Mining Features for Biomedical Data using Clustering Tree Ensembles

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Abstract

The volume of biomedical data available to the machine learning community grows very rapidly. A rational question is how informative these data really are or how discriminant the features describing the data instances are. Several biomedical datasets suffer from lack of variance in the instance representation, or even worse, contain instances with identical features and different class labels. Indisputably, this directly affects the performance of machine learning algorithms, as well as the ability to interpret their results. In this article, we emphasize on the aforementioned problem and propose a target-informed feature induction method based on tree ensemble learning. The method brings more variance into the data representation, thereby potentially increasing predictive performance of a learner applied to the induced features. The contribution of this article is two-fold. Firstly, a problem affecting the quality of biomedical data is highlighted, and secondly, a method to handle that problem is proposed. The efficiency of the presented approach is validated on multi-target prediction tasks. The obtained results indicate that the proposed approach is able to boost the discrimination between the data instances and increase the predictive performance.

Keywords: Tree-ensembles, Extremely randomized trees, Tree-embeddings, Biomedical data mining

1. Introduction

Significant progress has been made in biomedical data generation techniques and feature extraction methods. Microarrays, high-throughput sequencing, mass spectrometry and many others have been recognized as tools
5 of great importance. The scientific community exploits these technological advances to generate more data in the field of biomedicine. However, a thoughtful question would be how informative these data truly are to make predictive inferences.

More precisely, among all the scientific tools in biomedical informatics,
10 machine learning has proved to be of paramount importance, especially in predictive problems. It has provided contributions in a wide range of problems in biology and biomedicine [1, 2]. Protein function prediction, interaction prediction between drugs and proteins, knowledge discovery related to biomarkers are only some of the various examples. In particular, in the
15 framework of supervised learning several methods are provided to learn predictive models only from former observations of a system. In supervised learning, the instances are described by features (characteristics of each instance) and accompanied by targets. The goal is to learn a model on a training set of instances that can predict the target given the features [3].
20 This model is then used to predict the target of new unseen instances. If the target is numeric, the task is called regression. If the target is categorical (i.e., a class has to be predicted), the term classification is used. In some

prediction problems, rather than a single target, a *set* of targets needs to be predicted. The mentioned applications of gene function prediction or interaction prediction are instances of this so-called multi-target prediction task [4]. Multi-target prediction is a generalization of multi-target regression and multi-target classification. Multi-label classification can be considered as an instance of multi-target classification with only two nominal values for each target [5, 6]. These applications can be tackled by either transforming the multi-target problem into a set of single-target problems and applying a standard prediction algorithm, or by applying a specific multi-target prediction algorithm.

One of the most popular machine learning algorithms are the decision tree induction algorithms [7]. They have been applied extensively in biological and biomedical systems [2, 8]. Decision tree algorithms have many advantages over other machine learning methods. They provide interpretability of the induced models, providing transparency and insights to scientists, leveraging this way knowledge discovery. Their models are also scalable, computationally efficient and accurate. The predictive performance of decision trees is specifically boosted when they are combined with ensemble methods [9], providing state-of-the-art results. Decision tree learning and its ensemble extension have been extended to the multi-target prediction setting (i.e., multi-label classification and multi-target regression) [4]. Multi-label classification has received more attention than multi-target regression [10].

1.1. Problem Statement

In biomedicine and healthcare representing the data effectively is often a challenging task. In comparison to other fields, such as multimedia anal-

ysis or web mining, getting new features for an instance is a substantially
 more difficult task in biomedicine. In the case of a song or an image being
 50 under-represented one can easily get (extract) more features by collecting
 more information about the artist or applying an audio or image process-
 ing technique to the instance itself. However, this is not always possible in
 biomedicine. It requires significant time, expenditure, and the presence of
 human experts, as the features most of the times are the outcome of labora-
 55 tory work. Furthermore, in medicine the data are usually produced through
 the process of patient care and thereby issues of privacy are included [1]. In
 many countries, hospitals are equipped with inefficient database systems that
 are mainly designed for billing purposes. In addition, medical data inevitably
 contain many missing values and many non-numeric features. Many tradi-
 60 tional machine learning methods (e.g., SVM [11]) can not be applied on such
 data without preprocessing. These peculiarities of the data in healthcare and
 biomedicine often lead to non-variant data representations and inevitably the
 harassment of the performance of machine learning methods [12]. To this end,
 methodologies to handle this uniqueness of biomedical data are needed.

