Hierarchy exploitation to detect missing annotations on hierarchical multi-label classification

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Abstract. The availability of genomic data has grown exponentially in the last decade, mainly due to the development of new sequencing technologies. Based on the interactions between genes (and gene products) extracted from the increasing genomic data, numerous studies have focused on the identification of associations between genes and functions. While these studies have shown great promise, the problem of annotating genes with functions remains an open challenge. In this work, we present a method to detect missing annotations in hierarchical multi-label classification datasets. We propose a method that exploits the class hierarchy by computing aggregated probabilities to the paths of classes from the leaves to the root for each instance. The proposed method is presented in the context of predicting missing gene function annotations, where these aggregated probabilities are further used to select a set of annotations to be verified through in vivo experiments. The experiments on Oriza sativa Japonica, a variety of rice, showcase that incorporating the hierarchy of classes into the method often improves the predictive performance and our proposed method yields superior results when compared to competitor methods from the literature.

Genomic data has become exponentially available in the last decade, mainly due to the development of new technologies, including gene expression profiling generated with RNA sequencing (Ranganathan, Gibrskov, Nakai and Schönbach, 2019). Based on the interactions between genes (and gene products) extracted from the increasing genomic data, numerous studies have focused on the identification of associations between genes and functions (Rust, Mongin and Birney, 2002; Vandepoele, Quimbaya, Casneuf, De Veylder and Van de Peer, 2009; van Dam, Võsa, van der Graaf, Franke and de Magalhães, 2017).
Biologically, this task is usually addressed through in vivo experiments that require a significant investment of money, time, and effort given the combinatorial nature of the problem (i.e., a gene or a gene product may be associated with multiple functions and the number of functions is large (Zhou, Young, Santrosyan, Chen, Yan and Winzeler, 2005)). Approaches have emerged as alternatives to overcome these limitations by combining mathematical, probabilistic, and computational methods with biological data (see, e.g., Deng, Zhang, Mehta, Chen and Sun (2003); Luo, Yang, Zhong, Gao, Khan, Thompson and Zhou (2007); Jiang, Narjiai, Steffen, Kasif and Kolaczyk (2008); Cho, Berger and Peng (2016); Nakano, Lietaert and Vens (2019)). While these studies have shown great promise, the problem of annotating genes with functions remains an open challenge.

Gene functions, defined by Gene Ontology (GO), are structured in a hierarchy (Gene Ontology Consortium, 2019). For this reason, the problem of predicting gene functions (or functional annotation) is generally modeled as a hierarchical multi-label classification (HMC) task. The objective of HMC is to fit a predictor that maps a set of instances (e.g., genes of an organism) to a set of hierarchically organized labels (e.g., biological processes in the GO hierarchy), while respecting the hierarchy constraint among them. The hierarchy constraint states that if an instance is predicted to have a particular class, the ancestor classes must also be included in the prediction of such an instance (Vens, Struyf, Schietgat, Dzeroski and Blockeel, 2008; Silla and Freitas, 2011).

Gene functional annotation is generally addressed as a (hierarchical) multi-label classification problem, under the assumption that the functional information available (present annotations as well as the absent ones) can be trusted and can be used as a training set to construct an inductive model. However, it is well known that functional information of genes (and gene products) is incomplete (Valentini, 2009). Thus, it is important to use methods able to handle incomplete labeled data and that focus on detecting annotations that are missing (Yu, Zhu and Domeniconi, 2015; Sabzevari, Martínez-Muñoz and Suárez, 2018).

This work introduces hierRarchical multi-labEl cIAssification to dIScover mIssinG aNnotations (REASSIGN), a method to detect missing annotations based on HMC that exploits the class hierarchy to select a set of annotations (e.g., gene-function associations). Its specific purpose is twofold: first, it can be used to complete a given annotation dataset; second, the completed dataset can be used to create better supervised models.
To this aim, HMC classifiers based on tree ensembles are used to compute the probability of association of every instance-class pair (e.g., genes and biological functions). For each gene, aggregated probabilities are computed for the paths in the class hierarchy, where a path is a sequence of classes with ancestral relations from a leaf to the root of the hierarchy. Aggregated probabilities are used to group paths of classes instead of using single instance-pair associations. Based on the aggregated probabilities of the paths and genes, a set of annotations absent in the given annotation dataset and complying with the hierarchy constraint is selected as output.

The proposed method is evaluated on *Oryza sativa Japonica*, a variety of rice, and it is compared to different methods from the literature (Sabzevari et al., 2018; Nakano et al., 2019). In addition, eight HMC datasets of biological processes from the GO hierarchy for rice are introduced. These datasets correspond to subsets of rice genes and biological processes (GO sub-hierarchies), whose features are structural properties and embeddings of the gene co-expression network. The results show that the proposed method outperforms the comparison methods in most cases. We find that exploiting the hierarchy of functions helps to better identify gene-function associations. The evidence suggests that this is a promising approach for reducing the cost, time, and effort required for experimental verification in a lab.

The remainder of the paper is organized as follows. Section 1 provides some theoretical preliminaries. Section 2 reviews related work. Section 3 introduces the method to detect missing annotations exploiting the class hierarchy. Section 4 describes the datasets and experimental setup for the gene function prediction in *Oryza sativa Japonica*, followed by the results and discussion in Section 5. Finally, Section 6 draws concluding remarks and future research directions.

1 Preliminaries

This section presents preliminaries on hierarchical multi-label classification.

