Proceedings of the 2012 IEEE 12th International Conference on Bioinformatics & Bioengineering (BIBE), Larnaca, Cyprus, 11-13 November 2012

Evolving very-compact fuzzy models for gene expression data analysis

Miguel Arturo Barreto-Sanz, Alexandre Bujard and Carlos Andrés Peña-Reyes
University of Applied Sciences of Western Switzerland (HEIG-VD)
Vaud, Switzerland
Email: miguel-arturo.barreto-sanz@heig-vd.ch
alexandre.bujard@heig-vd.ch
carlos.pena@heig-vd.ch, c.penha@ieee.org

***Abstract*—Selecting predicitve gene pools from thousands of gene expression values is one of the main tasks in microarray data analysis. For this purpose multivariate techniques have proven much better, in terms of predicitve value and biological relevance, than univariate techniques as they are able to capture relevant relationships and interactions between genes. An additional goal for gene-expression profiling is finding models that, besides being predictive, are also understandable so as they can provide some insight on the underlying mechanisms. Models based on fuzzy logic might, potentially, exhibit both characteristics. However, accuracy and interpretability are usually contradictory objectives, and one must accept a trade off between them. Indeed, literature shows that the approaches based on fuzzy logic may be divided in two groups: accurate but complex models (i.e, with many rules using many variables per rule) on one hand, and models with only few short rules (thus, interpretable) but exhibiting limited accuracy. We present in this paper the application of Fuzzy CoCo, our cooperative coevolutionary fuzzy modelling approach, in order to deal efficiently with the accuracy-interpretability tradeoff. Fuzzy CoCo is able to find very compact fuzzy models, in terms of number of rules and number of variables per rule, while still exhibiting high predictive power. To validate the performance of our approach, we tested Fuzzy CoCo on four known data sets addressing each one a form of cancer: Leukemia, colon, lung, and prostate. We compared our results–in terms of maximum number of rules, number of variables per rule, and accuracy–with those of other similar works (i.e., based on fuzzy logic). Our models reached similar or better accuracy while being considerably smaller.**

I. Introduction

Microarray techniques allow measuring thousands of gene-expression values in a single experiment. Multiple microarray experiments, performed generally to investigate a given biological question, result in huge sets of data to be processed and analyzed. In order to make sense out of these complex data-sets, it is essential to count on methods that allow selecting relatively small subsets of genes associated to cell functions. In this context, many modeling techniques have been applied to microarray data, among which a plethora of univariate approaches, which test one feature at a time in order to discriminate individually-relevant variables. The top most significant features are then used to develop statistical models. In contrast, multivariate approaches consider the existence of synergies between genes; in other words, the fact that it may exist interactions between them that influence a given biological outcome rather than considering each gene's behavior as isolated. Although several multivariate methodologies have been successfully applied, there are still many remaining challenges [17].

In this work we address challenges related to the interpretability of the models, as very often they include a large number of variables and complex relationships that make difficult their interpretation. Fuzzy modeling constitutes a good approach to tackle such a challenge as it allows producing small, multivariate, and interpretable models. Algorithms implementing fuzzy modeling have proven worthwhile on numerous problems involving gene-expression data analysis [2], [5], [6], [8], [9], [11], [16], [21], [22]. Nevertheless, many reported approaches presents models with numerous and/or large rules, making difficult their interpretation. Conversely, approaches that generate models with few and/or short rules present lower accuracy than the former.

In order to find more compact models, in terms of number of rules and variables per rule, we present in this work the use of our Cooperative Coevolutionary Fuzzy approach (Fuzzy CoCo) [13]. Our specific goal is to take advantage of the characteristics of Fuzzy Coco creating very compact fuzzy models and using it to find models with a maximum of three rules and three variables per rule with a high discriminative power. For this aim we tested Fuzzy CoCo on a target of four known datasets: Leukemia (Golub et al. [3]), colon cancer (Alon et al. [1]), lung cancer (Gordon et al. [4]), and prostate cancer (Singh et al. [18]). Finally, we compare our results (in terms of maximum number of rules, number of variables per rule and accuracy) with these reported by other works using fuzzy logic based approaches.

