Application of neural networks in medicine – a review

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SUMMARY

The main aim of research in medical diagnostics is to develop more exact, cost-effective and easy-to-use systems, procedures and methods for supporting clinicians. In this paper the authors introduce a new method that recently came into the focus referred to as computer generated neural networks. Based on the literature of the past 5-6 years they give a brief review - highlighting the most important articles - showing the idea behind neural networks and where they are used in the medical field. The definition, structure and operation of neural networks are discussed. In the application section they discuss examples in order to give an insight into neural network application research. It is emphasized that in the near future completely new diagnostic equipment can be developed based on this new technology in the field of ECG, EEG and macroscopic and microscopic image analysis systems.

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INTRODUCTION

The implementation of human intelligence in scientific equipment has been the subject of scientific research for a long time and of the medical research in the last decade. In the 1950's computer simulation of biological neural network was first introduced. In 1951 McCullogh and Pitts stated the definition of the first artificial neuron [1]. In parallel with the evolution of computer technology, modeling of increasingly complicated neural functions and activity of simple neural clusters was defined. Mathematical models that could be applied for practical applications were developed between 1982 and 1987 based on the works of McLelland, Rummelhart, Hopfield and Kohonen [2,3,4]. In Hungary, T. Roska et al. achieved outstanding results in the field of cellular neural networks. Neural networks can be applied to medicine in four basic fields: modeling, bioelectric signal processing, diagnosing and prognostics (Table 1).

In this paper, after describing the basic elements of neural networks and sketching their operation, we discuss the main application fields of neural network technology in medicine.

1. Modelling: Simulating and modelling the functions of the brain and neurosensory organs.
2. Signal processing: Bioelecric signal filtering and evaluation
3. System control and checking: Intelligent artificial machine control and checking based on responses of biological or technical systems given to any signals
4. Classification: Interpretation of physical and instrumental findings to achieve more accurate diagnosis
5. Prediction: Neural network provide prognostic information based on retrospective parameter analysis

Table 1. Functional division of neural network applications.

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STRUCTURE AND OPERATION OF NEURAL NETWORKS

Artificial neural networks can be defined as mathematical algorithms that approach the functionality of small neural clusters in a very fundamental manner. In this short introduction let us focus on only the so-called Back Propagation neural network algorithm.

The artificial analogue of the biological neuron (Fig. 1a) is referred to as a 'Processing Element' (PE, Fig. 1b). A neural network consists of small numbers of PEs (tens to thousands). A PE has many input paths (dendrites, $X_{0..n}$) from adjoining PEs' outputs (axons). Input signals are combined usually by simple summation and are passed to the following PE through the axon.

Fig. 2 shows the basic structure of neural networks. PEs are usually organised into groups (layers). Generally there are three types of layers. The input layer collects information presented from the surroundings, the output layer generates a response to a given output. The layer between input and output layers is called the hidden layer. PEs in any one layers are joined with all PEs in the layer above.

The operation of a typical Back Propagation network can be described as follows.

1. After presenting signals to the input layer, information propagates through the network to the output layer (forward propagation). During this time input and output states for each PE will be set.

$$x_j^{[s]} = f(I_j^{[s]}) = f\left(\sum_i (w_{ij}^{[s]} * x_i^{[s-1]})\right)$$

where

$x_j^{[s]}$ denotes the current output state of the j^{th} PE in the current *[s]* layer,

$I_j^{[s]}$ denotes the weighted sum of inputs to the j^{th} PE in the current layer *[s]*,

f is conventionally the sigmoid function,

$w_{ji}^{[s]}$ denotes the connection weight between the i^{th} PE in the current layer *[s]* and the j^{th} PE in the previous layer *[s-1]*.

2. Global error is generated based on the summed difference of required and calculated output values of each PE in the output layer.

$$E_{glob} = 0.5 * \sum_k \left((r_k - o_k)^2\right)$$

where

E_{glob} means the global error,

Figure 1a. The biological neurone.