65 It is crucial for the performance of machine learning models that the fea-
 tures that describe the data instances are enriched with valuable information
 and are able to discriminate the data instances. However, there are many
 examples of broadly used benchmark biomedical datasets suffering from this
 phenomenon of lacking variance. An extreme version of the aforementioned
 70 phenomenon is the existence of biomedical datasets that contain identical
 feature vectors for different data instances. Some examples from the field
 of gene function prediction (e.g., [13], [14]) or interaction prediction (e.g.,

[15]) are shown in Table 1 [16, 17]. This is irrational as there are instances (e.g., genes), that have different targets (e.g., functions) but identical feature vectors.

Table 1: Datasets, the number of features, instances and unique feature vectors.

Context	Dataset	features	instances	unique feature vectors
Gene fct. prediction (<i>S. cerevisiae</i>)	church	27	3755	2352
	pheno	69	1592	514
	hom	47034	3854	3646
	seq	478	3919	3913
	struc	19628	3838	3785
(A. thaliana)	scop	2003	9843	9415
	struc	19628	11763	11689
Interaction prediction	drugs	660	1862	1779
(DPI network)	proteins	876	1554	683

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In the *pheno* dataset for example, 32% of the instances have a unique feature vector. As a unique feature vector we denote a feature vector that exists only once in the dataset after removing the replicates (i.e., instances that are described by exactly the same feature vectors). This dataset contains
80 an instance for every gene in the *S. cerevisiae* organism, and the instance corresponds to a mutant, i.e. an organism where the corresponding gene has been altered. There are 69 features corresponding to different growth medium (e.g., caffeine, sorbitol, benomyl,...), on which growth of the mutant is recorded. The values of the features correspond to the observed sensitivity

85 or resistance of the mutant: no effect, less growth or better growth compared
 to the wild type, or no data for the growth medium. The large number
 of replicates (i.e., instances that are described by exactly the same feature
 vectors) can be explained by two observations: (1) the data is very sparse,
 i.e. for many mutants few growth media have been tested, and (2) in many
 90 cases the tested growth media has no effect on the mutant. The *church*
 dataset also contains many instances with identical feature values. It consists
 of 27 mostly real-valued features. Interestingly, the replicate issue is not
 limited to datasets with few features. For example, *hom* contains homology
 information encoded by 47034 binary features, *struc* contains 19628 binary
 95 features related to predicted secondary structure of the protein. Moreover,
 apart from genes the aforementioned problem is also existing in interaction
 networks. In Table 1, an example of a drug-protein interaction network
 (DPI) [18] is presented where there are some drugs or proteins having the
 same feature vector. In drug-protein interaction networks connections are
 100 formed between drugs and proteins when the drug targets the protein. Both
 interaction parts are described by their own set of features, for example in
 the current dataset each drug is described by the presence or absence of
 660 chemical substances and each protein by the presence or absence of 876
 PFAM domains.

105 Lack of variance in the data representation can heavily impair the perfor-
 mance of machine learning algorithms. Indicatively, by applying an 1 nearest
 neighbor (1-NN) classifier to a training dataset (including the specific query
 instance), one expects to get 100% accuracy. However, in case there are in-
 stances in that dataset with exactly the same feature representation, it is not

110 guaranteed that an instance is mapped onto itself. As an example we could
 refer to [16] where ML-KNN [19] with $K = 1$ was applied on pheno dataset
 from Table 1 and it yielded a precision of only 51.59%. Moreover, instances
 with identical feature vectors will end up into the same leaf in case of decision
 trees or their ensemble extension. Although this is what is expected, it causes
 115 a performance issue if those instances (i.e., instances in the same leaf) have
 completely different labels. The algorithm is supposed to separate instances
 with very different labels into different leaves. In Fig. 1, the distances be-
 tween the feature vectors representing the 1592 data instances of pheno and
 the distances between the corresponding label vectors are displayed. More
 120 specifically, distances were computed between the feature vectors and be-
 tween the label vectors. Each cell (i, j) of the matrix was assigned a color
 based on the distance between the feature (label) vectors that correspond to
 instances i and j . White corresponds to distance equal to zero and black
 to distance equal to one. It is shown that instances represented by identical
 125 feature vectors (distance equal to zero) are associated with different labels.