1.1 Hierarchical Multi-label Classification

Classification problems may be defined using binary, multi-class, or multi-label prediction tasks, where predictions consist of a single class, a single class from a set of mutually exclusive classes, and a subset of classes, respectively.
Hierarchical multi-label classification is an extension of the multi-label classification, that addresses the task of structured output prediction where the classes are organized into a hierarchy (such as the GO) and instances may belong to multiple classes (Vens et al., 2008). Formally, a HMC task is defined as follows:

**Definition 1.** Let \( I \) be an instance space (set of instances) and \((C, \leq_h)\) a class hierarchy (where \( C \) is a set of classes and \( \leq_h \) is a partial order). The objective is to find a function \( \psi : I \rightarrow 2^C \) such that \( c \in \psi(x) \implies \forall c' \leq_h c : c' \in \psi(x) \) (i.e., \( \psi \) complies with the hierarchy constraint).

Silla and Freitas (2011) exposed that there are two types of methods to explore the hierarchical structure. First, local or top-down classifiers refer to partially predicting the classes in the hierarchy from top to bottom taking into account the predictions of parent classes. Second, global classifiers refer to a single classifier that considers the entire hierarchy at once.

Overlooking the class relationships often leads to situations where an instance is predicted to have a particular class, but the ancestor classes are not included in the prediction. In other words, the prediction does not satisfy the hierarchy constraint. Satisfying ancestral constraints is also referred as the true-path rule in biology (Valentini, 2009; Ashburner, Ball, Blake, Botstein, Butler, Cherry, Davis, Dolinski, Dwight, Eppig, Harris, Hill, Issel-Tarver, Kasarskis, Lewis, Matese, Richardson, Ringwald, Rubin and Sherlock, 2000).

## 2 Related Work

In this section, we present a literature overview of studies on hierarchical multi-label classification and prediction of gene (or gene products) functions.

Some studies have focused on hierarchical multi-label classification across different domains. For example, Dimitrovski, Kocev, Loskovska and Dzeroski (2010) presented a global approach that addresses HMC using random forests of predictive clustering trees (PCTs) to annotate images. Ramírez-Corona, Sucar and Morales (2016) introduced a local approach based on chained path evaluation. It used a classifier to train non-leaf classes (i.e., classes with at least one descendant) in the hierarchy, including information on ancestral relations through extra features with the prediction of parent classes.
Other studies have focus on the gene (or gene products) function prediction problem. For example, Jiang et al. (2008) proposed Hierarchical Binomial-Neighborhood, a probabilistic and local HMC approach to predict protein functions in yeast. Their results showed that their method outperforms approaches based on independent class prediction. However, it requires a high computational cost to compute probabilities of every protein-function pair. Yu et al. (2015) presented an approach to replenish the missing function labels and to predict functions for unlabeled proteins in a hierarchical manner assuming that the labeled data was incomplete. Their method combines the hierarchical structure of functions and the similarity between labels to identify interaction between proteins and functions using guilt by association (see Petsko (2009)).

Zhao, Fu, Wang, Guo and Yu (2019) presented Gene Ontology Hierarchy Preserving Hashing, a gene function prediction method that retains the hierarchical order between GO functions. It used a hashing technique based on the taxonomic similarity between functions to capture the GO hierarchy and predict gene functions. Their results showed that their method preserved the GO hierarchy and helped to improve prediction performance. Nakano et al. (2019) performed a comparison among publicly available HMC methods. According to their results, Clus-Ensemble, a random forest of predictive clustering trees adapted to HMC (Schietgat, Vens, Struyf, Blockeel, Kocev and Džeroski, 2010), provided superior results. However, the authors did not explicitly propose a method to identify missing annotations on HMC problems.

Zhou, Wang, Zhang, Guo and Yu (2020) presented an approach to predict functions of maize proteins, called Deep Graph Convolutional network model. It used amino acid sequences of proteins and the GO hierarchy to predict functions of proteins. Their results showed that their approach is a powerful tool to integrate amino acid data and the GO structure to accurately annotate proteins. Similarly, Cruz, De Meyer, Ampe, Sprenger, Herman, Van Hautegem, De Block, Inzé, Nelissen and Maere (2020) aimed to predict the phenotypes and functions associated to maize genes using (i) hierarchical clustering based on datasets of transcriptome (set of molecules produced in transcription) and metabolome (set of metabolites found within an organism), and (ii) GO enrichment analyses. Their results showed that profiling individual plants is a promising experimental design for narrowing down the lab-field gap.

Romero, Ramírez, Finke and Rocha (2022b) presented a method that combines the functional information with the gene co-expression network of an organism to extract features that capture the details of the GO hi-
erarchy using spectral clustering. Their results showed that the extracted features are key to improve the performance of the gene function prediction task on rice, using a global HMC approach of random forests of decision trees.

Other studies addressed gene function prediction, obtaining state-of-the-art performance for different case studies. However they do not take into account hierarchical dependencies between classes as they focus on multi-class problems instead (see, e.g., Abu-El-Haija, Kapoor, Perozzi and Lee (2018); Hamilton, Ying and Leskovec (2017); Kipf and Welling (2016); Makrodimitris, van Ham and Reinders (2020); Chen, Li, Tan, Qiao, Pan, Jiang and Chen (2021); Xiao, Wang, Dai and Guo (2021)). Therefore, such studies can not be compared directly to assess hierarchical multi-label classification.

3 The proposed method

In this section, we introduce a definition of the problem of predicting missing gene functions annotations and present a general method to detect missing annotations in HMC problems.

