Journal of Research Administration
Society of Research Administrators International

A REVIEW ON ARTIFICIAL NEURAL NETWORKS IN PHARMACEUTICAL TECHNOLOGY

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Abstract: Artificial Neural Networks (ANN) are one of the most powerful computational tools yet devised for mathematically modelling the human brain's neurophysiologic structure and function in order to imitate its process. Engineering, psychology, medicinal chemistry and pharmaceutical research are just few of domains where ANN can be used. Because of their capacity for making predictions, pattern recognition, and modelling, ANN have been very useful in many aspects of pharmaceutical research including modelling of the brain neural network, analytical data analysis, drug modelling, protein structure and function, dosage optimization and manufacturing, pharmacokinetics and pharmacodynamics modelling, and in-vitro in-vivo correlations due to their capacity for making predictions, pattern recognition and modelling. This article examines the differences between artificial and biological neurons, as well as ANN applications in pharmaceutical technology and the benefits and drawbacks of ANN modelling.

Keywords: Artificial neurons, biological neurons, pharmacokinetics and pharmacodynamics.

1. Introduction to Artificial Neural Networks

The ability of neural networks to emulate the brain's ability to learn by example has gained a lot of attention among scientists globally, being one of the greatest computational tools ever developed; this network makes decision and draws conclusions even when presented with incomplete information. It is a very good tool for many numeric as well as non-numeric calculations and is applied to numerous problems of considerable complexity in many fields, including engineering, psychology, medicinal chemistry, diagnostics, and pharmaceutical research [1]. ANN is a parallel, distributed information processing structure consisting of processing elements interconnected via unidirectional signal channels called connections. In simple words, they are computer systems developed to mimic the operations of the human brain by mathematically modelling its neurophysiologic structure and function [2]. ANN is capable of simulating neurological processing ability of the human brain. Average human brain contains about 100 billions of neurons with each neuron being connected with 1000-10,000 connections to others. The prediction of pharmaceutical responses based on ANN is widely accepted that mainly focuses on the optimisation and prediction of the best output in formulation development. Literature review revealed various applications of ANN modelling in pharmaceutical product formulations and some of them were briefly reviewed below.

Patel et al used ANN for the optimization of formulation of solid dispersion for fenofibrate using 3^2 full factorial designs [3]. **Prithviraj et al** applied the simultaneous optimization method incorporating artificial neural network using multi-layer perceptron model to develop buccoadhesive pharmaceutical wafers containing loratadine with an optimized physicochemical property and drug release [4].

Aksu et al used neuro-fuzzy logic models neural networks to analyse the impact of critical quality attributes, and critical process parameters on the evaluation tests like tablet hardness, friability and disintegration time on two different commercial superdisintegrants commonly used in oral dispersable tablets formulations (Ludiflash® and Parteck®) [5]. **Wen jin et al** prepared controlled porosity osmotic pump tablets for salvinolic acid and optimized with experimental design methods including ANN model [6]. **Aleksander Mendyk et al** used ANN as modeling tools for prediction of various drugs release patterns from hydrodynamically balanced systems composed with Metholose 90SH [7].

Advantages of ANN

- Effective use of incomplete data sets
- Rapid analysis of data
- Ability to accommodate more data and retrain the network
- Effective exploration of the total design space, irrespective of complexity
- Ability to accommodate constraints and preferences and
- Ability to generate understandable rules [2, 4 & 6].

Disadvantages of ANN

- Problems related to software and lack of development skills
- A number of features should be present before neural computing
- The problem must be numeric in nature, and reasonable quantities of data should be available to train an adequate model [2, 5 & 6].

2. Structure of Biological and Artificial Neurons

2.1. Biological neuron structure

Each biological neuron has three principal components, namely, dendrites, cell body and axon as shown in **Figure 1**. The dendrites are tree-like receptive networks of nerve fibres that carry electrical signals into the cell body. The cell body effectively sums and thresholds these incoming signals. The axon is a single long fibre that carries the signal from the cell body out to other neurons. The point of contact between an axon of one cell and a dendrite of another cell is called a synapse. A neuron is connected to other neurons through about 10,000 synapses (**Figure 2**).

