Designing an expert system for differential diagnosis of β-Thalassemia minor and Iron-Deficiency anemia using neural network

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Original Article

Abstract

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Introduction: Artificial neural networks are a type of systems that use very complex technologies and non-algorithmic solutions for problem solving. These characteristics make them suitable for various medical applications. This study set out to investigate the application of artificial neural networks for differential diagnosis of thalassemia minor and iron-deficiency anemia.

Methods: It is a developmental study with a cross-sectional-descriptive design. The statistical population included CBC results of 395 individuals visiting for premarital tests from 21 March to 21 June, 2013. For development of the neural network, MATLAB 2011 was used. Different training algorithms were compared after error propagation in the neural network. Finally, the best network structure (concerning diagnostic sensitivity, specificity, and accuracy) was selected, using the confusion matrix and the receiver operating characteristic (ROC).

Results: The proposed system was based on a multi-layer perceptron algorithm with 4 inputs, 100 neurons, and 1 hidden layer. It was used as the most powerful differential diagnosis instrument with specificity, sensitivity and accuracy of 92%, 94%, and 93.9%, respectively.

Conclusion: The artificial neural networks have powerful structures for categorizing data and learning the patterns. Among different training methods, the Levenberg-Marquardt backpropagation algorithm produced the best results due to faster convergence in network training. It also showed considerable accuracy in differentiating patients from healthy individuals. The proposed method allows accurate, correct, timely, and cost-effective diagnoses. In line with the application of intelligent expert systems, development of this system is presented as a new outlook for medical systems.

Key words: Anemia, Iron Deficiency, Beta-Thalassemia

Introduction:

Thalassemia as one of the most prevalent genetic disorders (of hemoglobin synthesis) is inherited from parents with thalassemia trait (1-4).

This type of anemia is more prevalent among people with Mediterranean, African and Southeast Asian descent, especially in malarious regions (1,3,5).

Normal hemoglobin comprises two alpha chains and two beta chains. Thalassemia syndromes are associated with reduced or absent synthesis of one of these two chains. Alpha thalassemia is less severe than beta and usually asymptomatic (1-5,7).

The severity of β-thalassemia depends on the involvement extent and intensity of hemoglobin chains (more than 200 types of mutations) (1-3).

Beta-thalassemia minor merely results in a type of simple microcytic anemia. Due to the development of a low mean corpuscular volume (MCV), it is confused with iron-deficiency anemia [8]. Iron-deficiency anemia is globally the most common type of anemia in all age ranges by affecting at least one-third of the world's population and causing 841,000 deaths per year (5-7,9).

In addition to severe form of anemia, β-thalassemia major is associated with several complications in different organs. Beta-thalassemia major can lead to a death within the first years of life. Frequent transfusion therapy may prolong this period to 20-30 years (1-3). There are over 25 thousand patients with thalassemia major and 2 million carriers in Iran, with a yearly increase of 1,000 new cases. This statistics highlights the importance of an early diagnosis. Thalassemia major is among the top health issues in Iran, especially in the southern provinces (4-11).

Detection of thalassemia carrier and provision of genetic counseling before marriage are two significant efforts to reduce the birth of affected new newborns. This goal is achieved only through identifying various aspects of thalassemia syndromes, using appropriate tests, being acquainted with the interpretation of tests, and employing modern techniques (3).

Beta-thalassemia is usually diagnosed with hemoglobin electrophoresis or genetic tests; whereas, the diagnosis of iron-deficiency anemia is confirmed through the measurement of serum iron, serum ferritin, and total iron binding capacity (TIBC) tests. These tests can be carried out only in large laboratories in capital cities. Therefore, patients usually receive simpler tests such as the complete blood count (CBC) and the measurement of hemoglobin in local laboratories, and only susceptible patients are referred to reference laboratories. Unfortunately, both diseases are categorized as hypochromic microcytic anemia, and thus indices such as the average volume of red blood cells and the mean corpuscular of hemoglobin (MCH) cannot differentiate thalassemia-susceptible patients with adequate sensitivity and specificity. England, Mentzer, and Shine, among others, have developed specific indices for distinguishing patients at high risk to receive additional and costly tests (11); however, these and other diagnostic indicators are not adequately conclusive (7). This study aimed to use modern medical technologies and knowledge to develop a simple, cost-effective, and accurate screening method for identification of thalassemia carriers and prevention of the birth of affected newborns (4).

