Artificial Intelligence in Drug Discovery and Development

Authors

Pressymol Benny
Department of Pharmaceutics, St. James' College of Pharmaceutical Sciences, Chalakudy, Kerala, India

Smitha K. Nair
Department of Pharmaceutics, St. James' College of Pharmaceutical Sciences, Chalakudy, Kerala, India
St. James Hospital Trust Pharmaceutical research centre (DSIR Recognized) Chalakudy, Kerala, India

K. Krishnakumar
Department of Pharmaceutics, St. James' College of Pharmaceutical Sciences, Chalakudy, Kerala, India
St. James Hospital Trust Pharmaceutical research centre (DSIR Recognized) Chalakudy, Kerala, India

Dineshkumar B
Department of Pharmaceutics, St. James' College of Pharmaceutical Sciences, Chalakudy, Kerala, India

Publication Month and Year: May 2020
Pages: 53
E-BOOK ISBN: 978-93-90002-11-5

Academic Publications
C-11, 169, Sector-3, Rohini, Delhi, India
Website: www.publishbookonline.com
Email: publishbookonline@gmail.com
Phone: +91-9999744933

Abstract

Artificial intelligence (AI) is defined as any techniques that allow the computer to mimic the human brain process to simulate intelligence process in human. Artificial intelligence (AI) is playing an important role in the field of drug discovery and drug development process. Computational power with advancements in Artificial intelligence technology has been used to modernize the drug development process. Currently, the pharmaceutical industry is having challenges to maintaining their drug development programmes due to more money investment in Research & development area. In this book, we mainly focused on an overview on AI, applications of AI in drug design, drug screening, drug interactions and drug development in the field of pharmaceutical sciences.

Introduction

Artificial intelligence (AI) is defined as any techniques that enable the computer to mimic the human brain to simulate human intelligence process [1].

The term “artificial intelligence” was coined by John McCarthy at the Dartmouth Conference in 1956 to describe “the science and engineering of making intelligent machines”. Artificial intelligence, one of the key technologies in the era of the 4th Industrial Revolution, is expected to greatly affect traditional drug discovery. Artificial intelligence is attracting attention as an innovative technology that can dramatically reduce the high cost and time required for the new drug discovery. At this stage, artificial intelligence is mainly used to search for candidate molecules during drug discovery, but it is likely to be actively used in drug discovery through open innovation in the future. In this book, it is presented the current state of artificial intelligence in each stage of a new drug discovery and prospect for the future usability.

Traditionally, the discovery of novel targeted drugs is an expensive long-term progress, costing billions of US dollars and more than 10 years. In the very beginning, a therapeutic drug target must be identified by traditional experimental methods. Then, structural biologists come to decipher the three-dimensional (3D) structures as well as their ligand-binding characteristics to reveal whether this is a druggable target. Subsequently, medicinal chemists and pharmacologists use high-throughput screening to find several highly effective lead compounds for further safety assessment as well as clinical trials. In general, the above procedures are costly and tedious. In November 2018, a study was conducted to estimate the total cost of trials for the development of novel Food and Drug Administration (FDA)-approved drugs. The result shows that the average cost of efficacy trials for the 59 new drugs approved by the FDA during 2015–2016 was $19 million. Therefore, it is necessary to overcome the limitations of the conventional drug discovery procedures by introducing efficient, low-cost and computational methods.

Compared with traditional drug discovery methods, rational drug design, mainly including computer-aided drug design (CADD), is more efficient and economical. Rational drug design integrates molecular docking to the ligand-binding pocket of a promising therapeutic target, computes the binding energy

of each docked small molecule compound, and selectively chooses the best ones as candidates for subsequent experimental procedures. Today, there are more than 100000 protein 3D structures deposited in Protein Data Bank (PDB) for molecular docking. In contrast to traditional methods, rational drug design has boosted the hit rate of drug screening by more than 100 times, from ~0.01% to 1%~2%. Moreover, CADD is a more multidiscipline method which integrates advanced bioinformatic techniques and sophisticated computational algorithms. Due to its relatively high hit rates, CADD method is becoming the fundamental basis of industrial drug discovery as well as academic research. Cancer-targeted drugs are the most successful drugs for the last three decades. A lot of cancer-related proteins have been identified as therapeutic targets by computational data mining of transcriptome data in databases such as The Cancer Genome Atlas (TCGA), The Human Protein Atlas (THPA) and so on. Unfortunately for other diseases, such as stroke, vascular-related diseases and other genetic diseases, there are no similar integrated omics databases to provide sufficient big data. However, there are increasingly more single cell transcriptome data of various diseases publicly available. Thus, such data will be precious goldmines in terms of the discovery of therapeutic targets for stroke, vascular-related diseases and other genetic diseases. Moreover, supercomputers are speeding up lead identification and evaluation. In this book, we provide an overview of how the integration of big data and AI could help us to discover new therapeutic targets and their targeted lead compounds, as well as their absorption, distribution, metabolism, excretion and toxicity (ADMET) properties [2].

What tasks is AI performing [3]?

Three broad categories: **Biology**, **Chemistry**, **Clinical Trials**

→ Identify disease targets and biomarkers, build confidence

→ Re-purpose existing drugs

→ Discover novel drugs

→ Design and recruit for clinical trials

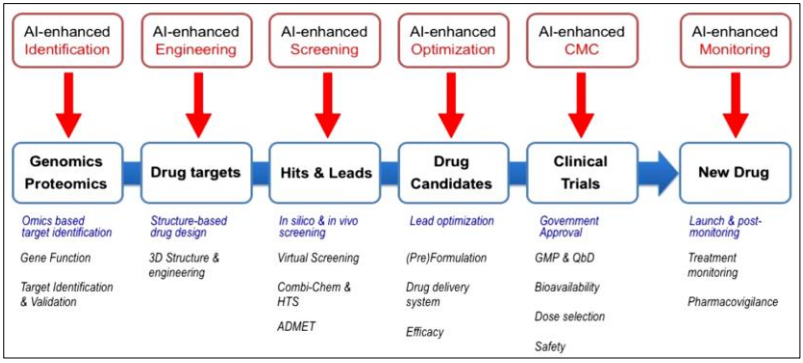
→ Synthesize and analyze real world evidence

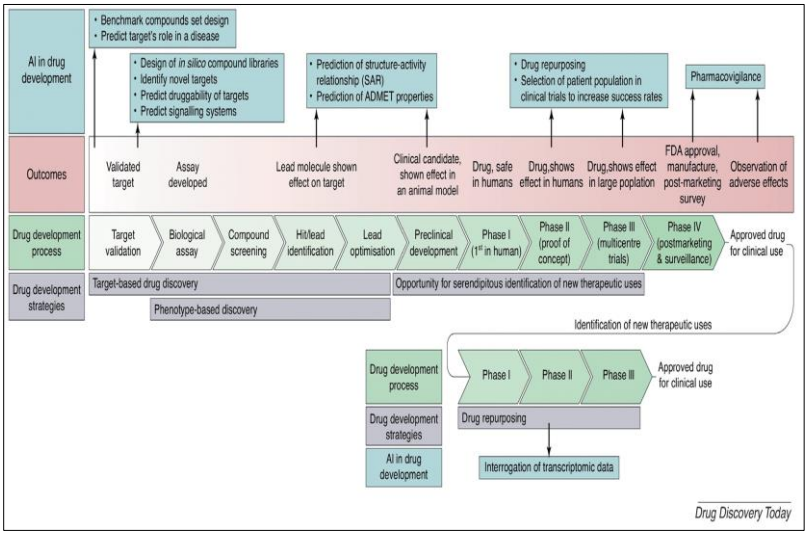
✓ **Brief History of Artificial Intelligence[4-9]**

