Artificial Neural Network in Drug Delivery and Pharmaceutical Research

Vijaykumar Sutariya[a,*], Anastasia Groshev[a], Prabodh Sadana[b], Deepak Bhatia[b] and Yashwant Pathak[a]

[a]*Department of Pharmaceutical Sciences, USF College of Pharmacy, University of South Florida, Tampa, FL 33612*

[b]*Department of Pharmaceutical Sciences, College of Pharmacy, Northeast Ohio Medical University, Rootstown, OH 44272*

Abstract: Artificial neural networks (ANNs) technology models the pattern recognition capabilities of the neural networks of the brain. Similarly to a single neuron in the brain, artificial neuron unit receives inputs from many external sources, processes them, and makes decisions. Interestingly, ANN simulates the biological nervous system and draws on analogues of adaptive biological neurons. ANNs do not require rigidly structured experimental designs and can map functions using historical or incomplete data, which makes them a powerful tool for simulation of various non-linear systems.ANNs have many applications in various fields, including engineering, psychology, medicinal chemistry and pharmaceutical research. Because of their capacity for making predictions, pattern recognition, and modeling, ANNs have been very useful in many aspects of pharmaceutical research including modeling of the brain neural network, analytical data analysis, drug modeling, protein structure and function, dosage optimization and manufacturing, pharmacokinetics and pharmacodynamics modeling, and in vitro in vivo correlations. This review discusses the applications of ANNs in drug delivery and pharmacological research.

1. INTRODUCTION

In 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 tools ever developed. Much of this excitement is due to the ability of neural networks to emulate the brain's ability to learn by example. This network makes decision and draws conclusionseven when presented with incomplete information. Moreover, at some primitive level, neural network imitates brain's creative process in adapting to a novel situation [1]. It is a very good statistical tool for many numeric as well as nonnumeric calculations. Specifically, 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 fields, including engineering [1], psychology, medicinal chemistry [2, 3], diagnostics [4, 5], and pharmaceutical research [6].
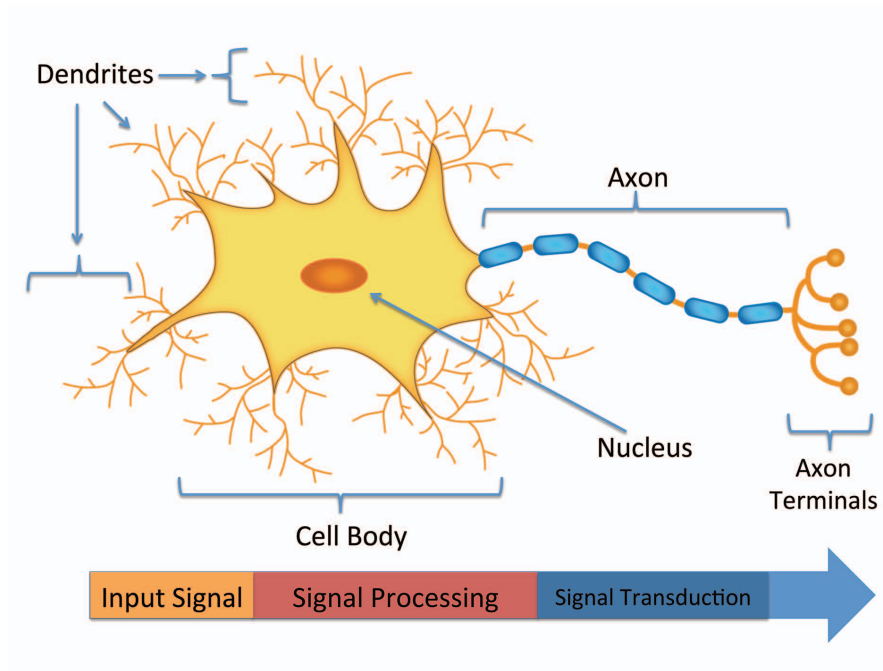
2. ARTIFICIAL NEURAL NETWORKS MODELING

