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A Fuzzy-GA Approach for Parameter Optimization of A Fuzzy Expert System for Diagnosis of Acute Lymphocytic Leukemia in Children

Rahil Hosseini[1], Farzaneh Latifi[2], Mahdi Mazinani[3]

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Abstract **- Hybrid fuzzy expert systems are one of the most practical intelligent paradigm of soft computing techniques with the high potential for managing uncertainty associated to the medical diagnosis. The potential of genetic algorithm (GA) by inspiring from natural evolution as a learning and optimization technique has been vastly concentrated for improving fuzzy expert systems. In this paper, the GA capabilities have been applied for optimization of the membership function parameters in a fuzzy inference system (FIS) for diagnosing of acute lymphocytic leukemia in children. The fuzzy expert system utilizes the high interpretability of the Mamdani reasoning model to explain system results to experts in a high level and combines it with the GA optimization capability to improve its performance. The hybrid proposed Fuzzy-GA approach was implemented in Matlab software and evaluated on the real patients' dataset. High accuracy of this system was achieved after GA tuning process with an accuracy about 98%. The results reveal the hybrid fuzzy-GA approach capability to assist computer-based diagnosis of medical experts, and consequently early diagnosis of the disease which is promising for providing suitable treatment for patients and saving more children's lives.**

Keywords **—Fuzzy expert system, genetic algorithm, acute lymphocytic leukemia, computer aided diagnosis.**

1-Introduction

Leukemia is the most common type of cancers affects children in Iran. According to the report published by Mahak Hospital this cancer includes 30% of the all types of cancers in the children [20]. Early diagnosis of the leukemia can increase the chance of treatment to more than 90%. Leukemia cancer begins from blood vessels. Early diagnosis of leukemia and consequently providing follow-up treatments play an important role in the patients' survival. Fuzzy expert aims at assisting the process of diagnosis by managing uncertainty issues related to the decision variables. Fuzzy expert system has high interpretability and can easily interact with human experts. A fuzzy expert system can model and manage imprecision and vagueness associated to the diagnosing acute lymphocytic leukemia in children which is performed using blood test results for the count of blood cells (C.B.C) and leukemia's symptoms. The result of fuzzy expert system is diagnosis of acute lymphocytic leukemia as shown in Figure 1.

1- Islamic Azad University, Shahr-e-Qods Branch, Tehran, Iran. (rahil.hosseini@qodsiau.ac.ir, rahilhosseini@gmail.com)
2,3- Islamic Azad University, Shahr-e-Qods branch, Tehran, Iran.

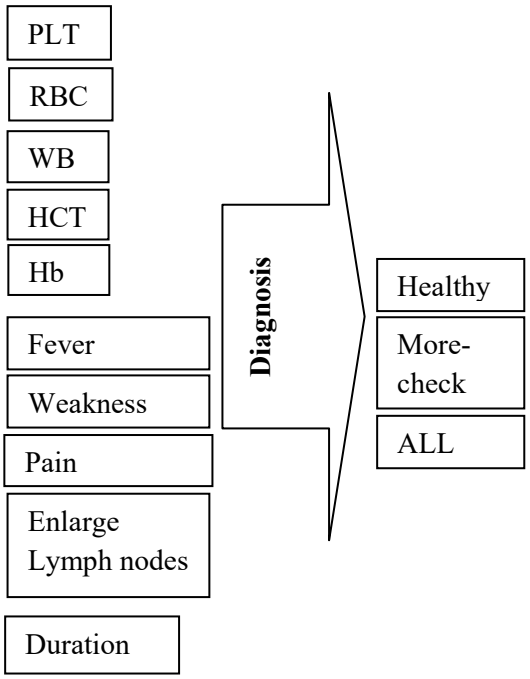

Figure 1. The inputs and output of the FES

During last decades, significant advances in medical field has occurred that attempts at incorporating computational techniques and artificial intelligence capabilities in medical diagnosis. Major advances has happened in prevention and detection of illness [1]. Decision making systems in different fields and expert systems as a kind of these systems has played an important role in medical field [2-4]