A neuron receives input from other neurons and then all inputs are combined. Once input exceeds a critical level, the neuron discharges a spike - an electrical pulse that travels from the body, down the axon, to the next neuron(s). The axon endings almost touch the dendrites or cell body of the next neuron. Transmission of an electrical signal from one neuron to the next is effected by neurotransmitters. Neurotransmitters are chemicals which are released from the first neuron and which bind to the second. This link is called a synapse. The strength of the signal that reaches the next neuron depends on factors such as the amount of neurotransmitter available.

It is the arrangement of neurons and the strengths of the individual synapses, determined by a complex chemical process that establishes the function of the neural network.

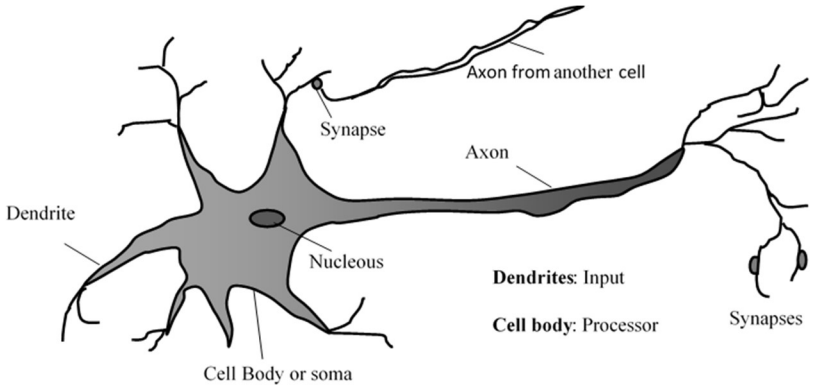

Figure 1. Structure of Biological neuron

Neural structures continue to change throughout life. These later changes tend to consist mainly of strengthening or weakening of synaptic junctions. New memories are formed by modification of these synaptic strengths. Thus, neurons have the capability to memorize, learn and expertise the data.

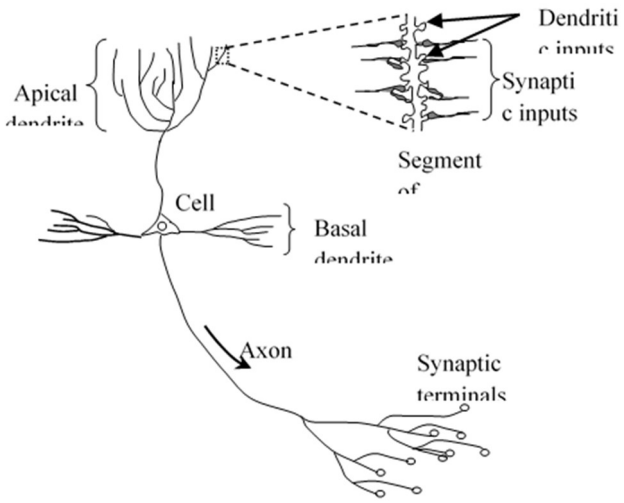

Figure 2. Biological neuron connection to other neurons

2.2. Artificial neuron structure

Each artificial neuron within the artificial neural network is usually an information processing unit which takes one or more inputs and produces an output (**Figure 3**). At each neuron, every input has an associated weight which modifies the strength of each input. The neuron simply adds together all the inputs and calculates the output to be passed on.