3.1 Problem definition

Given a set of genes $V$, a set of biological functions $A$, and an annotation function $\phi : V \rightarrow 2^A$, where each gene is associated with the collection of biological functions to which it is known to be related (e.g., verified through in vivo experiments). The goal is to use the information represented by $\phi$, together with additional information about $V$ (e.g., genomic sequences or gene co-expression data), to obtain a function $\psi : V \rightarrow 2^A$ that augments $\phi$ with previously undetected annotations. The problem of predicting gene functions is generally addressed as a HMC task, i.e., $V$ corresponds to the instance space $I$, the biological functions are structured in a hierarchy $(A, \leq_h)$ (e.g., Gene Ontology hierarchy), and the functions $\phi$ and $\psi$ comply with the hierarchy constraint. Associations between genes and functions not present in $\phi$ have either not (yet) been found through in vivo experiments or do not exist in a biological sense. The new associations identified by $\psi$ are a suggestion of functions that need to be verified through in vivo experiments. The function $\psi$ can be built from a predictor of gene functions, e.g., based on a supervised machine learning model.

Formally, the gene function prediction problem is defined as follows:
Definition 2. Let $V$ be a set of genes, $A$ a set of biological functions, and $\phi : V \rightarrow 2^A$ a function describing known annotations. The objective is to obtain a function $\psi : V \rightarrow 2^A$ that augments $\phi$ and complies with the hierarchy constraint.

3.2 REASSIGN

Given a HMC problem with instances $I$ and a class hierarchy $(C, \leq_h)$, we introduce hieRarchical multi-labEl clAsSification to diScover mIssinG aNnotations (REASSIGN), a method to detect missing annotations for $I$.

The input of the method are a dataset $X$ comprising $|I|$ instances and $|F|$ features, the class hierarchy represented as a tree with $|C|$ vertices (e.g., biological functions of genes), and an annotation function (e.g., $\phi$) represented as a label matrix $Y$ with an assignment of each instance in $I$ to a subset of classes from $C$ (i.e., $Y : I \times C \rightarrow \{0,1\}$). The output of the method is a suggestion of missing annotations in $Y$, i.e., a set of annotations whose value in $Y$ is originally 0, but which are believed to be false negatives. Naturally, the suggested annotations must still satisfy the hierarchy constraint.

HMC datasets often have a large and imbalanced label set, specially on deeper levels. In particular, despite being more informative, deeper classes in the hierarchy have less annotations (are sparse), leading to low predicted probabilities and predictive performance overall. As a possible solution, we propose a method that exploits the hierarchy of classes to compute an aggregated probability per instance and path of classes in the hierarchy, relying on the prediction probabilities provided by a HMC classifier. As a result, at most $I \cdot p$ aggregated probabilities are computed corresponding to all combinations between instances and paths, where $p$ is the total number of paths from the leaves to the root in the hierarchy. The aggregated probabilities of the paths are then used as the criterion to select a set of annotations.

The proposed method consists mainly of 3 steps. First, a HMC classifier is used to compute the probability of every instance-class association, i.e., compute $Y' : I \times C \rightarrow [0,1]$. Any local or global HMC classifier can be used (e.g., tree ensembles or neural networks), providing that the hierarchy constraint is satisfied.

Second, aggregated probabilities are computed for each instance and each path from the leaves to the root in the class hierarchy by using the predicted probabilities of the annotations in $Y'$. That is, only the paths
that go to leaves in the class hierarchy are considered, because the addressed problem is leaf mandatory (Silla and Freitas, 2011). Importantly, only new potential annotations are used to compute aggregated probabilities, i.e., instance-class associations satisfying

\[(\forall i, c : i \in I \land c \in C | Y[i, c] = 0 \land Y'[i, c] > 0).\]

Different ways of aggregating the probabilities can be used; in this work, we used the average, sum, and minimum. Each aggregation function is considered an independent variation of the proposed method:

- **REASSIGN (min)**: aggregates probabilities by using the minimum probability along the path considered. Paths are identified by their most informative (deepest) class;
- **REASSIGN (sum)**: aggregates probabilities by using the sum of the probabilities along the path considered. The longer and deeper the path, the larger the sum, and therefore, more informative classes are considered;
- **REASSIGN (average)**: aggregates probabilities by using the average of the probabilities along the path considered. It balances the probabilities of the more informative (deeper) and less informative (shallower) classes.

Fig. 1: Given an instance, aggregated probabilities are computed for every path in the class hierarchy from the leaves to the root using the average, sum and minimum of the probabilities of the annotations in the path. Only those annotations whose value is 0 in \(Y\) are considered in the paths. This Figure is best viewed in colors.

These variations are illustrated in Figure 1 where we exemplify how aggregated probabilities of the paths in the hierarchy are computed for a
given instance. Classes coloured with green denote that the instance \(i \in I\) is already associated to the class \(c \in C\) in \(Y\) (i.e., \(Y[i, c] = 1\)), while classes coloured in red denote that the instance is not associated to the class (i.e., \(Y[i, c] = 0\)). Since the method is focused in detecting missing annotations (i.e., instance-class pairs associations that have not been identified), only classes coloured with red are used to compute aggregated probabilities. Reinforcing the objective of detecting missing annotations through new paths in the hierarchy. Note that the path \(d \rightarrow a\) is not considered since it does not go to a leaf node.

**Algorithm 1**: Hierarchical multi-label classification to discover missing annotations (REASSIGN)

1. **input:**
   - \(X\): dataset
   - \((C, \leq_h)\): class hierarchy
   - \(Y : I \times C \rightarrow \{0, 1\}\): instance-class associations
   - \(f(\cdot)\): aggregation function
   - \(N_p\): Number of paths to select

2. **output:**
   - \(\text{top}_\text{annot} \subseteq \{(i, c) : i \in I \land c \in C\}\): subset of annotations

3. compute \(Y' : I \times C \rightarrow [0, 1]\) using a HMC method s.t. \(Y'\) complies to the hierarchy constraint.