The term “artificial intelligence” was coined by John McCarthy at the Dartmouth Conference in 1956 to describe “the science and engineering of making intelligent machines”. McCarthy’s original description still holds true today, albeit with some fleshing-out of the specifics. As a multidisciplinary field, AI involves integrating insights from diverse disciplines such as

computer science, mathematics, psychology, linguistics, philosophy, neuroscience, artificial psychology, and many others. Recent intellectual and engineering advances have helped the field progress from purely theoretical studies to the implementation of intelligent systems that solve problems in various aspects of our lives. The current scope of such applications includes fields and studies as heterogeneous as natural language understanding and processing, speech understanding and processing, mechanical/computer vision, autonomous/ intelligent robots, and domain expertise acquisition, to provide only a few examples. Despite the broad spectrum of problems that can be addressed by AI, there are some basic methods that play major roles in all cases, examples of which include knowledge acquisition and maintenance, knowledge representation, solution search, logic reasoning, and machine learning. In the mid-1930s, Alan Turing introduced the idea of what is today referred to as the "universal Turing machine", which could simulate any possible computer. To some extent in march-step with the advances of the computer hardware, the history of AI has been one of fits and starts, of boom and bust. The early, in the 1950s and 1960s, was fueled by pure optimism. During this period, symbolic methods were introduced for semantic processing, the concepts of logical reasoning and heuristic searching emerged, and man-machine interaction became feasible. The first machines with preliminary intelligence were conceived, for example, STUDENT (1964), a machine that could implement machine proofs of some mathematical theorems and logical inference of statements. Another early example was ELIZA (1966), a machine that could emulate human dialogue, albeit in a limited fashion. The rapid development of these and other instances of AI fueled a frothy reaction, leading to a cycle of irrational exuberance and eventual disappointment in the power of AI. The eventual cooling of such sentiments has been described as the first "AI winter". Importantly, and of note for AI evangelists past and present, there is no magic in AI, only probability and statistics, the proper applications of which are contingent on mathematics, the availability of suitable data, and on the capabilities of our hardware. AI had its second peak in the early 1980s. Substantial progress had been made in AI-related mathematical models, including the multilayer feed-forward neural network and the backpropagation algorithm. These tools allow for the construction of an abstract model of the world and provide a way to update the model given input (learning from feedback). This combination was the first to manage victory against a human chess player, and one that laid the foundation for much of the work done in the field to date. A first foray of such methods into the area of chemistry and molecular biology was achieved by the prediction of secondary structure from protein sequence information. At the

same time, various expert systems had entered the market. For example, Carnegie Mellon University had created an expert system for the DEC Company. This expert system allegedly helped DEC save about 40 million dollars per year by automated decision-making. Encouraged by this success, many countries, including Japan and the United States, invested heavily in the development of the so-called fifth-generation computers, also referred to as 'artificial intelligence computers'. However, an apparent drawback was their incapacity to learn algorithmically from data and to address uncertainty in reasoning. Moreover, the high maintenance costs of expert systems and the emergence of less expensive and faster desktop computers pioneered by Apple and IBM directly caused a collapse in the market for such systems, taking AI into the second winter with little apparent hope of re-emerging into the mainstream. Despite its withdrawal from the public eye and a corresponding reduction in funding, work on such matters did not cease entirely. Developments focused on enhancing the statistical validity of the reasoning produced by AI models. A Chemical Reviews new paradigm, machine learning, placed considerable emphasis on learning actionable insights from complex data and generated excitement within the wider scientific community. New key algorithms and methods were introduced, including expectation-maximization, Bayesian networks, support vector machines, and decision trees. Instead of being explicitly "programmed", as was the case for the expert systems, machine learning models are "trained" to Fig





✓ **Advantages of Artificial Intelligence[10,11]**

The purpose of making the first machines was only to assist people in daily tasks. However the only goal of today's machines is not only to help daily tasks. Day by day artificial intelligence is becoming more intelligent than people.

- **Making the daily life easier**

The most obvious advantage of artificial intelligence is helping daily life. People are need artificial intelligence because they are tired of many jobs in their daily lives. Whitby (2012) states that, "In the information technology revolution machines replaced much routine administrative work". When Artificial intelligence can use well, it will provide great convenience to people's life. For example Siri is a artificial intelligence developed by Apple. Siri has so many benefits in it. For example, there is a place we want to but we do not know how to go this place, Siri can show us a road map. In the future, artificial intelligence can do a lot of work such as chores, transportation. Therefore, artificial intelligence maintains an important place in people's lives.

- **Multitasking**

Another advantage of artificial intelligence is multitasking. Computers can do a lot of works at the same time as we know. For example people can surf the internet while listening to music with computer. Therefore, people can do only 2-3 at the same time. Whatever, artificial intelligence is always ahead

of them in this matter. Whitby (2012) states that, If you use search engine on the web, you will probably be using artificial intelligence technology or, at the very least, technology that has spun off from artificial technology. Indeed some search engines are now so sophisticated that their working has been said to throw light on ways in which human memory might work. Computers have much more sophisticated intelligence than humans. Moreover, computers have more information retrieval capacity. This means people can forget information but the informations we save on computers is unforgettable. Hence, computers do not forget when they learn a task and they can do so many task simultaneously.

✓ **Disadvantages**

Artificial intelligence has advantages but at the same time it has disadvantages. Such as unemployment, lack of privacy and the end of mankind. Sotala and Yampolskiy (2014) state that "Even if the intentions of their owners were benign. Narrow-AI systems are more autonomous and powerful. So that they take unanticipated and harmful actions before a human supervisor has a chance to react". Artificial intelligence is not reliable because they can't think like humans.

- **Unemployment**

With the development of technology, people started to work with machines. The early machines were used only for helping people at their jobs but as time goes by machines started to do jobs instead of humans.

People's feeling and daily life is affect their work performance but artificial intelligence can do whatever you want in any situations. Therefore, people might lose their jobs. The number of unemployment people might increase in turn. Because of that we must use artificial intelligence only a few jobs and we must take them under surveillance.

- **End of the Mankind**

The second major disadvantage of artificial intelligence is the end of mankind. In time, computers became more intelligent than humans. Yampolskiy and Fox (2012) states that "If AIs at human level and above are developed, the human species will be at risk, unless the machines are specifically designed to pursue human welfare, correctly defined, as their primary goal." Artificial intelligence has no learning limits because of that they are developed day after day. But all humans had a learning and intelligence limit. Therefore, artificial intelligence one day become more intelligence than humans. If they are intelligence than us maybe we can change

the roles in the future. Now robots or artificial intelligence is our tool but in the future maybe we will their tools. Maybe they will kill us in the future and this will be cause end of the mankind. Humans need to control artificial intelligence and artificial intelligence must be under surveillance.

- **Lack of Surveillance**

The last disadvantage of artificial intelligence is its negative effects on the privacy of the people. In the long run, artificial intelligence will become part of our lives such as smart phones, computers, tablets etc. These devices contain private information about everybody for example ID information, credit card information, passwords of social media accounts. The real life hackers first need to sneak into your computer, after that he/she try to deceive you. In the end if you are deceived your information's can be steal. But artificial intelligence don't need to deceive you because their data capacity or learning capacity is limitless. Because of that, they can be access everything they want and if artificial intelligence do that they can't be judge because our law system is for humans. Therefore, people can lose their money, their personal information's and the best critical problem is we can't judge them with our law system.

✓ **In what level can todays artificial intelligence do?**

Today's Artificial Intelligence (robotics) has the intensities to imitate human intelligence, performing various tasks that require thinking and learning, solve problems and make various decisions. Artificial Intelligence software or programs that are inserted into robots, computers, or other related systems which them necessary thinking ability [12]. So that Artificial intelligence can perform the task without errors. Robotics are also present in addition to AI. Artificial intelligence (AI) ability towards effectively performing every narrower and cognitive task considerably increases the peoples dependence towards the technology [13]. Artificial intelligence (AI) tools have the ability to process huge amounts of data by using computers, which control them and analyze all the information. Today, this considerably increases the threat which makes someone's ability to extract and analyze data in a massive way. Artificial intelligence is the artificial representation of human brain which tries to improve their learning process and the main aim is mimicking the human brain power. We have to reassure everyone that artificial intelligence equal to that of human brain which is unable to be created. Till now, we operate only part of our capabilities. As currently, the level of knowledge is rapidly developing, it takes only a part of the human brain. Human brain consist of approximately 100 trillion of electrically

conducting cells or neurons which have the computing power to perform the task rapidly and efficiently [14].

