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A FUZZY-MEMBRANE-IMMUNE ALGORITHM FOR BREAST CANCER DIAGNOSIS

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Abstract. The automatic diagnosis of breast cancer is an important medical problem. This paper hybridizes metaphors from cells membranes and intercommunication between compartments with clonal selection principle together with fuzzy logic to produce a fuzzy rule system in order to be used in diagnosis. The fuzzy-membrane-immune algorithm suggested were implemented and tested on the Wisconsin breast cancer diagnosis (**WBCD**) problem. The developed solution scheme is compared with five previous works based on neural networks and genetic algorithms. The algorithm surpasses all of them. There are two motivations for using fuzzy rules with the membrane-immune algorithm in the underline problem. The first is attaining high classification performance. The second is the possibility of attributing a confidence measure (degree of benignity or malignancy) to the output diagnosis, beside the simplicity of the diagnosis system, which means that the system is human interpretable.

1. Introduction

P Systems are used to search large, and often complex or exponential search spaces. They have proven worthwhile on numerous diverse problems, able to find optimal solutions, of course by creating exponential search space, in polynomial or even linear time. Fuzzy modeling can be considered as an optimization process where part or all of the parameters of a fuzzy system constitute the search space [6]. Works investigating the application of approximate techniques in the domain of fuzzy modeling had first appeared about a decade ago [18]. These focused mainly on the tuning of fuzzy inference

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systems involved in control tasks (e.g. cart-pole balancing, liquid level system, and spacecraft rendezvous operation)[2]. Approximate fuzzy modeling has been applied to number of domains, as chemistry, medicine, telecommunications, biology, and geophysics.

This paper uses the power of P systems with the clonal selection principle [14] to simulate solving the breast cancer diagnosis problem. The solution scheme depends on generating a fuzzy rule system for diagnosis. The fuzzy rule system itself could be found in a large or an exponential search space. We import from membrane computing The Intercellular communication between cells as depicted in figure 1. The proposed algorithm imports the positive/negative selection and proliferation from clonal selection principle.

This paper is organized as follows: section 2 gives an entry to P systems, section 3 gives an introduction to the problem to be solved, namely the Wisconsin breast cancer diagnosis problem; section 4 presents the used solution scheme. The section presents the fuzzy-membrane-immune algorithm and how to evolve a fuzzy system for the WBCD problem, after that the fuzzy-membrane-immune algorithm setup, in section 5 experimental results and testing are explained. Finally conclusions and future work are discussed in section 6.

2. An Entry to P systems

Membrane Computing is a branch of natural computing; which was introduced by Paun in [5] under the assumption that the processes taking place in the compartmental structure of a living cell can be interpreted as computations. The devices of this model are called P systems. A P system consists of a membrane structure, in the compartments of which one places multi-sets of objects which evolve according to given rules in a synchronous, non-deterministic maximally parallel manner.

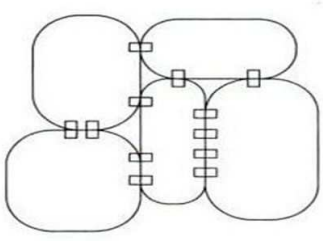

Figure 1. Intercellular communication

An important part of the cell activity is related to the passage of substances through membranes, and one of the most interesting ways to handle this trans-membrane communication is by coupling molecules. The process by which two molecules pass together across a membrane (through a specific protein channel) is called symport, see figure 2(a). When two molecules pass simultaneously through a protein channel in opposite directions is called antiport, see figure 2(b).

The symport and antiport operations could be formalized in an obvious way: (*ab, in*) or (*ab, out*), in symport rules, stating that a and b pass together through a membrane, entering in the former case and exiting in the latter case; similarly, (*a, out; b, in*) is an antiport rule, stating that a exits and, at the same time, b enters the membrane. Separately, neither a nor b can cross a membrane unless we have a rule of the form (*a, in*) or (*a, out*), called, for uniformity, the uniport rule. The used communication method in the fuzzy-membrane-immune algorithm is antiport.

