

Fuzzy Immune Approach to Biomedical Data Processing

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Abstract—Classification is an important data mining task in biomedicine. For easy comprehensibility, rules are preferable to another functions in the analysis of biomedical data. The aim of this work is to use a new fuzzy immune rule-based classification system for biomedical data. The performance of the proposed approach, in terms of classification accuracy and area under the ROC curve, was compared with traditional classifier schemes: C4.5, Naïve Bayes, K^* , and Meta END.

Index Terms—machine learning, fuzzy logic, artificial immune system, data mining

I. INTRODUCTION

Fuzzy logic has been applied to design classification systems due to its powerful capabilities of handling uncertainty and vagueness. A fuzzy rule-based classification system (FRBCS) is a special case of fuzzy modeling where the output of the system is crisp and discrete. Basically, the design of an FRBCS consists of finding a compact set of fuzzy IF-THEN classification rules to be able to predict a class for unknown example. The most challenging problem in the design of FRBCSs is the construction of rule-base for a task to be solved. Many approaches have been proposed to construct the rule-base from data. These include heuristic approaches [19], neuro-fuzzy techniques [34], clustering methods [33], genetic algorithms [20] and data mining techniques [13]. A quite novel approaches, among others, integrate Artificial Immune Systems (AISs) [12] and Fuzzy Systems to find not only accurate, but also linguistic interpretable fuzzy rules that predict the class of an example. The first AIS-based method for fuzzy rules mining was proposed in [2]. This approach, called IFRAIS (Induction of Fuzzy Rules with an Artificial Immune System), uses sequential covering and clonal selection to learn IF-THEN fuzzy rules. One of the AIS-based algorithms for mining IF-THEN rules is based on extending the negative selection algorithm with a genetic algorithm [16]. Another one is mainly focused on the clonal selection and so-called a boosting mechanism to adapt the distribution of training instances in iterations [1]. A fuzzy AIS was proposed also in [29], however that work addresses not the task of classification, but the task of clustering.

Efficient and effective classification is a core problem in biomedical data mining. The aim of this work is to use a new fuzzy immune approach derived from IFRAIS concept for biomedical data.

This paper is organized as follows. Section 2 describes methods used in the research, next Section 3 gives details of the proposed approach. Section 4 discusses the experimental results. Finally section 5 concludes the paper with future works.

II. BACKGROUND

A. Fuzzy rule-based classification system

A fuzzy rules can be expressed as a conditional statement in the form:

Rule R_j : IF x_1 is A_{j1} and ...and x_n is A_{jn} THEN Class C_j , where R_j is the label of the i -th rule, $x = (x_1, \dots, x_n)$ is an n -dimensional pattern vector, A_{in} is an antecedent fuzzy set, i.e. linguistic variable. A linguistic variable is a fuzzy variable. The set of fuzzy subsets of the linguistic variable is called a fuzzy partition.

Fuzzy reasoning includes two distinct parts: evaluating the rule antecedent (i.e. IF part of the rule) and applying the result to the consequent (i.e. THEN part of the rule). A truth membership grade of the rule consequent can be estimated directly from a corresponding truth membership grade in the antecedent [10]. A fuzzy rules can have multiple antecedents. All parts of the antecedents are calculated simultaneously and resolved in a single number, using fuzzy set operations (like intersection *min*).

Generation of fuzzy IF-THEN rules from numerical data consists of two phases: the first, fuzzy partition of attribute to number of linguistic variables and determine the membership function for each linguistic variables. The second, determination of fuzzy IF-THEN rules. For example, consider a two-class classification problem as in Fig.1, where black stars and open stars denote the pattern in class 1 and class 2, respectively. Fuzzy partitions are defined by triangular membership functions.

B. Clonal selection principle

Immunology has served as the foundations for Artificial Immune Systems (AIS), another biologically inspired approach, such as Artificial Neural Networks and Evolutionary Algorithms. The vast majority of developments within AIS focussed in three main immunological phenomena: clonal selection, immune networks and negative selection.