- ✓ **AI in Drug Design**
- **AI for primary drug screening**

Sorting and Classification of Cells by Image Analysis Using AI

AI technology has been very successful in recognizing images containing distinct objects or features. Recognizing images by traditional visual inspection is a very tedious task and becomes very inefficient for the analysis of big data. Hence, this is an ideal field for the application of AI-based computing technologies. For cell target classification or diagnosis, the AI model needs to be trained to rapidly and automatically identify the different features of cell types. For example, for the classification of breast cancer cells, the images of the cells are separated from the background by varying the image contrast. Tamura texture features and wavelet-based texture features are then extracted, and principal component analysis (PCA) is used to reduce the dimensions of the extracted features. AI-based methodologies are then trained to classify different cell types. Among the tested methods, the least-square support vector machine (LS-SVM) method, which is based on statistical learning theory using regression and classification techniques, shows the highest classification accuracy (95.34%) [15].

For cell sorting, AI-based image analysis decision-making needs to be sufficiently rapid that the robot has time to accurately separate different cell types in the sample. Most modern image-activated cell sorting (IACS) devices measure optical, electrical, and mechanical cell properties for highly flexible and scalable automation of cell sorting. These instruments allow high-speed digital image processing and decision-making within a few tens of milliseconds using AI-based convoluted deep neural network algorithms. This methodology was tested on high-content sorting of Chlamydomonas reinhardtii and human platelets, and showed excellent specificity and sensitivity. In addition to cell recognition and classification, AI has recently been used for interpretation of computerized electrocardiography (ECG), a step that plays a crucial role in clinical diagnosis/treatment workflows. This will reduce the time required for manual checking by an experienced practitioner. Digital ECG data and algorithmic deep learning (DL) will enhance the accuracy and scalability of automated ECG analysis.

- **AI in secondary drug screening**

1. Artificial Intelligence in Property Prediction

For a drug discovery process, the clinical candidate molecules must meet different criteria. Next to the right potency for the biological target, the compound should be selective against undesired targets and also show good physicochemical as well as ADMET properties (absorption, distribution, metabolism, excretion and toxicity properties). Therefore, compound optimization is a multidimensional challenge. Along with the optimization process, in-silico prediction methods are used for efficient compound design. In particular, several machine learning technologies have been successfully used, such as support vector machines (SVM), Random Forests (RF) or Bayesian learning.

One important aspect of the success of machine learning for property prediction is access to large datasets, which is a prerequisite for applying AI. In a pharmaceutical industry, huge amounts of datasets are collected during compound optimization for many different properties. Such large datasets for targets and anti-targets are available across different chemical series and are systematically used for training machine learning models to drive compound optimization.

DNNs have been widely used in numerous examples for property prediction. In these studies a comparison to other machine learning approaches has been performed which indicating, that DNNs show comparable or better performance than other machine learning approaches, eg. for different properties ranging from biological activity prediction, ADMET properties to physicochemical parameters [16].

QSAR and machine learning models are generally trained for one endpoint, although multiple endpoints can be used. DNNs provides the possibility to systematically combine predictions for several endpoints as multitask learning. Multitask learning can improve prediction quality has been shown by several studies, which compared the performance of single task vs. multitask models. Increased model performance is observed with multi task learning, while it appears to be stronger for certain tasks. A dataset shows an improved performance when it shares many active compounds with other tasks. The amount of data and the number of tasks are the two were described to beneficially influence multitask learning. In industry sized ADME datasets favorable effects for multitask learning could be identified, although the improvement appears to be highly dataset dependent [17].

Potential energies of small organic molecules predicted by Deep learning

method replacing a computational demanding quantum chemical calculation by a fast machine learning method. In case of large datasets, quantum chemically derived DFT potential energies have been calculated and used to train deep neuronal nets. The network predict the potential energy, called ANI-1, even for test molecules with higher molecular weight than the training set molecules. Deep learning has been extensively validated for a number of different datasets and learning tasks. DNNs show an improved performance as compared to well established machine learning technologies. In a large-scale comparison of different methods, in which the performance of DNNs was described as comparable to in-vitro assays. Nevertheless, many of the studies are performed retrospectively to show the applicability of deep learning architectures for property prediction and to compare the method to established machine learning algorithms. Often, public datasets like ChEMBL are used. In ChEMBL, biological data are only available for one target resulting in a thinly populated matrix, making cross-target learnings a significant challenge. DNNs clearly outweigh other machine learning approaches, in particular since training and parameter optimization is less demanding for many other machine learning methods. A promising development involves the self-encoding of the compound description by the learning engine, which will offer problem-dependent optimized compound descriptions.

2. Artificial Intelligence for de novo Design

De novo design was developed approximately 25 years ago aims to generate new active molecules without reference compounds. Numerous approaches and software solutions have been introduced. But de novo design has not seen a widespread use in drug discovery. This is at least partially related to the generation of compounds, which are synthetically difficult to access. In this field there are some revival recently due to developments in the field of artificial intelligence. An interesting approach is the variational auto encoder, which consists of two neural networks, an encoder network and a decoder network. Chemical structures defined by SMILES representations are translated by the encoder network into a real-value continuous vector as a latent space. The decoder part is able to translate vectors from that latent space into chemical structures. This characteristic was used to search for optimal solutions in latent space by an in-silico model and to back translate these vectors into real molecules by the decoder network. For most of the back translations one molecule dominates, but slight structural modifications exist with smaller probability. They used the latent space representation to train a model based on the QED drug-likeness score and the synthetic accessibility

score SAS. Molecules with improved target properties could be obtained. The performance of such a variational auto encoder was compared to an adversarial auto encoder. The adversarial auto encoder consists of a generative model producing novel chemical structures. A second discriminative adversarial model is trained to find apart real molecules from generated ones, while the generative model tries to fool the discriminative one. The adversarial auto encoder produced significantly more valid structures than the variational auto encoder in generation mode. Along with an in-silico model novel structures predicted to be active against the dopamine receptor type 2. A generative adversarial network (GAN) used to suggest compounds with putative anticancer properties.

Recursive neural networks (RNN) have also been successfully used for de novo design. Originally, they have been established in the area of natural language processing. This approach was also successfully used for the generation of novel peptide structures. Reinforcement learning was applied to bias the generated compounds towards desired properties. Transfer learning was also used to generate novel chemical structures with a desired biological activity. The novel chemical space explored by these methods with the property distribution of the generated molecules being similar to the training space. The first prospective application for this methodology was successful with 4 out of 5 molecules showing the desired activity [18]. Nevertheless, more experience need to be gained with respect to the size of the sampled chemical space and chemical feasibility of the proposed molecules.

3. Artificial Intelligence for Synthesis Planning

Organic synthesis is a critical part of small molecule drug discovery program. Along with the compound optimization path new molecules are synthesized and to identify molecules with improved properties. In some situations, synthetic challenges restrict the available chemical space available for design of molecules. Therefore synthesis planning is a main discipline in drug discovery. Based on this, numerous computational approaches have been developed to assist synthesis planning. Three different features can be distinguished: prediction of the outcome of a reaction with a given set of educts, prediction of the yield of a chemical reactions as well as retrosynthetic planning. Retrosynthetic planning is prevailed by knowledge-based systems, which are built on expert-derived rules or automatically extracted rules from reaction databases.

Artificial intelligence has also described for retrosynthetic analysis. Sequence-to-sequence based model used for retrosynthetic reaction

prediction. Reactants and products are coded by SMILES strings for RNNs and coupled to each other in an encoder-decoder architecture. These training allow spans 10 broad reaction types such as C-C bond formation, reductions, oxidations, heteroatom alkylation etc. and comprises 50,000 reactions. The performance of the technology overall was comparable to rule-based expert systems, but large differences have been observed over different reaction classes [19]. Different approach recommender systems have been used to identify reactants which yields a desired product in combination with a chemical reaction graph. Nevertheless, AUCs obtained in the validation indicated, that further improvement needs to be done.