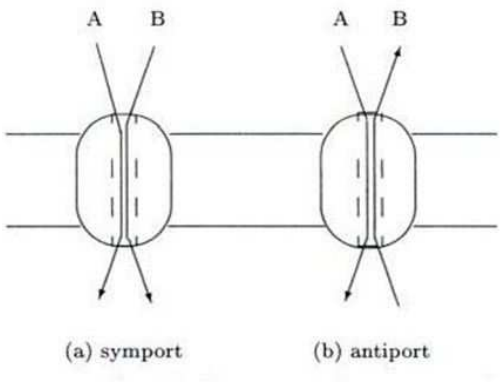

FIGURE 2. symport and antiport cellular communication

Beside the symport/antiport intercellular communication imported from membranes, the dividing and dissolution of membranes is be controlled using another nature inspired computation model, namely, the clonal selection principle, which is part of the immune system.

3. The Wisconsin breast cancer diagnosis problem

The Wisconsin breast cancer diagnosis problem [1, 2] is the test case of our proposed algorithm. Breast cancer is the most common cancer among women,

TABLE 1. The attributes in the Wisconsin data base

Clump thickness	V_1
Uniformity of cell size	V_2
Uniformity of cell shape	V_3
Marginal adhesion	V_4
Single epithelial cell size	V_5
Bare nuclei	V_6
Bland chromatin	V_7
Normal nucleoli	V_8
Mitosis	V_9

TABLE 2. The WCBD data representation

case	V_1	V_2	...	V_9	Diagnosis
1	1	2	...	8	Benign
2	2	4	...	3	Benign
...	...	...	...	...	...
683	4	8	...	1	Malignant

excluding skin cancer. The presence of a breast mass is an alert sign of a cancer, but it does not always indicate a malignant one. Fine Needle Aspiration (**FNA**) is an outpatient procedure that involves using a small-gauge needle to extract fluid directly from a breast mass. **FNA** procedure over breast masses is a cost-effective, non-traumatic, and mostly non-invasive diagnostic test that obtains information needed to evaluate malignancy. The Wisconsin Breast Cancer Diagnosis (**WBCD**) database [3] is the result of the efforts made at the university of Wisconsin hospital for accurately diagnosing breast masses based solely on a **FNA** test. Nine visually assessed characteristics of an **FNA** sample considered relevant for diagnosis were identified, and assigned an integer value between 1 and 10. The measured variables are described in table1.

The database itself consists of 683 cases. The general form of the database is described in Table 2. There exist some previous systems that achieved high classification ration, but these systems look like black boxes and with no explanation or interpretation about how the decision was taken. Further, the degree of benignity or malignancy is not provided. These two points are covered in this study besides a high classification ratio. In the next section, an entry about fuzzy modeling is given, as an entry to our problem solution scheme.

4. The solution scheme

The solution scheme we propose for the **WBCD** problem is depicted in Figure 3; Note that the fuzzy subsystem displayed to the left of figure 3 is the fuzzy inference system of Figure 4. Figure 3 consists of a fuzzy system and a threshold unit. The fuzzy system computes a malignancy value of the malignancy of a case, based on the input values, the threshold unit then outputs a benign or malignant diagnostic according to the fuzzy system's output. If the malignancy value is less than or equals 3, it is considered a benign case. Other than that, it is diagnosed as a malignant one. Look at figure 5.

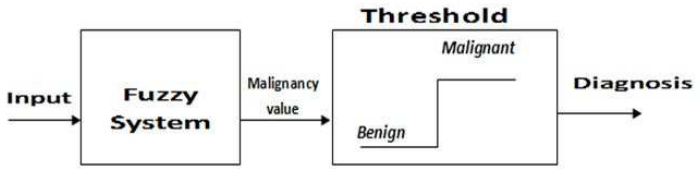

Figure 3. The proposed diagnosis system; the fuzzy subsystem displayed to the left is the fuzzy inference system in Figure 4