The main objective of the proposed fuzzy expert system for diagnosing acute lymphocytic leukemia in this study is to assist medical specialists for diagnosis of the disease in the early stage of its development. On the other hand, there are uncertainties associated to medical systems, i.e., the measurements provided in the blood test experiments and medical experts knowledge for diagnosis [17]. The main sources of uncertainty associated to diagnosis problems are described in [17]. Using optimization algorithms such as genetic algorithm, has been concentrated in the recent decade for designing rules (knowledge base) and database of a fuzzy expert system, e.g., for microarray data classification on leukemia dataset [21]. Selecting leukemia's gene was reported using genetic algorithm and support vectors machines in [22]. Ant colony algorithms applied to medical images through three basic steps: firstly, ant population generation, secondly, the upgrading and repetitive construction process which aimed at making the pheromone matrix, and finally, the decision process which is conducted based on the amount of pheromone [23]. This study takes advantages of hybrid intelligent systems to evolve a genetic algorithm for parameter optimizations of fuzzy expert systems. Fuzzy inference model manages the main sources of uncertainty in the diagnosis of leukemia. It also takes advantages of genetic algorithm for using natural evolution techniques such as selection, crossover, and mutation. The next section explains the acute lymphocytic leukemia and its symptoms and the diagnosis process in details. Section 3 explains the proposed fuzzy expert system and the GA evolved for parameter optimization of fuzzy system is explained in section 4. Performance evaluation and experimental results are presented in Section 5 and the paper is concluded in Section 6.

2. Diagnosing of an acute lymphocytic leukemia (ALL)

In the rest of this section, first the medical diagnosis process for the ALL is briefly described then it is followed by an overview of the current intelligent methods applied to the leukemia diagnosis.

2.1 Medical diagnosis process

Leukemia is the most common type of childhood cancers in Iran. According to the Mahak Hospital reports, it affects in average 4 children in every 100,000 population of Iranian children [20]. Diagnosis in the early stages of the leukemia development can increase the chance of treatment to more than 90%. The ALL can occur in adults too, but their treatment is different. It is caused by appearance of too many abnormal white blood cells (WBC) in the child's blood and bone marrow. It is acute because the WBC grows up very fast. The lymphoblastic refers to the WBC, which are also called lymphocytes. Normally, lymphocytes is an important part of the body's defense system against infections [8].

In its early stages, the ALL can look like other sicknesses such as the flu or a cold. The difference between the ALL and flu or a cold, fleeting infection is its persistence, and the fact that the child may begin to bruise easily.

Common symptoms for ALL include: fever, feeling weakness and tired and dizzy, pain, enlarged lymph nodes, bruises, Weight loss [8].

For diagnosis of the ALL, a doctor needs to look at the child's C.B.C test which is the kind of

test most children have had at least once by the time they are five years old in a routine physical exam. Then Cells must be counted. The cause of ALL is not known. However, some factors may increase a child's chance of developing it. Having an identical twin with ALL, inherited syndromes: such as Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, Ataxia-telangiectasia, Neuro fibromatosis [8]. There is no known way to prevent leukemia yet and there are no special tests that can find acute lymphocytic leukemia (ALL) in the early stages. The best way to find it is through asking questions from patients about any possible signs or symptoms of leukemia and take a medical history, and do a physical exam. Medical expert looks for any swollen lymph nodes, any fever or bruising, or signs of infection. If the doctor suspects leukemia, blood tests will be taken patients with ALL usually have too many WBC, not enough red cells, and not enough platelets. Many of the WBC will grow abnormal, and WBC don't work as usual which means a person has leukemia [9].

The main reason of the ALL, is unknown, but something cause the WBC rapidly grows more than normal. The red blood cells (RBC) needed to carry oxygen to tissues, and platelets that are needed to stop bleeding through clotting. When immature lymphocytes crowd out red blood cell production, a child's body does not receive all the oxygen it needs. As a result, child may develop anemia. When immature lymphocytes crowd out platelets, the child bleeds and bruises easily. As explained in this section, this process is associated with lots of uncertainty; i.e., vagueness and ambiguity with the patients' history and physical examination as well as imprecision associated to the blood test results. This fact clears the need for an intelligent expert system with the capability to manage uncertainty sources to assist the diagnosis process by clinicians.

2.2 Intelligent systems for diagnosis of the leukemia

In the recent decades, application of intelligent-based systems have been emerged for managing uncertainty issues associated to medical decision making. Such a systems are fuzzy expert system and application of learning mechanisms and clever algorithms such as Genetic algorithms. The rest of this section explains the related intelligent systems for diagnosis of leukemia and classified them into two categories: 1) Fuzzy expert systems, and 2) Learning and optimization methods such as Genetic algorithms (GAs) and Particle Swarm Optimization (PSO).