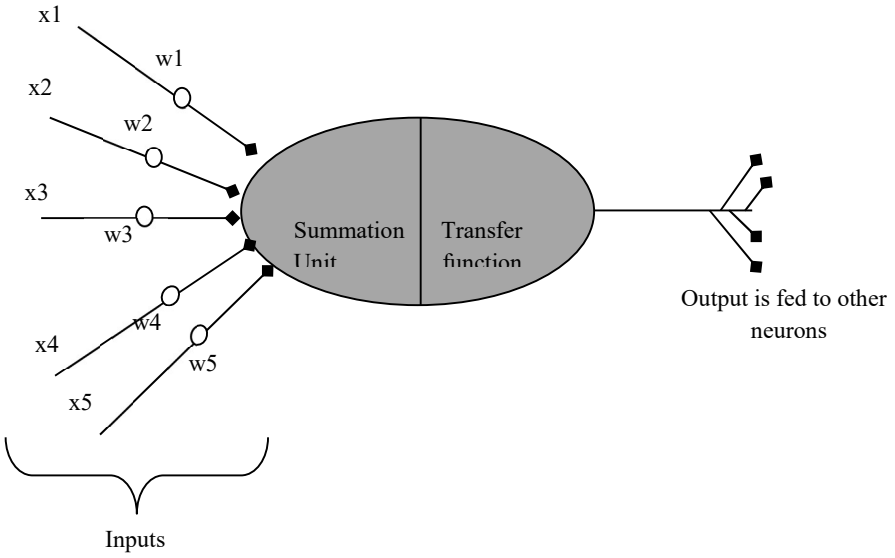

Figure 3. Model of artificial neuron

2.3. Analogy between biological and artificial neurons

An artificial neuron is an imitation of a human neuron. In ANN, the weight corresponds to the strength of a synapse, the cell body is represented by the summation and the transfer function, and the neuron output represents the signal on the axon. **Figure 4** shows the simplified schematic diagram of analogy between biological neuron and artificial neuron.

The model of the neuron which forms the basis of the design of artificial neural network has

i) A set of synapses or connecting links, each of which is characterized by weight or strength of its own ($x_j \times w_j$). Specifically, a signal x_j at the input synapse j, connected to the neuron k, is multiplied by the weight, w_j.

ii) an adder for summing the input signals, weighted by respective synapses of the neuron, the operation described here constitutes a linear combiner($\sum x_i w_i = x_0 w_0 + x_1 w_1 + \ldots + x_n w_n$ = output)

iii) An activation function for limiting the amplitude of output of the neuron (**Figure 4**).

