <- unlist(strsplit(flat.file, split="[.,_]"));
outname <- paste0(fname[-((length(fname)-1):length(fname))], collapse="_");
if(norm==TRUE && !(is.null(normtype)))
    outname <- paste0(outname,"_",normtype);
if(exptype == "ho"){
    save(S.hier, file=paste0(res.dir, outname, "_", hemdag.name, "_holdout.rda"), compress=TRUE);
}else{
    save(S.hier, file=paste0(res.dir, outname, "_", hemdag.name, ".rda"), compress=TRUE);
}
```

You can download the script as follow:

```
mkdir -p ~/hemdag/script/
cd ~/hemdag/script/
wget -nc https://raw.githubusercontent.com/marconotaro/hemdag/master/docs/playground/script/hemdag-call.R
```

Before executing the script be sure to have correctly installed the latest version of the HEMDAG package (and all its dependencies – see *Installation*) and the package optparse.

Note:

1. The output hierarchical score matrix of the called HEMDAG algorithm (whose name is saved in the output *.rda* file name) is stored in the folder `~/hemdag/res/(ho|cv)` depending on whether you chose to execute HEMDAG on either hold-out (ho) or cross-validated (cv) datasets. The HEMDAG elapsed time is printed on the shell.
2. By default, if no inputs parameters are specified in `hemdag-call.R`, the script executes the `isodescensTAU` algorithm on the hold-out dataset by tuning the parameter `tau` on the basis of AUPRC.
3. The tuning of the hyper-parameters can take from few minutes up to few hours depending on the size of the dataset and on the adopted evaluation metric (Fmax is slower than AUPRC).

5.1.1 Arguments Explanation

For the usage of the script, type in the shell under the `~/hemdag/script/` folder:

```
Rscript hemdag-call.R -h
```

For a detailed description of the input arguments *positive, bottomup, topdown, threshold, weight, metric, round, seed, fold, parallel, cores, norm, normtype*, please refer to the description of the input variables of the functions `(gpav|htd|tpr.dag).(holdout|cv)` in the HEMDAG reference manual.

Parametric-free arguments

To call a parametric-free HEMDAG algorithm the main required arguments are:

- `-b (--bottomup) none`
- `-t (--topdown) gpav|htd`

Note: GPAV can also be run in parallel simply by using the flag `-l (--parallel)` and by setting the number of cores `-n (--cores)`.

Parametric arguments

To call a parametric HEMDAG algorithm the main required arguments are:

- `-b (--bottomup) threshold.free|threshold|weighted.threshold.free|weighted.threshold|tau`
- `-t (--topdown) gpav|htd`
- `-c (--cut-off) 0.5|"seq(from=0.1, to=0.9, by=0.1)"`. Note the use of double quotes for the range of thresholds
- `-w (--weight) 0.5|"seq(from=0.1, to=0.9, by=0.1)"`. Note the use of double quotes for the range of thresholds

If a range of thresholds (or weights) is selected, the hyper-parameters are tuned on the basis of imbalance-aware performance metrics estimated on the training data – `-m (--metric) auprc|fmax`. By default the number of folds `-k (--fold)` is set to 5 and the seed `-s (--seed)` for the random generator is set to 23. Furthermore, if `-m (--metric) fmax` the parameter `-r (--round)` can be used to select the number of rounding digits to be applied for choosing the best Fmax (by default is set to 3).

Additional arguments

The following arguments are dataset-specific:

- `-o (--organism)` specifies the organism name (in the form <taxon>_<name>);
- `-d (--domain)` specifies the GO domain: bp (biological process), mf (molecular function), cc(cellular component);
- `-e (--exptype)` specifies the type of dataset where running HEMDAG: ho (holdout) or cv (cross-validated);
- `-f (--flat)` specifies the name of the flat classifier. In case the flat learning method returns a score and not a probability, the flat score matrix must be normalized before running HEMDAG. On the contrary, if the flat classifier already returns a probability there is no needed to normalize the flat score matrix, since the flat scores can be directly compared with the hierarchical ones. To normalize the flat score matrix we must "activate" the flag `-z (--norm)` (by default the flag `-z` is deactivate) and we need to choose a type of normalization (`-y (--normtype) maxnorm|qnorm`). The name of the chosen normalization is stored in the *rda* output file name.

5.2 Time-lapse hold-out experiments

Here, to show how to use HEMDAG in time-lapse hold-out experiments, we use a pre-built dataset of the organism *Drosophila melanogaster* (DROME) and, for simplicity, we consider the annotations of the GO domain molecular function (MF). To build the dataset we used the annotations of an old GO release (December 2017) as training set and the annotations of a more recent GO release (June 2020) as test set. The graph and the annotation matrix was built by adopting the pipeline. The flat score matrix was obtained by using the R interface of the machine learning library LiblineaR with the default parameter settings. For further details on the dataset, please refer to *HEMDAG: a*

family of modular and scalable hierarchical ensemble methods to improve Gene Ontology term prediction (submitted to Bioinformatics).

5.2.1 Download Data

All the required *.rda* files can be downloaded by using the following commands, by exploiting the beauty and power of the non-greedy positive lookbehind regex :

