Chapter 5

Artificial neural network modeling in Pharmaceutical research: theory and applications

5.1 INTRODUCTION

Artificial neural networks (ANNs) technology is a group of computer methods for modeling and pattern recognition, functioning similarly to the neurons of the brain. The brain learns from its experience. In the brain, a biological neuron receives inputs from many external resources, combines them, performs a non-linear operation, and then makes a decision based on the final results. The ANNs are a type of mathematical model that simulates the biological nervous system and draws on analogues of adaptive biological neurons. A major advantage of ANNs compared to statistical modeling is that they do not require rigidly structured experimental designs and can map functions using historical or incomplete data.

Over the past decade, neural networks have received a great deal of attention among scientists and engineers and they are being touted as one of the greatest computational tool ever developed. Much of this excitement is due to the apparent ability of neural networks to emulate the brain's ability to learn by example which is in term enables network to make decision and draw conclusion, when presented with complete information. Moreover, at some primitive level, neural network seem able to imitate brain's creative process to adapt to novel situation. It is a very good statistical tool for many numeric as well as non numeric calculation. It closely resembles the neural systems of animal in its performance[1].

ANNs are known to be a powerful tool to simulate various non-linear systems and have been applied to numerous problems of considerable complexity in many field including engineering, psychology, medicinal chemistry and pharmaceutical research. They are good recognizers of patterns and robust classifiers, with the ability to generate when making decision based on imprecise input data.

5.2 ARTIFICIAL NEURAL NETWORKS MODELING

Artificial neural networks are computer methods that simulate learning and generalization behavior of the human brain through data modeling and pattern recognition for completed multidimensional problems. A significant difference between an ANN model and a statistical model is that the ANN can generalize the relationship between independent and dependent variables without a specific mathematical function. Thus, an ANN works well for solving nonlinear problems of multivariate and multiresponse systems. An artificial neural network is a biologically inspired computational model designed to simulate neurological processing ability of human brain. The ANN mimics working of human brain. The ANN seem to fulfill cherished dream of scientist develop machines that can think like human beings. The ANN is formed from hundreds of single units, artificial units, artificial neurons, connected with coefficients (weights) which constitute the neural structure. They are also known as processing units (PE) as they process information. As average brain contains about 100 billion neuron, each of which has 1000-10000 connections with each other neurons. Neurons consist of a cell body which includes nucleus that controls the cell activity, many fine treads, dendrites, that carry information into cell, and one longer thread known as the axon which carries the signal away (figure 5.1).

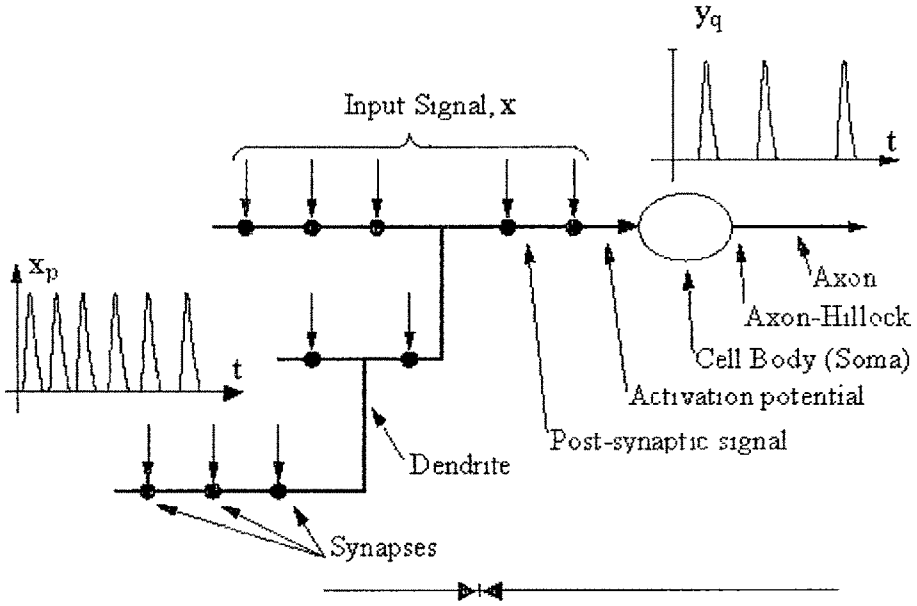


Figure 5.1. Conceptual structure of a biological neuron.

Impulses pass along the axon to the synapses, the junction between one neuron and the next one. The signals are passed from one to the next in all or none fashion. Neurons are organized in a fully connected network and act like messenger in receiving and sending impulses. The result is an intelligent brain capable of learning, prediction and recognition. There are many types of neural networks designed by now and new ones are invented every week but all can be described by the transfer functions of their neurons, by learning rule, and by the connection formula. Error back-propagation network developed by Rumehart et al. is most widely and successfully applied architecture[2]. The error back propagation network consists of input layer, one or more hidden layers and one output layer. The input layer provides data from the external world. The mapping of input data by neural network into interpretable results is done by a representative signal generated by output layer. The ability of neural networks to classify information separated by non-linear boundaries depends on hidden layers. The units in neighboring layers are fully connected to synapses. The neuron, building component of ANN receives many signals as weighted process variables from the response of other units. The strengths of connections between two units are called "weight". A common design of artificial neuron is given in figure 5.2[2,3].

