

Neural Computing: Application in Non-Invasive Cancer Detection

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The non-invasive cancer diagnosis represents one of the most practical but difficult challenges of contemporary medicine. Modern imaging methods have been recently developed to aid cancer diagnosis by discriminating between diseased and normal tissues. Neural networks, an information processing paradigm inspired by the way the human brain processes information, can be successfully trained on sample images of tumors, to discriminate between benign or malignant tumors. The aim of this paper is to demonstrate the efficiency of neural networks in the non-invasive diagnosis of malignant diseases, using endoscopic ultrasound elastography sample movies concerning pancreatic tumors. The intended audience consists of statisticians and researchers in Data Mining (including physicians) interested in computer-aided medical applications. An intermediate level of neural computing background is needed to understand the case.

1. Introduction

Palpation of the body, as part of the physical examination, is the classical method used by physicians to detect the presence of abnormalities that might indicate pathological lesions, usually because the mechanical properties of diseased tissue are typically different from those of the normal tissue that surrounds them. Palpation is, however, inherently limited to organs that are close to the skin surface. Recently developed methods in the management of cancer diseases designed to replace palpation include a routine use of a biopsy of the affected organ. However, a

biopsy is an invasive method, with inherent complications that may cause even the death of the patient. Consequently, the use of non-invasive alternatives is desired and necessary, since competitive computational technologies, which can be successfully employed towards this purpose, are currently available.

Endoscopic UltraSound (EUS) represents a high-resolution method of imaging of the GastroIntestinal (GI) tract and the nearby organs. It requires the usage of a

special video-endoscope coupled with a miniature ultrasound transducer located at the end of the endoscope. The ultrasound endoscope is then placed at the level of the targeted structure, inside the GI tract. EUS thus allows the precise delineation of the gastrointestinal wall structures, as well as of the nearby organs (pancreas, gallbladder, bile ducts, left adrenal, mediastinum, etc.). Moreover, EUS allows the precise guidance of fine needles, under real-time ultrasound control, inside the targeted structure (tumor, lymph node, etc.). The procedure is called EUS-guided Fine Needle Aspiration (EUS-FNA) and allows tissue sampling in order to obtain a confirmation of the diagnosis of malignancy. Recently, other imaging applications of EUS were further developed, including EUS elastography and contrast-enhanced EUS.

Endoscopic UltraSound Elastography (EUSE) is a newly developed imaging procedure that characterizes the differences in the hardness and strain between diseased tissues and normal tissues. This information can be obtained during real-time scanning with the results being displayed in color superimposed on the conventional grey-scale image. Colors express the difference in elasticity between healthy and diseased tissues. EUSE has been used in several pilot studies for the characterization and differentiation of benign and malignant lymph nodes, with sensitivity, specificity and accuracy which vary but are higher than with conventional EUS methods (Giovannini et al. (2006); Saftoiu et al. (2006)).

Classically, the images are analyzed by doctors in order to establish if an existing tumor is either malignant or benign. Unfortunately, this methodology exhibits a major disadvantage due to the subjective means in which clinician raters analyze a large range of color nuances, on the basis of which an objective decision regarding the type of the tumor is to be derived. Often, there are significant differences in the perception of close nuances which result in clinician-rate variation.

Due both to the usual medical methodology described above and to the inherent bias induced by the selection of images from a EUSE sample movie, the utility of using Data Mining techniques by digitalizing the dynamic images sequence and analyzing the corresponding hue histograms, may reduce variation and thus offer a more EUSE was performed during the EUS examinations, with two sample movies of 10 seconds recorded on the hard disk drive embedded in the ultrasound system, in order to minimize variability and to increase repeatability of acquisition. A two panel image with the usual conventional gray-scale B-mode EUS image on the right side and with the elastography image on the left side was

accurate way of using the EUSE technique (Gorunescu (2007); Saftoiu et al. (2007)).

The goal of this paper is to investigate the potential contribution of a technique of Artificial Intelligence - the neural network - in computer-aided cancer detection. Neural networks represent a Computer Science discipline concerned with adaptive information processing systems that develop associations between objects in response to their environment. In order to address the deficiency regarding the way in which the images are interpreted, we propose to employ a two-layer perceptron that will be trained to understand how to classify tumors as benign or malignant, based on the analysis of previously digitalized images.

