

MINING QUANTITATIVE ASSOCIATION RULES IN MICROARRAY DATA USING EVOLUTIVE ALGORITHMS

M. Martínez-Ballesteros, C. Rubio-Escudero, J. C. Riquelme
Department of Computer Science, University of Seville, Seville, Spain

F. Martínez-Álvarez
Department of Computer Science, Pablo de Olavide University of Seville, Seville, Spain

Keywords: Data mining, Evolutionary algorithms, Quantitative association rules, MicroArray.

Abstract: The microarray technique is able to monitor the change in concentration of RNA in thousands of genes simultaneously. The interest in this technique has grown exponentially in recent years and the difficulties in analyzing data from such experiments, which are characterized by the high number of genes to be analyzed in relation to the low number of experiments or samples available. In this paper we show the result of applying a data mining method based on quantitative association rules for microarray data. These rules work with intervals on the attributes, without discretizing the data before. The rules are generated by an evolutionary algorithm.

1 INTRODUCTION

The use of massive processing techniques has revolutionized the biotechnology research and it has highly increased the amount of data obtained (Durbin et al., 1998). In particular, microarray technology has revolutionized the biological research due to its ability to monitor changes in RNA concentration in thousands of genes simultaneously (Durbin et al., 1998). Research in molecular biology has traditionally focused on the study gene to gene, but nowadays we are in the genomic era and genes are studied in thousands or even whole genomes. Besides the genes, it is necessary to know the relationships between them.

In this context we present the result of applying a data mining technique, specifically, association rules, to gene expression data from experiments using microarray technology. The aim of this process of mining association rules is to discover the presence of pairs (attribute - value), which appear in a dataset with a certain frequency. This technique is applied to discover associations between genes from microarray datasets, in which gene expression is linked to another gene expression, $Gen1 \Rightarrow Gen2$.

There are many efficient algorithms to find these rules, most focused on discrete data. However in the real world, particularly in the problem to deal in this

paper, datasets consists of continuous attributes. In addition, the tools that work in continuous domains just discretize the attributes using a specific strategy and treat these attributes as if they were discrete (Vannucci and Colla, 2004). In this paper, the result of applying a genetic algorithm (GA) is presented. The algorithm can find association rules in databases with continuous attributes from microarray data, avoiding the discretization as a step in the process. The results will show that the rules obtained have been able to successfully characterize the data underlying and also to group relevant genes for the problem studied.

The rest of the paper is divided as follows. Section 2 provides the methodology used in this work. The results obtained by the algorithm developed are discussed in Section 3. Finally, Section 4 describes the achieved conclusions.

2 METHODOLOGY

2.1 Search of Rules

This work is focused on a continuous domain. It is necessary to group the sets of values in intervals to be able to express the membership of the values to each

group. Ranges have not been fixed for intervals. The Genetic Algorithm finds and adjust the most appropriate intervals to find quantitative association rules. Each individual in the population is a rule. The set of rules comprising the population undergo an evolutionary process in which mutation and crossover operators will be applied. The individual with the best fitness at the end of the process represents the best rule. The user can drive the search process because the fitness function has been provided with a set of parameters. Our proposal performs an IRL process (Iterative Rule Learning) (Venturini, 1993) to penalize instances already covered by rules in order to emphasize the covering of instances still not covered.

In the following sections we provide details of the general scheme of the algorithm, the fitness function, representation of individuals and genetic operators.

2.2 Scheme of the Algorithm

First, the rules population is initialized and evaluated. All rules are evaluated according to equation 1. Thus, in each iteration the selection operator is applied to select the best rules on the basis of the fitness function. Then, the crossover operator is applied to the selected rules while the population size is not completed. Individuals are randomly selected according to p_{mut} in order to apply the mutation operator. Finally, the new population is again evaluated by the fitness function and the evolutive process restarts. Note that the process will be repeated as many times as the maximum number of preset generations indicates.

2.3 Individuals Codification

The lower and upper limits of the intervals of each attribute will be represented by the different genes of an individual. Because the attributes are continuous, individuals are represented by an real coding. An individual consists of a not fixed number of attributes less than n , which represents the number of attribute in the database.

The representation of an individual consists in two data structures as shown in Figure 1. The upper structure includes all the attributes of the database, where i_j is the lower limit of the range and s_j is the upper limit. The bottom structure indicates the membership of an attribute to the rule represented by a individual. The type of each attribute t_j , can have three values: 0 when the attribute does not belong to the rule, 1 if it belongs to the antecedent of the rule and 2 when it belongs to the consequent part. If an attribute is wanted to be retrieved for a specific rule, it can be done by modifying the value equal to 0 of the type by a value

equal to 1 or 2 depending on the antecedent or consequent.

i_1	s_1	i_2	s_2	...	i_n	s_n
t_1		t_2		...		t_n

Figure 1: Representation of an individual of the population.

