ANN: A Revolutionary Biological Neuron Inspired Paradigm

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ABSTRACT:

There are problem categories that cannot be formulated as an algorithm. Many problems depend on many subtle factors. Without an algorithm a computer cannot predict like humans. Humans have a brain that can *"learn"*. Computers have some processing units and memory. They allow the computer to perform the most complex numerical calculations in a very short time, but they are not adaptive. Artificial neural networks (ANNs) technology is a group of computer methods for modeling and pattern recognition. The ANNs are a type of mathematical model that simulates the biological nervous system and draws on analogues of adaptive biological neurons.

Learning process is a human intelligence. This ability permits us to acquire various skills and expertise in numerous fields with reference to changing environment. Our reactions rather say outputs in different -different conditions are totally based on some previous experiences or inputs. So implementing these learning capabilities in machines and predicting the outputs by them is the central goal of Artificial intelligence. Some expert system can be developed to find application in various fields ranging from medicines, agriculture to computer design or etc. such expert systems or we can say models are computer programs which stimulates the expertise of human expert in solving problems. Artificial neural networks (ANNs) are such expert systems which are of simple processing elements (named 'neurons') operating on their local data and communicating with other elements. Basic principle is, each neuron in the network can receive input signals, process them and send an output signal in desired form.

So, by proper training and validation processes such generalized ANN model can be developed to predict the performance of various dosage forms.

KEY WORDS: ANN, Neuron, Learning, Artificial Intelligence, Pattern recognition.

1. INTRODUCTION:

India is known for its low cost and high quality generic medicine across the globe. It is the hub and heaven for the pharmaceutical industries, both tyro and virtuoso in the field of Formulation Development (F & D) and Research and Development (R & D). Continues development of new pharmaceutical formulation besides regular trouble shooting in existed formulation is very crucial task for pharmaceutical industries.

Performance of pharmaceutical product relays upon multiple factors and it is not possible to predict product performance in complex formulation development. One has to rely on empirical outcomes to understand the product performance along with experience of decades to select appropriate ingredients along with processing conditions to, even, find starting step of right pathway to develop successful formulation.

Traditionally, formulators use empirical method or statistical methods like response surface methodology and factorial design. However, such statistical method misleads in the case of complex formulation development. If numbers of the factors which are affecting formulations are more than five then very profound numbers of experiments are required to be performed.

1.1 WHAT IS ANN??

There are problem categories that cannot be formulated as an algorithm. Problems that depend on many subtle factors, for example the purchase price of a real estate which our brain can (approximately) calculate. Without an algorithm a computer cannot do the same. Therefore the question to be asked is: *How do we learn to explore such problems?* Exactly – we *learn*; a capability computer obviously does not have. Humans have a brain that can learn. Computers have some processing units and memory [1]. They allow the computer to perform the most complex numerical calculations in a very short time, but they are not adaptive.

Artificial neural networks (ANNs) technology is a group of computer methods for modelling and pattern recognition, functioning similarly to the neurons of the brain. It is a computational system inspired by the Structure Processing Method Learning Ability of a biological brain. In the brain, a biological neuron receives inputs from many external resources, combines them, performs a non-linear operation, and then makes a decision based on the final results.

The ANNs are a type of mathematical model that simulates the biological nervous system and draws on analogues of adaptive biological neurons. Similarly to a single neuron in the brain, artificial neuron unit receives inputs from many external sources, processes them, and makes decisions [2]. A major advantage of ANNs compared to statistical modelling is that they do not require rigidly structured experimental designs and can map functions using historical or incomplete data.

ANNs are known to be a powerful tool to simulate various non-linear systems and have been applied to numerous problems of considerable complexity in many field including engineering, psychology, medicinal chemistry and pharmaceutical research. They are good recognizers of patterns and robust classifiers, with the ability to generate when making decision based on imprecise input data.

Characteristics of Artificial Neural Networks:

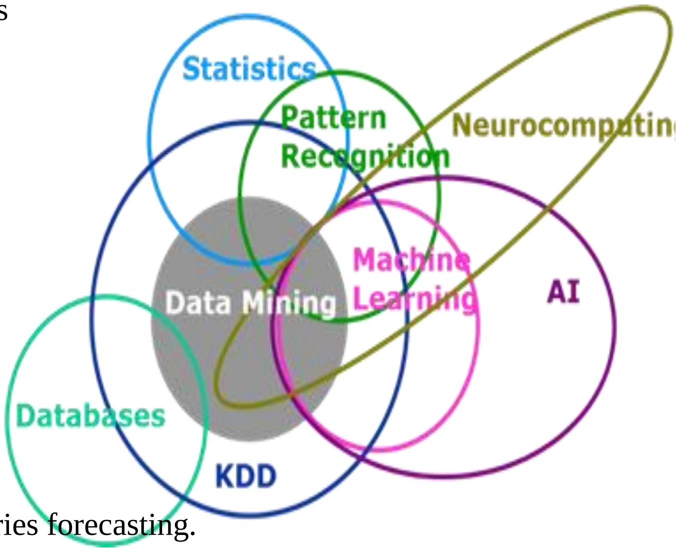
-A large number of very simple processing neuron-like processing elements

-A large number of weighted connections between the elements

-Distributed representation of knowledge over the connections

-Knowledge is acquired by network through a learning process

Applications of ANN: [3]



1. Pattern Classification Applications
    - Speech Recognition and Speech Synthesis
    - Classification of radar/sonar signals
    - Remote Sensing and image classification
    - Handwritten character/digits Recognition
    - ECG/EEG/EMG Filtering/Classification
    - Credit card application screening
    - Data mining, Information retrieval
2. Control, Time series, Estimation
    - Machine Control/Robot manipulation
    - Financial/Scientific/Engineering Time series forecasting.
    - Inverse modelling of vocal tract
3. Optimization
    - Travelling sales person
    - Multiprocessor scheduling and task assignment
4. Real World Application Examples
    - Real Estate appraisal
    - Credit scoring
    - Geochemical modelling
    - Hospital patient stay length prediction
    - Breast cancer cell image classification
    - Jury summoning prediction
    - Precision direct mailing
    - Natural gas price prediction
    - In drug discovery: Quantitative Structure-Activity Relationship (QSAR) , Quantitative Structure Toxicity Relationship (QSTR) , Virtual Screening (VS)

1.1.1 BIOLOGICAL NEURAL NETWORK VS ARTIFICIAL NEURAL NETWORK:

As biologically inspired computational model, 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.[4]

A single neuron consists of three major parts (Fig. **1**)—

- Dendrites (fine branched out threads)- carrying signals into the cell
- The cell body- receiving and processing the information
- The axon (a single longer extension) - carries the signal away and relays it to the dendrites of the next neuron or receptor of a target cell. The signals are conducted in all-or-none fashion through the cells.

All the connections in the brain enable it to learn, recognize patterns, and predict outcomes. Similarly to the brain, ANN is composed of numerous processing elements (PE), 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. [5-6]