Machine learning-based approaches can develop huge datasets, in which humans cannot handle in an unbiased manner. For synthesis planning, the combination of knowledge-based and machine learning based approaches used for prediction of chemical reactions. The purely machine-based approach capitalizing on a large reaction database shows an excellent performance. Nevertheless, one limitation remains for in-silico tools, is the capability to propose and to develop novel chemical reactions. Here, a detailed analysis is needed and will rely on the use of quantum chemical methods in the future.

4. Predicting Drug–Protein Interactions

QM or QM/molecular mechanics (MM) hybrid methods are useful for predicting protein–ligand (drug) interactions in drug discovery. These methods consider quantum effects for the simulated system (or the region of interest in the case of QM/MM) at the atomic level, therefore offering much better accuracy than classical MM methods. Because MM methods only apply simple energy functions based on atomic coordinates, the time-cost for QM-based methods is much larger than for MM methods [20]. The application of AI methods to QM calculations involves a tradeoff between the accuracy of QM and the favorable time-cost of MM models. AI models have been trained to reproduce QM energies from atomic coordinates, and can calculate speed of MM methods. AI is principally applied to atomic simulations and predictions of electrical properties, whereas DL has been used to predict the potential energies of small molecules, thereby replacing computationally demanding quantum chemistry calculations by a fast ML method. In case of large datasets, quantum chemistry-derived DFT (density functional theory) potential energies have been calculated and used to train DNNs. For example, in a study of two million elpasolite crystals, the accuracy of a ML model improved with increasing sample size and reached 0.1 eV/atom for DFT formation energies trained on 10000 structures. The model was then used for screening compositional alternatives for various properties.

✓ AI Application in Drug Development

The tasks of finding successful new drugs is daunting and predominantly the most difficult part of drug development. This is caused by the vast size of what is known as chemical space, which is estimated to be in the order of 1060 molecules. The technologies that incorporate AI have become versatile tools that can be applied ubiquitously in various stages of drug development, such as identification and validation of drug targets, designing of new drugs, drug repurposing, improving the R&D efficiency, aggregating and analysing biomedicine information and refining the decision-making process to recruit patients for clinical trials. These potential uses of AI provide the opportunity to counter the inefficiencies and uncertainties that arise in the classical drug development methods while minimising bias and human intervention in the process [21].

The other uses of AI in drug development include the prediction of feasible synthetic routes for drug-like molecules, pharmacological properties, protein characteristics as well as efficacy, drug combination and drug–target association and drug repurposing. Also, the identification of new pathways and targets using omics analysis becomes possible via the generation of novel biomarkers and therapeutic targets, personalised medicine based on omics markers and discovering the connections between drugs and diseases. DL has demonstrated outstanding success in proposing potent drug candidates and accurately predicting their properties and the possible toxicity risks. Circumventing past problems in drug development – such as analysis of large datasets, laborious screening of compounds while minimising standard error, requiring large amounts of R&D cost and time of over US$2.5 billion and a more than a decade – are now possible using AI methods. With AI technology, new studies can be carried out in assisting the identification of new drug targets, rational drug designing and drug repurposing.

a. AI in understanding the pathway or finding molecular targets

In drug development, AI has transformed the methods of pathway or target identification to treat diseases. This was possible owing to the incorporation of genomics information, biochemical attributes and target tractability. One study determined the plausibility of predicting therapeutic targets using a computational prediction application known as ‘Open Targets’ – a platform consisting of gene–disease association data – and it was reported that animal models exhibiting a disease-relevant phenotype with a neural network classifier of >71% accuracy provided the most predictive power. The application of AI in the process of drug development is proposed. IBM Watson

for Drug Discovery, an AI platform, has identified five new RNA-binding proteins (RBPs) linked to pathogenesis of a neurodegenerative disease known as amyotrophic lateral sclerosis (ALS).

b. AI in finding the hit or lead

The implementation of AI in the discovery of small drug-like molecules concerns the utilisation of chemical space. Chemical space provides the stage for identifying novel and high-quality molecules because it is possible to computationally enumerate the probable organic molecules. Additionally, ML techniques and predictive model software also contribute to the identification of target-specific virtual molecules and association of the molecules with their respective target while optimising the safety and efficacy attributes.

AI systems can reduce the attrition rates and the R&D expenditure by decreasing the number of synthesised compounds that are subsequently tested in either in vitro or in vivo systems. A variety of in silico techniques for profile selection such as virtual ligand or structure-based design approaches can be used with the available data on small-molecule modulator probes or their structural biology. DL becomes useful in instances where structural data are insufficient. Thus, phenotypic data or disease, biology or molecule network-based algorithms can be used. The validated AI techniques can be used to increase the success rates in drug development, whereas the AI techniques that are in development must be validated before applying to the drug development process. The most crucial part in the drug development process is the synthesis of chosen molecules. Thus, AI is valuable owing to its ability to prioritise molecules based on the ease of synthesis or develop tools that are effective for the optimal synthetic route.

c. AI in synthesis of drug-like compounds

Currently, several computer aided organic compound synthesis (CAOCS) systems are available to assist chemists in selecting the synthesis route; however, it is not a component of the computer-aided drug discovery (CADD) workflow**.**

d. Predicting the mode-of-action of compounds using AI

The prospect of having an AI platform that can predict the on- and off-target effects and in vivo safety profile of compounds before they are synthesised excites those involved in the drug development process – particularly medicinal chemists. The availability of such platforms reduces the drug development time, R&D costs and attrition rates. A few examples of such platforms are Deep Tox (predicts toxicity of new compounds) and PrOCTOR

(predicts the probability of toxicity in clinical trials) [22]. The predictive accuracy of these platforms could be improved if a bigger and refined dataset on toxicity and therapeutic profile of a varied set of compounds is made available. However, this can only be achieved if there is a willingness to share data among the industry.

e. AI in selection of a population for clinical trials

An ideal AI tool to assist in clinical trials should recognise the disease in patients, identify the gene targets and predict the effect of the molecule designed as well as the on- and off-target effects. A novel AI platform called AiCure was also developed as a mobile application to measure medication adherence in a Phase II trial of subjects suffering from schizophrenia, AiCure increased adherence 25% compared with the traditional 'modified directly observed therapy'. Patient selection for a clinical trial is a crucial process. Interrogating the relationship between human-relevant biomarkers and in vitro phenotypes affords a more predictable, quantifiable assessment of the uncertainty of therapeutic responses in a specific patient. The development of AI approaches to identify and predict human-relevant biomarkers of disease allows the recruitment of a specific patient population in Phase II and III clinical trials. The AI predictive modelling in selection of a patient population would increase the success rate in clinical trials.

f. AI in drug repurposing

With AI, the drug repurposing process becomes more attractive and pragmatic. The concept of applying an existing therapeutic to a new disease is advantageous because the new drug is qualified go directly to Phase II trials for a different indication without having to pass through Phase I clinical trials and toxicology testing again. In silico methods predicting pharmacological properties of drug and drug repurposing using transcriptomic data comprising various biological systems and conditions through DL applications were reported. The methods described are based on high-level representations of data utilising deep neural networks (DNNs), which is essentially a highly adaptive multilayer system comprising connected and interacting artificial neurons that perform various data transformation. In a study it was demonstrated that DNNs could classify complex drug action mechanisms on the pathway level, thus classifying drugs into therapeutic categories according to their functional class, efficacy, therapeutic use and toxicity. Additionally, the advances in precision medicine have resulted in the creation of next-generation AI that offers the ability to design drug molecules from the generative adversarial networks (GANs) [23]. GANs are an astounding

technology that uses DL to produce photo-realistic pictures from text descriptions. Thus, this platform can perform remarkable tasks beyond analysing data, such as imagining or creating new data modelled on real data. Essentially, the GAN technique is an adversarial game between two DNNs where, principally, one DNN evaluates the output of the other iteratively and, in that adversarial game, the two networks learn how to generate more perfect molecules.

g. AI in polypharmacology

Currently, the 'one-disease–multiple-targets' paradigm dominates over the 'one-disease–one-target' paradigm because of deeper understanding of pathological processes in diseases at the molecular level. One-disease–multiple-targets is termed polypharmacology. Many databases, such as ZINC, PubChem, Ligand Expo, KEGG, ChEMBL, Drug Bank, STITCH, Binding DB, Super target, PDB, among others, are available to integrate diverse information of molecular pathways, crystal structures, binding affinities, drug targets, disease relevance, chemical properties and biological activities. AI could be used to probe these databases to design polypharmacological agents.