This work is organized as follows: Section II introduce the Fuzzy CoCo approach and its advantages evolving very compact systems. Section III explain the data set used, the fuzzy modeling process, and the results we obtained. Finally, we discuss these results and we propose some tracks that could be pursued for improving and/or extending the reach and the relevance of the modeling approach.

978-1-4673-4358-9/12/$31.00 ©2012 IEEE

II. System and methods

A. Coevolutionary Algorithms

In the simplified models of evolution we consider individuals belonging to a single species, i.e., sharing the same genetic encoding and reproducing with each other. We assume this species evolves in isolation, in an almost unchanging environment. In nature, species live in the niches afforded by other species, modifying themselves and the environment and being affected by such modifications. Over time, the evolution of many species has been influenced by interactions with other species. Species that have mutually influenced one another's evolution are said to have coevolved. For instance, predator-prey interaction constitutes an example of competitive coevolution where the survival of individuals of one species requires the death of individuals from other species.

Coevolution has served as inspiration to propose a family of evolutionary algorithms capable of surmounting some of the limitations encountered by evolutionary computation. These coevolutionary algorithms deal particularly well with increasing requirements of complexity and modularity while keeping computational cost bounded.

Fuzzy CoCo applies cooperative coevolution to tackle the fuzzy-modeling problem.

B. Coevolutionary Computation

Inspired by natural coevolution, artificial coevolution refers to the simultaneous evolution of two or more species with coupled fitness. Such coupled evolution provides some advantages over non-coevolutionary approaches that render coevolution an interesting alternative when confronting certain problems. Among these advantages, we can mention :

- Coevolution favors the discovery of complex solutions whenever complex solutions are required.
- It helps preserve genetic diversity.
- It is suitable for parallel implementation.

In a competitive-coevolutionary algorithm, the fitness of an individual is based on direct competition with individuals of other species, which in turn evolve separately in their own populations. Increased fitness of one of the species implies a diminution in the fitness of the other species. This evolutionary pressure tends to produce new strategies in the populations involved so as to maintain their chances of survival. This "arms race" ideally increases the capabilities of each species until they reach an optimum.

C. Cooperative Coevolution

In nature, many species have developed cooperative interactions with other species to improve their survival. Cooperative coevolutionary algorithms involve a number of independently evolving species which together form complex structures, well-suited to solve a problem. The fitness of an individual depends on its ability to collaborate with individuals from other species. In this way, the evolutionary pressure stemming from the difficulty of the problem favors the development of cooperative strategies and individuals. As in nature the species are genetically isolated because they evolve in separate populations, because their genomes are genetically incompatible, or both.

D. A general model for cooperative coevolution

Potter and De Jong [14], [15] developed a general model for cooperative coevolution. Their hypothesis was that explicit notions of modularity are necessary in order to evolve complex structures in the form of interacting coadapted subcomponents.

Their model has the following characteristics:

1) Each species represents a subcomponent of a potential solution.
2) Complete solutions are obtained by assembling *representative* members of each of the species (populations).
3) The fitness of each individual depends on the quality of (some of) the complete solutions it participated in, thus measuring how well it cooperates to solve the problem.
4) The evolution of each species is controlled by a separate, independent evolutionary algorithm.
5) Given an ensemble of conditions, the number of species should itself be adapted by a mechanism of birth and death of species.

Figure 1 shows the general architecture of Potter's cooperative coevolutionary framework, and the way each evolutionary algorithm computes the fitness of its individuals by combining them with selected representatives from the other species. The representatives can be selected via a greedy strategy as the fittest individuals from the last generation.