For this, Table 1 provides an overview or comparison between some related works in diagnosis of blood cancer using fuzzy expert systems and their advantages and disadvantages and comparison between some efforts have been made for Leukemia diagnosis using optimization algorithms.

Table 2: The inputs and output of the FES

	Inputs	Explain	Range in Children
Blood Test Results	PLT	Platelets or thrombocytes, are blood cells that stop bleeding in the body.	More than ۴۷۵۰۰۰ and Lower than ۲۰۰۰۰۰ and Healthy Between200 000-47500
	RBC	Red blood cells or erythrocytes, are the most common type of blood cell that deliver oxygen to the body tissues.	Lower than 3.8 and More than 5.8 And Healthy Between3.8-5.8
	WBC	White blood cells or leukocytes or leucocytes, are the cells of the immune system that protect the body against both infectious disease and foreign invaders.	Lower than 4500 and More than 13500 and Healthy Between450 0-13500
	HCT	The percentage of red blood cells in a blood sample	Lower than 31% and More than 43%
	HB	RBC carry protein in the body and transports and delivers oxygen throughout the body.	Lower than 11 and More than 16 and Healthy Between11-16
Symptoms	Fever	High temperature	
	Weak ness	Feeling weakness	
	Pain	Feeling pain	
	Enlarg e lymph nodes	The growth in size of the lymph nodes	
	Time of sickne ss	The patients suffer from symptoms suddenly and their blood test is sick then child has ALL, if it is a long time that the patent is affected and blood test is abnormal then it is susceptible.	

3. The proposed fuzzy expert system

To design the fuzzy expert system for

Table 1: an overview of other related works of fuzzy systems

System's name	Methodology	Inputs	Outputs	Advantages	Disadvantages
Automated Blood Cancer Detection [10]	Diagnose leukemia with using images and fuzzy system. The method work on four different steps: Pre-Processed Image, Image segmentation, Fuzzy rule based decision System, Result	Size, shape and quantity (number of Infected cell) of image.	Diagnosing : ALL, healthy	Being automated and can help the physician as a tool for cancer diagnosis.	Having noisy data Because of using images in diagnosing and needs to device can take photo from blood. It's quality is low.
Clinical decision Support [11]	Diagnose Pneumonia by using fuzzy system (rule-based).	Pneumonia's symptoms	Diagnosing: Having Pneumonia or not	High accuracy, coverage area and less time requirement, managing uncertainty by using fuzzy systems	Systems have to trust to patient's answers.
VP-expert for diagnosing blood cancer [7]	Diagnose different types of blood cancer by asking some questions from patients and according to their answers.	Blood test, time of sickness and illness's symptoms.	Diagnosing: (ALL or AML or CLL or CML)	High accuracy, coverage area and less time requirement and can help to making decision.	It doesn't have clinical evaluation and Systems have to trust to patient's answers and can not work lonely yet.
Neuro-Fuzzy system [12]	It used Mamdani FIS and by providing leukemia's symptoms in three levels of low, middle and high from patients to diagnose leukemia. It used neural nets to find fuzzy system's parameters	Paleness Shortness of Breath Nose Bleeding Frequent infection Anaemia Epistaxis Bone pain Thrombocytopenia Granulocytopenia Asthenia Palpitation Digestive Bleeding Enlarge spleen Fatigue	With Leukemia, Might be Leukemia and Not Leukemia	By using combined systems (Neuro-fuzzy) can manage uncertainty and use training	Not having treatment part.
Designing an Expert System to Diagnose and Propose about Therapy of Leukemia [6]	This is an expert system presented for diagnosis of Leukemia using VP-Expert shell.	Blood test, time of sickness and illness's symptoms	Diagnosing: (ALL or AML or CLL or CML)	It can use as a tool for help to experts to make decision.	It doesn't have clinical evaluation and Systems have to trust to patient's answers.
The Proposed FES	It uses Mamdani FIS and it is a rule based system.	Blood test(C.B.C), ALL's symptoms, time-sickness.	Diagnosing: ALL in children	By using Mamdani FIS, easily to work and understand for each body and fuzzy systems can manage and modeling uncertainty and it's inputs are easily to achieve such as C.B.C and symptoms.	Not suggestion has provided for treatment.

