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Madrid, Spain, October 2001
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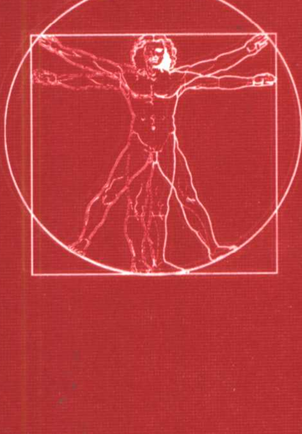

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Jose Crespo
Victor Maojo
Polytechnical University of Madrid
Artificial Intelligence Laboratory, Medical Informatics Group
28660 - Boadilla del Monte (Madrid), Spain
E-mail: {jcrespo/vmaojo}@fi.upm.es

Fernando Martin
Institute of Health Carlos III, Health Bioinformatics Unit
Ctra. de Majadahonda-Pozuelo Km.2
28220 Majadahonda (Madrid), Spain
E-mail: fmartin@isciii.es

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Preface

The 2nd International Symposium on Medical Data Analysis (ISMDA 2001) was the continuation of the successful ISMDA 2000, a conference held in Frankfurt, Germany, in September 2000. The ISMDA conferences were conceived to integrate interdisciplinary research from scientific fields such as statistics, signal processing, medical informatics, data mining, and biometrics for biomedical data analysis. A number of academic and professional people from those fields, including computer scientists, statisticians, physicians, engineers, and others, realized that new approaches were needed to apply successfully all the traditional techniques, methods, and tools of data analysis to medicine.

ISMDA 2001, as its predecessor, aimed to provide an international forum for sharing and exchanging original research ideas and practical development experiences. This year we broadened the scope of the conference, to included methods for image analysis and bioinformatics. Both are exciting scientific research fields and it was clear to the scientific committee that they had to be included in the areas of interest.

Medicine has been one of the most difficult application areas for computing. The number and importance of the different issues involved suggests why many data analysis researchers find the medical domain such a challenging field. New interactive approaches are needed to solve these problems.

In ISMDA 2001 we tried to enhance this interdisciplinary approach. Scientists from many areas submitted their papers. After a thorough peer-review process, 46 papers were selected for inclusion in the final program. We evaluated the 72 submitted papers according to their scientific originality, clear methodology, relevance, and results. All the papers were reviewed by at least two reviewers from the scientific committee and by additional reviewers. In addition, the volume contains three keynote lectures written by relevant invited speakers in areas of special interest. We did not include posters or "short papers" in the conference program. Thus, it was our aim that all the approved papers selected by the reviewers had a significant scientific content for their inclusion within the symposium proceedings.

We would like to thank all the people, institutions, and sponsors that have contributed to this symposium. Authors, members of the conference committees, additional reviewers, keynote speakers, and organizers collaborated in all aspects of the conference. Finally, we are specially grateful to SEIS, the Spanish Health Informatics Society, and its Executive Board, whose members have enthusiastically supported the conference from the very beginning.

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Medical Analysis and Diagnosis by Neural Networks

Rüdiger W. Brause

J.W. Goethe-University, Computer Science Dept.,
Frankfurt a. M., Germany.
Brause@cs.uni-frankfurt.de

Abstract. In its first part, this contribution reviews shortly the application of neural network methods to medical problems and characterizes its advantages and problems in the context of the medical background. Successful application examples show that human diagnostic capabilities are significantly worse than the neural diagnostic systems. Then, paradigm of neural networks is shortly introduced and the main problems of medical data base and the basic approaches for training and testing a network by medical data are described. Additionally, the problem of interfacing the network and its result is given and the neuro-fuzzy approach is presented. Finally, as case study of neural rule based diagnosis septic shock diagnosis is described, on one hand by a growing neural network and on the other hand by a rule based system.

