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# Predicting Biomedical Metadata in CEDAR: a Study of Gene Expression Omnibus (GEO)

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## Abstract

A crucial and limiting factor in data reuse is the lack of accurate, structured, and complete descriptions of data, known as metadata. Towards improving the quantity and quality of metadata, we propose a novel metadata prediction framework to learn associations from existing metadata that can be used to predict metadata values. We evaluate our framework in the context of experimental metadata from the Gene Expression Omnibus (GEO). We applied four rule mining algorithms to the most common structured metadata elements (sample type, molecular type, platform, label type and organism) from over 1,3 million GEO records. We examined the quality of well supported rules from each algorithm and visualized the dependencies among metadata elements. Finally, we evaluated the performance of the algorithms in terms of accuracy, precision, recall, and F-measure. We found that PART is the best algorithm outperforming Apriori, Predictive Apriori, and Decision Table.

All algorithms perform significantly better in predicting class values than the majority vote classifier. We found that the performance of the algorithms is related to the dimensionality of the GEO elements. The average performance of all algorithm increases due of the decreasing of dimensionality of the unique values of these elements (2697 platforms, 537 organisms, 454 labels, 9 molecules, and 5 types). Our work suggests that experimental metadata such as present in GEO can be accurately predicted using rule mining algorithms. Our work has implications for both prospective and retrospective augmentation of metadata quality, which are geared towards making data easier to find and reuse.

*Keywords:* data mining, prediction, metadata, GEO, CEDAR

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# 1. INTRODUCTION

Biomedical data is increasingly being viewed as a valuable commodity that can be mined for new insights beyond that for which it was created. Large community-focused databases such as the Gene Expression Omnibus (GEO) [1] or the database of Genotypes and Phenotypes (dbGAP) [2] offer a wealth of omics' data that have been used in developing diagnostic, prognostic, and therapeutic models [3, 4]. One crucial and limiting factor in the reuse of data lies in having access to accurate descriptions about the data - known as metadata. Community standards to describe an experiment (e.g. Minimum Information About a Microarray Experiment; MIAME [5]) are being widely promoted to highlight essential metadata, but creating good metadata can be challenging [6, 7].

Indeed, metadata is often of low quality, and many entries are absent, erroneous or inconsistent. The largest database of gene expression studies, the GEO microarray database, contains 50,000 studies, over 1.3 million samples, and is still growing [1]. Yet the description of these samples suffers from a lack of consistency and completeness. For example, a preliminary analysis revealed that there are 32 different ways to specify the age in GEO (e.g. age, Age, Age years, age year). Yet, these metadata are essential for researchers to find and reuse datasets of interest. When metadata are incomplete or inaccurate, researchers will miss relevant hits while being forced to sift through irrelevant results - resulting in lower productivity and potentially weaker scientific analyses. These issues are often attributed to lack of appropriate supporting infrastructure [8].

Metadata authoring applications such as ISA-Tools [9] or RightField [10] can be used to codify guidelines that specify multiple metadata elements and require users to use a set of controlled terms, such as terms from specified ontologies contained in the NCBO BioPortal [11]. Yet even with such tools, authoring good metadata is tedious and error-prone, and could benefit from more automation. The development of more effective platforms for metadata authoring and discovery is one of the goals of the Center for Expanded Data Annotation and Retrieval (CEDAR) [7, 8].

In this study, we examine the utility of supervised machine learning to predict metadata from existing metadata. This will help metadata submitter during the submission process. Predicting metadata could be a guideline for template authors during the process of metadata definition. This facility will not only significantly facilitate the template definition task but also will

38 make the resulting templates more comprehensive and reflective of the ac-  
 39 tual data. In CEDAR we also take advantage of emerging community-based  
 40 standard templates for describing different kinds of biomedical datasets, and  
 41 we investigate the use of computational techniques to help investigators to  
 42 assemble templates and to fill in their values [7].

43 Learning value sets from data will help ensure that template authors do not  
 44 miss important value sets that appear frequently in the data. Thus, data  
 45 submitters will be able to find the terms they need, hence improving the  
 46 quality of the metadata.

47 We use the increasing amounts of structured metadata to learn from as the  
 48 project progresses and learn value sets conditional on the experimental level  
 49 metadata. This incorporation of structural knowledge into the learning tech-  
 50 nology will allow us to infer common metadata patterns and their value sets  
 51 in the context of technology platform, organism, molecule, label or sample  
 52 type. Our key goal is to facilitate as much of the metadata collection process  
 53 as possible, by suggesting possible value sets for the fields based on available  
 54 data. This process will limit the value options, will reduce the burden of en-  
 55 tering metadata terms and will significantly shorten the time that is needed  
 56 for investigators to enter metadata.

57 We found that experimental metadata such as present in GEO can be accu-  
 58 rately predicted using rule mining algorithms. Our work has implications for  
 59 both prospective and retrospective augmentation of metadata quality, which  
 60 are geared towards making data easier to find and reuse.