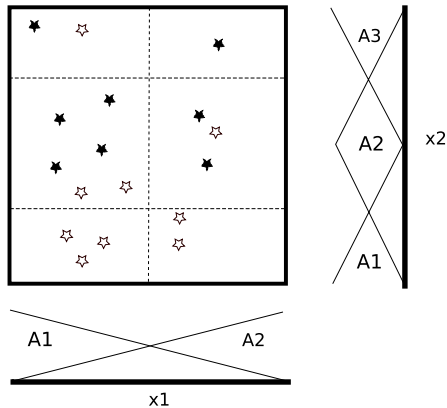


Fig. 1. An example of fuzzy partition by a simple fuzzy grid

A large part of AIS work has been based on the clonal selection theory. When antibodies on a B-cell bind with an antigen, the B-cell becomes activated and begins to proliferate. According to the clonal selection principle [5], it is important to note that only those B-cells will proliferate, which are capable of recognizing an antigenic stimulus. Next, exact copy of the parent B-cell are produced (B-cell clones), that then undergo somatic hypermutation and produce antibodies that are specific to the invading antigen. Clonal selection operates on both T-cells and B-cells. The B-cells, in addition to proliferating or differentiating into plasma cells, can differentiate into long-lived B memory cells. Memory cells circulate through the blood, lymph and tissues. After recovering from an infection, the concentration of antibodies against the infectious agent gradually declines over a time. The initial exposure to an antigen that stimulates an adaptive immune response is handled by a small number of B-cells. Storing some high affinity antibody producing cells from the first infection, so as to form a large initial specific B-cell clones for subsequent encounters, considerably enhances the effectiveness and speed of the immune response to secondary encounters.

Clonal selection algorithms evolve candidate solutions in terms of optimization, or pattern detectors in terms of learning. Evolving consists of a cloning, mutation and selection phase. Each of these algorithms have populations of B-cells (solution to be searched) that match against antigens (function to be optimized). These B-cells then undergo cloning (usually in proportion to the strength of the match) and mutation (usually, inversely proportional to the strength of the match). High affinity B-cells are then selected to remain in the population, some low affinity cells are removed and new random cells are generated.

Great efforts are made to handle with optimization problems by clonal selection applications, such as the work on CLONALG by de Castro and Von Zuben [6], the work by Cutello et al [11] and the work by Garrett [15] on parameter free clonal selection. As to applications dedicated to solve learning problems, AIRS by Watkins [35] [37], a distributed version of CLONALG by Watkins et al [36], DynamicCS by Kim and Bentley [24],

IFRAIS by Alves et al [2], and improved versions of IFRAIS by Mężyk and Unold [27] [28] [22] are to be noted.

III. FUZZY IMMUNE APPROACH

The use of Artificial Immune Paradigm for discovering comprehensible IF-THEN classification rules is much less explored in the literature when compared with other traditional rule induction in FRBSs. The presented fuzzy immune approach (FIA) inherits his architecture from IFRAIS [2], but differs from it in (1) using uniform population [28], (2) rules buffering in clonal selection algorithm [28], (3) and fuzzy partition learning [22].

Uniform population. The standard IFRAIS creates initial population of fuzzy rules at random. Note that random initial population may be created in the infeasible region, or all the rules in population may be in the nearest neighborhood and far away from a solution, or search of solution may stick to a local solution and we can not get rid of this local solution. Local solution in the task of classification is the rules that have no agreeable generalization ability. In FIA creating initial population is performed in a systematic way inspired by the uniform population method [23].

Rules buffering. The speed boosting extension was introduced to FIA. Boosting uses the hash table, which contains the saved pairs: a rule and fitness of a rule. The hash table accelerates rapidly the computation of rule fitness in clonal selection algorithm.

