COMPUTER-ASSISTED DIFFERENTIAL DIAGNOSIS AND MANAGEMENT

D. L. Hudson, Ph.D. — University of California, San Francisco

M. E. Cohen, Ph.D. — California State University, Fresno

M. F. Anderson, M.D. — VA Medical Center, Fresno

Abstract

A number of divergent techniques have been utilized in attempts to produce computerized decision aids. Medical applications have been particularly prominent areas for these applications, due in part to the inability of other methodologies to adequately address problems in medicine. The techniques used include rule-based expert systems, pattern classification, data base searching, statistical analysis, decision analysis, and most recently, neural network models. In this paper, a system is described which incorporates a number of these divergent techniques to produce a comprehensive system which can be utilized as an aid for differential diagnosis as well as an instructional tool for training of medical residents. The techniques used include rule-based expert systems, pattern classification, neural networks, and image analysis. The overall purpose of the system described here is to illustrate the practicality of combining these diverse technologies in a single decision making system.

Introduction

The current information explosion in medicine poses problems for physicians attempting to marshall all relevant facts to bear in the diagnosis of diseases while effectively using a bewildering array of diagnostic possibilities. It also poses problems in teaching the art and science of differential diagnosis to medical students and housestaff. Present trends show these problems will worsen as new medical information grows at an exponential rate. Computers, with the ability to handle huge amounts of data very rapidly, offer a natural tool for recording and organizing this information, if searching strategies can be incorporated to define relevant factors for each diagnostic problem. This same process can then be implemented as a teaching aid.

Computerized medical decision making has utilized a number of techniques, including rule-based expert systems, pattern classification techniques, statistical analysis, and most recently neural network techniques. No system has attempted to incorporate features from all of these methodologies to produce a comprehensive system which brings all available knowledge and types of analysis to bear on problems of differential diagnosis. Computer technology has now advanced to the point where it is feasible to develop such a system. This type of system is perfectly suited both for direct application as a differential diagnosis system and as an instructional technique for residents.

Early diagnostic systems utilized pattern classification techniques in an attempt to extract diagnostic strategies directly from data bases [1-5]. Although a number of these systems gave impressive results, they failed to gain acceptance in clinical practice because they did not appear to arrive at decisions through any recognizable strategy. More recently, a number of these systems have been implemented, and have proved useful in a number of clinical applications [6-8].

With the advent of MYCIN [9], a rule-based expert system modeled after the DENDRAL system in chemical synthesis [10], artificial intelligence techniques became prevalent in medical decision making [11-16]. These systems offered the advantage that, theoretically, the application could be changed by simple replacement of the rule base, without modification to the program. A number of expert system shells were developed for this purpose [17,18]. However, the difficult task remains for each application of defining the new knowledge base, usually through lengthy consultation with experts. Some attempts have been made to automate this process [19,20].

The field of neural networks is an old one in the history of artificial intelligence [21,22]. These techniques are based loosely on the structure of biological nervous systems [23], and have been used recently to construct connectionist expert systems [24]. Applications of neural networks have increased rapidly in the last two years [25-28], partially because of hardware advances in parallel processing, which offers a means of efficient implementation for neural networks. Neural networks use some of the same techniques as pattern recognition, in that information is extracted directly from data bases.

All of the above areas offer particular advantages in the decision making process. Pattern recognition allows the computer to diagnose by searching for complex patterns in the data which may not be readily apparent because of the number of parameters involved. Thus the decision making power is derived directly from the data. Rule-based systems are able to supply the user with a trace of the reasoning process. The knowledge base for these systems is derived from direct elicitation of expert opinion. Neural networks incorporate methods from pattern recognition, and are particularly well-suited for the new generation of parallel computers. It is also possible to use neural networks to set up decision making models and derive expert systems directly. All of these methods can be used as decision making tools, as well as providing a framework for teaching the decision making process.