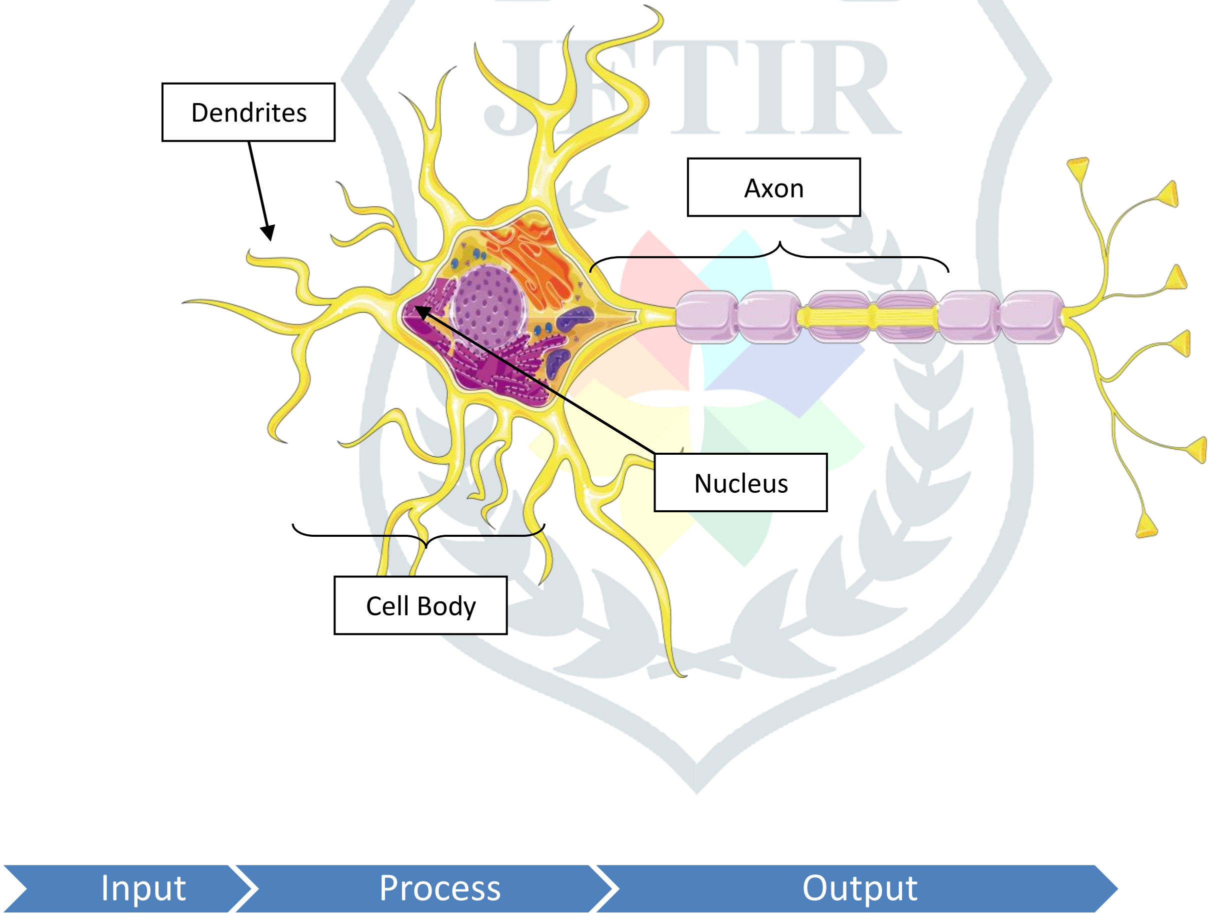


Figure 1: Structure of Neuron

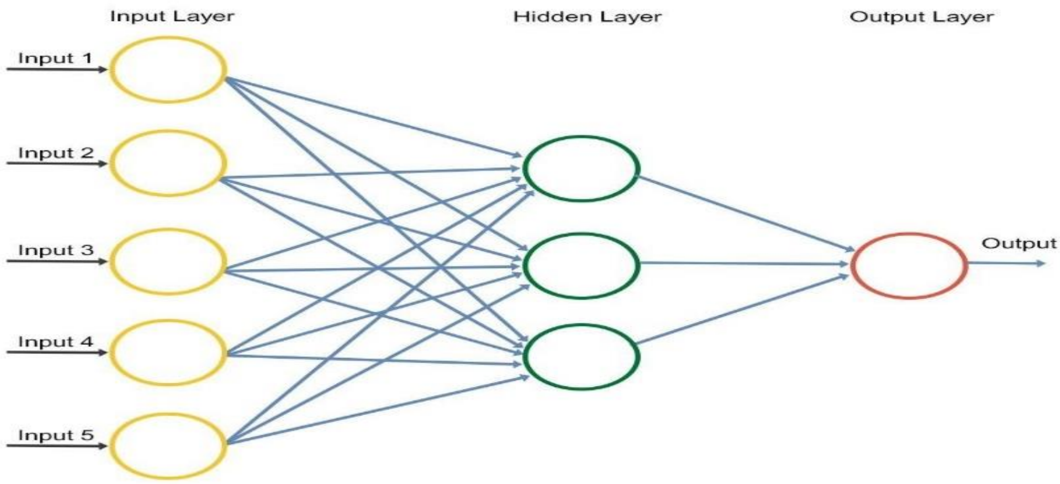


Figure 2 : A schematic diagram of Three-layered artificial network. Input layer units (in yellow) receive input signals (x1, x2, x3) and transfer the signal to the hidden layers via weighted connections. Output layer receives the signals and provides the representative output signal.

Basically, there are 3 different layers in a neural network:- [7]

1. Input Layer (All the inputs are fed in the model through this layer)
2. Hidden Layers (There can be more than one hidden layers which are used for processing the inputs received from the input layers)
3. Output Layer (The data after processing is made available at the output layer)

Biological Terminology	Artificial Neural Network Terminology
Neuron	Node/ Unit/ Neuron
Synapse	Connection/ Edge/ Link
Synaptic Efficiency	Connection Strength/ Weigh
Firing Frequency	Node Output

Table 1. Terminologies [8]

2. ARTIFICIAL NEURAL NETWORK MODEL DEVELOPMENT:

ANN models can be classified into three categories based on their functions: [9]

1. **Associating networks**: employed for data classification and prediction, need input (independent variable) and correlated output (dependent variable) values to perform supervised learning.
2. **Feature extracting networks**: which are used for data dimension reduction, need only input values to perform unsupervised or competitive learning.
3. **Nonadaptive networks:** need input values to learn the pattern of the inputs and reconstruct them when artificial neural networks (ANN) are computer presented with incomplete data set.