With the development of information technology applications, computer-based decision-making systems have become extremely important. In this regard, artificial intelligence, and especially expert systems, plays a major role (12).

Methodologies used for designing expert systems include data visualization methods, as well as statistical and machine-learning techniques. The concept of neural networks has been framed within the functional and theoretical framework of machine learning (12-15).

The artificial neural networks are regarded as a type of mathematical modeling of genuine neural systems and also as important and powerful instruments in the field of computational intelligence and machine learning (16).

Theorization of artificial neural network dated back to 1940s, when Mcculloch, a well-known psychologist, and Walter Pitts, a mathematician, coined it in 1943 (17,18). Since the first half of 1990s, a new generation of neural networks has been introduced, leading to practical, commercial, and hardware implementations of current neural networks (19).

Neural networks comprise a number of non-linear processors that operate in parallel. Capability in discovering hidden connections between non-linearly linked data, and finding linkages between the missing and erroneous data, has enabled these neural networks to compute a specific function, approximate an unknown pattern, recognize a pattern, process a signal, and eventually learn all of them. As a result, current artificial neural networks, as the processing core of expert systems, have been

widely investigated to achieve a human-like performance (20-21).

There is a view that categorizes neural networks into either feedforward or recurrent (feedbackward) groups in terms of reversibility, connection type, and weight connection. The majority of currently used neural networks (90-50%) have feedfoward topology. In this network, the information always moves from the input to the output without any feedback (loop).

The main objective of a neural network is learning. There exists a collection of instruments for a wide spectrum of learning algorithms with their unique advantages. Learning algorithms differ only in formulation and adjustment of synaptic weights or network parameters (22).

Learning algorithms in neural networks are either supervised (with a supervisor) or unsupervised (without a supervisor or self-organizing learning). Supervised learning algorithms analyze the neural network's inputs and samples. They, then, compare the network's output with ideal values and compute the error to adjust the network's parameters such as weight. In this way, the network becomes capable of detecting a completely different type of such samples. In contrast, unsupervised algorithms are not fed with samples of the function to be learned; rather, the training data comprises only examples of the input vectors. Parameters of the neural network are corrected and adjusted only with the system's responses (19,23). According to the studies, learning in the majority of common neural networks is based on a supervised algorithm (24).

Researchers have proved that medical analyses by means of artificial neural networks have produced more accurate and desirable results, as compared to the varieties of medical analysis techniques and statistical methods (such as linear and logistic regression) (25). In this study, the inputs (results of blood tests) versus outputs (diagnosis) were available. As a result, the structure of supervised multi-layer perceptron was used for differential diagnosis of patients with thalassemia minor, patients with iron-deficiency anemia, and healthy people, and also to assign input samples to these groups. At the end, the obtained results were analyzed.

Methods:

Since the present study resulted in the development of an expert system for differential diagnosis of thalassemia minor and iron-deficiency anemia, it was categorized as a developmental study. This system was devised aiming to make fast diagnoses, and prevent wasting of time and cost. Therefore, it was also categorized as an applied study with a cross sectional-descriptive methodology.

