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Intelligence supported drug design and development

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ABSTRACT

The process of Drug discovery and design (DDD) research is challenging, time consuming and expensive task which critically depends on a computerized mathematical systems, databases and novel disciplines. Computational methods can be used to assist and speed up the drug design and discovery process. Computer based DDD (CDDD) tools can act as a simulated shortcut, supporting in the expedition of this long process and theoretically reducing the cost of research and development. Moreover, cumulative information of organic structures, as well as increasing computer power have made it possible to use computational methods excellently in various phases of the drug discovery and development pipeline. This article focuses a brief overview of classical techniques in DDD with their limitations, and outlines current soft computing based techniques in drug design and discovery.

INTRODUCTION

Taking a medicinal drug to the market is a long term process that costs more. It is estimated that the cost associated with evolving and carrying a drug to the market has increased nearly 150% in the last years. The possibility of a failure in the drug discovery and development pipeline is high and 90% of the drugs entering clinical trials fail to get Federal Drug Administrative (FDA) approval and reach the consumer market. Approximately 75% of the cost is due to failures that happen along the drug discovery and design pipeline [1]. Currently with faster high throughput screening experiments, which can assay thousands of molecules with robotic automation, human labour associated with screening of compounds is no longer necessary. New methods for DD are therefore receiving considerable attention in the industry.

DRUG DISCOVERY

DD is a process of developing drugs for the harmless and operative handling of a disease. This process finds, assesses, and enhances compounds and molecules with chosen biological bustle against a stated target or function [1]. A target is a molecule within that plays a fundamental role at the onset or progression of a particular disease.

The DD process starts with a molecular target which instigates from the finding of a new gene or from the clarification of the molecular instrument of a genetic defect. Ensuing studies are completed to legalize the target. When appropriateness for DD has been recognized, new chemical units are acknowledged over arbitrary screening and/or normal drug design. The chemical mains with positive response in the screening process are particular and optimised as possible drug candidates. The result is a composite, or a small number of compounds that proceed to clinical trials for progress.

The DD process can be divided into four main steps: drug target identification, target validation, lead compound identification and lead optimisation. This process is depicted in figure 1 and described briefly in the section that follows.

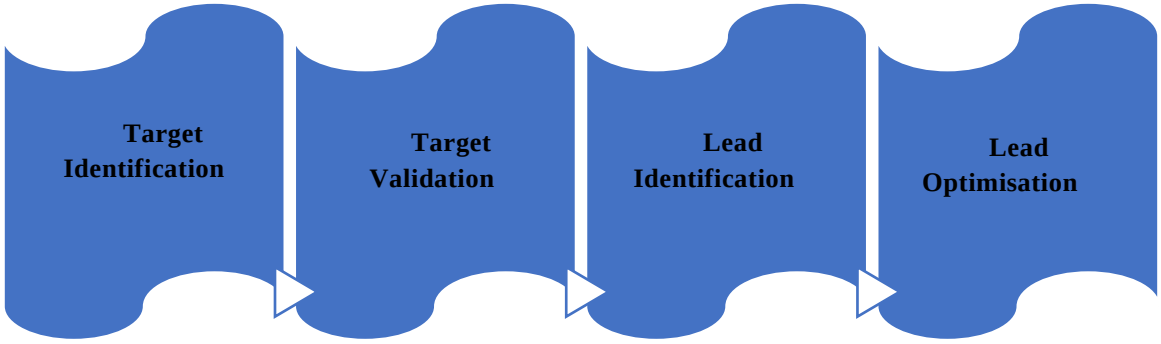

Fig. 1 Drug Discovery Process

NEURAL NETWORK METHODS

Mathematical representations and procedures, intended to copycat the data processing and information attainment of the human brain is known neural networks. They entail of many basic elements, termed artificial neurons, which accomplish alike responsibilities. A neuron receives a sequence of input indications and transmutes them into the output signal by a transfer function. In the progression of training, such a network of neurons 'learns' by shifting the weights of its neurons. Two different learning procedures can be distinguished as supervised and unsupervised learning.

Once learning is unsubstantiated, the neural network is providing by the input patterns. Later about restatements, it should settle down to a steady state. Entirely unsupervised learning systems take a overall optimization standard, for example the minimization of energy or distance, intensification of profit, and so forth, which is used for the assessment of the outcome at the end of each series. Since that retorts in a given system are identified for data points, the goal of supervised learning procedures is to find a model that properly associates the inputs with the targets.