The paper is organized as follows: Section 2 presents an example and the associated database. In Section 3 a classical neural network model, the two-layer perceptron, is presented along with the methodology. Section 4 presents the results of the study and Section 5 presents the conclusions.

2. Description of the data set

The study included 68 participants recruited within the Department of Gastrointestinal Surgery, Gentofte University Hospital, Copenhagen, Denmark and the Department of Gastroenterology, University of Medicine and Pharmacy, Craiova, Romania. For a database of EUSE sample movies, see <http://www.eusatlas.ro>; two tumors categories have been considered to be classified using neural networks: "malignant" and "benign".

An EUS, an EUS-FNA and an EUSE of the pancreas were performed during the same EUS examination using a Hitachi 8500 ultrasound system with an embedded SonoElastography module (Hitachi Medical Systems Europe Holding AG, Zug, Switzerland), used in conjunction with an EG 3830 Pentax linear endoscope (Pentax, Hamburg, Germany). All EUS examinations with EUS-FNA were performed by three endoscopists according to a common protocol to eliminate the introduction of variation. EUS-FNA procedures were performed with 22 G Sonotip 2, single-use biopsy needles (Medi-Globe Ltd, Achenmühle, Germany) or 22 G Olympus (Olympus Europe, Hamburg, Germany). considered. Two examples of such images are given in Figure 1 a and b.

Different elasticity values are marked with different (hue) colors (on a scale of 1 to 255) and the EUSE information is shown as a color sample movie. An EUSE sample movie (dynamic image) consists in a sequence of 125 frames

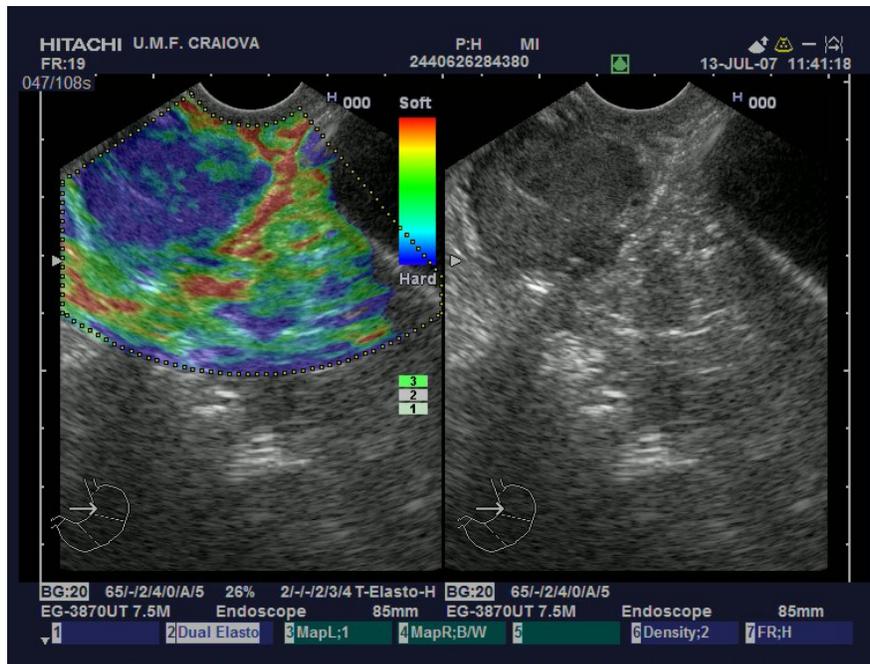


Figure 1a. EUSE sample movie frame showing a hard tumor mass (depicted with blue), in contrast with the soft surrounding tissues.

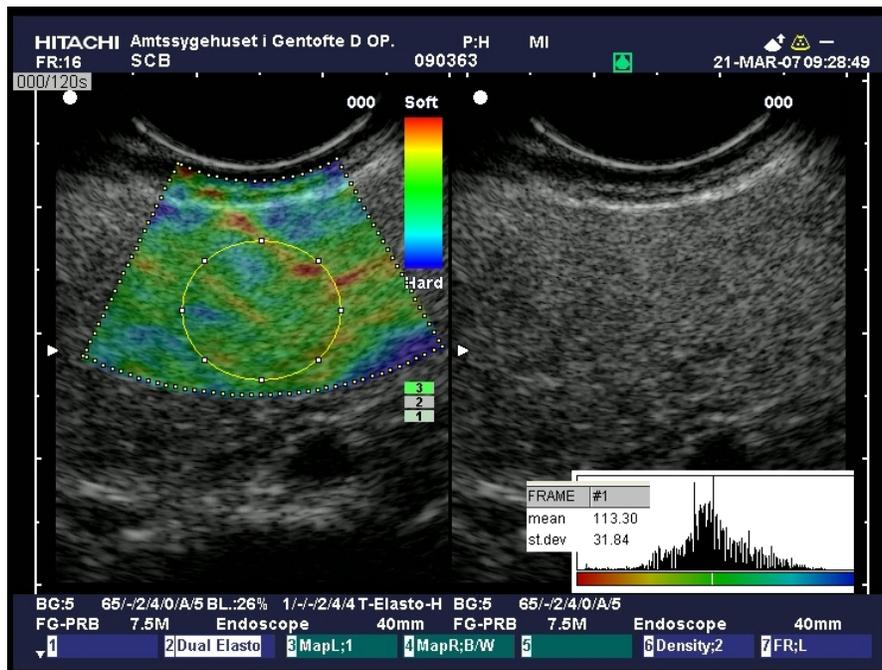


Figure 1b. EUSE sample movie frame displaying the color histogram for the selected area of the movie frame.

(static images). The system uses by default a rainbow color-coded map *red-green-blue* (RGB), where hard tissue areas are marked with dark blue, medium hard tissue areas with cyan, intermediate tissue areas with green, medium soft tissue areas with yellow, and soft tissue areas with red.

Each acquired EUSE sample movie was subjected to a computer-enhanced dynamic analysis, using a public domain Java-based image processing tool, developed at the National Institutes of Health, Bethesda, Maryland, USA (readers are referred to *ImageJ* at <http://rsb.info.nih.gov/ij/docs/intro.html>). Thus, the

system provides the corresponding (hue) color histograms of each frame of the sample movie; Figure 2 illustrates such a (hue) histogram.



Figure 2. Hue histogram corresponding to a EUSE sample movie.

In order to apply the neural network methodology to differentiate between the sample movies, characterizing either benign or malignant tumors, the movies needed to be digitalized. Since a EUSE sample movie (dynamic image) consists of a sequence of 125 frames (static images) displaying 255 colors, then, from a mathematical point of view, to each patient corresponds a 125×255 matrix (a_{ij}), each row corresponding to a certain frame of the sample movie and each column corresponding to a color.

Since the natural input of a Neural Network (NN) is represented by vectors, a method of summarizing the matrix corresponding to a EUSE sample movie in a vector pattern is needed. Since a_{ij} represents the frequency of the (hue) color j in the i -th frame, then $a_j = \frac{1}{125} \sum_{i=1}^{125} a_{ij}$ represents the mean frequency of the (hue) color j in the sample movie. Consequently, the vector $(a_1, a_2, \dots, a_{255})$ represents an average (hue) histogram summarizing the information provided by a EUSE sample movie.

3. Neural networks

The artificial neural network, commonly referred to as neural network (NN), is an information processing paradigm that is inspired by the way the brain processes information. The key to this paradigm is the novel architecture of the information processing system, consisting of a large number of highly interconnected processing elements (neurons) working together to solve specific problems. This complex processing system, storing experimental knowledge and making it available for use, offers an efficient mechanism to extract patterns

and detect trends that are too complex to be noticed by humans.

The basic elements of NN are the *neurons*, interconnected in a layered parallel structure –the network. The topology of the NN basically includes “single-layer” and “multi-layers” frameworks. While a single-layer network consists of input and output layers, the multi-layer network can also have one or more *hidden* layers. The hidden layers are so called because their inputs and outputs are only used for internal connections and are unavailable to the outside of the network.

The simplest neural network model is represented by the *perceptron*. The perceptron consists of a linear combiner followed by an activation function. The summing node of the perceptron computes a linear combination of the inputs applied to its synapses (weights). The resulting sum is applied to its activation function. Accordingly, the perceptron produces a certain output, depending on the activation function type. The synaptic weights of the perceptron can be adapted on an iteration-by-iteration basis. An example of a perceptron with two layers is displayed on Figure 3.

