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ARTIFICIAL NEURAL NETWORKS : IMPLICATIONS FOR PHARMACEUTICAL SCIENCES

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1. INTRODUCTION

Artificial Neural Networks (ANN) are machine based computational techniques which attempt to simulate some of the neurological processing ability of the human brain. Fundamentally, ANN are interconnected networks of processing units termed as 'neurons' which are responsible for the completion of the decision-making process. They have the ability to discern complex and latent patterns in the information presented to them. This feature of ANN, to extract latent information from the data presented to them, proves them to be powerful tools for modeling and predictive purposes and offers great potential for applications in a variety of disciplines. ANN have attracted the attention of many computer scientists and have been successfully applied to solve a multitude of problems in diverse areas of sciences, engineering and business.

However, pharmaceutical scientists do not appear, in general, to be fully aware of the great potential of this novel pattern-recognition technology. Hence, there is little pertinent literature in the pharmaceutical sciences. The implications and consequences of the current developments in neurocomputation and related sciences for the pharmaceutical

sciences have motivated us in writing this article. We have also attempted to review and constructively criticize the literature published in this and contiguous areas.

This review offers a basic explanation of the fundamental principles of the ANN technology. The details of the *'Back-propagation network architecture'* have been described to serve as an illustrative model. We have tried to identify various areas in the pharmaceutical sciences where the successful application of artificial neural networks can be envisaged. An evaluation of the performance of ANN technology as compared to standard statistical modeling techniques using the data published in literature has also been made.

2. PRINCIPLES AND PARADIGMS OF ANN

Among all organisms, the neurological processing ability of the human beings is truly remarkable. The possibility of 'machine-simulation' of this ability, even to a partial extent is desirable and enticing and has led to the development of ANN. ANN are parallel information processing systems that can develop adaptive responses to environmental information. Neural networks, adaptive systems, adaptive networks, neurocomputers and parallel distributed processors are all elements that can be found in various implementations of ANN. They also have massive potential for parallelism and excel at problems involving patterns- pattern mapping, pattern classification and pattern completion. Their performance has been shown to be superior to the traditional Von Neumann sequential approach and rule-based expert systems in certain applications(1,2).

2.1. Genesis and development

In the chronological sense, the history of ANN technology is still in its infancy. The genesis dates back to the pioneering efforts of McCulloch and Pitts in 1943, in which they demonstrated the ability of simple neural networks to compute arithmetic or logical functions (3). In 1949,

Hebb, in his book entitled '*The Organization of Behavior*', discussed the idea of learning and proposed a specific learning-law which inspired many of his contemporaries (4). In 1958, Rosenblatt and Wightman developed the first successful neurocomputer-the Mark-I perceptron (5).

In 1969, Minsky and Papert showed that the kinds of problems which could be solved by simple perceptrons was severely limited (6). As a consequence, progress in ANN research was stalled until the late seventies. However, In the early 1980s, new network architectures and learning algorithms became widely known- especially the back propagation algorithm and research in this area increased dramatically.

2.2. Some ANN Basics

Briefly, an ANN can be viewed as a network of interconnected processing elements or nodes. Each node receives weighted inputs from one or more sources and produces an output as a function of its inputs. Output values are passed on to other nodes or are used directly as one of the components of the final output of the entire network. By appropriately configuring the network and adjusting the weights on the interconnections between the nodes, it is possible to have a network act as a classifier, producing an appropriate coded output for each class of inputs, or to serve as a (multi-variable) function approximator , producing the appropriate mapped output for each set of input values.

Neural nets can vary in their architecture, i.e., the number of layers and nodes in the network and the topography of their interconnections. They can also vary with respect to the procedure that is used to determine the connection weights between the nodes. In some network architectures, weights are determined *a priori* as a function of the patterns to which the network is supposed to respond. For other classes of networks, algorithmic procedures-learning rules are known which can compute the necessary weights by making adjustments based on the difference between the actual output

of the network and the desired output. Thus, networks can be trained to respond by iteratively presenting to the network a series of input patterns, each with its target output, and adjusting the interconnection weights according to the learning rule until the network can correctly respond to all, or some predetermined proportion, of the input patterns. After this supervised training the network can be presented with new patterns and the output produced can be interpreted as a classification code or as a functional output value depending on the nature of the problem. One of the attractive features of trainable ANN is their ability to learn to classify patterns without being provided an explicit characterization or a mathematical model of the properties which serve as the basis for the classification.

3. THE ERROR BACK PROPAGATION ARCHITECTURE

The number of network architectures that have been or are being developed is large (7). However, the most widely used and successfully applied has been the error back-propagation paradigm or, more simply, the back-propagation network. The back-propagation network can be described as a totally connected, feedforward architecture in which the nodes are arranged into input and output layers, with one or more middle, or so called hidden layers, interposed between. Each node in a given layer is connected to each node in the adjacent layer (totally connected) and to only those nodes (feedforward). A generic back-propagation network is shown in Figure 1.

It should be mentioned that in the back-propagation network, the elements in the input layer do no processing and serve merely as distribution points to the first hidden layer. On the other hand, each element in the hidden and output layers processes by summing its weighted input from the previous layer and by then passing this sum through a non linear transfer function to its output. Some form of the sigmoidal function is commonly employed, although the only real requirement is that the function be differentiable. The

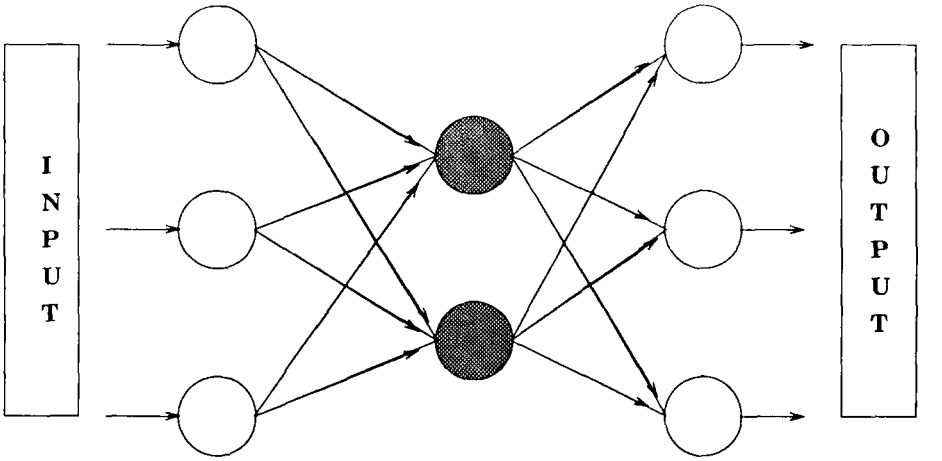

FIGURE 1
A three layered fully interconnected artificial neural network with a single hidden layer.

operation of the transfer function is graphically depicted in Figure 2.