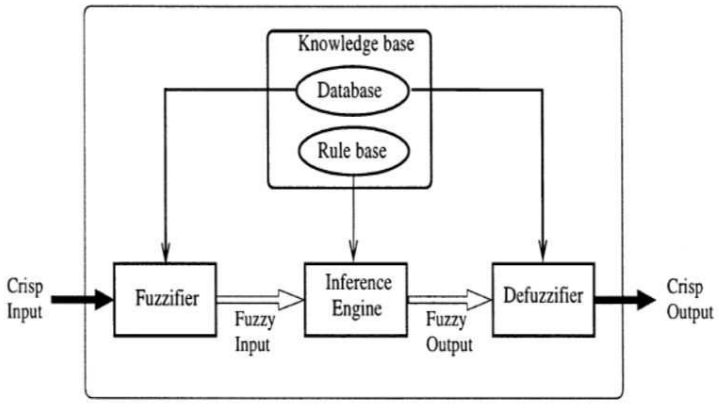

Figure 4. Basic structure of a fuzzy inference system

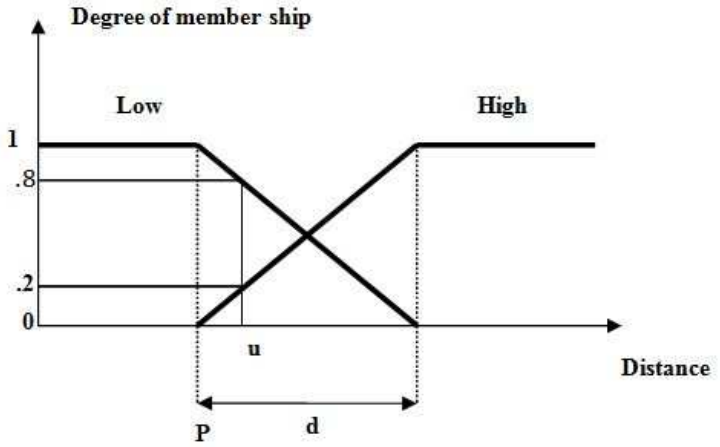

FIGURE 5. Example of a fuzzy variable length which has two possible fuzzy values, labeled low and high, and orthogonal membership functions, plotted above as degree of membership versus input values. P and d define the start point and the length of membership function respectively. The orthogonality condition means that the sum of all membership functions at any point is one. In the figure, an example: value u is assigned the membership values $\mu_{low}(u) = 0.8$ and $\mu_{high}(u) = 0.2$ (as it can be seen $\mu_{low}(u) + \mu_{high}(u) = 1$).

According to information obtained from previous work [1, 2], we have deduced the following knowledge: Systems with no more than four rules have been shown to obtain high performance. Rules with no more than four antecedents have proven adequate. Higher-valued variables are associated with malignancy [16, 17]. Some fuzzy models forgo interpretability in the interest of improved performance. Where medical diagnosis is concerned, interpretability, also called linguistic integrity, is the major advantage of fuzzy systems. This motivated us to take into account the following semantic criteria, defining constraints on the fuzzy parameters [8]:

- *Distinguishability*: To what extent the system is understood and has interpretability
- *Justifiable number of elements*: The number of membership functions of a variable. This number should not exceed the limit of 7 ± 2 distinct terms. The same criterion is applied to the number of variables in the rule antecedent; this is to be familiar for humans.

- *Orthogonality.* For each element of the universe of discourse, the sum of all its membership values should be equal to one.

4.1. **The fuzzy system setting.** In this subsection an explanation of the fuzzy system setting is shown.

Logical parameters

- *Reasoning mechanism*: singleton-type fuzzy system, i.e. Output membership functions are real values, rather than fuzzy ones.
- *Fuzzy operators*: min.
- *Input membership function type*: orthogonal, trapezoidal.
- *Defuzzification method*: weighted average.

Structural parameters

- *Relevant variables*: there is insufficient a priori knowledge to define them; therefore, this will be one of the algorithm's objectives.
- *Number of input membership functions*: two membership functions denoted Low and High.
- *Number of output membership functions*: two singletons are used, corresponding to the benign and malignant diagnostics.
- *Number of rules*: in our approach, this is a user-configurable parameter. Will there be only one rule? The rule itself is to be found by the fuzzy-membrane-immune algorithm.

