MACHINE LEARNING IN MEDICAL APPLICATIONS

George D. Magoulas[1] and Andriana Prentza[2]

[1] *Department of Informatics, University of Athens, GR-15784 Athens, Greece*
E-mail: magoulas@di.uoa.gr

[2] *Department of Electrical and Computer Engineering*
National Technical University of Athens, GR-15773 Athens, Greece
E-mail: aprentza@biomed.ntua.gr

ABSTRACT

Research in Machine Learning methods to-date remains centered on technological issues and is mostly application driven. This letter summarizes successful applications of machine learning methods that were presented at the *Workshop on Machine Learning in Medical Applications*. The goals of the workshop were to foster fundamental and applied research in the application of machine learning methods to medical problem solving and to medical research, to provide a forum for reporting significant results, to determine whether Machine Learning methods are able to underpin the research and development on intelligent systems for medical applications, and to identify those areas where increased research is likely to yield advances. A number of recommendations for a research agenda were produced, including both technical and human-centered issues.

INTRODUCTION

Machine Learning (ML) aims at providing computational methods for accumulating, changing and updating knowledge in intelligent systems, and in particular learning mechanisms that will help us to induce knowledge from examples or data. Machine learning methods are useful in cases where algorithmic solutions are not available, there is lack of formal models, or the knowledge about the application domain is poorly defined.

The fact that various scientific communities are involved in ML research led this scientific field to incorporate ideas from different areas, such as computational learning theory, artificial neural networks, statistics, stochastic modeling, genetic algorithms and pattern recognition. Therefore, ML includes a broad class of methods that can be roughly classified in symbolic and subsymbolic (numeric) according to the nature of the manipulation which takes place whilst learning.

The symbolic learning methods differ, in a theoretical sense, in the amount of knowledge required and in the level of inference performed. Inductive learning of symbolic rules, such as induction of rules (Clark and Niblett, 1989), decision trees (Quinlan, 1986), and logic programs (Lavrač and Dzeroski, 1994), statistical or pattern recognition methods, such as k-nearest neighbors or instance-based learning (Aha *et al.*, 1991; Dasarathy, 1990), discriminate analysis and Bayessian classifiers, are examples of symbolic learning methods.

On the other hand, artificial neural networks (Rumelhart *et al.*, 1986), genetic algorithms (Goldberg, 1989; Wnek and Michalski, 1994), probabilistic models (Weiss and Kulikowski, 1991) and reinforcement learning (Cichosz, 1995) belong to the subsymbolic category. Various attempts have been made to combine symbolic and subsymbolic learning algorithms to exploit the advantages of both categories, as for example in (Cios and Liu, 1992; Sankar and Mammone, 1991). A number of popular ML methods and examples of their applications are presented in the review papers of Kubat *et al.*, (1996) and Dutton *et al.* (1996). Another important contribution is the work of Dietterich (Dietterich, 1997) that provides an extensive discussion on important research issues related to the theory and practice of ML methods.

The diffusion of ML in various application areas is a subject of considerable ongoing research. The next section gives a brief overview of successful ML applications in medicine. Then, highlights of a one-day *Workshop on Machine Learning in Medical Applications* held on July 15th, 1999 and hosted by the ECCAI Advanced Course on Artificial Intelligence for 1999 (ACAI-99) are presented. This letter concludes with a general discussion on the development and use of ML methods in a medical context.

IMPLEMENTING MACHINE LEARNING METHODS IN A MEDICAL CONTEXT

ML provides methods, techniques, and tools that can help solving diagnostic and prognostic problems in a variety of medical domains. ML is being used for the analysis of the importance of clinical parameters and of their combinations for prognosis, e.g. prediction of disease progression, for the extraction of medical knowledge for outcomes research, for therapy planning and support, and for overall patient management. ML is also being used for data analysis, such as detection of regularities in the data by appropriately dealing with imperfect data, interpretation of continuous data used in the Intensive Care Unit, and for intelligent alarming resulting in effective and efficient monitoring. It is argued that the successful implementation of ML methods can help the integration of computer-based systems in the healthcare environment providing opportunities to facilitate and enhance the work of medical experts and ultimately to improve the efficiency and quality of medical care. Below, we summarize some major ML application areas in medicine.