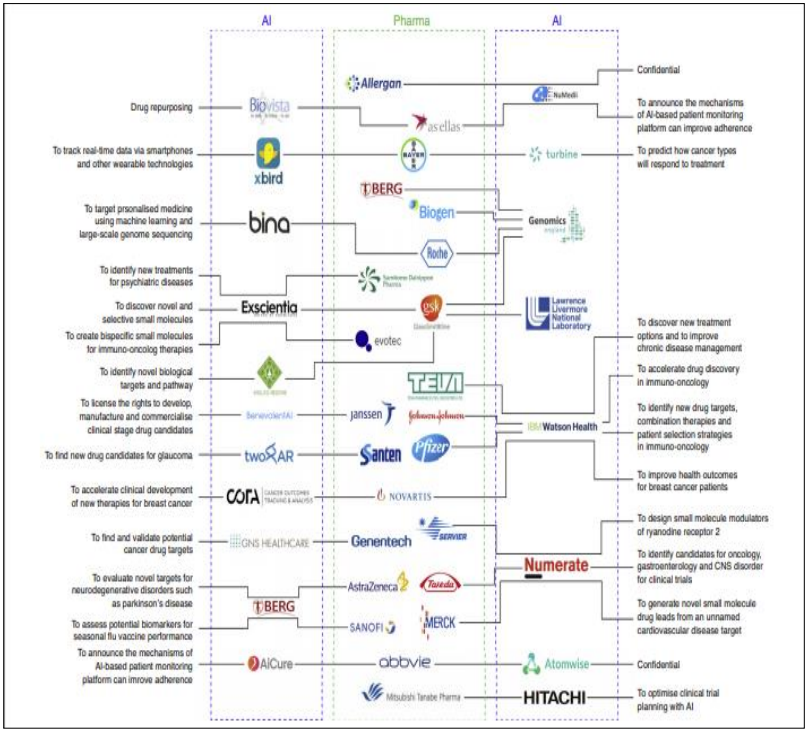
AI with pharmaceutical industry for drug develpoment

With the rapid introduction of AI in healthcare, especially in the years 2016 and 2017, numerous pharmaceutical companies have made investments in and have joint ventures with AI companies in the hopes of developing better healthcare tools. These include the improvements in diagnostics or biomarkers and the identification of drug targets and designing new drugs. The transition from general medicine to modern AI healthcare focuses on the basis of the data. The analyses of these underlying data coupled with ML or DL are subsequently formulated into algorithms – thereby strongly contributing to progressive modern healthcare that incorporates AI. Thus, numerous partnerships between pharmaceutical industries and AI companies were recently developed on a global scale. For instance, DeepMind Technologies, a subsidiary of Google, collaborated with Royal Free London NHS Foundation Trust to assist in the management of acute kidney injury [24].

Exscientia is an AI company that specialises in phenotypic drug discovery. Human analysis of extremely complicated datasets for high-content phenotypic drug discovery is outperformed by AI by a large margin. The ease in rapidly evolving drug designs is achievable through the testing of each newly designed compound and then comparing it with its anticipated performance and other molecules. Another notable AI start-up is Numerate. Numerate focuses on ligand chemistry, ADMET and combinatorial ML with

classical approaches, giving emphasis on the transformation of new medicine discovery by filling significant therapeutic gaps through analysing large datasets pertaining to drug development by applying algorithms.

A healthy spread of such partnerships covering various research areas, such as the identification of novel small molecules, the discovery of new treatment methods, monitoring the health data via wearable technologies, among others. These advances are forecasted to serve as contributing factors to the betterment of healthcare services, improvement in terms of efficiency in clinical trials, enhancement in stratified medicine and more. Presently, up to US$3 billion over the course of 15 years will be spent to bring a new drug to market. This trend is unsustainable and a change is inevitable because consumers are not willing to pay more for medicines and for the cost of the failures. Thus, a change in the business model is necessary, and AI offers such opportunity. These collaborations demonstrate the importance of AI technology in allowing us to explore a much bigger design space and discover rare molecules that have properties, which is beyond the conventional finds if we relied solely on traditional HTS [25]



✓ **Virtual screening to discover targeted lead compounds[26-29]**

Virtual screening technology is the core of CADD. Based on the 3D structure or the quantitative structure–activity relationship model of the target bio macromolecules, the theory of molecular biology and computer science and other related fields is used as a technical basis to select the compounds that meet the expectations from the known small-molecule databases. Then, one or more experimental methods are selected for targeted drug screening for specific diseases. In the pharmaceutical world, virtual screening is often considered as a top CADD tool to screen large chemical structural libraries and reduce them to a set of candidate compounds related to specific protein targets. At present, virtual screening has been regarded as a materialized tool, widely recognized in search for lead compounds and the enhancement of compound activity.

Virtual filtering process mainly include the following:

►► **Target selection:** This is the first step in virtual screening, and this step is crucial. Small molecular compounds target four large molecules: proteins, polysaccharides, lipids and nucleic acids. Proteins such as enzymes, ion channels and GPCR (G Protein-coupled Receptor) are often preferred as potential drug targets because they are highly specific and less toxic, such as the discovery of heat shock protein (Hsp90) inhibitors, the discovery of a selective inhibitor of Aurora A, the discovery of TASK-3 (KCNK9) channel blockers, the virtual screening for GPCR drug screening and so on.

►► **Prepare the compound database:** Before starting a new virtual screening, we need to collect all the compound structures for a specific drug target. In recent years, a number of compound databases have been developed which store not only the structure of the compound molecules, but also many chemical and biological information, such as ZINC, PubChem and others.

►► **Docking software:** Currently popular molecular docking software are Dock, Auto Dock, MolDock, Maestro and so on. These software are available for use and are easy to operate, but when the number of compounds involved in docking is too large (eg, 1 million), large-scale molecular docking methods and strategies need to be adopted. Linux-based virtual docking always plays an important role when we perform high-throughput docking.

►► **Scoring system:** Molecular docking is a computational method that predicts the preferred position of a molecule (ligand) relative to a second molecule (receptor) when the two molecules combine to form a stable complex, and then predict the binding strength or binding affinity between the receptor and the ligand. There are two main types of docking: rigid docking

and flexible docking. In rigid docking, the receptor and ligand are immobilized so that the bond angle and bond length are constant. This docking speed is very fast, but lacks practical application because flexible docking allows for conformational transformation. In flexible docking, the conformation of the ligand and acceptor can be converted at will during the calculation. This docking method requires relatively high computing power, but it can most accurately calculate the docking results and is suitable for the accurate investigation of the identification between molecules. Based on the position and binding energy, a docking score will be calculated.

►► **Biological experiment verification:** The candidate compounds of highest docking score are verified by both in vitro and in vivo biological experiments.

►► **Clinical study:** once all preclinical studies of these candidate compounds are proved to be effective, clinical studies will be performed on candidate compounds to determine their safety and effectiveness on patients.

- **Identification of ligand-binding pocket on the 3d protein model**

The interaction between protein and ligand usually occurs in a pocket formed by conserved amino acids. The protein function relies on the ligand-binding site on its 3D structure. The identification of the binding pocket helps to discover new drugs and better understand the mechanism of actions of drugs, such as the discovery of a conservative pocket of the guanylate cyclase heme domain. In the general molecular docking calculation, an indispensable step is to define the binding position of the ligand molecule, that is, its binding pocket. If the binding site is known, the ligand type and protein function can be determined by computer and experimental procedures, and can be used in drug design and to predict potential side effects. Bioinformatics is a cross-disciplinary discipline that solves biological problems through the use of computer, mathematical and statistical methods. The determination of binding pockets is very important for designing drugs. Traditional X-ray crystallography and nuclear magnetic resonance methods predict large amounts of protein structures that are time-consuming and expensive, but bioinformatics provides different tools to predict the 3D structure of proteins and reveal their binding regions. Its application is very promising, such as the identification of conserved binding pockets in ricin A chain, RASSF2 potential binding pocket prediction and so on.