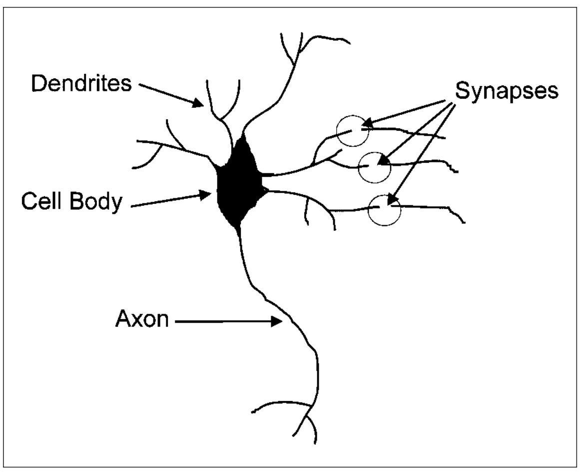


Figure 1b. 'Element structure' and function.

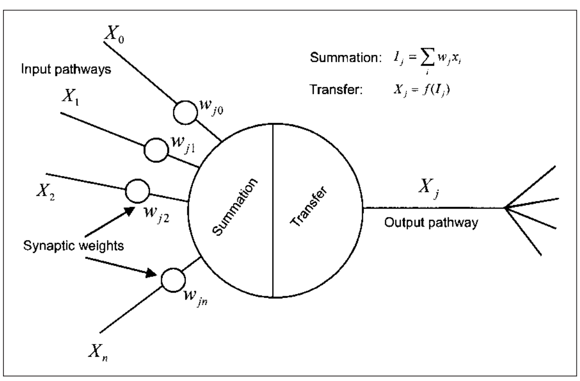
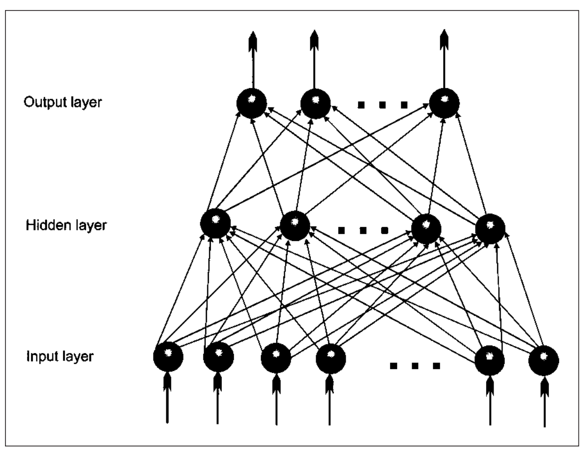


Figure 2. Neural network structure, layers.



$(r_k\text{-}o_k)$ denotes the difference of required and calculated output values.

Scaled local error for each PE in the output layer is calculated according to the following formula:

$$e_k^{(o)} = x_k^{[o]} * \left(1.0 - x_k^{[o]}\right) * \left(r_k - o_k\right)$$

This formula shows that local errors are scaled, based on their output activation values.

3. Global error is back-propagated through the network to calculate local error values and delta weights for each PE. Delta weights are modified according to the Delta-rule that strictly controls the continuous decrease of the synaptic strength of those PEs that are mainly responsible for the global error. In this manner, a regular decrease of global error is assured.

$$e_j^{[s]} = x_j^{[s]} * \left(1.0 - x_j^{[s]}\right) * \sum_k \left(e_k^{[s+1]} * w_{kj}^{[s+1]}\right)$$

where

$e_j^{[s]}$ is the scaled local error of the j^{th} PE in the current *[s]* layer.

$$\Delta w_{ji}^{[s]} = lcoef * e_j^{[s]} * x_i^{[s-1]}$$

where

$\Delta w_{ji}^{[s]}$ denotes delta weight of the connection between the current PE $(Pe_j^{[s]})$ and the joining PE $(Pe_i^{[s-1]})$,

lcoef denotes the learning coefficient, one of the training parameters.

4. Synaptic weights are updated by adding delta weights ($\Delta w_{ji}^{[s]}$) to the current weights.

Neural networks simulate neurotransmission by changing the strength of interneural connections (synaptic weight). Positive synaptic weights provide amplified neural signal and stronger effect to the joining PE. No modification in the information flow is modeled by 0 weight. Negative weights mean inhibition.