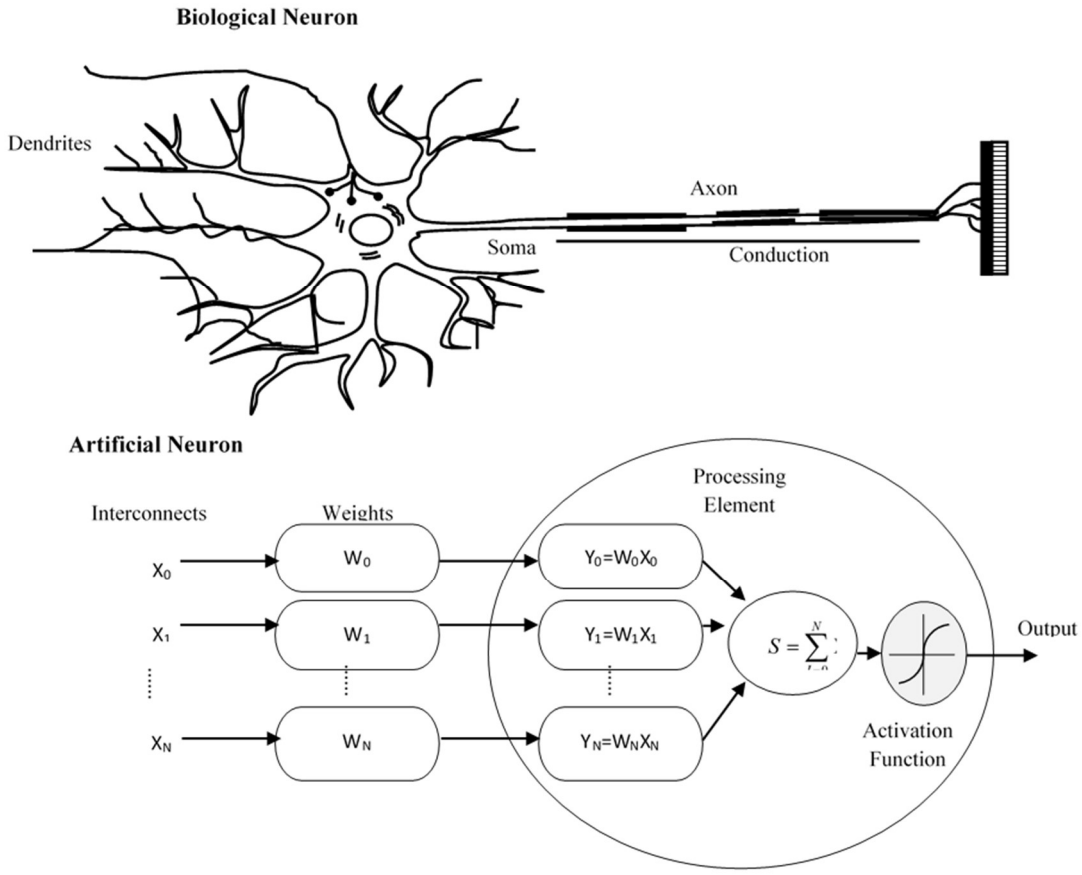

Figure 4. Biological Neuron and its equivalent artificial neuron

2.4. Input and output of a neuron

The variables applied to a neuron are called its inputs and the output of the neuron is its value. The graphical representation of a simple basic neuron is shown in **Figure 5**. The neuron's output (y) is a nonlinear combination of the inputs, $\{x_i\}$. These inputs are weighed by the parameters, $\{w_{ji}\}$, often termed weights, or synaptic weights. The neuron's output can be written as

$$y = f(x_1, x_2 \ldots x_i; v_j; w_{j1}, w_{j2}, \ldots, w_{ji})$$

Function [f(.)]is the activation function and v_j is termed as the bias input. The bias v_j, which a neuron has, is summed with the weighted inputs to form the net input. The function [f (.)] that is performed by neurons depends on the weight vector on the neurons. The weight vectors are usually determined in so called "training phase" using a learning algorithm. These weights determine the output of the neural network; therefore, it can be said that the connection weights form the memory of the neural network. **Figure 5.** shows the details of the elementary neuron structure with input as x_i.

Each input is weighted with an appropriate weight w_{ji}. The sum of the weighted inputs and the bias, v_j forms the input to the transfer function [f(.)]. Neurons can use any differentiable transfer function, [f(.)] to generate their output and is given by

$$\text{Output} = f(\text{input1} \times \text{weight1} + \text{input2} \times \text{weight2} + ...) = f\left(\sum_{i=1}^{n} x_i w_i\right)$$

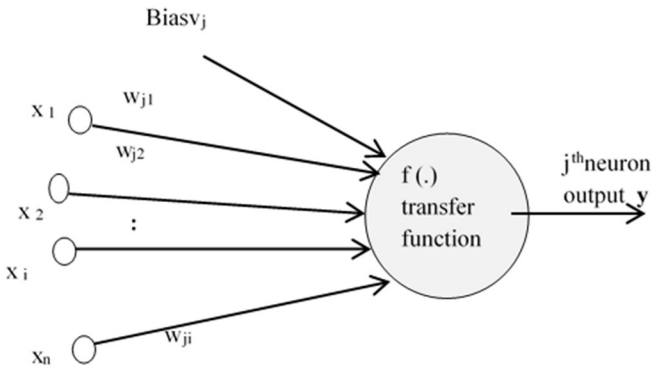

Figure 5.Inputs and output of neurons

In mathematical terms, ANN is defined as a directed diagram with the following properties:

- An input vector x_j associated with each node j (referred as neuron j)
- A real valued weight w_{ji} is associated with a link (referred as synapses) between two nodes j and i.
- A real valued bias (referred as activation threshold) v_j is associated with each node j
- A transfer function f_j [x_i, w_{ji}, v_j, ($i \neq j$)] is defined for each node j, which determines the state of the node as function of its bias, the weights of its incoming links and the states of the nodes connected to it by these links.

Nodes without links towards them are called input neurons and the output neurons are those without a link leading away from them. A feed forward network is one whose topology has no closed paths. The transfer function takes the form as given below.

$$f(z) = f(\Sigma_i w_{ji_i} x_i - v_j) \qquad (1)$$

Where, f (z) is either a discontinuous step function or smoothly increasing generalization known as a sigmoidal function.