Applying the back-propagation paradigm to a specific problem requires designing the specific network, training it using a set of training patterns, and only then using it on new patterns. Network design essentially means fixing the number of layers and the number of units in each layer. The number of input and output units is largely determined by the data in the problem. The number of hidden layers and the number of units is still based on mostly heuristic guidelines.

After a network has been designed and the initial weights assigned random small values , the network can be trained. Training is an (often long) iterative process and is accomplished by repeatedly choosing at random an input pattern from the training set, presenting the pattern at the inputs of the network, propagating the values through the network to determine the actual output of the network for that pattern, and then making weight adjustments to the network weights as a function of the error value. Each step

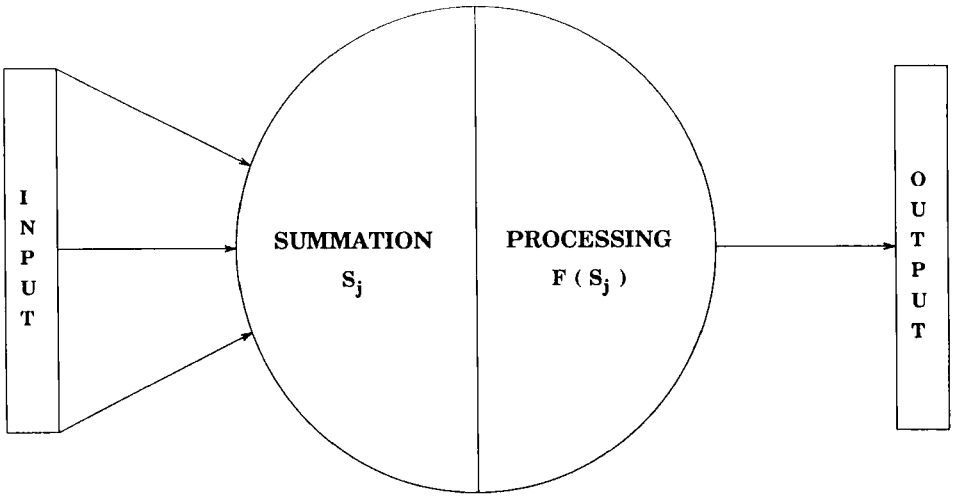

FIGURE 2
Representation of the operation of a transfer function.

of the training process can be shown to execute a gradient descent reduction of the squared error. Training continues until some error criterion set by the designer has been met, or in some cases, until a processing limit (number of cycles) has been reached.

The training procedure is sometimes described as a two-step process: the feedforward step and the back-propagation step.

3.1. Feedforward step

The feedforward step begins with the presentation of the input pattern and continues as activation levels continue to propagate through the hidden layers. In each hidden layer the processing unit sums its input and then applies the sigmoidal function to compute its output. Incoming connections to unit 'j' are at the left and originate at units in the layer below (Figure 1). Output values from these units arrive at unit 'j' and are summed by

$$S_j = \Sigma\, a_i w_{ji} \qquad \text{(Eq. 1)}$$

where a_i = the activation level of unit 'i'

w_{ji} = the weight from unit 'i' to unit 'j'

S_j = the weighted sum of the inputs to unit 'j'

After the incoming sum S_j is computed, a function F is used to compute $F(S_j)$. The output value for unit 'j' can then be defined in the following manner:

$$a_j = F(S_j) \qquad \text{(Eq. 2)}$$

where a_j = the output value of unit 'j'

$F(S_j)$ = the function applied to the weighted sum of inputs to unit 'j'

The function F used in a back-propagation network is a sigmoid function and is defined as :

$$F(x) = 1/(1 + e^{-x}) \qquad \text{(Eq. 3)}$$

where x belongs to Real numbers

The sigmoid function is continuous and differentiable throughout the real domain and can take any value between 0 and 1. Hence, the sigmoid function has the added advantage of differentiability, as well as all of the desired characteristics of the step function, which has a discontinuity at the point of activation. Some back-prop networks apply a bias unit to every layer except the output layer. The bias unit has a constant activation value of 1 and is sometimes helpful in improving the convergence properties of the network.

3.2. Back-propagation step

In this step, error values are calculated for all processing units and weight changes are calculated for all interconnections. The calculations begin at the output layer and progress backward through the network to the input layer. The error correction step takes place after a pattern is presented at the input layer and the forward propagation step is completed. The error value (δ) is computed for the output layer in a simpler manner than the hidden layers. If unit 'j' is in the output layer, then its error value is

$$\delta_j = [\, t_j - a_j \,]\, f'(S_j) \qquad \text{(Eq. 4)}$$

where δ_j = the error value of unit 'j'

t_j = the target value for unit 'j'

a_j = the output value for unit 'j'

$f'(x)$ = first derivative of the sigmoid function

S_j = weighted sum of inputs to unit 'j'

For a hidden layer the computation of the error is done as shown below

$$\delta_j = [\delta_k \, w_{kj}] \, f'(S_j) \qquad \text{(Eq. 5)}$$

The adjustment of connection weights is done using the 'δ' values of the processing unit. Each interconnection weight adjustment is done using the 'δ' value of the unit that receives input from that interconnection. The connection weight adjustment is done as shown below :

$$\Delta w_{ji} = (n) \, (\delta_j) \, (a_i) \qquad \text{(Eq. 6)}$$

where n = the learning rate of network

This is called the generalized 'delta rule'. The value of the learning rate is commonly between 0.25-0.75 and is chosen by the user of the neural network and reflects the rate of learning of the ANN. Higher values of 'n' may lead to unsatisfactory learning and smaller 'n' values may lead to excessively slow learning. Hence, the culmination of a pair of forward and backward propagation steps completes one iteration of the back-propagation network.

3.3. Convergence

The root mean squared (RMS) error is a quantitative measure of learning and reflects the degree to which the network has accomplished learning. Convergence is a process whereby the RMS value of the network gets closer to zero. This is not always easy and may sometimes take a very long time if the network gets stuck in a local minima. Convergence aims at reaching the global minimum error. Certain empirical remedies to improve the convergence properties of the network are the inclusion of a bias element and the optimal specification of the learning rate. It is also useful to hold the ratio of the number of data points to the number of controllable parameters in the network between 1.8 and 2.2 (8).