Fuzzy partition learning. In a basic IFRAIS approach three and only three linguistic terms (low, medium, high) are associated with each continuous attribute. Each linguistic term is represented by the triangular membership functions. FIA infers a fuzzy partition for each continuous attribute over the data set instead of stiff, and the same for different attributes partitioning. Fuzzy partitioning learning is based on a clonal selection algorithm. In such an approach a population of antibodies represent a set of partitions, and an antigen is a whole set of data.

FIA, as an Artificial Immune System evolves a population of antibodies representing the IF part of a fuzzy rule, whereas each antigen represents an learning example. Each rule antecedent consists of a conjunction of rule condition. FIA, like IFRAIS uses a sequential covering as a main learning algorithm. In the first step a set of rules is initialized as an empty set. Next, for each class to be predicted the algorithm initializes the training set with all training examples and iteratively calls clonal selection procedure with the parameters: the current training set and the class to be predicted. The clonal selection procedure returns a discovered rule and next the learning algorithm adds the rule to the rule set and removes from the current training set the examples that have been correctly covered by the evolved rule.

Clonal selection algorithm is used to induct rule with the best fitness from training set (see Listing 1). Basic elements of this method are antigens and antibodies which refers directly to biological immune systems. Antigen is an example from data set and antibody is a fuzzy rule. Similarly to fuzzy rule

structure, which consists of fuzzy conditions and class value, antibody comprises genes and informational gene. Number of genes in antibody is equal to number of attributes in data set. Each gene consists of a fuzzy rule and an activation flag that indicates whether fuzzy condition is active or inactive.

Listing 1: Clonal selection algorithm

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Input: training set, class value (c)
Output: fuzzy rule

CREATE uniformly antibodies population with size s
and class value c
FOR EACH antibody A in antibodies population
  PRUNE(A)
  COMPUTE-FITNESS(A, training set)
END FOR EACH
FOR i=1 TO number of generations n DO
  WHILE clones population size < s-1
    antibody to clone =
    TOURNAMENT-SELECTION(antibodies population)
    clones = CREATE x CLONES(antibody to clone)
    clones population = clones population + clones
  END WHILE
  FOR EACH clone K in clones population
    muteRatio = MUTATION-PROBABILITY(K)
    MUTATE(K, muteRatio)
    PRUNE(K)
    COMPUTE-FITNESS(K, training set)
  END FOR EACH
antibodies population =
SUCCESSION(antibodies population, clones population)
END FOR
result = BEST-ANTIBODY(antibodies population)
RETURN result

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In the first step the algorithm generates randomly antibodies population with informational gene equals to class value c passed in algorithm parameter. Next each antibody from generated population is pruned. Rule pruning has a twofold motivation: reducing the overfitting of the rules to the data and improving the simplicity (comprehensibility) of the rules [38]. Fitness of the rule is computed according to the formula

$$fitness(rule) = \frac{tp}{tp + fn} \cdot \frac{tn}{tn + fp} \quad (1)$$

where

tp - is number of examples satisfying the rule and having the same class as predicted by the rule;

fn - is the number of examples that do not satisfy the rule but have the class predicted by the rule;

tn - is the number of examples that do not satisfy the rule and do not have the class predicted by the rule;

fp - is the number of examples that satisfy the rule but do not have the class predicted by the rule.

Since the rules are fuzzy, the computation of the tp , fn , tn and fp involves measuring the degree of affinity between the example and the rule. This is computed by applying the standard aggregation fuzzy operator *min*

$$affinity(rule, example) = \min_{i=1}^{condCount}(\mu_i(att_i)) \quad (2)$$

where $\mu_i(att_i)$ denotes the degree to which the corresponding attribute value att_i of the example belongs to the fuzzy set associated with the i th rule condition, and *condCount* is