## 61 2. BACKGROUND

62 Supervised learning uses classification algorithms to learn from data and  
 63 make predictions. The goal of supervised learning is to build a model of  
 64 the distribution of class labels from instances [12]. The classifier can then  
 65 assign class labels to instances in which the values of the predictor features  
 66 are known, but the value of the class label is unknown. Numerous supervised  
 67 classification techniques have been developed including decision trees, arti-  
 68 ficial neural networks, and statistical techniques such as bayesian networks  
 69 [12]. Machine learning has been widely applied across domains including  
 70 the biomedical domain [13], such as protein function prediction [14], clinical  
 71 outcome prediction [15] and survival analysis [16].

72 As we mentioned earlier, this study specifically is about metadata and asso-  
 73 ciation between them. Therefore, using machine learning will be helpful to

mine the data, learn from the data, and find this association. In our study, we wanted to find the correlation between metadata elements and their values. Association rules are the main technique for data mining to find these correlations. Sharma et al., compared association rule mining algorithms (e.g. AIS and FP-Growth, and Apriori) [17]. Each algorithm has advantages and disadvantages according to their comparison. For example, AIS requires multiple scanning of the database, only rules that have one item in right side can be generated, and too many candidate itemsets are generated. FP-Growth also has some disadvantages such as the resulting FP-Tree is not unique for the same logical database and it cannot be used in interactive mining system. Apriori is scanning the complete database multiple times but still, it is easy to implement. Predictive Apriori algorithm overcomes this disadvantage of the Apriori algorithm with scanning the best  $n$  rules instead of scanning all rules. PART algorithm uses partial decision trees to generate the decision list that is shown in the output, but only this final list is what is used to make classifications and with that, we have better performance.

In previously published manuscript [18], we proposed a framework to predict structured metadata terms from unstructured metadata for improving quality and quantity of metadata, using the Gene Expression Omnibus (GEO) microarray database. Our framework consists of classifiers trained using term frequency-inverse document frequency (TF-IDF) features and a second approach based on topics modeled using a Latent Dirichlet Allocation model (LDA) to reduce the dimensionality of the unstructured data. Our results based on GEO database showed that structured metadata can be predicted with TF-IDF more accurate than LDA. And both TF-IDF and LDA are outperforming the majority vote baseline as well. Overall this is a promising approach for metadata prediction that is likely to be applicable to other datasets and has implications for researchers interested in biomedical metadata curation and metadata prediction. Considering that metadata is structured and unstructured in GEO and other resources, we decided to find the correlation between structured metadata. In this study, we found the correlation between selected structured metadata elements versus in previous work we predicted structure metadata from the free text. Structure metadata has a potential to be predicted and suggested to metadata template author or metadata submitter during the submission process based on each other.

Several studies have been done regarding GEO metadata prediction. For instance Buckberry et al., [19] presented a method for predicting the sex of

112 samples in gene expression microarray datasets. They believe that the meta-  
 113 data associated with many publicly available expression microarray datasets  
 114 often lacks sample sex information, therefore limiting the reuse of these data  
 115 in new analyses or larger meta-analyses where the effect of sex is to be con-  
 116 sidered. The package called *massiR* provides a method for researchers to  
 117 predict the sex of samples in microarray datasets. "This package implements  
 118 unsupervised clustering methods to classify samples into male and female  
 119 groups, providing an efficient way to identify or confirm the sex of samples in  
 120 mammalian microarray datasets" [19]. As it is clear this study is just about  
 121 particular field in GEO data and it is specialized to predict the sex of the  
 122 samples.

123 In this study, we propose methods to predict structured metadata. This  
 124 method is applicable to any structured metadata in biomedical field. We use  
 125 association rule mining (ARM) algorithms due to their interpretability and  
 126 good performance [20]. ARM is a method for discovering relations between  
 127 variables in large databases. [21]. ARM was defined by Agrawal in the early  
 128 90s in relation to a so called market basket analysis using APRIORI [20].  
 129 Since then, multiple studies have used this technique successfully to model  
 130 data [22]. For example, ARM has been used to predict infection detection  
 131 [23], to detect common risk factors in pediatric diseases [24], to understand  
 132 the interaction between proteins [25], to discover frequent patterns in gene  
 133 data [22], and to understand what drugs are co-prescribed with antacids [26].  
 134 To the best of our knowledge, ARM has not yet been applied for predicting  
 135 experimental metadata.

136

### 137 3. OBJECTIVE

138 We hypothesized that there are strong correlations between metadata el-  
 139 ements and their values that can be used to predict metadata. The goal  
 140 of this study is to predict the metadata based on the correlation between  
 141 them. For example, there is a correlation between platforms, organism, and  
 142 type. For GPL570 as a platform and *Homo Sapiens* as an organism a possi-  
 143 ble type of the study is RNA. We used four algorithms: Apriori, Predictive  
 144 Apriori, Decision Table and PART (see below). We used these algorithms to  
 145 find the association between metadata elements and to predict the value of  
 146 each element of interest. We then evaluated our approach using a standard  
 147 cross-validation of experimental metadata from GEO, a primary repository

148 of gene expression data.