In this paper, a comprehensive system is described which incorporates all of the above techniques for use in differential diagnosis. The aims of this project were to develop a comprehensive system which brings together applicable techniques from all the above areas to produce a system for:

1. assistance in differential diagnosis of difficult cases;
2. assistance in management strategies in specific disease processes;
3. instruction in differential diagnosis for residents;

The initial system is restricted to diagnostic radiology, but all underlying computer structures are general enough to subsequently incorporate other medical specialities. The system consists of a rule-based expert system which derives its knowledge base from expert input, a neural network decision model based on a pattern recognition learning algorithm which derives its knowledge direction from an accumulated application-specific data base, and a differential diagnosis package based upon a comprehensive data base of signs, symptoms, and test results. The diagnostic system utilizes all three of these decision models and in addition is supplemented by an on-line image manipulation capability, statistical analysis, and on-line literature searching.

Computers In Radiology

The ability of computers to handle very rapidly extremely large amounts of data has revolutionized radiology in several exciting ways which are shaping the future of medical imaging.

First, computers have allowed the processing of the digital data generated by the new imaging techniques, digital ultrasonography, digital subtraction angiography, computed tomography, and magnetic resonance imaging, as well as digital data obtained from standard analog images to provide a new range of images including 3-D reconstructions [29,30]. Filmless departments of radiology with computer networks, massive storage capabilities and sophisticated workstations where all images are digitized and stored on computers for processing, immediate access and interpretation are now quite feasible though expensive [31]. Computer networks will provide better communications between departments and improve patient care while teleradiology will extend geographically the availability of expert advice.

Secondly, the computerized environment of departments of radiology will enable the evaluation of diagnostic radiological procedures both by a) improving methods of image reconstruction and interpretation and b) by studying the proper selection of diagnostic tests and the development of principles of diagnosis from a knowledge of test characteristics [32,33]. From studies in decision analysis it has been possible to suggest rational diagnostic strategies for many clinical presentations and diseases [34] using a number of different approaches including signal detection theory which applies the receiver operating characteristic from industry [35], methods based on Bayesian probability [36], the use of expert systems [36] and pattern recognition [38].

Finally, with new very large memory capacities and high resolution graphics, computers are increasingly being used in the teaching of radiology and its precise role in the management of patients to students and housestaff [39-41].

Methodology

The major components of the system are: rule-based expert system, pattern recognition learning algorithm, neural network model, image analysis, differential diagnosis from symptom data base, statistical analysis, and on-line literature search. Of these, the approaches taken for the expert system, pattern recognition, neural network model, and image analysis have been developed by the authors, and are described below.

Expert Systems

EMERGE, a rule-based expert system developed by the authors [42], is based on a modified form of the production rule, where in addition to conjoined premises, one may have disjunctions or may require a certain number in a list to hold for substantiation of an antecedent. EMERGE rule searching is done in an hierarchical manner in order to provide rapid decision making, a necessity in emergency situations. Rules with far-reaching consequences are contained in a level zero control flow, which allow rapid focus of attention to areas pertinent to the case at hand. EMERGE, with the original rule base for evaluation of chest pain in the emergency room, has been extensively evaluated and shown to give accurate medical advice [43].

Recent work on EMERGE has centered on the handling of uncertain information which is always present in medical expert systems This uncertain information comes about from a number of sources, including the knowledge base itself, the data for a particular consultation, and the results. In the knowledge base, rule antecedents may in fact contribute to varying degrees, and are thus more appropriately weighted, rather than considered all to be of equal importance. Also, conclusions may not be absolute, in that a set of findings may be indicative of a condition but probably are not conclusive for that condition. In a specific consultation, symptoms are present to varying degrees. In order to incorporate nuances due to partial presence of symptoms, the "y/n/?" response was changed so that the user may enter a number between 0 and 10, inclusive, indicating a degree of presence of that symptom [44].

Pattern Recognition

Pattern recognition or classification is a method by which data sets can be grouped into two or more categories. It is useful in diagnosis from a number of viewpoints. In the simplest case, with two categories, it can be used to determine parameters which are important in establishing the presence or absence of a particular disease. In the multi-category case, it can be used to choose between disease alternatives. The method identifies parameters which are important in the decision making process, attaching a weight to each to indicate its relative degree of importance.

Weights are determined through a supervised learning approach based on previous work of Cohen and Hudson [45]. In this approach, data of known classification are used to determine weighting factors. The method is an adaptation of the potential function approach to pattern classification. The potential functions are the general class of Cohen multidimensional orthogonal polynomials [46].

