

Machine learning for medical diagnosis: history, state of the art and perspective

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Abstract

The paper provides an overview of the development of intelligent data analysis in medicine from a machine learning perspective: a historical view, a state-of-the-art view, and a view on some future trends in this subfield of applied artificial intelligence. The paper is not intended to provide a comprehensive overview but rather describes some subareas and directions which from my personal point of view seem to be important for applying machine learning in medical diagnosis. In the historical overview, I emphasize the naive Bayesian classifier, neural networks and decision trees. I present a comparison of some state-of-the-art systems, representatives from each branch of machine learning, when applied to several medical diagnostic tasks. The future trends are illustrated by two case studies. The first describes a recently developed method for dealing with reliability of decisions of classifiers, which seems to be promising for intelligent data analysis in medicine. The second describes an approach to using machine learning in order to verify some unexplained phenomena from complementary medicine, which is not (yet) approved by the orthodox medical community but could in the future play an important role in overall medical diagnosis and treatment. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Artificial intelligence is a part of computer science that tries to make computers more intelligent. One of the basic requirements for any intelligent behavior is learning. Most of the researchers today agree that there is no intelligence without learning. Therefore, machine learning [1–4] is one of major branches of artificial intelligence and, indeed, it is one of the most rapidly developing subfields of AI research.

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Machine learning algorithms were from the very beginning designed and used to analyze medical datasets. Today, machine learning provides several indispensable tools for intelligent data analysis. Especially in the last few years, the digital revolution provided relatively inexpensive and available means to collect and store the data. Modern hospitals are well equipped with monitoring and other data collection devices, and data is gathered and shared in large information systems. Machine learning technology is currently well suited for analyzing medical data, and in particular there is a lot of work done in medical diagnosis in small specialized diagnostic problems.

Data about correct diagnoses are often available in the form of medical records in specialized hospitals or their departments. All that has to be done is to input the patient records with known correct diagnosis into a computer program to run a learning algorithm. This is of course an oversimplification, but in principle, the medical diagnostic knowledge can be automatically derived from the description of cases solved in the past. The derived classifier can then be used either to assist the physician when diagnosing new patients in order to improve the diagnostic speed, accuracy and/or reliability, or to train students or physicians non-specialists to diagnose patients in a special diagnostic problem.

The aim of this paper is to provide an overview of the development of the intelligent data analysis in medicine from a machine learning perspective: a historical view, a state-of-the-art view and a view on some future trends in this subfield of applied artificial intelligence, which are, respectively, described in Sections 2–4. None of the three sections is intended to provide a comprehensive overview, but rather describe some subareas and directions which from my personal point of view seem to be important for medical diagnosis. In the historical overview, I emphasize the naive Bayesian classifier, neural networks, and decision trees. Section 3 presents a comparison of some state-of-the-art systems, one or two representatives from each branch of machine learning, when applied to several medical diagnostic tasks. The future trends are illustrated by two case studies. Section 4.1 describes a recently developed method for dealing with reliability of decisions of classifiers, which seems to be promising for intelligent data analysis in medicine. Section 4.2 describes an approach to using machine learning in order to verify some unexplained phenomena from complementary medicine, which is not (yet) approved by the orthodox medical community, but could in the future play an important role in overall medical diagnosis and treatment.

2. Historical overview

As soon as electronic computers came into use in the 1950s and 1960s, the algorithms were developed that enabled modeling and analyzing large sets of data. From the very beginning, three major branches of machine learning emerged. Classical work in symbolic learning is described by Hunt et al. [5], in statistical methods by Nilsson [6], and in neural networks by Rosenblatt [7]. Through the years, all three branches developed advanced methods [2]: statistical or pattern recognition methods, such as the k -nearest neighbors, discriminant analysis, and Bayesian classifiers, inductive learning of symbolic rules, such as top down induction of decision trees, decision rules and induction of logic programs, and artificial neural networks, such as the multilayered feedforward neural network with

backpropagation learning, the Kohonen's self-organizing network, and the Hopfield's associative memory.

2.1. The naive Bayesian classifier

I limit the historical overview of statistical methods to the naive Bayesian classifier. From the very beginning, I was very interested in it. The algorithm is extremely simple but very powerful, and later I discovered that it can provide also comprehensive explanations which was confirmed in long discussions with physicians.

I was fascinated with its efficiency and ability to outperform most advanced and sophisticated algorithms in many medical and also non-medical diagnostic problems. For example, when compared with six algorithms, described in Section 3, the naive Bayesian classifier outperformed all the algorithms on five out of eight medical diagnostic problems [8]. Another example is a hard problem in mechanical engineering, called mesh design. In one study, sophisticated inductive logic programming algorithms achieved modest classification accuracy between 12 and 29% [9,10], while the naive Bayesian classifier achieved 35%. The naive Bayesian classifier became for me a benchmark algorithm that in any medical domain has to be tried before any other advanced method. Other researcher had similar experience. For example, Spiegelhalter et al. [11] were for several man-months, developing an expert system based on Bayesian belief networks for diagnosing the heart disease for newborn babies. The final classification accuracy of the system was 65.5%. When they tried the naive Bayesian classifier, they obtained 67.3%.