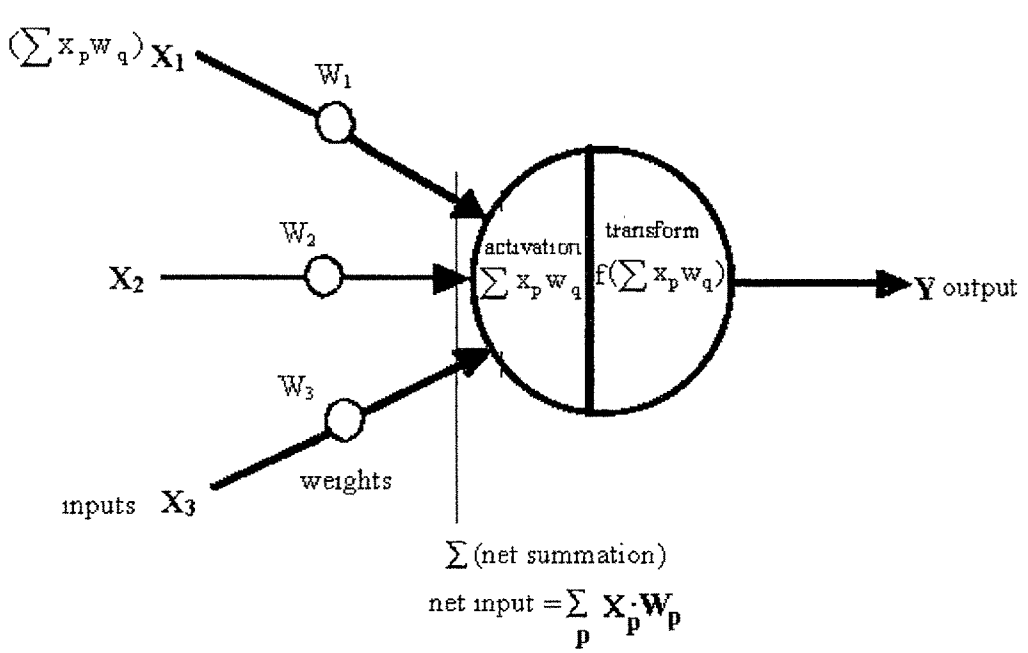


Figure 5.2. A common design of a node in an artificial neural network.

In each hidden layer and output layer the processing unit sums its input form previous layer and then applies the sigmoidal function to compute its output to the following layer according to the following equation.

$$y_q = \sum w_{pq} x_p \qquad (1)$$

$$f(y_q) = \frac{1}{1+\exp(-\alpha y_q)} \qquad (2)$$

Where, w_{pq} is the strength of the connections between unit q in the current layer to unit p in the previous layer, x_p is the output value from the previous layer, $f(y_q)$ is conducted to the following layer as an output value, and α is a parameter relating to the shape of the sigmoidal function. The advantage of this function is that it can accommodate large signal without saturation while allowing small signals to pass without excessive attenuation.

Nonlinearity of the sigmoidal function is strengthened with an increase in α. The ANN learns an approximate nonlinear relationship by a procedure called "training", which involves varying weight values. Training means a search process for the optimized set of weight values, which can minimize the squared error between the estimation and experimental data of units in the output layer. A back-propagation method has widely been applied for training ANNs[3]. Training is long iterative process, and an ANN often gets stuck in a local minima. Certain empirical techniques have been reported to improve the convergence of ANNs in the global minima [4]. We can greatly reduce the number of iterative training by using the extended Kalman filter algorithm, and also can avoid the ANN getting stuck in a local minima using the simulated annealing technique[5].

Carpenter and Hoffman introduced an equation relating to the number of units in the input layer, the hidden layer and the optimal output layer to enable reasonable prediction of each response[6]:

$$n_s = \beta\{n_h(n_i + 1) + n_0(n_h + 1)\} \quad (3)$$

Where, n_h is the number of hidden units, n_i is the number of input units, n_0 is the number of output units, and n_s is the number of training data pairs. The constant β is the parameter relating to the degree of over determination.

A cross-validation technique such as a ''leave-one-out (LOO) method'' should be applied to ensure the optimality of an ANN structure[7-9]. One data pair is systematically removed from the training data set, and the ANN is then trained by using the reduced data set. Akaike's information criterion (AIC) can be applied to evaluate the optimality of ANN[10]:

$$AIC = n_s \times \ln(SS) + 2 \times n_w \quad (4)$$

Where, n_s is the number of data pairs, n_w is the number of weights in the ANN, and SS is the residual sum of squares between observed and predicted response variables.

A very common approach to select the optimal number of hidden nodes is by trial and error method using the aforementioned rules as guidance. Jadid et al. proposed an upper limit of number of hidden nodes on an ANN model using the following equation[11].

$$N_{hidden} = \frac{N_{trn}}{[R + (N_{inp} + N_{out})]} \quad (5)$$

Where, N_{hidden} is the number of hidden nodes; N_{trn} is the number of training sample; R is a constant with values ranging from 5 to 10, N_{inp} is the number of inputs and N_{out} is the number of outputs.

The application of back-propagation technique to a problem requires three simple steps-network design, learning or training and usage. The number of process variables and response units are determined by data of problem after finalizing the number of layers and neurons in each layer. Then the network is subjected to learning process. The leaning

through weight adjustment can be supervised or unsupervised. The network is repeatedly presented with an input pattern and a desired output response in supervised learning. The training process terminates when error goal is near zero and neural network produces correct response for given input patterns. In unsupervised learning, no desired response is available to guide system and the learning is through input pattern alone. The neural network system itself then decides features to be used for grouping input data and this process is called self-organization or adaptation. The speed of learning is actually the rate of convergence between the current solution and the global minimum. Momentum helps the network to overcome obstacles (local minima) in the error surface and settle down at or near the global minimum. The most common training algorithm is based on the Delta rule, according to which each training iteration (frequently referred to as "epoch") is described by the following general equation:

$$\text{New weight change} = \text{Learning rule} * \text{Error} + \text{Momentum} + \text{Last weight change} \quad (6)$$

In feed forward step starts with presentation of process variable pattern and continues through activation level to propagate through hidden layers. The processing unit sums the input and applies sigmoidal function in the hidden layer to compute its response as shown in figure 5.3.

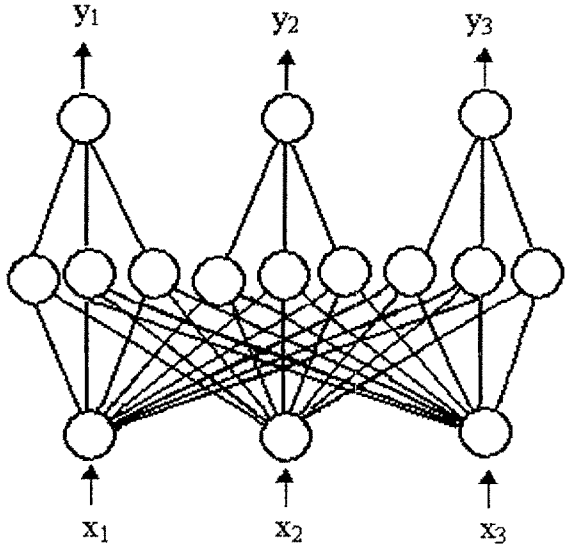


Figure 5.3. A three layered artificial network.