Connective parameters

- *Antecedents of rules*: to be found by the algorithm.
- *Consequent of rules*: the algorithm finds rules for the benign diagnostic; the malignant diagnostic is an else condition.
- *Rule weights*: active rules have a weight of value 1 and the else condition has a weight of 0.25.

Operational parameters

- *Input membership function values*: to be found by the evolutionary algorithm.
- *Output membership function values*: following the **WBCD** database, we used a value of 2 for benign and 4 for malignant.

4.2. **The fuzzy-membrane-immune algorithm description.** The clonal selection principle, or theory, is the algorithm used by the immune system to describe the basic features of an immune response to an antigenic stimulus [4, 10]. Clonal selection establishes the idea that only cells that recognize the antigens will proliferate where the rest will not, as depicted in figure 6 [11]. The most triggered cells selected as memory cells for future pathogens attacks

and the rest mature into antibody secreting cells called plasma cells [9, 11, 12, 15].

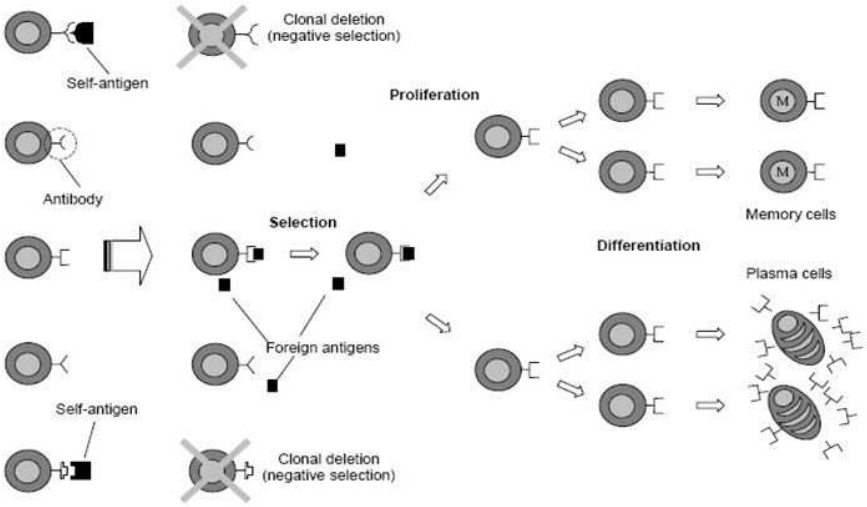

FIGURE 6. The clonal selection principle

Repertoire diversity is maintained by mutation. Mutation is random changes, these changes are introduced into the variable region genes and occasionally one such change will lead to an increase in the affinity of the antibody [20]. These higher-affinity variants are selected to enter the pool of memory cells [19]. Due to the random nature of the somatic mutation process, large proportions of mutating genes become non-functional or develop harmful antiself specificities. Those cells with low affinity receptors, or the self reactive cells, must be eliminated so that they do not significantly contribute to the pool of memory cells. The killing process here maintained by the selection algorithms. For this algorithm to work the receptor population or repertoire has to be diverse enough to recognize any foreign shape, we maintain the diversity by metadynamics. Metadynamics is adding randomly generated Abs into repertoire. A mammalian immune system contains a heterogeneous repertoire of approximately 10^{12} lymphocytes in human [9, 10, 13].

In the fuzzy-membrane-immune algorithm, the repertoire is a set of P systems, look at figure 7, each one consists of set of nested membranes, and each region has a set of solutions and a simple mutation algorithm that mutates all solutions in this region. These solutions are initialized randomly.

In every region there are a few solutions of the optimization problem to be solved and a mutation algorithm works on them. After the initial settings

all solutions are updated by the mutation algorithm placed in regions. Simultaneously, in every region, the best and worst solutions, with respect to the optimization criterion, are sent to the adjacent inner and outer regions, respectively. The best solution exists in the innermost region of a P system.

