کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Introduction of a New Diagnostic Method for Breast Cancer Based on Fine Needle Aspiration (FNA) Test Data and Combining Intelligent Systems

Mohammad Fiuzy¹, Javad Haddadnia¹, Nasrin Mollania², Maryam Hashemian³, Kazem Hassanpour³

Abstract

Background: Accurate Diagnosis of Breast Cancer is of prime importance. Fine Needle Aspiration test or "FNA", which has been used for several years in Europe, is a simple, inexpensive, noninvasive and accurate technique for detecting breast cancer. Expending the suitable features of the Fine Needle Aspiration results is the most important diagnostic problem in early stages of breast cancer. In this study, we introduced a new algorithm that can detect breast cancer based on combining artificial intelligent system and Fine Needle Aspiration (FNA).

Methods: We studied the Features of Wisconsin Data Base Cancer which contained about 569 FNA test samples (212 patient samples (malignant) and 357 healthy samples (benign)). In this research, we combined Artificial Intelligence Approaches, such as Evolutionary Algorithm (EA) with Genetic Algorithm (GA), and also used Exact Classifier Systems (here by Fuzzy C-Means (FCM)) to separate malignant from benign samples. Furthermore, we examined artificial Neural Networks (NN) to identify the model and structure. This research proposed a new algorithm for an accurate diagnosis of breast cancer.

Results: According to Wisconsin Data Base Cancer (WDBC) data base, 62.75% of samples were benign, and 37.25% were malignant. After applying the proposed algorithm, we achieved high detection accuracy of about “96.579%” on 205 patients who were diagnosed as having breast cancer. It was found that the method had 93% sensitivity, 73% specialty, 65% positive predictive value, and 95% negative predictive value, respectively.

If done by experts, Fine Needle Aspiration (FNA) can be a reliable replacement for open biopsy in palpable breast masses. Evaluation of FNA samples during aspiration can decrease insufficient samples. FNA can be the first line of diagnosis in women with breast masses, at least in deprived regions, and may increase health standards and clinical supervision of patients.

Conclusion: Such a smart, economical, non-invasive, rapid and accurate system can be introduced as a useful diagnostic system for comprehensive treatment of breast cancer. Another advantage of this method is the possibility of diagnosing breast abnormalities. If done by experts, FNA can be a reliable replacement for open biopsy in palpable breast masses. Evaluation of FNA samples during aspiration can decrease insufficient samples.

Keywords: Breast cancer; Fine needle aspiration; Artificial intelligent


Introduction

Breast cancer is a type of cancer with high mortality rates among women, and it is one of the most common causes of death in women [1]. According to National Cancer Institute statistics in America, one out of eight women suffers from breast cancer and 6 % of all deaths worldwide are caused
by this type of cancer [2]. In Iran, approximately 7500 new cases of breast cancer are diagnosed each year. In 2005, standardized incidence rate of breast cancer was 23.56 and 0.66 in females and males, respectively. Its standardized mortality rate was 3.31 in females which was the 4th leading cause of females' death due to cancer [3, 4]. It should be noted that the age of breast cancer in Iran is one decade lower than developed countries [5]. Early diagnosis is one of the major factors in the treatment of this disease [6]. Early diagnosis of breast cancer (maximum 5 years after the first cancer cell division) will increase survival chances from 56% to 86% [3]. Thus, a precise and reliable system is essential for the timely diagnosis of benign or malignant breast tumors [3]. Diagnosis of this cancer is done by samples with the help of surgery, which has the highest recognition accuracy among available methods, but it is an aggressive, time consuming and expensive procedure [4]. Fine Needle Aspiration (FNA) test is another method that can accurately identify breast cancer by using machinery learning techniques. Using Machinery Learning techniques, many studies have been done on diagnosing breast cancer based on WDBC database (back ground). A group of researchers, using the neural network [10, 11, 12, 42], Support Vector Machine (SVM) classifier with the Radial Basis Function (RBF) kernel [7-9] and a fuzzy classifier [10-12] attempted to resolve Wisconsin Breast Cancer issue, and reached about 95% accuracy in identifying breast cancer. A recent study shows that classification based on core is superior to other existing methods such as linear classification based on wavelet and neural networks [12]. In [16] 93% identifying accuracy was achieved using a combination of Decision Tree (DT) and Neural Network (NN) Algorithm, in [17] 94.4% identifying accuracy was achieved by combining GA and Decision Tree (DT). In [18] 93.6% identifying accuracy was reached by using expert systems. In [19] 94% identifying accuracy was obtained using genetic algorithms and artificial immune network, in [20] 92% identifying accuracy was achieved using Fuzzy Principal Component Algorithm (FPCA) algorithm. In all references [21-24] by using the expert system in [19] 94% identifying accuracy was achieved. Artificial neural networks and fuzzy systems, using Principal Component Algorithm and Dimension Reduction Method or by their combination, attempted to identify breast cancer. However, they had a fairly weaker accuracy than other methods. Many machine learning systems, due to inability to remove waste and undesirable features have low accuracy. Therefore, in order to select the best features and achieve the highest accuracy, a new and efficient algorithm was proposed in this study for feature selection, classification of samples, identification and modelling. Firstly, in this paper, the general method is described. Then the outline from Flowchart 1 will be discussed. Therefore, it is hoped that the study results despite being short could be significant in improving methods, treatment and diagnosis of breast cancer.