The theoretical basis for the successful applications of the naive Bayesian classifier (also called simple Bayes) and its variants was developed by Good [12,13]. We demonstrated the efficiency of this approach in medical diagnosis and other applications [14,15]. But only in the early 1990s, the issue of the transparency (in terms of the sum of information gains in favor or against a given decision) of this approach was also addressed and shown successful in the applications in medical diagnosis [16,17] (Table 2).

Lately, various variants and extensions of the naive Bayesian classifier have been developed. Cestnik [18] developed the *m*-estimate of probabilities that significantly improved the performance of the naive Bayesian classifiers in several medical problems. Kononenko [19] developed a semi-naive Bayesian classifier that goes beyond the "naivety" and detects dependencies between attributes. The advantage of fuzzy discretization of continuous attributes within the naive Bayesian classifier is described in [20]. Langley [21] developed a system that uses the naive Bayesian classifier in the nodes of the decision tree. Pazzani [22] developed another method for explicit searching of dependencies between attributes in the naive Bayesian classifier. The transparency of the naive Bayesian classifier can be further improved with the appropriate visualization [23].

2.2. Neural networks

After Rosenblatt [7] developed a basic delta learning rule for single-layered perceptrons, Minsky and Papert [24] proved that this rule cannot solve nonlinear problems. Only few scientists continued with research of neural networks. The field gained a prominent

impulse with the seminal works of Hopfield [25,26] on associative neural networks and even more with the publication of the backpropagation learning rule for multilayered feedforward neural networks [27]. This learning rule and its variants enabled the use of neural networks in many hard medical diagnostic tasks. However, neural networks were typically used as black box classifiers lacking the transparency of generated knowledge and lacking the ability to explain the decisions. Lately, many advanced variants of neural network algorithms were developed and some do provide for the transparency of decisions [28].

At the very beginning, I was very enthusiastic with neural networks. When I read papers by Hopfield [25,26] and Rumelhart et al. [27] for the first time in my life, I had a feeling that I understand how neurons in the brain can do useful computations. The early inspiration lead to my Ph.D. thesis on Bayesian neural networks [29], but later my research interest moved back to symbolic learning.

2.3. Symbolic learning

Probably the most promising area for medical data analysis was from the very beginning, the symbolic learning of decision trees and decision rules. Hunt et al. [5] used their Concept Learning System (CLS) for building decision trees in medical diagnosis and prognosis. They state as follows (p. 170).

In medicine fairly large files of records may be obtained in the course of routine hospital administration or from a special survey. Such records are often examined in order to plan an intensive, and perhaps expensive, specialized investigation. A drawback to this research strategy is that it is difficult to organize large files of records to reveal complex interactions in a manner that can be understood by the human investigator. Some help can be obtained by using computer oriented techniques of information retrieval, such as program to print selected two- and three-way tables plotting one variable against another. The investigator still must nominate the variable in which he is interested, since such programs have no way of discovering interesting patterns on their own. A CLS program, on the other hand, is designed to do precisely this.

Generating decision trees and decision rules became an active research area after Quinlan [30] developed the famous Iterative Dichotomizer 3 (ID3) algorithm and Michalski and Chilausky [31] successfully applied the system AQ in a plant disease diagnostic task. Bratko and Mulec [32] applied ID3 to a hard diagnostic problem in oncology, and later various descendants of ID3 were developed and successfully applied to various medical diagnostic problems. For example, our system Assistant [14,15] was applied to various problems in oncology (localization of primary tumor, prognosing the recurrence of breast cancer, lymphography), urology (lower urinary tract dysfunctions), and the prognosis of survival in hepatitis. Independently of ID3, Breiman et al. [33] developed the system CART and applied it to several diagnostic and prognostic tasks in cardiology and oncology.

A very incomplete and only illustratory list of applications of machine learning in medical diagnosis in the 1990s include applications in oncology [34], liver pathology [35],

diagnosis of thyroid diseases [36–38], rheumatology [39–41], diagnosing craniostenosis syndrome [42], dermatoglyphic diagnosis [43], cardiology [44–46], neuropsychology [47], gynecology [48], and perinatology [41].

In 1990s, the Relief algorithm and its successors were developed [49–51,53] that enabled the estimation of the quality of each attribute in the context of other attributes. This amazing algorithm not only significantly improved the applicability of the induction of decision trees and similar algorithms but also improved the transparency of decision trees. The structure of generated trees was more human-like, which was confirmed in several diagnostic tasks [8,52].

3. State of the art

In this section, we give a description of specific requirements that any machine learning system has to satisfy in order to be used in the development of applications in medical diagnosis. Several learning algorithms are briefly described. We compared the performance of all the algorithms on several medical diagnostic and prognostic problems, and their appropriateness for applications in medical diagnosis is discussed.