In feed back step, error values are calculated for all processing units and weight changes are calculated for all interconnections. The calculations start at output layer and progress backward through the network to input layer. Thus each neuron has one additional weight as an input that allows an additional degree of freedom when trying to minimize training error. The network is ready for use after design is completed and system is trained.

5.3 APPLICATION OF ANNs MODELING IN PHARMACEUTICAL RESEARCH

The potential applications of ANN methodology in the pharmaceutical sciences are broad. ANNs application can be summarized into classification or pattern recognition, prediction and modeling. The application of ANNs range from interpretation of analytical data (modeling the pharmaceutical analysis in quality control, drug modeling (QSAR and molecular modeling), protein structure and function prediction, dosage form design (optimization of manufacturing processes), and clinical pharmacy through biopharmacy (pharmacokinetics and pharmacodynamic modeling, in vitro in vivo correlation).

5.3.1-Pattern Recognition and Interpretation of Analytical Data

The ANNs can recognize patterns from a complex analytical data. The ANNs have applied to determine the composition of unknown sample when the spectrum of unknown is a superposition of known spectra. It used whole spectrum in identification process instead of only the individual peaks. The multiple linear regression (MLR) method is a tedious task requiring the specification of a polynomial function for each peak to be regressed and requires an iterative process, a spectrum decomposition and regeneration to systematically synthesized spectrum closely matching the true spectrum.

The ranitidine hydrochloride, an antihistaminic drug exists in polymorphic forms known as Form 1 and Form 2. Ranitidine hydrochloride tablets formulation is a multi-component tablet formulation in which there is significant overlap of spectral pattern of ingredients. S. Agatonovic-Kustrin et al. compared diffuse reflectance IR spectral analysis[12] and X-ray diffraction[13,14] with ANNs as a data modeling tool to develop a simple, sensitive and

rapid method for the qualitative and quantitative control of ranitidine-HCl. The ANN was trained to recognize specific patterns of constitutes of the formulations from the overall spectral pattern. The classification network identified and quantified all components in tablets when exposed to complex formulation containing only Form 1 crystals. There was no need to extract the active ingredient and Form 1 was successfully quantified in the presence of tablets excipients and additives.

Madden et al. have used ANN as the basis of computer-assisted optimization method for selection of optimal gradient conditions for anion separations[15]. The ANNs with 1-10-9 architecture has been found to be rapid and accurate in predicting retention times for anions in linear gradient elution ion chromatography with hydroxide eluents.

5.3.2 Preformulation

ANN model have been used in the preformulation tool to determine the physicochemical properties of amorphous polymers such as the hydration characteristics, glass transition temperatures and rheological properties by Ebube et al[16]. The relationships between the compositions of polymer blend and the water uptake profiles; the relationship between composition of polymers blends and viscosity of polymers solutions; and the relationship between moisture content of polymers and their glass transition temperatures were learned by the trained ANN model. The results of this study indicated that the ANN model accurately predicted the water-uptake, glass transition temperatures and viscosities of different hydrophilic polymers and their physical blends with a low prediction error (0-8%). It demonstrated the potential of the ANNs as a preformulation tool to evaluate the characteristics of amorphous polymers.

5.3.3 Optimization of Pharmaceutical Formulations

The prediction of pharmaceutical responses based on the polynomial equation and response surface methodology is often limited to low levels, resulting in the poor estimation of optimal formulations. In order to overcome these shortcoming, a multi-objective simultaneous optimization technique incorporating an ANN has been

developed[17,18]. The reliability of ANNs in optimizing controlled release capsules and ketoprofen hydrogel ointment has been demonstrated by Hussain et al[19]. A trained ANN model has been successfully employed to predict release profile and optimize formulation of various drug formulations such as aspirin extended release tablets[20,21], diclofenac sodium sustained release matrix tablets[22], salbutamol sulfate osmotic pump tablets[23] and transdermal ketoprofen hydrogel[24].

Takayama et al. applied an ANNs model to optimize controlled release theophylline tablets prepared with the mixture of hydroxypropylmethyl cellulose with lactose and cornstarch[25]. The plasma concentration profiles were simulated based on the pharmacokinetic parameters of theophylline. The results predicted by the trained ANN model agreed well with the observed values. Chen et al. has also used artificial neural network (ANN) and pharmacokinetic simulations in the design of controlled-release formulation[26]. Three out of the four predicted formulations showed very good agreement between the ANN predicted and the observed in vitro release profiles based on difference factor f_2.

Vaithiyalingam et al. used the ANN to model the effect of process and formulation variables, viz., coating weight gain, duration of curing, and plasticizer concentration on in vitro release profile of verapamil HCl from multi-particulate beads formulated with a novel aqueous-based pseudolatex dispersion[27]. The observed drug release data of the optimized formulations was close to the predicted release pattern, based on the ANN model

5.3.4 In Vitro In Vivo Correlations

The in vitro-in vivo correlations (IVIVC) are of great interest for pharmaceutical industry to avoid bioequivalence studies that are predicted to produce negative results. ANNs applied to in vitro-in vivo correlations have the potential to be a reliable predictive tool that overcomes some of the difficulties associated with classical regression methods, principally that of providing an a priori specification of the regression equation structure.

Dowel et al. has developed a number of unique ANN configurations to predict IVIVC from different formulations of same product[28]. Gobburu et al. has also applied a quantitative structure-pharmacokinetic relationship (QSPR) of beta-blockers using ANNs[29]. They reported that the ANN-predicted values that ANNs showed a good capability to predict in vivo results from in vitro experiments.

5.3.5 Quantitative Structure-Activity Relationships (QSAR)

Quantitative structure-activity relationships correlate structure or property descriptors of compounds with chemical or biological activities. All QSAR studies are based on the fundamental concept of interdependence of biological activities on physicochemical parameters. The physicochemical descriptors and topological parameters can be determined by computational methods.

Jaen-Oltra et al. has developed a new topological method to predict antimicrobial property of quinolones derivatives on the basis of their chemical structures[30].

An ANN with suitable set of topological descriptors and training algorithms was used to determine the minimum inhibitory concentration of quinolones. Gobburu et al. developed the neural networks to predict the quantitative structure pharmacokinetic relationships (QAPR) of beta adrenoreceptor antagonists in humans[31]. A neural network with congeneric series of ten bet-blockers having well established critical pharmacokinetic parameters was constructed and tested for its ability to predict the pharmacokinetic parameters from the octanol/water partition coefficient, the pK_a, or the fraction bound to plasma proteins. Neural networks predicted values showed better agreement with the experimental values than those predicted by multiple regression techniques (average difference = 47%).