As biologically inspired computational model, ANN is capable of simulating neurological processing ability of the human brain. Average human brain contains about 100 billions of neurons with each neuron being connected with 1000-10,0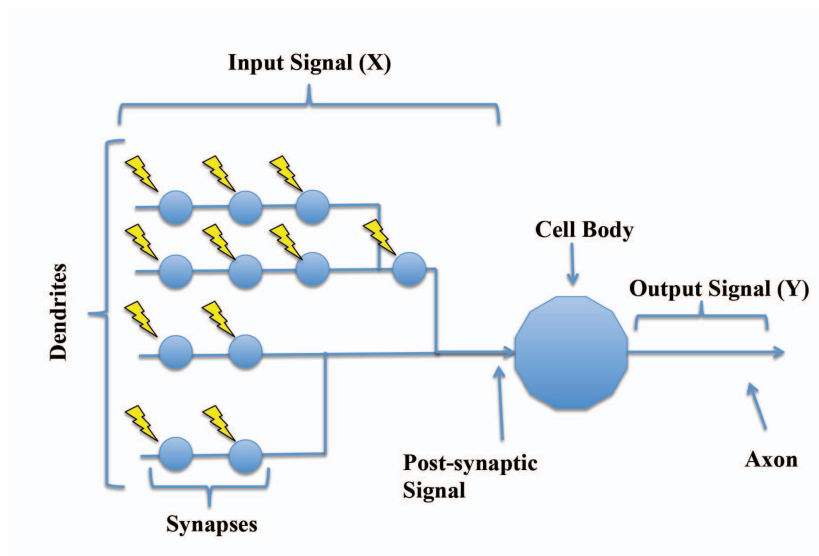00 connections to others. A single neuron consists of three major parts—dendrites (fine branched out threads) carrying signals into the cell, the cell body receiving and processing the information, and the axon (a single longer extension) (Fig. **1**). The axon carries the signal away and relays it to the dendrites of the next neuron or receptor of a target cell. The signals are conducted in all-or-none fashion through the cells. All the connections in the brain enable it to learn, recognize patterns, and predict outcomes.Similarly to the brain, ANN is composed of numerous processing units (PE), artificial neurons. The connections among all the units vary in strength, which is defined by coefficients or weights. The ANN mimics working of human brain and potentially fulfills the cherished dream of scientists to develop machines that can think like human beings.ANNs simulate learning and generalization behavior of the human brain through data modeling and pattern recognition for complex 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 such as space analysis in quantitative structure-activity relationships in pharmacokinetic studies [7] and structure prediction in drug development [8].

There are many types of neural networks with new ones being continually invented; however, all ANNscan be characterized by their transfer functions of their processing units (PE), the learning rules, and by the connections formulas. PE, building component of ANN, receives many signals as weighted process variables from the response of

*Address correspondence to this author at the Department of Pharmaceutical Sciences, University of South Florida College of Pharmacy, Tampa, Florida, 33612-4749, Tel: 813-974-1401; Fax: 813-974-9890; E-mail: vsutariy@health.usf.edu

(A)

(B)

Fig. (1). Conceptual structure of a biological neuron. (A) Schematic representing structure of biological neuron. Branched out dendrites receive the signal. The cell body processes the signal and relays it to the next target via axon, the elongated extension. **(B)** The input signals, represented by lightning bolts stimulate the dendrites in the synapses. The signals are relayed to the cell body, where they are processed and travel onto the axon as a single output signal.

other units [9]. The most commonly applied ANN layout is forward propagating network trained by error back-propagation developed by Rumehart *et al.* [10]. The forward propagation network consists of input layer, one or more hidden layers and one output layer (Fig. **2**) [11]. The input layer provides data from the external source. The mapping of the input data occurs by neural network hidden layers, then the final representative signal is generated by the output layer [10, 12]. The ability of neural networks to classify information depends on hidden layers, which are fully connected by the synapses to the neighboring layers.

In each hidden layer and output layer, the processing unit sums up its input from previous layer by the sigmoidal function to compute the output to the following layer according to the following equations (1) and (2) [13].
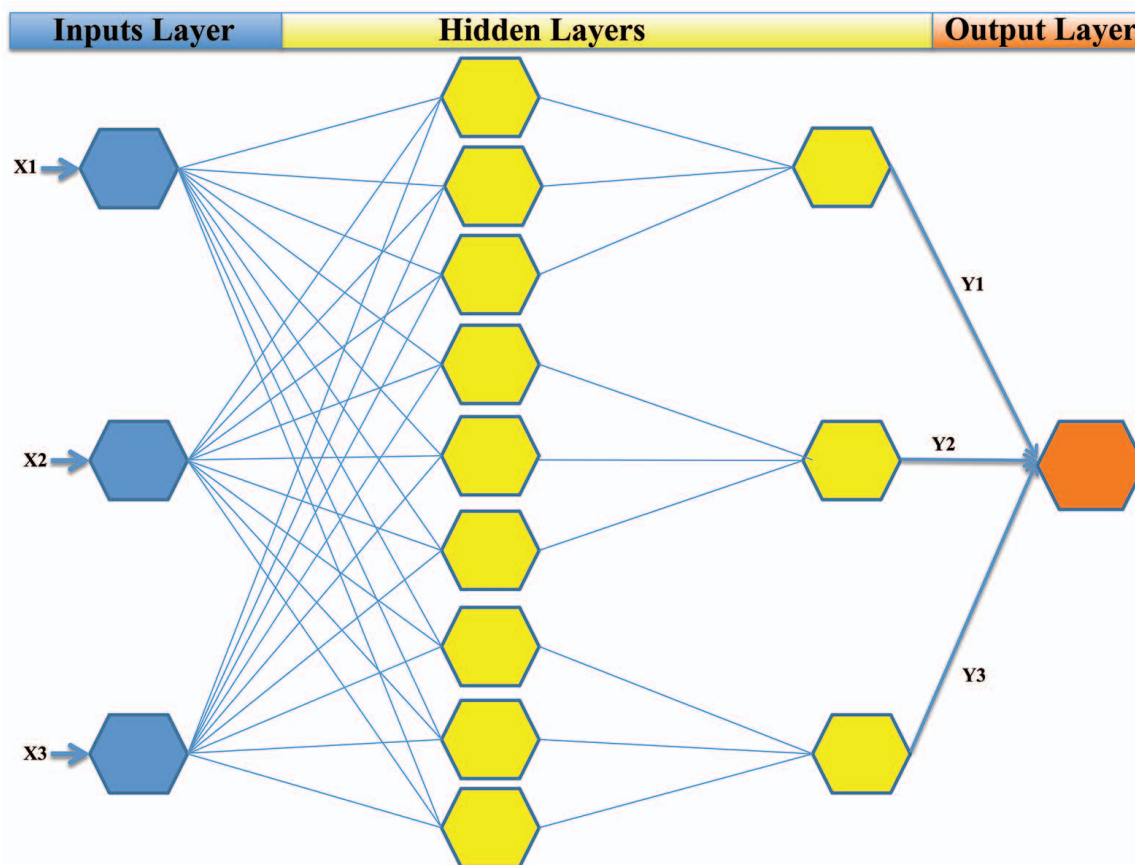
$$y_q = \sum w_{pq} x_p \tag{1}$$

