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Review Article

ARTIFICIAL NEURAL NETWORKS: FUNCTIONINGANDAPPLICATIONS IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

Artificial Neural Network (ANN) technology is a group of computer designed algorithms for simulating neurological processing to process information and produce outcomes like the thinking process of humans in learning, decision making and solving problems. The uniqueness of ANN is its ability to deliver desirable results even with the help of incomplete or historical data results without a need for structured experimental design by modeling and pattern recognition. It imbibes data through repetition with suitable learning models, similarly to humans, without actual programming. It leverages its ability by processing elements connected with the user given inputs which transfers as a function and provides as output. Moreover, the present output by ANN is a combinational effect of data collected from previous inputs and the current responsiveness of the system. Technically, ANN is associated with highly monitored network along with a back propagation learning standard. Due to its exceptional predictability, the current uses of ANN can be applied to many more disciplines in the area of science which requires multivariate data analysis. In the pharmaceutical process, this flexible tool is used to simulate various non-linear relationships. It also finds its application in the enhancement of pre-formulation parameters for predicting physicochemical properties of drug substances. It also finds its applications in pharmaceutical research, medicinal chemistry, QSAR study, pharmaceutical instrumental engineering. Its multi-objective concurrent optimization is adopted in the drug discovery process, protein structure, rational data analysis also.

Keywords: Artificial intelligence, QSAR, Optimization, Preformulation, Toxicity Prediction, Drug discovery

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INTRODUCTION

Artificial intelligence (AI) has been brought into existence for generating programming equipped for modern, wise, calculations like those that the specific brain routinely performs. It incorporates techniques, instruments, and frameworks to re-enact human strategies for legitimate and inductive learning procurement by brain activity of solving problems. Artificial intelligence is helpful for restorative finding and other demonstrative critical thinking. It gives a guide to expectation including vulnerability and ambiguity.

The following review was concentrated to elaborate the artificial neural networks in detail and its applications in the pharmaceutical field. Review and research article on ANN and its components that are available in journal databases such as Science Direct, Proquest, Springer from the year 2000-2018 were studied and in-depth knowledge on ANN was produced. Very few articles before the year 2000 were also considered.

Artificial Neural Network (ANN), an advancement of AI, are digitized models of a human brain, in which computer programs intended to mimic the way in which human brain forms data for desired outcome [1-2]. ANN perform through repeated or previous experience with suitable learning models similarly as individuals think, but not from programming. In other words, an ANN is a biologically developed computational model shaped from many single units, artificial neurons, associated with coefficients (weights) which constitute the structural neuron [3]. They are otherwise called processing elements (PE) as they process data. Every PE has an input of various weights, transfer function and gives as one output [4]. ANN has the capacity of handling broad measures of information, in any case, and making expectations that are very accurate. However, this does not make them keen on the usual 'human' feeling of the word, so computer knowledge might be a better method for depicting these functions. There are numerous sorts of neural systems planned at this point, and new ones are created every week. However, all can be represented by the exchange elements of their neurons, by the learning rule and connection formula [5]. ANN performs when the given data, called inputs are processed through a transfer function to deliver the output for that neuron, and the most ordinarily utilized exchange work is the sigmoid work. Dynamic networks can store information and expand it in time that is the favourable position of dynamic neural networks (contrasted with the static networks). Each input is investigated as a capacity of the previously submitted input [6]. The system recollects history; subsequently, the present output is coordination of previous data and the currently processed data of the system [7]. The neurons get several inputs, and it performs computation depending on the primitive function mentioned on the body of the neurons and depending on the threshold value mentioned the network decides whether to signal output or not. [8].

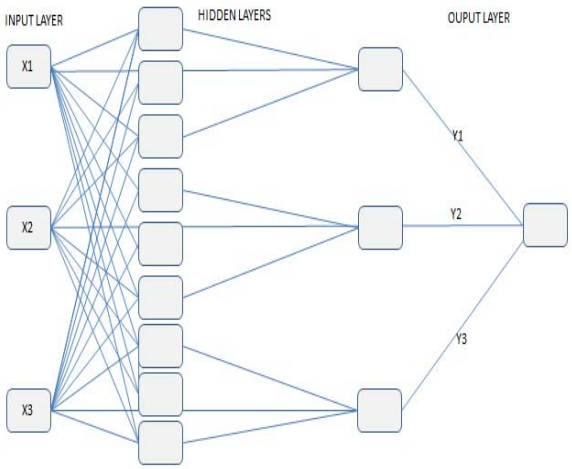

Fig. 1: Pictographic representation of four layered ANN network [3] Learning in ann

Among the various learning methods of ANN, Backpropagation rule [9] or delta rule is regularly utilized. The ANN reads the value of input and output from the training set of data and changes the estimation of the weighted connects to decrease the contrast between the anticipated and target esteems [10-11]. The blunder in expectation is limited to many training cycles until the point that the

system achieves indicated the level of accuracy. Preparing a system for more extended periods will results in overtraining, eventually losing its ability to perform the prescribed function.