```
mkdir -p ~/hemdag/data/ho/
cd ~/hemdag/data/ho/
curl -Ss https://github.com/marconotaro/hemdag/tree/master/docs/playground/data/ho | grep -oP '(?<=href=").*?(?=\">)' | grep '.rda$' | perl -pe 's/blob\///' | perl -pe 's/^/https\:\/\/raw.githubusercontent.com/' | wget -nc -i -
```

With the command above, we download the following datasets:

- `7227_drome_go_mf_ann_20dec17_16jun20.rda`: the annotation matrix;
- `7227_drome_go_mf_dag_20dec17_16jun20.rda`: the graph;
- `7227_drome_go_mf_testindex_20dec17_16jun20.rda`: the indexes of the examples of the test set;
- `7227_drome_go_mf_scores_svmlinear_holdout.rda`: the flat score matrix;

5.2.2 Programmatic Call

Below we show some examples of how to call HEMDAG in time-lapse hold-out experiments, but we leave the user the freedom to experiment with any another ensemble algorithm of the HEMDAG family.

Note:

1. the `hemdag-call.R` script must be called in `~/hemdag/script/`;
2. for the examples shown below, the tuning of hyper-parameters takes few minutes;
3. the output HEMDAG score matrices are stored in `~/hemdag/res/ho/`.

`GPAV` call (parallel version):

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -b none -t gpav -l -n 12
```

`isotprTF` call:

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -p children -b threshold.free -t gpav -l -n 12
```

`isotprW` call:

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -p children -b weighted.threshold.free -t gpav -w "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -k 5 -l -n 12
```

`isodescensTF` call:

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -p descendants -b threshold.free -t gpav -l -n 12
```

`isodescensW` call:

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -p descendants -b␣
↪weighted.threshold.free -t gpav -w "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -
↪k 5 -l -n 12
```

`isodescensTAU` call:

```
Rscript hemdag-call.R -o 7227_drome -d mf -e ho -f svmlinear -p descendants -b tau -t␣
↪gpav -c "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -k 5 -l -n 12
```

5.2.3 Check Hierarchical Constraints

All the HEMDAG score matrices respect the hierarchical constraints imposed by the underlying ontology. The script below checks that all the 6 HEMDAG matrices obtained with the commands shown above, do not violate the between-term relationships in the GO MF hierarchy. For further details refer to *Check Hierarchical Constraints*.

```
#!/usr/bin/Rscript

suppressPackageStartupMessages(library(HEMDAG));
library(optparse);

optionList <- list(
    make_option(c("-o", "--organism"), type="character", default="7227_drome",
        help="organism name in the form <taxon>_<name> (def 7227_drome)"),
    make_option(c("-d", "--domain"),  type="character", default="mf",
        help="gene ontology domain -- bp, mf, cc (def. mf)"),
     make_option(c("-e", "--exptype"), type="character", default="ho",
        help="type of dataset on which run HEMDAG. It can be: ho (hold-out) or cv␣
↪(cross-validated) -- def. ho"),
    make_option(c("-f", "--flat"), type="character", default="svmlinear",
        help="flat classifier (def. svmlinear)"),
    make_option(c("-a", "--algorithm"), type="character", default="isodescensTAU",
        help="hierarchical correction algorithm (def. isodescensTAU)")
);

optParser <- OptionParser(option_list=optionList);
opt <- parse_args(optParser);

## setting input argument
prefix    <- opt$organism;
taxon     <- strsplit(prefix,"_")[[1]][1];
organism  <- strsplit(prefix,"_")[[1]][2];
domain    <- opt$domain;
exptype   <- opt$exptype;
flat      <- opt$flat;
algorithm <- opt$algorithm;

## I/O
data.dir <- paste0("../data/", exptype, "/");
res.dir  <- paste0("../res/",  exptype, "/");
data.files <- list.files(data.dir);
res.files  <- list.files(res.dir);
if(!dir.exists(res.dir)){dir.create(res.dir, recursive=TRUE);}

## load data
```

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```
dag.file  <- data.files[grep(paste0(domain,".dag"), data.files)];
hier.file <- res.files[grep(paste0(organism, ".*", domain, ".scores.*", flat, ".",
↪algorithm), res.files)];

## check if flat|ann|dag exists
if(length(dag.file)==0 || length(hier.file)==0)
    stop("no dag|hier file found\n");

## check constraints violation
g <- get(load(paste0(data.dir, dag.file)));
S.hier <- get(load(paste0(res.dir, hier.file)));
root <- root.node(g);
g <- build.subgraph(colnames(S.hier), g);
check <- check.hierarchy(S.hier, g, root);
if(check$status=="OK"){
    cat(taxon, organism, domain, paste0(flat,'+',algorithm), "check passed :)","\n");
}else{
    cat(taxon, organism, domain, paste0(flat,'+',algorithm), "check failed :(","\n");
}
```

To download and use the hierarchical constraints script:

```
## download
mkdir -p ~/hemdag/script/
cd ~/hemdag/script/
wget -nc https://raw.githubusercontent.com/marconotaro/hemdag/master/docs/playground/
↪script/hemdag-checker.R

## call
Rscript hemdag-checker.R -o 7227_drome -d mf -e cv -f ranger -a isodescensTAU
```

You can call `hemdag-checker.R` by looping through more hierarchical ensemble methods:

```
algotihms=("gpav" "isotprTF" "isotprW" "isodescensTF" "isodescensW" "isodescensTAU")

for ((i=0; i<${#algotihms[@]}; i++)); do
    Rscript hemdag-checker.R -o 7227_drome -d mf -e ho -f svmlinear -a ${algotihms[
↪$i]}
done;

## example of stdout
7227 drome mf ranger+gpav check passed :)
7227 drome mf ranger+isotprTF check passed :)
7227 drome mf ranger+isotprW check passed :)
7227 drome mf ranger+isodescensTF check passed :)
7227 drome mf ranger+isodescensW check passed :)
7227 drome mf ranger+isodescensTAU check passed :)
```

Of course, you can loop `hemdag-checker.R` also through the arguments `-o, -d, -e, -f` according with the values of your interest.

5.2.4 Evaluation

To evaluate the generalization performance of HEDMAG in the time-lapse hold-out experiments performed above, you can use the *term-centric* and/or *protein-centric* evaluation metrics provided by the HEMDAG package itself. For

further details on the implemented performance metric refer to section *Performance Evaluation* of the HEMDAG tutorial.