There are two phases in neural information processing: the *training phase* and the *testing phase*. In the training phase, a training dataset is used to make progressive adjustments to the weighted interconnections (synaptic weights) that define the neural model. In this context, we speak of a *training paradigm* that refers to the process by which the free synaptic parameters of the NN are adapted to a process of stimulation by the environment in which the network is embedded. Training a neural network essentially means selecting a set of synaptic weights that minimizes the prediction error of the network. Technically, the training data are used to automatically adjust the weights in order to minimize this error. This process is equivalent to fitting the model represented by the network to the training data available. The error of a particular configuration of the network can be determined by running all the training cases through the network, comparing the actual output generated with the desired (or target) outputs. The differences are combined together by an *error function* to give the network error, or the error surface. Each of the N synaptic weights of the network is taken to be a dimension in space and the $(N + 1)$ -th dimension is the network error. For any possible configuration of synaptic weights, the error can be plotted in the $(N + 1)$ -th dimension, forming an error surface. The objective of the network training is to find the lowest point in this many-dimensional surface.

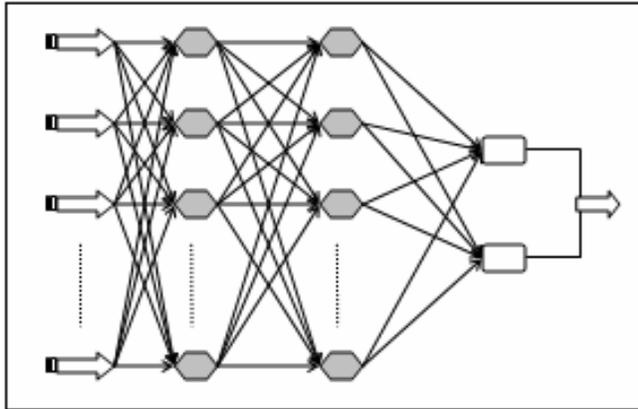


Figure 3. The two-layer perceptron basic architecture.

Afterwards, the trained neural model will be used in the testing phase to process testing patterns, yielding the true classification performance.

A NN is trained to associate outputs with input patterns. When NN is used, it identifies the input pattern and tries to output the associated output pattern. If a pattern that has no output associated with it is given as an input, NN gives the output that corresponds to a taught input pattern that is least different from the given pattern. For more details concerning NN, see for example Bishop (1995) and Haykin (1999).

The most popular network architecture in use today is represented by the *multi-layer perceptron* (MLP). This is the type of network discussed briefly above: each unit (processing element) performs a biased (which in NN terminology means that a constant term is included in the sum) weighted sum of its inputs and pass the activation level through a transfer (activation) function to produce its output, all the units being arranged in a layered feed-forward topology. Such networks can model functions of almost arbitrary complexity, with the number of layers and the number of neurons in each layer determined by the function complexity. An important issue in the MLP design includes the specification of the number of hidden layers and the number of neurons in these layers. A key observation in the practical use of MLP is that MLP with two hidden layers is theoretically sufficient to model almost any real-life problem (formal proof -Kolmogorov's Theorem (1957, see Bishop (1995))). This is our reason for choosing a two-(hidden) layer perceptron to discriminate between tumors types.

The best-known NN training algorithm is the *back propagation* (BP). In BP, the gradient vector of the error surface is calculated. Recall that the *gradient* (vector) of a scalar field is a vector field which points in the direction of the greatest rate of increase of the scalar field. This vector points in the direction of steepest descent from the

current point, so if we move along it a "short" distance, we will decrease the error. A sequence of such moves (epochs) will eventually find a minimum of some sort. Thus, the algorithm progresses iteratively through a number of epochs. On each epoch, the training cases are each submitted in turn to the network, target and actual outputs compared, and the error calculated as difference between them. These errors, combined by the error function into the error surface, are used to adjust the NN synaptic weights and the process then repeats. The initial network configuration is randomly built and the training stops when a given number of epochs elapse, or when the error reaches an acceptable level, or when the error stops improving.

4. Results

During the classification process of the tumors types, we have used a MLP with two hidden layers only. In order to evaluate the classification efficiency, two metrics have been computed: (a) the *training performance* (i.e. the proportion of cases which are correctly classified in the training process) and (b) the *testing performance* (i.e. the proportion of cases which are correctly classified in the testing process). Basically, the testing performance provides the final check of the NN classification efficiency, and thus is interpreted as the diagnosis accuracy using the neural networks support. Recall that the testing performance, corresponding to the neural networks-based diagnosis accuracy, involves only cases with unknown diagnosis for the neural network classifier. This represents an alternative to traditional classification performance measures, such as sensitivity, specificity etc. and is directly related to this Artificial Intelligence technique.