An example of one individual of the population is shown in Figure 2.

$A_1 \in [20.1, 23.5]$ and $A_2 \in [10.3, 15.8] \implies A_4 \in [54.4, 59.6]$.

20.1	23.5	10.3	15.8	70.4	78.2	54.4	59.6
1		1		0			2

Figure 2: Example of an individual of the population.

2.4 Initial Population

The number of attributes for each individual is randomly chosen to generate the initial population taking into account the desired format for the rules. In addition, the minimum and maximum numbers in the antecedents and consequents, the minimum and maximum number of attributes that belong to rule represented by an individual are controlled.

2.5 Genetic Operators

The genetic operators implemented in the propose genetic algorithm are: Selection, Crossover and Mutation.

- **Selection.** An elitist strategy replicating the individual with best fitness and a roulette selection-based method for the remaining individuals according to their fitness are used .
- **Crossover.** Two parents are chosen by the roulette selection-based method and they are combined to generate a new individual. The type of all the relevant attributes in both parents are analyzed.

If both parents have an equal type for the same attribute, it will assigned to offspring. The interval is obtained as a random value between the limits of the intervals of both parents.

Nevertheless, if both parents have a different type for the same attribute, one of the two parents is randomly chosen and offspring have the intervals and type attribute of the selected parent.
- **Mutation.** Individuals of the population are randomly selected in order to apply the mutation de-

pending on a mutation probability p_{Mut} . The mutation process consists in modifying individuals genes, according to a probability p_{MutGen} in the individuals selected. The mutation can be focused on the attribute type or on the intervals, in which are possible three separate cases: mutation of the upper limit, lower limit or both limits of the interval.

For this aim, a random value between 0 and 10% of the total domain in the attribute is generated and it is added or subtracted to the limit of the interval randomly selected.

2.6 Fitness Function

The fitness function calculation involves several measures that give us information about the rules. In particular, the most representative are the support and confidence that will positively affect the rule. However, it is necessary to take into account a number of factors with negative affect in the quality of the rule. In the amplitude of the intervals, the algorithm may try to extend the intervals to complete the domain of each attribute. For this aim, it is necessary to include a measure limiting growth of the intervals during the evolutive process.

The evaluation function f should be maximized in the evolutionary process is given by the equation . It consists in several parameters which values are calculated from the individual multiplied by a weight to calibrate the effect of each parameter in the overall evaluation.

$$f(i) = w_s \cdot sup + w_c \cdot conf - w_r \cdot recov + w_n \cdot nAttrib - w_a \cdot ampl \quad (1)$$

where sup is the support, $conf$ is the confidence, $recov$ is the number of recovered instances, $nAttrib$ is the number of attributes in the rule, $ampl$ is the average size of intervals of the attributes belong to the rule and w_s , w_c , w_r , w_n and w_a are weights in order to drive the process of search of rules.

The meaning of each parameters in the equation is:

- **Support (sop).** Percentage of records in the dataset covered by the rule.
- **Confidence (conf).** Conditional probability of consequent given the antecedent. Confidence is calculated dividing the support of the rule and the support of the antecedent.
- **Number of Recovered Instances (recub).** It is used to indicate a sample has already been covered by a previous rule. Rules covering different regions of search of space are preferred.

- **Number of Attributes (natrib).** Number of attributes (genes) belong to the rule (individual).
- **Amplitude (ampl).** Average of intervals size of the attributes belong to the rule.

3 RESULTS

The results of applying the algorithm proposed in Section 2 to a dataset acquired from a microarray experiment related to inflammation and immune response are presented. Inflammation is a critical process because the human body uses to protect itself from infections and lesions. In this experiment, conducted at the University of St. Louis, Missouri(Calvano et al., 2005), the blood of eight volunteers is analyzed, four treated with a toxin produces an inflammatory process and 4 with placebo. Samples has been taken at 6 time points over 24 hours, obtaining a total of 48 microarrays.

The algorithm was tested with the following parameters of AG: 100 for the size of the population, 100 for the number of generations, 20 for the number of rules to obtain, 0.8 for the mutation probability p_{Mut} of the individuals and 0.2 for the mutation probability p_{MutGen} of each gene in the individual. The fitness function weights are: 1 for w_s , 0.5 for w_c , 0.3 for w_r , 0.1 for w_n , and 0.1 for w_a . The reason to assign a high value to the weight w_s is to cover the maximum number of examples obtained by the rules. The weight associated to the instances covered by other rules and the size of the intervals are set to penalize rules whose intervals are too large and covering examples already covered by other rules.

The algorithm has been executed 10 times, and only those rules that cover a minimum of 6 samples out of 48 (support 12.5 %) have been taken into account, obtaining a total of 76 rules of the 200 possible rules (10 executions x 20 rules in each run). The limit of the support has been set at that value because 6 samples shows data from a complete volunteer, and such low limit for the support has been chosen because in this type of experiments we are interested both in frequent relations, but also in the not so frequent ones (McIntosh and Chawla, 2007).

