

REVIEW ARTICLES

Artificial Neural Networks: Current Status in Cardiovascular Medicine

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Artificial neural networks are a form of artificial computer intelligence that have been the subject of renewed research interest in the last 10 years. Although they have been used extensively for problems in engineering, they have only recently been applied to medical problems, particularly in the fields of radiology, urology, laboratory medicine and cardiology. An artificial neural network is a distributed network of computing elements that is modeled after a biologic neural system and may be implemented as a computer software program. It is capable of identifying relations in input data that are not easily apparent with current common analytic techniques. The functioning artificial neural network's knowledge is built on learning and experi-

ence from previous input data. On the basis of this prior knowledge, the artificial neural network can predict relations found in newly presented data sets. In cardiology, artificial neural networks have been successfully applied to problems in the diagnosis and treatment of coronary artery disease and myocardial infarction, in electrocardiographic interpretation and detection of arrhythmias and in image analysis in cardiac radiography and sonography. This report focuses on the current status of artificial neural network technology in cardiovascular medical research.

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Clinical decision-making is a challenging, multifaceted process. Its goals are precision in diagnosis and institution of efficacious treatment. Achieving these objectives involves access to pertinent data and application of previous knowledge to the analysis of new data in order to recognize patterns and relations. This process may be difficult because the data may be incomplete, imprecise or unavailable. Additionally, the analysis may be incomplete or imprecise, particularly if the data are viewed through a limited or incorrect window.

In clinical settings, cardiologists gather diagnostic data in several formats, including medical history, physical examination, electrocardiograms (ECGs), echocardiograms, nuclear studies and cardiac catheterization and angiographic studies. Practitioners apply various statistical techniques in processing these data to assist in clinical decision-making and to facilitate the management of patients. As the volume and complexity of these data have increased, use of digital computers to support data analysis has become a necessity. In addition to computerization of standard statistical analysis, several other techniques for computer-aided data classification and reduction, generally referred to as artificial intelligence, have evolved.

One promising new artificial intelligence technique being applied to cardiovascular medicine is the developing science of artificial neural networks. This article describes the computer technology of artificial neural networks and reviews the current utilization of artificial neural network technology in clinical cardiovascular research.

Artificial Neural Network Technology

Artificial neural networks are computational tools for pattern recognition that have been the subject of renewed research interest during the past 10 years. Artificial neural networks, employing several formats and learning algorithms, are being used in academic research and industrial applications. Research in neural networks began in the 1940s but had a brief decline in the late 1960s, when Minsky (1) showed that the artificial neural networks available at that time were unable to solve simple problems. Recently, artificial neural network research has been revitalized by the advent of new learning models. The field continues to grow, and a wide variety of network formats and learning rules are being explored.

Functional elements of artificial neural networks. An artificial neural network uses computer technology to model a biologic neural system both structurally and functionally. Like its biologic counterpart, an artificial neural network is a highly interconnected network of a large number of simple processing units (2). Figure 1 shows the architecture of a simple neural network with four inputs, one hidden layer and two outputs. The hidden and output layers process multiple inputs to produce outputs. Each processing unit in the hidden layer

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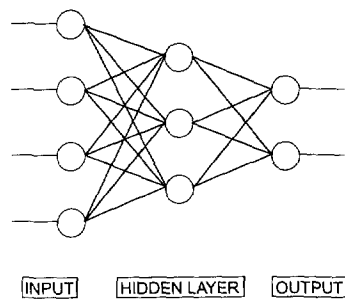


Figure 1. Diagram illustrating the architecture of a simple feed forward neural network with four inputs and two outputs. The network has three “hidden” neurons. These neurons are responsible for the pattern recognition capability associated with the network. Signals are presented to the input neurons, which weight them and pass them to the hidden layer. The hidden layer neurons sum the weighted signals and pass the sum through a transfer function. The transformed signals are then passed to the output neuron through the weighted connections (lines) between the hidden and output layers. The output neuron sums these weighted signals and passes this summed signal through its transfer function. This transformed signal becomes the output of the network. Circles = neurons.