```
#!/usr/bin/Rscript

start.time <- proc.time();

library(HEMDAG);
library(optparse);

optionList <- list(
    make_option(c("-o", "--organism"), type="character", default="7227_drome",
        help="organism name in the form <taxon>_<name> (def 7227_drome)"),
    make_option(c("-d", "--domain"),  type="character", default="mf",
        help="gene ontology domain -- bp, mf, cc (def. mf)"),
     make_option(c("-e", "--exptype"), type="character", default="ho",
        help="type of dataset on which run HEMDAG. It can be: ho (hold-out) or cv
↪(cross-validated) -- def. ho"),
    make_option(c("-f", "--flat"), type="character", default="svmlinear",
        help="flat classifier (def. svmlinear)"),
    make_option(c("-a", "--algorithm"), type="character", default="isodescensTAU",
        help="hierarchical correction algorithm (def. isodescensTAU)")
);

optParser <- OptionParser(option_list=optionList);
opt <- parse_args(optParser);

## setting input argument
prefix    <- opt$organism;
taxon     <- strsplit(prefix,"_")[[1]][1];
organism  <- strsplit(prefix,"_")[[1]][2];
domain    <- opt$domain;
exptype   <- opt$exptype;
flat      <- opt$flat;
algorithm <- opt$algorithm;

## I/O
data.dir <- paste0("../data/", exptype, "/");
res.dir  <- paste0("../res/",  exptype, "/");
if(!dir.exists(res.dir)){dir.create(res.dir, recursive=TRUE);}

## flat/ann/dag/testIndex file
files <- list.files(data.dir);
flat.file <- files[grep(paste0(organism, ".*", domain, ".scores.*", flat), files)];
ann.file  <- files[grep(paste0(domain,".ann"), files)];
dag.file  <- files[grep(paste0(domain,".dag"), files)];
## check if flat|ann|dag exists
if(length(flat.file)==0 || length(ann.file)==0 || length(dag.file)==0)
    stop("no flat|ann|dag file found\n");

if(exptype == "ho"){
    idx.file  <- files[grep(paste0(domain,".testindex"), files)];
    if(length(idx.file)==0)
        stop("no idx file found\n");
}

## hier file
files <- list.files(res.dir);
```

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```
hier.file <- files[grep(paste0(organism, ".*", domain, ".scores.*", flat, ".", algorithm), files)];

## load data
S <- get(load(paste0(data.dir, flat.file)));
S.hier <- get(load(paste0(res.dir, hier.file)));
g <- get(load(paste0(data.dir, dag.file)));
ann <- get(load(paste0(data.dir, ann.file)));
if(exptype == "ho")
    testIndex <- get(load(paste0(data.dir, idx.file)));

## if number of nodes between g and S mismatch -> shrink graph g to terms of matrix S
## eg. during flat learning you removed from S all those terms having less than N annotations
root <- root.node(g);
nd <- colnames(S);
class.check <- ncol(S) != graph::numNodes(g);
if(class.check){
    root.check <- root %in% colnames(S);
    if(!root.check)
        nd <- c(root, nd);
    g <- build.subgraph(nd, g, edgemode="directed");
    ann <- ann[, colnames(S)];
}

## remove root node S and S.hier score matrix (if any)
root <- root.node(g);
if(root %in% colnames(S)){
    S <- S[,-which(colnames(S)==root)];
    cat("root node removed from flat score matrix\n");
}
if(root %in% colnames(S.hier)){
    S.hier <- S.hier[,-which(colnames(S.hier)==root)];
    cat("root node removed from hierarchical score matrix\n");
}
## remove root node from annotation matrix (if any)
if(root %in% colnames(ann)){
    ann <- ann[,-which(colnames(ann)==root)];
    cat("root node removed from annotation matrix\n");
}

## shrink S to testIndex
if(exptype == "ho"){
    S <- S[testIndex, ];
    ann <- ann[testIndex, colnames(S)];
}

## compute flat perf
auc.flat  <- auroc.single.over.classes(target=ann, predicted=S, folds=NULL, seed=NULL);
prc.flat  <- auprc.single.over.classes(target=ann, predicted=S, folds=NULL, seed=NULL);
fmax.flat <- compute.fmax(target=ann, predicted=S, n.round=3, b.per.example=TRUE, folds=NULL, seed=NULL, verbose=FALSE);
pxr.flat  <- precision.at.given.recall.levels.over.classes(target=ann, predicted=S, folds=NULL, seed=NULL, recall.levels=seq(from=0.1, to=1, by=0.1));
cat(taxon, organism, domain, flat, algorithm, "flat performance done\n");
```

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```

## compute hier perf
auc.hier  <- auroc.single.over.classes(target=ann, predicted=S.hier, folds=NULL,␣
↪seed=NULL);
prc.hier  <- auprc.single.over.classes(target=ann, predicted=S.hier, folds=NULL,␣
↪seed=NULL);
fmax.hier <- compute.fmax(target=ann, predicted=S.hier, n.round=3, b.per.example=TRUE,
↪ folds=NULL, seed=NULL, verbose=FALSE);
pxr.hier  <- precision.at.given.recall.levels.over.classes(target=ann, predicted=S.
↪hier, folds=NULL, seed=NULL, recall.levels=seq(from=0.1, to=1, by=0.1));
cat(taxon, organism, domain, flat, algorithm, "hierarchical performance done\n");

## storing
outname <- gsub("scores", "perfmeas", hier.file)
save(auc.flat, prc.flat, fmax.flat, pxr.flat, auc.hier, prc.hier, fmax.hier, pxr.hier,
↪ file=paste0(res.dir, outname), compress=TRUE);