An n-dimensional vector $\underline{x} = (x_1,...,x_n)$ is defined, where each x_i represents a parameter which may be useful in the classification decision. For example, for the two-class problem of determining presence or absence of a particular disease, each x_i may represent a particular sign, symptom, or test result. Data of known classification is then used to attach a weighting factor to each parameter [47].

The supervised learning proceeds iteratively, until a separation of the data into correct categories is accomplished. In the process, weights are adjusted for each of the features. The decision hypersurface takes the form

$$D(x) = \sum_{i=1}^{m} w_i x_i + \sum_{i=1}^{m} \sum_{\substack{j=1 \\ i \neq j}}^{m} w_{i,j} x_i x_j \qquad (1)$$

Once weighting factors have been determined, in the decision making model, equation (1) produces a numerical value. The simplest interpretation of this value is

$$\begin{aligned} D(x) &> 0: \quad \textit{Class 1} \\ D(x) &< 0: \quad \textit{Class 2} \\ D(x) &= 0: \quad \textit{No decision} \end{aligned} \qquad (2)$$

However, the larger the absolute value, the more certain one can be that the vector belongs to the indicated category.

Neural Networks

A neural network model was developed based on a retrospective study of testing modalities in carcinoma of the lung undertaken by the authors [48,49]. A feed forward neural network was utilized. The input nodes, which have no incoming values associated with them, represent data values for signs, symptoms, and test results, which may assume continuous or discrete values. The interactive nodes account for the interactions which may occur between these parameters. At the top of the diagram are the output nodes that produce the final result. Each node above the input level computes an output which is the weighted sum of its inputs. This can be a final value or an input to another node. The output value V_i from node n_i is

$$V_i = \sum_{j=0}^{m} w_{i,j} n_j \qquad (3)$$

where m is the number of nodes contributing and n_j is the value of the jth node. The weighting factors $w_{i,j}$ must be determined through a learning algorithm. It is through this learning process that information is extracted from the data. Weights are determined through the supervised learning approach explained above under pattern recognition. A sample neural network was developed for the surgery decision, and is shown in figure 1. The weighting factors are determined using the learning algorithm described above, and result is an equation of the form:

$$D = 124 + 40x_1 - 25x_2 + 9x_3 + \ldots - 0.4x_9 + 3x_1x_2 + 6x_1x_3 + \ldots - 1.6x_8x_9. \qquad (4)$$

The interpretation is as follows: the multiplying coefficient for x_1 is $w_1=40$ as shown in figure 1, which corresponds to n_1; the coefficient of x_1x_2 is $w_{1,2}=3$, which corresponds to $n_{1,2}$. These weights are in relation to output node t , and again are labelled only by the originating node, for simplicity of notation. The interactive nodes are formed at an intermediate level with equal weights of 1 from input node to intermediate node.

The above procedure allows the reduction of necessary data items from 256 variables to only 10 variables. The parameters identified above are then elicited in question format. In addition, at this stage, rules suggested by the clinician are added.

The above method can be used to establish an overall decision making model [50]. Another option is to use the weighting factors and corresponding parameters to define rules directly. For example, assume that the learning algorithm identified the following parameters with the following weights:

$$D = 5x_1 + 2x_2 + x_3,$$

where x_1 is fvc, x_2 is bronchoscopy results, and x_3 is presence of local symptoms.

Following the rule format of the EMERGE system, which allows weighting factors for each premise, as well as partial presence of symptoms, one could arrive at a rule of the type

		Weight	Response
IF	*fvc is high*	*.625*	*8*
	bronchoscopy positive	*.250*	*10*
	local symptoms present	*.125*	*6*

THEN Surgery is appropriate

Note that the weighting factors have been normalized to add up to 1. The user will then be asked to enter information. The responses again will be numbers between 0 and 10, inclusive.