149

## 150 4. MATERIALS AND METHODS

### 151 4.1. Metadata

152 Our work focused on GEO [1], a large and well known database of gene  
 153 expression data which contains experimental metadata authored by the orig-  
 154 inal data submitters. We used the "GEOmetadb" package [27] in R [28] to  
 155 query and obtain the metadata for microarray experiments. GEOmetadb  
 156 implements an SQLite database that stores all the metadata associated with  
 157 all GEO data types including GEO samples (GSM), GEO platforms (GPL),  
 158 GEO data series (GSE). GEO itself stores curated gene expression DataSets  
 159 (GDS) that allows non-technical users to identify and visualize differentially  
 160 expressed genes in a given study. However, GEO DataSet curation is not  
 161 standardized across studies which preclude more powerful methods such as  
 162 integrated meta-analysis across multiple experiments to find robust gene sig-  
 163 natures. GDS have not been considered in this study.

164

Element	Description
Platform	A platform is a list of probes that define what set of molecules may be detected (GPLxxxxxx).
Type	Type of sample.
Organism	The organism(s) from which the biological material was derived for experiment.
Molecule	Type of molecule that was extracted from the biological material.
Label	The compound used to label the extract.

Table 1: Structured metadata elements in GEO. This table lists the structured metadata elements along with a description of each element [1].

165 The GEO database as of October 2015 contains 1,368,682 individual sam-  
 166 ple records in 50,000 studies or series. It includes 1.4 million samples now  
 167 (June 2016), which is decreased to 1.2 million samples after removing ele-  
 168 ments that occur less than 250 times. A series is identified with a series id  
 169 (i.e. GSExxxxxx) and each series consist of one or more samples. A sample  
 170 (identified with GSMxxxxxx) describes the set of molecules that are being



171 probed and references a platform (i.e. GPLxxxxx) used to representing the  
 172 molecular data [1]. Each study is annotated with up to 32 metadata fields  
 173 representing the conditions under which the sample was handled. There are  
 174 32 fields (16 for each channel of study including ch1 and ch2).  
 175 After discussion with the researchers in the field we considered five com-  
 176 mon structured elements for this study including (sample type, molecu-  
 177 lar type, platform, label type and organism (Table 1)) from 16 elements  
 178 (title, gsm, series-id, gpl, status, submission data, last-update-date, type,  
 179 sources name, organism, characteristics, molecule, label, treatment proto-  
 180 cols, extract-protocol, label -protocol). Other elements are date related (e.g.  
 181 last-update-date) or they are considered as unstructured (e.g. title) meta-  
 182 data. Therefore, we removed free text and date related information. We  
 183 also removed the studies with more than half missing value. We explained  
 184 the prediction for unstructured metadata such as title of the study in our  
 185 previous work. We define a structured element as a metadata element which  
 186 contains a single concept, such as the organism from which the material  
 187 was derived. More specifically, GEO metadata includes 5 sample types (e.g.  
 188 RNA, genomic), 9 types of molecules that were extracted from the biologi-  
 189 cal material (e.g., total RNA, cytoplasmic RNA), 12,431 different platforms  
 190 (e.g., GPL13653 for Affymetrix GeneChip Rat Genome U34A Array), 1,641  
 191 compounds used to label the samples (e.g., biotin, Cy3) and 2,434 organisms  
 192 (e.g. *mus musculus*). We removed elements that occur less than 250 times  
 193 to avoid the long tail, resulting in modeling 2,697 platforms, 5 types, 537  
 194 organisms, 9 molecule, and 454 labels (Table 2). We also made sure we did  
 195 not reduce the number of type and molecule with this set up threshold, which  
 196 they were not that many to begin with.

Element Name	classes	selected classes	Example Values
Platform	12431	2697	gpl570, gpl1261
Type	5	5	rna, genomic, sra
Organism	2434	537	homo sapiens, zea mays
Molecule	9	9	total rna, polya rna
Label	1641	454	biotin, cy3, cy5

Table 2: Number of classes in our experimental setup. This table shows the number of classes which constitute as well as example values, for each structured element.



#### 198 4.2. Association Rule Mining Algorithms

199 In this section, we describe the four different Association Rule Mining  
200 Algorithms (ARM) algorithms including Apriori, Predictive Apriori, Deci-  
201 sion Table and PART. These algorithms have been used to learn the rules  
202 and find the possible associations between five structural GEO elements and  
203 their values. We compared all four algorithms with the majority vote classi-  
204 fier representing the baseline model.