The process of updating and transporting solutions is repeated until a termination condition is satisfied. In our implementation a fixed number of iterations are used as a termination condition. The ratio of valid classification of cases is used as affinity measure of any solution. Each p system in the repertoire is supposed to be enhanced continuously by time because of maturation performed by mutation. The higher affinity solution will be found in the inner most region and cloning will performed proportional to this solution's affinity, i.e. a high membrane inner most solution affinity means a high cloning rate; a low membrane inner most solution affinity means a low cloning rate or a negative selection (clonal deletion). The concept of mutation is essential to fuzzy-membrane-immune algorithm, as it is the only way for repertoire diversification and maturation. Without sufficient mutation the population will tend to converge towards a few good solutions, possibly representing local optima. On the other hand, with too much mutation the search will have problems of focusing on potentially good solutions; this is the tradeoff between exploration and exploitation. According to our experiments we found that 0.1 mutation rate is suitable. To keep the repertoire diversity, a number of randomly generated P systems are added to the repertoire, our experiments showed that there is no need to perform this step, but in other problems it could be useful.

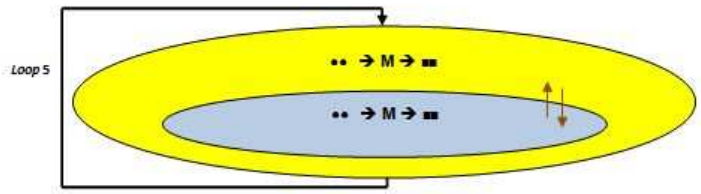

FIGURE 7. a single P system used in the fuzzy-membrane-immune algorithm

The proposed algorithm can be summarized as follows.

4.3. **The fuzzy-membrane-immune algorithm setup.** The membrane-immune algorithm used a repertoire size = 15 P systems, the algorithm maximum iterations = 30 times of +ve/-ve selection, single P systems perform 5