4. APPLICATIONS

ANN have been widely applied, effectively and efficiently, to solve numerous problems in a variety of disciplines. Typically, any problem which requires control and sensor processing is ideally suited for the application of ANN technology. Literature related to the application of ANN technology in the areas of image processing, speech processing, predictive modeling, optimization and fault diagnosis is available in plethora.

In contrast, the literature relevant to pharmaceutical sciences in this field is not very large. This observation is both surprising and intriguing. Hence, we have attempted to identify various possible areas in pharmaceutical sciences where this technology can be successfully exploited. It is our conviction that the nonlinear processing ability and the power to model a system without *a priori* knowledge of its mechanistic intricacies with neural networks can have significant implications for pharmaceutical sciences. We also wish to clarify that not all applications discussed here have been realized.

4.1. Epidemiology and Clinical pharmacy

Epidemiology is the research discipline concerned with the distributions and discriminants of various diseases in specific populations (9). Epidemiology aims at describing the health status of populations by quantifying the occurrence of diseases and discovering important 'trends' in their occurrence or resurgence. It also attempts to predict the number of occurrences of the disease and to achieve this objective, a variety of discriminant and stochastic modeling approaches have been employed. However, these approaches have not been found to be completely free of limitations. Typically, populations under study are considerably large which leads to difficulties in the identification and quantification of causative variables. Another crucial limitation of these approaches is their inadequacy to account for the effect of extraneous factors which are also many in number.

As ANN do not require the user to define the causative variables while modeling, we believe that it is interesting and worthy to evaluate the performance of this technology for modeling epidemiological occurrences. The inclusion of extraneous factors is conveniently possible as the user has complete freedom to decide the network topology and its elements. The advantage of discerning unknown interactions between causative variables or extraneous factors is also enticing. Hence, ANN technology seems to hold much potential for successful application in epidemiological research.

Clinical and community pharmacists struggle relentlessly to formulate better and efficient healthcare strategies for providing effective, safe and affordable healthcare. Hospital pharmacists vest the onerous responsibility of monitoring and managing serious epidemics, while clinical pharmacists play a critical role in the drug development process. We describe below certain strategies involving ANN technology which have been either realized or are worth a trial and would assist the healthcare personnel in realizing their objectives.

4.1.1. Medical decision-support systems

Healthcare personnel usually require incredibly large amounts of medical knowledge for rational and optimal therapeutic monitoring as a result of innumerable developments in the fields of medicine and elsewhere. Even experts have to labor diligently to keep themselves abreast of the current developments. Despite their utmost care and caution, misdiagnoses and mistreatments are not very rare and occur either due to the non-availability or the absence of the required expert. Such situations have motivated hospitals and physicians to accrue medical decision-support systems. These systems essentially are non-biological substrates, such as computers, which employ previous knowledge to analyze current data and assist in leading to a feasible solution. ANN in this field have stimulated much interest and have been proven to be promising. Stevens *et al.* have reported the ability of ANN to evaluate medical students' performances on

computer based simulations. They used ANN to model test selection patterns and found them to be 90% successful in judgment (10). We discuss below some relevant examples related to the treatment of cancer and cardiac diseases.

4.1.1.1. Cancer treatment

Maclin et al. have reported the use of ANN to diagnose cancer (11). They trained a network using the numerical ultrasound data of 52 patients and correctly identified renal cell carcinoma from renal cysts and other conditions without error. However, the method was not validated to yield statistically significant results. The ability of ANN to predict correctly the recurrence of breast cancer has been studied by Ravdin *et al.* (12). The network was trained using prognostic information from 1008 patients and its ability to determine the relapse probability was validated in a separate set of 960 patients. Ravdin and Clark also developed an ANN to predict the outcome of individual breast cancer patients over time using censored survival data and by including time as an additional prognostic variable (13). This network was validated to predict the probability of relapse at different times of follow up and allows plotting survival probability curves for individuals. Information from 1373 patients was used to train, predict and validate this network performance.

4.1.1.2. Cardiac diseases

Several clinical applications of ANN technology as aids in the treatment of cardiac diseases have been reported. Furlong and coworkers designed, trained and validated a network to predict the probability of acute myocardial infarction (AMI) based on the analysis of paired sets of cardiac enzymes (14). They also compared the performance of ANN with that of standard statistical techniques. They suggested that similar and broader applications are feasible within the domain of clinical decision-support. Baxt successfully designed an ANN to identify myocardial infarction in adult patients presented to an emergency

department with anterior chest pain and conclusively stated the network to be a valuable aid to clinical diagnosis of myocardial infarction (15). In another study, Baxt performed the analysis of the clinical variables driving decision in an ANN trained to identify the presence of myocardial infarction (16). He also developed a methodology to measure the impact of the input clinical variables on the diagnostic output. ANN technology has also been utilized for detecting coronary artery diseases noninvasively by the use of clinical examination variables and extracting information from the diastolic heart sounds associated with coronary occlusions. The fact that coronary stenosis produces sounds due to the turbulent flow of blood was successfully exploited to extract information regarding the pathologic status (17). Such methods are convenient, efficient and less time-consuming than conventional techniques. Tu and Guerviere made use of ANN to predict the length of stay in the intensive care unit following cardiac surgery (18). Their study was conducted in Canada where ICU facilities are limited and waiting lists exist for cardiac surgery. This study has been proven to be of immense value and lead to the improved utilization of ICU facilities and scheduling of patients and staff.

Clinical diagnostic aids using ANN technology have also been developed for hepatitis, thyroid disorders, radiographic diagnosis and sexually transmitted diseases (19-26). They have been found to be valuable for the efficient interpretation and utilization of pathological and laboratory data.

4.1.2. NDAs

New Drug Applications (NDA Form 356H) are documents furnished by manufacturers of new drug substances in the United States to the FDA requesting approval for the manufacture and marketing of the drug. The basic requirement of an NDA is the proof of safety and efficacy of the drug substance. A full report of all the clinical and preclinical studies in both animals and humans is to be included to

provide a better perception of the drug's safety. However, due to the myriad regulations, NDA submission has become a formidable task with regards to information compiling.