205 An association rule is an implication expression of the form  $X \rightarrow Y$ , where  
206  $X$  and  $Y$  are disjoint itemsets. The strength of an association rule can be  
207 measured in terms of its support and confidence. Support determines how  
208 often a rule is applicable to a given data set, while confidence determines  
209 how frequently items in  $Y$  appear in transactions that contain  $X$  [17].

210 The Apriori algorithm identifies association rules by identifying frequently  
211 occurring item sets [20]. An item set is called frequent when its support is  
212 above a defined minimum support. An item set  $X$  of length  $L$  is frequent if  
213 and only if all subsets of  $X$  with length  $L - 1$  are frequent. For every frequent  
214 item set  $T$  and every non-empty subset  $S$  of  $T$ , Apriori outputs a rule of the  
215 form  $S \Rightarrow (T - S)$  if and only if the confidence of that rule is above the  
216 user specified threshold. To run the algorithm some parameters had to be  
217 defined (e.g.  $T=0$ : The metric type which has been used to rank the rules.  
218 (default = confidence);  $C=0.9$ : The minimum confidence of a rule;  $D= 0.05$ :  
219 The delta by which the minimum support is decreased in each iteration;  $U$   
220  $=1.0$ : Upper bound for minimum support;  $M = 0.1$ : The lower bound for the  
221 minimum support). Apriori is easy to implement, but it is computationally  
222 and memory intensive.

223 Predictive Apriori [29] is a variant of Apriori that searches for the best 'n'  
224 rules using a support-based corrected confidence value. Since we just look  
225 at the best n rules is this algorithm, to run the algorithm we need to set  
226 the particular class attribute to predict as well ( $C$ = the class index for the  
227 chosen element to predict from 1 to 5) in each run. Predictive Apriori max-  
228 imizes the accuracy and minimizes the number of searches as compared to  
229 Apriori. A rule is added if the expected predictive accuracy of the rule is  
230 among the 'n' best and it is not subsumed by a rule with at least the same  
231 expected predictive accuracy [30].

232 A Decision Table [31] is a compact and easy to understand method to show  
233 the relationship between a series of conditions and resultant actions. It is  
234 based on a decision tree, where each node represents a feature and each  
235 branch represents a value that the node can assume. To run the algorithm

some other parameters had to be defined (e.g.  $D=1$  to set the forward search and  $N=5$  which is the number of non-improving nodes to consider before terminating search). A Decision Table can be translated into a set of rules by creating a separate rule for each path from the root to a leaf in the tree constructing an optimal binary. Finally, PART [32] is an algorithm that uses partial trees to generate near-optimal decision list. This list is what is used to make classifications. Once a partial tree has been build, a single rule is extracted from it. To run the PART algorithm considering previous parameters we also set minimum number of instances per leaf equal to  $M=2$ . The difference between heuristics for PART and heuristics for Decision Table is that the latter evaluate the average quality of a number of disjointed sets (one for each value of the feature that is tested), while PART only evaluate the quality of the set of instances that is covered by the candidate rule.

#### 4.3. Experimental Setup and Evaluation Framework

We used the four ARM algorithms to discover rules from our GEO dataset (Figure 1). We predicted each feature based on the other features (e.g. 'type' was predicted using molecule, label, platform, and organism). An example of a rule is: if organism=*Homo Sapiens*, molecule=total RNA then type=RNA. We performed 90:10 cross-validation in which we used 90% of the sample data for training and 10% for testing. Since the same sample can be used in another series, we partitioned the dataset by superseries such that samples that belong to the same study are either all in the training set or all in the test set. We assessed classifier performance based on the standard metrics for accuracy, precision, recall and F-measure [33]. The summary of the process of metadata prediction is shown in Figure 1.a. We then identified predictive features by counting the number of times a feature was selected as a feature in the model. We visualized the dependencies between all features as a network.

## Results

In this section, we discuss rules discovered with each of the four ARM algorithms over the experimental metadata from the GEO database. We report on the performance of each algorithm, and discuss associations within the rulesets.