3.1. Specific requirements for machine learning systems

For a machine learning (ML) system to be useful in solving medical diagnostic tasks, the following features are desired: good performance, the ability to appropriately deal with missing data and with noisy data (errors in data), the transparency of diagnostic knowledge, the ability to explain decisions, and the ability of the algorithm to reduce the number of tests necessary to obtain reliable diagnosis.

In this section, we first discuss these requirements. Then we overview a comparison study [8] of seven representative machine learning algorithms to illustrate more concretely the points made.

3.1.1. Good performance

The algorithm has to be able to extract significant information from the available data. The diagnostic accuracy on new cases has to be as high as possible. Typically, most of the algorithms perform at least as well as the physicians, and often the classification accuracy of machine classifiers is better than that of physicians when using the same description of the patients. Therefore, if there is a possibility to measure the accuracy of physicians, their performance can be used as the lower bound on the required accuracy of a ML system in the given problem.

In the majority of learning problems, various approaches typically achieve similar performance in terms of the classification accuracy, although in some cases some algorithms may perform significantly better than the others [2]. Therefore, a priori almost none of the algorithms can be excluded with respect to the performance criterion. Rather, several learning approaches should be tested on the available data and the one or few with best estimated performance should be considered for the development of the application.

3.1.2. Dealing with missing data

In medical diagnosis, very often the description of patients in patient records lacks certain data. ML algorithms have to be able to appropriately deal with such incomplete descriptions of patients.

3.1.3. Dealing with noisy data

Medical data typically suffer from uncertainty and errors. Therefore, machine learning algorithms appropriate for medical applications have to have effective means for handling noisy data.

3.1.4. Transparency of diagnostic knowledge

The generated knowledge and the explanation of decisions should be transparent to the physician. She should be able to analyze and understand the generated knowledge. Ideally, the automatically generated knowledge will provide to the physician, a novel point of view on the given problem, and may reveal new interrelations and regularities that physicians did not see before in an explicit form.

3.1.5. Explanation ability

The system must be able to explain decisions when diagnosing new patients. When faced with an unexpected solution to a new problem, the physician shall require further explanation, otherwise she will not seriously consider the system's suggestions. The only possibility for physicians to accept a "black box" classifier is in the situation where such a classifier outperforms by a very large margin all other classifiers, including the physicians themselves in terms of the classification accuracy. However, such situation is typically highly improbable.

3.1.6. Reduction of the number of tests

In medical practice, the collection of patient data is often expensive, time consuming, and harmful for the patients. Therefore, it is desirable to have a classifier that is able to reliably diagnose with a small amount of data about the patients. This can be verified by providing all candidate algorithms with a limited amount of data. However, the process of determining the right subset of data may be time consuming, as it is essentially a combinatorial problem. Some ML systems are themselves able to select an appropriate subset of attributes, i.e. the selection is done during the learning process and may be more appropriate than others that lack this facility.

3.2. Brief description of some state-of-the-art algorithms

In this subsection, we briefly describe seven representative algorithms from symbolic learning, statistical learning, and neural networks: three decision tree builders (Assistant-R, Assistant-I, and lookahead feature construction (LFC)), two variants of the Bayesian classifiers (the naive and the semi-naive Bayesian classifier), a state-of-the-art neural network which uses the backpropagation learning with weight elimination, and the k -nearest neighbors algorithm.

3.2.1. Assistant-R

Assistant-R is a reimplementation of the Assistant learning system for top down induction of decision trees [15]. The main difference between Assistant and its reimplementation Assistant-R is that ReliefF is used for attribute selection [53]. ReliefF is an extended version of RELIEF, developed by Kira and Rendell [49,50], which is a non-myopic heuristic measure that is able to estimate the quality of attributes even if there are strong conditional dependencies between attributes. In addition, wherever appropriate, instead of the relative frequency, Assistant-R uses the m -estimate of probabilities, which was shown to often improve the performance of machine learning algorithms [18].

3.2.2. Assistant-I

A variant of Assistant-R that instead of ReliefF uses information gain for the selection criterion, as the original Assistant does.

3.2.3. LFC

Ragavan and Rendell [54] and Ragavan et al. [55] used limited lookahead in their lookahead feature construction (LFC) algorithm for top down induction of decision trees to detect significant conditional dependencies between attributes for constructive induction. LFC generates binary decision trees. At each node, the algorithm constructs new binary attributes from the original attributes, using logical operators (conjunction, disjunction, and negation). From the constructed binary attributes, the best attribute is selected and the process is recursively repeated on two subsets of training instances, corresponding to two values of the selected attribute.

3.2.4. Naive Bayesian classifier

A classifier that uses the naive Bayesian formula to calculate the probability of each class C given the values V_i of all the attributes for an instance to be classified, assuming the conditional independence of the attributes given the class:

$$P(C|V_1, \dots, V_n) = P(C) \prod_i \frac{P(C|V_i)}{P(C)} \quad (1)$$

A new instance is classified into the class with maximal calculated probability. The m -estimate of probabilities makes the naive Bayesian classifier more robust [18].