ANN technology may be employed to justify further the primary objective of an NDA: demonstration of safety and efficacy of the drug substance. As NDAs are replete with information from clinical and preclinical studies, such data may be used to train networks and hence perform simulations under various conditions and constraints. If subjects with the required and desired pathological status to perform clinical trials are difficult to monitor or find, the results of such tests performed in a few subjects may be simulated using neural nets to provide additional supporting data and hence justify the drug's efficacy and safety. Additionally, neural nets may also be employed to elucidate the mode and mechanism of action of new drug substances.

The National Cancer Institute has used ANN technology in the drug screening program for the development of anti-cancer drugs. They can employ ANN to predict the mechanism of action of various candidate drugs for cancer from their patterns of activity (27). However, as the FDA is a very stringent regulatory agency, adequate caution should be exercised to validate and prove the results for statistical significance prior to submission.

4.1.3. Post-market surveillance

The possible applications of neural networks in the monitoring of adverse drug reactions and the investigation of product recalls are described here.

4.1.3.1. Adverse drug reactions

Although efficacy and safety of drug substances are provisionally established during clinical and preclinical studies, drugs are liable to be used by a large number of patients within highly variable populations after their approval. Multiple diseases, concomitant medications and several other factors such as ethnic, genetic and

environmental attributes may further complicate the monitoring of the drug's safety in such patient populations. Hence, monitoring adverse drug reactions (ADR) undetected during preclinical tests is critical for the assurance of drug safety. In the United States, FDA has initiated a computerized collection of all such ADR incidents. This compilation of data is referred to as the spontaneous reporting system (SRS), and processed nearly 600,000 reports related to various drugs in 1990 (28, 29). As ADR monitoring in populations with varied genetic, dietetic, pathologic, geographic and social backgrounds is fundamentally a pattern recognition problem similar to the one described under epidemiology, we believe it may be interesting to apply neural networks to realize such goals. Neural networks in conjunction with ADR databases such as SRS may be successful in predicting the adverse response of drugs in patients whose pathological disposition is different from that previously observed or reported. Such studies may prove to be worthy in alerting individuals suffering from certain diseases that may make them vulnerable to certain drugs.

4.1.3.2. Product recalls

In 1978, the FDA in the United States introduced the system of product recalls as a protective measure for removing or correcting consumer products that are in violation of the laws administered by the FDA (30). It is our opinion that the FDA should develop a recall database which is manufacture-specific and incorporate the reasons for the failure of the product and update it when necessary. In order to regulate the compliance to cGMP, FDA may periodically review the recall database of each manufacturer. It may be a fruitful proposition for the FDA to use neural nets to discern any unnoticeable and undesirable trends in the product recalls which may alert the FDA to order an investigation into the cGMP compliance of the manufacturer. Such an approach may be useful in the detection of production lapses and is of prophylactic utility.

4.2. Drug design and molecular graphics

With the demonstration that the biological activity of chemical compounds is a mathematical function of the physicochemical parameters of the molecule, Hansch and coworkers added a new dimension to rational drug design (31). This approach was actively fostered and further ramified into various branches which we know today as quantitative structure activity relationships (QSAR), quantitative structure pharmacokinetic relationships (QSPR), molecular graphics and molecular modeling. We describe below applications of neural networks to problems in the above fields which have stimulated much interest.

4.2.1. QSAR

The fundamental concept on which all QSAR studies are based is the correlation of biological activity to various physicochemical parameters. Models are constructed assuming

$$Y = b_o + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + \ldots \quad \text{(Eq. 7)}$$

where X_1-X_n : any physicochemical parameter
Y : biological activity
b_n : a regression coefficient

This equation is not only seemingly simple but also severely limited. Although, this equation theoretically allows the inclusion of higher order and cross product terms, the practical difficulties involved are overridingly huge and annul this advantage. As neural networks do not suffer from such shortcomings, investigators have adapted this modeling philosophy and success has been reported.

Andrea and Kalayeh have implemented ANN technology in the QSAR studies of dihydrofolate reductase (DHFR) inhibitors (32). They have demonstrated that neural networks lead to enhanced surface fits and predictions, apart from precluding the need to define 'indicator variables'. They also reported that neural nets lead to the successful understanding of local structure activity relationships. However, they did allude that the training time currently is inconveniently large and efforts to decrease it are desirable. So and

Richards also reported similar findings while studying the QSAR of diaminopyrimidines as DHFR inhibitors (33). They claimed that neural nets can outperform conventional techniques in QSAR studies. Tetko *et al.* have studied the QSAR of a small number of molecules using derivatives of carboquinone as an illustration (34). They concluded that the application of neural nets leads to unambiguous classification and also demonstrated that the predictive capacity could be improved by the combined application of statistical analysis and ANN technology.

Neural nets have also been used to classify physiologically active substances (35). Other pertinent literature demonstrating similar applications is available (36, 37, 38).

4.2.2. Molecular graphics

A frequently encountered problem in molecular graphics is the display and analysis of datasets which have a greater number of descriptive physiological parameters than the number of compounds in the dataset. Pattern recognition display techniques have been found to be very informative, especially during the initial investigations when redundant information has not yet been eliminated. Plots from principal component analysis (PCA) and nonlinear mapping (NLM) are two techniques used for linear and nonlinear dimension reduction of high dimensional datasets.

Livingstone *et al.* have reported a novel method for the display of multivariate data in molecular graphics using neural nets (39). A dataset consisting of physicochemical properties for sets of biologically active molecules calculated by computational chemistry methods has been used and the successful reduction of the dimensionality of these multivariate datasets to produce two dimensional plots has been achieved. The results were compared with that of two other standard linear and nonlinear dimension reduction techniques and were found to be either superior to or atleast comparable with that of the other techniques. The primary

advantage of these display techniques is their ability to produce synopses of very large data matrices and minimize the possibility of chance correlations.

4.3. Formulation and Analysis

Drugs should be delivered in the appropriate fashion to elicit the desired therapeutic response. This constraint compels pharmaceutical scientists to devise highly efficient and effective delivery systems. Upon the completion of formulation, it is also indispensable that the pharmacist evaluate the dosage form for the desired response profile. Hence, formulation and analysis of delivery systems form the core of much of the activity of many scientists in the pharmaceutical industry. In this section, we explore the applications of neural nets in these areas.

4.3.1. Pilot-plant experiment design

Design of pilot-plant experiments is imperative at the outset of any drug delivery development process. It is also a valid objective to try and incorporate a sense of rationality rather than proceeding on a merely empirical basis when planning such experiments. This aim can be readily realized using neural nets in conjunction with literature data. Previously published data may be employed to perform simulations using neural networks in order to achieve a better understanding of the right formulation and processing parameters. It should be realized that such an approach will considerably decrease the tendency of the formulator to digress from the correct path. In fact, with the completion of more experiments in the laboratory, the training set of the network may be updated and hence increase its potential to accurately model the system. Perhaps professional organizations such as American Association of Pharmaceutical Scientists (AAPS) could sponsor the exchange and exploitation of data for this purpose.

4.3.2. Optimization of manufacturing processes

Optimization techniques have become an integral part of rational drug delivery and dosage form design in the pharmaceutical industry over the last decade. Schwartz has comprehensively enunciated the intricate details of various techniques and their application in the industry (40).

ANN technology, from the perspective of predictive modeling, has provided a meaningful and interesting alternative to statistical techniques. Currently, there are no methods to determine optimized input/output sets for neural networks and hence statistical methods are superior to neural networks in optimization. But, ANN technology competes well with conventional statistical techniques in pattern recognition (41).

Hussain *et al.* have reported an interesting application of neural nets in the development of a controlled release hydrophilic matrix capsule containing blends of anionic and cationic cellulose ether polymers. They achieved optimization of the *in vitro* drug release profile from the matrix using neural networks and response surface methodology (RSM). Their conclusions suggest that ANN predictions are more accurate than those of RSM (42). ANN technology can also be employed to optimize the performance of chemical plants in the manufacture of bulk drugs (43). To optimize the yields of chemical reactors in bulk drug manufacture, it is sometimes desirable that the model predict input conditions for specified outputs. Conventional modeling techniques are 'unidirectional' and cannot be inverted. A unique advantage of neural networks is to allow for the convenient 'inversion' of a complex simulation. Hence, neural nets have massive potential for optimization purposes.

4.3.3. Quality control and assurance

Neural nets seem to have great potential in the area of quality control and assurance. Quality control requires strict vigilance over processing steps to yield control variables which are within acceptable limits of variation.

Neural nets may be utilized to discern seemingly latent patterns in the variation of control variables as a function of various processing parameters. A typical illustration would be the quality control of tablet manufacture. Suppose the control variables weight, hardness, friability and diameter of tablets need to be monitored as the response of the myriad processing parameters. This objective can be readily realized using neural nets. The first advantage is the freedom to choose and include any number of causative variables as inputs. Secondly, the network's predictive power keeps progressively increasing with time as more data is obtained and the training set of the network is being updated. Assuming that hardness of the tablets is exhibiting an increasing trend, this fact can be readily detected by running the network in the predictive mode. Hence, neural nets may be used as tools to detect problems in production and help make attempts to investigate and rectify the cause in advance.

4.3.4. Interpretation of analytical data

Data obtained from various analytical techniques may be successfully interpreted using neural networks. As an example, the spectroscopic data characterizing an unknown substance may be analyzed for chemical composition using neural nets. This concept may be extended to interpret NMR spectra of various chemical entities. The plethora of information available regarding the NMR spectra of various molecules may be utilized to train networks and successfully achieve atleast partially, if not completely accurate predictions.

The successful classification of immunoelectrophoretic patterns presented as three dimensional vectors to ANN has been reported by Søndergaard and coworkers (44). This example also illustrates the application of digital image processing, a visual recognition technique in conjunction with ANN technology. Kratzer *et al.* have devised a method for the analysis of serum electrophoretic data using neural networks

(45). This method could correctly differentiate the pathologic and physiologic patterns and had an 86% success rate in diagnosis. This technology has also been applied for the quantitative interpretation of UV circular dichroism spectral information (46). An ANN method which is faster and noise tolerant for *in vitro* and *in vivo* spectrophotometric applications has been developed by Lin et al. (47). This technique may be employed to quantitatively analyze the information content in difficult and distorted spectra. Nerella et al. have reported the use of ANN in the calibration and prediction of Near Infrared spectroscopic determinations (48). However, the major concern expressed in their study was the tediously long timespan involved in the training of networks.

4.4. Delivery of macromolecules

The term 'macromolecules', in this context, alludes to molecules whose molecular weight is considerably greater than that of common drug entities (eg. MW > 500) and encompasses protein and peptide drugs. Due to the far-reaching developments in biotechnology and related fields, the production of potent macromolecules with great therapeutic efficiency has become convenient and cost-effective. The major hurdle delaying the advent of such drugs in common clinical practice is the present inadequacy of the pharmaceutical industry to develop efficient delivery systems. We describe certain strategies involving neural nets which we believe are valuable in achieving this goal.

4.4.1. Identification/prediction of protein structure

Holley and Karplus have articulately reviewed the applications of ANN technology in solving the challenging task of predicting the structure of a protein from its amino acid sequence (49). They state that neural nets are being used for turn prediction, prediction of surface exposure and disulfide bonding of cysteines, as well as the prediction of the backbone distance constraints. They report that these

methods have an accuracy of 63-65%. They also suggest that altering the information encoding methods in input and output variables may lead to enhanced predictions. The effect of varying the number of hidden units on the accuracy of the network has been illustrated in Figure 3. Heijne, while reviewing the computer based analysis of DNA sequencing and protein secondary structure prediction has discussed the utility of neural nets (50). The author comments that ANN applications have lead to small, but significant improvements in the accuracy of prediction.

Friedrichs *et al.* have developed a method involving associative memory Hamiltonians for generalized protein tertiary structure recognition (2). Pancoska and coworkers have performed the neural network analysis of the relationship between fractions of protein secondary structural components derived from X-ray crystallography using literature data (51). They have concluded that the crystallographic data may have significant effects on the stability of the spectroscopic analyses (FTIR, Raman and UV circular dichroism) derived from such datasets.

A fully automated methodology to recognize conserved subsequences in a set of multiply aligned protein sequences using a back-prop algorithm has also been developed (52). A comprehensive review of the applications of ANN in the prediction of structural and functional features of proteins has been published by Hirst and Sternberg and the reader is referred to such reviews for further details (53). Thus, ANN technology has contributed significantly to enhance our power in protein structure prediction.