Image Analysis

Digital filtering is an important technique in numerous medical applications. A new class of digital filters based on an orthogonal function developed by Cohen has been developed. The resulting filters are applicable in both one and two dimensions. Comparisons with traditional filtering techniques show this new class fill a gap between known filters. The Legendre, or Optimal, Filter is a special case of this general class [51]. The general function is

$$F_n(m,a_t;s) = \sum_{k=0}^{n} \frac{\prod_{i=0}^{n-1} (m+a_i+a_k)^{x}}{\prod_{j=0}^{k-1} (a_j-a_k) \prod_{s=1}^{n-k} (a_{k+s}-a_k)} \qquad (5)$$

where

$$\prod_{j=0}^{k-1} (a_j-a_k) = (a_0-a_k)(a_1-a_k)\ldots(a_{k-1}-a_k) \quad k \geq 1$$

$$\prod_{s=1}^{n-k} (a_{k+s}-a_k) = (a_{k+1}-a_k)(a_{k+2}-a_k)\ldots(a_n-a_k) \quad n \geq k$$

This general function can be used to derive numerous three-pole and five-pole transfer functions to be used as high pass, low pass, or band pass filters [52].

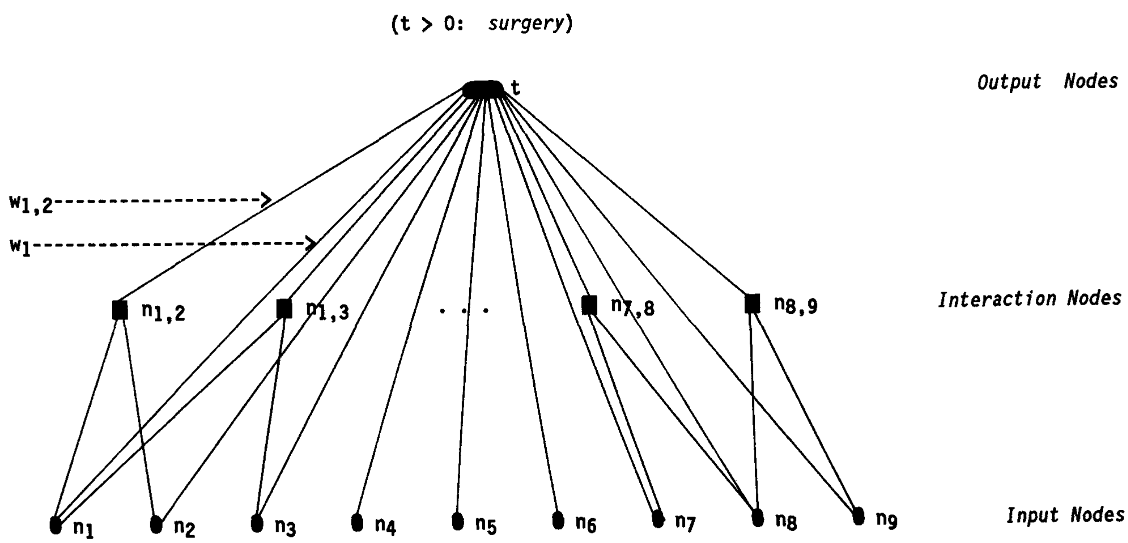


Figure 1: Sample Neural Network for Surgery in Lung Cancer

Implementation

Figures 2-4 show overall flow diagrams for the functioning of the system, which contains three subsections: system design and updating, instruction aid, and decision aid. As described above, the project combines a number of methodologies, including some pre-existing programs and some new techniques. Each subsection will be discussed in turn.

System Design and Updating

This portion of the system is illustrated in figure 2. It is updated as more information is obtained. It is modular in nature, but with automatic links to facilitate the distribution of new information to all components. The major components to arise from this portion are the neural network model and the expert system, both of which are utilized under decision aids.

Data Base Two data bases are utilized. The first consists of information obtained from literature searches for different areas of radiological diagnosis. The second is based on information from local cases.

Based on preliminary work of the authors on another project with Hypercard, a comprehensive computerized approach to the differential diagnosis of radiological findings was developed for all systems, for example, chest nodules, cerebral calcifications, and large kidneys.