Medical diagnostic reasoning is a very important application area of computer-based systems (Kralj and Kuka, 1998; Strausberg and Person, 1999; Zupan *et al.*, 1998). In this framework, expert systems and model-based schemes provide mechanisms for the generation of hypotheses from patient data. For example, rules are extracted from the knowledge of experts in the expert systems. Unfortunately, in many cases, experts may not know, or may not be able to formulate, what knowledge they actually use in solving their problems. Symbolic learning techniques (e.g. inductive learning by examples) are used to add learning, and knowledge management capabilities to expert systems (Bourlas *et al.*, 1996). Given a set of clinical cases that act as examples, learning in intelligent systems can be achieved using ML methods that are able to produce a systematic description of those clinical features that uniquely characterize the clinical conditions. This knowledge can be expressed in the form of simple rules, or often as a decision tree. A classic example of this type of system is KARDIO, which was developed to interpret ECGs (Bratko *et al.*, 1989).

This approach can be extended to handle cases where there is no previous experience in the interpretation and understanding of medical data. For example, in the work of Hau and Coiera (Hau and Coiera, 1997) an intelligent system, which takes real-time patient data obtained during cardiac bypass surgery and then creates models of normal and abnormal cardiac physiology, for detection of changes in a patient's condition is described. Additionally, in a research setting, these models can serve as initial hypotheses that can drive further experimentation.

Learning from patient data encounters several difficulties, since these datasets are characterized by incompleteness (missing parameter values), incorrectness (systematic or random noise in the data), sparseness (few and/or non-representable patient records available), and inexactness (inappropriate selection of parameters for the given task). ML provides tools for dealing with these characteristics of medical datasets (Lavrač, 1998). Subsymbolic learning methods, especially neural networks are able to handle these datasets and are mostly used for their pattern matching abilities and their human like characteristics (generalization, robustness to noise), in order to improve medical decision making (Akay *et al.*, 1994; Lim *et al.*, 1997; Micheli-Tzanakou *et al.*, 1993; Pattichis *et al.* 1995; Reategui *et al.*, 1996).

Another field of application is biomedical signal processing (Dawant *et al.*, 1990; Gindi *et al.*, 1991; Guo *et al.*, 1994; Kennedy *et al.*, 1997; Nekovei and Sun, 1995; Prentza and Wesseling, 1995; Rayburn *et al.* 1990; Yeap *et al.*, 1990). Since our understanding of biological systems is not complete, there are essential features and information hidden in the physiological signals which are not readily apparent. Also, the effects between the different subsystems are not distinguishable. Biological signals are characterized by substantial variability, caused either by spontaneous internal mechanisms or by external stimuli. Associations between the different parameters may be too complex to be solved with conventional techniques. ML methods rely on these sets of data, which can be produced easier, and can help to model the nonlinear relationships that exist between these data, and extract parameters and features which can improve medical care.

Computer-based medical image interpretation systems comprise a major application area providing significant assistance in medical diagnosis (Coppini *et al.*, 1995; Hanka, *et al.*, 1996; Ifeachor and Rosen, 1994; Innocent *et al.*, 1997; Karkanis *et al.* 1999; Lo *et al.*, 1995; Miller *et al.*, 1992; Phee *et al.*, 1998; Veropoulos *et al*, 1998; Zhu and Yan, 1997). In most cases, the development of these systems is considered as an attempt to emulate the doctor's expertise in the identification of malignant regions in minimally invasive imaging procedures (e.g., computed tomography, ultrasonography, endoscopy, confocal microscopy, computed radiography or magnetic resonance imaging). The objective is to increase the expert's ability to identify cancer regions while decreasing the need for intervention, and maintaining the ability for accurate diagnosis. Furthermore, it may be possible to examine a larger area, studying living tissue *in vivo*, possibly at a distance (Delaney, *et al.*, 1998), and thus minimize the shortcomings of biopsies, such as discomfort for the patient, delay in diagnosis, and limited number of tissue samples. The need for more effective methods of early detection such as those that computer assisted medical diagnosis systems aim to provide is obvious.