Over five thousand rules were generated from the analysis of the GEO

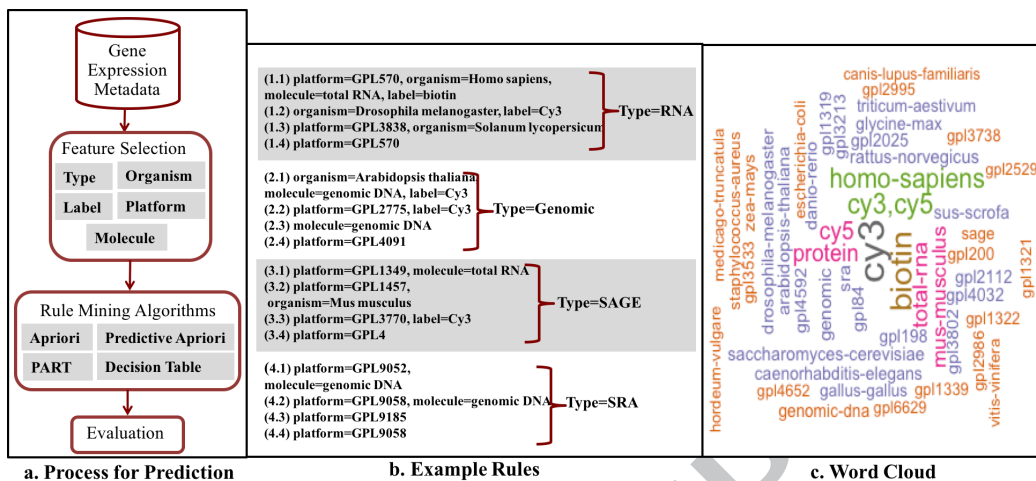


Figure 1: a. Overview of experimental design. b. Examples of rules generated by rule mining algorithms grouped by type and ordered by decreasing complexity. c. A word cloud containing high frequency values in rules from the PART algorithm.

database. We divided the rules into two kinds of rules: 1) complex rules having at least two elements in the antecedent, and 2) simple rules having only one element in the antecedent and one in the consequent. Figure 1.b. highlights rules to predict four metadata elements: RNA, Genomic, SAGE, and SRA. For example rule 1.1 is a complex rule to predict sample type using values from the other 4 features. This rule predicts RNA as type when the platform is GPL570 (i.e. the Affymetrix Human Genome U133 Plus 2.0 platform), the label is Biotin, the type of molecule that was extracted from the biological material is total RNA, and the sample was obtained from humans (*Homo sapiens*). In contrast, rule 3.4 is a simple rule that predicts the sample type as SAGE, when the platform used is GPL4. For the most common sample type, RNA, the generated rules have more variety with varying rule complexity (e.g. rule 1.1 with length 5 compared to rule 1.4, a simple rule). For the metadata element type, the value SRA is only predicted with the length of up to 3 (e.g. rules 4.1,4.2). Next, Figure 1.c. provides insight into reoccurring values in rules generated by the PART algorithm. For instance, the label Cy3 is most frequently used.

Next, we sought to understand how each of the four rule mining algorithms performed for each of the five selected features drawn from the GEO dataset. Figure 2 shows the performance using F-measure, precision, recall and accu-

291 racy for each of the four algorithms and the majority vote baseline. Our re-  
 292 sults indicate that PART is the best classifier. Also, only PART and Decision  
 293 Table consistently outperformed the majority vote classifier for predicting all  
 294 features that we examined. PART and Decision Table outperformed Apriori  
 295 and Predictive Apriori for Label, Organism, and Type. As shown in Figure  
 296 2 for each performance measurement we considered the confidence interval.  
 297 We calculated the confidence interval for 10 iterations for each algorithm. As  
 298 an example, Table S2 in supplementary materials shows the details regarding  
 299 the calculation of traditional confidence interval for all algorithms.