**Proposed Method and Algorithm**

![Flowchart 1. Proposed system](www.SID.ir)

At first, data are extracted from the database, and then delivered to Binary GA with neural network in its cost function. Binary genetic algorithm, based on optimal features selection at database, generates optimal answers (0 or 1) due to the cost function. The network output is then delivered to the classification algorithm "FCM" for reducing dimension, estimating accuracy of binary genetic algorithm and correcting the classification of patient from impatient. The output of this algorithm returns to the network again and this process is repeated in the cost function of genetic binary algorithm until the most optimal features for increasing maximum accuracy of feature selection are achieved. Flowchart 1 represents all stages in this study.

**Materials and Methods**

The FNA test involves extracting fluid from the breast tissue, and a visual examination of this sample under a microscope [8]. In smart detection, at first, this image turns to a gray level (it does not require
Then, the related software defines the cell core boundary based on the image processing techniques, and calculates the features for each core such as radius, texture, perimeter, area, compaction (square perimeter divided by area), flat (mean difference in length of lines radially adjacent), concavity, symmetry and fractal (border kernel of approximation coastline [27]). Finally, it calculates the mean square error and the mean of the three largest achieved values. Respectively, 30 features by factual values are gained for each sample. WDBC database is the data set involving a few FNA tests provided in the above description, which have been performed on 569 patients in Wisconsin hospitals and identified 212 malignant and 357 benign cases [28]. One sample of FNA test is shown in Figure 1.

**Pattern Recognition**

In fact, feature selection is the choice of features that have maximum power at output prediction [29]. To solve the problems which depend on optimal subset [26], feature selection algorithms are divided into two major categories. If features selection is done independent of any type of learning algorithm, it will be called Filter method, in which, the result of the selected features are determined before processing. If the assessment process is associated with a classified algorithm, the method of feature selection will be called Wrapper or Closed loop. This is a common pattern recognition system which consists of 4 sections: feature extraction and selection; designing and training classifier; and testing. In this study, feature extraction and testing by neural networks selected best features by GA algorithm, and FCM classifier was used for class and sample classification.

**Genetic Algorithm**

Genetic algorithm was developed for the first time by John Holland [30]. During 1960-1970 [31], the genetic algorithm was used to find approximate answers in optimization and search problems derived from natural concepts like heredity, mutation and recombination. The major objective in this algorithm is the chance to have good samples, to continue their life in the next generation, and improve the answers. The procedure of algorithm device is determined in pseudo-code [31]:

**Procedure: Applied Genetic Algorithm**

1. **Initialization**
   - Set population size or pop size, number of generation or max_gen, probability of crossover or pc, and probability of mutation or pm.
   - Initialize parent population \( P(t) \).
   - Evaluate \( P(t) \) and select the best solution \( \sigma^* \) with the optimum objective function among \( P(t) \).
   - While (no termination criteria) do
     - Regenerate \( C(t) \) from \( P(t) \) by applying the crossover and mutation operations.
     - Evaluate \( C(t) \) and select the current best solution \( \sigma^* \) with the minimum objective value among \( C(t) \).
     - Update the best solution \( \sigma^* \) solution, i.e., if \( \sigma^* < \sigma^* \), then \( \sigma^* = \sigma^* \).
     - Select \( P(t+1) \) from \( P(t) \) and \( C(t) \).
     - \( t = t+1 \).
     - End while;
   - End procedure

Here, the genetic algorithm was used from n-gene chromosomes to illustrate the problem space based on 30 features, for example, as a flowing vector. Many genes are “1” (effective in generation or effective features) and many are “0” (uneffective in generation or uneffective features).