3.2.5. Semi-naive Bayesian classifier

Kononenko [19] developed an extension of the naive Bayesian classifier that explicitly searches for dependencies between the values of different attributes. If such dependency is discovered between two values V_i and V_j of two different attributes, then they are not considered as conditionally independent. Accordingly, the term

$$\frac{P(C|V_i)}{P(C)} \frac{P(C|V_j)}{P(C)}$$

in Eq. (1) is replaced with

$$\frac{P(C|V_i, V_j)}{P(C)}$$

For such replacement, a reliable approximation of the conditional probability $P(C|V_i, V_j)$ is required. Therefore, the algorithm trades-off between the non-naivety and the reliability of approximations of probabilities.

3.2.6. Backpropagation with weight elimination

The multilayered feedforward artificial neural network is a hierarchical network consisting of two or more fully interconnected layers of processing units, neurons. The task of the learning algorithm is to determine the appropriate weights on the interconnections between neurons. Backpropagation of error in multilayered feedforward neural network [27] is a well-known learning algorithm and also the most popular among algorithms for training artificial neural networks. Well-known problems with backpropagation are the selection of the appropriate topology of the network and overfitting the training data. An extension of the basic algorithm that uses the weight-elimination technique [56] addresses both problems. The idea is to start with too many hidden neurons and to introduce into the criterion function, a term that penalizes large weights on the connections between neurons. With such criterion function, the algorithm, during training, eliminates an appropriate number of weights and neurons in order to obtain the appropriate generalization on the training data.

3.2.7. k -NN

The k -nearest neighbor algorithm. For a given new instance, the algorithm searches for k -nearest training instances and classifies the new instance into the most frequent class of these k instances.

3.3. An overview of comparison of algorithms on medical problems

We compared the performance of the algorithms on eight medical datasets [8]. In the following, we discuss how various algorithms fit the requirements. Table 1 summarizes the comparison of algorithms with respect to the appropriateness for developing applications in medical diagnostic and prognostic problems.

Among the compared algorithms, only decision tree builders are able to select the appropriate subset of attributes. With respect to the criterion of reduction of the number of tests, these algorithms have clear advantage over other algorithms.

Table 1
The appropriateness of various algorithms for medical diagnosis

Classifier	Performance	Transparency	Explanation	Reduction	Missing data handling
Assistant-R	Good	Very good	Good	Good	Acceptable
Assistant-I	Good	Very good	Good	Good	Acceptable
LFC	Good	Good	Good	Good	Acceptable
Naive Bayes	Very good	Good	Very good	No	Very good
Semi-naive Bayes	Very good	Good	Very good	No	Very good
Backpropagation	Very good	Poor	Poor	No	Acceptable
k -NN	Very good	Poor	Acceptable	No	Acceptable

With respect to the performance criterion, the algorithms are more similar. The best performance was achieved by the naive and semi-naive Bayesian classifiers. In medical datasets, attributes are typically relatively conditionally independent given the class. Physicians try to define conditionally independent attributes. Humans tend to think linearly and independent attributes make the diagnostic process easier. Therefore, it is not surprising that the Bayesian classifiers show clear advantage on medical datasets. It is interesting that the performance of the k -NN algorithm is also good in these domains.

With respect to the transparency and the explanation ability criteria, there are great differences between the algorithms.

3.3.1. k -Nearest neighbors

As k -NN does no generalization, the transparency of knowledge representation is poor. However, to explain the decision of the algorithm, a predefined number (k) of nearest neighbors from training set is shown. This approach is analogous to the approach used by domain experts who make decisions on the basis of previously known similar cases. Such explanation ability is assessed by physicians as acceptable.

3.3.2. Naive and semi-naive Bayes

Here, knowledge representation consists of a table of conditional probabilities which seems to be of interest to physicians. Therefore, such knowledge representation is assessed as good. On the other hand, the decisions of Bayesian classifiers can be naturally interpreted as the sum of information gains [17]. The amount of information necessary to find out that an instance belongs to class C is given by

$$-\log_2 P(C|V_1, \dots, V_n) = -\log_2 P(C) - \sum_i (-\log_2 P(C) + \log_2 P(C|V_i)) \quad (2)$$

Therefore, the decisions of the Bayesian classifiers can be explained with the sum of information gains from all attributes in favor or against the given class. In the case of the semi-naive Bayesian classifier, the process is exactly the same, except when the tuples of joined attribute/value pairs occur. In this case, instead of simple attribute values, the joined values are used.

Such information gains can be listed in a table to sum up the evidence for/against the decision. Table 2 provides a typical explanation of one decision [52]. Each attribute has an associated strength, which is interpreted as the amount of information in bits provided by that attribute. It can be in favor or against the classifier's decision. One of the main advantages of such explanation is that it uses all available attributes. Such explanation was found by physicians as very good and they feel that Bayesian classifiers solve the task in a similar way they diagnose. Namely, they also sum up the evidence for/against a given diagnosis.

