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Advances in Neural Networks for Pharmaceutical Applications

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Artificial neural networks (ANNs) are rapidly changing the landscape of the pharmaceutical industry. Their unique capabilities, including collective computing, adaptive learning, and fault tolerance, make them ideal for tackling complex challenges in drug discovery, analysis, and personalized medicine. This article summarizes the latest research progress in ANNs for pharmacy, highlighting breakthroughs in areas like QSAR modeling for drug design, pharmacokinetic prediction, and optimization of pharmaceutical preparations. With their immense potential to accelerate drug development, improve drug efficacy, and personalize healthcare, ANNs are poised to revolutionize the future of pharmaceuticals.

Keywords: Artificial neural network; research progress; pharmacy.

1. INTRODUCTION

Artificial neural network is associate approximate mathematical model supported biological neural network, which simulates the process mechanism of complicated data within the system of human brain, associated is an adjustive nonlinear dynamic network system composed of an oversized range of process units (neurons) connected with one another [1]. This

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system is composed of parallel computing ability, recovery ability, intelligent and self-help learning. It combines information processing and stockpile with distinct adaptive learning ability. Actually, it is a complicated network composed of a host of ordinary components, which is not only characterized by nonlinearity, but also a system capable of complex logical operations.

Artificial neural network does not need to know the mechanism of action of drugs, but can establish the relationship between them only by learning the information about input and output, and it is suitable for expressing complex multivariable nonlinear relations. Therefore, there are more and more attention on the application of artificial neural networks technology in the pharmaceutical field. This technology can solve many practical problems in the pharmaceutical field efficiently and conveniently, showing the good intelligent characteristics of ANN technology.

2. RESEARCH PROGRESS OF ARTIFICIAL NEURAL NETWORK

The definition of ANN is derived in 1943, and Warren McCulloch and Walter Pitts [2] first built an algorithm-based ANN computing model, called M-P model.By analoging the principle and process of biological neurons, the model presents the mathematical theory and network structure of artificial neurons, and certificates that individual neurons will implement the capability of logic, thereby opening the research era of artificial neural network. After the concept of ANN was put forward, it attracted wide attention of scholars, and more and more people devoted themselves to the study of ANN. However, after Minsky and Papert [3] discovered two key problems in dealing with the calculation of ANN in 1969, the research of ANN encountered bottlenecks. After that, the study of ANN stagnated because the logical reasoning limitation of perceptron could not be solved. A key factor to arouse interest of people in learning ANN again is the back propagation algorithm proposed by Paul Werbos [4] in 1974, which effectively solves the issue of insufficient computing power of computers and improves the possibility of multi-level network training. In 2006, by using the method of pre-training, Hinton [5] ameliorated the trouble of local optimal solution about ANN. eased the local optimal solution problem of ANN by using pre-training method, which set off a wave of learning about it. In 2016, the advent of AlphaGo brought research enthusiasm for deep learning to a new height.

Now ANN has been widely applied in various fields, such as image recognition [6-8], wireless signal processing [9-12], chemical process control and optimization [13-16], forecasting [17,18], security risk assessment [19], traditional Chinese medicine processing [20-22], aquatic products [23], intelligent driving [24,25], and so on.

The keywords associated with artificial neural networks are listed in Table 1 [26].

3. APPLICATION OF ARTIFICIAL NEURAL NETWORK IN PHARMACEUTICAL FIELD

3.1 Application in Pharmaceutics

ANN has the generalization ability, learning ability, self-adaptation, and the abilities of fault tolerance, it also has the characteristics of nonlinearity and high parallelism [27]. Since the upsurge of the second neural network in the early 1980s, artificial neural network has been extensively applied in design of new drugs, pharmaceutical preparations, pharmaceutical analysis, traditional Chinese medicine and clinical medicine with its unique abilities of simulation, learning and classification.