4.4.2. Formulation of protein drugs

Development of efficient delivery systems for protein drugs is one of the most challenging task currently being encountered by pharmaceutical formulators. Protein and peptide drugs being structurally complex and 'highly fragile' often cannot be formulated by conventional techniques. Primary concerns in the formulation of protein drugs have

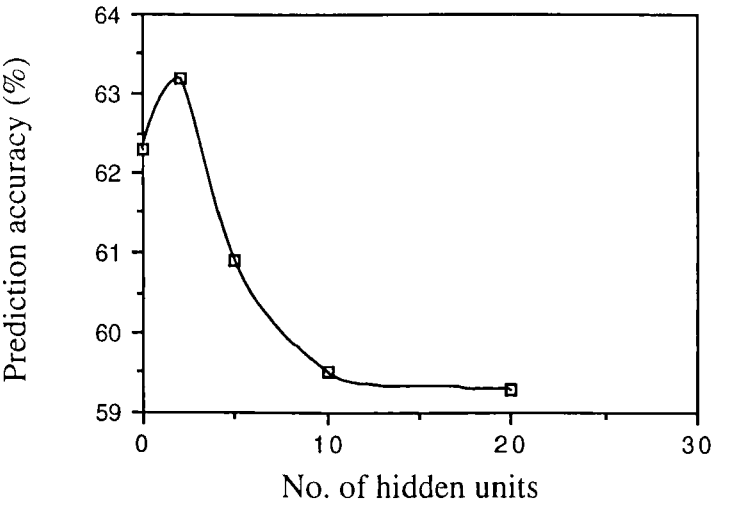

FIGURE 3
Dependence of prediction accuracy on the number of hidden units in the network. Data adopted from Ref. 48.

been comprehensively discussed by Chen (54). Inadequate *a priori* knowledge of the degradation pathways and conformational changes of these chemical entities in addition to current limitations to develop analytical methodologies has further slowed progress. We believe this problem may be appropriately addressed by utilizing neural nets. As neural nets have the ability to develop autonomous computational systems, the problem of optimizing protein drug formulation ideally suits the application of ANN technology.

It has been reported that proteins and peptides may have 'efficacy-specific sites' (partial fragments of the entire chemical chain) which are solely responsible for the therapeutic effect. Variations particular only to such sites will also lead to complete loss of therapeutic action and such information can neither be incorporated into nor extracted by conventional modeling techniques. Hence, the application of neural nets to model such situations is exciting and of great potential value.

The thermal behavior of protein and peptide drugs is often not governed by the conventional Arrhenius equation. Thus, neural nets may be employed to study the temperature dependence of protein drugs. This concept may be extended to encompass their dependence on variations in several environmental factors like pH and mechanical stress.

The application of neural networks to interpret UV circular dichroism spectra of proteins has already been mentioned. Bohm and coworkers have used a back-prop network to quantitatively analyze the protein far UV circular dichroism spectral data (46). They have successfully extracted information about five different secondary structure fractions with satisfactory correlations between calculated and measured structural data. Studies such as this suggest the potential applications of neural networks in the development of analytical strategies and delivery systems for protein drugs.

4.5. Biopharmaceutics

The efficiency of a drug delivery system depends to a significant degree on the fraction of the drug substance in the formulation that is actually delivered to the general systemic circulation in order to elicit its therapeutic effect. For this reason, the terms bioavailability and bioequivalence have gained importance in the recent past. FDA requires cogent quantitative justification of bioavailability or bioequivalence claims from all manufacturers. We will now investigate the implications of artificial neural nets for these purposes.

4.5.1. Modeling of bioavailability data

Bioavailability, essentially is the measure of the *in vivo* performance of any formulation (i.e., the rate and extent of drug absorption) However, the determination of the bioavailability of a formulation in a very large number of subjects is expensive and time-consuming and any methods to supplement this function are desirable. It may well be

feasible to explore the possibility of modeling bioavailability data of formulations using neural networks. One possibility is the determination of a correlation between the bioavailability of the formulation and its *in vitro* attributes. As an illustration, the bioavailability of a certain tablet formulation may be correlated to the dissolution profile, disintegration time and various other formulation factors of the tablets.

Another possibility is an attempt to decrease the number of subjects used for bioavailability testing. It may be possible to retain the same statistical power of prediction while using fewer subjects in the testing set by discerning certain complex correlative patterns in the bioavailability data. This goal, if realized will lead to considerable savings for the industry in terms of human and monetary resources. A third possibility may be to train networks using data obtained from bioavailability studies and later use them to predict the bioavailability of the formulation in a population with a certain pathological disposition. Hence, ANN technology has some very useful implications for the determination of bioavailability.

4.5.2. In vitro - In vivo correlations

For reasons of cost, time and safety *in vitro - in vivo* correlations are of great interest to the pharmaceutical industry. Over the last three decades, many efforts to realize this objective have been cited in the literature. As the correlation of *in vitro* and *in vivo* performance of a formulation is fundamentally a pattern recognition task, we believe that neural nets may hold immense potential in this area. The problem of predicting the *in vivo* performance of a formulation in a complex environment based on an artificial *in vitro* evaluation may be substantially simplified through the use of ANN. This also illustrates an instance where the convenient 'inversion' of the model is made possible due to the bidirectional nature of the neural networks. Required *in vitro* controls may be determined for specific *in vivo*

performance by interchanging the input and output variables of the network.

4.5.3. Bioequivalence testing

As has been described in the modeling of bioavailability data, two different formulations can also be evaluated for equivalent *in vivo* performance using ANN technology. Advantages like the freedom to include a large number of causative variables and potential for a possible decrease in the number of subjects used for testing, are also appropriate for bioequivalence testing. Hence, neural nets may be successfully employed in bioequivalence testing and, if indeed realized, may eventually lead to savings for the industry and reduced health care expenses for the public.

4.6. Pharmacokinetics

ANN technology has been widely applied for the purposes of sensor, cognizance and control processing. These objectives also form the pertinent interests of pharmacodynamics and thus, developments in neurocomputing will have significant consequences on the modeling approaches in pharmacodynamics.

4.6.1. Pharmacokinetic and Pharmacodynamic modeling

The primary goal of pharmacodynamics is to develop efficient quantitative modeling approaches to monitor the complex kinetic interactions between drug substances and the physiological system. ANN technology offers an exciting alternative to the many strategies which have been investigated to monitor complex kinetic processes. Veng-Pedersen and Modi have introduced the concept of neural network modeling and have added a new perspective to pharmacodynamic modeling (55). As an example, they have demonstrated the successful prediction of the effect of alfentanil on the heart-rate through the use of neural networks. The network performance was evaluated under

complicated conditions by employing a complex dosing regimen of alfentanil.