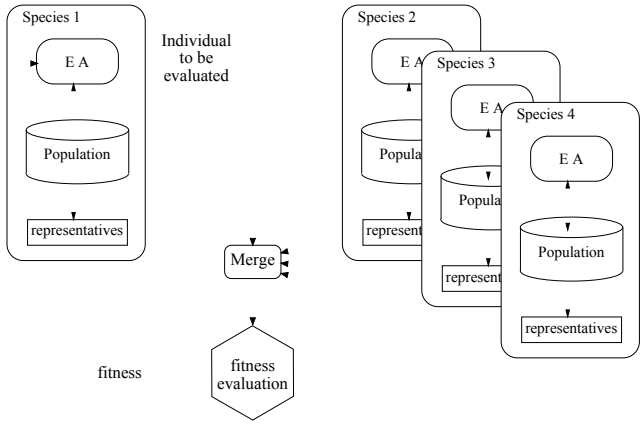

Fig. 1. Potter's cooperative coevolutionary system. The figure shows the evolutionary process from the perspective of Species 1. The individual being evaluated is combined with one or more *representatives* of the other species so as to construct several solutions which are tested on the problem. The individual's fitness depends on the quality of these solutions.

Results presented by Potter and De Jong [15] show that their approach addresses adequately issues like problem decomposition and interdependencies between subcomponents. The cooperative coevolutionary approach performs as good as, and sometimes better than, single-population evolutionary algorithms. Finally, cooperative coevolution usually requires less computation than single-population evolution as the populations involved are smaller, and convergence—in terms of number of generations—is faster.

E. Fuzzy CoCo

Fuzzy CoCo is a Cooperative Coevolutionary approach to fuzzy modeling wherein two coevolving species are defined: database (membership functions) and rule base. Fuzzy CoCo is conceived to allow a high degree of freedom in the type of fuzzy systems it can design in order to allow the user to manage the trade-off between performance and interpretability.

Fuzzy modeling can be thought of as two separate but intertwined search processes: (1) the search for the membership functions (i.e., operational parameters) that define the fuzzy variables, and (2) the search for the rules (i.e., connective parameters) used to perform the inference.

Fuzzy modeling presents several features which justify the application of cooperative coevolution: (1) The required solutions can be very complex, since fuzzy systems with a few dozen variables may call for hundreds of parameters to be defined. (2) The proposed solution—a fuzzy inference system—can be decomposed into two distinct components: rules and membership functions. (3) Membership functions are represented by continuous, real values, while rules are represented by discrete, symbolic values. (4) These two components are interdependent because the membership functions defined by the first group of values are indexed by the second group (rules).

Consequently, in Fuzzy CoCo, the fuzzy modeling problem is solved by two coevolving, cooperating species. Individuals of the first species encode values which define completely all the membership functions for all the variables of the system.

Individuals of the second species define a set of rules of the form:

if (v_1 **is** A_1) **and ... and** (v_n **is** A_n) **then** ($output$ **is** C),

where the term A_i indicates which one of the linguistic labels of fuzzy variable v is used by the rule. For example, a valid rule could contain the expression

if ... and ($Temperature$ **is** $Warm$) **and ... then ...**

which includes the membership function $Warm$ whose defining parameters are contained in the first species.

F. The algorithm

The two evolutionary algorithms used to control the evolution of the two populations are instances of a simple genetic algorithm [20]. Figure 2 presents the Fuzzy CoCo algorithm in pseudo-code format. The genetic algorithms apply fitness-proportionate selection to choose the mating pool (essentially, probabilistic selection according to fitness), and apply an elitist strategy with an elitism rate Er to allow some of the best individuals to survive into the next generation. The elitism strategy extracts E_S individuals—the so-called elite—to be reinserted into the population after evolutionary operators have been applied (i.e., selection, crossover, and mutation). Note that the elite is not removed from the population, participating thus in the reproduction process. Standard crossover and mutation operators are applied [10]: crossover between two genomes is performed with probability P_c by selecting at random (with uniform probability) a single crossover point and exchanging the subsequent parts to form two new offspring; if no crossover takes place (with probability $1 - P_c$) the two offspring are exact copies of their parents. Mutation involves flipping bits in the genome with probability P_m per bit. The condition under which the algorithm terminates is usually satisfied either when a given threshold fitness is attained, or when the maximum number of generations, G_{max}, is reached.