diagnosing ALL, studies have been conducted to understand leukemia illness, i.e., how the leukemia is diagnosed by doctors. This includes leukemia's symptoms or blood test results to determine inputs and outputs of proposed fuzzy expert system, i.e., C.B.C blood test results and ALL's symptoms such as fever, feeling weak and feeling tired and dizziness, pain in bones or joints, enlarged lymph nodes, as show in Table 2 and output are considered as ALL, Suspected, Healthy. The Mamdani FIS has been used in this study because of its simplicity and high interpretability. Rules have been suggested by physicians. Then, the membership functions (MFs) for the linguistic terms associated to the inputs and output fuzzy sets have been determined. The input variables of the FES are provided in Table 2. The design parameters of the fuzzy expert system are as follows:

AND METHOD:	MIN
OR METHOD:	MAX
IMPLICATION:	MIN
AGGREGATION:	MAX
DEFUZZIFICATION	CENTROID

The rules of the fuzzy expert system extracted using the knowledge of medical experts are described in Table 3.

Table 3: The proposed FES Rule-set

1. IF (PLT is LOW) and (RBC is LOW) and (WBC is HIGH) and (HCT is LOW) and (HB is LOW) and (FEVER is YES) and(WEAKNESS is YES) and (PAIN is YES) and(enlarge lymph nodes is YES) and (Time of sickness is SUDDENLY) then (DIAGNOSE is ALL)
2. IF (PLT is LOW) or (RBC is LOW) or (WBC is HIGH) or (HCT is LOW) or (HB is LOW) then (DIAGNOSE is MORE-CHECK)
3. IF (FEVER is YES) or (WEAKNESS is YES) or (PAIN is YES) or (enlarge is lymph nodes YES) or (Time of sickness is SUDDENLY) then (DIAGNOSE is MORE-CHECK)
4.IF (FEVER is YES) or (WEAKNESS is YES) or (PAIN is YES) or (enlarge lymph nodes is YES) or (Time of sickness is LONG) then (DIAGNOSE is ALL)
5. IF (PLT is MIDDLE) and (RBC is MIDDLE) and (WBC is MIDDLE) and (HCT is MIDDLE) and (HB is MIDDLE) and (FEVER is NO) and (WEAKNESS is NO) and (PAIN is NO) and (enlarge lymph nodes is NO) then (DIAGNOSE is HEALTH)
6. IF (PLT is HIGH) or(RBC is HIGH) and (WBC is LOW) and (HCT is HIGH) and (HB is HIGH) then (DIAGNOSE is MORE-CHECK)
7. If(PLT is LOW) or (RBC is LOW) or (WBC is HIGH) or (HCT is LOW) or (HB is LOW) or (FEVER is YES) or (WEAKNESS is YES) or (PAIN is YES) or(enlarge lymph nodes is YES) or (Time of sickness is LONG) then (DIAGNOSE is ALL)

4. The Proposed Fuzzy Genetic Algorithm (FGA) for Tuning The FES

The steps of the algorithm proposed for tuning the parameter of the membership functions of the FES using a fuzzy-GA hybrid algorithm are explained in the following steps:

1. Design the structure of the FLS: selecting input and output variables, its linguistic terms and the type of MFs, and the fuzzy rules for the FIS.

2. Identify the necessary parameters to represent the MFs of the input and output fuzzy sets.

3. Built a chromosome by sorting the parameters of the MF of each input/output variables.

4. Design an objective function.

5. Select the type of GA operations and their parameters.

6. Implement the necessary constraints to build valid individuals.

7. Execute the GA to evolve the FES: For tuning the proposed FES, first of all it is needed to design the fuzzy expert system for diagnosing ALL in children as described in part 3, and determined Gaussian MF parameters for all inputs/output linguistic terms. For fitness evaluation of the FES, the mean square error (MSE) was used. The chromosome representation method was real valued which was initialized using knowledge of physicians. By selecting and setting the parameters of genetic algorithm (such as mutation and crossover rate and their methods and selection method) that mutation rate was chosen as low rate because of saving genes with good fitness. The crossover rate was considered high because of more productivity of genes with high finesses.