Hussain *et al.* have investigated the feasibility of developing a neural network to predict the pharmacokinetic parameters in human beings using laboratory animal data (56). They compared the network performance with allometry, a conventional technique to achieve the same objective. Various network topologies and training algorithms have been employed to obtain satisfactory correlations. A comparison of the correlations between observed and predicted parameters using neural networks and allometry have proven neural networks to possess superior predictive ability.

In an effort to delineate the utility of the back-prop network, Erb has developed a network to estimate the creatinine clearance using gender, age, weight and serum creatinine as the input variables (41). He used two different sets, with 200 subjects each, for training and prediction and observed an excellent correlation between the ANN predictions and the observed clearance values. Hence, neural nets offer an effective and faster modeling alternative in pharmacodynamics.

4.6.2. Population pharmacokinetics

Population pharmacokinetics is concerned with the monitoring of complex kinetic interactions in large populations. Thus, additional limitations on the applicability and utility of conventional modeling practices are imposed leading to a boggling quandary. It is our firm conviction that the application of neural network modeling in such situations will prove to be a judicious solution. The phamacodynamic and pharmacokinetic information from such a large population will further enhance the network's ability to understand better and model the kinetic processes in the population. Limitations related to the very large number of causative variables and the inability to decipher effects of extraneous variables or interactions between causative variables are obviously precluded with neural networks.

5. COMPARISON WITH STATISTICAL TECHNIQUES

The hypothesis primarily emphasized in this article is the superior ability of neural networks to model poorly understood systems relative to the performance of conventional statistical techniques. ANN can autonomously develop an ability to extract hidden correlative patterns whereas classical statistical techniques require the explicit statement of such information by the user. Hence, the adaptive response of neural networks is of particular significance in the analysis of datasets with complicated correlation structures such as incomplete or irregular time-series of highly intercorrelated variables. Such problems are frequently encountered in pharmaceutical sciences and application of conventional statistical techniques to solve these problems is practically infeasible. This section will support the above hypothesis by citing pertinent examples. We have compared the performance of three standard statistical techniques with that of neural networks. In all cases, the data has been adapted from published reports.

5.1. Discriminant analysis

To investigate the utility of neural networks, Reibnegger et al. have compared the performance of neural networks and linear discriminant analysis (LDA) (19). The problem under study was the classification of three diseases [fatty liver (FL); chronic persistent non-A, non-B hepatitis (CPH); and chronic aggressive non-A, non-B hepatitis (CAH)] using concentrations of urine neopterin, serum aspartate aminotransferase (SAT) and serum alanine aminotransferase (SLT) as taxonomic discriminators.

The ability of neural networks to extract hidden information was demonstrated by designing two different networks with three and four inputs each (NN1 and NN2 respectively). The results of the simulations in all the three cases (NN1, NN2 and LDA) have been summarized in Table 1. Classification accuracy (CA) is the percentage of correct distinction and transinformation (TI) is the reduction in the

TABLE 1

Comparison of the Performance of Neural Nets and Discriminant Analysis. Data Adapted from Reference 19.

Method	Classification accuracy (CA)	Transinformation (TI)
NN1	95.24%	1.3381
NN2	97.62%	1.4231
LDA	76.19%	0.5432

uncertainty of the system, which signifies the efficiency of the method.

The superior predictive power of neural networks is obvious from the results. The only difference between NN1 and NN2 is the inclusion of SAT:SLT ratio as an input to NN2. Despite this difference, the performance of NN1 and NN2 is remarkably comparable. Moreover, the success rate of NN1 is approximately equal to that of NN2. This observation demonstrates the adaptive response of neural nets and their ability to sense the correlation between SAT and SLT presented to the network as separate inputs and compute the ratio on their own. The reduction in the uncertainty of the systems, measured quantitatively as TI, is also similar for NN1 and NN2 and is close to TI_{max} = 1.5538.

In contrast, the omission of SAT/SLT ratio leads to poor predictions by LDA. In fact, if the ratio was not explicitly stated, LDA could not differentiate between CPH and CAH and only FL could be correctly classified. This illustration unequivocally demonstrates the superior performance of neural nets in such applications.

5.2. Regression techniques

The extensive application of regression techniques in QSAR studies to fit large datasets has already been mentioned

(32, 33). The results from the QSAR study of DHFR inhibitors by Andrea and Kalayeh will be used to compare the performance of multiple linear regression techniques relative to neural networks. In this study, a dataset containing 256 DHFR inhibitory activities and their physicochemical properties was used to compare neural networks (NN), multiple linear regression without indicator variables (MLR) and multiple linear regression with indicator variables (MLRI). The results obtained by the application of all the three methods are compiled in Table 2.

An examination of the R^2 values and the number of outliers in this table reveals that neural networks gave the best R^2 values irrespective of the number of datapoints used. This fact is also demonstrated in Figure 4 where plots of R^2 values against the number of datapoints for NN and MLRI have been obtained. The plot for NN is a flat plateau and does not show any appreciable variance. In contrast, MLRI plots show great variance in the values of R^2. In fact, the best correlation (R^2 = 0.774) with MLRI is not comparable even with the worst correlation (R^2 = 0.794) using NN. Figure 5 shows similar plots of number of outliers against the number of datapoints. Here also, NN always showed minimum number of outliers and the variance amongst the outliers is not remarkable. Again, MLRI demonstrates higher number of outliers with great variance. These facts illustrate the ability of NN to produce better fits of data relative to conventional regression techniques. MLR, even after the cumbersome inclusion of indicator variables, does not compete with NN performance.

5.3. Response surface analysis

Hussain and coworkers have compared RSM and ANN analyses illustrating a neurocomputing application in pharmaceutical product development (42). Optimization of the *in vitro* drug release profile of a polymeric matrix capsule was the objective of the study. A four-component simplex mixture

TABLE 2

Comparison of the Performance of NN, MLR and MLRI in the QSAR Study of DHFR Inhibitors. Data adapted from Reference 32.

Method	R^2	No. of outliers	No. of datapoints
NN	0.850	12	256
MLR	0.494	61	256
MLRI	0.773	20	256
NN	0.794	10	245
MLR	0.244	41	245
MLRI	0.656	15	245
NN	0.815	4	132
MLR	0.387	23	132
MLRI	0.769	11	132
NN	0.796	1	113
MLR	0.268	5	113
MLRI	0.452	5	113

experimental design was used and dissolution half-time ($T_{0.5}$) and the release exponent (N) of the capsule were specified as the response variables.