the number of the rule antecedent conditions. The degree of membership is not calculated for an inactive rule condition, and if the i th condition contains a negation operator, the membership function equals to $(1 - \mu_i(att_i))$ (complement). An example satisfies a rule if $affinity(rule, example) > L$, where L is an activation threshold. Next, antibody to be cloned is selected by tournament selection from the antibodies population. For each antibody to be cloned the algorithm produces x clones. The value of x is proportional to the fitness of the antibody. Next, each of the clones undergoes a process of hypermutation, where the mutation rate is inversely proportional to the clone's fitness. Once a clone has undergone hypermutation, its corresponding rule antecedent is pruned by using the previously explained rule pruning procedure. Finally, the fitness of the clone is recomputed, using the current training set. In the last step the T -worst fitness antibodies in the current population are replaced by the T best-fitness clones out of all clones produced by the clonal selection procedure. Finally, the clonal selection procedure returns the best evolved rule, which will then be added to the set of discovered rules by the sequential covering.

IV. EXPERIMENTAL RESULTS

A. Datasets

In this study we used the following data sets obtained from UCI machine learning repository¹. We briefly describe the biological motivation for the data sets; interested readers should refer to the cited papers for details.

E.coli The objective of this data set is to predict the cellular localisation sites of E.coli proteins [18].

Attribute information:

1. sequence name: Accession number for the SWISS-PROT database,
2. mcg: McGeoch's method for signal sequence recognition,
3. gvh: von Heijne's method for signal sequence recognition,
4. lip: von Heijne's Signal Peptidase II consensus sequence score,
5. chg: Presence of charge on N-terminus of predicted lipoproteins,
6. aac: score of discriminant analysis of the amino acid content of outer membrane and periplasmic proteins,
7. alm1: score of the ALOM membrane spanning region prediction program,
8. alm2: score of ALOM program after excluding putative cleavable signal regions from the sequence.

Liver+Disorders - Bupa contains blood tests which are thought to be sensitive to liver disorders that might arise from excessive alcohol consumption.

Attribute information:

1. mcv: mean corpuscular volume,
2. alkphos: alkaline phosphatase,
3. sgpt: alamine aminotransferase,
4. sgot: aspartate aminotransferase,
5. gammagt: gamma-glutamyl transpeptidase,

¹<http://archive.ics.uci.edu/ml/datasets.html>

TABLE I
DATA SETS AND NUMBER OF ROWS, ATTRIBUTES, CONTINUOUS
ATTRIBUTES, AND CLASSES

Data set	#Rows	#Attrib.	#Cont.	#Class.
E.coli	336	7	2	8
Liver+Disorders	345	6	6	2
Hepatitis	80	19	6	2

6. drinks: number of half-pint equivalents of alcoholic beverages drunk per day,

7. selector: field used to split data into two sets.

Hepatitis - This data consists of 19 descriptive and clinical test result values for hepatitis patients [14].

Attribute information:

1. class: die, live,
2. age: 10, 20, 30, 40, 50, 60, 70, 80,
3. sex: male, female,
4. steroid: binary attribute,
5. antivirals: binary attribute,
6. fatigue: binary attribute,
7. malaise: binary attribute,
8. anorexia: binary attribute,
9. liver big: binary attribute,
10. liver firm: binary attribute,
11. spleen pappable: binary attribute,
12. spiders: binary attribute,
13. ascites: binary attribute,
14. varices: binary attribute,
15. bilirubin: 0.39, 0.80, 1.20, 2.00, 3.00, 4.00,
16. alk phosphate: 33, 80, 120, 160, 200, 250,
17. sgot: 13, 100, 200, 300, 400, 500,
18. albumin: 2.1, 3.0, 3.8, 4.5, 5.0, 6.0,
19. protime: 10, 20, 30, 40, 50, 60, 70, 80, 90,
20. histology: binary attribute.

Table I shows the number of rows, attributes, continuous attributes, and classes for each data set. Note that only continuous attributes are fuzzified.

B. Comparison of different methods

FIA was tested among several different machine learning methods. Here we briefly list the methods that we used to compare with our approach.