3.3.3. Backpropagation neural networks

Backpropagation neural networks have non-transparent knowledge representation and in general cannot easily explain their decisions. This is due to the large number of real-valued weights which all influence the result. In some cases, it is possible to extract symbolic rules from the trained neural network. However, the rules tend to be large and

Table 2

Semi-naïve Bayes: an explanation of a decision in the femoral neck fracture recovery problem^a

Attribute value	For decision (bit)	Against decision (bit)
Age: 70–80	0.07	
Sex: female		−0.19
Mobility before injury: fully mobile	0.04	
State of health before injury: other	0.52	
Mechanism of injury: simple fall		−0.08
Additional injuries: none	0.00	
Time between injury and operation >10 days	0.42	
Fracture classification according to Garden: Garden III		−0.30
Fracture classification according to Pauwels: Pauwels III		−0.14
Transfusion: yes	0.07	
Antibiotic profilaxis: yes		−0.32
Hospital rehabilitation: yes	0.05	
General complications: none		−0.00
Combination		
Time between injury and examination <6 h + hospitalization time between 4 and 5 weeks	0.21	
Artroplastic + anticoagulant therapy: yes	0.63	

^a Decision: no complications (correct).

relatively complex. Craven and Shavlik [57] compare rules extracted from a neural network with rules produced by Quinlan's [58] C4.5 system. The rules for a *NetTalk* dataset extracted from a neural network have on the average over 30 antecedents per rule compared to two antecedents for C4.5. Such rules are too complicated and hardly offer a useful explanation to a domain expert.

3.3.4. Decision trees (Assistant-I and Assistant-R)

Decision trees (Assistant-I and Assistant-R) can be used without the computer and are fairly easy to understand. Positions of attributes in the tree, especially the top ones, often directly correspond to the domain expert's knowledge. However, in order to produce general rules, these methods use pruning which drastically reduces the tree sizes. Correspondingly, the paths from the root to the leaves are shorter, containing only few, although most informative attributes. In many cases, the physicians feel that such a tree describes very poorly the diagnoses and is therefore not sufficiently informative [59]. However, as mentioned earlier, the structure of generated trees by Assistant-R is more human-like, which was confirmed in several diagnostic tasks [8,52].

3.3.5. Lookahead feature construction

LFC also generates decision trees. However, in each node a potentially complex logical expression is used instead of a simple attribute value. The generated trees can therefore be smaller. The expressions may represent valid concepts from the domain. However, on the lower levels of the tree, the expressions are often very specific and typically meaningless.

Due to complex logical expressions in nodes, the number of attributes used to classify an instance can be greater than in usual decision trees.

4. Future trends — two case studies

There are many directions in which future development of machine learning in medical diagnosis may take place. Some may rely on new trends in computer technology or technology of medical equipment, however, probably more important is going to be the development of new machine learning algorithms and the philosophy of medical diagnosis. We do not want to speculate all possible trends. Instead, we describe two case studies that illustrate the new trends in the development of machine learning algorithms and how machine learning methodology can support a possible change of philosophy of medical diagnosis.

The first case study describes a recently developed method for dealing with reliability of decisions of classifiers, which seems to be promising for intelligent data analysis in medicine. The second describes an approach to using machine learning in order to verify some unexplained phenomena from complementary medicine, which is not (yet) approved by the orthodox medical community, but could in the future play an important role in overall medical diagnosis and treatment.

4.1. Reliability of single prediction

4.1.1. Adding new instance to a learning set

When we apply a certain machine learning method, we usually estimate the overall reliability of the method, typically in terms of the classification accuracy, information score [60], or misclassification cost [61]. However, what we are really interested in when using the method to solve a given problem is the reliability of that method on this particular problem. This is also important when we use several classifiers and combine their decisions [52]. In such a case, we have to weight the contribution of each classifier to the final decision. The weights should be case dependent, i.e. we have to be able to estimate the reliability of each method on the given case.

A simple idea can be used for that purpose: the decision of a classifier is reliable on the given case when the decision (prediction, class, diagnosis) is not sensitive to adding this case, labeled with this or any other decision (diagnosis), to the learning set. We can verify the reliability simply by labeling the new case in turn with all possible decisions and by adding it to the learning set and rerunning the learning algorithm. If the decision does not vary a lot, we assume that the classifier is quite reliable. On the other hand, if the decisions are sensitive to adding a new case to the learning set, the final decision is not reliable.

Kukar [62] in his Ph.D. thesis has elaborated this basic idea much further. He developed several metrics for measuring distances between classifications, which are then used to measure the variation of classification. He compared several different reliability estimations and empirically showed that a metric based on scalar product of classification vectors performs best when combined with post-test probability. The experimental results on 15

domains confirm that the estimation of the reliability of single prediction provides useful information that can be used to improve the overall applicability of classifiers.

The same idea was used for weighted combination of answers of several classifiers. This approach improves the classification accuracy of a single classifier and considerably improves the robustness of the combined classifier with respect to noisy, random, and default classifiers.

The same idea was used also for problems with non-uniform misclassification costs. Cost-sensitive reliability estimations were used for cost-sensitive combination of different classifiers that do not need to be cost-sensitive by themselves. Experimental results show significant decrease of overall misclassification costs [62]. We illustrate the usefulness of the approach on the problem of diagnosing the ischaemic heart disease.