Considering the high prevalence of β-thalassemia major in southern regions of Iran (10,26), Bandarabbas was selected as the research site. The statistical population included couples visiting the Medical Center 5 (the reference center for premarital tests), from 21 March to 21 June, 2013. The CBC results of 395 couples were entered into an Excel form to be used in the study. In general, this study was conducted in six stages:

- The first stage (bibliographic studies): At this stage, books and articles existing in online databases such as Google Scholar, SID, Science Direct Scopus, PubMed, and Iran Medex were explored. The query was filtered to find only articles related to iron-deficiency anemia, β-thalassemia, expert systems, neural network, and artificial intelligence.
- The second stage: at this stage, determination of effective parameters and importance assessment of each CBC data (sex, MCV, HCT, HB, RBC, MCHC, MCH, and RDW-CW) were done with Clementine. Afterwards, the gathered data was refined and prepared. In addition, the missing values were imputed from the mean of the completed values of the respective parameters.
- The third stage: at this stage, the obtained dataset was randomly divided in learning (70%), and validation and test (30%) groups.
- The fourth stage: at this stage, the hardware structure of the networks (network's topology, number of layers, number of neurons in each layer, and type of group functions) was selected according to previous studies on artificial neural networks and their parameters such as

learning rate. The selected structure was then optimized using a trial and error technique.

- The fifth stage: at this stage, data in the learning group was fed into the designed neural network to be trained.
- The sixth stage: at this stage, data in the test and validation groups was fed into the network and then the network's performance was evaluated and validated in terms of the structure, topology, and algorithms, using the confusion matrix and the receiver operating characteristic (ROC) test. All algorithms were implemented with MATLAB 2011.

Concerning the nature of data and availability of the artificial neural network's outputs, this study used supervised neural networks. This study employed different types of common supervised artificial neural networks in the area of medical sciences including the (i) multi-layer Perceptron, (ii) RBF, (iii) LVQ, and (iv) support vector machine.

Results indicated that the SVM completely failed in identification of any support vector. Data was then loaded on RBF and LVQ. These networks were excluded due to showing low sensitivity, accuracy, and validity. Finally, the multilayer Perceptron, as a common supervised neural network, was used for categorization of subjects into beta thalassemia (minor), iron-deficiency anemia, and healthy groups, and produced acceptable outcomes.

Results:

The input parameters included sex, MCHC, MCH, MCV, HCT, HB, RBC, and RDW-CV data. The degree of importance of each parameter in the diagnosis was determined using Clementine (Table 1).

In general, the structure of the Perceptron includes an input layer, some hidden layers, and an output layer. In this structure, a number of neurons are used in each layer for the network's architecture. Moreover, the backpropagation, Trainlm-levenberg Marquardt, and TrainScg algorithms, which had the highest accuracy among the backpropagation algorithms, were used in the

structure of the multilayer Perceptron neural network. Concerning the degree of importance of each parameter, the number of inputs, hidden layers and their neurons was changed for each parameter, and then the results were evaluated.

Table 1. Degree of importance of input parameters in determination of network's output

Row	Parameter	Degree of Iimportance
1	MCH	0.187
2	MCV	0.1557
3	RBC	0.1392
4	MCHC	0.1388
5	HCT	0.1325
6	HB	0.1269
7	RDW-CV	0.0753
8	Gender	0.0445

The measurement criteria such as sensitivity, specificity, and accuracy were computed for each network. The best supervised network with backpropagation algorithm was the Levenberg–Marquardt with 4 inputs, 100 neurons, and 1 hidden layer (Figure 1).

In the neural networks, data of healthy individuals, as well as patients with iron-deficiency anemia and patients with β-thalassemia minor was randomly categorized into the learning, validation, and test groups. The accuracy and validity of diagnoses were evaluated using the results of the confusion matrix and the receiver operating characteristic curve. According to Figure 2, the prediction accuracy of the selected network was computed as 97.8% for learning data, 84.7% for validation and test, and 93.9% for overall network's accuracy.

The application of the ROC curve is an effective and common way for the evaluation of tests whose results are recorded in ordinal and quantitative scales. Therefore, the ROC curve was also used for the evaluation of all networks (28).