Next, Figure 3 shows the F-measure to predict the metadata element type

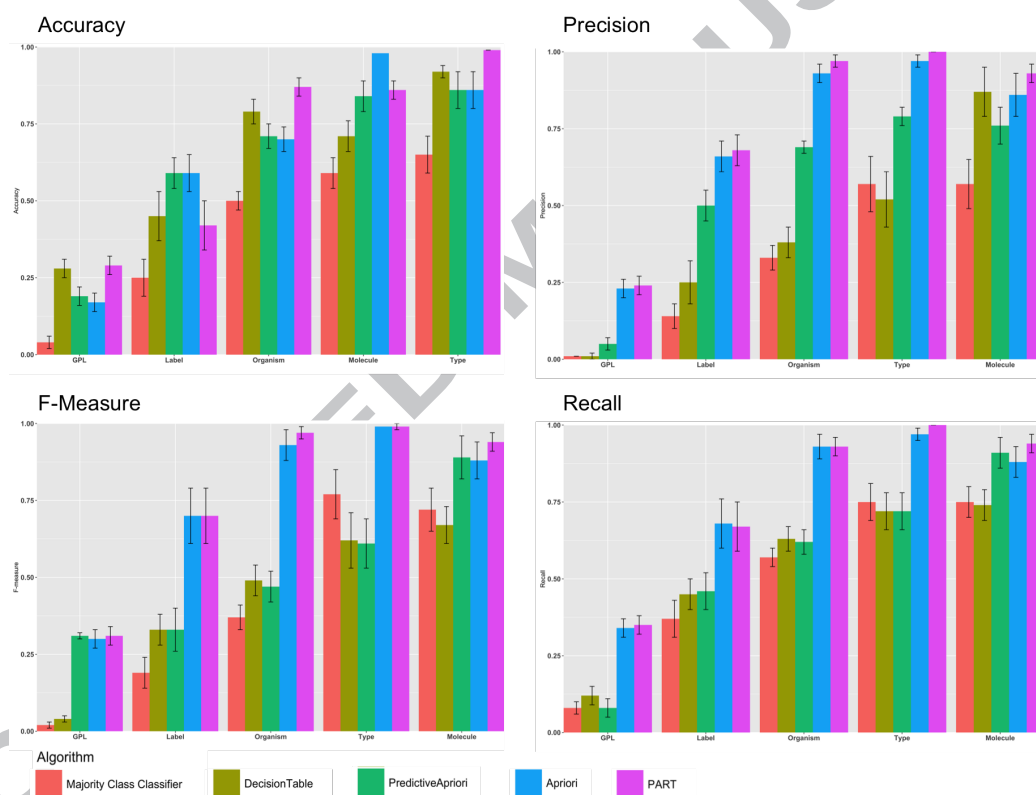


Figure 2: Evaluation Results: Performance measurements for weighted class averages for each element for all algorithms.

300 using all four algorithms. Our results suggest that the accuracy of pre-  
 301 dicting specific metadata values can vary significantly for each algorithm.  
 302 For instance, 'RNA', 'SRA', and 'GENOMIC' is near perfectly predicted by  
 303

304 PART, while lower performance is seen for predicting the 'PROTEIN' and  
 305 'SAGE' types. The Decision Table follows the same trend as PART, but is  
 306 less successful for each metadata value for this metadata element. Apriori  
 307 and Predictive Apriori predict 'RNA', but largely fail for the other values.  
 308 Apriori generates too many unnecessary candidates. A candidate itemset is  
 309 unnecessary if at least one of its subsets is infrequent. This is the major  
 310 reason that we have low performance in Apriori in general [34]. We report  
 311 the F-measure for all values for all metadata elements in the supplementary  
 312 materials (Table S1).

Next, we analyzed the rules to assess whether performance was influenced

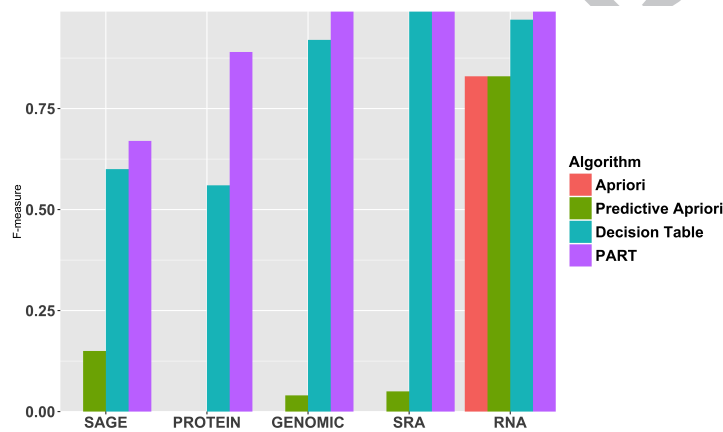


Figure 3: F-measure for predicting different values for the “type” element for each algorithm.

313 by length of rule. Figure 4 shows the rule length for all algorithms. We find  
 314 that the median length of rules is lowest for PART and Predictive Apriori  
 315 (length 2), while nearly all of the Decision Table rules have a length of 3.  
 316 Apriori appears to have the greatest variety in length of rules.

317 Finally, we investigated the associations that exist between GEO metadata,  
 318 at least as uncovered by each classifier.

319 Figure 5 shows the association network for rules generated by all algo-  
 320 rithms. The association network shows the dependency between elements in  
 321 each algorithm. On the other hand which elements can predict other ele-  
 322 ments. This association between elements also shows which element is more  
 323 predictable based on other elements and reveals the power of each element  
 324 to predict other elements. For example, in PART algorithm the platform  
 325

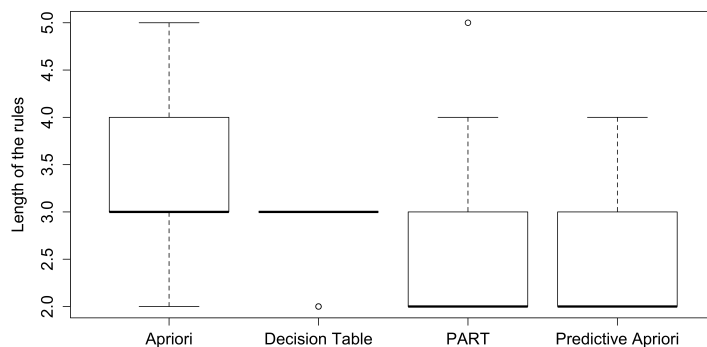


Figure 4: Box plot for the distribution of the rule length for all algorithms.

(GPL) has a power to predict all other elements. It means we can predict the possible organism, molecule, type and label which are associated with the particular platform. As it shown in Figure 5, there are tick arrows from platform to other elements, which shows the strong power of prediction of other elements based on the platform. The same description assigned to other algorithm based on the arrows in the network in Figure 5.