The issue of replicate feature vectors is an extreme example of the more
 general phenomenon of lacking variance in biomedical data. Although it
 is difficult to provide any algorithmic solution to the existence of replicate
 feature vectors, the scientific community should be aware of its presence.

130 1.2. Related Work

Whereas numerous studies have focused on feature selection [20, 21, 22],
 the more difficult task of feature construction or induction has received less
 attention. The main goal of feature construction is to augment the feature
 space by creating or inferring additional features [23].

Figure 1: Distance matrices for the features (left) and the labels (right) of the pheno dataset.

135 In [24], a feature construction method specifically focused on multi-label
 classification was presented. A distinct feature set was assigned to every
 label, increasing this way the performance of a classifier trained for that spe-
 cific label. The label-specific features were generated by first clustering the
 positive and negative instances (separately) of the label. Next, the distances
 140 of each instance to the obtained cluster centroids were calculated. Vens and
 Costa [25] proposed a feature induction technique based on random forest
 [9]. A metric transformation was proposed, mapping the identity of the tests
 performed in each node of a decision tree to a feature indicator. Next, the
 final representation is yielded by concatenating the features associated with
 145 the trees in the forest and encoding them with hashing. The method was
 demonstrated on binary and multi-label classification tasks. A similar work
 involving a set of random clustering forests was proposed in [26, 27]. The
 application was focused on the construction of visual vocabularies. More
 specifically, randomized trees were used to generate the new feature repre-

150 sentation. The feature generation process took into account the indices of
 the leaves of those trees. The proposed method generated a high dimensional,
 sparse, and binary feature set. In [28, 29], an unsupervised feature
 induction technique based on Extremely Randomized Trees [30] was pre-
 sented. The feature representation was also extended towards interaction
 155 data in [29] and [31]. Moreover, there have been many studies that adopted
 methods from the field of dimensionality reduction [32] for feature extraction.
 In [33], a comparison study between Principal Component Analysis (PCA),
 Independent Component Analysis (ICA), and Kernel Principal Component
 Analysis (KPCA) was performed. Furthermore, in [34], deep auto-encoder
 160 networks were used for dimensionality reduction, extracting features from
 high dimensional vectors. More specifically, an efficient approach was pro-
 posed to initialize the weights of these multi-layer neural networks, assisting
 auto-encoders to learn low-dimensional representations. Here, we focus on
 feature construction for multi-target prediction problems using scalable and
 165 inductive models that provide also interpretability (e.g., feature ranking).

1.3. *Introduction to the proposed method*

Motivated by the issue of lacking variance in biomedical data that was
 presented above we propose an efficient feature induction method that trans-
 forms the data into more variant and more informative representations. More
 170 specifically, we propose a method motivated by [25, 28]. The proposed ap-
 proach yields a feature set using Extremely Randomized Trees [30]. In partic-
 ular, the nodes of each tree of the forest are considered clusters that comprise
 the instances that pass through them. In the next step, binary vectors are
 produced. The existence of an instance in a cluster-node is associated with

175 those feature vectors. This way, a high dimensional and sparse feature representation is generated. It has to be mentioned that the proposed method is also inductive (i.e., new data are handled directly without the need of re-training the model). Moreover, different from [28, 29], the proposed approach follows the supervised learning setting and therefore the generated features
180 include information mined from the labels (i.e., the new features are constructed using label information). Different from [25, 28], we assign a weight to each cluster (node), based on the number of instances they contain. In addition, we extend our approach by converting the data from high dimensional feature vectors to low dimensional embeddings inducing as much variance as
185 possible. To achieve this, we employ Principal Component Analysis (PCA). Moreover, in this study we address both multi-label classification and multi-target regression settings. The obtained experimental results demonstrate the efficiency of the proposed approach.

The rest of the paper is organized as follows. In Section 2, the proposed
190 approach is described and the datasets used in this study are presented. The experimental evaluation is presented in Section 3. In Section 4, we draw conclusions and we discuss topics for future research.

2. Methods and Data

The proposed approach targets at boosting the representational power of
195 features. While the approach is valid for all kinds of prediction tasks, here we focus on multi-target prediction. We start with providing the theoretical background of our approach and presenting the ensemble method where our approach is based on. Next, we present the feature induction approach in

detail.