The area under the ROC curve was used to evaluate each diagnostic test. When the test becomes capable of making accurate and flawless diagnoses, the ROC curve forms a square above the diagonal and approaches the ideal mode (i.e. the area size of 1).
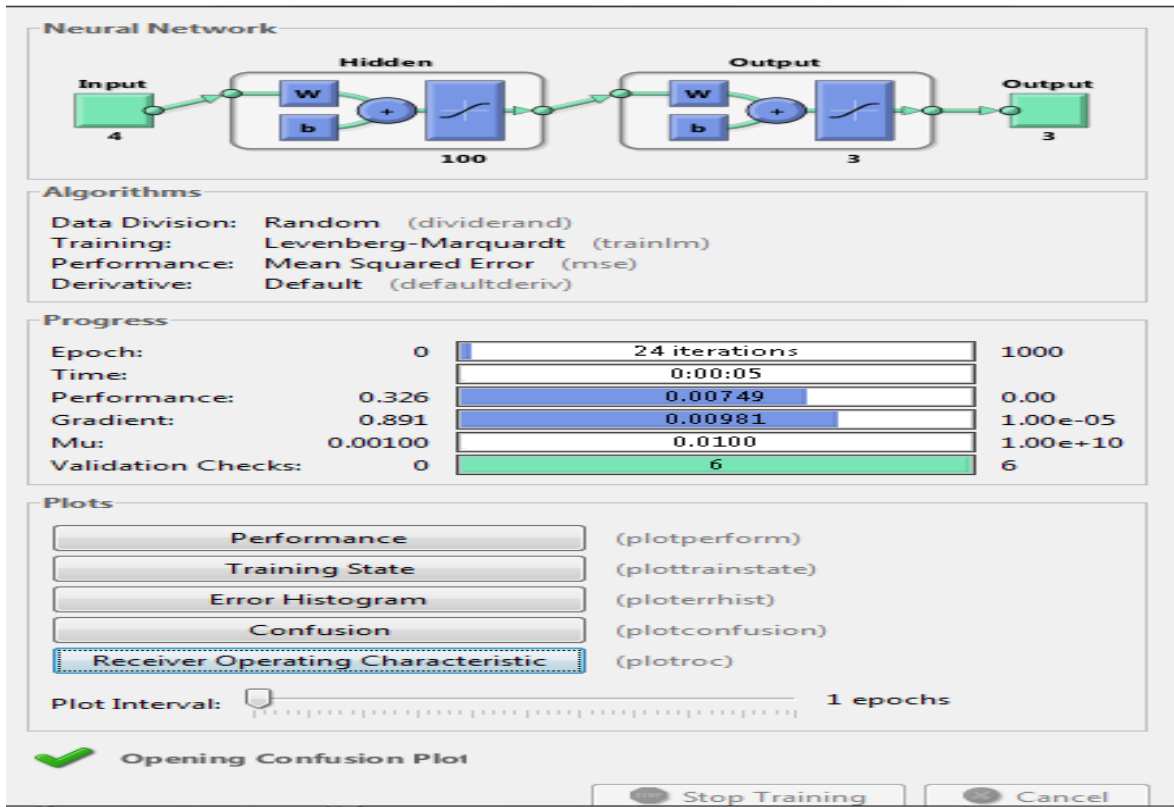
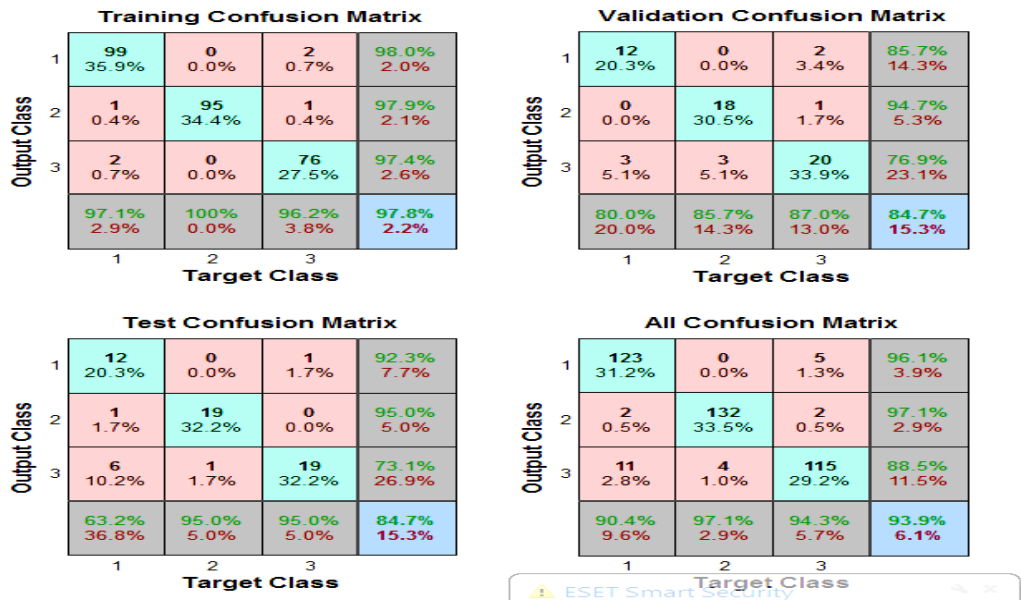**Figure 1. Specification of structure of multilayer Perceptron network**

Figure 2. Confusion matrix and diagnostic accuracy of learning, validation, test, and overall data
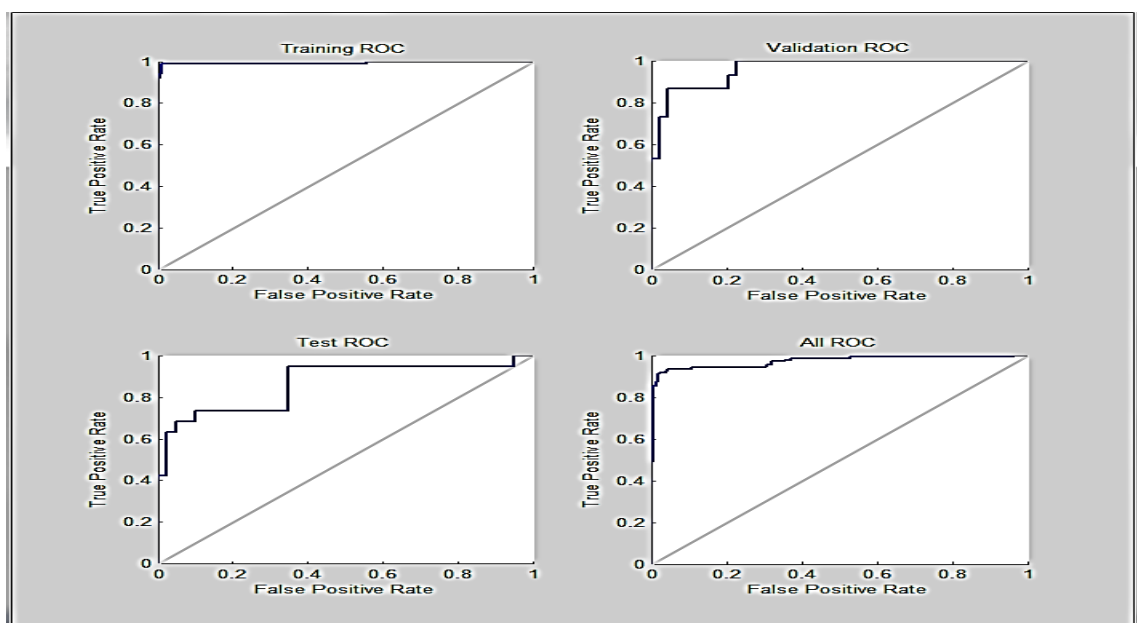
Figure 3. ROC curve for learning, validation, test, and overall data of the selected network

The ROC curve, as well as the area under versus above it indicates the high performance of the network, implemented based on the Levenberg–Marquardt propagation algorithm with aforementioned structure.