Connection formula

The neurons which link with each other has a significant impact on the processing of ANN. These neurons can get either excitatory or inhibitory data sources [12]. Excitatory information causes the summing system of the next neuron to include while the inhibitory information sources make it subtract. The system needs to 'pick' the most probability and repress all others, which is called as competition. Feedback is another connection where the output of one layer courses back to the contribution of a past layer, or to the same layer. Every neuron has extra leverage as information that will permit an extra level of flexibility when attempting to limit the preparation mistake. Such a system keeps a memory of past state, so that next state depends not just on input signal [13] yet additionally on the previous conditions of the system.

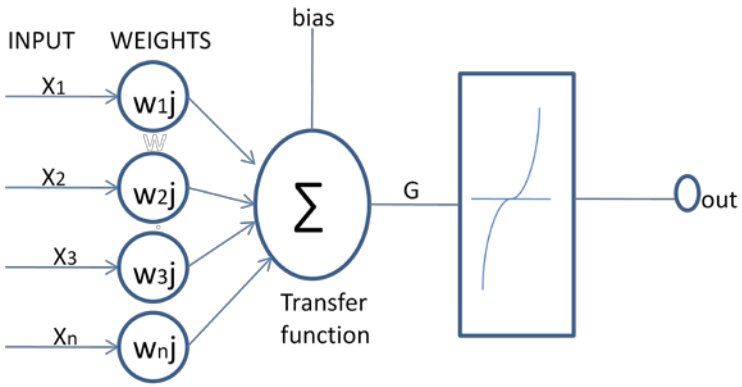

Fig. 2: Neuron transmission process model [3]

Approaches in ann

There are two ways to deal with training, i.e., supervised and unsupervised. The most frequently utilized ANN is a completely associated supervised network with back propagation learning standard [14]. Supervised learning is a type of relapse that depends on case sets of information where the input layer neurons get information from a document, and the output neurons give ANN reaction to the data. Processing neurons discuss just with different neurons and then decide an answer to the issue. This approach focuses mainly on the predicting one or more input variables. In case of unsupervised training, the system is given with inputs but not with the fixed output. The framework itself should then choose what feature will be required to enlist the input data. Therefore, this approach is called as adaptation or self-organization [15]. The goal of this approach is to develop a variable from which the observed variable, both input and output factors, can be anticipated.

Application of artificial neural network in the field of pharmaceutical aspects

The artificial neural network finds its application in the various fields of pharmaceutical sciences. Some of them are enlisted as below:

Structural screening in drug discovery process

The standard approach to predicting how active a chemical compound will be against a given target (usually a protein that needs to be inhibited) in the development of new medicines is to use machine learning models [16]. ANN-based QSAR models are broadly picked as the forecast strategies in the virtual screening. The essential part of Artificial Intelligence in patient care is quiet finding and picture examination, the future holds incredible potential for applying AI to enhance numerous parts of the patient care handle [17]. This approach is referred to as virtual screening. For example, if any basic structure of the compound is the input for a neural network, it displays various structure similar to those compounds screens over 1000 compounds, among them three compounds with high biologic activity can be identified [18].

Toxicity prediction

ANN can be used as an integral part of pharmacotoxicology, especially in Quantity Structure Toxicity Relationship (QSTR) contemplates. QSTR is a connection between the substance descriptors and its toxicological activity and can be associated to predict the lethality of compounds [19]. Like QSAR, the molecular descriptors of QSTR are predicted from physicochemical properties of the compounds and related to a toxicological reaction of intrigue through ANN. For example, topology method used as the input mode of a network; The ANN-QSTR model was approved by 23 substituted benzene derivatives. The connection coefficient amongst anticipated and real toxicological activities of these compounds was observed to be 0.9088 [20].