3.2 Application in the Design of New Drugs

In the design and expansion of new drugs, candidate drug molecules should have good physical and chemical properties, pharmacokinetics, and lower toxicity. The quantitative activity relationship (QSAR) study is to explore the quantitative bearing between the molecular construction of a compound and its biological competence, pharmacokinetics and other parameters by statistical methods. In the era of rapid progress and development of big data, machine learning method can be used to better construct high-accuracy QSAR model and apply this model to solve related problems, for instance, the structure of the compound was modified to improve its biological characteristics, so as to design compounds with required properties [28]. By predicting the process of drug absorption, metabolism, distribution, and excretion in human body, it can be used to screen and optimize the pharmacokinetic parameters of drugs in the early stage of drug development, which is salutary to improving the success rate and reducing the cost of drug research and development [29].

Table 1. Fields related to artificial intelligence

Keyword	Quantity	Keyword	Quantity	Keyword	Quantity	Keyword	Quantity
Neural network	678	Recurrent neural network	110	Prediction	64	Support vector regression	46
Artificial neural network	392	Extreme learning machine	106	Dimensionality reduction	59	Forecasting	46
Support vector machines	233	Clustering	103	Exponential stability	58	Serotonin	46
Classification	222	Dopamine	101	Cognition	58	Polymorphism	46
Machine learning	177	Face recognition	98	Artificial intelligence	57	Linear matrix inequality	45
Deep learning	169	Data mining	98	Adaptive control	56	Time-varying delay	45
Genetic algorithm	238	Pattern recognition	90	Stability	54	Reinforcement learning	44
Particle swarm optimization	145	Schizophrenia	85	Dementia	53	Botulinum toxin	43
Parkinson’s disease	129	Synchronization	78	Deep brain stimulation	52	Adhd	42
Feature extraction	128	Depression	76	Oxidativestress	52	Modeling	41
Optimization	125	Fuzzy logic	65	Electroencephalogram	51	Evolutionary algorithm	41
Feature selection	123	Hippocampus	64	Swarm intelligence	51		

In order to solve the problem of plasmodium resistance to antimalarial drugs [30], Yousefinejad et al. [31]. conducted QSAR model study on the activities of 33 imidazopiperazine compounds based on artificial neural network, which played an important role in antimalarial compounds for their design and modification. The artificial neural network based on stepwise multiple linear regression and Levenberg-Marquardt algorithm is an effective nonlinear method to correlate the relationship between antimalarial activity and molecular structure information. The results show that QSAR is an effective virtual screening method, and more effective antimalarial (3D7 and W2) active compounds are obtained. Imidazopiperazine is a good candidate compound. The use of QSAR method can intelligently change the structure and functional groups, thus enriching more effective compounds and reducing trial and error times in the synthesis process. Therefore, the artificial neural network method has a great forecast ability for the antimalarial activities of imidazopiperazine compounds and is a good virtual tool to reduce the cost of trial and error.

Mitogen-activated protein (MAP) kinases containing threonine and serine protein kinases are key signal molecules [32], which participate in a variety of cell activities and are latent target spots that have an effect on cancer and alternative connected diseases. MAP enzyme p38 responds to close stress and participates within the production of cytokines among the inflammatory method. This discovery of the effect of specific inhibitors of p38 block on inflammatory cytokines has aroused great interest in MAP kinase as a drug target. In vitro and animal experiments, several small molecular inhibitors of p38 MAP kinase have been proved to effectively block the production of some cytokines such as interleukin-1(IL-1) and tumor necrosis factor(TNF) [33]. Therefore, about 90 candidate drugs based on pyridyl imidazole with p38 MAP kinase inhibitory activity were selected, and adaptive neuro-fuzzy inference system (ANFIS) model was built for each combination by combining artificial neural network with ANFIS to predict the inhibitory activity [34]. Discovering a model that exactly combines input (structural descriptor) with output (biological activity) is the objective of ANFIS. Through the process, the most important descriptor (input) in fuzzy system is automatically recognized, and adaptive neuro-fuzzy inference system is simulated by MATLAB toolbox of fuzzy logic. However, due to the complex network structure, the amount of network parameters that can be adjusted expands exponentially with the amount of molecular descriptors, and ANFIS is proved to be not suitable for biological applications. Therefore, in practice, the number of descriptors is limited to 12 at most. Fig. 1 shows that the most influential figure is the input attribute LogP, which shows the results of selecting three input variables, among which Diam, Homo and LogP are the best combination, which can greatly show the significance of electronic, spatial and thermodynamic interactions between drugs and their targets in the distribution of compounds in biological systems and their interactions with competitive binding sites. However, the minimum error has not been significantly reduced from the model of best four-input, which shows that new attributes have not greatly improved the prediction.