Nestorov et al. compared the predictive performance of a mechanistically based model with an empirically ANN based model for the relationship between the tissue distribution and the lipophilicity of a homologous series of 5-n-alkyl-5-ethyl barbituric acids in the rat. The mean prediction error (ME) of the mechanistic model was 18 % (range, 20 to

57%), indicating a tendency for overprediction; the Mean squared prediction error (MSE) is 32% (range, 6 to 104%)[32]. The ANN model had almost no bias: the ME was 2% (range, 36 to 64) and had greater precision than the mechanistic model, MSE 18% (range, 4 to 70%).

5.3.6 Quantitative Structure-Property Relationship (QSPR)

Increasing number of neural network models are currently published for predicting various physicochemical properties from the molecular structures. In drug discovery phase, it would be valuable, if certain physicochemical properties could be calculated before synthesizing or purchasing a screening library. Lipophilicity and water solubility are properties, which can be used as rough early ADME screens to reject probable development failures as early as possible. Clark and co-workers used a data set containing 1085 compounds for developing a neural network model for $logP_{oct}$ prediction from the results of semi empirical AM1 calculations[33]. Subsequently, they proposed. Eros et al. developed neural network models for $logP_{oct}$ calculation using a database of 625 molecules, 98% of which are registered drugs showing high structural diversity[34]. The standard deviations of the fitting and prediction errors were s = 0.48 and s = 0.72, respectively.

Several research groups have modeled the normal boiling point of hydrocarbons. Predictive neural network models have been published for alkanes[35], alkenes[36] and for diverse hydrocarbons[37]. As expected, the models typically show good fitting and prediction statistics with less than ten simple descriptors. In the most recent work, Goll and Jurs[38] applied artificial neural network to predict the vapor pressures of hydrocarbons and halohydrocarbons from molecular structure. The neural network model with 7-3-1 architecture predicted the test set with a root mean square error of 0.209 (n = 52). Yaffe et al. modeled Henry's law constant using both fuzzy ARTMAP and feed forward neural network. The heterogeneous data set (n = 495) included compounds with oxygen, sulphur and nitrogen containing functional groups and halogens[39]. The logH values ranged from 26.72 to 2.87. Topological descriptors were used as input parameters. The average absolute errors for the test set of 74 members were 0.13 and 0.27 logH units for fuzzy

ARTMAP and the feed forward network, respectively. Liu et al. used five topological indices as input descriptors for the neural network with 5-5-3 architecture in predicting the refractive index, density and boiling point for alkenes. The training set contained 49 members[36]. Standard error of 0.13% was found the refractive index and 0.4% for density using a test set of 16 alkenes.

Sild and Karelson developed NN models for predicting dielectric constant and Kirkwood function using a data set of 155 organic liquids with extensive structural diversity and a range of 1.87–46.5 for the dielectric constant. Separate models with 5-5-1 configuration were developed for both dielectric constant and the Kirkwood function[40]. The average prediction error for the dielectric constant was 27.0% and for the Kirkwood function 4.1%. Tettech et al. have also developed a radial basis forward neural network for simultaneous prediction of flash point and boiling point[41]. The database contained 400 organic compounds with flash points between -60 °C and 200 °C. The average absolute error with for the test set in flash point prediction was 11.9 °C with a 26-36-2 configuration. Suzuki et al. developed an NN model for predicting liquid viscosity at a standard temperature of 20 °C[42] and subsequently, a temperature-dependent model[43]. The best model showed a root mean square error of 0.148 log units for the test set of 79 compounds and 133 data points.

5.3.7 Structure Retention Relationships (SRR) Methodology

Predicting chromatographic behavior from molecular structure is one of the main goals of the structure-retention relationships methodology. Tham et al. has applied artificial neural network in quantitative structure–gradient elution retention relationship of phenyl thiocarbamyl amino acids derivatives[44]. A five-descriptor nonlinear computational neural network model was used for estimation of chromatographic retention time values for a data set of 18 amino acids. The training set RMS error was 1.773 and the testing set RMS error was 0.8377. Based on the RMS errors of the training and testing sets and high correlation of predicted versus experimentally values (R>0.97), it is clear that a link exists between structure and chromatographic separation.

The usefulness of ANNs for modeling retention times in HPLC optimization to correlate the chromatographic behavior of solutes (capacity factors) with mobile phase composition and pH has been investigated by Agatonovic-Kustrin et al[45]. Computer simulation methods has been used to predict the separation as a function of simultaneous change in pH and solvent strength for reversed phase high- performance liquid chromatography[46,47] and hydrophobicity coefficients for the prediction of peptide elution profiles[48].

Agatonovic-Kustrin et al. have also developed an ANNs to correlate chromatograms retention times with mobile phase composition and pH, and with physical chemical properties of amiloride, hydrochloride and methyldopa and created a model for the prediction of retention values of unanalyzed molecules[49].

5.3.8 Prediction of Protein Structure and Function

ANNs are suitable for recognition of domains, classification of proteins, prediction of enzyme class, sequence classification of DNA/RNA and protein. These results are valuable for the further study of the relationship between the structure and function of proteins and which may also provide information regarding design and the prediction of protein tertiary structure. Murval et al. has developed a feed forward ANN consisting of six input and six hidden units with sigmoid transfer function for the recognition of domains in protein sequence[50]. A hierarchical network named PRED-CLASS to classify proteins into four classed such as transmembrane, fibrous, globular and mixed proteins has been used by Pasquier et al[51]. The PRED-CLASS trained using 50 protein sequences, correctly predicted 371 out of a set of 387 proteins with an accuracy of 96 percent. Livingstone at al. has discussed the advantage of networks in the simulation of drug molecules and protein structures[52]. Reidys et al. has applied ANNs with GA training algorithms in sequence alignment and assembly for both RNA and DNA molecules and in determining the folding and secondary structure of RNA strands[53]. Dosztanyl et al. has applied ANN based algorithms to identify, characterize and predict stabilization center elements from primary structure of single proteins and amino acid sequences of homologous proteins[54]. The stabilization center elements present in proteins stabilize

protein structures by preventing their decay. The prediction of long chain fatty acid transport protein FadL topology[55+], prediction of secondary structured of clostridial neuroprotein-C fragment[56], DNA/RNA and protein sequences analysis[57] are other applications where ANN technology has been exploited. The neural networks have been employed to predict eukaryotic protein phosphorylation sites[58], to recognize active sites and to predict enzyme class with high accuracy for novel protein structures[59].