There are two ways to find a pocket combination:

1. Proteins with known 3D structures can be searched from the PDB database, and related information can be downloaded directly from

the database;

2. Method of homology modelling, using I-TASSER, Swiss Model, Mod Web and other online servers based on homologous modelling to generate protein 3D structure, as well as to predict the ligand-binding pocket, for example, prediction of serotonin 1A receptor binding pocket.

- **Discovery of targeted lead compounds for a novel drug target**

The drug target is a special site formed by biomolecules, and the drug can be combined with it to produce pharmacological effects (targeted agonist/inhibitor) for the purpose of preventing and treating diseases. According to the biological characteristics of biomolecules, drug targets can be classified into receptors, enzymes, ion channels, DNA, hormones and growth factors. The research and development (R&D) of new drug is a work with high investment and low yield. The discovery and confirmation of drug target is the first step of the R&D of a new drug. However, the number of clinically validated drug targets is still very small, so there is an urgent need to discover more new drug targets. With the development of life science and bioinformatics, more and more target structures have been analyzed. Different from traditional drug research methods, big data mining is widely used in drug target research, such as using genetic algorithm and bagging-svm ensemble classifier to predict drug targets, mining and forecasting cancer-related database, and using genetic disease-related data to predict novel therapeutic targets by computational data mining methods. The human genome database shows that there are more than 20 000 proteins in the human body, while the Drug- Bank database indicates only about 500 have been identified in the past 100 years. Therefore, there are many potential targets to be discovered and confirmed. Thanks to structure biologists, a lot of new biological processes mediated by protein–protein interaction, protein–DNA interaction and protein–RNA interaction have been discovered. These above proteins may probably serve as potential novel drug targets in the near future. The information of the drug target database can be used to analyze the sequence characteristics and biochemical characteristics of structural features, and to establish a prediction model to discover new drug targets. Therefore, we set up a set of novel methods for potential cancer-related drug target discovery, such as the following procedures:

1. TCGA and Human Protein Atlas databases were used to mine the data of targets related to prediction of cancer prognosis in the database.

2. Then use the computer to correlate with known cancer prognosis-related targets and score according to the correlation strength.
3. Then review the research progress of the target according to the score table and explore the 3D structural information of the drug target in the PDB database.
4. According to the integrated information, select the appropriate targets for further biological verification.

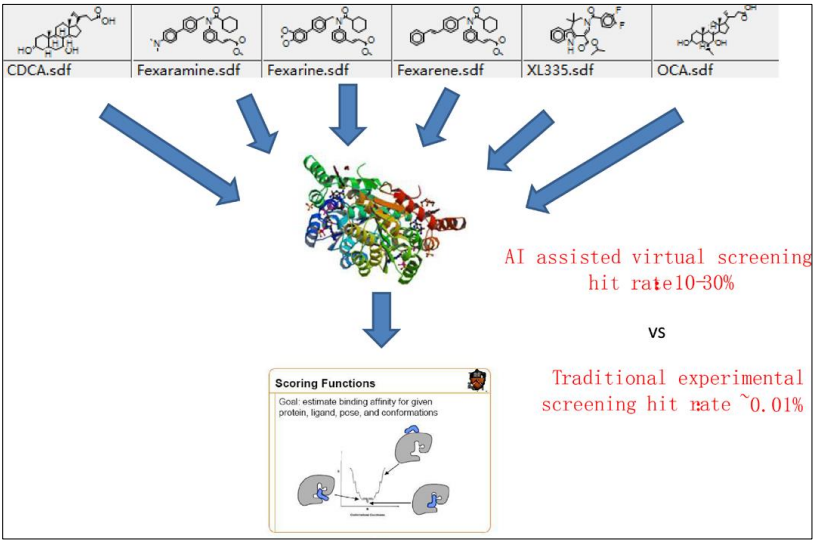
After successful verification of the novel therapeutic targets in vitro and in vivo, the virtual screening molecular docking-based drug screening can be performed according to the novel targets. This process has greatly reduced the time and cost compared with traditional drug development. In the past few years, discovered 73 novel compounds as well as 12 FDA-approved drugs targeting more than 30 potential novel therapeutic targets. Moreover, four FDA-approved Drugs will be used for clinical trial tests to cure multiple sclerosis in the near future.

- **Reverse docking done to find drug targets of an old drug**

Drug repositioning, is also known as drug repurposing, defines new indications for existing drugs and can be used as an alternative to drug development. The advantages of repositioning are the availability of chemical materials and previously generated data, so that the potential for R&D is significantly greater than the time required and cost of bringing new drugs to market. In meta-analysis, a study showed the class III antiarrhythmic amiodarone was active in neurodegeneration assays and could also selectively remove embryonic stem cells, and that the antipsychotic trifluoperazine was active in neurodegeneration assays. Apart from traditional molecular docking, reverse docking is used for identifying receptors for a given ligand among a large number of crystal structures. Generally, the following steps are required to perform a drug repositioning by reverse docking (drug repositioning):

1. Data set collection;
2. Data set partition;
3. Molecular descriptor calculation and modelling;
4. Ensemble learning;
5. Retrospective screening campaigns;
6. Building positivity predictive value surfaces and choosing an adequate score threshold value;
7. Prospective virtual screening;
8. Molecular docking;
9. Reverse docking scoring.

The results of the reverse docking were then verified by biological experiments. There are reports that they have implemented a computer-aided drug repurposing campaign to discover new inhibitors of falcipain-2. Four hits were acquired and tested against the enzyme, among that two of them confirming inhibitory activity. The dropped drug odanacatib show competitive inhibition, while the antibiotic methacycline showed inhibitory effects through non-competitive inhibition. Therefore, it is feasible to find the target of the old drug through reverse docking. This method saves a lot of time and can reduce many experimental costs and experimental steps. In the past few years, discovered 13 new targets for eight FDA-approved drugs by this.



Schematic procedure of artificial intelligence (AI)-assisted virtual screening

Millions of structurally diverse chemical compounds are docked to a specific therapeutic target. AI scoring function is used to select the best hits from millions of docked results. Reverse-docking the old drugs to all ligand-binded structures extracted from PDB (>100 000 proteins;).

The new indications and adverse effects of these old drugs have been revealed through biological verification for those reverse-docked targets.

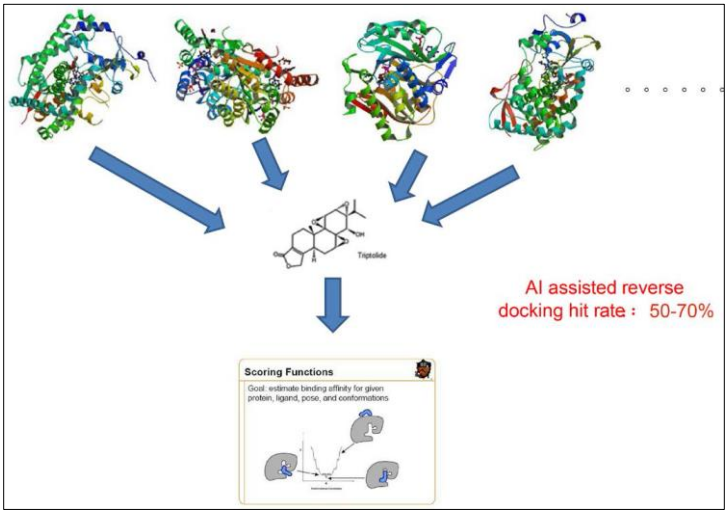
- **AI for the prediction of a compound's admet**

The ADMET of chemicals plays a key role in drug discovery and development. High-quality drug candidates should not only have sufficient efficacy for the treatment target, but should also display appropriate ADMET characteristics at the therapeutic dose. Moreover, ADMET's predictions not

only reduce the risk of late-stage attrition of new compounds and compound libraries but also help researchers optimize screening and testing by looking at only the most promising compounds. Just relying on biological experiments to verify the ADMET of a compound is a waste not only of time but also a lot of human and material resources. With the increase in computer speed and the implementation of quantum chemistry methodology, pharmacodynamic and pharmacokinetic issues have become computationally easier to handle. Quantum mechanics helps to study pharmacokinetic problems at the molecular level prior to laboratory preparation and testing. In order to realize ADMET for predicting compounds by computer, we need to do a lot of work in the early stage:

1. Data collection and preparation (this is a crucial step);
2. calculate ADMET-related properties based on the collected data;
3. Definition of the ADMET score;
4. Validation of the ADMET score.