3. ANN Modelling

Alike the brain, ANN is composed of numerous processing units, artificial neurons. The connections among all the units vary in strength, which is defined by coefficients or weights. The ANN mimics working of human brain and potentially fulfils the cherished dream of scientists to develop machines that can think like human beings. ANNs simulate learning and generalization behaviour of the human brain through data modelling and pattern recognition for complex multidimensional problems. A significant difference between an ANN model and a statistical model is that the ANN can generalize the relationship between independent and dependent variables without a specific mathematical function. Thus, an ANN works well for solving nonlinear problems of multivariant and multiresponse systems such as space analysis in quantitative structure-activity relationships in pharmacokinetic studies [8] and structure prediction in drug development [9].

Three simple steps involved in neural networking are:

- Network design
- Learning or training
- Usage or testing phase.

In the network design, stage the number of connections and layers is selected based on the type of application. Then, the training stage requires selection of training set of data and remodelling of the network to minimize the error. And lastly, following the training ANN is suitable to use network design. Number of hidden layers is essential to the purpose and function of an ANN as it influences the number of connections in the network and, thus, its performance. Examples of applications of ANN in pharmaceutical product formulations are shown in **Table 1** & **Table 2.**

Table 1. Examples of Applications of ANN in Immediate Release Oral Formulations

S.NO	ANN APPLICATION EXAMPLES	Ref. No.
1.	Direct compression tablet formulation of hydrochlorothiazide using ANN in order to maximize tablet strength and select the best lubricant	10
2.	Application of ANN tablet formulation of caffeine in order to relate both formulation (diluent type and concentration, binder concentration) and processing variables (type of granulator, method of addition of binder) with granule and tablet properties (friability, hardness, and disintegration time).	11
3.	Optimization of crushing strength and disintegration time of a high-dose plant extract tablet using ANN.	12

4.	Prediction of drug content and hardness of intact tablets of theophylline mixed with microcrystalline cellulose from their near-infrared spectra using neural networks.	13
5.	Application of ANN for predicting the dissolution of 28 diltiazem immediate release tablet formulations.	14

Table 2. Examples of Applications of ANN in Controlled Release Oral Formulations

S.NO	ANN APPLICATION EXAMPLES	Ref. No.
1.	Optimization of diclofenac sodium sustained release matrix tablets using ANN, where different formulation variables like concentrations of cetyl alcohol, PVP K30 and magnesium stearate, and sampling time were chosen as inputs.	15
2.	Application of ANN model in optimization of controlled release theophylline tablets prepared with mixture of HPMC with lactose and cornstarch.	16
3.	A generalized regression neural network (GRNN) was used in the design of extended-release aspirin tablets using eudragit RS PO compression pressure as casual factors.	17, 18
4.	Use of neural networks in the formulation of salbutamol sulfate osmotic pump tablets, using different amounts of HPMC and PEG present in the cellulose acetate coating, in addition to the coating weight, as control factors and predicting the release parameters for 1000 formulations; from which they selected an optimised formulation with the desired release pattern.	19
5.	Application of both multi-layer perceptrons and recurrent neural networks to modelling the release of theophylline from a matrix controlled release pellet formulation prepared using extrusion and spheronization.	20
6.	Comparison of response surface methodology and neural networks for modelling and optimizing the effect of the process and formulation variables on the release profile of verapamil hydrochloride.	21
7.	Compression of fluidized bed manufactured, enteric-coated, omeprazole pellets into tablets using neural networks where tablet strength and the concentration of the microcrystalline cellulose are used as a compression aid.	22

5. Conclusion

ANNs are one of the greatest computational tools which make decisions and draws conclusions even with incomplete information for numeric and non-numeric calculations in different fields of engineering, psychology, diagnostics etc. It is widely used in prediction of pharmaceutical responses like finding optimal composition of inclusion complexes, solid dispersions, and prediction of various drug release patterns based on the description of the formulation as well as chemical structure of drug.

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