multiplies each initial input by the associated connection or synaptic weight derived from the training phase. These are subsequently summed in each hidden processing unit and passed through a transfer function that scales the output to a value within a limited range (e.g., between 0 and 1). The output then becomes an input for the next layer. In this simple example, the next layer is the output layer. The output layer processing units then multiply the inputs from the hidden layer with the weights connecting the two layers. These resulting signals are processed by the transfer functions and become the output of the network. In short, each processing unit, or neuron, sums weighted inputs and passes the results through a transfer function on to the next level neuron, which finally activates the output unit and produces the artificial neural network output (3). The choice of transfer function allows one to tailor to the specific task at hand. Use of logarithmic or hyperbolic tangent functions is frequently preferred because both functions and their mathematic derivatives are continuous, a characteristic that simplifies many artificial neural network training algorithms. These nonlinear characteristics provide saturation functions; more excitation above some maximal firing level has no further effect on the output.

Training methods for artificial neural networks. Artificial neural networks can be divided into two main classes—those using supervised learning and those employing unsupervised learning. Supervised learning techniques, which are used most commonly, associate inputs with learned outputs. Unsupervised learning is generally used for data base classification.

For supervised learning, a network is trained rather than programmed. Most commonly, a neural network is trained by the process of back propagation, although alternative processes, such as cascade correlation and general regression, are available. In back propagation training, a technique first introduced by Rumelhart et al. (4) in 1986, the network is

presented with a set of input values and an associated set of output values. The network is required to set interlayer weights that provide correct output functions for each case in the set. An error occurs when there is a discrepancy between the network’s output and the true output for a training set. Errors occur because the interlayer weights are not correct. A learning rule then causes the network to change its connection weights to more closely approximate the true output. Thus, an error determines a weight modification and allows the network to learn by modifying its interlayer weights. At the end of the training process, the connecting weight patterns represent the final values that associate inputs to outputs for a given data base. An alternative learning algorithm, cascade correlation, trains one hidden unit at a time and adds units as needed to minimize output error. This is a somewhat faster training algorithm than the back propagation method.

After training the network, testing for learning and generalization, rather than memorization, is performed by using a test set. Generalization is the ability of the trained neural network to produce a correct output for input that it has not seen previously. Generalization is tested for by presenting test data unknown to the neural network and evaluating the neural network output with respect to the known actual output of the test data. If there is agreement between the actual output and the neural network output, generalization and learning have been successful.

Currently, neural network architectures are derived primarily by trial and error, although rules for neural network optimization are under development. Decisions about the number of neurons in a hidden layer, the number of hidden layers in use, the pattern of neuron connections and the types of transfer functions are largely an empiric process.

Neural networks provide an approach to data analysis that uses mathematic pattern recognition. Artificial neural networks learn complex interactions among inputs and produce an output as they train on a known set of data. Artificial neural networks use this training to produce an output for new inputs. Artificial neural networks are thus capable of identifying relations in input data not apparent to human analysis. In a broad sense, an artificial neural network develops “clinical judgment” based on previous learning and experience.

Neural network technology has been widely applied to problems in engineering and computers. Recently, medical applications have been developed in various fields, including cardiology, radiology, urology and laboratory medicine. The remainder of this report will focus on the current status of neural network technology in cardiovascular medicine.

Artificial Neural Networks in Cardiovascular Medicine

The science of artificial neural networks has been applied in efforts to solve several problems in four general areas of cardiovascular medicine. These areas are: coronary artery disease, electrocardiography, cardiac image analysis and car-

liovascular drug dosing. The artificial neural network reports relating to coronary artery disease may be divided into those addressing the general diagnosis and treatment of coronary artery disease and those specifically related to acute myocardial infarction. The ECG studies are concerned with general ECG interpretation, arrhythmia identification and arrhythmia localization. A small number of studies (5-7) have also been published that relate artificial neural networks to miscellaneous areas of interest to the cardiovascular specialist.