Designing of preformulation parameters

ANN modelling has been utilized to enhance pre-formulation parameter and to estimate the physicochemical properties of amorphous polymers. They predict the absorption, glass temperatures and viscosities of different hydrophilic polymers and their physical substance with a low expectation mistake (0-8%) [21]. It demonstrated the potential of ANN as a preformulation tool by prediction of the relationship between the composition of polymer substance and the water uptake profiles, a viscosity of polymers solutions, moisture content and their glass transition temperatures. [22]. In the presence of multiple Active Pharmaceutical Ingredient (API) this model could test 14 APIs after progressing the strategy of utilizing self-sorting out maps recognizing the goal to extend the database of quick release tablet and to concentrate the impact of Programming interface on the tablet properties [23-24]. It has been precious in the pre-formulation outline and would help to decrease the cost and length of preformulation contemplate.

Optimization of pharmaceutical formulation

It addresses the multi-objective oriented concurrent optimization issues in the pharmaceutical industry to establish the relationship between reaction factors and insignificant factors [25]. The prediction of pharmaceutical responses in the polynomial equation and response surface methodology (RSM) has been broadly used as a part of formulation optimization [26-27] However; this prediction is small scale due to a low success rate of estimation. An optimization method consolidating an ANN has been created to overcome these shortcomings and to anticipate release profile and improve detailing of different drug formulations. For example, aspirin or diclofenac sodium prolonged-release tablets [28-29]. The

results calculated by the trained ANN model satisfy well with the theoretically observed values including *in vitro* release pattern which helps to improve the effectiveness of process and formulation variables.

Quantity structure-activity relationship (QSAR)

ANN has been shown to be a useful tool to establish this type of relationship and predict the activities of new compounds [30]. QSAR links physicochemical parameters of compounds with substance or biological activities [31-32]. These parameters include molecular weight, log p-value, electronic properties, hydrophobicity, steric effects, a hydrogen donor, molar volume and molar refractivity. Experimental determination of such properties can be the time-consuming process, and in a few cases, there may occur experimental variation and errors [33]. An initial phase in QSAR contemplates figuring a massive number of structural descriptors as mathematical illustrative of chemical structure [33]. The relation of structure and activity with the physicochemical descriptors and topological parameters can be controlled by computational techniques. For example, ANN has been utilized by Grobburu and associates to foresee the quantitative structure QSPR of beta-adrenoceptor antagonist in human [32]. In the examination, ANN with the congeneric arrangement of ten beta-blockers having high set up pharmacokinetic parameters was developed and tried for its ability to predict the pharmacokinetic parameters [33-34]. Testing an enormous number of possible combination of descriptors might take a lifetime to succeed. A more efficient path is to utilize algorithm calculations such as computational models of advancement, combined with Artificial Neural Network [35-36]. "Back-propagation (ANN) were trained with topological indices, molecular connectivity, and novel physicochemical descriptors to predict the structure-activity relationship of a large series of analogues" [37-41]. It generates valuable models of the aqueous solubility inner arrangement of fundamentally related medications with necessary auxiliary parameters [42]. Topological descriptors interface the compounds with their aqueous solubility [43]. ANN predicted properties exhibited better correlation with the experimentally determined values than those predicted by various multiple regression methods. Correlation studies of the prescient performance of an automated model with an observational ANN display in ascertaining the connection between the tissue distributions furthermore, the lipophilicity of a homologous arrangement of 5-n-alkyl-5-ethyl barbituric acids in the rats have been distributed and exhibited the scope of ANN in this application [43]. Further, ANN has been valuable in QSAR investigation of antitumor movement of acridinone subordinates [44]. Moreover developed mode allowed to recognize the critical variables adding to the antitumor movement such as lipophilicity. Therefore, ANN is not just valuable in predicting QSARs yet additionally in distinguishing the part of the particular components relevant to the action of interest. It has been exhibited in the earlier investigation by Uesawa also, partners in their QSAR investigation of tumor-specificity of 1,2,3,4-tetrahydroisoquinoline subordinates [45]. ANN can also be exceptionally helpful in predicting synthetic properties of compounds. A few research groups have displayed the typical breaking point of hydrocarbons. Predicting neural system models have been distributed for alkanes, alkenes, and assorted hydrocarbons. Of course, the models commonly demonstrate great fitting and expectation insights with under ten necessary descriptors. Goll and Jurs also connected the simulated neural system to anticipate the vapor weights of hydrocarbons and halo hydro-carbons from sub-atomic structure [46].

Pharmacokinetics and pharmacodynamics

ANN monitors human pharmacokinetics parameters from the set of data on physicochemical properties of medications such as partition coefficient, protein binding, dissociation constant and animal pharmacokinetic parameter [47-48]. Medication doses and drug choice are resolved by information of the drug's pharmacokinetics and pharmacodynamics [49]. They are adapted to estimate the pharmacodynamics profiles precisely for a broad assortment of pharmacokinetic and pharmacodynamics relationship without requiring any data of active metabolite [50-52]. As they do not require any structural information, it provides an idea over usual dependent conventional methods. ANN is a quick and straightforward method for predicting and identifying covariates [53-54]. For example, the rate of clearance, protein-bound fraction of drug and also volume distribution can be determined by incorporating them in monitoring various PK interactions in the biological system and anticipation of PD parameters. Because of their computational adaptability, they have been used as a tool for population pharmacokinetic investigation and result concludes ANN as a better estimate tool in comparison with NONMEM. Hussain *et al.* used ANN in the prediction of PK parameters from data obtained in animal studies. Further, Ritchel *et al.* predicted human PK parameters utilizing information from the data set of physiochemical properties like dissociation constant, protein binding, a volume of distribution, partition coefficient in association with animal PK parameters [55]. Corrigan *et al.* connected neural system to predict the concentration of gentamicin in a general doctor's facility population [56]. Their outcomes demonstrated that neural networks offered a few favorable advantages over traditional dose prediction techniques. Kenji *et al.* connected an ANN simulation to link the pharmacokinetic of aminoglycoside anti-microbial utilizing physiological estimation in patients with extreme disease [57].

Proteomics and genomics

In the detachment of peptides in ion exchange chromatography, ANN predicts peptide separation. Due to their ability to identify the pattern, ANN is appropriate for the arrangement of proteins, prediction of enzyme class, characterization of DNA/RNA and protein [58]. A hierarchical network named PRED-CLASS have been used to group proteins into four categories, for example, transmembrane, stringy, globular and blended proteins. The PRED-CLASS prepared by studying 50 protein arrangements, predicted 371 out of an arrangement of 387 proteins with an accuracy of 96 percent [59]. These properties are highly significant in the investigation of protein structure and function. They could assist in the prediction of protein tertiary structure, for example, a data of six input and six hidden units with sigmoid transfer function developed by Murvaiet *et al.* for the acknowledgment of areas in protein succession [60]. Cai and colleagues utilized ANN for predicting secondary protein structure to pair coupled amino acid sequence. Furthermore, the study exhibited that ANN is an appropriate technique for prediction of the secondary structure of proteins. The neural systems have been utilized to predict eukaryotic protein phosphorylation sites to identify active sites and to predict protein class with high accuracy for novel protein structures in peptide sequence and enhancement protein confinement and arranging prediction [61]. Additionally, ANN-based algorithms have been utilized to recognize, characterize and anticipate stabilization center elements from the essential structure of single proteins and amino acid sequence of homologous proteins.

Disease diagnosis

ANN has been applied in the diagnosis of various diseases by the input of clinical data [62]. It exhibits good results in the early prediction of cardiovascular risk or myocardial infarction, diagnosis of Alzheimer's disease, prediction of outcome in epilepsy surgery, prediction of development of pregnancy-induced hypertensive disorders, diagnosis of pigmented skin lesions Moreover, it has also been used to predict responses in pharmacotherapy, hormonal treatment in metastatic breast malignancy and clinical result for individual patients [63-68]. Compared to conventional strategies, the level of certainty for the prediction can achieve 90% by employing ANN [70, 71], and this can make a significant advancement towards individualized treatment in the future.

***In vitro in vivo* correlation**

The *in vitro in vivo* relationships (IVIVC) are of great interest to the pharmaceutical industry to dodge bioequivalence subjects which exhibits considerable variability in results. They can predict the IVIVC of the same product with different formulations and also they can skip constraints related to regression methods. For example, the absence of design acknowledgment powers breaking down multivariable

informational collections with the high level of variety [72-75]. Jovanovic *et al.* determine IVIVC of salbutamol in the lungs in healthy and asthmatic volunteers even without *in vivo* information. The medication drug level was estimated in urine and compared with the pulmonary function. The investigation inferred that ANN is helpful in anticipating *in vivo* reaction with given *in vitro* information [76].

Table 1: List of neural networking software

Software	Applications
Statistica Neural network	Signal processing, and Classification, Pattern recognition, Medical diagnostics and monitoring, Image and speech analysis, Stock market and forecasting [77]
Tns2server	Genetic Algorithm solutions, Statistical Analysis, Linear and Nonlinear Optimization, Mathematical modeling
Applied Analytic System, Inc.	
Data engine	Functionality for all the phases of data analysis
Environment for Computer-Aided Neural Software Engineering (eCANSE)	Data Analysis, Experiment design and actual experimentation, Analyzing and packaging results [78]
Fast Artificial Neural Network (FANN)	Backpropagation training, Evolving topology training, Graphical interface
Brian Neural Network simulator	Plotting and analysis of auditory system modelling, Electrophysiological data
Neural Simulation Language	Supporting neural network layer, Programming of neural elements
Neuroshell	Large library of technical analysis, Prediction analysis, Genetic Optimization and Multicore Distributed Optimization, Multiple Time Frame analysis, Batch Processing [79]

Conclusion and future perspectives

The application of ANN in pharmaceutical development can be successfully applied in various fields especially pattern classification, function approximation, optimization, prediction of improved therapeutic effect. Adapting in the pharmaceutical area have been of great interest due to its capacity to design a process that can't be satisfactorily represented by statistical methods. Its key advantage falls in the process of drug discovery in pharmaceutical research by viewing the accurate data prediction. At present, ANN has the potential to predict toxicity, physicochemical and biological activity and diagnosis of disease. Furthermore, ANN it was already successfully applied in some of the pharmaceutical processes such as medicinal chemistry, clinical chemistry, the study of pharmacokinetic aspects to provide solutions for large-scale manufacturing and improvement of physical and biological properties by ANN suggested modifications.

ABBREVIATIONS

AI = artificial intelligence, ANN = artificial neural network, API =active pharmaceutical ingredient, eCANSE= environment for computer aided neural, software engineering, FANN= fast artificial neural network, IVIVC= *in vitro in vivo* correlation, PE= processing elements, PD= pharmacodynamics, PK= pharmacokinetics, QSAR= quantitative structure-activity relationship, QSPR = quantitative structure-property relationship, QSTR= quantitative structure-toxicity relationship, RSM= response surface methodology.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Wesolowski M, Suchacz B. Artificial neural networks: theoretical background and pharmaceutical applications: a review J. AOAC Int 2012;95:652-68.
2. Carpenter H, M WC. Understanding neural network approximations and polynomial approximations helps neural network performance. AI Expert 1995;2:31-3.
3. Agatonovic Kustrin S, Beresford R. Basic concepts of the artificial neural network (ANN) modeling and its application in pharmaceutical research. J Pharm Biomed Anal 2000;22:717-27.
4. Ferrari S, Stengel RF. Smooth function approximation using neural networks. IEEE Trans Neural Netw (a publication of the IEEE Neural Networks Council) 2005;16:24-8.
5. Erb RJ. Introduction to backpropagation neural network computation. Pharm Res 1993;10:165-70.
6. Liu F, Er MJ. A novel efficient learning algorithm for self-generating a fuzzy neural network with applications. Int J Neural Syst 2012;22:21-35.
7. Bourquin J, Schmidli H, Van Hoogevest P, Leuenberger H. Basic concepts of artificial neural networks (ANN) modeling in the application to pharmaceutical development. Pharm Dev Technol 1997;2:95-109.
8. Chen CP, Zhang CY. Data-intensive applications, challenges, techniques, and technologies: a survey on big data. Information Sciences. Asian J Pharm Clin Res 2014;275:314-47.
9. Holmstrom L, Koistinen P. Using additive noise in backpropagation training. IEEE Trans Neural Netw 1992;3:24-38.
10. Pukrittayakamee A, Hagan M, Raff L, Bukkapatnam ST, Komanduri R. Practical training framework for fitting a function and its derivatives. Neural Netw IEEE Trans 2011;22:936-47.
11. Wu J, Mei J, Wen S, Liao S, Chen J, Shen Y. Self-adaptive genetic algorithm-artificial neural network algorithms with leave-one-out cross-validation for descriptor selection in QSAR study. J Comput Chem 2010;31:1954-68.
12. Bouleimen K, Lecocq H. A new efficient simulated annealing algorithm for the resource-constrained project scheduling problem and its multiple mode versions. Eur J Oper Res 2003;148:268-81.
13. Inden B, Jin Y, Haschke R, Ritter H. Evolving neural fields for problems with large input and output spaces. Neural Net 2012;28:24-39.
14. Jadid MN, Fairbairn DR. Neural-network applications in predicting moment-curvature parameters from experimental data. Eng Appl Artif Intell 1996;9:309-19.
15. Livingstone DR, Manallack DT, Tetko IV. Data modeling with neural networks: advantages and limitations. J Comput Aided Mol Des 1997;11:135-42.
16. Olier I, Sadawi N, Bickerton GR, Vanschoren J, Grosan C, Soldatova L, *et al*. Meta-QSAR: a large-scale application of meta-learning to drug design and discovery. Mach Learn 2018;107:285-311.
17. Gawad J, Bonde C. Artificial intelligence: future of medicine and healthcare. Asian J Pharm Clin Res 2017;11:355-60.
18. Hu L, Chen G, Chau RM. A neural network-based drug discovery approach and its application for designing aldose reductase inhibitors. J Mol Graph Model 2003;24:244-53.
19. Gao DW, Wang P, Liang H, Peng YZ. A study on prediction of the bio-toxicity of substituted benzene based on the artificial neural network. J Environ Sci Health B 2003;38:571-9.
20. Jaen Oltra J, Salabert Salvador MT, Garcia March FJ, Perez Gimenez F, Tomas-Vert F. Artificial neural network applied to prediction of fluoroquinolone antibacterial activity by topological methods. J Med Chem 2000;43:1143-8.