In general, it seems that as the healthcare environment is becoming more and more reliant on computer technology, the use of ML methods can provide useful aids to assist the physician in many cases, eliminate issues associated with human fatigue and habituation, provide rapid identification of abnormalities and enable diagnosis in real time.

THE PAPERS

The *Workshop on Machine Learning in Medical Applications* was held on July 15th, 1999 at Chania, Island of Crete, in Greece, and aimed at presenting some of the advances that have been achieved in the field of application of ML methods in medicine. The workshop comprised eleven referred papers and one invited, which looked at the theories and approaches that underpin the use of ML methods in the medical context. Next, a brief description of these contributions is presented.

M. Schurr, from the Section for Minimal Invasive Surgery of the Eberhard-Karls-University of Tuebingen, gave an invited talk on endoscopic techniques and the role of ML methods in this context. He referred to current limitations of endoscopic techniques, which are related to the restrictions of access to the human body, associated to endoscopy. In this regard, the technical limitations include: restrictions of manual capabilities to manipulate human organs through a small access, limitations in visualizing tissues and restrictions in getting diagnostic information about tissues. To alleviate these problems, international technology developments focus on the creation of new manipulation techniques involving robotics and intelligent sensor devices for more precise endoscopic interventions. It is acknowledged that this new generation of sensor devices contributes to the development and spread of intelligent systems in medicine by providing ML methods with data for further processing. Current applications include suturing in cardiac surgery, and other clinical fields. It was mentioned that particular focus is put by several research groups on the development of new endoscopic visualizing and diagnostic tools. In this context, the potentials of new imaging principles, such as fluorescence imaging or laser scanning microscopy, and machine learning methods are very high. The clinical idea behind these developments is early detection of malignant lesions in stages were local endoscopic therapy is possible. Technical developments in this field are very promising, however, clinical results are still pending and ongoing research will have to clarify the real potential of these technologies for clinical use.

Moustakis and *Charissis'* work (Moustakis and Charissis, 1999) surveyed the role of ML in medical decision making and provided an extensive literature review on various ML applications in medicine that could be useful to practitioners interested in applying ML methods to improve the efficiency and quality of medical decision making systems. In this work the point of getting away from the accuracy measures as sole evaluation criteria of learning algorithms was stressed. The issue of comprehensibility, i.e. how well the medical expert can understand and thus use the results from a system that applies ML methods, is very important and should be carefully considered in the evaluation.

The paper by *Alexopoulos*, *Dounias*, and *Vemmos* (Alexopoulos *et al.*, 1999) was focused on the application of inductive ML methods in medical diagnosis of stroke. The proposed approach was based on the See5 algorithm, which is an updated version of the C4.5 algorithm. In the experiments reported, this approach showed the capability to learn from examples and to handle missing information by constructing a decision tree, which was possible to be transformed to IF/THEN rules. Special attention was given to the determination of the complexity and comprehensibility of the acquired decision rules, in collaboration with medical experts.

In the paper of *Zelič, Lavrač, Najdenov,* and *Rener-Primec* (Zelič *et al.*, 1999) ML methods, like the Mangus assistant decision tree learner and the Bayessian classifier, were used for the diagnosis and prognosis of first cerebral paroxysm. Despite the fact that best predictions were obtained using the naïve Bayessian classifier, the most interesting results from a medical point of view were achieved using the Magnus Assistant decision tree learner. Data and attributes which were considered by expert neurologists as obvious and meaningless turned out to be very important for automatic diagnosis and prognosis. In this case, ML methods provided a different estimation of some clinical attributes and motivated clinicians to generate new hypotheses and ultimately to improve their standard diagnostic and prognostic processes.

An interactive system for the ascertainment of visual perception disorders was presented in the paper of *Ruseckaite* (Ruseckaite, 1999). The system performed data analysis and extracted interesting dependencies between visual perception disorder and damage of the brain by applying a modified version of the ML algorithm Charade. Preliminary results indicated the effectiveness of the proposed approach in rehabilitating persons with certain brain anomalies.