![Figure 1. FNA Test and Samples, Figure 1a. Biopsy, Figure 1b By Ultrasound, Figure 1c. Benign Sample, Figure 1 d. Malignant Sample](image)

The rotating selection (roulette wheel) is used to select chromosomes to combine and generate [32]. The method applied for mutation is in the inverse way. In this method, a sub-collection of chromosome’s gene is selected and then it is reversed in replacement. To combine chromosomes with the above mentioned structure, the Partially Mapped cross over (PMX) method is used [33]. The objective function is the equation that gets merits for each generation. It seems that accuracy in identifying is more important than the small selected subsets. Although the two series have the same accuracy, the smaller set is preferred, so we suggest the following fitness function:

\[
\text{Fitness} = \alpha \cdot \text{Accuracy} + \beta \cdot \frac{|p| - |k|}{|p|} \quad (\text{Eq.1})
\]
Which $|n|$ is the number of the total features and $|s|$ is the number of selective features. First sentence is the carefully identified coefficient and the second sentence is the rate coefficient of reduced features.

Table 1. GA Properties

<table>
<thead>
<tr>
<th>ALG</th>
<th>Binary GA</th>
<th>POPsize</th>
<th>Maxiter</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA</td>
<td>250</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>Maxiter</td>
<td>Var low</td>
<td>600</td>
<td>0.4</td>
</tr>
<tr>
<td>Var high</td>
<td>Recom Percent</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Max generation</td>
<td>Mut Percent</td>
<td>0.4</td>
<td>Selection</td>
</tr>
</tbody>
</table>

Multi layer progressive algorithm located in genetic algorithm cost function

Progressive (feed forward) multi-layer neural networks are composed of many processing elements that are in connection with each other, which are called neurons [34]. Generally, the input neurons (P) are added and their weights are multiplied (w), and applied by bias (b) (width from sources), and result in activation function (f), and then the results (a) will be transferred to the next layer (Figure 2). Feed Forward Multi-Layer Neural Network is one of the most important types of static neural networks, and used in many applications such as system identification problems, control, etc [34]. Error Back Propagation algorithm or BP model was introduced as a training algorithm for network by this model.

This algorithm provides a solution for reducing gradient to minimize errors in the network. In this project, we used 3 layers of feed forward network with sigmoid activation function for input layer (i) and output layer (k) with linear function for input layer (i) Figure 3 with adoption of [34].

At first, we selected 30 neurons for input in [26]. Then, we selected the middle layer of network for the best selection of the structure. Then, to achieve the best result, 15 neurons were selected in the middle layer. The number selection of the middle layer neurons is very important. If their number is low, Network will be faced with a shortage of learning resources for solving complex and nonlinear problems and if their number is high, the two following problems are caused: first, learning takes much time. Second, unimportant training data may be learned and the system network would be weak to solve the problems [35, 41, 42]. In this method, the error is passed to the back. In each layer, necessary reforms are carried out on weights. In this process, the quite long error coverage reaches to minimum amount or Error Global coverage becomes equal to times of maximum repetition, which is predetermined. Error Global should be set so that it
Table 2. Neural Network (NN) Properties

<table>
<thead>
<tr>
<th>Properties</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurons</td>
<td>30/15/1</td>
</tr>
<tr>
<td>Input/Output</td>
<td>30/1</td>
</tr>
<tr>
<td>Learning Algorithm</td>
<td>BP</td>
</tr>
<tr>
<td>MSE</td>
<td>0.002</td>
</tr>
<tr>
<td>Error Global</td>
<td>0.02</td>
</tr>
<tr>
<td>Maximum iteration</td>
<td>1000</td>
</tr>
<tr>
<td>1st Activation Function</td>
<td>Sigmoid</td>
</tr>
<tr>
<td>2nd Activation Function</td>
<td>Linear</td>
</tr>
</tbody>
</table>

FCM or fuzzy c-means algorithm

In 1969, Ruspini, proposed the first clustering model with fuzzy idea [36]. In this method, the amount of any membership or data belonging to each data to any cluster in matrix member is determined.

avoids the Network from learning. In this project, 250 has been considered as the number of repetition. Error global value has also been determined 0.02. Properties of the suggested neural network are expressed in Table 2.