The goals serve not only as a measure for how well the system has been skilled, but also effect the improvement of each weight. More complex neural networks are just models with more hidden layers and that means more neurons and more connections between neurons. And this more complex web of connections is what allows the neural network to "learn" the complicated relationships hidden in the data. Neural networks can be applied to four basic types of applications association, clustering, transformation, modelling. Below is the diagram of a simple neural network with five inputs, 5 outputs, and two hidden layers of neurons which is depicted in Figure 2. Also, how the neural network learns from its mistake using a process known as back propagation.

The architecture or design of the network is given by:

- The number of inputs and outputs;
- The number of layers;
- The number of neurons in each layer;
- The number of weights in each neuron;
- The way in which the weights are linked together, within or between the layer(s);

- Which neurons receive the correction signals.

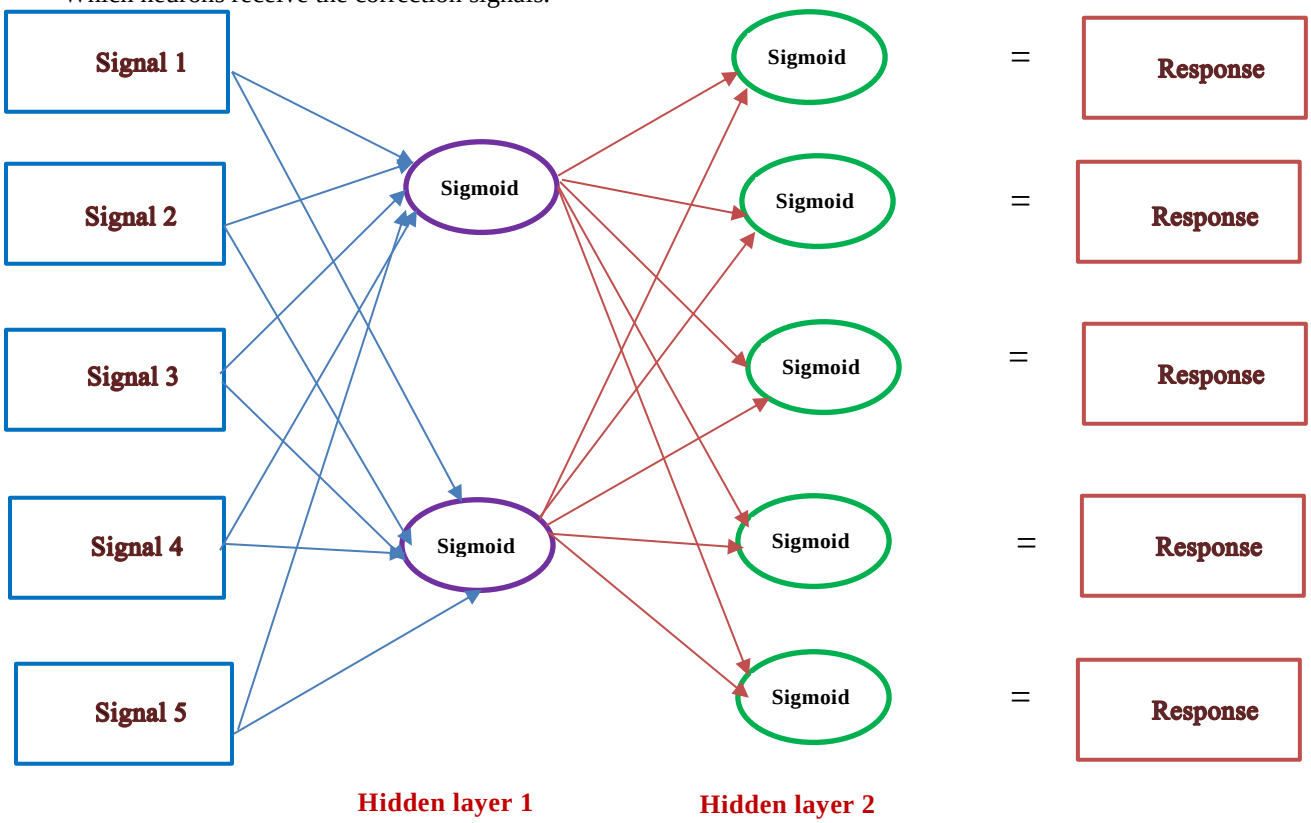

Fig. 2 Neural Network Scheme

USE OF NEURAL NETWORKS IN DRUG DESIGN

Neural networks can be employed for the following applications in drug design

- Study of multi-dimensional facts
- Sorting and prophecy of biological activity and ADME-Tox (absorption, distribution, metabolism, excretion, and toxicity) properties
- Prime discovery
- Evaluation of compound libraries
- Scrutiny of the similarity and diversity of combinatorial libraries and analysis of data

GENETIC ALGORITHM

Genetic algorithms (GAs) belong to a class of probabilistic evolutionary techniques (EAs were introduced by Holland, and mimic nature's adaptive heuristic method of adapting to a changing environment (i.e.) selection, cross-over, mutation and accepting. The initial point is a population of individuals, independently representing a probable solution to a problem. Each individual is assigned a fitness measure conferring to the quality of the solution it produces. The fittest individuals endure to the next generation although the that produce undesirable solutions are eliminated.

The metamorphosis from one generation to the next is through imitation among the individuals that continue. Reproduction consequences in new individuals that share approximately of the features taken from both of the parents. They are stochastic optimization techniques and offer a influential means to reach directed random searches in a large problem space as encountered in chemometrics and drug design.

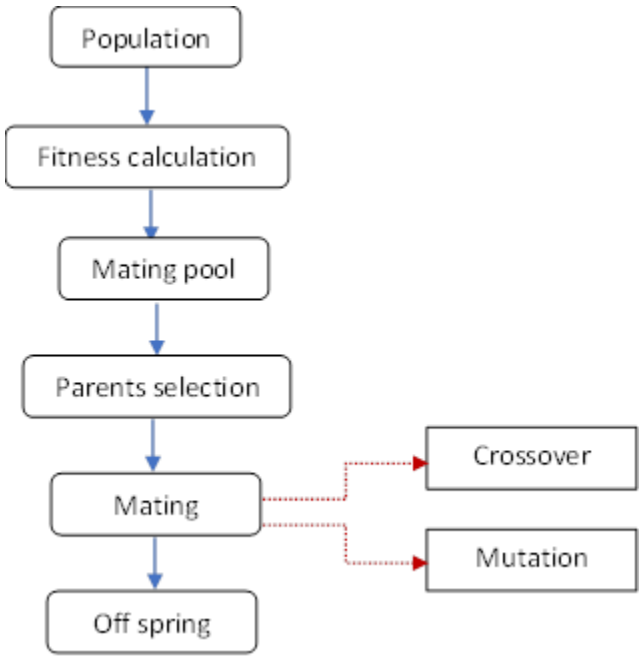

Fig. 3 Genetic algorithm steps

APPLICATIONS OF GAS IN DRUG DESIGN

An extensive series of investigation in QSAR gain advantage from the use of GAs. Investigators enhanced the predictive value of a QSAR model by variable selection using a GA. Fitness is evaluated by a PLS (partial least squares) cross validation. GA-based variable selection has also proved to be advantageous in comparative molecular field analysis. Pharmacophore are three dimensional models generated from a set of analogous molecules, perception for receptors with an unknown 3D structure can be carried out by comparing the spatial and electronic requirements of a set of ligands that are known to bind to the receptor of interest. One group produced a GA for the superimposition of it's of flexible molecules. Molecules were represented by a chromosome that encodes angles of rotation about flexible bonds and mappings between hydrogen bond donors, acceptor lone pairs and centre features in pairs of molecules.

The molecule with the smallest number of features in the data set was used as a template onto which the remaining molecules were fitted. The algorithm was applied to several well-known pharmacophore elucidation problems including benzodiazepine antagonists, 5-HT3 antagonists, dopamine D2 antagonists and others. The pharmacophores were generated rapidly and showed good agreement with those derived by alternative means. Such a comparison is performed by the structural alignment of these ligands. Docking of flexible ligands to macromolecules is paramount in structure-based drug design. Molecular docking sets out to predict the bound conformations of either ligand-receptor or protein receptor interactions. GAs have also been used to refine the accuracy of more traditional docking programs such as PRO_LIGAND. Some programs that work with a GA also enable automated docking. Another application of GAs is the automated generation of small organic molecules. Traditionally, lead compounds in medicinal chemistry have come from the bioassay of natural products. Over the last couple of years, the power of computers has been harnessed to generate large sets (called libraries) of sometimes millions of molecules made up from molecular fragments which are scored against some type of test protocol such as a fit to a three dimensional pharmacophore in an attempt to produce novel lead compounds with good bioactivity.

CONCLUSION

Speeding up drug discovery and development is of central interest in all pharmaceutical companies. It has been shown that neural networks and genetic algorithms are powerful tools with a wide range of applications in the field of drug design field, including QSAR, QSPR, variable selection, conformation searching, receptor docking, pharmacophore development, molecular design and combinatorial libraries. Other areas of soft computing including fuzzy logic, fractals, chaos and cellular automata are currently less frequently used, but may become more popular as new applications are found. The large number, variety and flexibility of the applications found suggest the newly designated field of soft computing is likely to flourish within the field of drug design in the future.

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