4. set \(\text{all}_\text{paths} = \{\}\)

5. **foreach** instance \(i \in I\)
   - **foreach** path \(\in (C, \leq_h)\)
     - **foreach** \(c \in \text{path}\)
       - **if** \(Y[i, c] = 0 \land Y'[i, c] > 0\)
         - add \(Y'[i, c]\) to \(\text{probs}\)
         - add \((i, c)\) to \(\text{annot}\)
       - end
     - end
   - add \((f(\text{probs}), \text{annot})\) to \(\text{all}_\text{paths}\)
   - end
   - end
   - sort \(\text{all}_\text{paths}\) in decreasing order
   - set \(\text{top}_\text{paths} = \text{all}_\text{paths}[0 \ldots N_p]\)
   - set \(\text{top}_\text{annot} = \{\}\)
   - **foreach** \((x, \text{annot}) \in \text{top}_\text{paths}\)
     - add \(\text{annot}\) to \(\text{top}_\text{annot}\)
   - end

7. remove duplicates from \(\text{top}_\text{annot}\)

8. **return** \(\text{top}_\text{annot}\)

At last, some paths are selected using their aggregated probability as selection criterion. The number of paths to be selected is a parame-
ter denoted as $N_p$. All annotations within the top $N_p$ paths with higher aggregated probability are selected. Note that there might be common annotations between the paths, so duplicates have to be removed. For instance, paths $i \rightarrow f$ and $h \rightarrow f$ in Figure 1 share the class $f$, hence in case both paths are selected, the association between the instance and class $f$ will be duplicated. The resulting number of annotations is denoted as $N$ and used for comparison with other methods. A detailed description of the proposed method is presented in Algorithm 1.1.

4 Experimental setup

In this section, a detailed description of the employed databases, comparison methods, and evaluation measures is presented.

4.1 Datasets

Two datasets are built using the functional information and the gene co-expression network (GCN) for *Oryza sativa Japonica*, a variety of rice (Kurata and Yamazaki, 2006; Childs, Davidson and Buell, 2011; Sakai, Lee, Tanaka, Numa, Kim, Kawahara, Wakimoto, Yang, Iwamoto, Abe, Yamada, Muto, Inokuchi, Ikemura, Matsumoto, Sasaki and Itoh, 2013).

The functional information depicts associations between genes and functions previously identified through *in vivo* or *in silico* experiments. For this work, the functional information is imported from DAVID Bioinformatics Resources (Huang, Sherman and Lempicki, 2009), that contains annotations of biological processes, i.e., pathways to which a gene contributes. Note that genes may be associated to several biological processes, and biological processes may be associated to multiple genes. The datasets are built using two different versions of the functional information of rice. That is, each dataset has a different label matrix, but they share the instances and features. One dataset (the older version) is used to train and build the models, whereas the other one is used to evaluate the detected missing annotations.

The first version of the functional information is from 2018 and it comprises 3 531 biological processes and 6 367 hierarchical relations that are part of the GO hierarchy (Gene Ontology Consortium, 2019). A total of 197 194 associations between genes and functions are considered in this version. The second version is from 2021 and since it is only used for
performance evaluation, the same set of biological processes and hierarchical relations are considered. This version comprises a total of 289,407 associations.

The GCN is built using the co-expression information imported from the ATTED-II database (Obayashi, Aoki, Tadaka, Kagaya and Kinoshita, 2018) (version r17c). A GCN is represented as an undirected and weighted graph where each vertex represents a gene and each edge the level of co-expression between two genes (Aoki, Ogata and Shibata, 2007; Vandepoele et al., 2009). The GCN of rice \( G = (V, E, w) \) comprises 19,663 vertices (genes) and 550,813 edges. In this case, a mutual rank threshold of 100 is used as the cut-off measure for \( G \), i.e., \( E \) contains edges \( e \) that satisfy \( w(e) \leq 100 \). Note that the lowest value is assigned to the strongest connections.

Biological processes are a subset of the functions in the GO hierarchy, where each function in the topmost level represents a sub-hierarchy. However, as functions can have more than one parent, sub-hierarchies might not be independent (i.e., functions might belong to multiple sub-hierarchies) and there might be several paths between two functions. The topological-sorting traversal algorithm presented by Romero, Finke and Rocha (2022a) is used to transform the hierarchy into a tree so that there is unique path between all pair of function in the sub-hierarchies and all sub-hierarchies are independent. Each sub-hierarchy is denoted as \( H = (A, \leq_h) \), where \( A \) is the subset of biological processes and \( \leq_h \) the binary relation representing ancestral relations between pairs of biological processes, i.e., \( a \leq_h b \) means that function \( b \) is parent of function \( a \) in the sub-hierarchy.

As a result, 8 sub-hierarchies of biological processes are used. Table 1 describes each sub-hierarchy \( H \), starting by the root term and its description, followed by the number of biological processes \( A \), the number of genes, the number of new annotations (i.e., 0s that became 1s from 2018 to 2021 version), and the number of functions per level. Note that the functional information from 2021 includes more annotations (i.e., 0s that became 1s), but also drops some of them (i.e., 1s that became 0s). Annotations are dropped from one version to other because it was experimentally verified that such associations between genes and functions do not exist. The prediction approach is applied to each sub-hierarchy \( H \) independently.

