ARTIFICIAL NEURAL NETWORKS: FUNCTIONING AND APPLICATIONS 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

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].

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 result 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 regression 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 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].
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 such a 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 were 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 acridine 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 pharmacokinetic parameters [33-34]. Testing an enormous number of possible combination of descriptors might take a lifetime to succeed. 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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 pharmaco kinetic 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 animals studies. Further, Ritchel et al. predicted human PK parameters utilizing information from the data set of physicochemical 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 has been used to group proteins into four categories, for example, transmembrane, stringy, globular and blended proteins. The PREDCLASS 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 Murvai 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]. 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 IVIC 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].

**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 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, QSTR= quantitative structure-property relationship, RS= response surface methodology.

**AUTHORS CONTRIBUTIONS**

All the authors have contributed equally

**CONFLICT OF INTERESTS**

Declared none

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