The learning process of the neural network (training) is similar to the learning function of the brain. During training, samples are presented to the input layer that yield changes of the activation state of the output PEs. The calculated output value is compared to the required value that is also given in the training set. Depending on the difference between the required and the calculated output values, the network adjusts synaptic weights whose distribution constitutes the basis of the problem solving algorithm. The network processes the elements of the training set in cyclical order until the difference becomes lower than a given value.

In the second part of the training process the system is tested. The test set is fundamentally similar to the training set, but it contains different data. If testing fails, network structure or learning parameters are then modified.

Neural network research led to the development of several algorithms, many of which are currently used world-wide. Different algorithms are suitable for different solutions. Back Propagation model is one of the most wide-spread, all purpose, and simple algorithms developed by David Rummelhart and Robert McLelland. Information flows from the direction of the input layer towards the output layer. The term 'Back Propagation' refers to the principle that calculation of synaptic weight changes proceeds in reversed direction (from the output layer towards the input layer).

COMPARISON OF NEURAL NETWORKS TO CONVENTIONAL COMPUTATIONAL SYSTEMS

In the course of conventional computational problem solving, software designers and programmers use algorithm-based procedures and linear or nonlinear functions. Thus an algorithm is defined that clearly describes the whole problem solving procedure and is then transformed into mathematical functions. On the other hand neural networks are developed through training. Making an appropriate network is relatively simple using computerized simulator software. The well-defined network is able to self-adapt to the exercise and prepares its own solving algorithm based on the cyclical processing of the training samples. The problem solving algorithm is included in the neural network synaptic weight matrix. The manner in which such a neural network makes its decision is currently unknown. Neural networks can improve on conventional rule-based systems in their flexibility and ability to adapt (Table 2).

There are, however, several disadvantages of neural networks compared to algorithm-based systems. Although easy to produce tuning a neural network for a specific task requires long experience. There are no appropriate data in the literature describing what type of network to create for a given task,

	Algorithm-based Systems	Neural Network
Variables	pre-processed parameters	raw bioelectric signas, pre-processed parameters
Classification	algorithmic, pre-defined differentiating factors	training set, training process
Reproducibility of decision process	available	not available
Decision process	decision borders and pathways predefined by experts	automatic self-made decision based on learning process

Table 2. Comparison of algorithm-based systems to neural networks.

Discipline	Application field	Reference
Cardiology	diagnostics, prognostics	5 , 6, 7, 8, 9, 58
ECG	diagnostics	10, 11, 12, 59
Intensive care	prediction	13, 14, 43, 60
Gastroenterology	prediction	16
Pulmonology	diagnostics	17, 18
Oncology	diagnostics, prognostics	19, 20, 21, 61
Paediatrics	diagnostics	26
Neurology	signal processing, modelling	22, 23, 27
EEG	diagnostics	25
Otology-Rhinology-Laryngology	signal processing, modelling	28, 29, 30, 35
Obstetrics and Gynaecology	prediction	32, 33
Ophthalmology	signal processing, modelling	34, 62
Radiology	signal processing (x-ray, US, CT)	37, 63
Clinical chemistry	signal processing, diagnostics	51, 52, 53, 54, 55
Pathology	diagnostics, prognostics	39, 40, 42, 44, 47
Cytology	diagnostics, re-screening	45, 46
Genetics	diagnostics	48, 49, 50
Biochemistry	protein sequence, structure	64, 65

Table 3. Summary of applications of neural networks in the medicine.

how to set learning parameters or how long to train. During training three types of error can occur: training the network too accurately will result in a loss of flexible problem solving; with a short training process the network will be unfit for proper accuracy; and finally incorrect learning parameter settings result in reaching a dead end (local minima) - this means that training for any further length of time can not lead to a better result. Training accuracy depends not only on the training parameter settings and the number of learning iterations, but also on the samples of the training set.

Neural networks' ability to adapt flexibly to a problem makes them suitable for solving classification problems based on mainly qualitative differences. On the other hand algorithm-based systems can be used for reaching mathematically exact results. Examples will be introduced in the following chapters.