## timing
timing.s <- proc.time() - start.time;
timing.m <- round(timing.s/(60),4);
timing.h <- round(timing.m/(60),4);
cat("\n");
cat("elapsed time:", timing.s["elapsed"], "(seconds)", "|", timing.m["elapsed"],
↪"(minutes)", "|" , timing.h["elapsed"], "(hours)", "\n\n");
```

To download and use the HEMDAG evaluation script:

```
## download
mkdir -p ~/hemdag/script/
cd ~/hemdag/script/
wget -nc https://raw.githubusercontent.com/marconotaro/hemdag/master/docs/playground/
↪script/hemdag-eval.R

## call
Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a gpav
```

Chunk evaluation (optional)

The above R call evaluates the performance of an HEMDAG algorithm just on a single dataset. Since HEMDAG can be virtually applied on top of any flat classifier, the Perl script below generates "chunks" of HEMDAG evaluation calls.

Note: The parameter regulating the number of chunk is `$m`, set by default to 12. Increase (resp. decrease) this value to rise (reduce) the number of HEMDAG evaluation calls to be executed in parallel.

```
#!/usr/bin/perl

use strict;
use warnings;
use Getopt::Long 'HelpMessage';

GetOptions(
    "org=s"   => \(my @orgs=""),
```

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```
    "flat=s" => \(my @flats=""),
    "alg=s"  => \(my @algs=""),
    "dmn=s"  => \(my @onts=""),
    'exp=s'  => \(my $exp='ho'),
    'chk=i'  => \(my $chk='12'),
    'help'   => sub {HelpMessage(0)},
) or HelpMessage(1);

@orgs=  split(/,/,join(',',@orgs));
@flats= split(/,/,join(',',@flats));
@algs=  split(/,/,join(',',@algs));
@onts=  split(/,/,join(',',@onts));

print "#!/bin/sh\n\n";
print "tot_start=\$(date +%s)\n\n";

my $k=0;  ## cpu number on which binding a task
foreach my $org (@orgs){
    foreach my $flat (@flats){
        foreach my $alg (@algs){
            foreach my $ont (@onts){
                $k++;
                my $cpu= $k-1;
                print "taskset -c $cpu Rscript hemdag-eval.R -o $org -d $ont -e $exp -f $flat -a $alg > $org"."_go_"."$ont"."_"."$flat"."_"."$alg"."_perfmeas.out 2> /dev/null &\n";
                if($k % $chk ==0){
                    print "\n";
                    print "wait\n";
                    print "\n";
                    $k=0;
                }
            }
        }
    }
}

print "\n";
print "tot_end=\$(date +%s)\n";
print "tot_elapsed_s=\$((tot_end-tot_start))\n";
print "tot_elapsed_m=\$((tot_elapsed_s/60))\n";
print "tot_elapsed_h=\$((tot_elapsed_m/60))\n";
print "printf \"grand total elapsed time:\t\$((tot_elapsed_s)) SECONDS\t\$((tot_elapsed_m)) MINUTES\t\$((tot_elapsed_h)) HOURS\"\n";
print "echo\n\n";

print "echo \"compute performance done\"\n\n";

__END__

=pod

=head1 NAME

call-hemdag-chunk - generate HEMDAG evaluation calls chunks

=head1 SYNOPSIS
```

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```
63
64      --org,-o    organism list. The list can have one or more elements. The elements␣
    ↪must be comma separated (7227_drome,9031_chick,..)
65      --flt,-f    flat classifier list. The list can have one or more elements. The␣
    ↪elements must be comma separated (svmlinear,ranger,..)
66      --alg,-a    hierarchical correction algorithm list. The list can have one or more␣
    ↪elements. The elements must be comma separated (gpav,isodescensTF,isodescensTAU,..)
67      --dmn,-d    gene ontology domain list. The list can have one or more elements.␣
    ↪The elements must be comma separated (bp,mf,cc)
68      --exp,-e    type of dataset on which evaluate HEMDAG. It can be: ho or cv (def.␣
    ↪ho)
69      --chk,-c    number of parallel evaluations to be computed before going to the␣
    ↪next block (def 12)
70      --help,-h   print this help
71
72  =cut
```

To download and use the Perl script that generates "chunks" of HEMDAG evaluation calls:

```
## download the perl script
mkdir -p ~/hemdag/script/
cd ~/hemdag/script/
wget -nc https://raw.githubusercontent.com/marconotaro/hemdag/master/docs/playground/
↪script/hemdag-chunk.pl

## generate chunk evaluation calls
perl hemdag-chunk.pl -o 7227_drome -d mf -f svmlinear -a gpav,isotprTF,isotprW,
↪isodescensTF,isodescensW,isodescensTAU -e ho -c 6 > hemdag-ho-eval.sh

## evaluate HEMDAG in chunks
bash hemdag-ho-eval.sh > out &
```

You can generate the calls that you wish, simply by extending the arguments of the arrays *@orgs, @flats, @algs, @onts* with the wanted values. For instance, by setting `-d bp,mf,cc`, the Perl script `hemdag-chunk.pl` returns 2 chunks of evaluation calls, the first made of 12 calls and the second one of 6 calls:

```
## call
perl hemdag-chunk.pl -o 7227_drome -d bp,mf,cc -f svmlinear -a gpav,isotprTF,isotprW,
↪isodescensTF,isodescensW,isodescensTAU -e ho -c 12