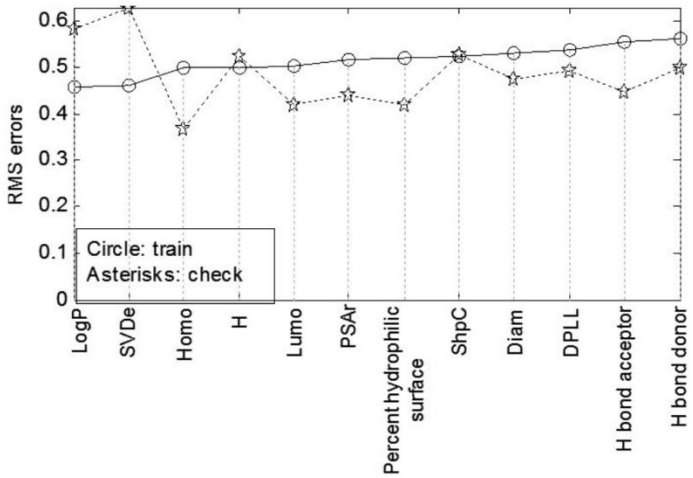

Fig. 1. Effect of each input variable on drug activity

Comparing their root mean square prediction error(RMSE) values with the inspection data, ANFIS prediction can be compared with the linear regression model, and the inspection numbers of adaptive neuro-fuzzy inference system model are 0.535, 0.646 and 0.573 respectively. The RMSE value of linear regression is higher (6.547), while the RMSE value of ANFIS method is close to zero, which indicates that the description is suitable, indicating that ANFIS method is superior to linear regression, and QSAR modeling using ANFIS-ANN method is superior to multiple linear regression (MLR) method.

3.3 Application in Pharmacokinetic Model

Corynoxeine (CX) isolated from Uncaria rhynchophylla extract is a promising compound to preven vascular diseases and its treatment [35]. Ma et al. used the average concentration of corynoxeine in four different dosage groups to establish a back propagation artificial neural network(BP-ANN) model for pharmacokinetic study [36]. After completing the model simulation which establishing by using Matlab R2011a, four groups of concentration data are chosen and examined. The predicted concentrations of the model are 0.1, 0.2, 0.3, 0.6, 0.9, 1.2, 1.8, 2.4, 3.6, 4.8 and 7.2. After 2000 simulations, the performance of the model in four groups of concentration indicators (mean square error, gradient size, verification times and correlation coefficient) is shown in Table 2. The results show high precision of the estimation of the BP-ANN model(R^2 > 0.99) at four different doses, and the model is applicable to forecast the concentration of CX. The prediction and measurement time-concentration curve of CX is shown in Fig. 2.

3.4 Application in Pharmaceutical Preparations

Parikh et al. [37] used I-optimal mixing design and ANN to optimize and compare key parameters (oil dosage, surfactant dosage and cosurfactant dosage) influencing the size of microspheres in drug delivery system of self-emulsifying. Through comparative study, the contour map and three-dimensional map generated by artificial neural network show that the interaction between input and output data is better and the selected output parameters are more predictable. At the same time, the R^2 value of I-optimal mixed design method is 0.9867, and that of artificial neural network technology is 0.99548, so the output of artificial neural network is more predictable and the optimization effect is better.

One of the things to firstly consider the development of tabletting technology in pharmaceutical process is the performance of compressed powder mixture in tabletting machine [38]. The fluidity of powder mixture must be good enough, and almost the same quality of powder needs to enter it every time the mold is filled. Kachrimanis et al. [39] took lactose, Emcompress and starch as the research objects and studied the effects of different factors(volume, shape, particle size and density) on circular hole velocity with lactose, emcompress and starch as the research objects, they established a model by using artificial neural network and compared the predicted results with the flow equation put forward by Jones et al. [40]. And the research shows that the artificial neural network is better than flow equation, because it has no need to regress each attribute separately, and its prediction ability is higher. With the development of dosage forms, a large data set and suitable mathematical tools were created. Zawbaa et al. [41] combined artificial neural network with variable selection algorithm and obtained the result that pressure had the greatest influence on the strength of tension and the porosity of tablets.