Although it is not guaranteed that the predicted results are completely consistent with the later experimental results, the introduction of AI can reduce many unnecessary troubles for later research. Machine learning (including AI) methods are accompanied by verification procedures in many cases and are often used in conjunction with other methods. Therefore, this makes them an excellent and attractive hybrid tool for reducing false predictions and model errors.



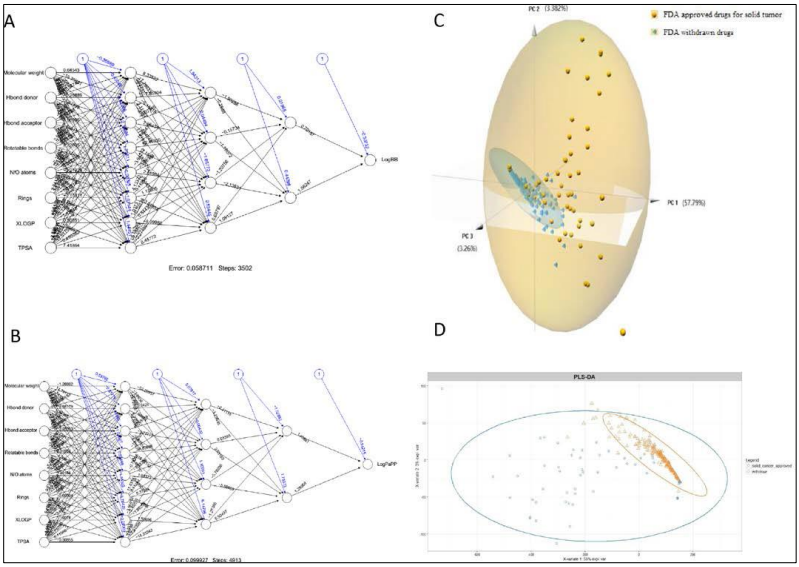
Schematic procedure of artificial intelligence (AI)-assisted reverse docking

More than 100 000 structurally diverse protein structures are reversely docked to a specific chemical compound/natural product. AI scoring function is used to select the best hits from millions of docked results.

In the past few years, several new ADMET prediction tools based on deep learning AI was developed, such as prediction for logBB and logPapp to calculate the overall ADMET properties of a specific compound. Toxicity of a compound is very difficult to predict, mainly because it depends not only on its own chemical structure but also its direct actions on the target proteins. Hence, we collected all FDA-approved/ withdrawn drugs to perform batch reverse docking with all ligand-binded structures extracted from PDB. Every docked target of each drug was scored and each drug can be considered as an N-dimensional vector in an N-dimensional space. Therefore, FDA-approved/ withdrawn drugs can be referred as training data set to predict the toxicity of any given compounds.

- **Mining cancer data base to discover novel therapeutic drug targets**

Targeted drug design has become a hot topic because it is one of the key technologies for the discovery of therapeutic drugs. However, it is very difficult to find new drug targets through traditional experiments and methods and it is often difficult to achieve the desired results. Therefore, bioinformatics technology can be used to discover and identify new drug targets by mining cancer database. With the complete information of cancer genome/ transcriptome sequencing accumulated in recent years, a variety of publicly available biological databases have provided us with a multidisciplinary goldmine of big data; especially the cancer genomic/transcriptomic/ proteomic research has taken a big step forward. TCGA is a project jointly supervised by the National Cancer Institute and the National Human Genome Research Institute. It aims to use high-throughput genome analysis technology to help people to better understand the occurrence and development of cancer, in order to achieve the purpose of prevention, diagnosis and treatment. For example, as of 2012, the genomes and epigenetic groups of lung squamous cell carcinoma have not been fully elucidated, but through the genomic and epigenetic analyses of about 180 lung SQCCs (Squamous Cell Carcinoma), TCGA has successfully screened out molecular targeting drugs for SQCC.



AI-assisted ADMET properties prediction. (A) Deep learning algorithm to calculate logBB for a specific chemical compound. (B) Deep learning algorithm to calculate logPapp for a specific chemical compound. (C) PCA (Principal Component Analysis) analysis on 48 186 reverse-docked proteins for 55 FDA-approved drugs (yellow dots) and 224 FDA-withdrawn drugs (blue dots). (D) PLS-DA (Partial Least Squares Discriminant Analysis) analysis on 48 186 reverse-docked proteins for 55 FDA-approved drugs (blue dots) and 224 FDA-withdrawn drugs (yellow dots).

ADMET, absorption, distribution, metabolism, excretion and toxicity; AI, artificial intelligence; FDA, Food and Drug Administration; TPSA, total polar surface area for ovarian serous cystadenocarcinoma, which is not optimistic in diagnosis and treatment at present, some potential therapeutic targets have been found through the comprehensive analysis of ovarian serous cystadenocarcinoma with higher grade by TCGA. In this way, the mining of the cancer database plays an important role in finding new therapeutic druggable targets. By mining TCGA and THPA, our lab has discovered more than 10 potential novel therapeutic targets in various cancers, such as pancreatic cancer, lung cancer, triple negative breast cancer, colorectal cancer and so on, as well as their targeted compounds recently. For other diseases (such as stroke, cardiovascular diseases, neurological diseases and so on), there is no such intact database for the data mining to discover novel therapeutic targets. However, single cell transcriptomic sequencing data have been accumulated rapidly in the recent years, and these data will be helpful for new therapeutic target discovery in the near future.

- **Animal models and their limitations**

In order to study the physiological and biochemical processes of human diseases and to explore the pharmacodynamics and pharmacokinetics of drugs in vivo, many animal models of various diseases have been introduced to preclinical studies. The most popular animal models are mouse, rat and monkey. Particularly, specific genes knock-out/ knock-in mouse models have revolutionized our ability to study specific gene and protein functions in vivo and to better understand their molecular pathways and mechanisms.

Although there are animal models used as powerful support for modern medical research in preclinical studies of many diseases, the new drug therapy is still difficult to convert from laboratory to clinical, because it is not feasible to mimic all aspects of a human disease in an animal model, especially a heterogeneous disease with complex pathophysiology such as stroke, and most of its studies are carried out in young animals without any complications. These models are physiologically different from real stroke, which especially affects the elderly with a variety of cerebrovascular risk factors. Therefore, in stroke studies, more than 1000 drugs were candidates in stroke models, but only 17 were tested in humans. Recently, many Alzheimer's disease (AD) candidate drugs have shown great effects in mouse models but all failed during clinical trials. Perhaps this is because the tissues, organs and systems of animals are always different from those of human beings, and their reactions and effects to drugs are also different. An animal model cannot involve all aspects of a human disease. The age, sex and species of animals, tissue and organ damage, or the increase, deletion and change of genes caused by the establishment of animal models may have a significant impact on the experimental results. Furthermore, another big problem of an animal model is the genetic difference between the animal protein and human protein. According to ENSEMBL genome database, orthologous genes have been analyzed in human, chimpanzee, mouse and rat. Surprisingly, there are only 7043 orthologous genes (single copy common genes) shared in these four species. For chimpanzee and human, a set of 13 454 pairs of human and chimpanzee genes with unambiguous 1:1 orthology have been identified.