The second limitation, called normalization constraints, was that the total membership of all clusters must be equal to “1” in each data class.

$$\sum_{c=1}^{n} u_{ij} = 1 \quad \forall \ j \in \{1, \ldots, n\}$$  \hspace{1cm} (Eq. 4)

FCM tries for any data set, finds the parts that minimize the following cost Equation 1 or objective function.

$$J_f(X, U_f, C) = \sum_{c=1}^{c} \sum_{i=1}^{n} u_{ij}^{m} d_{ij}^2$$  \hspace{1cm} (Eq. 5)

Where in it, \( d_{ij} \) is data distance between \( X_i \) and the \( i \)th cluster center. \( m \in [1, \infty) \) is degree of fuzziness. If \( "m" \) goes to one, clustering will be more difficult or crisp. On the contrary, if \( "m" \) goes to infinity, clustering will be fuzzier. Supposedly as demonstrated in Figure 4 we supposedly classified 1000 random data in 2 classes.

Fuzzy –C- Means or “FCM” methods consist of 4 stages:

1. If function cannot be minimized directly, repeat algorithm could be used. To solve this problem, the optimal replacement scheme was used as follows: select the proper values for \( m, C \) and small positive number for \( "\varepsilon" \). The matrix \( C \) is randomly filled (middle or center of clusters) finally, set \( t = 0 \).

2. In \( (t = 0) \) membership matrix is calculated, and in \( (t > 0) \) updated membership matrix is determined. This means that the degree of membership for fixed parameters of clusters is optimized such as Equation 5 in the flowing:

$$u_{ij}^{t+1} = \frac{d_{ij}^{-2(m-1)}}{\sum_{c=1}^{c} d_{ij}^{-2(m-1)}} = \frac{1}{\sum_{j=1}^{c} \left( \frac{1}{d_{ij}^{2(m-1)}} \right)^{1/(1-m)}}$$  \hspace{1cm} (Eq. 6)

for \( i = 1, \ldots, c \) and \( j = 1, \ldots, N \)

3. The final step is updating the center of the clusters with optimized membership matrix. In addition to these parameters, how the distance is measured is of prime importance.

4. Repeating Steps 2 and 3 until

\[ \left\| C^{t+1} - C^t \right\| < \varepsilon \] or \[ \left\| U^{t+1} - U^t \right\| < \varepsilon \] by all above steps are applied on the random test data (Figure 4) and the second cluster is created. The result can be observed in Figure 5.

Shown in practice researches, this method does not get stuck on local peaks, and today FCM probable method is used as an inceptor in many clustering ways. More details exist on this method [36- 40].
Results
MATLAB® is used for simulation. In this implementation, trained neural network is performed at one time. All weights will change for each input or for one row of data collection. The gained results are presented in Table 3. There were 202 patients during the evaluation process in [7], in the second evaluation [10-12] there were 202 patients, 198 patients in evaluation in [16], in evaluation [17] 201 patients, in evaluation [18] approximately 194 patients, in evaluation [19] 199 patients, in evaluation [20] 195 patients. Approximately 204 patients were identified in the proposed method.

Table 3. Compare and Result

<table>
<thead>
<tr>
<th>Patient</th>
<th>Best answer</th>
<th>Accuracy test</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>202</td>
<td>Not Available</td>
<td>95.61%</td>
<td>SVM [7]</td>
</tr>
<tr>
<td>202</td>
<td>---</td>
<td>&gt; 95%</td>
<td>RBF+FCM and SVM [10,11,12]</td>
</tr>
<tr>
<td>~198</td>
<td>---</td>
<td>&gt; 93%</td>
<td>DT + NN [16]</td>
</tr>
<tr>
<td>~201</td>
<td>---</td>
<td>94.4%</td>
<td>GA + DT [17]</td>
</tr>
<tr>
<td>~194</td>
<td>---</td>
<td>&gt; 93.6%</td>
<td>Exp Sys [18]</td>
</tr>
<tr>
<td>~195</td>
<td>---</td>
<td>&gt; 94%</td>
<td>GA+ AI [19]</td>
</tr>
<tr>
<td>~195</td>
<td>---</td>
<td>&gt; 92%</td>
<td>FPRCA [20]</td>
</tr>
<tr>
<td>~205</td>
<td>96.579%</td>
<td>96 %</td>
<td>Proposed algorithm</td>
</tr>
</tbody>
</table>