For each sub-hierarchy, we compute and combine two sets of features: structural properties and node embeddings of the GCN. Given a sub-hierarchy \( H \) and its associated genes, structural properties of the GCN
Table 1: Resulting sub-hierarchies of biological processes for rice. The identifier and description of each root function \( r \) is presented in the first and second columns, respectively. The following columns show the number of functions \( A \) within each sub-hierarchy, the number of genes associated to it, and the number of new annotations (i.e., 0s that became 1s). The last column shows the number of functions per level, e.g., the first sub-hierarchy has 4 levels and there are 8, 10, 6, and 1 function on each level.

| Root       | Description                                | Functions | Genes | 0 → 1 | Functions per level |
|------------|--------------------------------------------|-----------|-------|-------|---------------------|
| GO:0032501 | multicellular organismal process            | 26        | 538   | 184/8/10/7/1 | 4/9/21/31/16/5/1/1 |
| GO:0019752 | carboxylic acid metabolic process           | 63        | 505   | 180/7/15/23/15/2 | 7/15/23/15/2 |
| GO:0032502 | developmental process                       | 68        | 871   | 537/10/19/25/11/2 | 10/19/25/11/2 |
| GO:0006796 | phosphate-containing compound               | 73        | 1142  | 669/9/16/22/16/7 | 9/16/22/16/7 |
| GO:0051179 | metabolic process                           |           |       |       |                     |
| GO:0008152 | biological regulation                       | 514       | 5348  | 14601/14/47/149/98/72/60/45/18/8/1/1 | 3/19/57/94/69/23/13/8/3/1 |
| GO:0000905 | cellular process                            | 594       | 5967  | 16520/12/67/117/144/93/66/46/16/10/1/1 | 4/9/21/31/16/5/1/1 |

are computed as features. In this case, the properties included for each gene \( u \) are the following:

- degree: number of edges incident to \( u \) (including \( u \));
- average neighbor degree: average degree of the neighbors of \( u \);
- eccentricity: maximum shortest distance from \( u \) to any node in its connected component;
- clustering coefficient: ratio between the number of triangles (3-loops) and the maximum number of 3-loops that could that pass through \( u \);
- closeness centrality: reciprocal of the average shortest path length from \( u \);
- betweenness centrality: the amount of influence that \( u \) has over the interactions of other nodes in the network, measured as the number of shortest paths that pass through \( u \);
- Kleinberg’s hub scores: defined as the principal eigenvector of \( \mathbf{A} \mathbf{A}^T \), where \( \mathbf{A} \) is the adjacency matrix of the graph (Kleinberg, 1999). Hubs are vertices linked to many other vertices.
- Kleinberg’s authority score: defined as the principal eigenvector of \( \mathbf{A}^T \mathbf{A} \). Authorities are the most central vertices on a network, which are connected to many different hubs.
- coreness: the highest order \( k \)-core containing the vertex \( u \), where a \( k \)-core is a maximal subgraph in which each vertex has at least degree \( k \).

These measures are computed using igraph (Ju, Li, Yu and Zhang, 2016), an open source and free collection of network analysis tools.
tionally, a low-dimension embedding of the GCN is computed to capture gene expression patterns. Embeddings are continuous representations of nodes into a low-dimensional space that captures node similarity and network structure. The goal is for properties in the embedded representation to approximate properties in the original network (Grover and Leskovec, 2016). In other words, embeddings are vector representations that capture characteristics of the nodes by using less data, thus being more tractable for machine learning. The dimension of the embedding for each sub-hierarchy corresponds to the number of biological processes in it (i.e., $|A|$).

### 4.2 Comparison methods

In this work, we employ 6 methods for comparison. More specifically, we present a comparison method from the literature, followed by 2 baseline methods and 3 variants of our proposed method.

Despite providing insights on how prediction probabilities may be used, Nakano et al. (2019), the most recent work in this context, did not explicitly propose a method to identify missing annotations on HMC problems. These authors have, however, showed that random forests have superior predictive performance than other HMC methods. For this reason, we used a global HMC classifier based on random forests of decision trees as the baseline classifier for all methods (including the proposed one), where all functions of the sub-hierarchy are considered at once. The parameter values used for random forest classifiers are: 200 estimators ($n_{\text{estimators}}$) and minimum number of samples of 5 ($\text{min}_{\text{samples}}_{\text{split}}$), whereas the number of folds used is $k = 5$.

The work of Yu et al. (2015) could be employed as a comparison, nonetheless the authors addressed the problem of identify missing functional annotations of proteins using a probabilistic model based on similarities between functions and guilt by association. Their method associates a protein and a function based on the correlation of functions in the hierarchy and the information of related proteins in the protein-protein interaction network (i.e., guilt by association). Thus, it can not be seen or extended as a HMC method.

Apart from that, the literature presents several works that are capable of identifying missing or wrong annotations in binary classification (Cao, Kwong and Wang, 2012; Sluban, Gamberger and Lavrač, 2014; Sabzevari et al., 2018; Samami, Akbari, Abdar, Plawiak, Nematzadeh, Basiri and Makarenkov, 2020; Zhang, Chen, Shen, Hao, Zhu and Savvides, 2020). Unfortunately, these works require adaptation since they were evaluated
in the context of binary classification. Among these, the recently proposed method presented by Sabzevari et al. (2018) seems to be the most related to the proposed method, since it relies specifically on random forests, and it can be straightforwardly adapted to HMC. In this work, this method is referred to as Noise detect.