begin Fuzzy CoCo
  g:=0
  for each species S
    Initialize populations $P_S(0)$
    Evaluate population $P_S(0)$
  end for
  while not done **do**
    for each species S
      g:=g+1
      $E_S(g) =$ Elite-select$[P_S(g-1)]$
      $P'_S(g) =$ Select$[P_S(g-1)]$
      $P''_S(g) =$ Crossover$[P'_S(g)]$
      $P'''_S(g) =$ Mutate$[P''_S(g)]$
      $P_S(g) = P'''_S(g) + E_S(g)$
      Evaluate population $P_S(g)$
    end for
  end while
end Fuzzy CoCo

Fig. 2. Pseudo-code of Fuzzy CoCo. Two species coevolve in Fuzzy CoCo: membership functions and rules. The elitism strategy extracts E_S individuals to be reinserted into the population after evolutionary operators have been applied (i.e., selection, crossover, and mutation). Selection results in a reduced population $P'_S(g)$ (usually, the size of $P'_S(g)$ is $\|P'_S\| = \|P_S\| - \|E_S\|$). The line "Evaluate population $P_S(g)$" is elaborated in Figure 3.

G. Fitness evaluation

A more detailed view of the fitness evaluation process is depicted in Figure 3. An individual undergoing fitness evaluation establishes cooperations with one or more representatives of the other species, i.e., it is combined with individuals from the other species to construct fuzzy systems. The fitness value assigned to the individual depends on the performance of the fuzzy systems it participated in (specifically, either the average or the maximal value).

Representatives, or *cooperators*, are selected both fitness-proportionally and randomly from the last generation in which they were already assigned a fitness value (see Figure 2). In Fuzzy CoCo, N_{cf} cooperators are selected probabilistically according to their fitness, favoring the fittest individuals, thus boosting the exploitation of known good solutions. The other N_{cr} cooperators are selected randomly from the population to represent the diversity of the species, maintaining in this way exploration of the search space.

III. Implementation

A. Implementation and data sets

In order to compare our modeling results with those obtained by other authors we selected several benchmark data

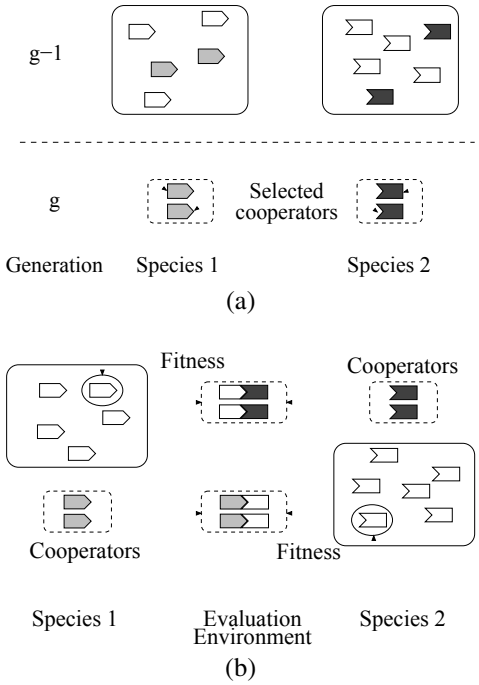

Fig. 3. Fitness evaluation in Fuzzy CoCo. (a) Several individuals from generation $g-1$ of each species are selected both randomly and according to their fitness to be the representatives of their species during generation g; these representatives are called "cooperators." (b) During the evaluation stage of generation g (after selection, crossover, and mutation—see Figure 2), individuals are combined with the selected cooperators of the other species to construct fuzzy systems. These systems are then evaluated on the problem domain and serve as a basis for assigning the final fitness to the individual being evaluated.

sets, namely: (i) the well-known leukemia data studied by Golub et al. [3]. In this dataset, there are 38 observations, each of which is described by the gene expression levels of 7129 genes and a class attribute with two distinct labels: acute myeloid (AML) and lymphoblastic leukemia (ALL); (ii) the colon cancer data set used by Alon et al. [1]. This data set contains 62 observations. There are 40 tumor samples, and 22 normal samples. From about 6000 genes represented in each sample in the original data set, only 2000 genes were selected by Alon et al.; (iii) the prostate cancer data set studied by Singh et al. [18] containing 52 prostate tumor samples and 50 non-tumor prostate samples with a total number of genes of 12600; (iv) the lung cancer dataset reported by Gordon et al. [4], which contains samples of malignant pleural mesothelioma (MPM) and adenocarcinoma (ADCA) of the lung, and consists of 181 tissue samples (31 MPM, 150 ADCA). Each sample is described by 12,533 genes.