Fifteen different polymeric compositions of the matrix were formulated and the values for $T_{0.5}$ and N for each formulation were determined. This dataset was used for both ANN and RSM analyses. A separate test-set of eight different formulations was also formulated and the values for the response variables of this set were determined. ANN and RSM predictions were made for the test set and compared with the experimentally determined values.

The difference between the observed and predicted values of $T_{0.5}$ and N are listed in Tables 3 & 4 respectively. These

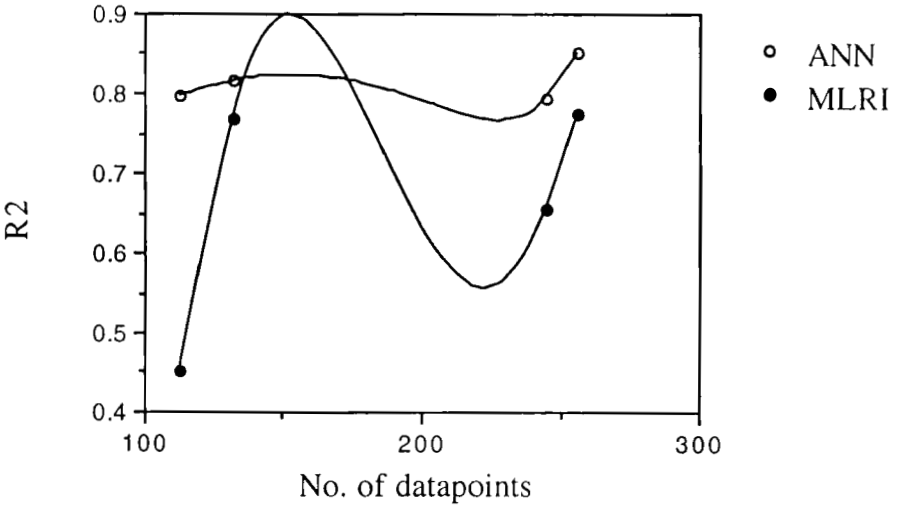

FIGURE 4
Comparison of the performances of ANN and MLRI. Plots of R^2 against the number of datapoints in the set. Data adopted from Ref. 32.

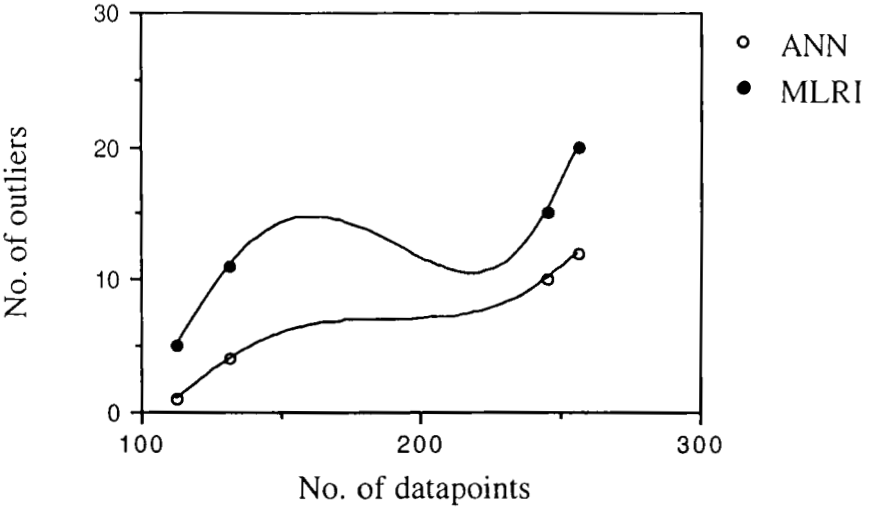

FIGURE 5
Comparison of the performances of ANN and MLRI. Plots of number of outliers against the number of datapoints in the set. Data adopted from Ref. 32.

TABLE 3

Prediction Errors for Release Exponent (N) using ANN and RSM Analyses. Prediction Error (PE) was calculated as the difference of observed and predicted values. Data adapted from Reference 42.

Formulation No.	PE (ANN)	PE (RSM)
1	-0.03	0.08
2	0.02	0.13
3	-0.05	0.07
4	0.04	0.14
5	-0.08	0.10
6	-0.05	0.05
7	-0.02	0.07
8	-0.06	0.02

TABLE 4

Prediction Errors for Dissolution Half Time ($T_{0.5}$) using ANN and RSM Analyses. Prediction Error (PE) was calculated as the difference of observed and predicted values. Data adapted from Reference 42.

Formulation No.	PE (ANN)	PE (RSM)
1	-0.63	-2.16
2	0.04	-1.80
3	-0.28	-2.32
4	-0.03	-1.73
5	0.28	-1.45
6	0.45	-1.55
7	0.13	-1.68
8	0.00	-1.76

tables show smaller error values between predicted and observed responses when ANN was used than those obtained using RSM analysis. This fact further justifies the hypothesis of superior performance by neural networks.

Livingstone and Manallack have investigated the occurrence of 'chance correlations' amongst variables in neural network analysis (8). They concluded that the possibility of chance effects in ANN analysis cannot be completely eliminated and found the ratio of connections to observations to be an important determinant in their occurrence. They have also suggested optimal values for this ratio in regression and discriminant analysis using neural nets. Cross-validation with real datasets to examine the predictive ability and objectively eliminate the possibility of chance effects has been strongly recommended.

6. CONCLUSION

Artificial neural networks have lead to the evolution of a novel modeling philosophy as a feasible alternative to conventional modeling techniques in pharmaceutical sciences. Preliminary work in this area has been promising, and there is great scope for future investigations. In particular, the unique advantages of neural networks, such as nonlinear processing capacity and an ability to model poorly understood pharmaceutical systems, are not only enticing but also have consequential implications for pharmaceutical sciences. However neural nets are not useful in illustrating the mechanistic nature of the correlation established between variables. Rather, they behave as 'blackboxes' for information processing. Presently, the training time for networks may be long which is inconvenient. However, the applications of neural networks are limited only by our imagination.

Developments, such as those cited in this article re-emphasize the need for pharmaceutical scientists to participate in communion with their colleagues elsewhere to accomplish successfully challenging tasks being faced by our

industry. Pharmaceutical scientists should be abreast of the current innovations in esoteric and diverse areas and demonstrate a willingness to collaborate.

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