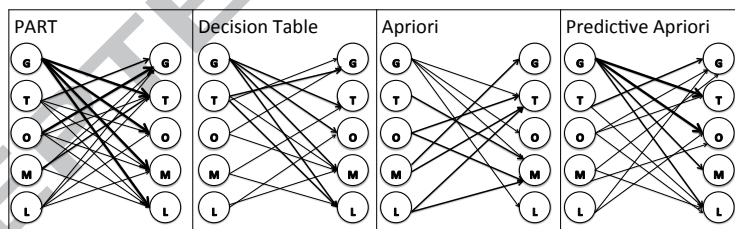


Figure 5: A network diagram illustrating associations between all elements (GPL for platform, Type, Organism, and Molecule) in rules generated by all algorithms. This association shows which element is more predictable based on other elements. It also reveals the power of each element to predict other elements. Thick lines indicate associations of bigger than 0.5 (strong association), medium lines indicate associations between 0.05 and 0.5. Associations of strength less than 0.05 are thin lines (weak association).

## 5. DISCUSSION

In this work, we explored the use of ARM algorithms to predict structured metadata. Our results, based on the analysis of a subset of GEO's metadata elements, support the hypothesis that associations between certain metadata elements exist and can be used by ARM algorithms in a predictive manner. Our goal is to simplify the authoring of metadata as much as possible for metadata submitter with predicting the metadata value and recommend that to the metadata submitter during the submission process. We show that algorithms, which have been used in this study, particularly PART and Decision Tables, perform better than using the most frequently occurring metadata value for a particular metadata element (i.e. majority vote classifier). We found differences in the length of rules generated by different algorithms and the quality of their predictions. While our work focused on the metadata in the GEO database, we anticipate that our approach can be applied to other databases of experimental metadata with similar levels of success.

Our research has important implications for initiatives aimed at improving the quantity and quality of metadata in a prospective and retrospective manner. Several efforts are devoted to prospective metadata authoring - they specify metadata that can, should, and minimally must be provided. BioSharing.org [6] catalogs guidelines, standards, and the policies for databases, journals, and funders. Metadata authoring applications such as ISA-Tools [9] or RightField [10] can be used to codify guidelines and enable users to author metadata using ontologies from the NCBO BioPortal [11]. Authoring good metadata is tedious and error-prone, and could benefit from more automation. Our work shows that a subset of metadata elements can be predicted with sufficiently high accuracy. Thus, our predictive approach could be useful for metadata authoring. It could vastly reduce the amount of metadata authoring a submitter must do, but also potentially improve the quantity and quality of metadata. Generating higher quality metadata with less effort is a key part of our NIH BD2K Center for Data Annotation and Retrieval (CEDAR) [7], which is developing intelligent tools for metadata authoring and discovery [8]. We believe that the application of ARM and other machine learning algorithms will greatly accelerate metadata authoring, and improve the quality of research data submissions; failure to do so will likely continue the present situation wherein guidelines are variably applied [35]. Additionally, metadata prediction can be useful retrospectively. Our predictive framework can be used to highlight metadata values that differ from our



370 predictions and may need to be more closely examined. We also anticipate  
 371 that we could use the approach to predict missing metadata, subject again to  
 372 further validation by professional users in the field or possibly through crowd-  
 373 sourcing, which has been applied to find and categorize errors in Linked Data  
 374 [36]. Our work is not without limitations. First, a key limitation in ARM al-  
 375 gorithms lies in the vast number of discovered rules and the arbitrary thresh-  
 376 olds applied to limit these rules. The main drawback is that the arbitrary  
 377 thresholds may reduce the amount of information and affect the performance  
 378 of the classifier specifically when we have the high variety of the values (e.g.  
 379 values for the platform). Existing approaches employ different parameters  
 380 to search for interesting rules [37, 38, 22]. This fact and a large number of  
 381 rules make it difficult to compare the output of ARM algorithms. Several  
 382 methods for solving this problem such as rule reduction methods, associa-  
 383 tion rule refinement and association rules for supervised classification have  
 384 been proposed [38]. Most studies suggest the latest one is the more effective  
 385 one [38, 30, 22]. Second, our method is currently focused on learning rules  
 386 from structured metadata. However, databases of experimental metadata  
 387 often contain textual descriptions which could not be used directly in our  
 388 approach. In previous work, we showed that experimental metadata could  
 389 be predicted using classifiers trained with term frequency-inverse document  
 390 frequency (TF-IDF) based models [18].  
 391 Finally, while our work showed promise in predicting some of the metadata  
 392 values in GEO, it remains to be seen how well the approach will be with  
 393 other experimental databases. We expect that our approach will work well  
 394 with well structured data sets such as the Sequence Read Archive (SRA),  
 395 but perhaps do less well on data sets with less metadata. Further study on  
 396 data sets comprised of different sizes, different varieties of the values for each  
 397 element, and different combination of structured and unstructured elements  
 398 is needed. It is also unclear whether data from one database can be usefully  
 399 combined with data from other databases to improve prediction.