Keywords: Statistical Classification, Adaptive Prediction, Neural Networks, Neurofuzzy Medical Systems

1 Introduction

Almost all the physicians are confronted during their formation by the task of learning to diagnose. Here, they have to solve the problem of deducing certain diseases or formulating a treatment based on more or less specified observations and knowledge. Certainly, there is the standard knowledge of seminars, courses and books, but on one hand medical knowledge outdates quickly and on the other hand this does not replace own experience. For this task, certain basic difficulties have to be taken into account:

- The basis for a valid diagnosis, a sufficient number of experienced cases, is reached only in the middle of a physician's career and is therefore not yet present at the end of the academic formation.
- This is especially true for rare or new diseases where also experienced physicians are in the same situation as newcomers.
- Principally, humans do not resemble statistic computers but pattern recognition systems. Humans can recognize patterns or objects very easily but fail when probabilities have to be assigned to observations.

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These principal difficulties are not widely known by physicians. Also studies who revealed that about 50% of the diagnoses are wrong do not impede the self-conscience of some physicians. It is not by chance that the disease AIDS which manifests by a myriad of infections and cancer states was not discovered directly by treating physicians but by statistical people observing the improbable density of rare cancer cases at the U.S. west coast.

An important solution for the described problem lies in the systematic application of statistical instruments. The good availability of computers ameliorate the possibilities of statistically inexperienced physicians to apply the benefits of such a kind of diagnosis:

- Also physicians in the learning phase with less experience can obtain a reliable diagnosis using the collected data of experienced colleagues.
- Even in the case of rare diseases, e.g. septic shock, it is possible to get a good diagnosis if they use the experience of world-wide networked colleagues.
- New, unknown diseases can be systematically documented even if this induces complex computations which are not known to the treating physician.
- Also in the treatment of standard diseases a critical statistical discussion for the use of operation methods or medical therapies may introduce doubts in the physicians own, preferred methods as it is propagated by the ideas of evidence based medicine EBM16.

A classical, early study 8 in the year 1971 showed these basic facts in the medical area. At the university clinic of Leeds (UK) 472 patients with acute abdominal pain where examined and diagnosed. With simple, probability-based methods (Bayes classification) the diagnostic decision probabilities were computed based on a data base of 600 patients. Additionally, a second set of probabilities were computed by using a synthetic data base of patients build on the interviews of experts and questionnaire sheets about 'typical' symptoms.

Then, the 472 cases were diagnosed by an expert round of 3 experienced and 3 young physicians. The results of this experiment was as follows:

- Best human diagnosis (most experienced physician): *79.7%*
- Computer with expert data base: *82.2%*
- Computer with 600 patient data: *91.1%*

The conclusion is clear: humans can not ad hoc analyze complex data without errors. Can neural networks help in this situation?

2 The Prognostic Capabilities of Neural Networks

Let us shortly review the prognostic capabilities of adaptive systems like those of neural networks. There is a long list of successful applications of neural networks in medicine, e.g. 13,27. Examples are given below:

Myocardial Infarction [1]

From 356 patients of a heart intensive care unit 120 suffered from acute myocardial infarction. Based on these data, Baxt (1990) trained a network and obtained a sensitivity of 92% and a specificity of 96% for heart attack prediction.

Back Pain [3]

145 responses of a questionnaire represented the input, 4 possible diagnosis results were the output (simple lower back pain SLBP, root pain RP, spinal pain SP, abnormal illness behavior AIB). After training with 50 example cases the following correct percentage for 50 test cases were observed (Table 1):

Table 1 Diagnostic correctness of back pain

Method	SLBP %	RP %	SP %	AIB %	average %
Network	63	90	87	95	83
Neuro-surgeon	96	92	60	80	82
orthoped. surg.	88	88	80	80	84
common phys.	76	92	64	92	81

For this application, the network has (in the average) roughly the same success as the human, experienced experts. Nevertheless, for the non-critical case of simple lower back pain the network was worse than the physicians; for the important case of spinal symptoms where a quick intervention is necessary the network was better than the experts.