3.5 Application in the Pharmaceutical Analysis

The drug analysis often involves multi-component determination or principal component determination of interfering components, such as drug quality evaluation and multi-component content determination. In recent years, many studies have combined ANN method with various analytical methods, which can directly determine multi-components without prior separation.

Arabzadeh et al. [42] established an ultraviolet spectrophotometric analysis method, which is based on three models of artificial neural network, partial least squares regression and principal component regression, and by using them, emtricitabine and tenofovir fumarate in AIDS virus drugs were simultaneously determined [43]. Three algorithms, including Levenberg-Marquardt algorithm, momentum gradient descent algorithm and adaptive learning rate back propagation algorithm, are adopted. Result data shows that Levenberg-Marquardt algorithm is better than adaptive learning rate back

propagation algorithm. In addition, the root mean square error and recovery rate of those methods show that partial least squares regression model is better than principal component regression model. Moreover, compared with the root mean square prediction error and determination coefficient (R^2) of the three methods, results show that ANN method has better prediction effect.

Dorián et al. [44] used a large number of information based on collective near infrared and Raman spectroscopy on the drug production line [45] to have a prediction on the dissolution of tablets by establishing a ANN model. The slow-release preparations were prepared under 37 different conditions with the model drug of Triverine Hydrochloride (DR) and moreover, the contents of DR, hydroxypropyl methylcellulose (HPMC) and pressure are variables. Through recording the near infrared spectrum and raman spectrum of tablets with methods of transmission and reflection respectively, the partially least squares prediction model of DR and HPMC content was established. Input data is the predicted values and the measured compression force of artificial neural network model. It comes out that the artificial neural network model has more accurate precision (Table 3).

Table 2. Fitness of BP-ANN model

Quota	1 mg	2 mg	4 mg	8 mg
Mean square error	0.0276	1.3619	192.2058	0.2867
Gradient size	5.1×10^{-3}	7.8×10^{-6}	4.5×10^{-3}	1.5×10^{-2}
Verification check	0	0	0	0
Correlation coefficient (R^2)	1	0.99997	0.99839	0.99926

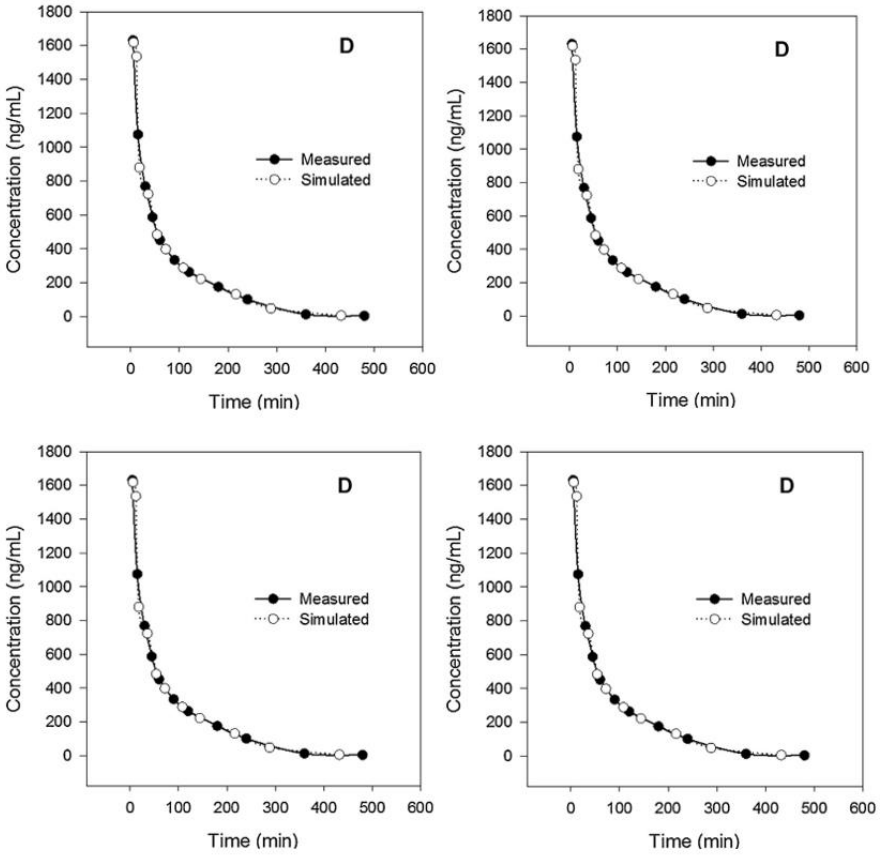

Fig. 2. Determination of CX in rats and pharmacokinetic characteristics of its predicted concentration