Coronary artery disease. *Diagnosis and treatment.* Millions of patients present each year for evaluation of symptoms of coronary artery disease. The initial evaluation typically includes analysis of history and physical as well as noninvasive testing for ischemia. The relations among these clinical and noninvasive variables are often subtle and complex. Currently, coronary artery disease is assessed by several noninvasive methods, including exercise stress testing, nuclear imaging and echocardiography. There are many limitations to these technologies, including time requirements and patient inconvenience. In addition, gender differences in sensitivity and specificity can limit diagnostic accuracy. For example, women have a higher rate of false positive exercise ECGs than do men, and breast attenuation is a problem in nuclear imaging studies. A technology that could minimize these limitations would be beneficial in the diagnosis and treatment of coronary artery disease. Alternatively, a technology that could take into account the limitations of noninvasive testing and combine the noninvasive results with the history and physical variables would also be extremely useful in the clinical setting. Investigators are exploring the potential of artificial neural networks to achieve these goals.

Akay (8) utilized history and physical examination data, as well as preprocessed recordings of diastolic heart sounds, to diagnose coronary artery disease with a back propagation trained artificial neural net. The positive predictive accuracy was 84% and the negative predictive accuracy was 89% in this study of 63 abnormal and 37 normal subjects.

Our group (9) also assessed the significance of coronary artery disease by using an artificial neural network. We trained a personal computer-based artificial neural network, using back propagation of errors in a single layer, to identify patients with significant coronary artery disease on the basis of 23 noninvasive variables. These variables included history and physical examination data as well as results of noninvasive testing such as exercise treadmill testing. The artificial neural network was trained to recognize significant coronary artery disease, defined as >50% obstruction of the left main coronary artery or other epicardial vessels. We identified significant coronary artery disease with a positive predictive accuracy of 80% and a negative predictive accuracy of 92%. It appeared from that study that artificial neural networks may be useful in excluding patients with significant coronary artery disease and could potentially eliminate the need for further invasive testing in these patients.

There has been one report of artificial neural network use to facilitate treatment of coronary artery disease. In a study by

Gindi et al. (10), tissue fluorescence spectra were analyzed with the use of an artificial neural network to assist with laser angioplasty procedures by helping to differentiate normal from abnormal atherosclerotic tissue. In that study, a back propagation-trained artificial neural network was useful in distinguishing normal from abnormal tissue.

Artificial neural networks at this time do not significantly improve current noninvasive technologies for diagnosing and treating coronary artery disease. With continued research, roles for such networks may be developed. For example, they may become useful in risk stratification of patients who present with unstable angina, and the technology may ultimately assist in identifying patients who will respond to medical therapy.

Acute myocardial infarction. In the era of health care reform, when cost containment efforts are being mandated by both governmental and private third-party payers, the accurate detection of acute ischemic heart disease in patients presenting to the emergency room with chest pain of suspected cardiac origin and a nondiagnostic ECG has become particularly important. Artificial neural networks have been tested for identifying patients with cardiac chest pain and more specifically those with acute myocardial infarction.

In one of the first studies of this subject, Baxt (11) retrospectively analyzed 356 patients admitted to a coronary care unit with chest pain. With the history, physical examination findings and ECG data, Baxt used back propagation to train a neural network to identify patients with myocardial infarction. He validated the diagnosis of myocardial infarction with confirmatory serum enzyme levels or with an ECG showing new pathologic Q waves. The network correctly identified 92% of patients with and 96% of patients without a myocardial infarction.

In a subsequent study, using the artificial neural network trained on the initial patients, Baxt (12) prospectively studied 331 adult patients with precordial chest pain. He compared diagnostic sensitivity (True positives/True positives + False negatives) and specificity (True negatives/True negatives + False positives) between attending emergency room physicians and neural networks in identifying the diagnosis of acute myocardial infarction. The physicians had a diagnostic sensitivity of 78% and a specificity of 85%, whereas the neural network had a sensitivity of 97% and a specificity of 96%. Baxt (13) further evaluated the process by which the artificial neural network diagnosed myocardial infarction. The most important diagnostic variable was the presence of ST segment depression or elevation in the admission ECG. More interesting was the finding that the network predicted infarction by placing more diagnostic importance on the finding of rales on auscultation than on the patient's age and gender or a history of hypertension or diabetes mellitus. Rales as a clinical finding had not previously been shown to be predictive of infarction.