Bourlas, Giakoumakis, and *Papakonstantinou* (Bourlas *et al.*, 1999) extended previous work on medical expert systems for ECG diagnosis by incorporating ML methods to continuously improve the knowledge base of a medical expert system. Their new system exhibited continual learning capabilities using an extended version of the ID3 algorithm to extract from time to time a set to diagnosis rules based on a training set of ECGs. The extracted rules were merged into the older ones and the duplicates were removed. In order to optimize the performance of the system, a knowledge management subsystem provided monitoring of the performance of the final rules, in terms of their diagnostic accuracy, and modified the knowledge base.

The work of *Neves, Alves, Nelas, Romeu,* and *Basto* (Neves *et al.,* 1999) demonstrated the need for Health Care Unit's medical imaging models and introduced the concept of a generic and deductive/inductive model of operation, which supports scheduling, forecasting, and accounting. Following this approach, several agents concurred in generating hypotheses, each one of them having a different role in evaluating parts of the data, and neural networks were used to discover associations in the dataset.

Asteroth and *Möller* (Asteroth *et al.*, 1999) investigated the use of neural network-based approximation of structural information to the identification of individualized models of the human cardiovascular system. This approach allowed them to achieve robust real-time identification.

The problem of identifying the structure of a population of patients with brain disorder was investigated in the paper of *Pranckeviciene* (Pranckeviciene, 1999). The similarity among patients electroencephalograms (EEGs) was evaluated by a single layer neural network. Experiments indicated that this approach successfully revealed similarities in the electrical activity of the brain of different patients.

In the paper of *Jankowski* (Jankowski, 1999) the use of incremental neural networks was suggested for approximation and classification tasks. The proposed model was based on neurons with a new form of rotated bi-radial transfer functions and was dynamically generated to match the complexity of the training data. The model exhibited superior generalization performance when compared with other popular methods for the classification of medical data in the simulations.

The last two papers proposed the use of textural descriptors for the discrimination of cancer regions in endoscopic images. In the paper of *Karkanis, Magoulas, Grigoriadou,* and *Schurr* (Karkanis *et al.,* 1999) a simple scheme consisting of a feature extraction stage and a classification stage was applied. Second order gray level statistics were used for the texture description and a multi-layer feedforward neural network was employed to detect abnormalities in colonoscopic images with high accuracy.

The paper of *Karkanis, Galousi,* and *Maroulis* (Karkanis *et al.,* 1999a) outlined a new approach to texture classification applied on lung endoscopic images. Feature selection was based on the texture spectrum of the image and a clustering method was used to distinguish the features with the most discriminative ability.

DISCUSSION

The workshop gave the opportunity to researchers working in the ML field to get an overview of current work of ML in medical applications and/or gain understanding and experience in this area. Furthermore, young researchers had the opportunity to present their ideas, and received feedback from other workers in the area. The participants acknowledged that the diffusion of ML methods in medical applications can be very effective in improving the efficiency and the quality of medical care, but it still presents problems that are related to both theory and applications.

From a theoretic point of view, it is important to enhance our understanding of ML algorithms as well as to provide mathematical justifications for their properties, in order to answer fundamental questions and acquire useful insight in the performance and behavior of ML methods.

On the other hand, some major issues which concern the process of learning knowledge in practice are the visualization of the learned knowledge, the need for algorithms that will extract understandable rules from neural networks, as well as algorithms for identifying noise and outliers in the data. The participants also mentioned some other problems that arise in ML applications and should be addressed, like the control of overfitting and the scaling properties of the ML methods so that they can apply to problems with large datasets, and high-dimensional input (feature) and output (classes-categories) spaces.

A recurring theme in the recommendations made by the participants was the need for comprehensibility of the learning outcome, relevance of rules, criteria for selecting the ML applications in the medical context, the integration with the patient records and the description of the appropriate level and role of intelligent systems in healthcare. These issues are very complex, as technical, organizational and social issues become intertwined. Previous research and experience suggests that the successful implementation of information systems (e.g., (Anderson, 1997; Pouloudi, 1999)), and decision support systems in particular (e.g., (Lane *et al.*, 1996; Ridderikhoff and van Herk, 1999)), in the area of healthcare relies on the successful integration of the technology with the organizational and social context within which it is applied. Medical information is vital for the diagnosis and treatment of patients and therefore the ethical issues presented during its life cycle are critical. Understanding these issues becomes imperative as such technologies become pervasive. Some of these issues are system-centered, i.e., related to the inherent problems of the ML research. However, it is humans, not systems, who can act as moral agents. This means that it is humans that can identify and deal with ethical issues. Therefore, it is important to study the emerging challenges and ethical issues from a human-centered perspective by considering the motivations and ethical dilemmas of researchers, developers and medical users of ML methods in medical applications.