21. Eros D, Kovesdi I, Orfi L, Takacs Novak K, Acsady G, Keri G. Reliability of logP predictions based on calculated molecular descriptors: a critical review. Curr Med Chem 2000;9:1819-29.
22. Yan A, Chen X, Zhang R, Liu M, Hu Z, Fan BT. Predicting the standard enthalpy (deltaH0f) and entropy (S0) of alkanes by artificial neural networks. SAR. QSAR. Environ Res 2000; 11:235-44.
23. Liu S. Neural network-topological indices approach to the prediction of properties of the alkene. J Chem Inform Computer Sci 1997;37:1146-51.
24. Kirkpatrick S, Gelatt CDJR, Vecchi MP. Optimization by simulated annealing. Science 1983;220:671-80.
25. Glass BD, Agatonovic Kustrin S, Wisch MH. Artificial neural networks to optimize formulation components of a fixed dose combination of rifampicin, isoniazid, and pyrazinamide in a microemulsion. Curr Drug Discovery Technol 2005;2:195-201.
26. Takahara J. Multi-objective simultaneous optimization technique based on an artificial neural network in sustained release formulations. J Controlled Release 1997;11:11-20.
27. Ibric S, Jovanovic M, Djuric Z, Parojcic J, Petrovic SD, Solomun L, *et al*. Artificial neural networks in the modeling and optimization of aspirin extended release tablets with Eudragit L 100 as matrix substance. AAPS Pharm Sci Tech 2003;4:E9.
28. Zupancic Bozic D, Vrecer F, Kozjek F. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur J Pharm Sci 1997;5:163-9.
29. Aoyama T, Suzuki Y, Ichikawa H. Neural networks applied to quantitative structure-activity relationship analysis. J Med Chem 1990;33:2583-90.
30. Agatonovic Kustrin S, Zecevic M, Zivanovic L. Use of ANN modeling in structure-retention relationships of diuretics in RP-HPLC. J Pharm Biomed Anal 1999;21:95-103.
31. Myint KZ, Wang L, Tong Q, Xie XQ. Molecular fingerprint-based artificial neural networks QSAR for ligand biological activity predictions. Mol Pharm 2012;9:2912-23.
32. Nirouei M, Ghasemi G, Abdolmaleki P, Tavakoli A, Shariati S. Linear and non-linear quantitative structure-activity relationship models on indole substitution patterns as inhibitors of HIV-1 attachment. Indian J Biochem Biophys 2012;49:202-10.
33. Takayama K, Fujikawa M, Nagai T. Artificial neural network as a novel method to optimize pharmaceutical formulations. Pharm Res 2011;16:1-6.
34. Nestorov IS, Hadjitodorov ST, Petrov I, Rowland M. Empirical versus mechanistic modeling: comparison of an artificial neural network to a mechanistically based model for quantitative structure pharmacokinetic relationships of a homologous series of barbiturates. AAPS Pharm Sci 1999;1:17.
35. Vaithiyalingam S, Khan MA. Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion. Int J Pharm 2002;234:179-93.
36. Erturk MD, Saban MT, Novic M, Minovski N. Quantitative structure-activity relationships (QSARs) using the novel marine algal toxicity data of phenols. J Mol Graph Model 2012;38:90-100.
37. Yaffe D, Cohen Y, Espinosa G, Arenas A, Giralt F. Fuzzy ARTMAP and back-propagation neural networks based quantitative structure-property relationships (QSPRs) for octanol-water partition coefficient of organic compounds. J Chem Inform Computer Sci 2002;42:162-83.
38. Myint KZ, Wang L, Tong Q, Xie XQ. Molecular fingerprint-based artificial neural networks QSAR for ligand biological activity predictions. Mol Pharm 2012;9:2912-23.
39. Wu CH. Artificial neural networks for molecular sequence analysis. J Computer Chem 1997;21:237-56.
40. Sachdeva J, Kumar V, Gupta I, Khandelwal N, Ahuja CK. A dual neural network ensemble approach for multiclass brain tumor classification. Int J Numer Method Biomed Eng 2012;28:1107-20.
41. Luque NR, Garrido JA, Ralli J, Laredo JJ, Ros E. From sensors to spikes: evolving receptive fields to enhance sensorimotor information in a robot arm. Int J Neural Syst 2012; 22:12500-13.