The average support obtained for the 151 rules has been 47.17% with a confidence close to 100% for most of them. The average amplitude of intervals in the rules was 24.7%, which justifies the use of quantitative rules in place of the classical rules in which the whole domain of the attribute is taken into account.

The rules obtained have accurately characterized dataset treated, having two types of rules: those with a support value between 75 % and 100 %, and those

Table 1: Analyzed Rules.

Id	Rule	Sup. (%)	Conf. (%)	Ampl. (%)
1	215091_s_at ∈ [98.35 , 376.99] and 215760_s_at ∈ [527.04 , 1168.82] ⇒ 203944_x_at ∈ [890.80 , 5308.61]	52	100	17
2	205119_s_at ∈ [783.83 , 1527.60] and 215597_x_at ∈ [8301.78 , 9819.85] ⇒ 212967_x_at ∈ [2076.59 , 2592.60]	20	100	16
3	222099_s_at ∈ [859.491 , 1425.210] ⇒ 49327_at ∈ [1517.45 , 2239.45]	55	100	17

with support values less than 50 % where in almost cases cover records or endotoxin-treated group or placebo group.

The number of rules covering the placebo group is significantly higher, which makes sense because this group has gene expression values more stable and frequent than the group treated with endotoxin (Rubio-Escudero, 2007). To examine the relevance of the rules obtained in the studied problem, we have used the Onto-CC software (Romero-Zliz et al., 2008), which retrieves information regarding the functionality of a set of genes that is passed as a query, and a PI value (the probability of intersection) associated with the relevance of these genes appear together in one rule. PI is a value to minimize between 0 and 1 and considered relevant those obtained under 0.05.

The results of only 3 rules are listed in Table 1 for readability. When Onto-CC is applied, the PI values obtained for every rule are quite low, indicating the relevance of grouping these three genes with respect to these terms, immune response and related terms are explicitly included.

4 CONCLUSIONS

In this paper we present the result of applying an evolutive technique for extracting association rules from microarray data. We have seen the rules obtained are able to successfully characterize the dataset applied, either covering almost all samples, or covering samples only one of the two groups in the data: treated with endotoxin or treated with placebo. In addition, the mean amplitude of the intervals was 24.7%, which justifies the use of quantitative rules in place of the classical rules.

We have shown the relevance of the rules obtained for the problem studied using the Onto-CC program. The PI values obtained show significance in the group of genes found in the rules, and secondly the terms obtained querying Gene Ontology are closely related to the problem of inflammation.

Thus, we conclude that the use of quantitative association rules, in particular those obtained by the algorithm proposed, is a valid method for analyzing microarray data, and we consider it a starting point

for future work, applying this technique to other microarray data, comparing with other analytical techniques and seeing the importance of the influence antecedent-consequent obtained by the rules with regard to genetic networks.

ACKNOWLEDGEMENTS

The financial support from the Spanish Ministry of Science and Technology, project TIN 2007-68084-C-02, and from the Junta de Andalucía, project P07-TIC-02611, is acknowledged.

REFERENCES

- Calvano, S. E., Xiao, W., Richards, D. R., Felciano, R. M., Baker, H. V., Cho, R. J., Chen, R. O., Brownstein, B. H., Cobb, J. P., Tschoeke, S. K., Miller-Graziano, C., Moldawer, L. L., Mindrinos, M. N., Davis, R. W., Tompkins, R. G., Lowry, S. F., and Large Scale Collab Res Program, I. A. (2005). A network-based analysis of systemic inflammation in humans. *Nature*, 437.
- Durbin, R., Eddy, S., Krogh, A., and Mitchison, G. (1998). *Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids*. Cambridge University Press.
- McIntosh, T. and Chawla, S. (2007). High-confidence rule mining for microarray analysis. *IEEE/ACM Transactions on Computational Biology and Bioinformatics*, 4(4):611–623.
- Romero-Zliz, R., del Val, C., Cobb, J., and Zwir, I. (2008). Onto-cc: a web server for identifying gene ontology conceptual clusters. *Nucleic Acids Res*, 36(4):W352–W357.
- Rubio-Escudero, C. (2007). *Fusion of Knowledge towards Identification of Genetic Profiles in the Systemic Inflammation Problem*. Ph.D Thesis. Universidad de Granada.
- Vannucci, M. and Colla, V. (2004). Meaningful discretization of continuous features for association rules mining by means of a som. In *Proceedings of the European Symposium on Artificial Neural Networks*, pages 489–494.
- Venturini, G. (1993). SIA: a Supervised Inductive Algorithm with genetic search for learning attribute based concepts. In *Proceedings of the European Conference on Machine Learning*, pages 280–296.