200 2.1. *Extremely randomized trees for multi-target prediction*

In decision tree learning the trees are usually constructed with a top-down induction method [7]. The first node is called the root node and it is associated with the complete training set. The nodes are recursively split based on a test that is applied to one of the features that describe the instances. The best split is selected among all features and their corresponding split points based on a split quality criterion. This split criterion can vary. For classification tasks it is often information gain and for regression tasks variance reduction is often used. The tree growing procedure stops when the data contained in a node is pure w.r.t. the target, or when another stopping criterion holds. Then the node is called a leaf and a label is assigned to it. For classification, the assigned label is the majority class of the training instances in the leaf. For regression, the value assigned to a leaf is the average of the target values that are associated with the training instances contained in the leaf. As for the test instances, the labels are obtained by letting the instances traverse the tree ending up in a leaf node. Here, the used decision tree learning methods follow the Predictive Clustering Tree (PCT) [35] framework. More precisely, PCTs emphasize on the hierarchical clustering setup of decision trees. In each split, the split criterion is to maximally reduce the intra-cluster variance.

220 A disadvantage of PCTs (or of decision trees in general) is the instability and the overfitting effect. These disadvantages are surpassed by extending the PCT framework to ensembles of trees. Various tree ensemble models exist. Here, we consider the ensemble method of Extremely Randomized Trees

(ERT) [30]. In an ERT ensemble, each tree is constructed by considering
 225 only a random set of split candidates at each node. More precisely, a random subset of features is picked, and for each feature, a random split point is selected. From these candidates, the candidate yielding the best value for the split criterion (i.e., variance reduction computed on the labels) is chosen. The tree growing process is terminated when no further splitting can be
 230 performed or a stopping criterion has been reached (e.g., maximum depth, minimum number of instances to split, etc.). Due to the explicit randomization of the splitting threshold and feature in combination with ensemble averaging ERT achieve stronger bias-variance reduction than other methods. ERT was shown to have a better predictive performance than the more popular
 235 Random Forest [30] and it is also computationally less expensive due to the node splitting process that is followed.

Apart from their extension to ensembles, PCTs have also been extended towards structured-output tasks, such as in the multi-target prediction case [4]. In a multi-target prediction problem for each instance the set of targets is
 240 represented as a vector of size equal to the total number of targets. Then, the possible splits are evaluated by calculating the variance reduction over these vectors, instead of over single values. Next, the average of the target vectors of the instances that are present in a leaf is computed. Once the model has been built, it can be used for prediction of new (unseen) instances.

2.2. Feature induction with ERT

The proposed approach starts by applying Extremely randomized trees to the original feature set. Let $\mathbf{N} = \{n_1, n_2, \dots, n_{|N|}\}$ be the nodes of all trees in the ensemble. The tree-nodes are treated as clusters. The instances contained

Figure 2: Illustration of the proposed approach. An instance traverses the trees and the corresponding feature vector is constructed.

in those clusters are the ones that pass through them while traversing the tree.

250 The original feature set is denoted as $\mathbf{X} \in \mathbb{R}^{|S| \times |M|}$ and the generated one as $\mathbf{F} \in \mathbb{R}^{|S| \times |N|}$, where $|S|$ and $|N|$ correspond to the number of instances and the number of the generated features of the dataset, respectively. Although the trees of the ensemble may contain different number of nodes, all the instances traverse all the trees and therefore the corresponding generated

255 feature vectors are of equal size (i.e., the total number of nodes $|N|$). The clusters $n_j \in \mathbf{N}$ are treated as features of the feature set $\mathbf{F}$. Each $f_{ij} \in \mathbf{F}$ equals to 1 if the instance $i \in \mathbf{S}$ is contained in cluster (node) $j \in \mathbf{N}$ and 0 otherwise, as shown in equation (1). When it comes to new (unseen) instances, they also traverse the trees of the ensemble, generating feature

260 vectors. In Fig. 2, the tree-ensembles part of the feature induction approach is illustrated.

$$f_{ij} = \begin{cases} 1, & \text{if } i \in n_j \\ 0, & \text{otherwise.} \end{cases} \quad (1)$$

In order to generate a better feature representation the features corresponding to the cluster nodes of every tree are weighed and filtered based on the number of instances they contain (i.e., weight of the cluster). In order