REFERENCES

Aha, D., Kibler, D., and Albert, M. (1991). "Instance-based learning algorithms". *Machine Learning,* 6, 37-66.

Akay, Y.M., Akay, M., Welkowitz, W., and Kostis, J.B. (1994). "Noninvasive detection of coronary artery disease using wavelet-based fuzzy neural networks". *IEEE Engineering in Medicine and Biology*, 761-764.

Alexopoulos, E., Dounias, G.D., and Vemmos, K. (1999). "Medical diagnosis of stroke using inductive machine learning". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 20-23.

Anderson, J.G. (1997). "Clearing the way for physician's use of clinical information systems". *Communications of the ACM*, 40, 8, 83-90.

Asteroth, A. and Möller, K. (1999). "Identification of individualized models of the human cardiovascular system". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 43-48.

Bourlas, Ph., Sgouros, N., Papakonstantinou, G., and Tsanakas, P. (1996). "Towards a knowledge acquisition and management system for ECG diagnosis". In *Proceedings of 13th International Congress Medical Informatics Europe-MIE96*, Copenhagen.

Bourlas, Ph., Giakoumakis, E., and Papakonstantinou, G. (1999). "A knowledge acquisition and management system for ECG diagnosis". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 30-36.

Bratko, I., Mozetic, I., and Lavrač, N. (1989). *KARDIO: A study in deep and qualitative knowledge for expert systems*, Cambridge, Massachusetts: MIT Press.

Cichosz, P. (1995). "Truncating temporal differences: on the efficient implementation of the TD(λ) for reinforcement learning". *Journal of AI Research*, 2, 287-318.

Cios, K. and Liu, N. (1992). "A machine learning method for generation of a neural network architecture: a continuous ID3 algorithm". *IEEE Transactions on Neural Networks,* 3, 2, 280-290.

Clark, P. and Niblett, T. (1989). "The CN2 induction algorithm". *Machine Learning,* 3, 4, 261-283.

Coppini, G., Poli, R., and Valli, G. (1995). "Recovery of the 3-D shape of the left ventricle from echocardiographic images". *IEEE Transactions on Medical Imaging*, 14, 301-317.

Dasarathy, B.V. (ed.) (1990). *Nearest Neighbor (NN) Norms: NN Pattern Classification Techniques.* IEEE Computer Society Press, Los Alamitos, CA.

Dawant, B.M., Ozkan, M., Sprenkels, H., Aramata, H., Kawamura, K., and Margolin, R.A. (1990). "A neural network approach to magnetic resonance imaging tissue characterization". *Communication, Control, and Signal Processing,* Arikan E., (ed.), 2, 1803-1809, Bilkent University, Ankara, Turkey. Elsevier, Amsterdam.

Delaney, P.M, Papworth, G.D, and King, R.G. (1998). "Fibre optic confocal imaging (FOCI) for in vivo subsurface microscopy of the colon". In *Methods in disease: Investigating the Gastrointestinal Tract,* Preedy, V.R. and Watson, R.R. (eds.), Greenwich Medical Media, London.

Dietterich, T. G. (1997). "Machine learning research: Four current directions". *AI Magazine*, 18, 4, 97-136.

Dutton, D., and Conroy, G. (1996). "A review of machine learning", *The Knowledge Engineering Review,* 12, 4, 341-367.

Gindi, G.R., Darken, C.J., O' Brien, K.M., Sterz, M.L., and Deckelbaum, L.I. (1991). "Neural network and conventional classifiers for fluorescence-guided laser angioplasty". *IEEE Transactions on Biomedical Engineering*, 38, 3, 246-252.

Goldberg, D. (1989). *Genetic Algorithms in Search, Optimization, and Machine Learning.* Addison-Wesley.

Guo, Z., Durant, L.G., Lee, H.C., Allard, L., Grenier, M.C., and Stein, P.D. (1994). "Artificial neural networks in computer-assisted classification of heart sounds in patients with porcine bioprosthetic valves". *Medical, Biological Engineering and Computing*, 32, 311-316.