Other investigators have evaluated the use of artificial neural networks for the diagnosis of myocardial infarction. Furlong et al. (14) used analysis of cardiac enzyme data to diagnose myocardial infarction. The artificial neural network, trained by back propagation of cardiac enzyme data, was used

to identify 24 patients with and 29 patients without acute myocardial infarction. The positive predictive accuracy was 100% and the negative predictive accuracy 93%.

These studies suggest that an artificial neural network may be able to find a useful pattern in the unique combination of signs, symptoms and laboratory results that each patient brings to the clinical encounter. With this ability, it appears that artificial neural networks can be used to assist in the evaluation of cardiac chest pain and in the diagnosis of myocardial infarction and to bring a greater level of confidence to this process.

Electrocardiography. General interpretation. For many years computer technology has been used in the analysis and interpretation of ECGs (15,16). Recently, artificial neural network technology has been incorporated into the efforts for automated analysis and interpretation. Bortolan et al. (17) compared artificial neural network interpretation of ECGs to statistical analysis of conventional linear discriminant analysis and multigroup logistic discriminant analysis. Edenbrandt et al. (18) evaluated artificial neural network ECG ST-T segment classification and compared it with clinical interpretation. They found that artificial neural network classification accuracy was 80%, when compared with the classification of experienced cardiologists.

Although interesting preliminary studies have been reported in this area, few have had clinical relevance, and to date no work has shown the feasibility of artificial neural networks performing routine ECG analysis. Suzuki and Ono (19) showed the most promising use of an artificial neural network in the automation of interpretations in a noisy ECG record. This application seems to have a potentially wide utility but needs to be studied further.

A more fruitful area of research is the use of artificial neural networks in the ECG diagnosis of myocardial infarction. Heden et al. (20) studied the ability of artificial neural networks to make the diagnosis of myocardial infarction from the analysis of the ECGs of 1,107 patients who had undergone diagnostic cardiac catheterization. The performance of the artificial neural networks in the diagnosis of anterior and inferior myocardial infarction was compared with the conventional automated ECG interpretation with the Glasgow program (15). For anterior infarction, the artificial neural network sensitivity was 81% and the conventional program sensitivity 68%. For inferior infarction, the artificial neural network sensitivity was 78% and the conventional program sensitivity 66%. Artificial neural network interpretation of anterior and inferior myocardial infarction appears to be more sensitive than the Glasgow program, a frequently utilized rule-based computer system. Yang et al. (21) demonstrated that using a back propagation neural network in combination with the deterministic Glasgow program yielded better diagnostic outcomes for inferior wall myocardial infarction than did either the deterministic program or the neural network used alone.

Arrhythmia identification. There are numerous studies using artificial neural network for arrhythmia detection, identification and treatment. Yang et al. (22) evaluated artificial

neural networks as an aid to improving the sensitivity and specificity of a commercial ECG interpretation program (15) in diagnosing atrial fibrillation. Only minor differences were noted in the sensitivities and specificities of the commercial program alone, the artificial neural network and the combination of commercial program and artificial neural network. The initial conclusion was that utilization of an artificial neural network did not lead to any appreciable gains in the diagnosis of atrial fibrillation, although several years of development were required to achieve the degree of precision present in the deterministic program. In a subsequent report, Yang et al. (23) suggest that the artificial neural network technique can improve the deterministic logic program's sensitivity from 88.5% to 92% without losing specificity (92.3%).

An important use of artificial neural networks may be in the accurate identification of ventricular tachycardia. In a study by Dassen et al. (24), a back propagation artificial neural network correctly identified 95% of ventricular tachycardias. The clinical utility of this process was limited because the input data were not automated. Manual measurements of ECG variables and subsequent neural net input is a more cumbersome process than simple visual interpretation in the immediate clinical setting. Lee (25) described a rate of ventricular tachycardia identification >95% with the use of an artificial neural network. The importance of this study may be in the application of this artificial neural network to implantable cardioverter-defibrillators. The sensing characteristics of the device, which enable it to recognize a wide range of arrhythmias, are crucial to the delivery of appropriate shocks. Current, implantable cardioverter-defibrillators use rate-based systems, which have limitations in the identification of the origin of the tachyarrhythmia.