265 to preserve the inductive setup of the proposed method these weights are

computed only once (i.e., in the training phase) and they are not subject to new instances (i.e., they are not updated when new instances arrive). The weight of every node j is computed as in equation 2.

$$w_j = \frac{1}{\log(|n_j|) + e} \quad (2)$$

Where $|n_j|$ is the number of the instances contained in the cluster (node) j and e a very small value ($e \ll 1$) in order to guarantee the numerical stability of the fraction (i.e., the denominator of the fraction is never equal to 0). The features that correspond to the nodes close to the root are not so informative as they often contain approximately all the instances of a dataset. By discarding the nodes containing more than $p\%$ of the instances, the number of generated features is reduced making the subsequent learning phase more efficient. Based on this strategy, one can keep all the nodes from root to leaves, discard the root nodes and some nodes close to them, or keep only the leaves. Next, the data are transferred from a high dimensional space to a low dimensional space through maximizing the variance in the data representation. This is performed by applying PCA. The high dimensional feature vectors are converted to a low dimensional orthogonal basis set. The fitted model can then be also used for new instances as well. Note that we also suggest the removal of many components. By keeping only few of the first components, which are the most informative (most variant), we achieve noise removal and make the generated feature set more computationally efficient for subsequent machine learning analysis. Although the new features cannot be interpreted, the ERT employed in the first phase of the method provides a feature ranking output that could help scientists that want to get some insights from their features. This is the same level of interpretability one gets

290 by applying ERT or another tree-ensemble learner to the original features.

The proposed feature set is more informative than the original one due to the feature selection strategy followed by ERT. The non-informative features are not included in the procedure (i.e., no split occurs on these features). The induced features are generated by computing clusterings over
295 the whole dataset and therefore information from the whole instance space is used. Noisy instances and outliers can be discriminated easily, as separating an outlier from the rest of the instances leads to large variance reduction. Moreover, one can control the growing of the trees by setting specific stopping criteria.

300 At this point we should state that any hierarchical clustering approach could yield a similar feature representation. However, the proposed feature induction method is benefited by the use of ERT exploiting all the advantages of the tree ensembles methods and ERT in particular. Extremely randomized trees is a tree-ensemble model and thereby robust to minor data
305 perturbations. The induced features are also more noise invariant due to the feature selection mechanism adopted by ERT. Furthermore, the proposed feature induction method inherits the advantages of tree ensembles. It can treat both numerical and non-numerical values and in contrast to many other methods, it handles missing values. The presented method provides also a
310 feature ranking output. There is no need of parameter tuning and it follows the inductive setup (i.e., new data are handled directly without the need of re-training the model).

Table 2: The datasets used in the evaluation procedure are presented.

<i>Dataset</i>	<i> instances </i>	<i> Features </i>	<i> targets </i>	<i>Type of Targets</i>
ERN	1164	445	154	<i>Binary</i>
SRN	1821	9884	113	<i>Binary</i>
MN	668	325	668	<i>Binary</i>
PPI	984	325	984	<i>Binary</i>
Medical	978	1449	45	<i>Binary</i>
Yeast	2417	103	14	<i>Binary</i>
WQ	1060	16	14	<i>Numeric</i>
SG	735	113	18	<i>Numeric</i>

2.3. Datasets

In our study, we used in total 8 datasets from the fields of biology and
315 biomedicine: 2 multi-target regression datasets and 6 multi-label classification ones. The summarization of the datasets and their characteristics is shown in Table 2. It contains the number of instances, original features, and targets of each dataset.

In particular:

- 320 • **E. coli regulatory network (ERN)** [36]. This dataset corresponds to a regulatory network. It consists of 1164 genes of E. coli. Each gene is represented by 445 expression values (i.e., these are the features). The binary targets represent the interactions between these genes and 154 Transcription Factors (TFs).