5.3.9 Prediction of Skin Permeability of Drug

Agatonovic-Kustrin et al. have developed a quantitative structure–permeability relationship of penetration across polydimethylsiloxane membranes[60], which were expected to be the model of skin permeation[61,62]. A set of 254 compounds and their maximum steady state flux was collected from the literature[64,65]. Twelve of 42 molecular descriptors were selected for ANN modeling of maximum steady-state flux by the use of genetic algorithm, that include molecular shape and size, inter-molecular interactions, hydrogen-bonding capacity of drugs, and conformational stability. For the 12-descriptor neural network model, the training set relative means square error was 0.36 and the testing set relative mean square error was 0.59. When the prediction power was evaluated using an external prediction set, the relative mean square error was 0.60, indicating that the quality of the model would be ensured.

Lim et al. have also proposed a method for predicting the human skin permeability (log K p) of compounds from three-dimensional molecular structure using a combination of molecular orbital (MO) calculations and ANN. For 92 compounds that was listed in the Flynn's data[66], their molecular descriptors, such as dipole moment, polarizability, sum of charges of nitrogen and oxygen atoms (sum (N,O)), and sum of charges of hydrogen atoms bonding to nitrogen or oxygen atoms (sum (H)), were calculated from MO calculations. The correlation between these molecular descriptors and log Kp was examined using a feed-forward back-propagation neural net work. To improve the generalization capability of a neural network, the network was trained with input patterns given 5 % random noise[67]. The neural network model with a configuration of 4-4-1 for input, hidden, and output layers was much superior to the conventional multiple linear

regression model in terms of root mean square errors (0.528 vs. 0.930). Moreover, a 'leave-one-out' cross-validation revealed that the neural network model could predict skin permeability with a reasonable accuracy (predictive relative mean square error of 0.669). The ANN modeling of skin permeability for 45 compounds based on MO-calculated descriptors has been performed by Fu et al[68]. When external validation was conducted for eight compounds, the ANN model gave a mean prediction error of 2.6%, whereas the prediction error of the multiple linear regression model with the same descriptors was 32.09%.

Degim et al. analyzed skin permeability of 40 compounds by an ANN and compared its predic-tability with the multiple linear regression model obtained by Pugh et al[69,70]. According to the linear model of Pugh et al., the partial charges of the penetrants, their molecular weight, and their calculated octanol–water partition coefficient (log $P_{oct/w}$) were used as molecular descriptors. While the linear equation gave a regression coefficient (r^2) of 0.672, the ANN produced log K_p values that correlated well with the experimental ones (r^2 = 0.997). In addition, they experimentally determined human skin permeability for some compounds that have not been previously investigated, and found that their experimental data can be predicted well from the ANN model developed.

5.3.10 Pharmacokinetic and Pharmacodynamics

Turner et al. used ANNs for the prediction of clearances, fraction bound to plasma proteins, and volume of distribution of a series of structurally diverse compounds[70]. Correlations for test compounds ranged from 0.855 to 0.992. Predicted values agreed closely with experimental values for total clearance, renal clearance, and volume of distribution, while predictions for protein binding were encouraging.

The ANN technology offers an exciting alternative to monitor complex interactions between drug substance and physiological system that are usually monitored by pharmacodynamics. Haidler et al. reported on a predictive PK/PD model for an oral hypoglycemic agent (repaglinide) using ANNs. They concluded that ANNs were a quick and simple method for predicting and identifying significant covariates[72].

Gobburu et al. also applied an ANN to PK/PD analysis and concluded that it is a versatile computational tool and exhibits clear advantage over conventional model-independent PK/PD analysis. Chow et al. compared the predictive ability of ANNs with that of NNMEM for tobramycin plasma levels in pediatric patients and conclude that ANNs have the potential to become a useful analytical tool for population pharmacokinetic data analysis[73]. Reports of the prediction of human PK/PD data from physicochemical properties of drugs and animal PL/PD data have been published. The feasibility of using ANNS to predict human PK parameters from animal PK data was reported by Hussain et al[74]. Ritchel et al. used ANNs to predict human pharmacokinetics parameters (total clearance and distribution volume) from a combined data set of physicochemical properties of drugs (protein binding, partition coefficient, dissolution constant) and animal pharmacokinetic parameters (total clearance and distribution volume)[75].

Recently, Moon et al. reported the PD model for dose determination of HMG-Co-A-reductase inhibitors using ANNs[76]. An ANN model for dosing HMG-CoA reductage inhibitors demonstrated an ability to predict appropriate dosing, but a larger sample size may be necessary for the development of a more accurate model. Corrigan et al. applied neural network to predict gentamicin concentration in a general hospital population[77]. Their results indicated that neural networks offered some advantages over traditional dose prediction methods for gentamicin. Kenji et al. applied an ANN simulator to predict the pharmacokinetic of amino glycoside antibiotic using physiological measurement in patients with severe illness[78]. ANN analysis using standardized data showed reasonable predictive performance.

5.3.11 Diagnosis of Disease

ANNS have been applied in the diagnosis of cancers based on clinical chemical data[79], diagnosis of acute myocardial infarction[80], prediction of cardiovascular risk[81], prediction of the development of pregnancy-induced hypertensive disorders[82], diagnosis of Alzheimer's disease[83], diagnosis of benign focal liver disease[84], AIDS research and diagnosis[85], Parkinsonian tremor[86], urologic oncology[87], diagnosis of pigmented skin

lesions[88], lung nodule detection[89], prediction of outcome in epilepsy surger[90] and identify the presence of myocardial infarction[91].

5.4 CONCLUSIONS

The ANNs modeling are newly developed strategies and an alternative to conventional modeling techniques. The utility of ANNs in the pharmaceutical field and drug discovery has recently grained enormous due to their ability to model process that can not be modeled by classical methods. The ANNs need no special computer as neural nets are described using mathematical models and implemented using ordinary computer software. Training time for networks is long but the advantages are overwhelming. The ANNs is better than response surface methodology because they allow incorporation of literature and experimental data to solve common problems in pharmaceutical industry. It is capable of solving problems involving complex pattern recognition which is advantageous in pharmaceutical product development. The use of artificial neural network in pharmaceutical research drug discovery is growing at a fast rate.