In a study by Farrugia et al. (26), a traditional rate-based classifier was compared with an artificial neural network sensed event classifier to evaluate both waveform configuration and heart rate variability. The artificial neural networks produced significantly better results than did the conventional rate-based classifiers. The absolute error rate (percent of the total number of patterns misclassified) was 7.1% for the artificial neural networks in contrast to 17% for the rate-based system. Ventricular tachycardia was also more effectively discriminated from sinus tachycardia by the artificial neural networks. Thus, artificial neural network-based systems that considered waveform configuration of the ventricular intracardiac ECGs in conjunction with rate were superior in arrhythmia recognition to rate-based systems alone. Iwata et al. (27) have used neural network technology to compress ECG data for more efficient ambulatory ECG (Holter) monitor functioning.

Arrhythmia localization. Radiofrequency catheter ablation has become the treatment of choice for patients with symptomatic or life-threatening cardiac arrhythmias related to preexcitation syndromes and accessory pathways. Currently, the initial noninvasive localization of accessory pathways is based on clinical interpretation of surface ECGs. However, because this method is nonspecific and successful catheter

ablation is dependent on highly accurate localization of the bypass tract, a more accurate preprocedure method of localization is required. Additionally, accurate localization can potentially minimize procedure time and radiation exposure to both the patient and the operator. In this area artificial neural networks have been tested and show great promise.

Morytko et al. (28) evaluated the use of artificial neural networks to localize accessory pathways before performing radiofrequency ablation. Artificial neural networks were trained with retrospective data from 60 patients who had undergone ablation. The output of each of the networks indicated the presence or absence of the accessory pathway site for which the network was trained. The networks were then applied to eight random patients not used in training. Accessory pathway locations were localized with a sensitivity of 75% and specificity of 100%. The positive predictive value was 95% and overall accuracy 96%.

Dassen et al. (29) also used an artificial neural network to localize atrioventricular accessory pathways in patients with the Wolff-Parkinson-White syndrome. After the artificial neural network was trained on manually generated data from 60 cases, 25 cases were used to test the network. The network interpreted 23 cases correctly. In 15 cases, predicted locations and actual locations were exact fits; in 8 cases, a border zone between two locations was predicted by the network; and in 2 other cases, prediction was incorrect. The investigators concluded that artificial neural networks can be useful in these types of studies even where causal relations between physiologic mechanisms and ECG findings are only partially understood.

In the area of arrhythmia localization, artificial neural networks show the potential to analyze subtle, complex ECG patterns and to successfully predict accessory pathway location and determine the focus of ventricular tachycardia. This area of investigation is exciting and offers great promise. By refining the technique of ablation with preprocedure localization of an accessory pathway, artificial neural networks can potentially reduce procedure time, minimize radiation exposure and avoid ineffective energy applications and increase overall success rates.

Cardiac image analysis. Noninvasive imaging data including stress echocardiographic images and nuclear scintigraphic images require computer preprocessing before interpretation. The importance of preprocessing is illustrated by the technology of automated border detection. Proponents of automated border detection state that it can offer pathophysiologic insights and improve clinical and perioperative management of patients with acute and chronic coronary syndromes, congestive heart failure and valvular heart disease (30). The utility of automated border detection can be illustrated in the interpretation of stress echocardiography. Standard, subjective visual interpretation of wall motion changes may be enhanced and made more sensitive by automated border detection. Artificial neural networks are under investigation in the fields of image processing and interpretation. They are being used to process

images, to facilitate complex pattern recognition, which will aid classification of images into clinically relevant categories.

In medical applications outside of cardiology, artificial neural networks have been trained to recognize lesions imaged on mammography as benign or malignant, hepatic ultrasound images and avascular necrosis of the femoral head in magnetic resonance images (1). In cardiovascular applications investigators are using artificial neural networks to automate the segmentation and recognition of structures or regions of interest in echocardiographic and scintigraphic images.

Cios et al. (31) evaluated echocardiographic images by neural networks for separation into regions of interest for diagnosis. The investigators found specificities of >70% for all diagnostic classes such as hypertrophic cardiomyopathy and posterior myocardial infarction. Using a similar concept, Fujita et al. (32) found that a neural network analyzed thallium-201 myocardial single-photon emission computerized tomographic bull's-eye images to make a corresponding diagnosis. The diagnosis was more accurate than that of a junior resident but less accurate than that of a staff radiologist. The accuracy rate was 77% for an artificial neural network, 69% for a junior resident and 83% for a staff radiologist. The data from these investigators are preliminary but appear promising with further refinements.