Figure 3 shows the shape of ROC curve in the selected network. This shape represents the results of the ROC curve for learning, validation, test, and overall data.

Conclusion:

Results from the Clemente and evaluation of the selected network showed that among blood cells count parameters (e.g. MCH, MCV, RBC, and MCHC), four parameters had the maximum impact on the final diagnosis. The application of RBC, MCV, and MCH for diagnostic purposes has been frequently emphasized in several articles and the instructions of the National Program for Prevention of Beta-Thalassemia Major (32).

Many studies indicate the inefficiency of manual formulas used commonly in laboratory centers, and also the costly process of specialized tests for diagnosis of beta-thalassemia minor. Zandian in an investigation, entitled "CBC-RBC based Routine Lab Diagnostic Tests, Effective Indices, Accuracy, and Validity of Them in Diagnosis of Beta-Thalassemia Minor," reported that the quantitative measurement of hemoglobin A2 and F were more

costly than globin chain synthesis and DNA mutation tests, and thus were not used for screening (26,27).

Previous studies on diagnosis, made upon manual interpretation of routine lab tests, suggested that these test not adequately valid. They also strongly recommended avoiding the application of manual CBC and RBC indices for examining the carriers of thalassemia minor. These formulas cannot be used for children, pregnant women, and patients with iron-efficiency anemia. In addition, their diagnostic accuracy ranges from 80% to 90% (29-31).

Manual formulas are useful only in simple cases and a definitive diagnosis requires more examinations. These types of formulas produce false results in cases with pregnancy, malnutrition, malabsorption, rheumatoid arthritis, tuberculosis, renal failure, and malaria, and those on cytotoxic drugs, and also after hemorrhage (4).

Ghafori et al. suggest that the sensitivity of MDHL and Shine indices for diagnosis of thalassemia minor is far less than what is expected from a screening test. The sensitivity of Mentzer and England indices is only near 90% that is, to some extent, acceptable for screening individuals susceptible to thalassemia minor (11).

Keykhani et al. put that none of the available indices including England and Fraser, Srivastava,

Mentzer, Green and King, Shine and Lal, Red Blood Cell (RBC) Count, Red Blood Cell Distribution Width, Red Blood Cell Distribution Width Index (RDWI), Mean Cell Hemoglobin Density (MCHD), and Mean Density of Hemoglobin Per Liter of Blood (MDHL) have adequate specificity and sensitivity for differential diagnosis of iron-deficiency anemia and β-thalassemia minor. In a study by Kara et al. in Turkey, similar results were obtained for adults (32, 33).

It seems that blood test indices and/or manual indicators extracted from CBC tests are not adequately efficient for the diagnosis of β-thalassemia minor, and thus the application of alternative methods is essential to minimize false negative results. This study shows that the artificial neural networks can substitute for conventional manual and/or costly methods.

Extensive research has been conducted in the field of diagnosis and treatment of various diseases, using artificial neural networks. Orhan (2008) puts that the multilayer neural network successfully substitutes for conventional diagnostic methods in disease diagnosis systems, and also backpropagation algorithms are powerful instruments for training the multilayer neural networks. They used the Levenberg–Marquardt algorithm in their study and concluded that this algorithm had faster convergence and better results than their counterparts (34).

Many similar studies also emphasized the role of neural networks in quality promotion of disease diagnosis and treatment (35-37). The artificial neural networks have powerful structures for data categorization and pattern learning. Results of this study showed the categorization accuracy of 93.9% for the proposed Levenberg–Marquardt based artificial neural network. In general, this system seems successful in differential diagnosis of healthy individuals, patients with beta-thalassemia minor, and patients with iron-deficiency anemia. As a result, it can be used to achieve precise, accurate, timely, and cost-efficient diagnosis. The development of this system is presented as a route to the application of intelligent expert systems in the field of medical systems.

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