Hanka, R., Harte, T.P., Dixon, A.K., Lomas, D.J., and Britton, P.D. (1996). "Neural networks in the interpretation of contrast-enhanced magnetic resonance images of the breast". In *Proceedings of Healthcare Computing,* Harrogate, UK, 275-283.

Hau, D., and Coiera, E. (1997). "Learning qualitative models of dynamic systems". *Machine Learning*, 26, 177-211.

Ifeachor, E.C., and Rosen, K. G. (eds.) (1994). *Proceedings of the International Conference on Neural Networks and Expert Systems in Medicine and Healthcare*, Plymouth, UK.

Innocent, P.R., Barnes, M., and John, R. (1997). "Application of the fuzzy ART/MAP and MinMax/MAP neural network models to radiographic image classification". *Artificial Intelligence in Medicine*, 11, 241-263.

Jankowski, N. (1999). "Approximation and classification in medicine with IncNet neural networks". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 53-58.

Karkanis, S., Magoulas, G.D., Grigoriadou, M., and Schurr, M. (1999). "Detecting abnormalities in colonoscopic images by textural description and neural networks". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 59-62.

Karkanis, S., Galoussi, K., and Maroulis, D. (1999a). "Classification of endoscopic images based on texture spectrum". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 63-69.

Kennedy, L.R., Harrison, R.F., Burton, A.M., Fraser, H.S., Hamer, W.G., MacArthur, D., McAllum, R., and Steedman, D.J. (1997). "An artificial neural network system for diagnosis of acute myocardial infarction (AMI) in the accident and emergency department: evaluation and comparison with serum myoglobin measurements". *Computer Methods and Programs in Biomedicine*, 52, 93-103.

Kralj, K. and Kuka, M. (1998). "Using machine learning to analyze attributes in the diagnosis of coronary artery disease". In *Proceedings of Intelligent Data Analysis in Medicine and Pharmacology-IDAMAP98*, Brighton, UK.

Kubat, M., Bratko, I., and Michalski, R. (1996). "A review of machine learning methods". In *Machine Learning and Data Mining: Methods and Applications*, Michalski, R.S., Bratko, I., and Kubat, M. (eds.), John Willey and Sons.

Lane, V.P., Lane, D., and Littlejohns, P. (1996). "Neural networks for decision making related to asthma diagnosis and other respiratory disorders". In *Proceedings of Healthcare Computing*, Harrogate, UK, 85-93.

Lavrač, N. (1998). "Data mining in medicine: Selected techniques and applications". In *Proceedings of Intelligent Data Analysis in Medicine and Pharmacology-IDAMAP98*, Brighton, UK.

Lavrač, N., and Dzeroski, S. (1994). *Inductive Logic Programming: Techniques and Applications.* Ellis Horwood, Chichester.

Lim, C.P., Harrison, R.F., and Kennedy, R.L. (1997). "Application of autonomous neural network systems to medical pattern classification tasks". *Artificial Intelligence in Medicine*, 11, 215-239.

Lo, S.-C. B., Lou, S.-L. A., Lin, J.-S., Freedman, M.T., Chien, M.V., and Mun, S.K. (1995). "Artificial convolution neural network techniques and applications for lung nodule detection". *IEEE Transactions on Medical Imaging*, 14, 711-718.

Micheli-Tzanakou, E., Yi, C., Kostis, W.J., Shindler, D.M., and Kostis, J.B. (1993). "Myocardial infarction: Diagnosis and vital status prediction using neural networks". *IEEE Computers in Cardiology*, 229-232.

Miller, A.S., Blott, B.H., and Hames, T.K. (1992). "Review of neural network applications in medical imaging and signal processing". *Medical and Biological Engineering and Computing*, 30, 449-464.

Moustakis, V. and Charissis, G. (1999). "Machine learning and medical decision making". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 1-19.

Nekovei, R. and Sun, Y. (1995). "Back-propagation network and its configuration for blood vessel detection in angiograms". *IEEE Transactions on Neural Networks*, 6, 1, 64-72.