Cardiac drug dosing. One important goal of clinical decision making is the institution of efficacious treatment. Studies concerning the effectiveness of artificial neural networks as drug therapy monitors have been reported. Poli et al. (7) describe "Hypernet," an artificial neural network-based system that utilizes 24-h blood pressure monitor input to diagnose and analyze therapeutic interventions for ambulatory hypertensive patients. In a test set of 35 patients (10 normotensive and 25 hypertensive), the therapeutic recommendations of Hypernet were tested against those of an experienced specialist. In this comparison, Hypernet achieved a sensitivity of 92% and a specificity of 96% when evaluated for both diagnosis and treatment efficacy.

Narayanan and Lucas (33) reported the result of an artificial neural network utilized to assist the physician in choosing a warfarin dose to optimize patients' international normalized ratio. This type of program may help shorten hospital stay, for example in patients who have had coronary artery stent placement. These studies illustrate the potential of artificial neural networks in tailoring pharmacotherapy.

Other areas of research. Several reports on neural networks have been published in miscellaneous areas of interest to cardiovascular medicine. Scott and Palmer (5) reported the use of artificial neural networks in the interpretation of ventilation-perfusion lung scans. Ebell (6) described their use for predicting the outcome of in-hospital cardiopulmonary resuscitation. Lette et al. (34) suggested that artificial neural networks may be useful in predicting cardiac complications after noncardiac surgery. Tu and Guerriere (35) used an artificial neural network to predict length of stay in the intensive care unit after cardiac surgery. Foo et al. (36) used an artificial neural network to detect the lack of heart rate

variability, a viable index to predict sudden cardiac death. Cathers (37) described the development of a neural network-based classifier for phonocardiographic output. Georgiadis et al. (38) recently described a neural network-based analysis of Doppler signals representing microemboli in patients with prosthetic cardiac valves.

Discussion

Artificial neural networks are a new application of computer technology. They have varied utilization in current cardiovascular medical research, but there are current limitations to the technology. Artificial neural network techniques are initially cumbersome. It is time-intensive to collect and preprocess data and to train the networks. Once training is completed, further tasks can be carried out with relative ease.

Another limitation is that, unlike rule-based systems, the artificial neural networks cannot easily explain their reasoning. Many clinicians may have difficulty putting faith in a "black box" whose logic is not clear. However, clinical medicine comprises empiric observations. Clinicians use empiric data and "clinical judgment" to make clinical decisions on a daily basis. As one reviewer of this technology (39) wrote, "Artificial neural networks should not be considered to be mystical black boxes. The only mystery lies in how something so simple, such as a network of elementary decision nodes, can solve problems as complex as the diagnosis of an myocardial infarction or the interpretation of a V/Q scan."

A third limitation of this technology, particularly of back propagation training methods, is its restricted range. The technique performs best in the setting of a well defined problem with a limited number of diagnostic options—for example, the presence or absence of a myocardial infarction. This can be a limitation in that in many diagnostic problems, multiple disorders may be present concurrently. An excellent example of this problem is illustrated in the study by Yang et al. (21) in which the presence of left ventricular hypertrophy reduces the specificity of a neural network in the diagnosis of inferior wall myocardial infarction.

Artificial neural networks are not meant to replace clinical judgment or classic statistical approaches; they are meant to enhance clinical decision-making. Though they are relatively new, they are one of a number of techniques for interpreting cardiovascular medical data. One value of artificial neural networks as a new tool may be that they can be developed relatively quickly if data are available, as opposed to certain deterministic logistic programs which, as pointed out by Macfarlane and Yang and their co-workers (15,22,23), may require significantly more developmental time. Another potential value of the newly developing artificial neural network tool may be that it assists in recognizing patterns and relations among sets of clinical and experimental information that previously have not been accessible because of limitations in the analytic methods. There may be profound truths that have not been appreciated because observers have been looking

through the wrong window. At the very least, artificial neural networks open a new window.

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