Algorithms were then developed for the radiological approach to clinical situations which will indicate the most appropriate work-up for a patient presenting with a given set of symptoms and signs. The general specifications for each test with its sensitivity and specificity, as well as its disadvantages, are established from the radiological literature. Data are from accumulated experience and predicted values obtained using the incidence of disease at the VA Medical Center, Fresno. Initially, data collection is centered on the diagnosis of cancer, including specifically carcinoma of the lung, prostate, colon, and pancreas. Data currently collected for carcinoma of the lung is being used, and the same procedure will be followed for other carcinomas.

As the project progresses, the local data base will become large enough to detect local variations to patterns presented in the literature. Separate data collection forms are designed for each phase of the diagnostic and management processes.

Pattern Recognition Pattern recognition techniques developed by the authors which were described above determine important parameters in the decision making process. This involves several stages, since the overall system deals with a number of diagnostic problems. Information is obtained from the data bases discussed above.

BMDP Statistical Package The BMDP Statistical Package [53], first developed at UCLA, provides a wide range of analytical capabilities that range from plots and simple data descriptions to advanced statistical techniques. Specific techniques used include analysis of variance, chi-squared, discriminant analysis, and regression.

Neural Networks The learning algorithm from the pattern recognition methodology is used to produce neural network models of the diagnostic processes. In addition, rules are generated from this phase for the decision making strategies.

Rules Decision making rules are determined both through direct expert consultation, and utilizing the data bases above. These rules are then be used in the EMERGE expert system shell.

Certainty Factors Results from statistical analysis, pattern recognition, and expert consultation are used to determine certainty factors to be utilized in conjunction with the rules in the expert system.

Expert System The rule-based expert system component is based upon the expert system shell of the EMERGE system, which is described above. Techniques of approximate reasoning are used to handle uncertain information.

Instruction Aid

The instructional aspect of the system uses the decision support aspects of the system, which are discussed in detail in the following section, as well as functional system descriptions and image analysis, as shown in figure 3.

Functional Systems Hierarchical information derived from a Hypercard teaching aid developed by the authors was used to obtain a structured approach to the radiological components. These include the following functional systems: skull and brain; face and neck; spine; bones, joints, and soft tissues; cardiovascular system; chest; gastrointestinal and abdomen; genital/urinary, and retroperitoneum.

Image Analysis An image enhancement program is set up to analyze digitized radiographs. The system includes algorithms for high pass, low pass, and band pass filtering, edge detection, histogram adjustment, and pixel averaging.

Decision Aid

As a decision aid, the system calls upon a number of components to allow complete analysis of the given situation, as illustrated in figure 4. These include the expert system and neural network model as described above, as well as the capability to do on-line literature

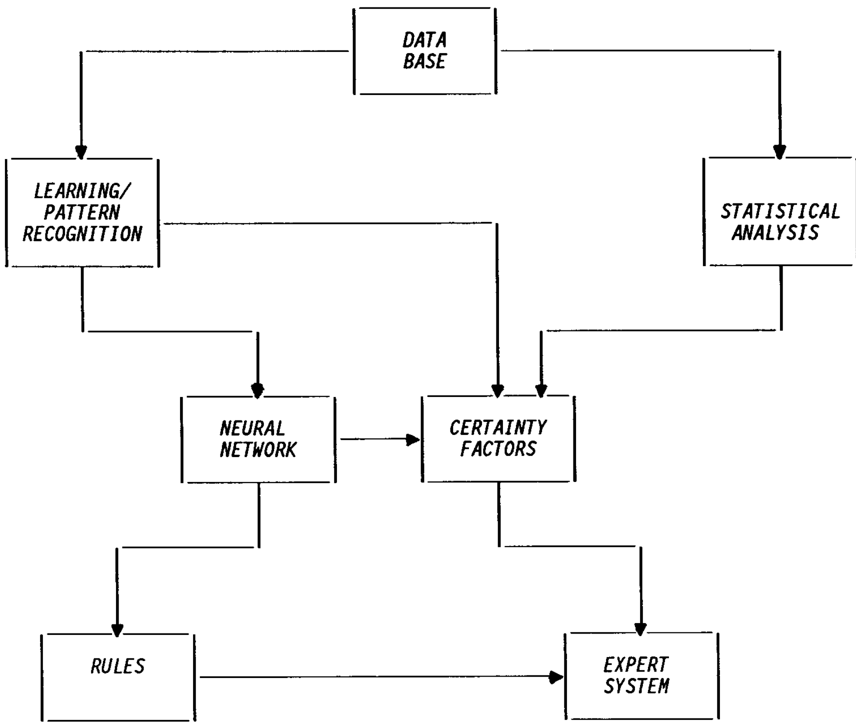
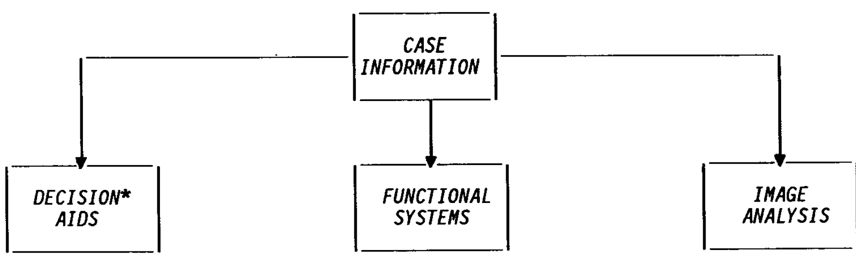