Below, we present a more detailed description of each method included in our experiments:

- **Noise detect**: Sabzevari et al. (2018) recently proposed a method that employs an ensemble of decision trees to identify mislabeled instances in binary classification. More specifically, an instance is marked as noise if its misclassification rate is higher than a threshold, where the misclassification rate is defined as the proportion of predictors in which the instance is misclassified based on the number of predictors where the instance is out-of-bag. In this work, we adapt this method by selecting the top $N$ annotations with higher misclassification rate;

- **No aggr**: A variant of our proposed method that does not consider the hierarchy of classes. That is, no aggregation method is employed, and the predictions are employed directly from the classifier. This variant is included to highlight the importance of the hierarchical relationships;

- **Random**: A baseline random method that selects annotations without any criterion and complies with the hierarchy constraint. This method is included as reference point to validate the use of machine learning methods;

- **REASSIGN (min)**: A variant of our proposed method that aggregates probabilities by using the minimum probability along the path considered;

- **REASSIGN (sum)**: A variant of our proposed method that aggregates probabilities by using the sum of the probabilities along the path considered;

- **REASSIGN (average)**: A variant of our proposed method that aggregates probabilities by using the average of the probabilities along the path considered;

Since Noise detect was built for binary classification problems, a default threshold of 0.5 is used to define the labels. However, in HMC, the predicted probabilities vary according to their level in the hierarchy, the deeper a class is, the lowest the probabilities get. For this reason, we adapt this method by using a different threshold for each function according to the level in the hierarchy.
its level in the sub-hierarchy. The threshold is set as \( t = 0.5 \cdot 0.75^{l-1} \) (similar to weights proposed by Vens et al. (2008)), where \( l \) is the level of the function. For instance, a threshold \( t = 0.5 \) is used for functions in the first level and \( t = 0.88989 \) is used for functions in the seventh level.

### 4.3 Evaluation measures

The performance evaluation of the methods is based on the true positive and false positive measures, because the aim of this work is to detect missing annotations (i.e., identifying 0s that became 1s) and there are two versions of the datasets available that allows us to verify the predictions. That is, the evaluation is focused on annotations that are not detected, but might show up in the future and can be verified using the newer version of the datasets.

We use precision@\( N \) as the first evaluation metric. Given \( N \), the number of annotations selected in a dataset (derived from the number of paths to be selected \( N_p \)), the precision for the selected annotations is computed as

\[
\text{precision@}N = \frac{tp_N}{tp_N + fp_N}.
\]

Moreover, different values of \( N \) are used to avoid bias in the prediction and evaluation, hence the number of selected paths can be set according to the resources available for \textit{in vivo} biological experimentation.

In addition, we use the area under the curve generated between the different values of \( N \) (in the \( x \)-axis) and the precision@\( N \) (in the \( y \)-axis) as second evaluation metric, denoted as, AUP@NC. This metric aims to analyze the performance of the methods regardless of the value of \( N \) and to remove subjectiveness caused by using only one value for each method and dataset. The area under the precision@\( N \) curve is defined as

\[
\text{AUP@NC} = \sum_{N_i} \text{area}(N_i, \text{precision@}N_i)
\]

where \( N_i \) represents the different values of \( N \).

The number of paths to be selected \( N_p \) by the proposed method is defined as a proportion of the number of 1s in the older version of the dataset, i.e., the total number of associations between genes and functions occurring in \( Y \). In particular, we set \( n \in [0, 1] \) as the proportion of occurring annotations and \( N_p = \sum Y \cdot n \). The number of annotations within the top \( N_p \) paths after removing duplicates is denoted as \( N \). That
is, \( N \) and \( n \) have a positive proportional relationship, i.e., lower values of \( n \) lead to lower values of \( N \), and higher values of \( n \) lead to higher values of \( N \). We use 20 different values of \( n \), from \( n = 0.01 \) incremented in steps of 0.01 up to \( n = 0.2 \). Note that the values of \( N_p \) and \( N \) are different for each dataset, whereas the values of \( n \) are the same for all datasets.

Furthermore, in order to provide statistical evidence, the Friedman-Nemenyi test is used. At first, the Friedman test verifies if any of the compared methods performs statistically significantly different from others. Next, the Nemenyi test ranks the methods where methods with superior results are ranked in higher positions. Graphically, methods connected by a horizontal bar, of length less or equal to a critical distance, are not statistically significantly different. As input to this test, we employ the area under the precision@\( N \) curve.

5 Results and discussion

In this section, the experiments and results are presented. At first, we analyze the predictive performance of the proposed and comparison methods using the precision@\( N \) measure, followed by a discussion on how our method differs from its comparison counterparts through the area under the precision@\( N \) curve. Lastly, we analyze the deepness of the annotations predicted by the proposed method.

5.1 Comparison between all methods of the precision@\( N \)

Figure 2 illustrates the predictive performance of all sub-hierarchies measured with the precision@\( N \). Sub-hierarchies are shown in the same order of Table 1, from smallest (top left) to largest (bottom right). The predictive performance of the methods is measured based on a selection of the same number of annotations for each dataset.

As can be seen, the variants of our method are mostly associated with superior performance. More specifically, we highlight the results of \textit{REASSIGN (avg)} on the datasets GO:0051179, GO:0008152 and GO:0009987, where its curve is majoritarily above the others considering most values of \( n \). A noteworthy advantage in performance is seen in the GO:0008152 dataset where \textit{REASSIGN (avg)} achieved 5\% higher precision than the closest competitor, \textit{No aggr}, for all values of \( n \).

The other variants of our method, \textit{REASSIGN (min)} and \textit{REASSIGN (sum)}, also provided superior results in three cases: GO:0006796, GO:0051179 and GO:0009987. Precisely, in the GO:0006796 dataset, both
Fig. 2: Precision@N of all sub-hierarchies for 20 different values of \( n \) (\( N \) is derived from \( n \)) considering all evaluated methods. This Figure is best viewed in colors.
methods are remarkably preferable over the competitors due to superior performance in all values of \( n \). Likewise, these variants also yielded the best results in the GO:0051179 (\textit{REASSIGN (sum)}) and GO:0009987 (\textit{REASSIGN (min)}) datasets when \( n = 0.01 \) is considered. The performance of these methods, associated with the performance of \textit{REASSIGN (avg)}, endorses the necessity of incorporating the hierarchical relationships among the classes.