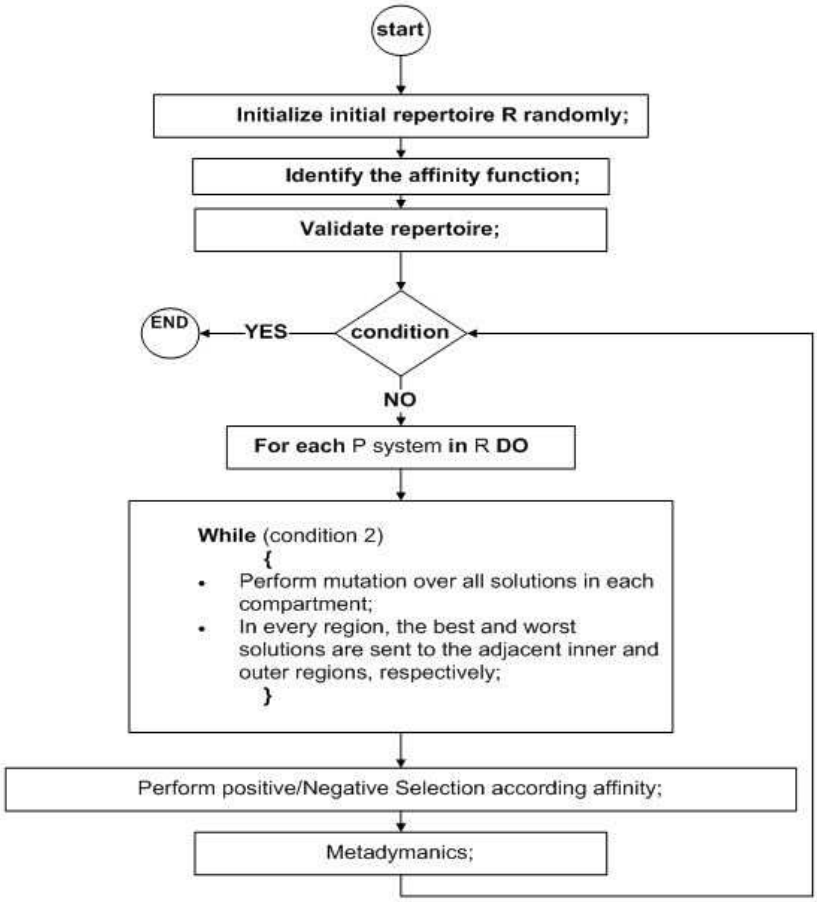

FIGURE 8. the fuzzy-membrane-immune algorithm

iterations, and every single P system has 2 regions (compartments) as depicted in figure 7. Mutation rate = 0.1. Selection and Cloning is proportional to the inner most genome's affinity. The algorithm terminates when the maximum number of iterations is reached. A flowchart of the used algorithm is depicted in figure 8. The used parameters are chosen heuristically and using try and error technique.

The algorithm applies Pittsburgh-style structure learning, the algorithm searches for three parameters, the relevant variables, the input membership function values and the antecedents of rules. They are constructed as follows: There are nine variables ($V_1 - V_9$), each variable has two parameters P and

d, defining the start point and the length of the membership function edges, respectively. The i^{th} rule has the form: $if(V_1 is A_i^1) and ... and (V_9 is A_i^9)$ *then (output is benign)* where A_i^j represents the membership function applicable to variable V_j. A_i^j can take the values: 1 (Low), 2 (High), or 0 or 3 (Other). Relevant variables are searched for implicitly by letting the algorithm choose non-existent membership functions as valid antecedents; in such a case, the respective variable is considered irrelevant.

TABLE 3. Parameters encoding of a genome, total genome length is 54+18= 72

Parameter	Values	Bits	Quantity	Total bits
P	1-8	3	97	27
d	1-8	37	9	27
A	0-3	2	9	18

TABLE 4. Database

p_1	d_1	p_2	d_2	p_3	d_3	p_4	d_4	p_5	d_5	p_6	d_6	p_7	d_7
3	5	4	1	2	8	5	1	7	7	2	5	5	5
p_8	d_8	p_9	d_9	A_1	A_2	A_3	A_4	A_5	A_6	A_7	A_8	A_9	
7	2	4	7	1	1	3	3	3	1	3	1	1	

TABLE 5. Rule Base

Rule	If ((v_1 is low) and (v_2 is low) and (v_6 is low) and (v_8 is low) and (v_9 is low)) then(output is benign)
Default	Else(output is malign)

The parameters encoding are described in Table 3, which form a single individual's genome. Table 4 shows a sample genome and table 5 shows an interpretation of that genome. a population size of 200 individuals showed to be sufficient for generating the fuzzy inference system; no significant enhancements appear by increasing the population above 200 individuals , and fitness-proportionate selection. The algorithm terminates when the maximum number of generations is reached.

5. Experimental Results and testing

To gain an intuitive understanding of how a classification value is computed, let us sketch a simple example. Referring to the system produced by the fuzzy-membrane-immune algorithm table 5, assume that the following values in table 6 (these represent case number 1 of the WBCD database), are presented as inputs, then the membership value of each variable is then computed in accordance with the (evolved) fuzzy rule. The result of membership values are represented in table 7. This completes the fuzzification phase.

Having computed these membership values, the inference engine can now go on to compute the so-called truth value of each rule. This truth value is computed by applying the fuzzy *'and'* operator to combine the antecedent clauses (the membership values) in a fuzzy manner; this results in the output truth value, namely, a continuous value which represents the rule's degree of activation. Thus, a rule is not merely either activated or not, but in fact is activated to a certain degree represented by a value between 0 and 1. In our example, the activation value for a rule is 0.6 and for the default case is 0.25.