- 325 • **S. cerevisiae regulatory network (SRN)** [37]. This dataset corresponds to a regulatory network. It consists of 1821 genes of *S. cerevisiae* regulated by 113 Transcription Factors (TFs). Each gene is represented by 1685 expression values and 8199 motifs features. The binary targets represent the connections between the Transcription Factors (TFs) and

330 their target genes.
- 335 • **Metabolic Network (MN)** [38] This dataset represents an homogeneous metabolic network. The network is composed of 668 *S. cerevisiae* enzymes. The 668 targets have binary values and they represent the edges of the network. There is an edge (i.e, target value is equal to 1) between two enzymes when these two enzymes catalyse successive reactions. Each enzyme is described by 325 features (a concatenation of expression data, phylogenetic profiles, and localization data).
- 340 • **Protein-Protein Interaction Network (PPI)** [39] This dataset represents an homogeneous protein-protein interaction network. The network is composed of 984 *S. cerevisiae* proteins. The 984 targets have binary values and they represent the edges of the network. There is an edge (i.e, target value is equal to 1) between two proteins when these two proteins interact with each other. Each protein is described by 325 features (a concatenation of expression data, phylogenetic profiles, and

345 localization data).
- 345 • **Yeast** [40] This dataset contains information about a set of 2417 Yeast cells described by 103 features. The task is to determine the localization site of each cell. The dataset contains 14 binary targets.

- **Medical** [41] This dataset contains 978 instances of clinical text documents described by 1449 features. The dataset contains 45 binary targets.
- **Water Quality (WQ)** [42]. The Water Quality dataset represents 1060 instances described by 16 input features. These features correspond to physical and chemical water quality parameters. The dataset contains 14 target values that refer to the relative representation of plant and animal species in Slovenian rivers.
- **S. cerevisiae genes (SG)** [43]. It consists of 735 genes of *S. cerevisiae*. Each gene is described by 113 binding motifs. The 18 targets are numeric and represent expression levels.

3. Results and Discussion

In this section the experimental evaluation of the methods proposed above is presented. First, the evaluation protocol is described. Next, the obtained results are demonstrated and discussed.

3.1. Experimental set-up

The evaluation measures that were employed for multi-label classification were the area under precision recall curve (AUPR) and the area under the receiver operating characteristic curve (AUROC). A PR curve is defined as the Precision ($\frac{TP}{TP+FP}$) against the Recall ($\frac{TP}{TP+FN}$) at various thresholds. A ROC curve plots the true positive rate ($\frac{TP}{TP+FN}$) on the y axis against the false positive rate ($\frac{FP}{FP+TN}$) on the x axis at various thresholds. The true-positive rate is the same as recall, and is also known as *sensitivity* while the false

positive rate is also known as $(1 - \textit{specificity})$. The aforementioned measures were employed in a micro-average setup. For multi-target regression, the Relative Root Mean Squared Error (RRMSE) was used as in equation (3).

$$RRMSE(y_i, \hat{y}_i) = \sqrt{\frac{\sum_1^T (y_i - \hat{y}_i)^2}{\sum_1^T (\bar{Y}_i - \hat{y}_i)^2}} \quad (3)$$

Where $\hat{y}_i$ is the predicted value of the i -th instance, y_i is the corresponding true value, $\bar{Y}_i$ is the mean value of the target variable over the training set, and T is the number of the test instances. The measure was applied in a uniform averaging setup (i.e., the errors of all outputs were averaged with a uniform weight). For evaluation purposes, the 5-fold cross validation setting was followed. The proposed approach is denoted as Low dimensional Clustering Tree Features (*LCTF*) and was compared to the original feature representation (*ORF*), Kernel PCA features (*KPCAF*), and Random Forest feature induction (*RFFI*) [25]. For the training of the tree ensembles (*LCTF*), the number of trees was set equal to 200. As stopping criterion, the minimum number of instances that have to be present in a leaf was used and it was set equal to 5. These parameters do not affect significantly the training procedure (e.g., one could use 100 or 300 trees and 3 or 8 as a stopping criterion without observing major differences in the results). Moreover, the tree node weight scheme was applied as described in Section 2.2 and the nodes containing more than 90% of all the data instances were removed (i.e., mainly the root nodes and some nodes close to them). For KPCA, the radial basis function (RBF) kernel (i.e., $K(\chi, \psi) = -\gamma ||\chi - \psi||^2$) was employed and the γ parameter was set equal to $1/|M|$, where M is the number of the original features. For RFFI, we used 200 trees (in the original paper [25] the algo-

395 rithm converged at this number) and a stopping criterion of 5 instances per
 leaf (the same as in our algorithm). In order to evaluate the efficiency of the
 generated feature representation in multi-label classification, the ML-KNN
 (Multi-Label K-Nearest Neighbor) [19] algorithm was employed. Multiple
 numbers of nearest neighbors were used and the smoothing parameter was
 400 set equal to 1 (i.e., Laplacian smoothing, as in the original paper [19]). For
 multi-target regression, we used the k-NN regressor (i.e., for each test, the
 target vector is predicted by averaging the target vectors associated with the
 nearest neighbors in the training set). Multiple numbers of nearest neighbors
 were used. The computation of the nearest neighbors was based on Euclidean
 405 distances. As we are interested in evaluating the contribution of the features
 we selected a relatively simple predictor. For the implementation and experi-
 mental evaluation we used the machine learning library Scikit-learn (Python)
 [44], and the libraries NumPy and matplotlib [45].