42. Gobburu JV, Shelver WH. Quantitative structure-pharmacokinetic relationships (QSPR) of beta blockers derived using neural networks. J Pharm Sci 1995;84:862-65.
43. Samarasinghe S. Neural networks for applied sciences and engineering; auerbach publications: New York, NY, USA; 2006.
44. Basheer IA, Hajmeer M. Artificial neural networks: fundamentals, computing, design, and application. J Microbiol Methods 2000;4:3–31.
45. Dearden JC, Hewitt M. QSAR modeling of bioconcentration factor using hydrophobicity, hydrogen bonding, and topological descriptors. SAR. QSAR. Environ Res 2010;21:6671-80.
46. Chen Y, McCall TW, Baichwal AR, Meyer MC. The application of an artificial neural network and pharmacokinetic simulations in the design of controlled-release dosage forms. J Controlled Release 1999;59:33-41.
47. Gobburu JV, Chen EP. Artificial neural networks as a novel approach to integrated pharmacokinetic-pharmacodynamic analysis. J Pharm Sci 1996;85:505-10.
48. Ritschel WA, Akileswaran R, Hussain AS. Application of neural networks for the prediction of human pharmacokinetic parameters. Methods Find Exp Clin Pharmacol 1994;19:629-43.
49. Brier ME, Zurada JM, Aronoff GR. Neural network predicted peak and trough gentamicin concentrations. J Pharm Res 1995;12:406–12.
50. Haidar SH, Johnson SB, Fossler MJ, Hussain AS. Modeling the pharmacokinetics and pharmacodynamics of a unique oral hypoglycemic agent using neural networks. J Pharm Res 2002;19:87-91.
51. Gaweda AE, Jacobs AA, Brier ME, Zurada JM. Pharmacodynamic population analysis in chronic renal failure using artificial neural networks–a comparative study. Neural Net 2003; 16:841–5.
52. Chow HH, Tolle KM, Roe DJ, Elsberry V, Chen H. Application of neural networks to population pharmacokinetic data analysis. J Pharm Sci 1997;86:840-5.
53. Hussain AS, Johnson RD, Vachharajani NN, Ritschel WA. Feasibility of developing a neural network for prediction of human pharmacokinetic parameters from animal data. J Pharm Res 1993;10:466-9.
54. Veng Pedersen P, Modi NB. Neural networks in pharmacodynamic modeling. Is the current modeling practice of complex kinetic system. J Pharmacokinet Biopharm 1992; 20:397–412.
55. Leung FHF, Lam HK, Ling SH, Tam PKS. Tuning of the structure and parameters of a neural network using an improved genetic algorithm. IEEE trans Neural Net 2003;14:79-88.
56. Andreas Breindl BB, Timothy Clark, Robert C Glen. Prediction of the n-Octanol/water partition coefficient, logp, using a combination of semiempirical calculations and a neural network. J Mol Model 1997;3:142-55.
57. Gobburu JV, Chen EP. Artificial neural networks as a novel approach to integrated pharmacokinetic-pharmacodynamic analysis. J Pharm Sci 1996;85:505-10.
58. Hasani M, Moloudi M, Emami M. Spectrophotometric resolution of ternary mixtures of tryptophan, tyrosine, and histidine with the aid of principal component-artificial neural network models. Anal Biochem 2007;370:68-76.
59. Baczek T, Bucinski A, Ivanov AR, Kaliszan R. Artificial neural network analysis for evaluation of peptide MS/MS spectra in proteomics. Anal Biochem 2004;76:1726-32.
60. Murvai J, Vlahovicek K, Szepesvari C, Pongor S. Prediction of protein functional domains from sequences using artificial neural networks. Genome Res 2001;11:1410-7.
61. Zhao W, Davis CE. A modified artificial immune system based pattern recognition approach--an application to clinical diagnostics. Artif Intell Med 2011;52:1-9.
62. Torrent M, Andreu D, Mogues V, Boix E. Connecting peptide physicochemical and antimicrobial properties by a rational prediction model. PloS One 2011;6:16968.
63. Koba M. Application of artificial neural networks for the prediction of antitumor activity of a series of acridinone derivatives. J Med Chem 2012;8:309-19.