## stdout

#!/bin/sh

tot_start=$(date +%s)

taskset -c 0 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a gpav >␣
↪7227_drome_go_bp_svmlinear_gpav_perfmeas.out 2> /dev/null &
taskset -c 1 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a gpav >␣
↪7227_drome_go_mf_svmlinear_gpav_perfmeas.out 2> /dev/null &
taskset -c 2 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a gpav >␣
↪7227_drome_go_cc_svmlinear_gpav_perfmeas.out 2> /dev/null &
taskset -c 3 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a isotprTF␣
↪> 7227_drome_go_bp_svmlinear_isotprTF_perfmeas.out 2> /dev/null &
taskset -c 4 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a isotprTF␣
↪> 7227_drome_go_mf_svmlinear_isotprTF_perfmeas.out 2> /dev/null &
```

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```
taskset -c 5 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a isotprTF␣
↪> 7227_drome_go_cc_svmlinear_isotprTF_perfmeas.out 2> /dev/null &
taskset -c 6 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a isotprW >
↪ 7227_drome_go_bp_svmlinear_isotprW_perfmeas.out 2> /dev/null &
taskset -c 7 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a isotprW >
↪ 7227_drome_go_mf_svmlinear_isotprW_perfmeas.out 2> /dev/null &
taskset -c 8 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a isotprW >
↪ 7227_drome_go_cc_svmlinear_isotprW_perfmeas.out 2> /dev/null &
taskset -c 9 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a␣
↪isodescensTF > 7227_drome_go_bp_svmlinear_isodescensTF_perfmeas.out 2> /dev/null &
taskset -c 10 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a␣
↪isodescensTF > 7227_drome_go_mf_svmlinear_isodescensTF_perfmeas.out 2> /dev/null &
taskset -c 11 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a␣
↪isodescensTF > 7227_drome_go_cc_svmlinear_isodescensTF_perfmeas.out 2> /dev/null &

wait

taskset -c 0 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a␣
↪isodescensW > 7227_drome_go_bp_svmlinear_isodescensW_perfmeas.out 2> /dev/null &
taskset -c 1 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a␣
↪isodescensW > 7227_drome_go_mf_svmlinear_isodescensW_perfmeas.out 2> /dev/null &
taskset -c 2 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a␣
↪isodescensW > 7227_drome_go_cc_svmlinear_isodescensW_perfmeas.out 2> /dev/null &
taskset -c 3 Rscript hemdag-eval.R -o 7227_drome -d bp -e ho -f svmlinear -a␣
↪isodescensTAU > 7227_drome_go_bp_svmlinear_isodescensTAU_perfmeas.out 2> /dev/null &
taskset -c 4 Rscript hemdag-eval.R -o 7227_drome -d mf -e ho -f svmlinear -a␣
↪isodescensTAU > 7227_drome_go_mf_svmlinear_isodescensTAU_perfmeas.out 2> /dev/null &
taskset -c 5 Rscript hemdag-eval.R -o 7227_drome -d cc -e ho -f svmlinear -a␣
↪isodescensTAU > 7227_drome_go_cc_svmlinear_isodescensTAU_perfmeas.out 2> /dev/null &

tot_end=$(date +%s)
tot_elapsed_s=$((tot_end-tot_start))
tot_elapsed_m=$((tot_elapsed_s/60))
tot_elapsed_h=$((tot_elapsed_m/60))
printf "grand total elapsed time:   $((tot_elapsed_s)) SECONDS  $((tot_elapsed_m))␣
↪MINUTES  $((tot_elapsed_h)) HOURS"
echo

echo "compute performance done"
```

5.3 Cross-validated experiments

Here, to show how to use HEMDAG in cross-validated experiments, we use a pre-built dataset of the organism *Drosophila melanogaster* (DROME) that covers the annotations of the GO domain molecular function (MF). The graph and protein-GO term associations belong to the GO release of December 2017. The graph and the annotation matrix was built by adopting the following pipeline. The flat score matrix was obtained by using the random forest as flat learning method (model *ranger* in the R library caret package with the default parameter settings). For further details on the dataset, please refer to *HEMDAG: a family of modular and scalable hierarchical ensemble methods to improve Gene Ontology term prediction (submitted to Bioinformatics)*.

5.3.1 Download Data

All the required *.rda* files can be downloaded by using the following commands:

```
mkdir -p ~/hemdag/data/cv/
cd ~/hemdag/data/cv/
curl -Ss https://github.com/marconotaro/hemdag/tree/master/docs/playground/data/cv | grep -oP '(?<=href=").*?(?=\">)' | grep '.rda$' | perl -pe 's/blob\///' | perl -pe 's/^/https\:\/\/raw.githubusercontent.com/' | wget -nc -i -
```

Note: Note the change of the last directory from `ho/` to `cv/` compared to the data downloaded in the *Time-lapse hold-out experiments*.

With the command above, we download the following datasets:

- `7227_drome_go_mf_ann_20dec17.rda`: the annotation matrix;
- `7227_drome_go_mf_dag_20dec17.rda`: the graph;
- `7227_drome_go_mf_scores_pearson_100_feature_ranger_5fcv.rda`: the flat score matrix;

5.3.2 Programmatic Call

To execute any HEMDAG algorithm on cross-validated datasets, basically you must replace `-e ho` with `-e cv` in the various calls shown in section *Programmatic Call* for the time-split hold-out experiments.

Note:

1. the `hemdag-call.R` script must be called in `~/hemdag/script/`;
2. for the examples shown below the tuning of hyper-parameters takes around one hour;
3. the flat classifier adopted for the cross-validated experiments performed here is not the *svm* (`-f svmlinear`), but the *random forest* (`-f ranger`);
4. the output HEMDAG score matrices are stored in `~/hemdag/res/cv/` (note the shift of the last directory);

For instance, to call the 6 HEMDAG on cross-validated datasets just type:

```
## GPAV
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -b none -t gpav -l -n 12

## isotprTF
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -p children -b threshold.free -t gpav -l -n 12

## isotprW
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -p children -b weighted.threshold.free -t gpav -w "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -k 5 -l -n 12

## isodescensTF
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -p descendants -b threshold.free -t gpav -l -n 12

## isodescensW
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -p descendants -b weighted.threshold.free -t gpav -w "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -k 5 -l -n 12
```