Table 6. case number 1 of the WBCD database

attribute	V1	V2	V3	V4	V5	V6	V7	V8	V9
value	5	1	1	1	2	1	3	1	1

Table 7. The membership value of each variable in table 6 using the generated database of table 5.

attribute	V1	V2	V3	V4	V5	V6	V7	V8	V9
m_Low	3/5	1	-	-	-	1	1	1	-
m_High	2/5	0	-	-	-	0	0	0	-

The inference engine now goes on to apply the aggregation operator (Min), combining the continuous rule activation values to produce a fuzzy output with a certain truth value (the point marked 'fuzzy output' in Figure 4) as follows:

Degree of activation(rule 1) = $\mu_{low}(V_1)$ and $\mu_{low}(V_2)$ and $\mu_{low}(V_6)$ and $\mu_{low}(V_7)$ and $\mu_{low}(V_8)$= min{ $\mu low(V_1)$, $\mu low(V_2)$, $\mu_{low}(V_6)$, $\mu_{low}(V_7)$, $\mu_{low}(V_8)$ }= min{0.6, 1, 1, 1, 1}= 0.6.

After that the defuzzifier then kicks in (Figure 4), producing the final continuous value of the fuzzy inference system; this latter value is the appraisal value that is passed on to the threshold unit (Figure 3). In our example the appraisal value is 2.44 (i.e. benign), which is true classification according to the WCBD data base, and computed as explained below.

$$appraisal = \frac{0.6*2+0.25*4}{0.6+0.25} = 2.44$$

The membrane-immune algorithms reached a valid classification ratio equal to 97.36% using only one fuzzy rule, i.e. 665 valid diagnosis cases from 683 cases.

TABLE 8. Comparison of the best systems evolved by our approach with four other rule-based diagnostic approaches

rules number	Setiono	Setiono&Liu	Taha&Ghosh	Pen&Sipper[1]	Pena&Sipper[2]	Our study
1	95.42(2)	-	-	96. 35(3)	97.07(4)	97.36(4)
2	-	-	-	96.65(7)	-	-
3	97.14(4)	97.21(4)	-	-	-	-
4	-	-	-	-	-	-
5	-	-	96.19(1.8)	-	-	-

Table 8 presents a five related works that solved the same problem. Setiono [16], Setiono&Liu [17], and Taha&Ghosh [7] are based on boolean rule bases extracted from trained neural networks. Pen&Sipper[1], Pen&Sipper[2] are based on genetic algorithms.

Column one in table 8 represents the number of rules included in every generated fuzzy rule system. Sentio in [16] reached a valid classification ration = 95.42% with one rule and two variables in this rule. The same work reached 97.14% valid classification ratio using three rules and the average number of variables in each rules = four. Sentio and Liu [17] reached 97.21% valid classification ration with three fuzzy rules and four variables per each in average. Taha and Ghosh [7] reached 96.19% valid classification ration with five rules and average number of variables =1.8. Pen and Sipper in [1] reached 96.35% using one rule and three variables per each rule in average, 96.65% using two rules and seven variables per rule in average. In [2] the last authors reached 97.07% with one rule using four variables. Our work is explained in the last column; we reached the highest valid classification ration 97.36% using only one rule and only four variables in this rule.

The fitness measure of the fuzzy-membrane-immune algorithm can take into consideration with the number of rules to be developed in the fuzzy system, the number of variables included in each rule to improve the system's interpretability. This means smaller number of variables in rules implies higher interpretability. Table 8 shows that the fuzzy-membrane-immune algorithm produced the fuzzy system with the highest valid classification ration in comparison with other techniques in table 8. We run the membrane-immune algorithm 90 times. In every run the algorithm finds a solution of a classification ration = 97.36% as depicted in figure 9, in the other hand the best solutions of genetic algorithm have classification ratio between 94.5% to 97.07%, as mentioned in [1]. As depicted in figure 10 about half of the solutions have

classification performance less than 96.5. Thus the proposed algorithm surpasses genetic algorithm in terms of the best solution and also in the average classification ration of produced systems. From these observations we can claim that the membrane-immune is a promising algorithm in solving similar optimization problems.