- **Survival probability** after severe injury [21]
- For 3 input variables (Revised Trauma Score RTS, Injury Severity Score ISS, age) and 2 output variables (life, death) a network was trained with 4800 examples. Compared to the traditional score method TRISS and a variant ASCOT which separate special risk groups before scoring, resulted in the following diagnostic scores for juvenile patients (Table 2):

Table 2 Diagnostic success for severe injury of juvenile patients

Diagnose	TRISS	ASCOT	NNet
sensitivity %	83,3	80,6	90,3
specificity %	97,2	97,5	97,5

The significant higher sensitivity of the neural network can be deduced to the superiority of the adaptive approach of the neural net compared to the fixed linear weighting of the scores (as e.g. APACHE). A linear weighting corresponds to only one layer of linear neurons (e.g. the *output layer*); the categorical score input corresponds to fixed nonlinear neurons (e.g. the *hidden units*).

Beside the high number of successful medical applications (MedLine [18] listed about 1700 papers for the keywords "artificial neural network" in spring 2001) there are many reviews for the use of artificial neural networks in medicine, see e.g. [9,24,26]. In this contribution, only the basic principles of neural networks will be presented in the next section in order to set the base for applications like the one in section 4.

3 Basic Principles of Neural Networks

Let us start by modelling the artificial neurons. Like in nature neural networks consist of many small units, the formal neurons. They are interconnected and work together. Each neuron has several inputs and one output only. In Fig. 1 a biological neuron and an artificial neuron are shown.

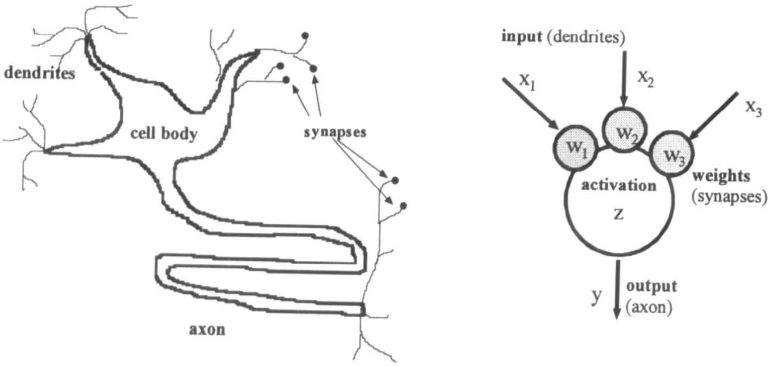

Fig. 1 A biological neuron and an artificial one

Our formal neuron has inputs x_i, each one weighted by a weight factor w_i. We model all of the neural inputs from the same neighbour neuron by just one weighted input. Typically, the activation z is modelled by a weighted sum of the n inputs

$$z = \sum_{i=1}^{n} w_i x_i \tag{1}$$

The output activity y is a function S of the activation, generally a nonlinear one.

Nonlinear predictions are provided by nonlinear neurons, i.e. neurons with a nonlinear function $S_i(z)$ for the i-th neuron, e.g. a radial basis function (RBF)

$$S_i(z) = e^{-z^2} \text{ with } z^2 = \frac{(\mathbf{c}_i - \mathbf{x})^2}{2\sigma_i^2} \tag{2}$$

This bell-shaped function provides a local sensitivity of each neuron i for an area of width σ_i centred at point $\mathbf{c}_i$.

If we arrange several neurons in parallel and then in different layers, we get a mapping from input to output ("feedforward network"). Given a certain task, what kind of network should we choose? To resolve this question, we should know: what is in general the power of a network? For a two layer network (Fig. 2) containing at least one nonlinear layer we know that we can approximate any function as close as desired. For a more precise notation of this property, see e.g. [15].

For our purpose, we have to decide whether we want to solve a classification or prediction task, based on a number of known cases, or if we want to make a kind of data mining approach, discovering new proportions of the data. In the first case we should take a multi-layer decision network with a learning algorithm based on the classification probability, not on a distance measure like the mean square error of approximation. The classification might be done either by a multi-layer-perceptron MLP or a radial basis function network RBF, see [12]. In either case, the network is trained to do a certain classification job by presenting the patient data and the correct classification to the network. It is the task of the network to predict the class of an unknown patient from the presented data, giving rise to appropriate treatments.