Figure 6. Regression plot for output and target in validation and final result (train, test, valid) or all

Table 4. Table for Comparing MD (Medical result) method with proposed ALG

<table>
<thead>
<tr>
<th></th>
<th>Medical result (MD)</th>
<th>Proposed ALG</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEN (%)</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>SPE (%)</td>
<td>99</td>
<td>73</td>
</tr>
<tr>
<td>ACC (%)</td>
<td>99</td>
<td>96</td>
</tr>
<tr>
<td>PPv (%)</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>NPv (%)</td>
<td>98</td>
<td>95</td>
</tr>
</tbody>
</table>

To review the performance of the proposed system, the below parameters are defined which have an important role in the final decision:

\[ \text{Sensitivity} = \frac{T_p}{T_p+F_n} = 93\% \]  
\[ \text{Specificity} = \frac{T_n}{T_n+F_p} = 73\% \]  
\[ \text{Positive Predictive Value} = \frac{T_p}{T_p+F_p} = 65\% \]  
\[ \text{Negative Predictive Value} = \frac{T_n}{T_n+F_n} = 95\% \]  
\[ \text{Accuracy} = \frac{T_p+T_n}{\text{Total}} = 96\% \] number of true diagnosis

For better comparison of the proposed algorithm and the medical method, their results are expressed in Table 4.

Therefore, the suggested method is precise and optimal. The best and most effective selected features in this suggested method are obtained in the following vector: this vector represents seven effective features (3, 6, 12, 18, 21, 25, 27) from all the features involved in the diagnosis of breast cancer.

Figure 6 includes the obtained results in the final stage drawn in terms of factual result.
system has better performance. In each of the 2 charts of the proposed system and real results (MD system), we used 2 new parameters: True Positive Fraction: Expresses the proportion of false positives to benign or

\[ TPF = \frac{F_p}{A} \]  

(Eq.12)

and False Positives Fraction: Expresses whether the ratio of false negative is a true malignancy or

\[ FPF = \frac{F_n}{B} \]  

(Eq.13)

This chart is displayed in Figure 7.

Given the two graphs, it is clear that the proposed system has a good performance. The results of the system are close to the real results.

Conclusion

Breast FNA is a quick test, which takes 10 to 20 seconds for each sample, and this procedure may be repeated several times until the doctor is convinced that a good sample is collected. The examination and FNA procedure will generally take around 20 to 30 minutes for ultrasound guidance and 45-60 minutes for mammographic guidance. Breast FNA should be done after careful medical examination and imaging tests such as mammogram or ultrasound as part of the “triple test” to ensure the correct diagnosis is made. Breast FNA is done by specialist doctors experienced in breast needle biopsy procedures. Breast cancer is the most common disease that leads to the women’s deaths around the world. Due to necessity of early and timely disease diagnosis, a new method based on a combination of intelligent systems is presented in this research. Many researchers are interested in using this tool, but the challenge of neural networks training is their most important concern. Combination of evolutionary algorithms and data mining systems could be used to train these networks to identify and select properties, and therefore lead to their accurate performance. Simulation results show that using data mining process can increase accuracy and efficiency of the network training. The main goal of this research is to achieve 100% accuracy, so to guarantee those artificial intelligence systems and furnish them with practical aspects, we need adequate knowledge, and satisfactory control over intelligent systems, data mining, and breast cancer.

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Conflict of Interest

The authors have no conflict of interest in this article.

Authors’ Contribution

Mohammad Fiuzy conceived, designed the study, interpreted the results, drafted the manuscript and carried out the data analyses. Javad Haddadnia, Maryam Hashemian, Kazem Hassanpour; participated in writing and revising the manuscript, while Javad Haddadnia revised the final manuscript. All authors read and approved the final manuscript.

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