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```
## isodescensTAU
Rscript hemdag-call.R -o 7227_drome -d mf -e cv -f ranger -p descendants -b tau -t␣
↪gpav -c "seq(from=0.1, to=0.9, by=0.1)" -m auprc -s 23 -k 5 -l -n 12
```

5.3.3 Check Hierarchical Constraints

To check that HEMDAG does not violate hierarchical constraints imposed by the GO MF hierarchy in the cross-validated datasets obtained above, just replace replace `-e ho` with `-e cv` and `-f svmlinear` with `-f ranger` in the *Check Hierarchical Constraints* script:

```
algotihms=("gpav" "isotprTF" "isotprW" "isodescensTF" "isodescensW" "isodescensTAU")

for ((i=0; i<${#algotihms[@]}; i++)); do
    Rscript hemdag-checker.R -o 7227_drome -d mf -e cv -f ranger -a ${algotihms[$i]}
done;
```

5.3.4 Evaluation

To evaluate HEMDAG in the cross-validated experiments performed above, just replace replace `-e ho` with `-e cv` and `-f svmlinear` with `-f ranger` in the *Evaluation* script:

Note: the evaluation of the cross-validated dataset used here takes around 30 minutes – the slowest metric is `PXR`.

```
## single evaluation call
Rscript hemdag-eval.R -o 7227_drome -d mf -e cv -f ranger -a gpav

## generate chunk evaluation calls
perl hemdag-chunk.pl -o 7227_drome -d mf -f ranger -a gpav,isotprTF,isotprW,
↪isodescensTF,isodescensW,isodescensTAU -e cv -c 6 > hemdag-cv-eval.sh

## evaluate HEMDAG in chunks
bash hemdag-cv-eval.sh > out &
```

CHAPTER 6

Frequently Asked Questions

6.1 Where are the questions?

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

CHAPTER 7

Cite HEMDAG

If you use HEMDAG package please cite the following references:

- Notaro M, Marco Frasca, Alessandro Petrini, Jessica Gliozzo, and Giorgio Valentini. HEMDAG: a family of modular and scalable hierarchical ensemble methods to improve gene ontology term prediction. Submitted to Bioinformatics.
- Marco Notaro, Max Schubach, Peter N. Robinson, and Giorgio Valentini. Prediction of Human Phenotype Ontology terms by means of hierarchical ensemble methods. *BMC Bioinformatics*, 18(1):449, December 2017. doi:10.1186/s12859-017-1854-y.

CHAPTER 8

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:

8.1 Types of Contributions

8.1.1 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.

8.1.2 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.

8.1.3 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.

8.1.4 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.

8.1.5 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 :)

8.2 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
:::::::::
```