Among these three types of ANN models, associating networks can be employed to develop controlled release formulations, since the relationship between the drug release profiles of the controlled release drug delivery systems and formulation and process factors is not linear, and is not well understood. Associating ANN models can map the relationship between the formulation and process variables, and response such as in vitro drug release profiles through learning or training processes. These networks can then be used to predict the response such as in vitro drug release profiles of new formulations that are prepared with different composition and manufacturing processes. Hence, the focus of this research work is the usefulness of associating network models to design and formulate modified release drug delivery systems.

A network can be developed in two ways [10]:

1. **Single layer network**: Model has just 2 layers of nodes (input nodes and output nodes). Often called a *single-layer* network on account of having 1 layer of links, between input and output. It is not having any hidden layers.

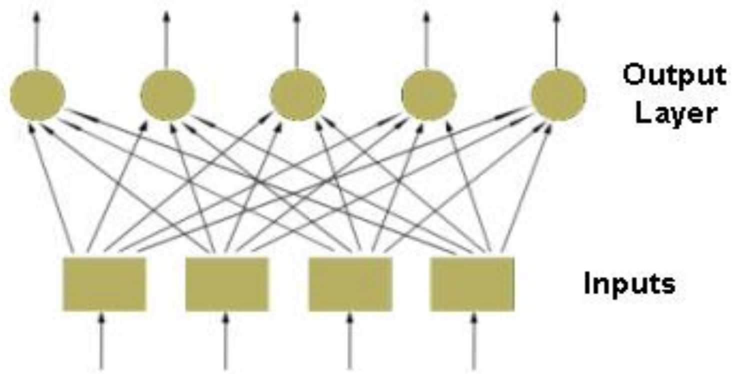


Figure 1: Single layer Perceptron

2. **Multi layer network**: A multilayer perceptron (MLP) is a class of feed forward artificial neural network. A MLP consists of, at least, three layers of nodes: an input layer, a hidden layer and an output layer. Except for the input nodes, each node is a neuron that uses a nonlinear activation function. MLP utilizes a supervised learning technique called back propagation for training. Its multiple layers and non-linear activation distinguish MLP from a linear perceptron. It can distinguish data that is not linearly separable.

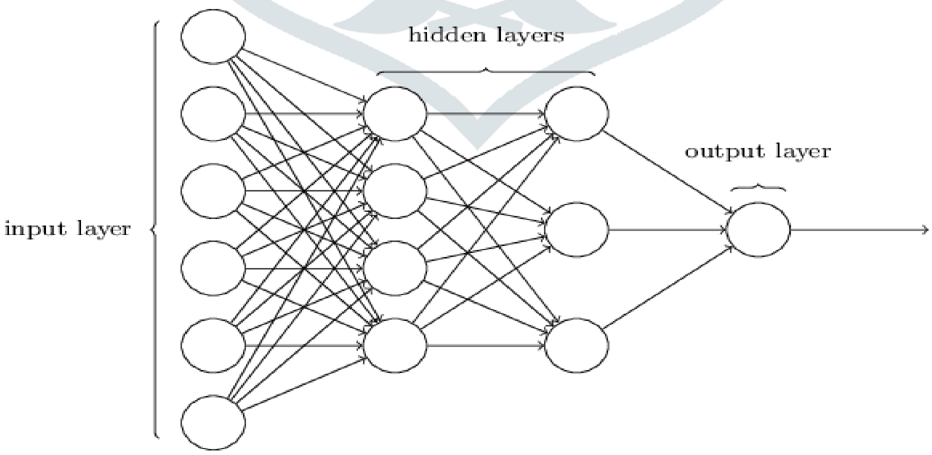


Figure 2: Multi layer Perceptron

Single layer network is limited to linear functions only. Multilayer networks solve the classification problem for non linear sets by employing *hidden layers*, whose neurons are not directly connected to the output. The additional hidden layers can be interpreted geometrically as additional hyper-planes, which enhance the separation capacity of the network.

Artificial model development includes number of operations like training, validation or testing. So to develop any artificial neural network few steps have to be performed which are as follows:

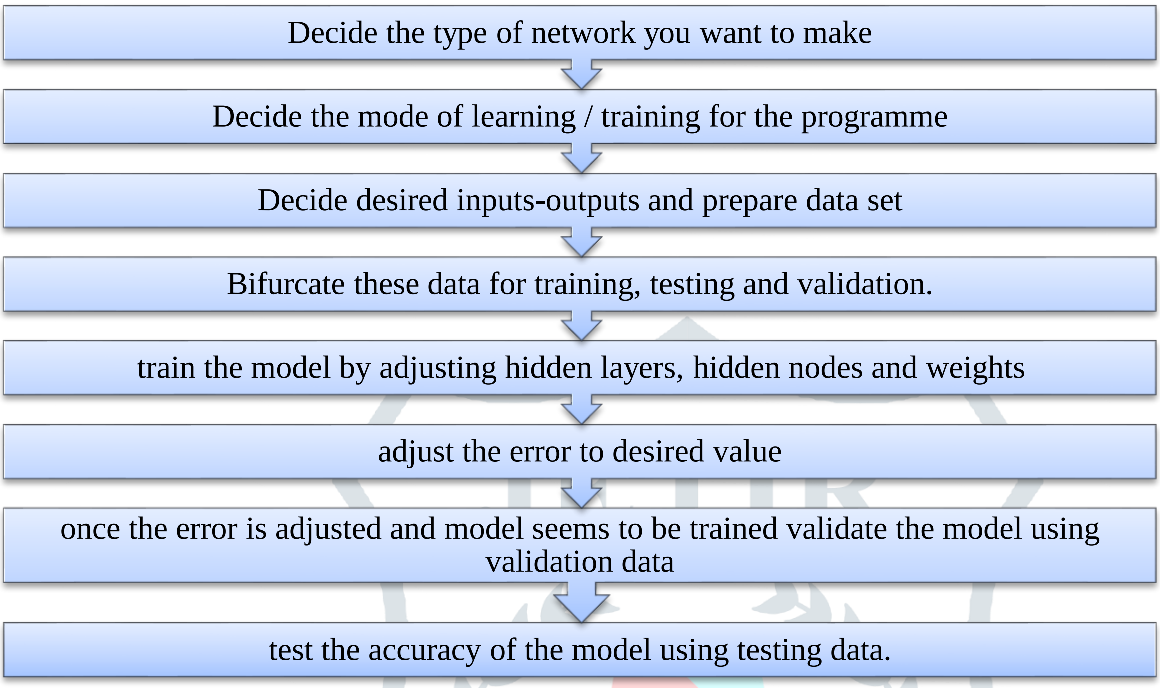


Figure 3: Hierarchy of ANN model development.

2.1. How does a model *"learn"*?

Learning process is a human intelligence. This ability permits us to acquire various skills and expertise in numerous fields with reference to changing environment. Our reactions rather say outputs in different -different conditions are totally based on some previous experiences or inputs. So implementing these learning capabilities in machines and predicting the outputs by them is the central goal of Artificial intelligence.

Based on the topology, the connection of ANN could be feedforward and feedback. In a feedforward ANN model, the connections between the nodes do not form cycles. In a feedback or recurrent ANN model, there are cycles in the connections.

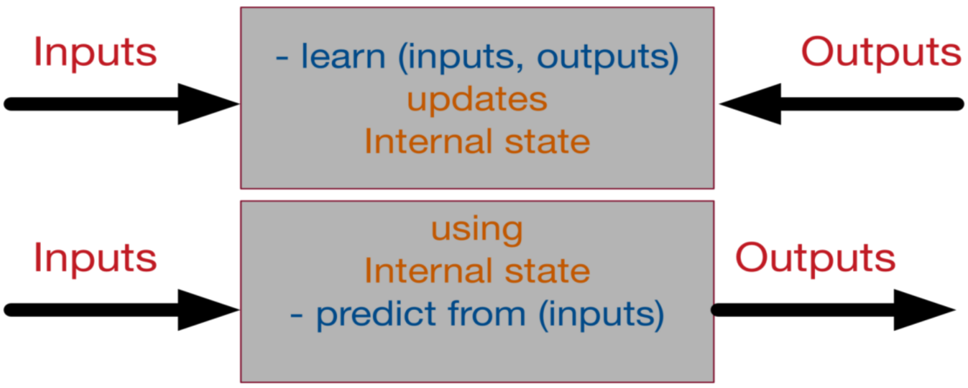


Figure 4: Feedforward and Feedback models

Feed forward network works on bases of randomly assigned weigh values and apply the activation function and gives the output. While feedback model first decreases error between predicted output and real output and after that it gives the final output. In some feedback ANN models, each time an input is presented, the ANN model must iterate for a potentially long time before it produces a response. Feedback ANN models are usually more difficult to train than feedforward ANN models.

2.2. Basic back-propagation architecture: [11]

Back-propagation ANN models have multi-layered architecture. The first layer is called the input layer, which does not have computing activity. It is simply used to input independent variables such as various significant formulations and process factors (inputs), to the first hidden layer. The last layer is called the output layer, which is used to process outcome for the dependent variables.

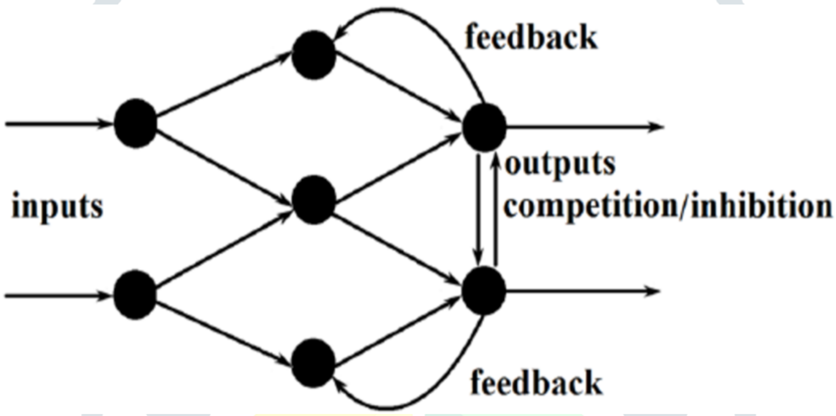


Figure 5: Back propagation Model

Hidden layers are the connections between input and output layers which can be one or multiple. These connections can be fully connected or partially connected. In fully connected connections all nodes in first layers are connected with all nodes in second layer while in partial connection it is not necessary that nodes of first layers are connected with all nodes in second layer. The building components in ANN are processing elements, which are called artificial neurons or nodes. These artificial nodes process information based on weighted inputs using their transfer function and send out outputs. The nodes in adjacent layers are fully or partially interconnected with weighted links.

3. TRAINING OF THE ANN MODEL:

Neural network has the power of a universal approximator, i.e. it can realise an arbitrary mapping of one vector space onto another vector space. The main advantage of neural networks is the fact, that they are able to use some a priori unknown information hidden in data. Process of 'capturing' the unknown information is called 'learning of neural network' or 'training of neural network'.

Each neuron is connected at least with one neuron, and each connection is evaluated by a real number, called the weight coefficient, that reflects the degree of importance of the given connection in the neural network. In mathematical formalism to learn means to adjust the weight coefficients in such a way that some conditions are fulfilled. The weights are adjusted, based on the training set of data, until the error is minimized.

There exist two main types of training process: [12]

1. **Supervised training**: Simply it means it requires teacher to teach and supervise outcomes. It is presented with input / output data sets. Supervised training (e.g. multi-layer feed-forward (MLF) neural network) means, that neural network knows the desired output and adjusting of weight coefficients is done in such way, that the calculated and desired outputs are as close as possible.
2. **Unsupervised training**: Simply it means it does not require teacher to supervise outcomes. In this ANN model is presented with input data alone, and the model learns to recognize patterns in the data. It (e.g. Kohonen network [13]) means, that the desired output is not known, the system is provided with a group of facts (patterns) and then left to itself to settle down (or not) to a stable state in some number of iterations.

ANN models learn from experience, which is acquired through a training process. The training process involves fitting of the data to a neural network model. Training is supervised for an associating ANN model in which the model is presented with input /output data sets. When training data is presented to the model, it adjusts the weights between the nodes. These adjusted weights will be freeze once error is optimized during the training operation.

3.1. Selection of training data set:

In back-propagation learning, we usually start with a training set and use the back-propagation algorithm to compute the synaptic weights of the network. The hope is that the neural network so designed will generalize. A network is said to generalize well when the input-output relationship computed by network is correct (or nearly correct) for input/output patterns never used in training the network. Generalization is not a mystical property of neural networks, but it can be compared to the effect of a good non-linear interpolation of the input data [S]. Principle of generalization is shown in Fig. 6a [14]

When the learning process is repeated too many iterations (i.e. the neural network is overstrained or over fitted, between overtraining and overfitting is no difference), the network may memorize the training data and therefore be less able to generalize between similar input-output patterns. The network gives nearly perfect results for examples from the training set, but fails for examples from the test set. Overfitting can be compared to improper choose of the degree of polynom in the polynomial regression (Fig. 6b). Severe overfitting can occur with noisy data, even when there are many more training cases than weights.

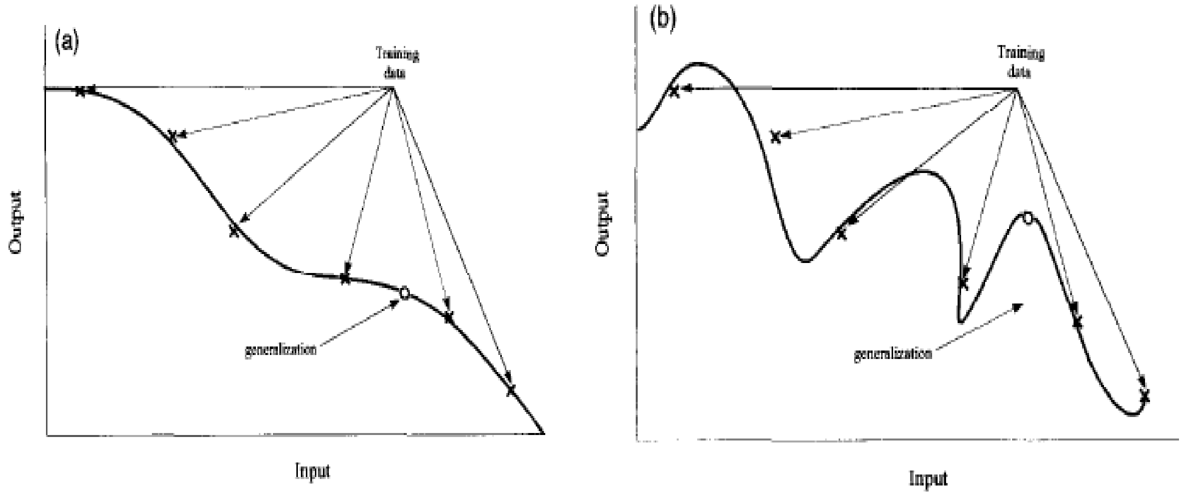


Figure 6: Principle of generalization of input data

The basic condition for good generalisation is sufficiently large set of the training cases. This training set must be in the same time representative subset of the set of all cases that you want to generalise to. The importance of this condition is related to the fact that there are two different types of generalisation: Interpolation and extrapolation.

Interpolation applies to cases that are more or less surrounded by nearby training cases; everything else is extrapolation. In particular, cases that are outside the range of the training data require extrapolation. Interpolation can often be done reliably, but extrapolation is notoriously unreliable. Hence it is important to have sufficient training data to avoid the need for extrapolation. Methods for selecting good training sets arise from experimental design.

These training data sets can be presented to a model network in 2 ways:

Incremental training [10]: "example-by example". In this method the weights are updated after processing each sample for the incremental training.

Batch training: "whole batch". Weights are updated after processing the entire training set for the batch training process.

3.2. Selection of numbers of hidden layers and weight adjustment:

The weight factors of the links between the processing nodes play a critical role during the learning process by the ANN model. They are part of the memory capacity of the ANN model, since the numerical values of the weight factors change according to the training data sets, in order to minimize the difference between the actual outputs and model predicted outputs. Thus, the relationship between causal factors and response is mapped during the learning process. The method used to adjust the weight factor is called training algorithm.

The numbers of number of hidden nodes in each layer and hidden layers totally depend on complexity of the problems like number of input training data set, test data set or accuracy required. Yet optimum numbers of hidden nodes can be decided referring:

- numbers of input and output nodes
- number of training data sets
- amount of noise in the targets
- complexity of the function or classification to be learned
- architecture
- type of hidden node activation function
- training algorithm

Optimum limit is required because less numbers of layers can cause under learning because hidden layers plays a role of memory of the model. So less number of layers means less memory of model and that can hamper the learning capability of the ANN model. While too many will result in overfitting of the data set.

Some rules of thumb are proposed by some investigators to select the hidden nodes.few examples are as follows:

- *Kolomogorov's theorem:* "twice the number of input variables plus one is enough hidden nodes to compute any arbitrary continuous function [15]
- *Jadid et al*. proposed an upper limit of number of hidden nodes using the following equation [16]

  $N_{hidden} = N_{trn} / [R + (N_{inp} + N_{out})]$

  Where, N_{hidden} = number of hidden layers

  N_{trn} = number of training samples

  R = constant ranging from 5 to 10

  N_{inp} = number of inputs

  N_{out} = number of outputs.
- Carpenter [17] introduced an equation based on the number of inputs and outputs, and the number training sample set.

  $N_{hidden} = (N_{trn} / \beta- N\ out) / (N_{inp} + N_{out} + 1)$

  Where, N_{hidden} = number of hidden layers

  N_{trn} = number of training samples

  β = parameter related to degree over determination.

  N_{inp} = number of input nodes

  N_{out} = number of outputs nodes.

A very common approach to select the optimal number of hidden nodes is by trial and error method using the aforementioned rules as guidance.

3.3. Learning Process:

The training mode begins with arbitrary values of the weights - they might be random numbers – and proceeds iteratively. Each iteration of the complete training set is called an epoch. In each epoch the network adjusts the weights in the direction that reduces the error (see back-propagation algorithm). As the iterative process of incremental adjustment continues, the weights gradually converge to the locally optimal set of values. Many epochs are usually required before training is completed.

The back-propagation learning rate (h) and the momentum coefficient (m) are two parameters that need to be defined for the back-propagation ANN model training. The learning rate (h) is an adjustable factor that controls the speed of the learning process. With a faster learning rate, the ANN model will learn faster. However, if the learning rate is too high, the oscillation of weight change can impede the convergence of the error surface, and may lead to overshooting of a near-optimal weight factor *w*. In contrast, if the learning rate is too slow, the ANN model may get caught in a local error minimum instead of the global minimum. The learning process can be facilitated by starting with a high learning rate initially, followed by a gradual reduction in the learning rate. A constant learning rate of 0.1–10 throughout the training process has also been proposed by Wythoff [18] and 0.3–0.6 has been proposed by Zupan et al. [19]

Momentum coefficient (m) is used in weight updating for back-propagation ANN to avoid local minima and to reduce oscillation of weight change. To obtain faster learning without oscillation, the weight change is related to the previous weight change to provide a smooth effect. The momentum coefficient determines the proportion of the last weight change that is added into the new weight change.

Convergence is the process of searching a set of weight factors for the ANN model so that the prediction errors can be reduced to a minimum. When all errors become within the range set by a designer the model network has learned properly is developed with optimal numbers of hidden layers, nodes, learning rate and momentum.

4. APPLICATION OF ANN MODEL IN FORMULATION AND DEVELOPMENT OF DOSAGE FORMS:

The ANN model can be used at various stages of formulation and development of controlled release matrix tablet like optimization [20] of formulations and manufacturing processes. ANN models have been used in the preformulation [21] stage of designing oral controlled release dosage forms. An ANN model was built by Ebube et al. [22] to predict the physicochemical properties such as the hydration characteristics, glass transition temperatures and rheological properties of hydrophilic polymers and blends of hydrophilic polymers, which are commonly used for preparing controlled released matrix tablets. The relationships between the composition of polymer blend and water uptake, composition of polymer blend and viscosity of polymer solutions were trained by ANN model. Result of study showed that prediction of water uptake and viscosities could be accurately predicted by the trained model within prediction error (0-8%). Thus it can be useful in preformulation stage.

Such developed and trained model can also be used to predict the release study of any formulated dosage form by providing formulation conditions and parameters as inputs and release study as outputs for training purpose. ANN model can learn the latent relationship between the causal factors (formulation variables) and responses [23]. A formulation optimization program based on the ANN model was developed to optimize salbutamol sulfate osmotic pump tablets by Wu et al. [24]. The amounts of hydroxypropylmethylcellulose (HPMC), polyethylene glycol 1500 (PEG 1500) in the coating solution, and the coat weight were selected as the causal factors. Both the average drug release rate *v* for the first 8 h, and the correlation coefficient r of the cumulative amount of drug released versus time were used as response variables. Twenty sets of data were employed as training set. Ten sets of data were used as test data. An ideal release rate and zero-order release characteristics were used as optimal response to optimize formulation factors. The optimal formulation factors were obtained using trained ANN model. The optimized formulation was prepared and tested in vitro. The release rate and correlation coefficient for the optimized formulation coincided well with the predicted results.

Several ANN models were developed to predict dissolution profiles of matrix-controlled release theophylline pellets prepared with microcrystalline cellulose (MCC) and glyceryl monostearate (GMS) by Peh et al. [25]. An artificial neural network (ANN) was developed to optimize a transdermal ketoprofen hydrogel containing *O*-ethylmenthol (MET) as percutaneous absorption enhancer by Takayama et al. [26].

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