B. Modeling goals

The modeling problem tackled in this work involves discriminating two classes for each of the aforementioned four data sets based on their gene-expression profiles. For each data set, it admits a relatively high number of variables and consequently, a huge search space. An initial, exploratory number of evolutionary fuzzy modeling runs, and the subsequent analysis showed that many different models were capable of satisfactorily solving the pursued discrimination problem. Furthermore, we observed that there exist many, radically-different, pools of genes that may lead to highly accurate models with very few rules and variables.

C. Evolutionary parameters

The main parameters used are shown in Table I

TABLE I
Evolutionary-fuzzy modeling setup for the data-set

Parameter	Values
Population size	100
Maximun generations	300
Crossover probability	0.8
Mutation Probability	0.025 for each bit in the genome
Elitism	5 per individual population
Maximum number of variables per rule	1 to 3
Maximum number of rules per system	1 to 3

D. Fitness function

The fitness function combines three criteria: (1) The sensitivity, computed as $TP/(TP+FN)$ (2) The specificity, computed as $TN/(TN+FP)$ (3) The root mean square error (rmse) between predicted and actual values.

The sensitivity and specificity are the most important measures of performance. We used them in combination instead of the accuracy since we can avoid some balancing problems if the number of cases for each class is not equal. The rmse is used to cause a fitness difference among models with similar classification performance and also to move away prediction from the threshold value. The fitness value assigned to an individual is :

$$\frac{w1 * sensitivity + w2 * specificity + w3 * 2^{-rmse}}{w1 + w2 + w3}$$

, where $w1 = w2 = 1.0$ and $w3 = 0.2$.

E. Experimental modeling setup

Bootstrapping was used for validating the performance of the obtained fuzzy models. We performed resampling with replacement from the original data in order to create the training set on which Fuzzy CoCo tested the candidate solutions. Resampling was applied until there remained only 37% of all cases that were not included in the training set. This 37% of unseen cases were used, as a validation set, to test the performance of the best fuzzy model emergeing out of a given evolutionary run. We repeat this operation 300 times for each one of the nine model configurations tested (i.e., one to three rules times one to three variables per rule). In this way, we conducted a total of 2700 modeling runs obtaining the same number of candidate models.

IV. Results and Discussion

A global summary of the results obtained for accuracy, sensitivity and specificity are presented in Figures 4, 5 and 6 respectively. Table II shows the results obtained when modeling with Fuzzy CoCo alongside, for comparison purposes, with those reported in other papers. Note that, even though we evolved our models on the base of sensitivity and specificity, Table II presents only accuracy figures as this is the measure used by almost all the referenced works. From these results we can observe that in the case of the leukemia data, Fuzzy CoCo presents the best possible accuracy (i.e., 100% on the validation set) and the second lowest reported number of rules and variables per rule. The second and third best accuracies are presented by Viterbo and Huerta, but they also present the highest number of rules and variables per rule. On the other hand, works reporting compact fuzzy models–i.e., with few rules and few variables per rule–also exhibit lower accuracy. Thus, for this data set, as Fuzzy CoCo presents the best accuracy and the second most compact models, it exhibits the best trade-off between these two goals. Regarding the performance of Fuzzy CoCo on the colon cancer data as compared with the model reported by Huerta, one can observe higher accuracy using a considerably-lower number of genes. For prostate and lung cancer datasets, Ho and Wang report fuzzy models of similar size in terms of number of rules and variables per rule than those obtained by Fuzzy CoCo. However, our models exhibit a (much) better accuracy.