Complementary, \textit{No aggr}, the variant that overlooks the hierarchy, managed to have the upperhand only in a few cases, such as in the datasets GO:0032501, GO:0032502, GO:0019752 and GO:0065007, specially when the value of \( n \) is small. We suspect that this is related to size of the sub-hierarchies. As presented in Table 1, the datasets GO:0032501, GO:0032502 and GO:0019752 have relatively smaller sub-hierarchies, thus incorporating the hierarchy does not necessarily lead to better results. The behaviour observed in GO:0065007 seems peculiar since it was the only dataset where the method \textit{Noise detect} yields the highest performance, followed by \textit{No aggr}, specially when smaller values of \( n \) are employed. However, it is worth mentioning that this difference is marginal, as their performance ranges from approximately 6.5% to 4%, when compared to our proposed method using the average as the aggregation method.

As opposed to that, \textit{Random} provides very underwhelming results in most of the experiments where its performance is barely superior than 0, making it negligible. Curiously, in some very specific scenarios, \textit{Random} was capable of overcoming the \textit{Noise detect} method, as seen in the GO:0032502, GO:0006796, GO:0051179 and GO:0009987, when larger values of \( n \) are analyzed. We attribute this counter-intuitive finding to the performance of \textit{Noise detect} as a whole. As shown in the Figure 2, there is a perceivable deterioration in performance as the value of \( n \) increases, whereas a less prominent worsening was detected in the other methods.

Such deterioration is expected, since smaller values of \( n \) lead directly to smaller subsets of annotations to be evaluated, artificially increasing the value of the precision. Hence, selecting a smaller subset of annotations does provide relatively better results.

Despite yielding superior results when compared to the literature, our method shows that detecting missing annotations is a rather challenging task, as seen in datasets such as GO:0065007 and GO:0006796 where the best methods merely achieved 6% and 8% precision. We suspect that the low availability of annotations, specially in deeper levels of the hierarchy, plays a significant role in this matter.
5.2 Analysis of the area under the precision@N curve

Table 2 shows the area under the precision@N curve for all methods and sub-hierarchies. For each sub-hierarchy the best method is highlighted with boldface. In all cases, variations of our method always provide the highest AUP@NC. More specifically, \textit{REASSIGN(avg)} provides the best performance in 4 datasets, followed by \textit{No aggr} and \textit{REASSIGN(min)} on 3 and 1, respectively. The competitor method \textit{Noise detect} did not manage to have the best performance in any dataset.

Among the 3 cases where \textit{No aggr} had the upperhand, its superiority was more pronounced only in one dataset, GO:0032501, where it yielded 0.0208 AUP@NC and the second best method, \textit{REASSIGN(avg)}, provided only 0.0137. In the other two cases, GO:0032502 and GO:0065007, \textit{No aggr} was only marginally better.

A different behaviour is seen in \textit{REASSIGN(avg)} where its performance was considerably better in 3 out of the 4 cases. Precisely, in GO:0051179, GO:0008152 and GO:0009987, \textit{REASSIGN(avg)} provided visibly superior results in comparison to the runner-up method. When compared solely against \textit{Noise detect}, our most prominent variant, \textit{REASSIGN(avg)} is consistently superior.

| Root      | \textit{REASSIGN (avg)} | \textit{REASSIGN (sum)} | \textit{REASSIGN (min)} | \textit{No aggr} | \textit{Random} | \textit{Noise detect} |
|-----------|-------------------------|-------------------------|-------------------------|------------------|----------------|---------------------|
| GO:0032501| 0.0137                  | 0.0121                  | 0.0114                  | **0.0208**       | 0.0063         | 0.0129              |
| GO:0019752| **0.0141**              | 0.0128                  | 0.0113                  | 0.0139           | 0.0027         | 0.0096              |
| GO:0032502| 0.0111                  | 0.0075                  | 0.0111                  | **0.0122**       | 0.0033         | 0.0067              |
| GO:0006796| 0.0040                  | 0.0060                  | **0.0071**              | 0.0039           | 0.0028         | 0.0025              |
| GO:0051179| **0.0286**              | 0.0249                  | 0.0139                  | 0.0166           | 0.0047         | 0.0088              |
| GO:0065007| 0.0057                  | 0.0028                  | 0.0055                  | **0.0066**       | 0.0022         | 0.0055              |
| GO:0008152| **0.0339**              | 0.0203                  | 0.0191                  | 0.0233           | 0.0048         | 0.0160              |
| GO:0009987| **0.0225**              | 0.0213                  | 0.0180                  | 0.0207           | 0.0046         | 0.0087              |

Table 2: Area under the curve generated between the different values of \(n\) (in the x-axis) and the precision@N (in the y-axis), i.e., AUP@NC. The proposed method (\textit{REASSIGN (avg)}) outperforms \textit{No aggr} and \textit{Noise detect} methods in 5 and all sub-hierarchies, respectively.

These results are further attested in the Friedman-Nemenyi presented in Figure 3. It can be seen that there is a significant difference between \textit{REASSIGN (avg)} and the competitor method \textit{Noise detect}, nonetheless no significant difference is observed among the variant of our proposal.

Precisely, \textit{REASSIGN (avg)} is ranked in the first position followed by \textit{No aggr}, \textit{REASSIGN (sum)} and \textit{REASSIGN (min)}. The competitor
method Noise detect, the variant REASSIGN (min) and Random are not statistically significantly different.

Fig. 3: Friedman–Nemenyi test evaluating the area under the precision@N curve, i.e., the curve generated between the different values of \( n \) (in the \( x \)-axis) and the precision@N (in the \( y \)-axis). Methods connected by a horizontal bar, of length less or equal to a critical distance, are not statistically significantly different. The proposed method is significantly different from the noise detection and the random methods.