5. Experimental Results and Performance Evaluation of the proposed Fuzzy-GA Approach

The proposed FES and the FGA were designed in MATLAB software. Figure 4 and Figure 5 represent the MFs defined for input and output variables before optimization and after optimization by GA, respectively. As shown in this figures, the uncertainty between different linguistic terms (the overlapped areas) have been adjusted after the tuning. Furthermore the Gaussian membership function parameters (i.e., mean and standard deviation) associated to fuzzy sets of linguistic terms have been tuned using the GA optimization process.

For performance evaluation, the FES results

have been compared to the real patients' results and the mean square error (MSE) was computed as performance measure. The FES was evaluated with a dataset including 100 patients (children), some affected by leukemia. The dataset of the examined children has been collected from physician and blood test results collected from laboratory and provided from different clinical centers such as Khatamol-Anbia hospital, Hakin and Mehr Laboratories. In this dataset, 30 samples were abnormal and 32 samples were healthy and 38 samples were susceptible. Thus, 30% of samples are abnormal, 32% of them are healthy samples and 38% are suspected children.

The parameters of the GA operators have been heuristically chosen after trying different reasonable values as show in Table 4. The mutation rate was chosen low because of saving genes with good fitness. The crossover rate was considered high for more production of genes with high finesses. After selecting and setting the parameters of genetic algorithm, the hybrid GA approach has run for 100 generation. The plot of best result and mean of fitness function in each generation of the GA are shown in Figure 6. As shown in this figure, the MSE error has increased significantly after 50 generations of the GA and the algorithm has converged after 90 generations of the GA.

Table 4: comparison of different GA operators' parameters and their effect of the FES accuracy

$P_{Mutation}$	0.05	0.001	0.15	0.1	**0.25**
$P_{CrossOver}$	0.5	0.6	0.7	0.9	**0.9**
Fitness (Mean)	0.035	0.038	0.014	0.011	**0.010**

The comparison of some FES methods and optimization techniques for diagnosis of Leukemia and their accuracy are represented in Tables 5 and 6, respectively.

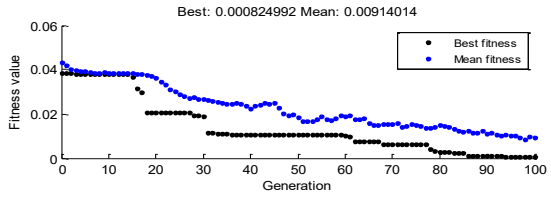

Figure 6: Plot of the best and average performance of GA evolving the FES

The main advantages of this work compared to other related works are summarized as follows:

1. The evaluation process of the proposed method in this study has been conducted using real patients' dataset. In some of the studies it has just been mentioned that the method provides a high accuracy but the details of the evaluation process has not properly provided.
2. Its high interpretability to interact with medical experts through using Mamdani FIS. This system can be used as an assistant for providing second opinion during diagnosis process.
3. The hybrid fuzzy-GA method is capable of randomly initializing the FES parameters for diagnosing acute lymphocytic leukemia (ALL) in the children, compared to existing methods which have used expert knowledge for parameter initialization of the FES.
4. It is promising for early diagnosis of this type of cancer in children because of its high performance and consequently providing suitable treatment.

Table 5: comparison of accuracy of the FESs

Method's names	**Accuracy**
Neuro-Fuzzy system [12]	Not reported
Model of experts for decision support in the diagnosis of leukemia patients [18]	Not reported
Designing an Expert System to Diagnose and Propose about Therapy of Leukemia [6]	Not reported
Implementation of Fuzzy Inference System For White Blood Cell Cancer Detection Using DSP [19]	Just mentioned High accuracy
Automated Blood Cancer Detection [10]	High accuracy in comparison other traditional methods
The proposed system before evolving GA[this work]	96%
The proposed system after evolving GA[this work]	98

Table 6: comparison of accuracy of the GA based Methods

Method's names	**Accuracy**
Gene selection using PSO & GA [24]	95.1%
Gene selection using(GA&SVM)[22]	100%
Selecting Informative Genes with PGA[25]	0.93
Gene Selection in Cancer Classification using PSO/SVM and GA/SVM[26]	100%
Proposed method after tuning[this work]	98%

The proposed fuzzy-GA approach is promising to assist early diagnosis of other types