8.3 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
```

8.4 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.

8.5 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 `NEWS.md` file.

CHAPTER 9

Authors

in alphabetical order

- Marco Notaro (maintainer)
- Max Schubach
- Giorgio Valentini

CHAPTER 10

History

10.1 HEMDAG 2.7.4

10.1.1 Changes

- remove extra input parameter `f.criterion` from `tpr.dag.cv`, `tpr.dag.holdout`, `find.best.f` and `compute.fmax`: type of F-measure used to select the best F-measure is always the harmonic mean between the average precision and recall (`f.criterion="F"`) and never the F-measure computed as average across examples (`f.criterion="avF"`);
- fix a minor bug in `tpr.dag.holdout`;
- add warning checks in `tpr.dag.cv` and `tpr.dag.holdout`;
- improve some test cases and manual;

10.2 HEMDAG 2.7.3

10.2.1 New Features

- add `build.scores.matrix.from.list`;
- add `build.scores.matrix.from.tupla`;
- add several test cases;

10.2.2 Changes

- streamline and lighten HEMDAG's hierarchical functions (namespace clearer and lighter);
- rename the following functions:
  - htd-dag:

    * Do.HTD -> htd.vanilla;
    * Do.HTD.holdout -> htd.holdout;
  - obozinski heuristic methods:
    * heuristic.max -> obozinski.max;
    * heuristic.and -> obozinski.and;
    * heuristic.or -> obozinski.or;
    * Do.heuristic.methods -> obozinski.methods;
    * Do.heuristic.methods.holdout -> obozinski.holdout;
  - gpav:
    * GPAV -> gpav;
    * GPAV.over.examples -> gpav.over.examples;
    * GPAV.parallel -> gpav.parallel;
    * Do.GPAV -> gpav.vanilla;
    * Do.GPAV.holdout -> gpav.holdout;
  - tpr-dag:
    * TPR.DAG -> tpr.dag;
    * Do.TPR.DAG -> tpr.dag.cv;
    * Do.TPR.DAG.holdout -> tpr.dag.holdout;
  - utility functions:
    * get.parents -> build.parents;
    * get.parents.top.down -> build.parents.top.down;
    * get.parents.bottom.up -> build.parents.bottom.up;
    * get.parents.topological.sorting -> build.parents.topological.sorting;
    * get.children.top.down -> build.children.top.down;
    * get.children.bottom.up -> build.children.bottom.up;
    * check.DAG.integrity -> check.dag.integrity;
    * do.subgraph -> build.subgraph;
    * do.submatrix -> build.submatrix;
    * do.stratified.cv.data.single.class -> stratified.cv.data.single.class;
    * do.stratified.cv.data.over.classes -> stratified.cv.data.over.classes;
    * do.unstratified.cv.data -> unstratified.cv.data;
    * do.edges.from.HPO.obo -> build.edges.from.hpo.obo;
  - performance metrics:
    * AUPRC.single.class -> auprc.single.class;
    * AUPRC.single.over.classes -> auprc.single.over.classes;

    * `AUROC.single.class` –> `auroc.single.class`;
    * `AUROC.single.over.classes` –> `auroc.single.over.classes`;
    * `compute.Fmeasure.multilabel` –> `compute.fmax`;
- remove the following functions (no more needed):
  - `Do.flat.scores.normalization`;
  - `Do.full.annotation.matrix`;
- improve manual;
- make HEMDAG's documentation clearer and less redundant;

10.3 HEMDAG 2.6.1

10.3.1 Changes

- fix `stringsAsFactors` issue – link;

10.4 HEMDAG 2.6.0

10.4.1 Changes

- fix NAMESPACE notes in CRAN checks;
- add link to the GitHub repository `obogaf::parser`;
- adjust link to read the docs;

10.5 HEMDAG 2.5.9

10.5.1 New Features

- add `build.consistent.graph`;

10.5.2 Changes

- add some warning checks in functions that compute performance metrics;
- improve some graph utility functions;
- improve manual;
- improve tutorial on read the docs – link;
- make namespace clearer;
- fix minor bugs;
- remove defunct functions;

10.6 HEMDAG 2.4.8

10.6.1 Changes

- fix a minor bug in `Do.GPAV.holdout`;
- improve package description;

10.7 HEMDAG 2.4.7

10.7.1 New Features

- fix degenerate case in `precision.at.all.recall.levels.single.class` (labels are all negatives/positives);
- fix degenerate case in `precision.at.given.recall.levels.over.classes` (labels in a fold are all negatives/positives);
- fix degenerate case in `do.stratified.cv.data.single.class` (sampling of the labels with just one positive/negative);
- add 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`;

10.7.2 Changes

- improve manual;

10.8 HEMDAG 2.3.6

10.8.1 New Features

- add `lexicographical.topological.sort`;

10.8.2 Changes

- fix minor bugs;
- improve manual;

10.9 HEMDAG 2.2.5

10.9.1 New Features

- precision-recall performance computed through `precrec` package:
  - add `precision.at.all.recall.levels.single.class`;
  - `PXR.at.multiple.recall.levels.over.classes` –> `precision.at.given.recall.levels.over.classes`;
- improve IO functions: the extension of the input or output file can be or plain text (`.txt`) or compressed (`.gz`);

10.9.2 Changes

- fix minor bugs;
- improve manual;

10.10 HEMDAG 2.2.4

10.10.1 Changes

- fix `CRAN` Package Check Results: remove unneeded header and define from `GPAV C++` source code

10.11 HEMDAG 2.2.3

10.11.1 New Features

- add `GPAV` algorithm (Burdakov et al., *Journal of Computational Mathematics*, 2006 – link);
- Embed `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");`

10.11.2 Changes

- improve manual;

10.11.3 AUTHOR

- add **Alessandro Petrini** as author for his contribution in writing the `C++` code of `GPAV` algorithm;

10.12 HEMDAG 2.1.3

10.12.1 Changes

- various fixes from 2.1.2

10.13 HEMDAG 2.1.2

10.13.1 New Features

- improve performance metrics:
  - add `compute.Fmeasure.multilabel`;
  - add `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**;
- improve the high-level hierarchical ensemble functions:
  - embed the new performance metric functions;
  - add the parameter `metric`: maximization by `FMAX` or `PRC` (see manual for further details);
  - add some checkers (warning/stop messages) to make the library more user-friendly;

10.13.2 Changes

- improve manual;

10.14 HEMDAG 2.0.1

10.14.1 Changes

- fix bug in `do.stratified.cv.data.single.class`;

10.15 HEMDAG 2.0.0

10.15.1 New Features

- add `TPR-DAG`: function gathering several hierarchical ensemble variants;
- add `Do.TPR.DAG`: high-level function to run `TPR-DAG` **cross-validated** experiments;
- add `Do.TPR.DAG.holdout`: high-level functions to run `TPR-DAG` **holdout** experiments;
- The following `TPR-DAG` and `DESCENS` high-level functions were remove:
  - `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`;

NOTE: all the removed functions can be run opportunely by 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);

10.15.2 Changes

- improve manual;

10.16 HEMDAG 1.1.1

10.16.1 New Features

- add `DESCENS` algorithm;
- add Heuristic Methods `Max`, `And`, `Or` (Obozinski et al., Genome Biology, 2008 – link);
- add `tupla.matrix` function;

10.16.2 Changes

- improve manual;
- add link to the GitHub repository `HPOparser` (note: from version `2.6.0` `HPOparser` was changed in `obogaf::parser`);
- add `CITATION` file;

10.17 HEMDAG 1.0.0

10.17.1 Package Genesis

CHAPTER 11

HEMDAG License

11.1 GNU GENERAL PUBLIC LICENSE

Version 3, 29 June 2007

11.2 Preamble

The GNU General Public License is a free, copyleft license for software and other kinds of works.

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The precise terms and conditions for copying, distribution and modification follow.

11.3 TERMS AND CONDITIONS

11.3.1 0. Definitions.

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11.3.2 1. Source Code.

The "source code" for a work means the preferred form of the work for making modifications to it. "Object code" means any non-source form of a work.

A "Standard Interface" means an interface that either is an official standard defined by a recognized standards body, or, in the case of interfaces specified for a particular programming language, one that is widely used among developers working in that language.

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The "Corresponding Source" for a work in object code form means all the source code needed to generate, install, and (for an executable work) run the object code and to modify the work, including scripts to control those activities. However, it does not include the work's System Libraries, or general-purpose tools or generally available free programs which are used unmodified in performing those activities but which are not part of the work. For example, Corresponding Source includes interface definition files associated with source files for the work, and the source code for shared libraries and dynamically linked subprograms that the work is specifically designed to require, such as by intimate data communication or control flow between those subprograms and other parts of the work.

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```
<one line to give the program's name and a brief idea of what it does.>
Copyright (C) <year>  <name of author>

This program is free software: you can redistribute it and/or modify
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```

Also add information on how to contact you by electronic and paper mail.

If the program does terminal interaction, make it output a short notice like this when it starts in an interactive mode:

```
<program>  Copyright (C) <year>  <name of author>
This program comes with ABSOLUTELY NO WARRANTY; for details type `show w'.
This is free software, and you are welcome to redistribute it
under certain conditions; type `show c' for details.
```

The hypothetical commands ‘show w’ and ‘show c’ should show the appropriate parts of the General Public License. Of course, your program's commands might be different; for a GUI interface, you would use an "about box".

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Bibliography

[1] Oleg Burdakov, Oleg Sysoev, Anders Grimvall, and Mohamed Hussian. *An O(n2) Algorithm for Isotonic Regression*, chapter 83, pages 25–33. Springer US, Boston, MA, 2006. URL: https://doi.org/10.1007/0-387-30065-1_3, doi:10.1007/0-387-30065-1_3.

[2] Yuxiang Jiang, Tal Ronnen Oron, Wyatt T. Clark, Asma R. Bankapur, Daniel D'Andrea, Rosalba Lepore, Christopher S. Funk, Indika Kahanda, Karin M. Verspoor, Asa Ben-Hur, Da Chen Emily Koo, Duncan Penfold-Brown, Dennis Shasha, Noah Youngs, Richard Bonneau, Alexandra Lin, Sayed M. E. Sahraeian, Pier Luigi Martelli, Giuseppe Profiti, Rita Casadio, Renzhi Cao, Zhaolong Zhong, Jianlin Cheng, Adrian Altenhoff, Nives Skunca, Christophe Dessimoz, Tunca Dogan, Kai Hakala, Suwisa Kaewphan, Farrokh Mehryary, Tapio Salakoski, Filip Ginter, Hai Fang, Ben Smithers, Matt Oates, Julian Gough, Petri Törönen, Patrik Koskinen, Liisa Holm, Ching-Tai Chen, Wen-Lian Hsu, Kevin Bryson, Domenico Cozzetto, Federico Minneci, David T. Jones, Samuel Chapman, Dukka BKC, Ishita K. Khan, Daisuke Kihara, Dan Ofer, Nadav Rappoport, Amos Stern, Elena Cibrian-Uhalte, Paul Denny, Rebecca E. Foulger, Reija Hieta, Duncan Legge, Ruth C. Lovering, Michele Magrane, Anna N. Melidoni, Prudence Mutowo-Meullenet, Klemens Pichler, Aleksandra Shypitsyna, Biao Li, Pooya Zakeri, Sarah ElShal, Léon-Charles Tranchevent, Sayoni Das, Natalie L. Dawson, David Lee, Jonathan G. Lees, Ian Sillitoe, Prajwal Bhat, Tamás Nepusz, Alfonso E. Romero, Rajkumar Sasidharan, Haixuan Yang, Alberto Paccanaro, Jesse Gillis, Adriana E. Sedeño-Cortés, Paul Pavlidis, Shou Feng, Juan M. Cejuela, Tatyana Goldberg, Tobias Hamp, Lothar Richter, Asaf Salamov, Toni Gabaldon, Marina Marcet-Houben, Fran Supek, Qingtian Gong, Wei Ning, Yuanpeng Zhou, Weidong Tian, Marco Falda, Paolo Fontana, Enrico Lavezzo, Stefano Toppo, Carlo Ferrari, Manuel Giollo, Damiano Piovesan, Silvio C.E. Tosatto, Angela del Pozo, José M. Fernández, Paolo Maietta, Alfonso Valencia, Michael L. Tress, Alfredo Benso, Stefano Di Carlo, Gianfranco Politano, Alessandro Savino, Hafeez Ur Rehman, Matteo Re, Marco Mesiti, Giorgio Valentini, Joachim W. Bargsten, Aalt D. J. van Dijk, Branislava Gemovic, Sanja Glisic, Vladmir Perovic, Veljko Veljkovic, Nevena Veljkovic, Danillo C. Almeida-e-Silva, Ricardo Z. N. Vencio, Malvika Sharan, Jörg Vogel, Lakesh Kansakar, Shanshan Zhang, Slobodan Vucetic, Zheng Wang, Michael J. E. Sternberg, Mark N. Wass, Rachael P. Huntley, Maria J. Martin, Claire O'Donovan, Peter N. Robinson, Yves Moreau, Anna Tramontano, Patricia C. Babbitt, Steven E. Brenner, Michal Linial, Christine A. Orengo, Burkhard Rost, Casey S. Greene, Sean D. Mooney, Iddo Friedberg, and Predrag Radivojac. An expanded evaluation of protein function prediction methods shows an improvement in accuracy. *Genome Biology*, 17(1):184, Sep 2016. URL: https://doi.org/10.1186/s13059-016-1037-6, doi:10.1186/s13059-016-1037-6.

[3] Marco Notaro, Max Schubach, Peter N. Robinson, and Giorgio Valentini. Prediction of Human Phenotype Ontology terms by means of hierarchical ensemble methods. *BMC Bioinformatics*, 18(1):449, December 2017. URL: http://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-017-1854-y (visited on 2021-02-01), doi:10.1186/s12859-017-1854-y.

[4] G. Obozinski, G. Lanckriet, C. Grant, Jordan. M., and W.S. Noble. Consistent probabilistic output for protein function prediction. *Genome Biology*, 9:135–142, 2008. URL: http://europepmc.org/articles/PMC2447540, doi:10.1186/gb-2008-9-s1-s6.

[5] Giorgio Valentini. True path rule hierarchical ensembles for genome-wide gene function prediction. *IEEE/ACM Trans. Comput. Biology Bioinform.*, 8(3):832–847, 2011. URL: https://doi.org/10.1109/TCBB.2010.38, doi:10.1109/TCBB.2010.38.