4.1.2. Application in the ischaemic heart disease diagnosis

Ischaemic heart disease is one of the world's most important causes of mortality, so any improvements and rationalization of diagnostic procedures are very useful. The four diagnostic levels consist of the evaluation of signs and symptoms of the disease and ECG (electrocardiogram) at rest, sequential ECG testing during the controlled exercise, myocardial scintigraphy, and finally coronary angiography. The diagnostic process is stepwise and the results are interpreted sequentially, i.e. the next step is necessary only if the results of the former are inconclusive. Because of the possible suggestibility, the results of each step are interpreted separately and only the results of the highest step are valid.

On the other hand, machine learning methods may be able to objectively interpret all available results for the same patient and in this way increase the diagnostic accuracy of each step. The performance of different diagnostic methods is usually described as classification accuracy, sensitivity, specificity, ROC curve, and post-test probability. We shall discuss only the latter, the other performance criteria are discussed in [61].

In our study, we used a dataset of 327 patients with performed clinical and laboratory examinations, exercise ECG, myocardial scintigraphy, and coronary angiography. In 229 cases, the disease was angiographically confirmed and in 98 cases it was excluded. The patients were selected from the population of the approximately 4000 patients who were examined at the Nuclear Medicine Department of University Clinical Center in Ljubljana, Slovenia, in years 1991–1994. For the purpose of our study, we selected only the patients with complete diagnostic procedures (all four steps).

The positive and the negative diagnosis of the ischaemic heart disease are defined to be reliable if the probability of presence or absence of the disease, respectively, is greater than 0.90 [63]. For that purpose, the tabulated pretest probabilities and the results of various diagnostic steps together with the sensitivity and specificity are used in order to calculate the post-test probabilities [64].

The standard procedure of the lookup table can be replaced by machine learning algorithms. Kukar and Grošelj [65] showed that for the stepwise calculation of post-test probabilities machine learning algorithms are able to improve the number of reliably classified positive and negative cases for 6%, which is an important improvement (Table 3; stepwise calculation of post-test probabilities). When we allow the machine learning algorithm to deal with all attributes at once, the improvement is even higher, however this result is not useful, as the number of incorrectly classified negative cases also increases

Table 3
Results of various classifiers in the ischaemic heart disease diagnosis [62]^a

Classifier	Positive cases		Negative cases	
	Reliable (%)	Errors (%)	Reliable (%)	Errors (%)
Physicians	73	3	46	8
Stepwise calculation of post-test probabilities				
Semi-naïve Bayes	79	5	46	3
Assistant-I	79	5	49	8
Neural network	78	4	49	8
Using all attributes at once to calculate post-test probabilities				
Semi-naïve Bayes	90	7	81	11
Assistant-I	87	8	77	6
Neural network	86	5	66	9
Using all attributes at once to evaluate the reliability of classification of single new cases				
Naïve Bayes	89	5	83	1
Semi-naïve Bayes	91	6	79	2
Assistant-I	77	18	55	18
Assistant-R	81	5	77	2
k-NN	64	12	80	12
Neural network	81	11	72	11

^a The percentage of reliably diagnosed cases together with the amount of wrongly classified cases is given both for the positive and negative cases.

(Table 3; using all attributes at once to calculate post-test probabilities). On the other hand, Kukar [62] has shown that if machine learning algorithms use the estimation of the reliability of a single prediction, the results can be significantly better (Table 3; using all attributes at once to evaluate the reliability of classification of single new cases). The naïve and the semi-naïve Bayes and Assistant-R achieved excellent results. Compared to physicians, the naïve Bayesian classifier improves the number of reliably classified positive cases for 17% and the number of reliably classified negative cases for 37%!

4.2. Machine learning in complementary medicine

4.2.1. Kirlian effect — a scientific tool for studying subtle energies

The history of the so-called Kirlian effect, also known as the gas discharge visualization (GDV) technique (a wider term that includes also some other techniques is bioelectrography), goes back to 1777 when G.C. Lihtenberg in Germany recorded electrographs of sliding discharge in dust created by static electricity and electric sparks. Later, various researches contributed to the development of the technique [66]: Nikola Tesla in the USA, J.J. Narkiewich-Jodko in Russia, Pratt and Schiemmer in Prague until the Russian technician Semyon D. Kirlian together with his wife Valentina noticed that through the interaction of electric currents and photograph plates, imprints of living organisms developed on film. In 1970, hundreds of enthusiasts started to reproduce Kirlian photos and the research was until 1995 limited to using a photo-paper technique. In 1995, a new

approach based on CCD video techniques and computer processing of data was developed by Korotkov [66,67] and his team in St. Petersburg, Russia. Their instrument Crown-TV can be routinely used which opens practical possibilities to study the effects of GDV.