5.3 Comparison of true positives through the GO hierarchy levels

To further evaluate the two best methods, REASSIGN (avg) and No aggr, we have investigated their performance per level. More specifically, we analyze the precision per level on two datasets: GO:0032501 (Table 3) and GO:0009987 (Table 4). These were selected due to their difference in hierarchy size (4 and 11 levels, respectively) and in performance.

As can be seen in Table 3, No aggr focuses substantially on annotations present in the first level of the hierarchy where it correctly predicts 26 annotations, whereas REASSIGN (avg) managed to obtain only 10. In the second and third level, however, REASSIGN (avg) was capable of accurately identifying more missing annotations. We believe that the aggregation function is responsible for this difference, as classes located in deeper levels are often associated to very low prediction probabilities, making their selection very unlikely by No aggr.

A slightly different behaviour in performance is noticed at Table 4 where REASSIGN (avg) had the upper hand with 1712 over 1624 provided by No aggr. Despite of that, a similar tendency in the distribution of the annotations was noticed: the missing annotations identified by No aggr are mostly located in the shallow levels of the sub-hierarchy, specially on the second level in this case, whereas REASSIGN (avg) seeks
### Table 3: Number of predicted annotations per level for the proposed REASSIGN (avg) and No aggr methods for the sub-hierarchy GO:0032501.

The second column shows the number of missing annotations (0s that became 1s) per level, followed by the number of true positives, the number of predicted annotations and the precision per level for both methods. The last row shows the total number of missing annotations in the sub-hierarchy and the total number of true positives predicted by each method.

| Level | # 0 → 1 | REASSIGN (avg) | No aggr |
|-------|---------|----------------|---------|
| 1     | 97      | 10/77 (12.99%) | 26/185 (12.05%) |
| 2     | 51      | 6/87 (6.90%)   | 3/24 (12.50%)   |
| 3     | 33      | 1/50 (0.02%)   | 0/5 (0%)        |
| 4     | 3       | 0/0 (0%)       | 0/0 (0%)        |
| Total | 184     | 17/214 (7.94%) | 29/214 (13.55%) |

### Table 4: Number of predicted annotations per level for the proposed REASSIGN (avg) and No aggr methods for the sub-hierarchy GO:0009987.

The second column shows the number of missing annotations (0s that became 1s) per level, followed by the number of true positives, the number of predicted annotations and the precision per level for both methods. The last row shows the total number of missing annotations in the sub-hierarchy and the total number of true positives predicted by each method.

| Level | # 0 → 1 | REASSIGN (avg) | No aggr |
|-------|---------|----------------|---------|
| 1     | 2334    | 581/2871 (20.24%) | 261/1913 (13.64%) |
| 2     | 3976    | 502/3121 (16.08%) | 938/7458 (12.58%) |
| 3     | 3833    | 302/2748 (10.99%) | 221/2025 (10.91%) |
| 4     | 2402    | 202/2197 (9.19%)  | 116/1268 (9.15%)  |
| 5     | 1729    | 87/1625 (5.35%)   | 76/793 (9.58%)    |
| 6     | 1109    | 20/699 (2.86%)    | 6/52 (11.54%)     |
| 7     | 721     | 12/271 (4.43%)    | 5/46 (10.87%)     |
| 8     | 304     | 6/34 (17.65%)     | 1/16 (6.25%)      |
| 9     | 85      | 0/19 (0%)         | 0/14 (0%)         |
| 10    | 24      | 0/0 (0%)          | 0/0 (0%)          |
| 11    | 3       | 0/0 (0%)          | 0/0 (0%)          |
| Total | 16 520  | 1712/13585 (12.00%) | 1624/13585 (11.95%) |
deeper annotations. Nevertheless, \textit{REASSIGN (avg)} detects in average the double of missing annotations than \textit{No aggr} in all levels, except for the second one.

Hence, we may assume that \textit{No aggr} is more likely to provide desirable results when sub-hierarchies with fewer levels (in this case, 4) are considered. As opposed to that, employing the average as the aggregation function is preferred when deeper, and possibly more complex, sub-hierarchies are investigated. However, it is worth mentioning that detecting missing annotations in deeper levels still remains a challenge since no method was able to detect them in the deepest level of both hierarchies.

6 Conclusion and Future Work

In this work, we have presented a novel method to detect missing annotations in HMC datasets. More specifically, we proposed a method, with 3 possible variants, that exploits the class hierarchy by computing aggregated probabilities (e.g., average, sum and minimum) of the paths of classes from the leaves to the root for each instance. Furthermore, the proposed method is presented in the context of predicting missing gene function annotations, where these aggregated probabilities are further used to select a set of annotations to be verified through \textit{in vivo} experiments.

Experiments on \textit{Oriza sativa Japonica}, a variety of rice, showcased that our proposed method yields superior results when compared to competitor methods from the literature. Furthermore, we could also identify that incorporating the hierarchy of classes into the method often improves the results. Precisely, averaging the probabilities leads to the identification of missing annotations in deeper levels of the hierarchy, which is often regarded as more informative. Despite of that, our results also highlight how challenging this task is.

Hence, as future work, we highlight two main lines. First, considering other ways of aggregating the probabilities, may lead to improved results, specially on deeper levels of the hierarchy. Additionally, we may also explore transfer learning, specifically domain adaptation, to enrich the training of HMC classifiers. Using information from other organisms can not only result in higher prediction performance, but may also allow the application of HMC to organisms without functional information available.

Even though the proposed method is focused in detecting missing annotations in the datasets, detecting annotations that were removed
instead of added, may be of interest to identify wrong associations and to improve the quality of the datasets.

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