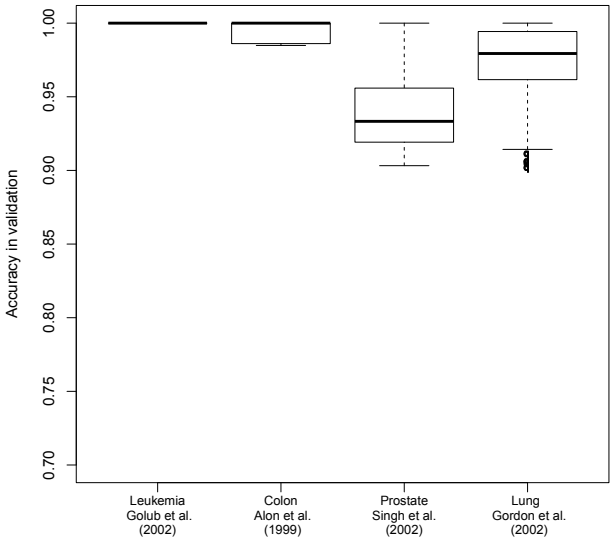

Fig. 4. Accuracy in validation for each of the four data set analyzed. The accuracy is used as measure of performance in the papers cited in this work. Nevertheless, we consider that sensitivity and specificity must be also presented, since accuracy in some cases can hide interesting patterns than can be highlighted when observing the sensitivity and specificity.

V. Conclusion

Designing interpretable systems is a prime goal of Fuzzy Coco approach. It allows to create fuzzy systems providing high numeric precision, while incurring as little a loss of interpretability as possible. Thus, creating very compact fuzzy systems with a high accuracy. These features make of Fuzzy CoCo a perfect technique to select relatively small subset of genes associated to cell functions from thousands of microarray gene expression data. After testing Fuzzy CoCo on a four benchmark problems, namely: leukemia (Golub et al.), colon cancer (Alon et al.), lung cancer (Gordon et al.) and prostate cancer (Singh et al.), we showed that in all cases, Fuzzy CoCo produces systems both of high performance and high interpretability, comparable (if not better) than the best models demonstrated to date. However, although Fuzzy CoCo allow to find very compact fuzzy models it still the open question of which of that models are the most biologically correct. In addition, to find a good fuzzy model is not limited to finding the most accurate model, but it is also related with which genes are involved in such models, looking for relevant indications

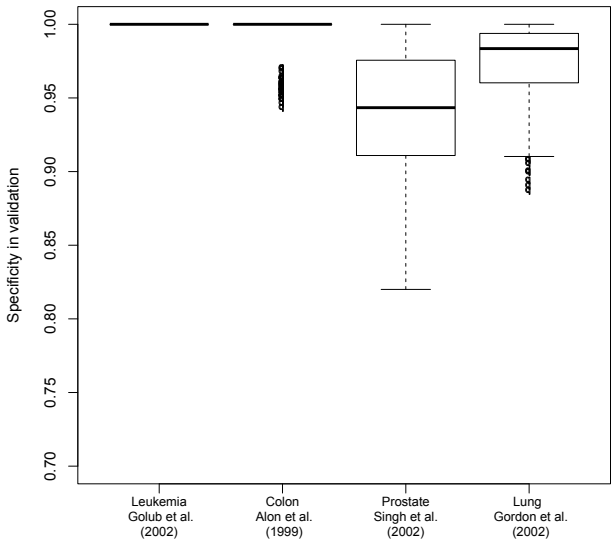

Fig. 5. Specificity in validation for each of the four data sets analyzed.