Figure 2: System Design and Updating



* *Utilizes decision aid subsystem*

Figure 3: Instruction Aid

searching, statistical analysis (as described above), and the use of the RECONSIDER data base for differential diagnosis.

On-line Literature Search Through the University of California Computer network, MEDLINE can be accessed. The on-line access to the MEDLINE data base has citations and abstracts of journal articles published in the biomedical sciences in the last three calendar years, and references over 3,400 biomedical journals.

RECONSIDER RECONSIDER, authored by M.S. Blois et al. of University of California, San Francisco [54], is a prompting aid which suggests diseases for inclusion in the differential diagnosis. Among its advantages are its breadth of coverage (3262 diseases are currently represented in it), its simplicity (which makes its operation readily comprehensible to the user-physician), and its rapid response. It is specifically intended as an aid to memory, a feature in which computers are frequently superior to humans, and not as a substitute for human inference or judgment, where at the present they may perform less well.

Linkages

Data transfer among the various components described above is accomplished through ASCII file input and output coordinated through a system manager written in C.

Conclusion

Advantages of the combined approach include:
1. maximum flexibility in choice of methodology;
2. availability of information from divergent sources for decision making, including expert opinion, relevant data analysis, image interpretation, and literature citations;
3. ability of the student to learn to combine and reason with information from divergent sources for use in the diagnostic process.

The system is in the testing process for diagnosis of carcinoma. Data collection will then be expanded to encompass other areas of radiological diagnosis. Testing of the system is proceeding separately for its two uses as an instructional tool and a decision making aid.

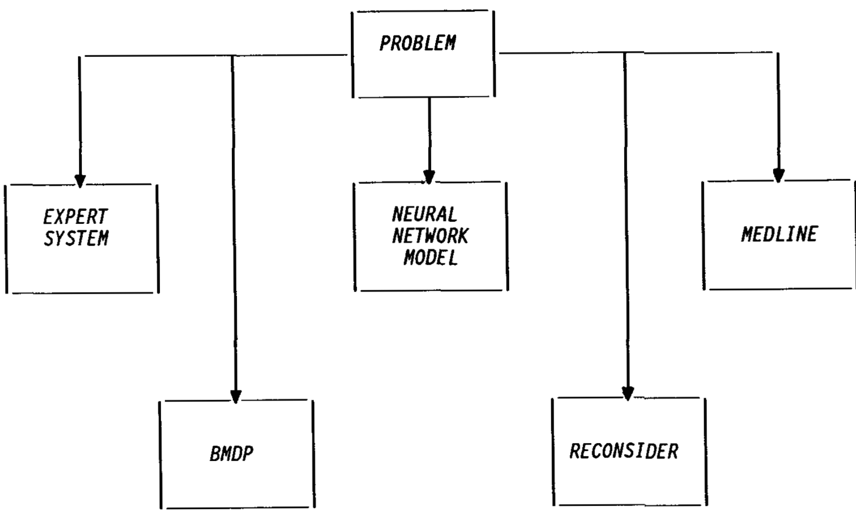


Figure 4: Decision Aid

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