5.5 REFERENCES

1. Lippman RP, An introduction to computing with neural nets, IEEE AASP Mag, 4, 4-22, 1987.

2. Agatonovic-Kustrin S, Beresford R, Basic concept of artificial neural network (ANN) modeling and its application in pharmaceutical research, J Pharm Biomed Anal, 22, 717-727, 2000.

3. McClelland JL, Rumelhart DE, Explorations in parallel distributed processing, MIT Press, Cambridge, MA, 1998.

4. Erb RJ, Introduction to backpropogation neural network computation, Pharm Res, 10, 487-493, 1993.

5. Kirkpatrick S, Gelatt CD, Vechi MP, Optimization by simulated annealing. Science, 220, 671-680, 1983.

6. Carpenter WC, Hoffman ME, Understanding neural network approximations and polynomial approximations helps neural network performance, AI Expert March, 2, 31-33, 1995.

7. Aoyama T, Suzuki Y, Ichikawa H, Neural networks applied to quantitative structure-activity relationship analysis, J Med Chem, 33, 2583-2590, 1990.

8. Lim CW, Fujiwara S, Yamashita F, Hashida M, Prediction of Prediction of human skin permeability using a combination of molecular orbital calculations and artificial neural network, Biol Pharm Bull, 25, 361-366, 2002.

9. Fujiwara S, Yamashita F, Hashida M, Prediction of Prediction of Caco-2 cell permeability using a combination of MO-calculation and neural network, Int J Pharm, 237, 95-105, 2002.

10. Takayam K, Morva A, Fujikawa M, Hattori Y, Obata Y, Nagai T, Formulation and optimization of theophylline controlled release tablet based on artificial neural networks, J Cont Rel, 68, 175-186, 2000.

11. Jadid MN, Fairbairn DR, Predicting moment curvature parameters from experimental data, Eng Appl Artif Intell, 9, 303-319, 1996.

12. Agatonovic-Kustrin S, Tucker IG, Schmierer D, Powder diffractmetric assay of two polymorphic forms of ranitidine hydrochloride, Pharm Res, 16, 1479-1484, 1999.

13. Agatonovic-Kustrin S, Wu V, Rades T, Saville D, Tucker IG, Powder diffractmetric assay of two polymorphic forms of ranitidine hydrochloride, Int J Pharm, 184, 107-114, 1999.

14. Agatonovic-Kustrin S, Wu V, Rades T, Saville D, Tucker IG, Ranitidine hydrochloride X-ray assay using a neural network, J Pharm Biomed Anal, 22, 985-992, 2000.

15. Maden JE, Avdalovic N, Haddad PR, Havel J, Prediction of retention times for anion in liner gradient elution ion chromatography with hydroxide eluent using artificial neural networks, J Chromatogr A, 910, 173-179, 2001.

16. Ebube NK, Owusu A, Adeyeye CM, Preformulation studies and characterization of the physicochemical properties of amorphous polymers using artificial neural networks, Int J Pharm, 196, 27-35, 2000.

17. Takahara J, Takayama K, Nagai T, Multi-objective simultaneous optimization based on artificial neural network in sustained release formulations, J Cont Rel, 49, 11-20, 1997.

18. Takahara J, Takayama K, Isowa K, Nagai T, Multi-objective simultaneous optimization based on artificial neural network on a ketoprofen hydrogel formula containing O-ethylmenthol as a percutaneous absorption enhancer, Int J Pharm, 158, 203-210, 1997.

19. Hussain S, Yu X, Johnson RD, Application of neural computing in pharmaceutical product development, Pharm Res, 8, 1248-1252, 1991.

20. Ibric S, Jovanovic M, Djuric Z, Parojcic J, Solomum L, The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit ((R)) RSPO as matrix substance, J Cont Rel, 82, 213-222, 2002.

21. Ibric S, Jovanovic M, Djuric Z, Parojcic J, Petrovic SD, Solomum L, Stupar B, Artificial neural network in the modeling and optimization of aspirin extended release tablets with eudragit L 100 as matrix substance, AAPS Pharm Sci Tech, 2003, 4, Article 9 (www.pharmscitech.org).

22. Zupanic BD, Vreer F, Kozjek F, Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network, Eur J Pharm Sci, 5, 163-169, 1997.

23. Wu T, Pan W, Chen J, Zhang R, Formulation optimization technique based on artificial neural network in salbutamol sulfate osmotic pump tablets, Drug Dev Ind Pharm, 26, 211-215, 2000.

24. Takayama K, Fujikawa M, Nagai T, Artificial neural network as a novel method to optimized pharmaceutical formulations, Pharm Res, 16, 1-6, 1999.

25. Takayama K, Morva A, Fujikawa M, Hattori Y, Obata Y, Nagai Y, Formula optimization of theophylline controlled release tablet based on artificial neural networks, J Cont Rel, 68, 175–186, 2000.

26. Chen Y, MaCall TW, Baichwal AR, Meyer MC, The application of an artificial neural network and pharmacokinetic simulations in the design of controlled-release dosage forms, J Cont Rel, 59, 33-41, 1999.

27. Vaithiyalingam S, Khan MA, Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion, Int J Pharm, 234, 179-193, 2002.

28. Dowel J, Hussain JA, Devane J, Young D, Artificial neural networks applied to the in vitro in vivo correlation of an extended-release formulation: initial trials and experience, J Pharm Sci, 88, 154-160, 1999.

29. Gobburu JVS, Chen EP, Artificial neural networks as a novel approach to integrated pharmacokinetic pharmacodynamic analysis, J Pharm Sci, 85, 505-510, 1996.

30. Jaen-Oltra J, Salabert-Salvador MT, Garcia-March FJ, Perez-Gimenes F, omas-Vert F, Artificial neural network applied to prediction of fluoroquinolone antibacterial activity by topological methods, J Med Chem, 43, 1143-1148, 2000.

31. Gobburu JVS, Shelver WH, Quantitative structure pharmacokinetic relationship (QSPR) of beta blockers derived using neural network, J Pharm Sci, 84, 862-865, 1995.

32. Nestorov I, Rowland M, Empirical versus mechanistic modeling: Comparison of an artificial neural network to a mechanistically based model for quantitative structure pharmacokinetic relationship of a homologous series of barbiturates, AAPS Pharm sci, 1999, 1, article 17, (www.pharmsci.org).