Neves, J., Alves, V., Nelas, L., Romeu, A., and Basto, S. (1999). "An information system that supports knowledge discovery and data mining in medical imaging". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 37-42.

Pattichis, C., Schizas, C., and Middleton, L. (1995). "Neural network models in EMG diagnosis". *IEEE Transactions on Biomedical Engineering*, 42, 5, 486-496.

Phee, S.J., Ng, W.S., Chen, I.M., Seow-Choen, F., and Davies, B.L. (1998). "Automation of colonoscopy part II: visual-control aspects". *IEEE Engineering in Medicine and Biology*, May/June, 81-88.

Pouloudi, A. (1999). "Information technology for collaborative advantage in health care revisited". *Information and Management*, 35, 6, 345-357.

Pranckeviciene, E. (1999). "Finding similarities between an activity of the different EEG's by means of a single layer perceptron". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 49-52.

Prentza, A. and Wesseling, K.H. (1995). "Catheter-manometer system damped blood pressures detected by neural nets". *Medical and Biological Engineering and Computing*, 33, 589-595.

Quinlan, J.R. (1986). "Induction of decision trees". *Machine Learning,* 1, 1, 81-106.

Rayburn, D.B., Klimasauskas, C.C., Januszkievicz, A.J., Lee, J.M., Ripple, G.R., and Snapper, J.R. (1990). "The use of back propagation neural networks to identify mediator-specific cardiovascular waveforms". In *Proceedings of the International Joint Conference on Neural Networks,* 2, 105-110.

Reategui, E.B., Campbell, J.A., and Leao, B.F. (1996). "Combining a neural network with case-based reasoning in a diagnostic system". *Artificial Intelligence in Medicine,* 9, 5-27.

Ridderikhoff, J. and van Herk, B. (1999). "Who is afraid of the system? Doctors' attitude towards diagnostic systems". *International Journal of Medical Informatics* 53, 91-100.

Rumelhart, D.E. and McClelland, J.L. (eds.) (1986). *Parallel Distributed Processing, Vol. 1: Foundations.* MIT Press, Cambridge, MA: MIT Press.

Ruseckaite, R. (1999). "Computer interactive system for ascertainment of visual perception disorders". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 27-29.

Sankar, A. and Mammone, R. (1991). "Combining neural networks and decision trees". *Applications of Artificial Neural Networks 2,* SPIE, 1469, 374-383.

Strausberg, J. and Person, M. (1999). "A process model of diagnostic reasoning in medicine". *International Journal of Medical Informatics,* 54, 9-23.

Veropoulos, K., Campbell, C., and Learmonth, G. (1998). "Image processing and neural computing used in the diagnosis of tuberculosis". *Colloquium on Intelligent Methods in Healthcare and Medical Applications*, York, UK.

Weiss, S. and Kulikowski, C. (1991). *Computer Systems that Learn-Classification and Prediction Methods from Statistics, Neural Nets, Machine Learning and Expert Systems*, Morgan-Kaufmann.

Wnek, J. and Michalski, R. (1994). "Comparing symbolic and subsymbolic learning: three studies". In *Machine Learning: a multistrategy approach.,* Michalski, R and Tecuci, G. (eds.), 4, Morgan-Kaufmann.

Yeap, T.H., Johnson, F., and Rachniowski, M. (1990). "ECG beat classification by a neural network". In *Proceedings of the 12th Annual International Conference of the IEEE Engineering in Medicine and Biology Society,* 3, 1457-1458, Philadelphia, Pennsylvania, USA.

Zelič, I., Lavrač, N., Najdenov, P., Rener-Primec, Z. (1999). "Impact of machine learning to the diagnosis and prognosis of first cerebral paroxysm". In *Proceedings of Workshop on Machine Learning in Medical Applications, Advance Course in Artificial Intelligence-ACAI99*, Chania, Greece, 24-26.

Zhu, Y. and Yan, H. (1997). "Computerized tumor boundary detection using a Hopfield neural network". *IEEE Transactions on Medical Imaging*, 16, 55-67.

Zupan, B., Halter, J.A., and Bohanec, M. (1998). "Qualitative model approach to computer assisted reasoning in physiology". In *Proceedings of Intelligent Data Analysis in Medicine and Pharmacology-IDAMAP98,* Brighton, UK.