APPLICATION IN THE MEDICINE

Between 1990 and 1997 applications of neural networks were introduced in near 2000 papers. Table 3 gives an overview of the main disciplines; some papers from each field are cited here. Detailed description of applications of most importance is included in the remainder of this paper.

Cardiology

Serum enzyme level analysis forms the basis of acute myocardial infarction (AMI) diagnostics. A neural network has been trained for the analysis of these heart enzyme levels. Diagnostic accuracy proved to be 100% with an 8% false positive rate [5]. Later, the same research group developed an integrated decision support system in which a neural network was trained not only by enzymatic data, but also by EKG-phenomena, subjective symptoms and changes after administration of nitroglicerine [6].

Neural networks were used by Farruggia et al. to study the sophisticated control of cardioverter defibrillators. Neural networks have been used to model heart rate regulation [7,8], while Ortiz et al. used them to examine heart failure [9].

Analysis of ECGs

Computational ECG-analysers are widely used in clinical practice. Currently available systems are based on mostly rule-based mathematical and statistical algorithms for the analysis of ECG-signals. There are several attempts to use neural networks to improve the diagnostic accuracy and achieve more faultless operation even in the presence of complicating factors. Evaluation of long term ECG recordings (Holter-monitor) requires automated recognition of events that occur infrequently; human evaluation of nearly 90.000 ECG-complexes a day is a time consuming and exhausting procedure. An adequately trained neural network can recognize given disorders with up to 99.99% sensitivity [10,11,12].

Intensive care

The evaluation of clinical parameters and especially the use of alarm signals in an intensive care unit is currently done on a one by one basis. An alarm system that is able to evaluate changes and interactions of physical, chemical and thermodynamical parameters simultaneously would be most ideal. Conventional technology would have to assume a full knowledge of clinical relationship for such a system. Because these relations are only incompletely known, neural networks' ability for learning and adaptation could be expected to be utilized [13]. In anesthetic practice, physicians are required to monitor more and more displays and evaluate an increasing number of signals. Processing of this amount of data requires experienced and skilled clinicians to ensure intelligent, high-level systematisation and timely evaluation of theirs input. Neural networks can definitely support physicians by initiating necessary responses in case of emergency (within 17 seconds instead of the 45 seconds average by clinicians) [14,15].

Gastroenterology

Determination of the prognosis of patients undergoing hepatectomy is an overlapping field of gastroenterology and oncology. Hamamoto et al. trained a back propagation neural network with clinical findings of 54 patients; data of 11 patients were used for testing. The prognosis in the test patients were reproduced with 100% accuracy [16].

Pulmonology

Pulmonologists and radiologists have worked together on the development of a system for the classification of solitary pulmonary nodules [17]. According to their results, neural network analysis of such disorders was less successful than conventional classification methods. In contrast, neural networks were more accurate than 2 well-trained experts for the diagnosis of pulmonary embolism in 1064 patient [18].

Oncology

There are several systems available for the diagnosis and selection of therapeutic strategies in breast cancer. A neural network judged the possible recurrence rate of tumors correctly in 960 of 1008 cases by using data from lymphatic node positive patients (tumor size, number of palpable lymphatic nodules, tumor hormone receptor status, etc.) [19]. Baker et al. reported that they came to similar results by neural network evaluation of the parameters of the BI-RADS standardized code system [20]. Fogel stated in his paper on neural network recognition of breast cancer that evaluation of mammographic, cytological and epidemiological findings in an integrated system is thought to be useful in the diagnostic process [21].

Neurology

The sometimes difficult differential diagnosis between Alzheimer disease and vascular dementia can be assisted by neural network analysis of brain SPECT image data. An 86% sensitivity rate was achieved in one study [22]. Guigo et al. studied and modeled the learning process of the prefrontal cortex. This theoretical study could promote development of more complex artificial neural network structures [23].