Fig. (2). A schematic of four-layered artificial network. Input layer units (in blue) receive input signals (x_1, x_2, x_3) and transfer the signal to the hidden layers via weighted connections. Output layer receives the signals and provides the representative output signal.

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

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 a 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 is the search process for the optimized set of weight values to minimize the squared error between the estimation and experimental data of units in the output layer. Most commonly used methods is back-propagation method, whichrequires three simple steps—network design, learning or training, and usage [11]. In the network design stage the number of connections and layers is selected based on the type of application. Then, the training stage requires of selection of training set of data and remodeling of the network to minimize the error. And lastly, following the training ANN is suitable to use.

Network design. Number of hidden layers is essential to the purpose and function of an ANN as it influences the number of connections in the network and, thus, its performance. A very common approach to select the optimal

number of hidden nodes is by trial and error method using the training rules as guidance; however, the upper limit of number of hidden nodes on an ANN model can be determined using the following equation (3) [14].

$$n_s = \beta \{ n_h(n_i + 1) + n_o(n_h + 1) \} \qquad (3)$$

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 final number of process variables and response units depends on the type of the problem and is determined by the data for the analysis. After finalizing the number of layers and neurons in each layer ANN is ready for training.

Training. The process of training involves a search for the most optimal network state by adjustments of the weights of the connections between PEs. The weights are adjusted, based on the training set of data, until the error is minimized. At some point the network may become stuck in local minima, where the error is lower; however, less than optimal confirmation is achieved. The momentum can aid the network to continue sampling confirmations making training is a long iterative process.Certain empirical techniques have been reported to improve the convergence of ANNs in the global minima [15]. Kalman filter algorithm [16, 17] may help to reduce the amount of iterative trainingand prevent the ANN getting stuck in local minimaby using the simulated
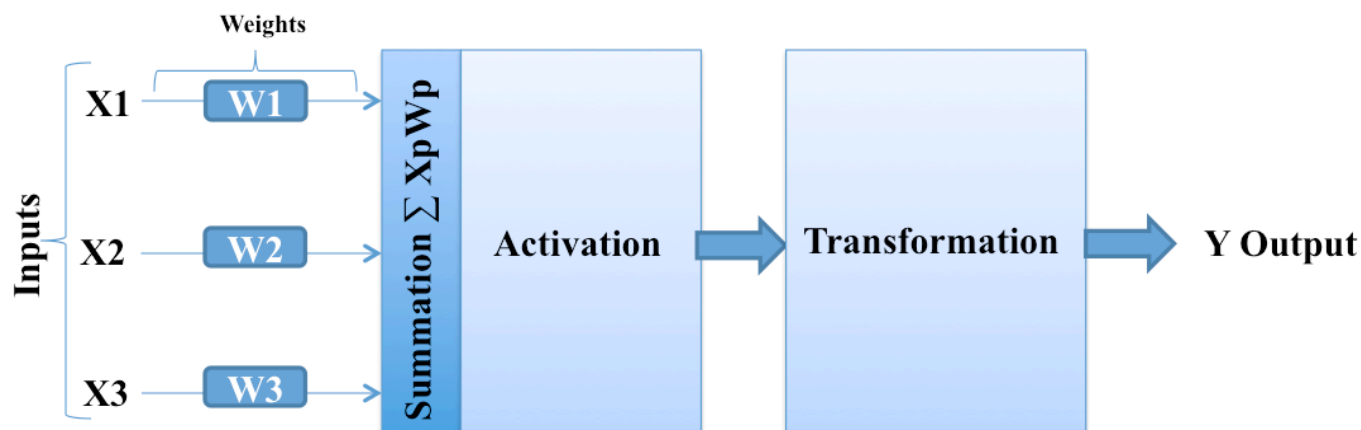
Fig. (3). A common design of a node in an artificial neural network. The input signal travels to the unit though weighted connection. Multiple signals are summated, processed, and transformed based on the specific function. An output signal is relayed to the following nodes in the network.

annealing technique where the global minima can be more specified making the training process quicker and more efficient [18-20].

The amount of training is important because undertrained ANNs yields larger errors in the output signal and overtrained ANNs lose the ability to generalize and recognize patterns. Equation (4) relating to the number of units in the input layer, the hidden layer and the optimal output layer may be used for reasonable prediction of number of training pairs [21]:

$$AIC = n_s \mathrm{x} \ln(SS) + 2 \mathrm{x} \imath \qquad (4)$$

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 that relates to the degree of over determination.

Further, a cross-validation technique such as a ''leave-one-out (LOO) method'' may be applied to ensure the optimality of an ANN structure [22-24]. 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 (Equation (6)) [25]:

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

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 [26].

The learning 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 of the training iterations (frequently referred to as "epoch") are described by the following general equation:

New weight change = learning rule * Error + Momentum + Last weight change (6)

The 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 Fig. (**3**). 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.

In the training process, it may become necessary to change the number of units in the hidden layers, especially in multilayer networks where overfitting may occur. Pukrittayakamee *et al*. described two types of overfitting that may occur during the training process when both function and its derivatives and recommended pruning or adjusting the number of PEs in the network to overcome this issue [27].

Based on the design and purpose of the ANN, the training may reach termination in the state of minimal error or continue evolving and learning though interactions with datasets. If the data is noisy, overtraining of the ANN may be of a concern as it may lose the ability to generalize and recognize the patterns. However, evolving ANNs are often used for modeling brain activity and artificial intelligence [28], space perception [29], and analysis of data requiring large inputs and large outputs [30] among other applications.

3. APPLICATION OF ANNS MODELING IN DRUG DELIVERY AND PHARMACEUTICAL RESEARCH

The potential applications of ANN methodology in the pharmaceutical sciences are broad as ANNs capabilities can

be summarized bymodeling, pattern recognitionand prediction. Thus, applications of ANNs includedrug modeling, dosage design, protein structure and function prediction, pharmacokinetics and pharmacodynamics modeling, as well as, interpretation of analytical data, and *in vitro/in vivo* correlations.

3.1. ANNs Applications Analytical Data Analysis and Structure Retention Relationship (SRR) Methodology in Pharmacological Research

As ANNs can recognize patterns from complex sets of analytical data, they become very useful in data analysis of pharmacological research due to their ability to recognize even non-linear relationships from noisy data. For instance, ANNs can be applied in analysis of spectral data of multi-component samples such as mixtures forquantification of the concentrations in the mixture using the whole spectrum in the identification process [31-33]. Hasani *et al.* used ANNs for detection and calibration of amino acids with similar structures and spectrums such as tryptophan, tyrosine, and histidine [32]. Moreover, ANNs are capable of assisting in determining of concentrations of a chiral sample and enantiomeric excess in a single spectrophotometric measurement due to their ability to identify non-linear relationships [34]. For instance, ranitidine hydrochloride, one of the most commonly prescribed antihistamines, exists in two forms, Form 1 and 2. Application of ANNs in development of method of quantification of ranitidine-HCL using diffuse reflectance IR spectral data and X-ray diffraction allows for sensitive and quick identification of Form 1 concentration in a multi-component tablet without extraction of active ingredient and Form 1 [35-37]. Usefulness of ANNs in analysis of peptide MS/MS spectral data has been also demonstrated. The constructed ANN was used to analyze the data generated by Sequest, a widely used protein identification program. ANN was demonstrated to classify automatically as either "good" or "bad" the peptide MS/MS spectra otherwise classified manually. An appropriately trained ANN proves to be a high-throughput tool facilitating examination of Sequest's results and authors recommended a routine use of this approach in handling large MS/MS data sets [38].

ANNs can also be used as the basis of computer-assisted optimization method for selection of optimal gradient conditions for anion separations in chromatography [39-41]. 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.Tham *et al.* applied ANNs in quantitative structure–gradient elution retention relationship of the compounds such as phenyl thiocarbamyl amino acids derivatives with estimation of the chromatographic retention times [42]. This study found the training set RMS error to be 1.773 and the testing set RMS error— 0.8377. Based on the RMS errors of the training and testing sets and high correlation of predicted versus experimental values (R>0.97), it is clear that the correlation between the structure and the chromatographic separation can be predicted by ANNs. Similarly, ANNs can assist in HPLC optimization by finding correlation of the chromatographic behavior of solutes (capacity factors) with mobile phase composition and pH to predict retention times

[43], the separation as a function of simultaneous change in pH and solvent strength [44, 45], and hydrophobicity coefficients for the prediction of peptide elution profiles [46]. ANNmodel have used in successful prediction of retention values of unanalyzed molecular in studies done by Agatonovic-Kustrin by determining the correlations of chromatograms retention times with mobile phase composition and pH, and with physical chemical properties of amiloride, hydrochloride and methyldopa [47]. Recently, Chen *et al.* have used ANNs in combination with generic algorithms (GA) for method optimization of detection of two similar biophenols blood levels even at trace amounts and small sample volume [48]. ANNs can serve as a great tool in optimization stage of the method development to help save time and cost during this stage of research. Further, ANNs may help to detect relationships in analysis of challenging sets of data such as characterization of mixtures.

3.2. Preformulation

ANN model has been used in the design and optimization of preformulation to determine the physicochemical propertiesof amorphous polymers [49]. A study by Ebubeet. al. 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 as trained ANNs model enables prediction of the relationships between the compositions of polymer blend and the water uptake profiles, the relationships between composition of polymers blends and viscosity of polymers solutions, and the relationship between moisture content of polymers and their glass transition temperatures.

In the phase design, it may be important to consider the effect of active pharmaceutical ingredients (API) on the tablet itself, especially if multiple APIs are present. Using ANNs,Onukiet. al. were able to test 14 APIsafter optimizing the formulation base using self-organizing maps in order to expand the fast-release tablet database and study the effect of API on the tablet properties [50]. Moreover ANNs also have been successfully used in design of stable formulations for multiple active components, such as rifampicin and isoniazid microemulsions [51]. ANNs are certainly very useful in the preformulation design and would help reduce the cost and length of preformulation study.

3.3. Optimization of Pharmaceutical Formulations

The prediction of pharmaceutical responses based on the polynomial equation and response surface methodology (RSM) has been widely used in formulation optimization but may be limited to low volumes, resulting in the poor estimation of optimal formulations. In order to overcome these shortcomings, a multi-objective simultaneous optimization technique incorporating an ANN has been developed [52, 53]. For example, the reliability of ANNs in optimizing controlled release capsules and ketoprofen hydrogel ointment has been demonstrated by Hussain et al [54]. 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 [55, 56], diclofenac sodium sustained release matrix tablets

[57], salbutamol sulfate osmotic pump tablets [58], transdermal ketoprofen hydrogel [59], and nimodipine floating tablet formulation [60].

Takayama *et al.* applied an ANN 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 ANN and pharmacokinetic simulations in the design of controlled-release formulation [61]. 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. Vaithiyalingam *et al.* used the ANN to model the effect of process and formulation variables, 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 [62]. The observed drug release data of the optimized formulations was close to the predicted release pattern, based on the ANN model. Recently, Atkas *et al.* have utilized ANNs in developing a carvedilol controlled release tablets, where the formulation resisted the pH-dependent solubility of carvedilol [63]. No significant difference between ANN-derived predictions and experimental values were observed during this study. Similar findings of ANNs application in formulation optimization have been reported by Patel et. al., in their study ANN was used to design low and pH-dependent tablet formulation [64]. Optimization process variables included drug amount, osmotic pressure of promoting agent rage, polymer content and weight of the coating, demonstrating that ANNs may be valuable in optimization of the formulations.

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 IVIVC have the potential to be a reliable predictive tool that overcomes some of the limitations associated with classical regression methods such as lack of pattern recognition powers analyzing multivariable data sets with high degree of variation. ANN configurations are very useful in prediction of IVIVC from different formulations of same product [65]. ANNs can also be applied in quantitative structure-pharmacokinetic relationship (QSPR) of beta-blockers using ANNs demonstrating that ANNs are capable of prediction *in vivo* results from *in vitro* experiments [66]. IVIVC has been applied in prediction of absorption of salbutamol in the lungs in healthy and asthmatic volunteers based on published *in vivo* data [67, 68]. The drug concentrations were measured in urine and compared to the lung function. The study concluded that ANNs are useful in predicting in vivo response based on in vitro data based on the squared correlations between predicted and experimental values of 0.83 and 0.84 for urine and lung function data.Recent studies by Paixãoet. al. predicting drug clearance by hepatocytes based on in vitro data (train r=0.953 and test

r=0.804) show that ANNs may be a valuable tool in prediction of metabolic clearance of new drugs [69].

3.5. Quantitative Structure-Activity Relationships (QSAR) and Quantitative Structure-Property Relationship (QSPR)

QSAR correlate structure or property descriptors of compounds with chemical or biological activities and increasing number of neural network models are currently published for predicting various physicochemical properties from the molecular structures [70-73]. All QSAR studies are based on the fundamental concept of interdependence of biologecta activities on physicochemical parameters. The relationships of structure and function with the physicochemical descriptors and topological parameters can be determined by computational methods. For instance, ANNs have been used by Grobburu and colleagues to predict the quantitative structure QSPR of beta adrenoreceptor antagonists in humans [74]. In the study, ANNs with congeneric series of ten beta-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%). Comparison studies of the predictive performance of a mechanistic model with an empirical ANN model in calculating the relationship between the tissue distribution and the lipophilicity of a homologous series of 5-n-alkyl-5-ethyl barbituric acids in the rat have been published and demonstrated the superiority of ANNs in this application [75]. 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%).

On other hand, 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%). ANNs have also been applied in prediction of antimicrobial activities of quinolone derivatives and detection of their minimum inhibitory concentrations using a topological method based on chemical structure of quinolone derivatives [76]. Morerecently, an improved prediction model of antimicrobial activity has been published by Torrent et. al. allowing for projection of antimicrobial potency accounting even for factors such as protein aggregation [77]. ANN also has been utilized in the development of four-parameter counter propagation (CP) QSAR model of *Dunaliellat-ertiolecta* in predicting toxicity for freshwater alga *Pseudokircheneriellasubcapitata* [78] and in screening of antibacterial activity of 3-hydroxypyridine-4-one derivatives [79].

Further, ANN has been useful in QSAR study of antitumor activity of acridinone derivatives [80]. Correlation of predicted values to the experimental data was 0.9484; moreover, the developed model allowed also to identify the important factors contributing to the antitumor activity such as lipophilicity. Thus, ANNs are not only useful in prediction QSARs but also in identifying the role of the

specific factors relevant to the activity of interest. This has been demonstrated in the earlier published study by Uesawa and colleagues in their QSAR analysis of tumor-specificity of 1,2,3,4-tetrahydroisoquinoline derivatives, where ANN allowed for identification of water-accessible surface area and quantum chemical descriptors as factors in estimating tumor specificity of compounds [72].

Calculation of certain physicochemical properties before synthesizing or purchasing screening library would be especially valuable drug discovery phase. Lipophilicity and water solubility are properties related to the octanol-water partition coefficient, 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 octanolpartition coefficient prediction from the results of semi empirical AM1 calculations [81] and Eros et al. developed neural network (fitting and prediction errors were s = 0.48 and s = 0.72 respectively)from database of 625 molecules, 98% of which are registered API showing high structural diversity [82]. Similarly, more recent studies based on QSPR ANN model predicted octanol-water partition coefficients for 209 chlorinated trans-azobenzene derivatives, contaminants in herbicides [83]. QSPR ANN model was also used by Noorizadeh *et al.* to calculate the polar surface area of 32 drug molecules [84]. Application of ANNs in prediction of API solubility has been demonstrated by Louis and colleagues in comparison study of MLR, ANN, and SVM methods with ANN yielding the best prediction data set [85]. Squared correlation coefficient values were 0.814, 0.823, and 0.835 for MLR, ANN, and SVM respectively.

ANNs can also be very useful in predicting chemical properties of compounds. Several research groups have modeled the normal boiling point of hydrocarbons. Predictive neural network models have been published for alkanes [86, 87], alkenes [88] and for diverse hydrocarbons [89]. As expected, the models typically show good fitting and prediction statistics with less than ten simple descriptors. Goll and Jursalso applied artificial neural network to predict the vapor pressures of hydrocarbons and halohydrocarbons from molecular structure [90]. The neural network model with 7-3-1 architecture predicted the test set with a root mean square error of 0.209 (n =52). Recently, Piliszek and colleagues utilized property parameterization model (RM1) and density functional theory (DFT) followed by ANN analysis in prediction of subcooled vapor pressures and classification of 399 polychlorinated trans-azoxybenezenes [91]. 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 [92]. The log Hvalues ranged from 26.72 to 2.87 and topological descriptors were used as input parameters. The average absolute errors for the test set of 74 members were 0.13 and 0.27 logHunits 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 and the training set contained 49 members [88]. Standard error for refractive

index was found to be 0.13% and 0.4% for density using a test set of 16 alkenes.

Sild and Karelson developed ANN 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 [93]. Separate models with 5-5-1 configuration were developed for both dielectric constant and the Kirkwood function. 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 [94]. The database contained 400 organic compounds with flash points between -60 ºC and 200 ºC. The average absolute error for the test set in flash point prediction was 11.9 ºC with a 26-36-2 configuration. Suzuki et al. developed an ANN model for predicting liquid viscosity at a standard temperature of 20 ºC [95] and subsequently, a temperature-dependent model [96]. 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.

Although ANNs have surprisingly vast number of applications, it appears that ANNs may also yield the best prediction results in development of QSAR and QSPR models when used in combination with other statistical methods. For example GA may be implemented in the optimization process during the network training in search for optimal data training set, such as demonstrated by a recent study on indole substitutions that could inhibit HIV-1 attachment found GA-ANNs the best model in comparison with MLR and MLR-ANN [71, 97]. As there are numerous potential combinations, further studies are needed on development of these statistical models based on the field of study and the nature of the problem in consideration.

3.6. ANNs Application in Proteomics and Genomics

Due to their ability to recognize patterns, ANNs are suitable for recognition of domains, classification of proteins, prediction of enzyme class, sequence classification of DNA/RNA and protein. These properties are especially useful in the study of the protein structure and function and could assist in prediction of protein tertiary structure such as a feed forward ANN consisting of six input and six hidden units with sigmoid transfer function developedby Murvai et. al. for the recognition of domains in protein sequence [98]. Cai and colleagues used ANNs for predicting secondary protein structure based on pair-coupled amino acid sequence and demonstrated that ANNs is a suitable method for prediction of the contents of prominent secondary structures of the proteins [99, 100]. Further, as ANNsare able to recognize the patterns based on the original sequences, it becomes possible to group large number of proteins by predefined classifications. A hierarchical network named PRED-CLASS have been used to classify proteins into four classes such as transmembrane, fibrous, globular and mixed proteins [101]. The PRED-CLASS trained using 50 protein sequences, correctly predicted 371 out of a set of 387 proteins with an accuracy of 96 percent. Artificial neural networks have been applied for predicting the separation of peptides in strong anion exchange chromatography. Such capability allows researchers to predict peptide separation

and assist with required data mining steps such as protein identification [102].

Additionally, ANNs enable simulation of drug molecules and protein structures and help determine the folding and secondary structure of RNA strand [103, 104]. Also, ANN based algorithms have been used to identify, characterize and predict stabilization center elements from primary structure of single proteins and amino acid sequences of homologous proteins [105]. 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 [106], prediction of secondary structured of clostridialneuroprotein-C fragment [107], DNA/RNA and protein sequences analysis [108] are other applications where ANN technology has been exploited. The neural networks have been employed to predict eukaryotic protein phosphorylation sites [109], to recognize active sites and to predict enzyme class with high accuracy for novel protein structures [110], in peptide design and optimization [111], protein localization and sorting prediction [112, 113].

3.7. ANNs Application in Pharmacokinetics

It has been established that ANNs have wide applications in pharmacology, including in pharmacokinetics (PK) and pharmacodynamics (PD)—in monitoring multiple PK interactions in biological systems and in prediction of PD parameters such as clearance rates, protein bound fractions, and volume distribution [114, 115]. Due to their computation versatility, ANNs have been utilized as analytical tool for population pharmacokinetic data analysis and was found superior to NONMEM with lesser average absolute errors and significantly lesser average prediction errors than NONMEM [66, 116]. ANNs have been tested in prediction of Hussain et al. tested application of ANNs for prediction of PK parameters from those determined in animal studies [117]. Further, Ritchel *et al.* was able to predict human PK parameters using data set of physiochemical properties (protein binding, partition coefficients, dissociation constant, total clearance and volume of distribution) in combination with animal PK parameters [118]. Corrigan *et al.* applied neural network to predict gentamicin concentration in a general hospital population [119]. Their results indicated that neural networks offered some advantages over traditional dose prediction methods for gentamicin. Kenji *et al.* applied an ANN simulation to predict the pharmacokinetic of amino glycoside antibiotic using physiological measurement in patients with severe illness [120]. Recently, Moon *et al.* reported the PD model for dose determination of HMG-Co-A-reductase inhibitors using ANNs [121]. An ANN model for dosing HMG-CoA-reductase inhibitors demonstrated an ability to predict appropriate dosing, but a larger sample size may be necessary for the development of a more accurate model. ANN analysis using standardized data showed reasonable predictive performance.

3.8. Prediction Permeability of Skin and Blood Brain Barrier

Development of an accurate skin permeability model is becoming increasingly important as skin has been more utilized in recent development of drug delivery methods. Also, the studies on absorption of toxic compounds through the skin are scarce with animal skin such as rodent and pig as a weak substitute [122]. Similar studies by Agatonovic-Kustrin *et al.* and Cheng *et al.* have published on use of ANNs in determining the quantitative structure–permeability relationship of penetration across skin or polydimethylsiloxane membranes as the model of skin permeation [123-126]. A set of over 200 compounds and their maximum steady state flux was collected from the literature [127, 128]. In Agatonovic-Kustrin *et al.* study, 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 [123]. 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. Chen *et al.* study also confirmed the suitability of ANNs for prediction of skin permeability based on molecule descriptors such as molecular weight and partial charge [123].