33. Breindl A, Beck B, Clark T, Glen RC, Prediction of the n-octanol/water partition coefficient, logP using a combination of semiempirical MO-calculations and a neural network, J Mol Model, 3, 142–155, 1997.

34. Eros D, Kovesdi I, Orfi L, Takacs-Novak K, Acsady G, Keri G, Reliability of logP predictions based on calculated molecular descriptors: a critical review, Curr Med Chem, 9, 1819–1829, 2002.

35. Cherqaoui D, Villemin D, Use of a neural network to determine the boiling point of alkanes, J Chem Soc Faraday Trans, 90, 97–102, 1994.

36. Liu S, Zhang R, Liu M, Hu Z, Neural network topological indices approach to the prediction of properties of alkenes, J Chem Inf Comput Sci, 37, 1146–1151, 1997.

37. Espinosa G, Yaffe D, Cohen Y, Arenas A, Giralt F, Neural network based quantitative property relations (QSPRs) for predicting boiling points for aliphatic hydrocarbons, J Chem Inf Comput Sci, 40, 859–879, 2000.

38. Goll ES, Jurs PC, Prediction of vapor pressures of hydrocarbons and halohydrocarbons from molecular structure with a computational neural network, J Chem Inf Comp Sci, 39, 1081–1089, 1999.

39. Yaffe D, Cohen Y, Espinosa G, Arenas A, Giralt F, Fuzzy ARTMAP and back-propagation neural networks based quantitative structure–property relationships (QSPRs) for octanol–water partition coefficient of organic compounds, J Chem Inf Comput Sci, 42, 162–183, 2002.

40. Sild S, Karelson M, A general QSPR treatment for dielectric constants of organic compounds, J Chem Inf Comput Sci, 42, 360–367, 2002.

41. Tettech J, Suzuki T, Metcalfe E, Howells S, Quantitative structure–property relationships for the estimation of boiling point and flash point using a radial basis function neural network, J Chem Inf Comput Sci, 39, 491–507, 1999.

42. Suzuki T, Ebert RU, Schuurmann G, Development of both linear and nonlinear methods to predict the liquid viscosity at 20 °C of organic compounds, J Chem Inf Comp Sci, 37, 1122–1128, 1997.

43. Suzuki T, Ebert RU, Schuurmann G, Application of neural networks to modeling and estimating temperature dependent liquid viscosity of organic compounds, J Chem Inf Comput Sci, 41, 776–790, 2001.

44. Tham SY, Agatonovic-Kustrin S, Application of the artificial neural network in quantitative structure gradient elution retention relationship of phenyl thiocarbamyl amino acids derivatives, J Pharm Biomed Anal, 28, 581–590, 2002.

45. Agatonovic-Kustrin S, Zecevic M, Zivanovic L, Tucker IG, Application of artificial neural networks in HPLC method development, J Pharm Biomed Anal, 17, 69-76, 1998.

46. Lewis JA, Lommen DC, Raddatz WD, Dolan JW, Snyder LR, Molnar I, Computer simulation for the prediction of separation as a function of pH for reverse phase high performance liquid chromatography: I. Accuracy of a theory based model, J Chromatogr A, 592, 183-195, 1992.

47. Lewis JA, Dolan JW, Snyder LR, Molnar I, Computer simulation for the prediction of separation as a function of pH for reversed phase high-performance liquid chromatography: II. Resolution as a function of simulation change in pH and solvent strength, J Chromatogr A, 592, 197-208, 1992.

48. Hearn MT, Aguilar MI, Mant CT, Hodges RS, High performance liquid chromatography of amino acids, peptides and proteins: LXXXV. Evaluation of

the use of hydrophobicity coefficients for the prediction of peptide elution profiles, J Chromatogr, 438, 197-210, 1988.

49. Agatonovic-Kustrin S, Zecevic M, Zivanovic L, Use of ANN modeling in structure retention relationships of diuretics in RP-HPLC, J Pharm Biomed Anal, 21, 95-103, 1999.

50. Murvai J, Vlhovicek K, Szepesvari C, Pongor S, Prediction of protein functional domains fro sequences using artificial neural networks, Genome Res, 11, 1410-1417, 2001.

51. Pasquier C, Promponas VJ, Hamodrakas SJ, Cascading neural networks for generalized protein classification and genome wide applications, Protein, 44, 361-369, 2001.

52. Livingstone DJ, Manallack DT, Tetko IV, Data modeling with neural networks: advantages and limitations, J Comput Aided Mol Des, 11, 135-142, 1997.

53. Reidys C, Stadler PF, Schuster P, Generic properties of cominatory maps: neural networks of RNA secondary structures, Bull Math Biol, 59, 339-397, 1997.

54. Dosztanyi Z, Fiser A, Simon I, Stabilization centers in proteins: identification, characterization and predictions, J Mol Biol, 272, 597-612, 1997.

55. Cristalli G, Dirusso CC, Black PN, The amino terminal region of the long chain fatty acid transport protein FadL contains an externally exposed domain required for bateriophase T2 binding, Arch Biochem Biophys, 377, 324-333, 2000.

56. Lebeda FJ, Umland TC, Sax M, Olsan MA, Accuracy of secondary structure and solvent accessibility predictions for a clostridial neurotoxin C-fragment, J Protein Chem, 17, 311-318, 1998.

57. Wu CH, Artificial neural networks for molecular sequence analysis, Compt Chem, 21, 237-256, 1997.

58. Blom N, Gammeltoft S, Brunak S, Sequence and structure based prediction of eukaryotic protein phosphorylation sites, J Mol Bio, 294, 1351-1362, 1999.

59. Stabl M, Taroni C, Schneider G, Mapping of protein surface cavities and prediction of enzyme class by a self organizing neural network, Protein Eng, 13, 83-88, 2000.

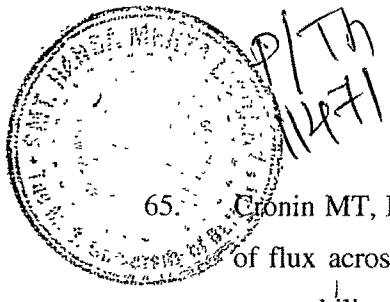
60. Agatonovic-Kustrin S, Beresford R, Yusof AP, ANN modeling of the penetration across a polydimethylsiloxane membrane from theoretically derived molecular descriptors, J Pharm Biomed Anal, 26, 241–254, 2001.