3.2. *Experimental Results and Discussion*

410 In Fig. 3, the 2D (two dimensional) data distribution of 4 datasets is
 displayed (see supplementary files for all the 2D and 3D projections). The
 original feature sets (ORF) were projected to 2D using PCA. Using the origi-
 nal features, it is noted that no manifold is detected and the data projections
 are similar to a random projection. This is particularly obvious in cases of
 415 wq and ern datasets. As reflected, the LCTF generates better data repre-
 sentations than original features. More specifically, it is shown that using
 LCTF adds variance between the instances and improves the data represen-
 tation in cases where the original features can not sufficiently discriminate
 the instances.

Figure 3: 2D projections of 4 datasets used in our evaluation procedure.

Figure 4: Average AUROC and AUPR results for various numbers of nearest neighbors.

420 In Table 3, the obtained comparison results for multi-label classification are illustrated. We compared our generated feature set to the original features, to the feature representation yielded by KPCA and to the Random Forest induced feature representation. Standard deviations are also provided in parenthesis and the best results are indicated in bold. For ML-KNN, 425 9 nearest neighbors ($k = 9$) were used. As shown in Table 3, the proposed approach outperforms the compared ones in terms of both AUROC and AUPR. Only in two cases (i.e., ERN, SRN datasets) LCTF is slightly outperformed by other approaches. More specifically, in the SRN dataset, the RFFI achieves better results and in the ERN, the ORF and KPCAF 430 slightly surpass the proposed LCTF.

In Fig. 4, the average AUPR and AUROC results for all datasets are shown for various numbers of nearest neighbors. The results obtained by LCTF surpass the ones of the compared approaches. The obtained results for multi-target regression are illustrated in Table 4. It is shown that LCTF 435 is better than all the compared approaches. The number of nearest neigh-

Table 3: AUPR and AUROC results for the compared approaches.

AUPR				
Data	LCTF	ORF	KPCAF	RFFI
MN	0.214 (± 0.05)	0.095 (± 0.01)	0.095 (± 0.01)	0.147 (± 0.026)
PPI	0.155 (± 0.042)	0.131 (± 0.042)	0.131 (± 0.042)	0.148 (± 0.034)
ERN	0.356 (± 0.04)	0.363 (± 0.029)	0.363 (± 0.029)	0.354 (± 0.036)
SRN	0.13 (± 0.014)	0.047 (± 0.005)	0.045 (± 0.002)	0.161 (± 0.012)
Medical	0.786 (± 0.051)	0.697 (± 0.046)	0.703 (± 0.039)	0.772 (± 0.051)
Yeast	0.703 (± 0.009)	0.699 (± 0.005)	0.699 (± 0.005)	0.697 (± 0.01)
Average	0.391 (± 0.034)	0.339 (± 0.023)	0.339 (± 0.021)	0.38 (± 0.028)
AUROC				
Data	LCTF	ORF	KPCAF	RFFI
MN	0.818 (± 0.023)	0.735 (± 0.015)	0.735 (± 0.015)	0.782 (± 0.025)
PPI	0.789 (± 0.022)	0.774 (± 0.028)	0.774 (± 0.028)	0.778 (± 0.022)
ERN	0.82 (± 0.03)	0.82 (± 0.031)	0.82 (± 0.031)	0.819 (± 0.028)
SRN	0.792 (± 0.012)	0.766 (± 0.006)	0.761 (± 0.005)	0.811 (± 0.009)
Medical	0.952 (± 0.013)	0.948 (± 0.01)	0.947 (± 0.012)	0.951 (± 0.016)
Yeast	0.836 (± 0.004)	0.832 (± 0.004)	0.832 (± 0.004)	0.831 (± 0.005)
Average	0.835 (± 0.017)	0.813 (± 0.016)	0.812 (± 0.016)	0.829 (± 0.018)

Table 4: RRMSE results for the compared approaches.