64. Giordano A, Giuliano M, Laurentiis DE, Eleuteri A, Iorio F, Tagliaferri R, *et al*. Artificial neural network analysis of circulating tumor cells in metastatic breast cancer patients. Breast Cancer Res Treat 2011;129:451-8.
65. Bahari MH, Mahmoudi M, Azemi A, Mirsalehi MM, Khademi M. Early diagnosis of systemic lupus erythematosus using ANN models of ds DNA binding antibody sequence data. Bioinform 2010;5:58-61.
66. Pedersen SM, Jorgensen JS, Pedersen JB. Use of neural networks to diagnose acute myocardial infarction. I. A clinical application. Clin Chem 1996;42:613-7.
67. Baxt WG. Analysis of the clinical variables driving decision in an artificial neural network trained to identify the presence of myocardial infarction. Anal Emerg Med 1992;21:1439-44.
68. Leoncini G, Sacchi G, Viazzi F, Ravera M, Parodi D, Ratto E, Vettoretti S, TomolilloC,Deferrari G, and Pontremoli R. Microalbuminuria identifies overall cardiovascular risk in essential hypertension: an artificial neural network-based approach. J. Hypertens2002;20:1315-21.
69. Mello G, Parretti E, Ognibene A, Mecacci F, Cioni R, Scarselli G, *et al*. Prediction of the development of pregnancy-induced hypertensive disorders in high-risk pregnant women by artificial neural networks. Clin Chem Laboratory Med 2001;39:801-5.
70. Deng X, Li K, Liu S. Preliminary study on application of artificial neural network to the diagnosis of Alzheimer's disease with magnetic resonance imaging. Chin Med J 1999;112:232-37.
71. Sardari S, Sardari D. Applications of the artificial neural network in AIDS research and therapy. Curr Pharm Des 2002;8:659-70.
72. Schmid P, Wischnewsky MB, Sezer O, Bohm R, Possinger K. Prediction of response to hormonal treatment in metastatic breast cancer. Oncology 2002;63:309-16.
73. Jaen Oltra J, Salabert Salvador MT, Garcia March FJ, Perez Gimenez F, Tomas-Vert F. Artificial neural network applied to prediction of fluoroquinolone antibacterial activity by topological methods. J Med Chem 2000;43:1143-8.
74. Caramella C, Ferrari F, Bonferoni MC, Sangalli ME, De Bernardi, Di Valserra, *et al*. *In vitro*/*in vivo* correlation of prolonged release dosage forms containing diltiazem HCl. Biopharm Drug Dispos 1993;14:143-60.
75. Dowell, Hussain JA, Devane D, Young JD. Artificial neural networks applied to the *in vitro–in vivo* correlation of extended-release formulations: initial trials and experience. J Pharm Sci 1999;88:154–60.
76. Parojcic J, Ibric S, Duric Z, Jovanovic M, Corrigan OI. An investigation into the usefulness of generalized regression neural network analysis in the development of level a *in vitro–in vivo* correlation. Eur J Pharm Sci 2007;30:264–72.
77. Munishpuri, Yashwant P, Vijay Kumar S, Tipparaji M. Artificial neural network as helping tool for drug formulation USA; 2016. p. 270-2.
78. Torii K, Matsumoto K, Nakakoji K, Takada Y, Shima K. An Environment for computer-aided empirical software engineering. IEEE Trans Neural Netw 1999;25:474-92.
79. Alfredo W, Michael A, Amanda A. The neural simulation language: a system for brain modeling. The MIT Press; 2002.