## 401 6. CONCLUSION

402 We have shown that predicting metadata using ARM algorithms is pos-  
 403 sible using an existing large biomedical database such as GEO. Future work  
 404 will focus on expanding this application to other databases such as Biosam-  
 405 ple datasets (e.g. SRA), more comprehensive metadata as well as aggre-

gation with other models from our previous works on both structured and unstructured metadata [18]. GEO database includes both structured and unstructured metadata as well as other resources. We will extend our methods from previous work such as LDA and TF-IDF to other unstructured data (e.g. abstract of the related manuscript associated with the studies) to improve additional information to improve classification. However, an ensemble classifier could be considered to combine predictions given by different methods, i.e. from rule-based algorithms trained on structured metadata and from other machine learning methods trained on textual features. Predictive metadata can be used both prospectively to facilitate metadata authoring, and retrospectively to improve, correct and augment existing metadata in biomedical databases.

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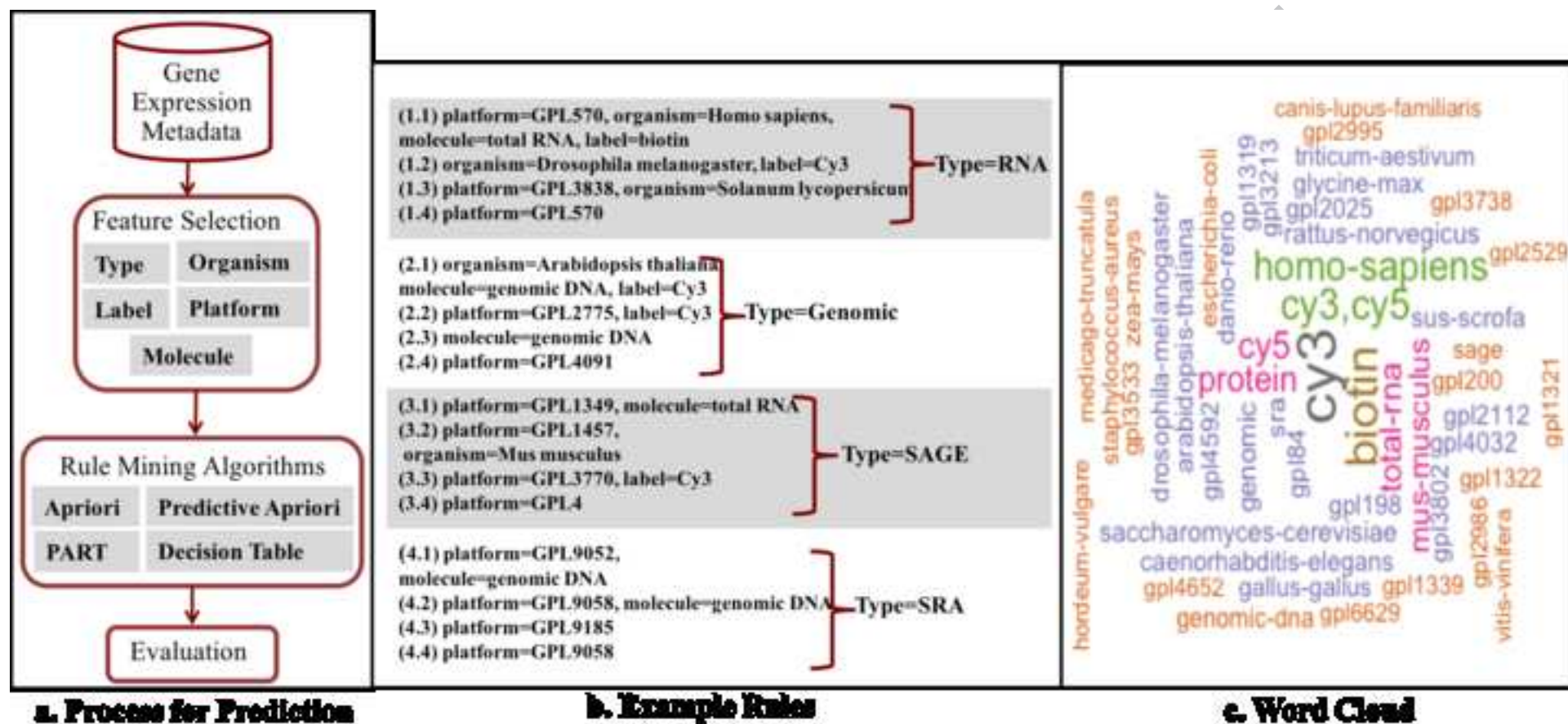
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## Highlights

- Associations between certain metadata elements exist and can be used by ARM algorithms in a predictive manner.
- Particularly PART and Decision Tables, perform better than using the most frequently occurring metadata value for a metadata element.
- Our predictive approach could be useful for metadata authoring. It could vastly reduce the amount of metadata authoring a submitter must do, but also potentially improve the quantity and quality of metadata.