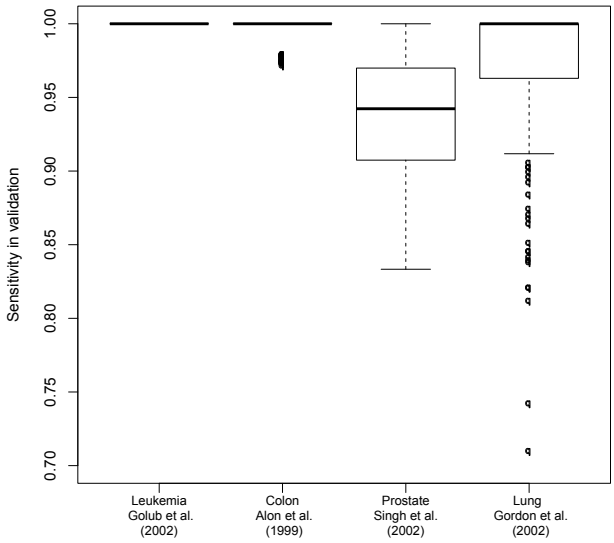

Fig. 6. Sensitivity in validation for each of the four data sets analyzed.

TABLE II

COMPARISON OF THE RESULTS OBTAINED MODELING WITH FUZZY COCO WITH THOSE REPORTED BY THE REFERENCED PAPERS. THE MODELS ARE ANALYSED IN TERMS OF ACCURACY AND COMPACTNESS (MEASURED BY NUMER OF RULES AND NUMBER OF VARIABLES PER RULE). TO FACILITATE THE COMPARISON, WE MENTION EXPLICITELY WHETHER THE RESULTS CORRESPOND TO A SINGLE SYSTEM (BEST) OR TO THE AVERAGE OVER A LARGE NUMBER OF MODELS (MEAN).

Data set information								
Name	Number of genes used	Cases used	Number of classes	Paper	Number of rules	Variables (Genes) used	Accuracy	AUC
Acute myeloid and lymphoblastic leukemia (Golub et al.)	5327	72	2	Ohno-Machado et al. [11]	2 (best)	2 (best)	0.79 (best)	
	5327	72	2	Vinterbo et al. [19]	35 (mean)	21.8 (mean)	*	0.95 (mean)
	5327	72	2	Ho et al. [5]	3.5 (mean)	4.1 (mean)	0.94 (mean)	
	1360	62	2	Huerta et al. [6]	*	30 (best)	1 (best)	
	5327	72	2	**Barreto-Sanz et al.**	**2.3 (mean)**	**1.8 (mean)**	**1 (mean)**	**1 (mean)**
Colon data set (Alon et al.)	2000	62	2	Huerta et al. [6]	*	17 (best)	0.90 (best)	
	2000	62	2	**Barreto-Sanz et al.**	**2.6(mean)**	**2.41 (mean)**	**0.99 (mean)**	
Prostate tumor (Singh et al.)	10509	102	2	Ho et al. [5]	2.4 (mean)	4.1 (mean)	0.91 (mean)	
	10509	102	2	**Barreto-Sanz et al.**	**2.3 (mean)**	**2.1 (mean)**	**0.93 (mean)**	
Lung cancer (Gordon et al.)	12533	181	2	Wang et al. [22]	3 (best)	2 (best)	0.91 (best)	
	12533	181	2	**Barreto-Sanz et al.**	**2.1 (mean)**	**2.08 (mean)**	**0.97 (mean)**	

"*" The results are not listed in the original papers

about the relationships between them. For instance to finding groups of models and genes with the highest repeatability. This analysis makes part of our future work.

REFERENCES

[1] U. Alon, N. Barkai, D. A. Notterman, K. Gish, S. Ybarra, D. Mack, and A. J. Levine. Broad patterns of gene expression revealed by clustering analysis of tumor and normal colon tissues probed by oligonucleotide arrays. *Proceedings of the National Academy of Sciences of the United States of America*, 96(12):6745–6750, June 1999.

[2] Madara Gasparovica, Natalia Novoselova, and Ludmila Aleksejeva. Using fuzzy logic to solve bioinformatics tasks. *J. Riga Technical University*, 42:99–105, 2010.

[3] T. R. Golub, D. K. Slonim, P. Tamayo, C. Huard, M. Gaasenbeek, J. P. Mesirov, H. Coller, M. L. Loh, J. R. Downing, M. A. Caligiuri, and C. D. Bloomfield. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. *Science*, 286:531–537, 1999.