Table 3. Average f2 value of the best ANN models compared to partial least squares (PLS) models using the same input

Modeling Method	Raman	NIR	NIR-Raman
ANN	74.27	71.84	73.07
PLS	65.63	65.01	65.79

The selection and optimization of separation and determination conditions are often encountered in the process of drug analysis. In addition to a large amount of tests, the method of artificial neural network can also be applied. D'archivio et al. [46] used artificial neural network method to simulate the effects of column temperature, mobile phase flow rate and gradient of mobile phase linear concentration on the biological activity of water-soluble components of saffron separated by UPLC method [47-48], and then established an effective prediction model of separation conditions, which not only reduced peak overlap, but also detected new crocetin derivatives.

3.6 Application in Chinese Medicine

The chemical composition of traditional Chinese medicine is complex and varied, and there are also differences between authentic herbs. The laws behind these complex identification problems are difficult to describe with conventional mathematical models, and artificial neural network has advantages in dealing with such complex problems with its unique learning, generalization and adaptive ability. Yang et al. [49] established a Chinese herbal medicine identification model which combined near infrared spectroscopy with artificial neural network, which is used to identify Chinese herbal medicine raw materials with similar appearance and difficult to identify by visual inspection. When comparing with other detective methods, it is found that near infrared has the strong points of no damage, celerity and convenient accessibility [50]. Among the research, ANN is used to assay absorption spectrum of herbs, and a model that can identify 30 different herbs is successfully established. The recognition rate of the best recognition model is 99.67% on the training data of 600 samples, 100% on the testing set of 300 samples,and therefore, this is an efficient and simple model method.

3.7 Application in Clinical Medicine

Adverse drug reactions (ADR) sometimes occur in clinic, which have no or unexpected harmful reactions with the purpose of drug use under normal usage and dosage. At present, the general practice of treating ADR in most hospitals is to pay attention to drug users and deal with ADR after it is found, but such measures have great lag. Using artificial neural network technology can predict whether patients will have ADR after taking drugs in advance, and take preventive measures as soon as possible to reduce the harm caused by ADR to patients. Lai et al. [51] used three technical algorithms of ANN, support vector machine (SVM) and random forest to predict results of hepatotoxicity of anti-tuberculosis drugs, calculated their accurate, sensitive and specific degree, and operating characteristic curve lower area of receivers. Then they compared the traditional model, genome model and combination model of the three technologies. The results show that the ANN combined with clinical and genomic factors performs best in the test set, its accurate, sensitive and specific degree reach 88.67%, 80% and 90.4% respectively, which has obvious advantages, so artificial neural network technology can be an effective innovative tool for predicting and preventing adverse drug reactions.

4. CONCLUSION

With the advent of the information age, there are more and more combinations of experiments and model algorithms. Because of its unique characteristics, artificial neural network is extensively used in multiple domains. With the continuous development of artificial neural network's theory and technology, it can better solve the existing limitations such as over-fitting and nonlinearity, and its application in pharmaceutical-related fields is more and more effective, which promotes the far-reaching development of pharmaceutical-related fields and further promotes human health. However, like other mathematical models, artificial neural network technology also has large errors due to model structure and algorithm, so it can be optimized and analyzed by trying to choose the appropriate algorithm and network structure in different aspects and combining with the specific experimental characteristics.

Besides new drug design, pharmacokinetics, pharmaceutical preparations, pharmaceutical analysis, traditional Chinese medicine identification and clinical pharmacy, there are many other aspects in the pharmaceutical field, such as drug mass production, workshop design and so on. Therefore, better exploration and research are needed in this field to find the potential development direction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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