Since the database contains a small number of cases (68), the classical 10-fold cross-validation was used as a testing method. Accordingly, the classification accuracy is computed ten times, each time leaving out one of the sub-samples from the computations and using that sub-sample as a testing sample for cross-validation, so that each sub-sample is used nine times in the training sample and just once as the testing sample. Technically, 60 cases are randomly selected each time and used for training, 8 cases remaining for testing; this procedure is repeated ten times to complete a cross-validation cycle. In order to assess the robustness of this method, we have run the application 20 times and considered the standard deviation of the training/testing performances as a robustness measure. The main results are displayed in Table 1.

Table 1 summarizes results of the two-layer perceptron applied to discriminate between benign and malignant

Table 1. The two-layer MLP performance

Average (Std. Dev.) hidden neurons	Average (Std. Dev.) training performance	Average (Std. Dev.) testing performance
15 (9)	96% (2 perc.points.)	90% (5 perc. points)

tumors using digitalized EUSE sample movies. Firstly, notice that a testing performance of 90% on average has been obtained (90% of cases are correctly classified in the testing process), together with a high training performance equaling 96% on average (96% of cases are correctly classified in the training process). Thus, the neural networks-based diagnosis accuracy is 90% on previously unknown cases, proving a good potential for this methodology. Usually, the training performance is higher than the testing performance, since the latter concerns unknown cases. In this case, the two measures are close enough (difference of 6 percentage points only), indicating a low over-learning level, that is a balanced training/testing process. Moreover, the corresponding standard deviations equaling 2 and 5 percentage points respectively, indicate a high stability of the model, especially in the training case. Note that, as training progresses, the training error naturally drops; it is desirable that the testing error should decrease as well as the training error as training progresses. If the difference between the two errors increases too much, this indicates that the network is starting to over-learn the data and thus it is applicable to other datasets anymore.

Secondly, the mean number of hidden processing units (neurons) in the network equals 15, with a relative high standard deviation, equaling 9. This means that a two-hidden layer MLP with 15 neurons on average is able to provide a 90% diagnosis accuracy. Moreover, it is possible to build a neural network model with 4 neurons only, that is a simple neural structure, and obtain a good enough accuracy. On the other hand, more than 24 neurons are not necessary to obtain a better classification. Thus, we can conclude that it is possible to have a relative simple network structure (i.e. a small number of hidden neurons), that is a fast NN with a very good performance (about 90%). Recall that an efficient neural computing solution to real-life problems implies the selection of the simplest NN architecture with high performance.

5. Conclusions

Different types of elasticity imaging procedures have recently been described in the medical literature, with clinical applications already developed for the diagnosis of different types of cancer. The EUSE was reported to offer supplemental information that appears to obtain a better characterization of tissue and that might enhance conventional elasticity imaging procedures.

The methodology we have developed in this paper, based on processing EUSE digitalized sample movies of tumors, enables the exploration and analysis by automatic means of large quantities of data generated by both the process of image digitalization and the potentially large number of patients. This provides a method which is an alternative to traditional human-based techniques, and optimally predicts the presence or absence of cancer by using a noninvasive methodology.

The application of neural networks models in non-invasive cancer diagnosis, using EUSE sample movies, represents a promising complementary method, enhancing and supporting the differential diagnosis of benign and malignant tumors made by physicians, in real time and with a high degree of accuracy, compared to traditional methods, but much faster. Future work must compare the results obtained using the neural network methodology with other diagnostic methods. Moreover, a classification performance analysis based on ROC curves is also needed to complete the study.

Acknowledgements. We would like to thank Gabriel Lucian Popescu and Alexandru Iordache, from the IT Center, University of Medicine and Pharmacy of Craiova, Romania, for providing the data in digitalized form.

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Appendix: Data information

The data set included with this article is arranged as follows:

- each row is related to a patient EUSE sample movie, digitalized and summarized as a vector (formula in the paper). For 68 patients there are 68 rows (input vectors hue histograms).
- each column (except the last one) represents the mean percentages of the same (hue color) in the 68 EUSE sample movies (details in the paper).
- the last column describes the tumors type (benign/malignant), corresponding to each patient.

To summarize, each row in the dataset corresponds to a certain patient and each column to a certain hue color (and the diagnosis-the last one).