[4] Gavin J. Gordon, Roderick V. Jensen, Li li Hsiao, Steven R. Gullans, Joshua E. Blumenstock, Sridhar Ramaswamy, William G. Richards, David J. Sugarbaker, and Raphael Bueno. Translation of microarray data into clinically relevant cancer diagnostic tests using gene expression ratios in lung cancer and mesothelioma. *Cancer Res*, 62:4963–4967, 2002.

[5] Shinn-Ying Ho, Chih-Hung Hsieh, Hung-Ming Chen, and Hui-Ling Huang. Interpretable gene expression classifier with an accurate and compact fuzzy rule base for microarray data analysis. *Biosystems*, 85(3):165–176, September 2006.

[6] E. B. Huerta, B. Duval, and J. K. Hao. Fuzzy logic for elimination of redundant information of microarray data. *Genomics, proteomics & bioinformatics / Beijing Genomics Institute*, 6(2):61–73, June 2008.

[7] H. Juillé. *Methods for Statistical Inference: Extending the Evolutionary Computation Paradigm*. PhD thesis, Brandeis University, May 1999.

[8] Mehdi Khashei, Ali Zeinal Hamadani, and Mehdi Bijari. A fuzzy intelligent approach to the classification problem in gene expression data analysis. *Know.-Based Syst.*, 27:465–474, March 2012.

[9] Ricardo Linden and Amit Bhaya. Evolving fuzzy rules to model gene expression. *Biosystems*, April 2006.

[10] Z. Michalewicz. *Genetic Algorithms + Data Structures = Evolution Programs*. Springer-Verlag, Heidelberg, third edition, 1996.

[11] Lucila Ohno-Machado, Staal A. Vinterbo, and Griffin Weber. Classification of gene expression data using fuzzy logic. *Journal of Intelligent and Fuzzy Systems*, 12(1):19–24, 2002.

[12] J. Paredis. Coevolutionary computation. *Artificial Life*, 2:355–375, 1995.

[13] Carlos Andrés Peña-Reyes. *Coevolutionary Fuzzy Modeling*, volume 3204 of *Lecture Notes in Computer Science*. Springer, 2004.

[14] M. A. Potter. *The Design and Analysis of a Computational Model of Cooperative Coevolution*. PhD thesis, George Mason University, 1997.

[15] M. A. Potter and K. A. De Jong. Cooperative coevolution: An architecture for evolving coadapted subcomponents. *Evolutionary Computation*, 8(1):1–29, spring 2000.

[16] Robert Reynolds, Habtom W. Ressom, Mohamad T. Musavi, and Christian Domnisoru. Improving robustness of fuzzy gene modeling. In Michel Verleysen, editor, *ESANN*, pages 51–56, 2002.

[17] Yvan Saeys, Iñaki Inza, and Pedro Larrañiaga. A review of feature selection techniques in bioinformatics. *Bioinformatics*, 23(19):2507–2517, October 2007.

[18] Dinesh Singh, Phillip G. Febbo, Kenneth Ross, Donald G. Jackson, Judith Manola, Christine Ladd, Pablo Tamayo, Andrew A. Renshaw, Anthony V. D'Amico, and Jerome P. Richie. Gene expression correlates of clinical prostate cancer behavior. *Cancer Cell*, 1(2):203–209, 2002.

[19] Staal A. Vinterbo, Eun-Young Kim, and Lucila Ohno-Machado. Small, fuzzy and interpretable gene expression based classifiers. *Bioinformatics*, 21(9):1964–1970, May 2005.

[20] M. D. Vose. *The Simple Genetic Algorithm*. MIT Press, Cambridge, MA, August 1999.

[21] Z. Wang and V. Palade. Building interpretable fuzzy models for high dimensional data analysis in cancer diagnosis. *BMC Genomics*, (12(S2):S5), 2011.

[22] Zhenyu Wang and Vasile Palade. Multi-objective evolutionary algorithms based interpretable fuzzy models for microarray gene expression data analysis. In *BIBM*, pages 308–313, 2010.