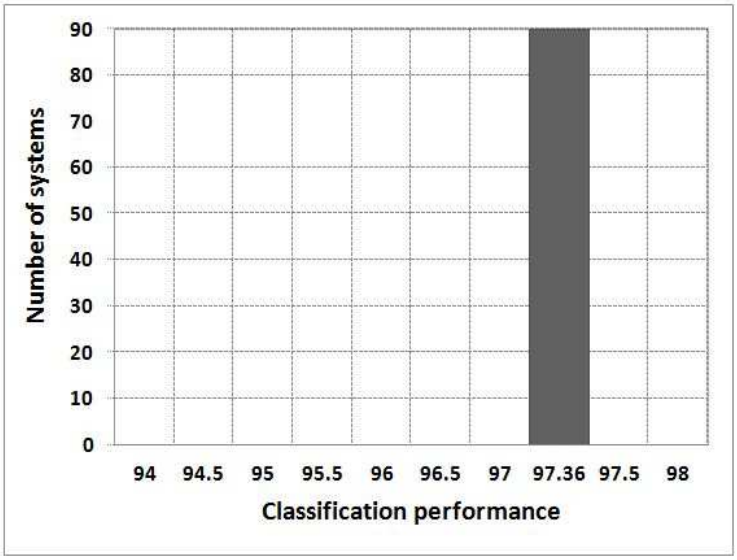

FIGURE 9. Summary of results of 90 runs. The histogram depicts the number of systems Exhibiting a given performance level.

6. Conclusions and Remarks

The proposed algorithm can be hybridized by many approaches other than artificial immune system, e.g. genetic algorithms, swarm intelligence, rough sets, etc. There are many possibilities for improving the proposed algorithm, for example different termination conditions could be used, i.e. one can terminate execution if the good solution is not changed during a predetermined number of steps, considering metadynamics in the earlier execution in the algorithm could enhance performance, metadynamics may be useful in some applications and in other not, Metadynamics needs a deeper view, and it could be implemented by applying very high mutation rates to a number of selected members besides adding some new randomly generated ones. Instead of performing cloning according the affinity of the inner most solution, it could be

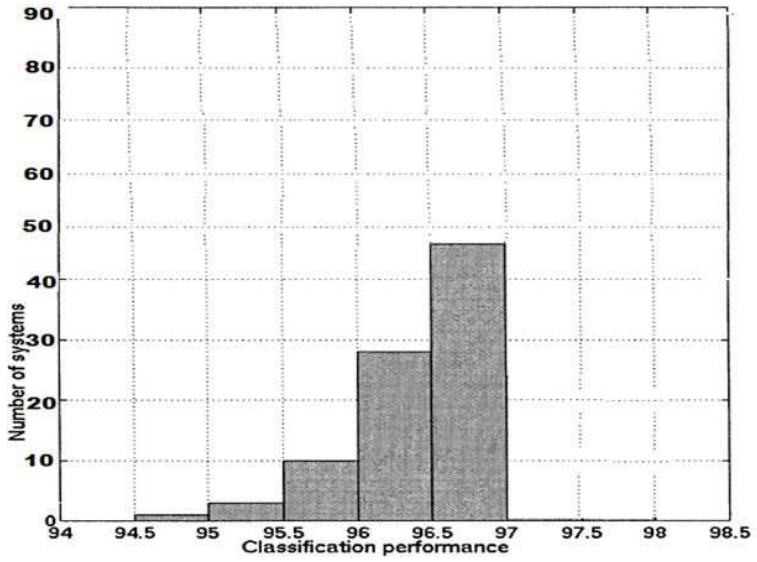

FIGURE 10. Summary of results of 90 evolutionary runs using GA. The histogram depicts the number of systems Exhibiting a given performance level at the end of the evolutionary run.

performed according to the average value of all solutions for a P system; the first mechanism takes into consideration the affinity of one solution to perform cloning but the latter counts for all solutions' affinity in a p system.

The repertoire has a number of independent P systems so; the algorithm will be easily implemented in parallel, distributed, or grid computing systems which indicates a better performance. Each p system itself could be implemented in a parallel system as it contains a number of independent regions all of them has its solutions and maturation/mutation technique. Different mutation techniques may be more suitable for different optimization problems like mutation per solution or Swap Mutation. The best mutation rate for repertoire is an open point; mutation may be high in early iteration and get smaller by time. The proposed structure could be involved in more complex structures as well. Finally, our positive results support the idea that our algorithm is a suitable approach for tackling highly constrained optimization problems.

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