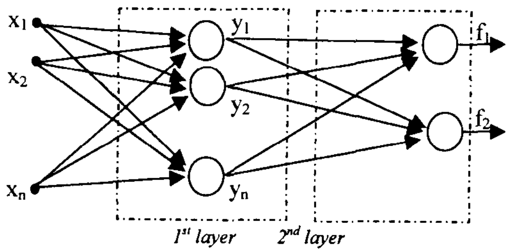

Fig. 2 A two-layer network

Preprocessing the Data

Very important for medical data analysis, especially for retrospective evaluations, is the preprocessing of the data, see [23]. The problems are listed below.

- The **data set** in single studies is often **too small** to produce reliable results.
- Often, medical data material is very **inhomogeneous**, coming from multivariate time series with irregularly measured time stamps.
- **Typing errors** are detected by checking bounds of the variables.
- A lot of variables shows a high number of **missing values** caused by faults or simply by seldom measurements.
- **Feature variables** should be **selected** to avoid the so called "curse of dimensionality"

For our task we heavily rely on the size of the data and their diagnostic quality. If the data contains too much inaccurate or missing entries we have no chance of building up a reliable system even if it is principally possible.

Training and Testing

In general, the networks have to be trained in order to get the parameters set for a proper function. We distinguish between two modes: the *supervised training* where we add to each training sample input (patient data) also the desired network output information (e.g. the correct classification), and the *unsupervised training* which is used to extract statistical information from the samples. The latter is often used for signal preprocessing, e.g. PCA and ICA, see [12].

How do we get the parameters of the chosen network, e.g. σ_i and $\mathbf{c}_k$ of eq.(2) ? 1 **Changing the parameters** at fixed network: The parameters are updated such that an objective function R(w) is optimised. 2 **Growing networks** with fixed parameters: Starting with one neuron, for each data sample which causes a high error in the prediction a new neuron is added to the network. All parameters are set such that the error is decreased.

It is well known that the performance of learning systems on the training data often does not reflect the performance on unknown data. This is due to the fact that the system often adapts well on training to the particularities of the training data. Therefore, the training data should be randomly chosen from all available data. It should represent the typical data properties, e.g. the probability distribution. If you have initially a bias in the training data you will encounter performance problems for the test data later.

In order to test the real generalization abilities of a network to unknown data, it must be tested by classified, but yet unknown data, the *test data* that should not contain samples coming from patients of the training data. We have to face the fact that patient data is very individual and it is difficult to generalize from one patient to another. Ignoring this fact would pretend better results than a real system could practically achieve.

Interfacing the Results

One of the most important questions for diagnosis is the design of the user interface. Why?

Neural networks are seldom designed to explain what they have learned. The approach of using the experience of the physician and explaining the diagnosis by proper medical terms is crucial for the question whether a diagnostic system is used or ignored. In general, all diagnostic systems, even the most sophisticated ones, are worthless if they are not used. So, the importance of acquiring the necessary knowledge and presenting the results in a human understandable, easy way can not be overestimated.

Now, with the appearance of fuzzy systems which use vague, human-like categories [20] the situation for knowledge-based diagnosis has changed. Based on the well-known mechanisms of learning in RBF networks, a neuro-fuzzy interface can be used for the input and output of neural systems. The intuitive and instructive interface is useful in medical applications, using the notation and habits of physicians and other medically trained people. In Fig. 3 this concept is visualized.

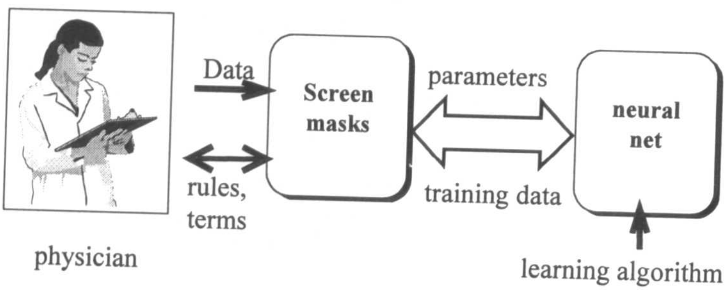

Fig. 3 Interactive transfer of vague knowledge

Here, the user interface must use the typical human properties and formulate the diagnosis by the vague, inexact language of physicians. The following notational habits of physicians for variables and possible outcomes have to be reflected by the user interface: