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Review

Basic concepts of artificial neural network (ANN) modeling and its application in pharmaceutical research

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Abstract

Artificial neural networks (ANNs) are biologically inspired computer programs designed to simulate the way in which the human brain processes information. ANNs gather their knowledge by detecting the patterns and relationships in data and learn (or are trained) through experience, not from programming. An ANN is formed from hundreds of single units, artificial neurons or processing elements (PE), connected with coefficients (weights), which constitute the neural structure and are organised in layers. The power of neural computations comes from connecting neurons in a network. Each PE has weighted inputs, transfer function and one output. The behavior of a neural network is determined by the transfer functions of its neurons, by the learning rule, and by the architecture itself. The weights are the adjustable parameters and, in that sense, a neural network is a parameterized system. The weighed sum of the inputs constitutes the activation of the neuron. The activation signal is passed through transfer function to produce a single output of the neuron. Transfer function introduces non-linearity to the network. During training, the inter-unit connections are optimized until the error in predictions is minimized and the network reaches the specified level of accuracy. Once the network is trained and tested it can be given new input information to predict the output. Many types of neural networks have been designed already and new ones are invented every week but all can be described by the transfer functions of their neurons, by the learning rule, and by the connection formula. ANN represents a promising modeling technique, especially for data sets having non-linear relationships which are frequently encountered in pharmaceutical processes. In terms of model specification, artificial neural networks require no knowledge of the data source but, since they often contain many weights that must be estimated, they require large training sets. In addition, ANNs can combine and incorporate both literature-based and experimental data to solve problems. The various applications of ANNs can be summarised into classification or pattern recognition, prediction and modeling. Supervised associating networks can be applied in pharmaceutical fields as an alternative to conventional response surface methodology. Unsupervised feature-extracting networks represent an alternative to principal component analysis. Non-adaptive unsupervised networks are able to reconstruct their patterns when presented with noisy samples and can be used for image recognition. The potential applications of ANN methodology in the pharmaceutical sciences range from interpretation of analytical data, drug and dosage form design through biopharmacy to clinical pharmacy.

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1. Artificial intelligence

Artificial intelligence (AI) has been established as the area of computer science dedicated to production software capable of sophisticated, intelligent, computations similar to those that the human brain routinely performs. It includes methods, tools and systems devoted to simulate human methods of logical and inductive knowledge acquisition, reasoning of brain activity for solving problems. There are two main categories of AI developments. The first includes methods and systems that simulate human experience and draw conclusions from a set of rules, such as expert systems. The second includes systems that model the way the brain works, for example, artificial neural networks (ANNs) (Table 1).

Expert systems are knowledge-based systems, an extension of conventional computing and are sometimes called the fifth generation of computing. This knowledge base allows an expert to define the rules that simulate a process of thinking and provides a simple way to draw conclusions and solve problems by following a set of rules. The idea of expert systems is that logical thinking can be modelled by compiling lists of logical propositions and performing logical transformations upon them. Expert systems are useful for medical diagnosis, and other diagnostic problem solving [1,2]. It provides a guide for prediction and decision making in environments involving uncertainty and vagueness. Medical practice, for example, is often hampered by incomplete and inexact scientific models of human health and disease, and incomplete or sometimes inaccurate data about individual patients.

Table 1
Differences in approach between conventional computing and ANNs

Characteristics	Conventional computing (including expert systems)	Artificial neural networks
Learning method	By rules (didactically)	By example (Socratically)
Functions	Logically	Perceptual pattern
Processing style	Sequential	Parallel

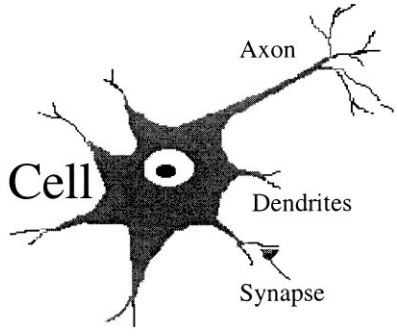

Fig. 1. Neuron cell.

ANNs are digitized models of a human brain, computer programs designed to simulate the way in which human brain processes information. ANNs learn (or are trained) through experience with appropriate learning exemplars just as people do, not from programming. Neural networks gather their knowledge by detecting the patterns and relationships in data. The brain is an excellent pattern recognition tool. When we look at a pen, we know it is a pen because biological neurons in a certain area of our brain have come across a similar input pattern on previous occasions and have learned to link that specific pattern with the object description 'pen'. Since our brain contains billions of neurons which are fully interconnected, we can learn and recognize an almost endless variety of input patterns.

An average brain contains ~ 100 billion neurons, each of which has 1000–10 000 connections with other neurons. Neurons consist of a cell body which includes nucleus that controls the cell activity, many fine treads, dendrites, that carry information into the cell, and one longer thread known as the axon which carries the signal away (Fig. 1). Impulses pass along the axon to the synapse, the junction between one neuron and the next and signals are passed from one to the next in an all-or-none fashion. Neurons are organised 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.

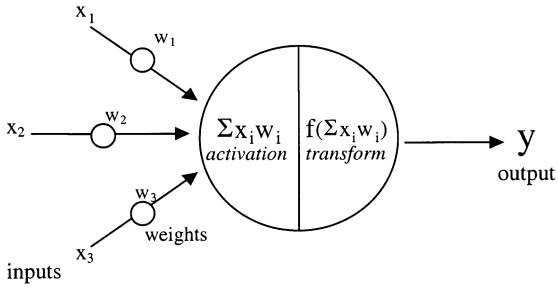

Fig. 2. Model of an artificial neuron.

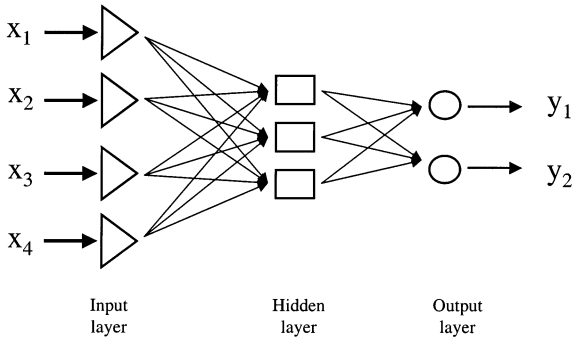

Fig. 3. Feedforward network.

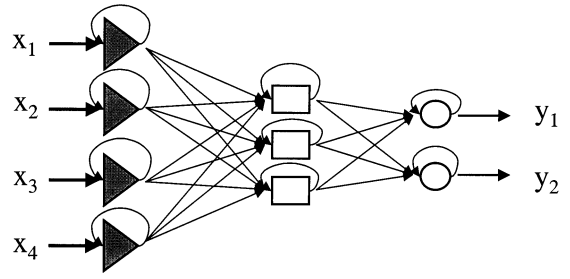

Fig. 4. Feedback network.

2. Artificial neural networks

An artificial neural network [3,4] is a biologically inspired computational model formed from hundreds of single units, artificial neurons, connected with coefficients (weights) which constitute the neural structure. They are also known as processing elements (PE) as they process information. Each PE has weighted inputs, transfer function and one output. PE is essentially an equation which balance inputs and outputs. ANNs are also called connectionist models as the connection weights represent the memory of the system.

Although a single neuron can perform certain simple information processing functions, the power of neural computations comes from connecting neurons in a network. The supposed intelligence of artificial neural networks is a matter of argument. Artificial neural networks rarely have more than a few hundred or a few thousand PEs, while the human brain has ~ 100 billion neurons. Artificial networks comparable to a human brain in complexity are thus still far beyond the creative capacity of the human brain. The human brain is much more complex and, unfortunately, many of its intellectual functions are still not well known. ANNs are capable of processing extensive amounts of data, however, and making predictions that are sometimes surprisingly accurate. This does not make them intelligent in the usual 'human' sense of the word, so the term computer intelligence may be better way of describing these systems.

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 the learning rule, and by the connection formula.

2.1. Neurons

The artificial neuron is the building component of the ANN designed to simulate the function of the biological neuron. The arriving signals, called inputs, multiplied by the connection weights (adjusted) are first summed (combined) and then passed through a transfer function to produce the output for that neuron. The activation function is the weighed sum of the neuron's inputs and the most commonly used transfer function is the sigmoid function (Fig. 2.).

2.2. Connection formula

The way that the neurons are connected to each other has a significant impact on the operation of

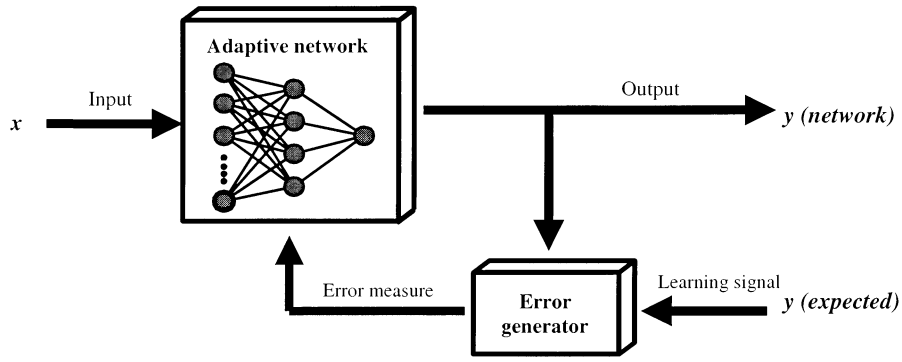

Fig. 5. Supervised network with backpropagation learning rule.

the artificial neural network. Just like 'real' neurones, artificial neurons can receive either excitatory or inhibitory inputs. Excitatory inputs cause the summing mechanism of the next neuron to add while the inhibitory inputs cause it to subtract. A neuron can also inhibit other neurons in the same layer. This is called lateral inhibition. The network wants to 'choose' the highest probability and inhibit all others. This concept is also called competition.

Feedback is another type of connection where the output of one layer routes back to the input of a previous layer, or to same layer. Two types of architecture may be identified according to the absence or presence of feedback connection in a network. Feedforward architecture does not have a connection back from the output to the input neurons and therefore does not keep a record of its previous output values (Fig. 3). Feedback architecture has connections from output to input neurons. Each neuron has one additional weight as an input that will allow an additional degree of freedom when trying to minimize the training error (Fig. 4). Such a network keeps a memory of previous state so that next state depends not only on input signals but also on the previous states of the network.

2.3. Learning rule

There are many different learning rules but the most often used is the Delta rule or Back-propagation rule. A neural network is trained to map a set of input data by iterative adjustment of the weights. The use of the weighted links is essential to the ANN's recognizing abilities. Information from inputs is fed forward through the network to optimize the weights between neurons. Optimization of the weights is made by backward propagation of the error during training or learning phase. The ANN reads the input and output values in the training data set and changes the value of the weighted links to reduce the difference between the predicted and target values. The error in prediction is minimized across many training cycles until network reaches specified level of accuracy. If a network is left to train for too long, however, it will overtrain and will lose the ability to generalise.

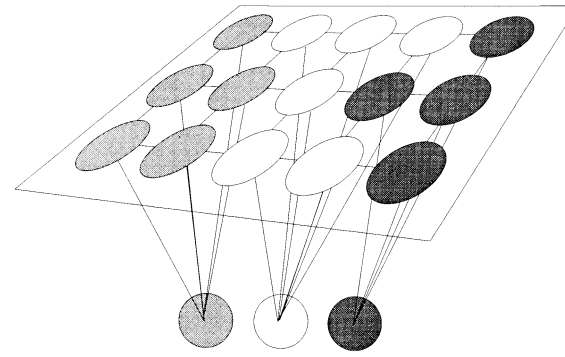

Fig. 6. Kohonen or Self Organizing Map with unsupervised learning algorithm.

3. ANN models and learning algorithm

There are many different types of ANNs, some of which are more popular than others. When neural networks are used for data analysis, it is important to distinguish between ANN models (the network's arrangement) and ANN algorithms (computations that eventually produce the network outputs). Once a network has been structured for a particular application, that network is ready to be trained. There are two approaches to training, supervised and unsupervised. The most often used ANN is a fully connected, supervised network with backpropagation learning rule (Fig. 5). This type of ANN is excellent at prediction and classification tasks. Another is the Kohonen or Self Organizing Map with unsupervised learning algorithm, which is excellent at finding relationships among complex sets of data (Fig. 6).

3.1. Associating networks with supervised learning

The goal in supervised learning is to predict one or more target values from one or more input variables. Supervised learning is a form of regression that relies on example pairs of data: inputs and outputs of the training set.

This type of network is a system of fully interconnected neurons organized in layers, the input layer, the output layer, and the hidden layers between them. The input layer neurons receive data from a data file. The output neurons provide ANN's response to the input data. Hidden neurons communicate only with other neurons. They are part of the large internal pattern that determines a solution to the problem. Theory says that most functions can be approximated using a single hidden layer [5].

The information that is passed from one processing element to another is contained within a set of weights. Some of the interconnections are strengthened and some are weakened, so that a neural network will output a more correct answer. The most commonly used learning algorithm is back propagation of error. The error in prediction is fed backwards through the network to adjust the weights and minimize the error, thus preventing the same error from happening again. This process is continued with multiple training sets until the error is minimized across many sets. This results in the mapping of inputs to outputs via an abstract hidden layer.

The number of neurons in the hidden layer influences the number of connections. During training phase inputs are adjusted (transformed) by the connection weights. Therefore, the number of connections has a significant effect on the network performance. Too few hidden neurons will hinder the learning process and too many will depress prediction abilities through overtraining. By increasing the number of the hidden neurons the ANN more closely follows the topology of the training data set. However exceeding an optimum number results in tracing the training pattern too closely.

When the ANN produces the desired output (i.e. is trained to a satisfactory level) the weighted links between the units are saved. These weights are then used as an analytical tool to predict results for a new set of input data. This is a recall or prediction phase when network works only by forward propagation of data and there is no backward propagation of error. The output of a forward propagation is the predicted model for the validation data.

Pattern association is usually supervised learning. ANNs compete well with statistical methods in pattern recognition, especially when the systems contain high level of noise and variation.

3.2. Feature-extracting networks with unsupervised learning

In unsupervised training, the network is provided with inputs but not with desired outputs. The system itself must then decide what features it will use to group the input data. This is often referred to as self-organization or adaptation. The self-organising behaviour may involve competition between neurons, co-operation or both. Neurons are organised into groups of layers. In competitive learning, neurons are grouped in such a way so that when one neuron responds more strongly to a particular input it suppresses or inhibits the output of the other neurons in the

group. In co-operative learning the neurons within each group work together to reinforce their output. The training task is to group together patterns that are similar in some way, extract features of the independent variables and come up with its own classifications for inputs. ANNs considers the data they are given, discover some of the properties of the data set and learn to reflect these properties in their output. The goal is to construct feature variables from which the observed variables, both input and output variables, can be predicted. Feature-extracting networks can be regarded as principal component analysers (PCA). They are used as an alternative to classical PCA for data reduction purposes, to transform the data set into a new space with retained information in data set but with a reduced number of variables (dimensionality). The goal is to construct a network that will map the entire training data (both inputs and outputs variables) at once.

4. Application of ANN in pharmaceutical research

The ANN methodology is based on the attempt to model the way a biological brain processes data. It is thus quite different from standard statistical methods of analysis.

ANN represents a promising modeling technique especially for data sets having the kind of non-linear relationships, which are frequently encountered in pharmaceutical processes. Neural networks require less formal statistical training, are able to detect complex non-linear relationships between dependent and independent variables and all possible interactions without complicated equations, and can use multiple training algorithms. In terms of model specification, artificial neural networks require no knowledge of the data source but, since they often contain many weights that are estimated, they require large training sets. In addition, ANNs can combine and incorporate both literature-based and experimental data to solve problems. The use of ANNs is a new but expanding area in the field of pharmaceutical research [6–10].

The various applications of ANNs can be summarised into classification or pattern recognition, prediction and modeling.

Supervised associating networks can be applied in pharmaceutical fields as an alternative to conventional response surface methodology (RSM). Unsupervised feature-extracting networks, which can map multidimensional input data sets onto two-dimensional spaces, represent an alternative to principal component analysis (PCA). Non-adaptive unsupervised networks map data sets and are able to reconstruct their patterns when presented with noisy samples; they can thus be used for image recognition.

The potential applications of ANN methodology in the pharmaceutical sciences are broad, based on these abilities. They range from interpretation of analytical data (modeling the pharmaceutical analysis in quality control), drug design (QSAR and molecular modeling) and dosage form design (optimization of manufacturing processes) to clinical pharmacy through biopharmacy (pharmacokinetic and pharmacodynamic modeling, in vitro/in vivo correlation).

4.1. Pattern recognition and modeling analytical data

Neural networks are able to recognise patterns even from noisy and complex data in which there is a considerable degree of variation and to estimate non-linear relationships. Therefore, ANNs are useful in all fields of research where the recognition of peak-shaped signals in analytical data is important, for example spectral data.

ANNs are useful in determining the composition of an unknown sample when the spectrum of the unknown is a superposition of known spectra. One feature of this technique is that it uses the whole spectrum in the identification process instead of only the individual peaks.

The conventional multiple linear regression (MLR) method involves an iterative process of spectrum decomposition and regeneration to mathematically synthesised spectrum closely matching the true spectrum. This is a tedious task requiring the specification of a polynomial function for each peak to be regressed. Each polynomial equation can be regarded as a separate model.

Ranitidine hydrochloride is antihistaminic drug, one of the 20 most frequently prescribed drugs. It

exists in two polymorphic forms known as Form 1 and Form 2. Diffuse reflectance IR spectral analysis [11] and X-ray diffraction [12] were combined with ANNs as a data modeling tool to develop a simple, sensitive and rapid method for the qualitative and quantitative control of ranitidine-HCl. Method was used to analyse bulk drug and to quantify ranitidine-HCl Form 1 from tablets without prior extraction in the presence of other components. The technique could simultaneously distinguish between two crystal modifications, and identify polymorphic transition and even quantify it, thus enabling the purity of the bulk drug substance to be checked. The ranitidine hydrochloride tablet is a multicomponent tablet formulation in which there is a significant overlap of the spectral pattern of ingredients. Using ANN as a data-modeling tool solved this problem. The ANN was trained to recognize specific patterns of constituents of the formulations from the overall spectral pattern. When the classification ANN was exposed to complex tablet formulation samples containing only ranitidine-HCl Form 1 crystal modification, it successfully identified and quantified all components in tablet formulation down to a concentration of $0.7 \pm 1.88\%$. There was no need to extract the active ingredient and Form 1 was successfully quantified in the presence of tablet excipients and additives.

4.2. Modeling the response surface

The usefulness of artificial neural networks for response surface modeling in HPLC optimization [13–15] was compared with (non-) linear regression methods. Retention mapping describes the chromatographic behaviour of solutes by response surface, which shows the relationship between the chromatographic behaviour of solutes and components of the mobile phase. The capacity factor of every solute in the sample can then be predicted, rather than performing many separations and simply choosing the best one obtained. Experiments confirmed that predicted capacity factors of solutes obtained by ANNs were better than those obtained with multilinear stepwise regression model.

A non-linear transformation function with a back-propagation algorithm was used to describe and predict the chromatographic data for assessing chromatographic peak purity [16]. Simulation data and practical analytical data for both pure and mixture samples were analysed with satisfactory results.

4.3. Structure-retention relationships

Predicting chromatographic behaviour from molecular structure of solutes is one of the main goals of structure-retention relationship (SRR) methodology. Artificial neural networks (ANNs) were used to find molecular parameters related to the RP retention times and to predict the retention as a function of changes in mobile phase pH and composition, along with molecular structure descriptors of separated solutes. An ANN model was used to correlate the liquid chromatographic behaviour of a group of structurally diverse diuretics with their physical chemical and molecular descriptors and to create a model for the prediction of retention values of unanalysed molecules [17].

A novel method of untangling overlapped peaks in chromatograms was proposed [18]. The basic idea was to find a set of parameters that characterize the shape of the overlapped peaks and to use a supervised network to quantitatively correlate the parameters with the percentage area of an individual peak. The proposed method performed very well with high accuracy and less computing time compared with other, conventional methods.

4.4. Application of ANNs in pharmaceutical product development

The pharmaceutical product development process is a multivariate optimization problem. It involves the optimization of formulation and process variables. These relationships are difficult to model using classical methods. One of the difficulties in the quantitative approach to formulation design is the understanding of relationships between causal factors and individual pharmaceutical responses. Furthermore, a desirable formulation for one property is not always desirable for the other characteristics. The use of ANNs seems

to be most suitable for dealing with complex multivariate non-linear relationships. ANNs can identify and learn correlative patterns between input and output data pairs. Once trained, they may be used to predict outputs from new sets of data. One of the most useful properties of artificial neural networks is their ability to generalise. These features make them suitable for solving problems in the area of optimization of formulations in pharmaceutical product development.

A response surface methodology (RSM) has usually been applied to solve problems of optimal formulations. Prediction of pharmaceutical responses based on the second order polynomial equation that is commonly used in RSM is often limited to a low level, resulting in the poor estimation of an optimal formulation. ANN models showed better fitting and predicting abilities in the development of solid dosage forms in investigations of the effects of several factors (such as formulation, compression parameters) on tablet properties (such as dissolution) [19–21]. Important relationships were acknowledged with the ANN model only, whereas the RSM model ignored them. In vitro dissolution rate was successfully predicted as a function of product formulation changes. Predicted optimal formulations gave a satisfactory release profile and observed results coincided well with predictions.

ANNs provided a useful tool for the development of microemulsion-based drug-delivery systems in which experimental effort was minimised [22]. ANNs were used to predict the phase behaviour of quaternary microemulsion-forming systems consisting of oil, water and two surfactants. The phase behaviour of a four component mixture at fixed pressure and temperature can be represented using a tetrahedron. Full characterization of such systems would require a large number of experiments. Only three inputs (percentages of oil and water and HLB of the surfactant blend) and four outputs (oil in water emulsion, water in oil emulsion, microemulsion, and liquid crystal containing regions) were used. Detailed experimental data were gathered from several 'slices' within a tetrahedron region. Samples used for training represented $\sim 15\%$ of the sampling space. After training, the ANN was reasonably successful in predicting other regions of that tetrahedron and had an accuracy of 85.2–92.9%. In most cases the errors in the prediction were confined to points lying along the boundaries of regions and for the extrapolated predictions outside the ANN's 'experience'.

Another approach was to include a fifth component [23], a cosurfactant, for the formulation of pharmaceutically acceptable drug-delivery systems and predict the pseudo-ternary phase diagrams for these systems using only computed physicochemical properties for the cosurfactants involved.

ANN was also used to simulate aerosol behaviour, with a view to employing this type of methodology in the evaluation and design of pulmonary drug-delivery systems. It is concluded that carefully tailored, well trained networks could provide valuable tools not just for predicting but also for analysing the spatial dynamics of pharmaceutical aerosols [24].

4.5. Quantitative structure-property relationship (QSPR) and molecular modeling

Louis Hammett [25] (1894–1987) first correlated electronic properties of organic acids and bases with their equilibrium constants and reactivity. Since then, many mathematical models that correlate structure with have been developed. Quantitative structure-activity relationships (QSAR) methods correlate structural or property descriptors of compounds with their chemical or biological activities. The general assumption in QSPR modeling is that molecular structure is responsible for the observed behaviour of a compound. These physicochemical descriptors, which include parameters to account for hydrophobicity, topology, electronic properties, and steric effects, are determined empirically or, more recently, by computational methods.

A number of commercial software products for physical property prediction exist. Experimental determination of such properties can be time consuming and in some cases, be subject to experimental variation and errors.

A first step in QSAR studies is to calculate a multitude of structural descriptors as mathematical representative of chemical structure. The sub-

set of descriptors that best encodes the investigated property must be found. Testing large number of all possible combinations of descriptors might take a lifetime. A more efficient way is to use genetic algorithms [26–28] (GA), as computational models of evolution, coupled with ANN. A GA is an optimization system that uses selection and recombination processes to generate new sample points with higher fitness. Once a subset of descriptors is found the descriptors can be mapped to the property of interest using a non-linear computational neural network.

Back-propagation artificial neural networks (ANNs) were trained with topological indices, molecular connectivity, and novel physicochemical descriptors to model the structure-activity relationship of a large series of capsaicin analogues [29]. The ANN QSAR model produced a high level of correlation between the experimental and predicted data. After optimization, the developed model correctly classified 34 of 41 inactive compounds and 58 of 60 active compounds of 101 capsaicin analogues

Topological connectivity indexes were used to detect the microbiological activity in a group of heterogeneous compounds [30]. The methods followed were stepwise linear discriminant analysis (linear analysis) and artificial neural network (non-linear analysis). Although both methods are appropriate to differentiate between active and inactive compounds, the artificial neural network was better and showed in a test set a prediction success of 98%, versus the 92% obtained with linear discriminant analysis.

Neural networks produced useful models of the aqueous solubility within series of structurally related drugs with simple structural parameters [31,32]. Topological descriptors were used to link the structures of compounds with their aqueous solubility.

A three-layer, feed-forward neural network has been developed for the prediction of human intestinal absorption (HIA%) of drug compounds from their molecular structure [33]. The data set contained 86 drug and drug-like compounds whose molecular structure was described with six descriptors. Given the structural diversity and bias of the data set, this is a good attempt at modeling human intestinal absorption using QSPR methods. The process of intestinal absorption of drug compounds depends both on complex biological processes and on the compounds' physicochemical properties. This model does not produce an exact rank ordering, but is clearly differentiates the well absorbed compounds from the purely absorbed ones and thus illustrates the potential of using QSPR methods to aid the drug development process.

A four layer genetic neural network (GNN) model was used to predict the degree of drug transfer into breast milk, depending on the molecular structure descriptors and was compared with the current models [34]. The set of 60 drug compounds and their experimentally derived M/P values used in this study were gathered from the literature. A total of 61 calculated structure features including constitutional descriptors, topological descriptors, molecular connectivity, geometrical descriptors, quantum chemical descriptors, physicochemical descriptors and liquid properties were generated for each of the 60 compounds. The M/P values were used as the ANN output and calculated molecular descriptors as the inputs. The best GNN model with 26 input descriptors is presented, and the chemical significance of the chosen descriptors is discussed. Strong correlation of predicted versus experimentally derived M/P values (R^2 greater than 0.96) for the best ANN model confirmed that there is a link between structure and M/P values. The strength of the correlation was measured by the quality of the external prediction set. With an RMS error of 0.425 and a good visual plot, the external prediction set ensures the quality of the model. Unlike previously reported models, the GNN model described here does not require experimental parameters and could potentially provide useful prediction of M/P ratio of new potential drugs and reduce the need for actual compound synthesis and M/P ratio measurements.

4.6. Protein function and structure prediction

As a technique for computational analysis, neural network technology is well suited for the anal-

ysis of molecular sequence data. It has been applied successfully to a variety of problems, ranging from gene identification to protein structure prediction and sequence classification [35,36]. These results are valuable for the further study of the relationship between the structure and function of proteins. Such methods can be extremely useful because a structural similarity may represent an evolutionary relationship that is undetectable by sequence analysis. It may also provide important information about protein design and the prediction of protein tertiary structure.

Livingstone et al. [37] has discussed the advantage of networks in the simulation of drug molecules and protein structures. It is also possible to compare three-dimensional protein structures in a similar manner to sequence database searching. A back-propagation ANN was used for pattern recognition in protein side-chain-side-chain contact maps [38]. The network was trained on a set of patterns that are common in side-chain contact maps of protein structures. The resulting network could distinguish between original and randomized patterns with an accuracy of 84.5% and a Matthews' coefficient of 0.72 for the testing set. ANNs with GA training algorithms have been used in sequence alignment and assembly for both RNA and DNA molecules and in determining the folding and secondary structure of RNA strands [39–41] and acknowledged the quantitative similarity among tRNA gene sequences. These results demonstrated the efficiency of the artificial neural network method in sequence analysis of biological molecules [42].

4.7. Pharmacokinetics

Drug dosages and drug choices are determined by knowledge of the drug's pharmacokinetics and pharmacodynamics. Often, insufficient information is available to determine the pharmacokinetics of a drug or which drug will have a desired effect for an individual patient. ANNs represent a novel model-independent approach to the analysis of pharmacokinetic (PK)-pharmacodynamic (PD) data [43,44]. ANNs have been shown to be flexible enough to predict PD profiles accurately for a wide variety of PK-PD relationships (e.g. effect compartment linked to the central or peripheral compartment and indirect response models). In addition ANNs could accurately predict PD profiles without requiring any information regarding the active metabolite. Since structural details are not required, ANNs exhibit a clear advantage over conventional model-dependent methods.

4.8. Molecular de novo design and combinatorial libraries

Structure based drug design is better than the traditional approaches to designing new drugs as it can save large amounts of time and money. One goal of computational chemistry is to develop quantitative models that are able to predict activities of compounds quickly and accurately. These models can be based on the number of hydrogen bonds, hydrophobic surface area, interaction energies, desolvation or other calculations. The quality of the model is then subject to the description of these parameters.

There are at least two possible ways to find a compound that can fit into the active site. One possibility is to search through databases of known structures and to identify those entities that fit into the active site. However, this approach does not address the issue of conformational flexibility and the number and variety of structures is limited by the size of the database used. Another approach uses a library of fragments (or molecules). These fragments are then connected to form a single molecule. There are several advantages to this approach. It is very fast and due to the large number of possible fragment combinations the variety of molecules that can be generated is enormous.

Molecular similarity searching has, in recent years, become a popular way of providing useful leads in the search for new or improved bioactive molecules. It involves evaluating a large range of chemical structures to find those that show either similarity with each other or complementarity with a target structure. With the advancement of computer technology and improved search algorithms, evaluation of large databases of chemical structures can be performed efficiently to guide the design of novel molecules with appro-

priate properties. GAs can be used to reduce the number of potentially useful molecules to controllable numbers of possibly lead compounds.

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