The basic idea of GDV is to create an electromagnetic field using a high-voltage and high-frequency generator. After a threshold voltage is exceeded, the ionization of gas around the studied object takes place and as a side effect, the quanta of light photons are emitted. So the discharge can be fixed optically by a photo, photosensor or TV-camera. Various parameters influence the ionization process [66]: gas properties (gas type, pressure, gas content), voltage parameters (amplitude, frequency, impulse waveform), electrode parameters (configuration, distance, dust and moisture, macro- and microdefects, electromagnetic field configuration), and studied object parameters (common impedance, physical fields, skin galvanic response, etc.). So the Kirlian effect is the result of mechanical, chemical and electromagnetic processes, and field interactions. Gas discharge acts as means of enhancing and visualization of super-weak processes.

Due to the large number of parameters that influence the Kirlian effect, it is very difficult or impossible to control them all, so in the development of discharge there is always an element of vagueness or stochastic. This is one of the reasons why the technique has not yet been widely accepted in practice as results did not have a high reproducibility. All explanations of the Kirlian effect apprehended fluorescence as the emanation of a biological object. Due to the low reproducibility, in academic circles there was a widely spread opinion that all observed phenomena are nothing else but fluctuation of the crown discharge without any connection to the studied object. With modern technology, the reproducibility became sufficient to enable serious scientific studies.

Besides studying non-living objects, such as water and various liquids [66], minerals, the most widely studied are living organisms: plants (leaves, seeds, etc. [66,68]), animals [69], and of course humans. For humans, most widely recorded are coronas of fingers [66,70] and GDV records of blood excerpts [71]. Principal among these are studies of the psycho-physiological state and energy of a human, diagnosis [72], reactions to some medicines, reactions to various substances, food [70], dental treatment [73], alternative healing treatment, such as acupuncture, 'bioenergy', homeopathy, various relaxation and massage techniques [66], GEM therapy, applied kineziology and flower essence treatment [74], leech therapy, etc. and even studying the GDV images after death [67]. There are many studies currently going on all over the world and there is no doubt that the human subtle energy field, as visualized using the GDV technique, is highly correlated to the human's psycho-physiological state, and can be used for diagnostics, prognostics, therapy selection, and controlling the effects of the therapy.

4.2.2. *Verifying the map of organs*

Korotkov's team has developed a computer program that generates the corona of the whole human body from coronas of all 10 fingertips. The program is based on a map, known from traditional Chinese medicine and described in Mandel's book [75]. This map defines regions (sectors) of each finger's corona to be related with a specific organ or organ system in the body. For example, the corona of the left little finger contains sectors that correspond to the coronary vessels, heart, kidney, respiratory system, small intestine, and ileum. Korotkov [66] and his team slightly modified Mandel's map.

For the orthodox medicine, this map is meaningless, there is no physiological evidence for the connection of fingertips with different organs. Besides, the Kirlian camera is considered to provide only noisy pictures that are not related to human state of health.

In order to verify the map and the hypothesis that Kirlian camera provides useful information, we performed several experiments [76–78]. In the following, we briefly describe one such experiment.

We recorded all 10 fingertips of 105 persons that also filled in a questionnaire where they described their health problems. We wanted to distinguish persons, that in the questionnaire had answered that they had no health problem, from persons who had problems with the throat (majority class contained 52.4% of cases). The cases were described by 75 numeric attributes that correspond to areas of sectors of coronas according to the map. We used the C4.5 learning system [58] and the result of 10-fold cross-validation was 14.5% of error. This indicates that coronas in fact contain useful information for diagnosis.

Even more interesting was the structure of trees. For the root of the tree, the algorithm selected most of the times, out of 75 attributes describing sectors of fingers, a sector that corresponds to the throat. There are two such sectors out of 75 sectors (the probability that this could happen by chance for one tree is $2/75 = 0.027$). The other two most important attributes corresponded to jaw and kidney. Jaw is, also by orthodox medicine, related to throat while kidney is by traditional Chinese medicine directly connected with the throat.

This result and several similar studies [76–78] indicate that the map of organs makes sense and that it would be beneficial for medicine to study this phenomena and eventually discover the underlying principles.

4.2.3. Overview of other studies

We use Kirlian camera to indirectly record subtle bioelectromagnetic field of living organisms, mostly humans. The obtained images are then described with a set of numerical parameters that serve as an input to statistical and ML algorithms. The subtle energies are not recognized by current orthodox scientific community, and the aim of our studies is to verify “knowledge” of many practitioners in complementary medicine, who claim that living organisms besides physical body contain also non-measurable subtle levels, such as emotional and mental body.

We have performed several studies in which we analyzed the influence of various parameters on plant and human bioelectromagnetic field.

4.2.3.1. Apple skin. We recorded the coronas of apple peels that were cut off from apples in a standard way. We used four sorts of apples of two different ages. We succeeded by the means of ML to extract useful information for distinguishing apples of different sorts and of different ages (the achieved classification accuracy was low but significantly higher than random classification). We were unable to extract any information to distinguish sun/shadow sides of apples [77].

4.2.3.2. Grapes. The aim of the study was to verify whether the Kirlian camera could be used to describe grapevines and if the berry bioelectromagnetic field is influenced by disease. With the Kirlian camera, we recorded coronas of grape berries. We tested this method on eight grapevine cultivars, performing different tests using ML algorithms. The

results show that the coronas of grapevine berries contain significant information about the cultivars and their sanitary status [79].