EEG analysis

Several neurological disorders are routined examined by EEG analysis. Differentiation between physiological and pathological alterations requires the flexibility and excellent adaptation capability of neural networks through the processing and recognition of huge amounts of various EEG-complexes. In a laboratory model, a back propagation neural entwork was trained to recognize spontaneously occurring HVS-patterns (High Voltage spike-and-wave Spindle) in rats. This well-trained and optimized network could detect the presence of HVS in EEGs recorded for 12 night hours with 93-99% sensitivity. However, falsely detected events (non-HVS, artefacts) varied over a wide range (18-40%). This attempt does, however, demonstrate the potential usefulness of neural networks in the recognition of EEG patterns and consequent construction of automated EEG evaluation systems for detection, observation and tracking of epileptiform patterns [24]. Gabor et al. has reached a similar conclusion by identifying typical epileptiform alterations of the EEG in an epileptic seizure [25].

There are several neural network classifiers that derive data from the EEG by data pre-processing. Examining the capability to classify sleep stages in infants using artificial neural networks, Pfurtscheller et al. reported a 65-80% accuracy in the classification of EEG patterns into 6 classes [26]. In Boston, EOG (electrooculogram) and EMG (electromyogram) data in addition to EEG patterns were used for neural network training to study sleep stages. The investigators achieved a remarkable accuracy of 93.3% [27].

Otorhinolaryngology

Neural networks have proven to be a new and effective method for modeling hearing [28]. This technique could become useful for understanding, modeling and treating speech and hearing impairments [29,30].

Hearing-aids can well be improved by using neural networks for noise filtering and optimization of parameter settings [31].

Obstetrics and Gynecology

Benesova et al. used neural networks to determine the teratogenity of perinatal administrated drugs [32]. Lapeer and his group applied neural networks for similar predictive tasks, attempting to pick out perinatal parameters influencing birthweight [33].

Ophthalmology

Maeda et al. applied neural networks to videokeratography pattern interpretation in the diagnosis of shape abnormalities of the cornea that relate to several abnormalities. Cornea maps (183) were divided into a training set (108) and a test set (75). The network achieved correct classification for all the maps in the training set, and an 80% rate for the test set. Slightly better results were observed in automated visual field diagnosis using neural network analysis[34].

Radiology

To date, the application of neural networks seems to be most interesting and most powerful in the field of radiology. Images contain much information and they are so complicated that it's all but impossible to interpret them using conventional rule based systems. By selecting an appropriate training set and learning process, neural network modeling becomes suitable for noise filtering and for recognition of unusual images.

For cold lesion detection and localization in SPECT images a neural network was trained using images with different sizes and noise levels. The network scanned the whole image and recognized alterations with a high sensitivity, and with only a few false-positive errors [35]. Another specific application uses a back propagation algorithm for the detection of 7 coronary artery disorders on the basis of myocardial SPECT images. A neural network has also been applied for the detection of microcalcification on digital mammograms. The program is able to locate regions of interest and differentiate pathological alterations from false-positive ones.

Conventional image analysis systems process information row by row. However, newer decision supporting systems use parameters derived from the image by pre-processing. These parameters are obtained from the features of the image.

Abdominal ultrasound and laboratory investigations do not usually provide enough data for the differentiation of liver diseases. Based on ultrasonographic and laboratory findings, a neural network was created to diagnose five classes of liver diseases. The network achieved a recognition accuracy somewhere between the results of residents and those of certified radiologists [36]. Prater et al. reported similar results with ultrasonographic examination of the prostate [37].

In another study, experienced radiologists designed a database classifying 14 features of mammographic images. A back propagation neural network trained by this database achieved a higher classification accuracy then the experienced radiologists [38]. There is also a neural network available for the interpretation of breast cancer ultrasonographic images. Data for the training for this network was also obtained by feature extraction pre-processing.

Pathology

Dawson et al. created a neural network to establish the grading of breast carcinoma. They examined features extracted from light microscopic images [39]. A similar technique used to differentiate tubular carcinoma from sclerosing adenosis seems also to be useful [40]. According to Wolberg et al. routine diagnosis of breast cancer can be aided by neural networks [41]. Kolles created a system for grading astrocytomas based on immunohistochemically and DNA stained microscopic images [42]. Even prostate cancer spread can be evaluated using neural networks [43].