C4.5 Algorithm

C4.5 builds decision trees from a set of training data using the concept of information entropy. It is based on ID3 (Iterative Dichotomiser 3). Both algorithms were proposed by Ross Quinlan [31].

Naïve Bayes

The Naïve Bayes algorithm is based on conditional probabilities. It uses Bayes' Theorem, a formula that calculates a probability by counting the frequency of values and combinations of values in the historical data [32]. It is naive because it assumes attribute independence.

K^*

TABLE II
ACCURACY RATE AND AUC ON THE TEST SET. THE BEST RESULTS ARE IN
BOLD.

Data	FIA	IFRAIS	C4.5	Naïve	K^*	Meta
	Acc AUC	Acc AUC	Acc AUC	Acc AUC	Acc AUC	Acc AUC
Bupa	70.72 0.72	60.00 0.59	66.38 0.65	54.80 0.64	67.00 0.71	66.38 0.65
Hepatitis	96.25 0.94	86.25 0.89	79.74 0.67	83.89 0.85	80.79 0.82	79.74 0.67
E.coli	86.90 0.93	80.36 0.86	83.34 0.96	85.48 0.99	81.91 0.98	85.19 0.98

K^* is an instance-based classifier using an Entropic Distance Measure. It provides a consistent approach to handling of symbolic attributes, real valued attributes and missing values [7].

Meta END

The main idea of meta-classification is to represent the judgment of each classifier (SVM based) for each class as a feature vector, and then to re-classify again in the new feature space. The final decision is made by the meta-classifiers instead of just linearly combining each classifiers judgment [25].

C. Criteria and results of comparison

All experiments were repeated 10-times using 5-fold cross-validation. A dataset is randomly split into five equal-sized subsets, four of which are combined as the training dataset and another one is taken as the testing dataset. The training-testing process is repeated five times such that each subset is used as the testing dataset once.

The statistical analysis was based on the area under the Receiver Operating Characteristics (ROC) curve [17]. This value is equivalent of the Mann-Whitney U statistic [3] normalized by the number of possible pairings of positive and negative values. The area under the ROC curve (AUC) actually represents the probability that a randomly chosen positive example is correctly rated (ranked) with greater suspicion than a randomly chosen negative example. Moreover, this probability of correct ranking is the same quantity estimated by the non-parametric Wilcoxon statistic [4]. Bradley [4] has compared popular machine learning algorithms using AUC, and found that AUC exhibits several desirable properties compared to accuracy. For example, AUC has increased sensitivity in Analysis of Variance (ANOVA) tests, is independent to the decision threshold, and is invariant to a priori class probability distributions.

Table II shows for each data set the average accuracy rate (ACC) and AUC. As shown in Table II the FIA obtained better results than any other algorithm presented in the Table, with the exception of AUC measure for Naïve Bayes approach.

Table III contains an exemplary set of the inferred rules by FIA for Hepatitis data set (96.25 of an accuracy, and 0.94 of AUC).

TABLE III
THE INFERRED RULE SET FOR HEPATITIS

No.	Rule
1.	IF PROTINE!=0 and HISTOLOGY=0 THEN class = 2
2.	IF ASCITES!=1 and BILIRUBIN=0 and ALK PHOSPHATE!=2 THEN class = 2
3.	IF SGOT=1 and ALBUMIN!=0 THEN class = 2
4.	IF AGE!=0 and LIVER BIG=0 and PROTINE!=0 and HISTOLOGY!=0 THEN class = 1

V. CONCLUSION

In this paper we focused on the problem of classification of biomedical data using the fuzzy immune approach. The proposed algorithm outperforms compared approaches, not only in terms of the accuracy, but in terms of AUC statistic too.

Nevertheless, there are several possible directions for future work. For example, it would be interesting to investigate if a use of more sophisticated membership functions would yield to further improvement. Since many biological datasets are very high-dimensional, a dimensionality reduction before classification is also required.

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