Another method for predicting the human skin permeability (log K p) of compounds has been developed based on 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 [129], 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 Kpwas examined using a feed-forward back-propagation neural network. To improve the generalization capability of a ANN, the network was trained with input patterns given 5% random noise [130]. 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 RMS 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, with 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% [131].

Degim *et al.* [132] analyzed skin permeability of 40 compounds by an ANN and compared its predictability with the multiple linear regression model obtained by Pugh *et al.* [114]. 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.

The ability of ANNs to recognize and predict patterns may be applied in studying the blood-brain distribution (BBD) of a compound, which is commonly expressed as logarithmic function of the ratio of brain concentration to blood concentration of a compound. Experimental values of each concentration, however, are time consuming and expensive to obtain [133]. Therefore, reliable prediction model is necessary, which is possible from the molecular structure of a compound and by QSAR/QSPR models.

Numerous models have been developed and published for prediction of BBD. Narayan and Gunturi have developed MLR method based model for BBD prediction by four descriptors of 88 compounds (r=0.8638, q=0.8479 and SE=0.3929) [134]. In 2006, improved ANNs have been built based on chemical descriptors of the molecules—Katritzkyet.al. usedfive descriptors (r^2=0.781 and s=0.123) and Garg and Verma used seven descriptors (for training r=0.90 and for testing r=0.89) [135, 136]. A benchmark of predictive accuracy in the area of QSAR models for blood-brain barrier (BBB) permeation prediction was established by Konovalov *et al.* in developing a predictive log BB-QSAR model based on MLR method [137]. Afterward, Yan *et al.* carried out comparison study involving over 300 compounds by 19 global molecular descriptors, eight shape descriptors, 88 2D autocorrelation vectors, and 1024 3D property weighted RDF descriptors using MLR, SVM, and ANN [138]. ANN was found to have similar prediction abilities as MLR and SVM.

3.9. Diagnosis of Disease

ANNs have been applied in the diagnosis based on clinical chemical data of many diseases—cancers [139-141]; early diagnosis of lupus erythmatosus [142]; diagnosis of acute myocardial infarction [143, 144]; prediction of cardiovascular risk [145]; prediction of the development of pregnancy-induced hypertensive disorders [146]; diagnosis of Alzheimer's disease [147]; diagnosis of benign focal liver disease [148]; prediction of metabolic syndrome [149]; AIDS research and diagnosis [150]; Parkinsonian tremor [151]; urologic oncology [152]; diagnosis of pigmented skin lesions [153]; lung nodule detection [154]; prediction of outcome in epilepsy surgery [155]; and in assisting in making diagnosis decisions in emergency room [156].

In addition, ANNs have also been used to predict responses to pharmacotherapy. Cases in point, ANNs have been used to predict the response to hormonal treatment in metastatic breast cancer [157]. They can be used to predict the clinical outcome for individual patients. In contrast to conventional methods, the level of confidence for the predictions can reach 90% and more using ANNs. Such predictive power will be a big step towards individualized therapy in the future.

4. CONCLUSIONS AND FUTURE PERSPECTIVES

The application of ANN in medical decision making has been immensely successful especially as it applies to disease diagnosis, classification and modeling. The ANNs are newly developed strategies as an alternative to conventional modeling techniques. Applications of ANNs in the pharmaceutical field have been of increased interest due to their ability to model process that cannot be adequately represented using classical statistical methods. The ANNs do not need special computer as neural nets are described using mathematical models and implemented using ordinary computer software. Training time for networks is long but considerably advantageous. ANNs are an improvement over 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 with very promising prospects.

Due to their capacity to learn, recognize patterns, and generalize, ANNs are a great tool in data analysis and modeling. The scope of current uses that ranges from spacial perceptions to chemical properties, activity, diagnosis and toxicology indicates the true potential of ANNs in analyzing the data and making predictions. This exciting versatility allows ANNs be utilized almost in any area of science requiring analysis of large, variable, and/or multivariate data; thus, applications of ANNs are expected to continue expanding into many more disciplines.

ABBREVIATIONS

ADME	=	absorption, distribution, metabolism, and excretion
ANNs	=	Artificial neural networks
API	=	active pharmaceutical ingredient
GA	=	generic algorithms
HPLC	=	high performance liquid chromatography
MLR	=	multiple linear regression
PE	=	processing units
PD	=	pharmacodynamics
PK	=	pharmacokinetics
RDF	=	radial distribution function
RMS	=	root mean squared error
RSM	=	response surface methodology
QSAR	=	Quantitative Structure-Activity Relationships
QSPR	=	Quantitative Structure-Property Relationship
SRR	=	= Structure Retention Relationship
SVM	=	support vector machine

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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