4.2.3.3. Menstrual cycle. For the preliminary study, we recorded coronas of all 10 fingertips of 13 female students in 4 weeks, one recording per week. Each recording was classified into one of four menstrual phases. The results of the analysis indicate that the coronas seem to be correlated with menstrual phases and that sectors of organs make sense. Out of 225 numerical parameters, we automatically extracted 15 most important parameters. Total 14 of those parameters corresponded to sectors of three fingers which by Chinese medicine are directly connected with organs that are by official medicine affected by/responsible for the menstrual cycle [77].

4.2.3.4. T-shirts. We wanted to evaluate the effect of different T-shirts on the human bioelectromagnetic field: color T-shirts developed by physicist Dr. Tom Chalko from University of Melbourne, ‘healing’ T-shirt developed by Vitalis from Slovenia, and an ordinary black and ordinary white T-shirt.

We measured five groups of people (with a control group). The analysis confirmed that black and white T-shirts have no significant influence on the coronas, while Vitalis and color T-shirts do have positive influence — they improve in time, the coronas of human fingers by means of larger area and lower fragmentation [77].

4.2.3.5. Glass 2000. Vili Poznik from Ceije, Slovenia, uses organ technology to encode information into a glass which affects in some way the water with which you fill the glass (this is of course nonsense for orthodox science). We recorded coronas of 34 persons before and after drinking the tap water from an ordinary glass and from a Glass 2000, coded by Vili Poznik. The results show that there was a significant improvement of coronas (larger area and lower fragmentation) when drinking water from Glass 2000, while the effect of drinking from ordinary glass was insignificant [79].

4.2.3.6. The art of living. We performed three studies in order to verify the effects of the art of living program (exercises in communication, relaxation, and breathing) on its participants. The results showed significant improvement of coronas (larger area) for participants of a 2 h meeting and of a 6-day seminar compared to control groups which had no significant differences [80].

4.2.3.7. Mobile telephones. We recorded coronas of all 10 fingertips of five groups of persons that were carrying the mobile telephone above their heart for a period of 1 h under different conditions: without any protection, with two different energetic protections (which are nonsense for orthodox science), with placebo (fake) protection and a control group (without mobile telephones). Results indicate that mobile telephones negatively affect the human BEM field, that energetic protections work well while the placebo protection does not work [81].

4.2.3.8. Energetic diagnosis. We recorded coronas of all 10 fingertips of 110 persons for whose the extrasense healer provided the energetic diagnosis. We used machine learning to

interpret the GDV coronas in order to verify three hypothesis: (a) the GDV images contain useful information about the patient, (b) the map of organs on coronas of 10 fingers does make sense, and (c) the extrasense healer is able to see by himself (with his natural senses) the energetic disorders in the human body. The results support all three hypotheses [78].

5. Discussion

The historical development of machine learning and its applications in medical diagnosis shows that from simple and straightforward to use algorithms, systems and methodology have emerged that enable advanced and sophisticated data analysis. In the future, intelligent data analysis will play even a more important role due to the huge amount of information produced and stored by modern technology. Current machine learning algorithms provide tools that can significantly help medical practitioners to reveal interesting relationships in their data.

Our experiments show that in medical domains, various classifiers perform roughly the same. So one of the important factors when choosing which classifier to apply is its explanation ability. Our experiments show that the physicians prefer explanations as provided by the Bayesian classifiers and decision tree classifiers: Assistant-R and LFC. However, instead of selecting a single best classifier, it seems that the best solution is to use all of them and combine their decision when solving new problems. The physicians found that the combination of classifiers was the appropriate way of improving the reliability and comprehensibility of diagnostic systems. The combination should be done in an appropriate way and the reliability of each classifier on the given new case should be taken into account, as the results of Kukar [62] clearly demonstrate.

Regarding the future role of machine learning in medical diagnosis, our views are as follows.

- Machine learning technology has not been accepted in the practice of medical diagnosis to an extent that the clearly demonstrated technical possibilities indicate. However, it is hard to expect that this disproportion between the technical possibilities and practical exploitation will remain for very much longer.
- Among the reasons for slow acceptance, perhaps the most reasonable one is that the introduction of machine learning technology will further increase the abundance of tools and instrumentation available to physicians. Any new tool has the undesirable side effect of further increasing the complexity of the physician's work which is already sufficiently complicated. Therefore, machine learning technology will have to be integrated into the existing instrumentation that makes its use as simple and natural as possible.
- Machine learning-based diagnostic programs will be used as any other instrument available to physicians: as just another source of possibly useful information that helps to improve diagnostic accuracy. The final responsibility and judgement whether to accept or reject this information will, as usual, remain with the physician.
- Complementary medicine is becoming in recent years more and more important, which can be seen also by the amount of money people spend on various complementary

medicine treatments. Physicians are becoming aware of the efficiency and the benefits of complementary medicine and they need verification procedures in order to acknowledge the benefits and issue licences for the use of complementary approaches. Machine learning can play an important role in this process in particular due to the transparency of data analysis.

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