Analysis of DNA flow cytometric histograms by neural networks yields benefits in breast cancer screening and estimating risk. In a study reported from Australia, patients were divided into low risk and high risk groups. To increase diagnostic precision, neural network analysis was used in conjunction with conventional statistical rule-based techniques [44].

Cytology

Perhaps the most widely-known application of neural networks in medicine is the PAPNET system. It is designed and used for automated cytological screening of cervical smears. Boon pointed out that the number of false-negative cases can be reduced using the PAPNET for revising negative cases [45]. Brouwer's work confirms that malignant cervical cells can be recognised by neural networks [46].

In our own work, we compared the usefulness of linear discriminant analysis and back propagation neural networks for the evaluation of parameters that were obtained by quantitative morpho- and densitometric cytological examination of gastric imprint smears. According to our results neural networks yield slightly better results compared to traditional statistical techniques in the classification of normal, dysplastic and malignant cases [47].

Genetics

Errington and Graham trained a neural network for chromosome classification based on pre-processed data representing the shape, size and banding of chromosomes [48]. They stated in an earlier publication that the classification accuracy of a neural network can be improved by redesigning the training set; however traditional algorithms must be redefined in the event of inaccurate operation [49].

Burstein et al. designed a neural network model for studying the entire spatial and temporal embryogenesis and genetic pattern formation in Drosophila [50].

Clinical chemistry

Intelligent evaluation of the results from clinical chemistry analysers and programmed answers for unexpected events has been the subject of several studies [51,52]. Neural networks created the conditions for automatic result control and the subsequent need for further determinations [53]. By automated evaluation of electrophoretic patterns, effectiveness and efficiency is increased [54,55]

Biochemistry

The ProCANS (Protein Classification Artificial Neural Networks) system has been designed for superfamily classification of proteins. Training was based on the official protein sequence database (Protein Identification Resource). The performance of the network on the Cray supercomputer was convincing: 90% classification accuracy and less than 0.1 seconds per sequence classification rate [56].

The relationship of primary protein structure to the features of complex organisation is well-known. However, the laws of this mechanism are currently unknown. A simple back propagation neural network was trained based on the features and amino acid sequences of two types of oligopeptide chains each containing 130 amino acids. The study determined that neural networks are suitable for representation of amino acid sequence - structure relation [57].

STEPS AND TOOLS IN NEURAL NETWORK RESEARCH

The starting point of designing a neural network is the definition of the problem to be evaluated. When working with bioelectrical signals, collecting and measuring data has its difficulties. Routine diagnostic systems pre-process measured signals immediately after obtaining them, providing only calculated and determined parameters. Conventional evaluation techniques use these modified parameters. However, pre-processing of these signals results in an alteration in the information content of the original data.

After obtaining the original measured signal (or derived parameters if they are clearly suitable) a training set should be designed with enough data to control for biological variability. Reference methods should be used for the determination of 'required values' (namely the required classes) of the training set. The whole group of samples should be divided into training and test groups.

Definition and training of neural networks can be made with the help of custom-developed modules, shareware or commercial software packages. Among these the Stuttgarter Neural Network Simulator (SNNS) is widely used and can be accessed free via the Internet. For a more professional purpose, NeuralWorks Professional Plus (NeuralWare Inc, Pittsburgh, USA) or ANSIM (Science Application International Corporation, California, USA) are available among many others. The Gerenia program package is a promising development in Hungary (Aktív Rekord Kft, Budapest, Hungary).

User manuals, references and literature can help the user in selecting the best model and training parameters.

NEURAL NETWORKS: ARTIFICIAL INTELLIGENCE IN THE FUTURE?

As yet, neural networks have not broken through many of the barriers to applied sciences. This technique was been applied only for testing mathematical models developed for simple problem solution in practice. Application of neural networks must currently be supported by conventional mathematical methods. In this way, neural networks can result in more success in pattern recognition and classification compared to purely conventional techniques. To become more widespread, development of new models are required that are able to manage complicated and complex real-world problems.

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