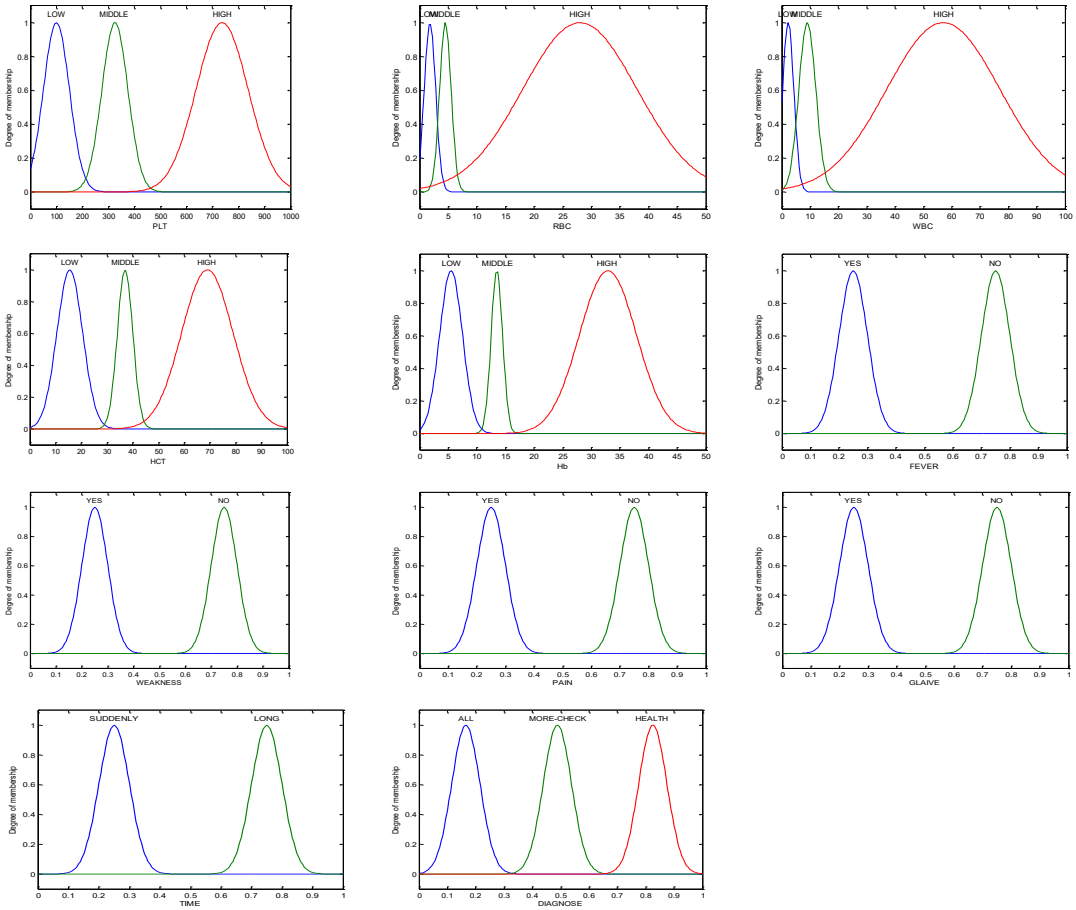

Figure 4: MFs of proposed FES before optimizing

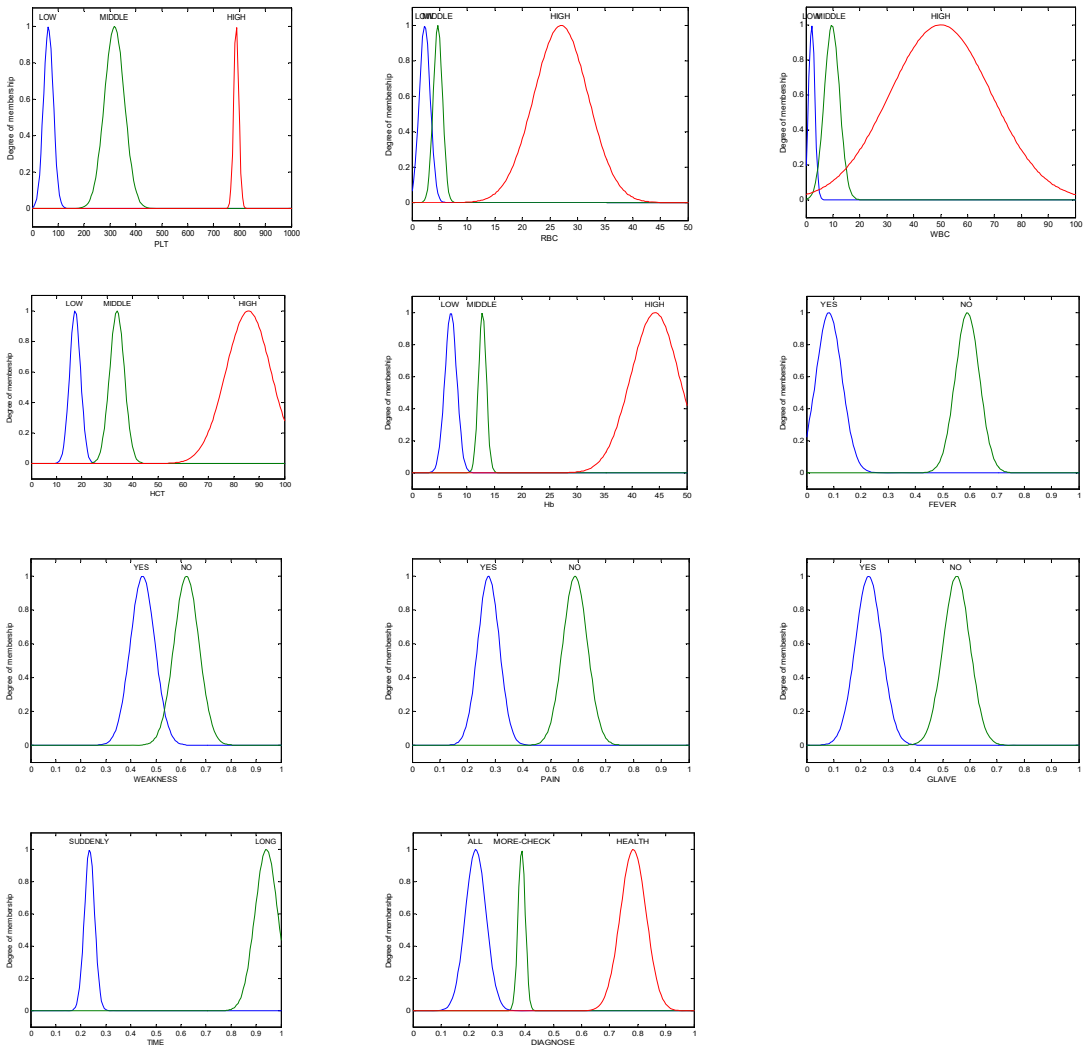

Figure 5: MFs of proposed FES after optimization

of the cancer, specifically leukemia by providing a second opinion during the diagnosis process. This can significantly save cost and reduce the time required for diagnosis and consequently save more children lives. It, also can help to manage uncertainty sources associated to measurements and to the knowledge of medical experts due to incompleteness of the medical science for diagnosing unknown types of a particular disease such as cancers. The intra and inter uncertainty issues in the knowledge of one medical expert and between clinicians can affect the process of knowledge extraction in the design of a fuzzy expert system. The evolutionary optimization techniques such as GA can improve this issue by randomly exploring the search space in an optimized manner inspired from nature.

6. Conclusions

This paper has proposed a fuzzy expert system to diagnose acute lymphocytic leukemia in children. The parameters of system have been tuned using a genetic algorithm (GA). This approach takes advantages of evolutionary nature of the GA for parameter optimization of a fuzzy expert system. The GA random initialization capability can help to manage uncertainty associated to the knowledge of medical experts. It is also beneficial for multi-dimensional optimization problems as our leukaemia cancer diagnosis problem. The Fuzzy-GA method was evaluated on real patients' dataset. This system can assist experts' decision making for diagnosis of the ALL cancer in children and also is applicable for early diagnosis of even suspected people. This approach is promising to assist early diagnosis of this type of cancer in the children and consequently providing suitable follow-up and treatment to save more children lives.

Our future work is to extend the FES for diagnosis of other types of the leukemia. Furthermore, apply other intelligent meta-heuristic evolutionary algorithms for tuning and optimization of the FES.

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