RRMSE				
Data	LCTF	ORF	KPCAF	RFFI
WQ	0.988 (± 0.034)	0.997 (± 0.022)	0.997 (± 0.022)	0.996 (± 0.036)
SG	0.938 (± 0.018)	0.96 (± 0.013)	0.958 (± 0.012)	0.949 (± 0.007)
Average	0.963 (± 0.026)	0.9785 (± 0.018)	0.978 (± 0.017)	0.973 (± 0.022)

bors was set equal to 9. The average results for various numbers of nearest neighbors are illustrated in Fig. 5.

It has to be mentioned that for evaluation purposes in the aforementioned experiments no PCA or KPCA generated components were removed. However, as stated in Section 2.2, the removal of many components is suggested. We conducted experiments removing each time a different percentage of components (i.e., amount of information). We compared the obtained results of the proposed approach (LCTF) to KPCAF, Independent Component Analysis (ICA) [46], Truncated SVD (similar to PCA), Locally Linear Embedding (LLE) [47], and Isomap [48] [32]. The results are shown in Figs. 6 and 7, for multi-label classification (ML-KNN, $k = 9$) and multi-target regression (KNN, $k = 9$), respectively. LCTF outperforms all the compared approaches. As it is shown the performance of LCTF is not decreased by the reduction of the components. It is interesting to notice that the best performance is achieved when 80% – 90% of the components are removed. This way, it can be deducted that the proposed method succeeds in generating a compact low

Figure 5: Average RRMSE results for various numbers of nearest neighbors.

dimensional feature representation, enriching the information contained in the data, inducing variance between the instances and removing the existing noise in the original representation.

455 In our evaluation process we computed the AUPR and AUROC in a micro-average setup. Nevertheless, one could argue that a macro-average setup is more suitable when it comes to class imbalanced datasets, as micro-average calculates a global measure using the total number of TP, TN, FP, FN and therefore can be biased towards the majority class. In Fig. 8, macro-averaged AUPR and AUROC results for multiple numbers of nearest neighbors are illustrated for the Yeast dataset. However, the computation of the macro-averaged measures presents a problem in cases of extreme class imbalance, where there are targets containing very few (sometimes only one) positive labels. In such cases, multiple folds may be left without any positive labels for some targets, leading to an undefined recall. This case is present 460 in the rest of the multi-label datasets used here (i.e., MN, PPI, ERN, SRN,

Figure 6: Average AUROC and AUPR results for various percentages of removed components.

Figure 7: Average RRMSE results for various percentages of removed components.

Figure 8: Macro-averaged AUPR and AUROC results for various numbers of nearest neighbors (Yeast dataset).

Figure 9: Macro-averaged AUPR and AUROC results for various numbers of nearest neighbors (Medical, MN, PPI, ERN, SRN datasets).

Medical). In order to surpass this impediment, in these datasets, we erased the targets that contain less than 5 positive labels and then computed the macro-averaged AUPR and AUROC scores in the remaining ones, applying a 2-fold CV. This approach is often used in cases of extreme class imbalanced data [49, 50]. The obtained results are illustrated in Fig. 9. As shown in both Figs. 8 and 9 the results are consistent with the micro-averaged ones, reaffirming the effectiveness of the proposed approach.

4. Conclusions

475 This study aims at highlighting the issue of lacking variance in biological and biomedical data representations and inform the scientific community about it. We also demonstrated the effect on machine learning algorithms. In addition, an efficient feature induction approach was proposed converting the data to a more informative feature representation. The data transformation process is done maximizing the variance between the instances. The
480 generated feature set is compact and therefore computationally efficient. The proposed approach was based on Extremely Randomized Trees inheriting all the advantages of tree ensembles, such as scalability, feature ranking, ability to handle various types of data without the need of preprocessing, and ability to handle missing values. The efficiency of the method was demonstrated
485 experimentally and the obtained results affirmed its potential.

A possible idea for future work is the employment of different node weighting schemes. An interesting extension could be also the application of deep learning. More specifically, the high dimensional tree induced feature vectors
490 could be converted to low dimensional encodings using auto-encoders.

ACKNOWLEDGMENTS

The authors acknowledge the KU Leuven research funding.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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