61. Addicks WJ, Flynn GL, Weiner N, Chiang CM, Drug transport from thin applications of topical dosage forms: development of methodology, Pharm Res, 5, 377–382, 1988.

62. Jetzer WE, Huq AS, Ho NF, Flynn GL, Durais WL, Condie L, Permeation of mouse skin and silicone rubber membranes by phenols: relationship to in vitro partitioning, J Pharm Sci, 75, 1098–1103, 1986.

63. Chen Y, Yang WL, Matheson LE, Prediction of flux through polydimethylsiloxane membranes using atomic charge calculations, Int J Pharm, 94, 81–88, 1993.

64. Chen Y, Vayuhasuwan P, Matheson LE, Prediction of flux through polydimethylsiloxane membranes using atomic charge calculations: application to an extended data set, Int J Pharm, 137, 149–158, 1996.



65. Cronin MT, Dearden JC, Gupta R, Moss GP, An investigation of the mechanism of flux across polydimethylsiloxane membranes by use of quantitative structure permeability relationships. J Pharm Pharmacol, 50, 143–152, 1998.

66. Flynn GL, Physicochemical determinants of skin absorption, in: G.T.R.C.J. Henry (Ed.), Principles of Route-to-route Extrapolation in Risk Assessment, Elsevier, New York, 93–127, 1990.

67. Holmstrom L, Koistinen P, Using additive noise in back propagation training, IEEE Trans Neural Networks, 3, 24–38, 1992.

68. Fu XC, Ma XW, Liang WQ, Prediction of skin permeability using an artificial neural network, Pharmazie, 57, 655–656, 2002.

69. Degim T, Hadgraft J, Ilbasmis S, Ozkan Y, Prediction of skin penetration using artificial neural network (ANN) modeling, J Pharm Sci, 92, 656–664, 2003.

70. Pugh WJ, Degim IT, Hadgraft J, Epidermal permeability penetrant structure relationships: 4, QSAR of permeant diffusion across human stratum corneum in terms of molecular weight, H-bonding and electronic charge, Int J Pharm, 197, 203–211, 2000.

71. Turner JV, Maddalena DJ, Cutler JD. Pharmacokinetic parameter prediction from drug structure using artificial neural networks. Int J Pharm 2004; 270: 209–219.

72. Haidar SH, Johnson SB, Fossler MJ, Hussain AS, Pharmacokinetics and pharmacodynamics of an unique oral hypoglycemic agent using neural networks, Pharm Res, 19, 87-91, 2002.

73. Chow HH, Tolle KM, Roe DJ, Eldberry V, Chen H, Application of neural networks to population pharmacokinetic data analysis, J Pharm Sci, 86, 840–845, 1997.

74. Hussain S, Johnson RD, Vachharajani NN, Ritschel WA, Feasibility of developing a neural network for prediction of human pharmacokinetic parameters from animal data, Pharm Res, 10 466-469, 1993.

75. Ritschel WA, Akileswaran R, Hussain AS, Application of neural networks for the prediction of human pharmacokinetic parameters, Methods Find Exp Clin Pharmacol, 17, 629-643, 1995.

76. Moon A, Smith T, A preliminary evaluation of neural network analysis for pharmacodynamic modeling of the dosing of the hydroxymethylglutaryl coenzyme A-reductase inhibitors simvastatin and atorvastatin, Clin Ther 24, 653-661, 2002.

77. Corrgan BC, Mayo PR, Jamali F, Application of neural networks for gentamicin concentration prediction in a general hospital population, Drug. Monitoring, 1997, 19, 25-28, 1997.

78. Kenji N, Massaki H, Shigeo Y, Yahunori M, Akio K, Toru M, Yasuhiro Y, Prediction of plasma levels of aminoglycoside antibiotic in patients with severe illness by means of an artificial neural network simulator, J Pharm Pharamceut Sci, 1, 95-101, 1998.

79. Shan Y, Zhao R, Xu G, Liebich HM, Zhang Y, Application of probabilistic neural network in the clinical diagnosis of cancers based on clinical chemistry data, Anal Chim Acta, 471, 77–86, 2002.

80. Pedersen SM, Jorgensen JS, Pedersen JB, Use of neural networks to diagnose acute myocardial infarction. II. A clinical application, Clin Chem (Washington, DC), 42, 613–617, 1996.

81. Leoncini G, Sacchi G, Viazzi F, Ravera M, Parodi D, Ratto E, Microalbuminuria identifies overall cardiovascular risk in essential hypertension: An artificial neural network based approach, J Hypertens, 20, 1315–1321, 2002.

82. Mello G, Parretti E, Ognibene A, Mecacci F, Cioni R, Carselli G, Prediction of the development of pregnancy induced hypertensive disorders in high risk pregnant women by artificial neural networks, Clin Chem Lab Med, 39, 801–805, 2001.

83. Deng X, Li K, Liu S, Preliminary study on application of artificial neural network to the diagnosis of Alzheimer's disease with magnetic resonance imaging, Chin Med J, 112, 232–237, 1999.

84. Rudzki K, Hartleb M, Sadowski T, Rudzka J, Focal liver disease: neural network-aided diagnosis based on clinical and laboratory data, Gastroenterol Clin Biol, 21, 98–102, 1997.

85. Sardari S, Sardari D, Applications of artificial neural networks in AIDS research and therapy, Curr Pharm Design, 8, 659–670, 2002.

86. Edwards R, Beuter A, Glass L, Parkinsonian tremor and simplification in network dynamics, Bull Math Biol, 61, 157–177, 1999.

87. Douglas TH, Moul JW, Applications of neural networks in urologic oncology, Semin Urol Oncol, 16, 35–39, 1998.

88. Rubegni P, Cevenini G, Burroni M, Perotti R, Dell'Eva G, Sbano P, Automated diagnosis of pigmented skin lesions, Int J Cancer, 101, 576–580, 2002.

89. Penedo MG, Carreira MJ, Mosquera A, Cabello D, Computer-aided diagnosis: a neural-network-based approach to lung nodule detection, IEEE Trans Med Imag, 17, 872–880, 1998.

90. Arle JE, Perrine K, Devinsky O, Doyle WK, Neural network analysis of preoperative variables and outcome in epilepsy surgery, J Neurosurg, 90, 998–1004, 1999.

91. Baxt WG, Analysis of the clinical variables driving decision in an artificial neural network trained to identify the presence of myocardial infarction, Ann Emerg Med, 21, 439–1444 1992.