In humans and chimpanzee the orthologous proteins are similar, with ~ 29% are identical and the typical orthologue differ by two amino acids, one per lineage. Compared with ~25 000 genes in each of these four species, 7043 orthologous genes are ~28%, which means the other ~72% expressed non-orthologous proteins in these four species are very different in their protein sequences. Even if humans and chimpanzees are considered as the closest primate relatives in the animal kingdom, only 13 454 pairs of orthologue genes

are identified consisting ~50% of their own expressed genes, which means the other ~50% expressed non-orthologous proteins are very different in their amino acid sequences. Taken together this above genetic evidence, it is very clear that if the drug target of the animal model is structurally different from the one of human, drugs targeting the animal protein will perform a significantly different effect between animal experiment and clinical experiment. The interaction between drug and its target is caused by hydrogen bonds, Van der Waals force and π-π interaction, which are exerting their interactive forces within less than 4 Angstrom. One or two amino acid mutations within the binding pocket of the drug target can make a big difference.

Cancer-targeted drugs are much more successful compared with targeted drugs developing for stroke and AD. Perhaps there are two major reasons. First, in the field of cancer-targeted drug R&D, there are a lot of mouse models carrying humanized genes (such as mouse carrying humanized immune system) to mimic the human immunity system. Second, patient-derived xenograft models (mouse carrying clinical human cancer tissue) have been widely introduced in the preclinical studies of cancer-targeted drugs. For stroke, AD and rare diseases, similar humanized animal models carrying human drug target protein must also be introduced in the preclinical studies in the near future.

- ✓ **Artificial Intelligence and Big Data**

Facilitated Targeted Drug Discovery [25]

Traditionally, the discovery of novel targeted drugs is an expensive long-term progress, costing billions of US dollars and more than 10 years. In the very beginning, a therapeutic drug target must be identified by traditional experimental methods. Then, structural biologists come to decipher the three-dimensional (3D) structures as well as their ligand-binding characteristics to reveal whether this is a druggable target. Subsequently, medicinal chemists and pharmacologists use high-throughput screening to find several highly effective lead compounds for further safety assessment as well as clinical trials. In general, the above procedures are costly and tedious. In November 2018, a study was conducted to estimate the total cost of trials for the development of novel Food and Drug Administration (FDA)-approved drugs. Surprisingly, the average cost of efficacy trials for the 59 new drugs approved by the FDA during 2015–2016 was $19 million. Therefore, it is necessary to overcome the limitations of the conventional drug discovery procedures by introducing efficient, low-cost and computational methods. Compared with

traditional drug discovery methods, rational drug design, mainly including computer-aided drug design (CADD), is more efficient and economical. Rational drug design integrates molecular docking to the ligand-binding pocket of a promising therapeutic target, computes the binding energy of each docked small molecule compound, and selectively chooses the best ones as candidates for subsequent experimental procedures. Today, there are more than 100 000 protein 3D structures deposited in Protein Data Bank (PDB) for molecular docking. In contrast to traditional methods, rational drug design has boosted the hit rate of drug screening by more than 100 times, from ~0.01% to 1%~2%. Moreover, CADD is a more multidiscipline method which integrates advanced bioinformatics techniques and sophisticated computational algorithms. Due to its relatively high hit rates, CADD method is becoming the fundamental basis of industrial drug discovery as well as academic research. Cancer-targeted drugs are the most successful drugs for the last three decades. A lot of cancer-related proteins have been identified as therapeutic targets by computational data mining of transcriptome data in databases such as The Cancer Genome Atlas (TCGA), The Human Protein Atlas (THPA) and so on. Unfortunately for other diseases, such as stroke, vascular-related diseases and other genetic diseases, there are no similar integrated omics databases to provide sufficient big data. However, there are increasingly more single cell transcriptome data of various diseases publicly available. Thus, such data will be precious goldmines in terms of the discovery of therapeutic targets for stroke, vascular-related diseases and other genetic diseases. Moreover, supercomputers are speeding up lead identification and evaluation.

Artificial Intelligence in Pharmaceutical Product Formulation: Neural Computing [30-35]

The development of a commercial product, like a capsule, tablet or oral liquid or a controlled release formulation (e.g. an implant), is always a time-consuming and complicated process. The primary formulation consist of one or more drugs mixed with various ingredients (excipients) is prepared, and, as development progresses, the choice of these and their levels, and the process of manufacturing, are changed and optimized as a result of intensive, time consuming experimentation. These iterations, in turn, result in the generation of large amounts of data, the processing and understanding of which is challenging. In reality, the formulator has to work in a design space that is multi-dimensional and virtually impossible to conceptualize. The advantage of this method are generating clearly expressed models with associated confidence factors. However, for more than three or four inputs, statistical

approaches rapidly become unwieldy, so that the formulator is tempted to oversimplify the problem (for example, restricting a study to three input variables) in order to model it. Statistics also often require the assumption of a functional form (for example, linearity) in order to generate a model and such assumptions can be inappropriate for complex tasks like formulation. In recent years, it has been shown that neural networks can provide an alternative approach.

Neural networks are mathematical constructs, capable of "learning" relationships within data, with no prior knowledge required from the user. The neural network made no assumptions about the functional form of the relationships; it generates and assesses a range of models to determine one that will best fit the experimental data provided to it. As such, increasingly, artificial neural networks (often referred to as ANNs) are used to model a complex behavior in problems like pharmaceuticals formulation and processing. The models generated by neural networks allow "what if" possibilities to be investigated easily manner. However, their capabilities are enhanced substantially by combining them with other technologies. For example, optimization process done by using genetic algorithm, along with neural networks models, proved to be exceptionally powerful when the formulator must develop a formulation to meet stringent, often conflicting, objectives. The objectives for the optimization can easily and intuitively be defined by another artificial intelligence technology, fuzzy logic. Fuzzy logic is valuable when conflicting properties (for example, hard tablets that disintegrate quickly) are desired. Efforts have been made to integrate the technologies, creating new methodologies like neuro fuzzy logic, which combines the ability of neural networks to "learn" from data, with fuzzy logic's capacity to express complex concepts in a simple fashion. These techniques are capable of "mining" the information directly from data, presenting it in the form of easy to understand, actionable rules that can guide the formulator's future work.

- **Neural Networks**

Neural networks learn directly from input data. The learning algorithms take two main forms. Unsupervised learning, where the network is presented with input data and learns to recognize patterns in the data, is useful for organizing amounts of data into a smaller number of clusters. For supervised learning, which is analogous to "teaching" the network, the network is presented with a series of matching input and output examples, and it learns the relationships connecting the inputs to the outputs. Supervised learning has proved most useful for the formulation, where the goal is to determine cause-

and effect links between inputs (ingredients and processing conditions) and outputs (measured properties). The basic component of the neural network is the neuron, a simple mathematical processing unit that takes one or more inputs and produces an output. In neuron, every input has an associated weight that defines its relative importance, and the neuron simply computes the weighted sum of all the outputs and calculates an output. This is then modified by means of a transformation function (sometimes called a transfer or activation function) before being forwarded to another neuron. This simple processing unit is known as a perceptron, a feed-forward system in which the transfer of data is in the forward direction, from inputs to outputs, only. A neural network consists of many neurons organized into a structure called the network architecture. Although there are many possible network architectures, one of the most popular and successful is the multilayer perceptron (MLP) network. This consists of identical neurons all interconnected and organized in layers, with those in one layer connected to those in the next layer so that the outputs in one layer become the inputs in the subsequent layer. Data flow into the network via the input layer, pass through one or more hidden layers, and finally exit via the output layer. In theory, any number of hidden layers may be added, but in practice multiple layers are necessary only for those applications with extensive nonlinear behavior, and they result in extended computation time. It is generally accepted that the performance of a well-designed MLP model is comparable with that achieved by classic statistical techniques. Unlike conventional computer programs, which are explicitly programmed, supervised neural networks are "trained" with previous examples. The network is presented with example data, and the weights of inputs feeding into each neuron are adjusted iteratively until the output for a specific network is close to the desired output. The method used to adjust the weights is generally called back propagation, because the size of the error is fed back into the calculation for the weight changes. There are a number of possible back propagation algorithms, most with adjustable parameters designed to increase the rate and degree of convergence between the calculated and the desired (actual) outputs. Although training can be a relatively slow process, especially if there are large amounts of data, once trained, neural networks are inherently fast in execution.

- **Fuzzy Logic**

Conventional logic demands that a proposition is either true or false. This leads to a conventional set theory, so that a hypothesis lies either in the "true" set, or lies wholly outside it.

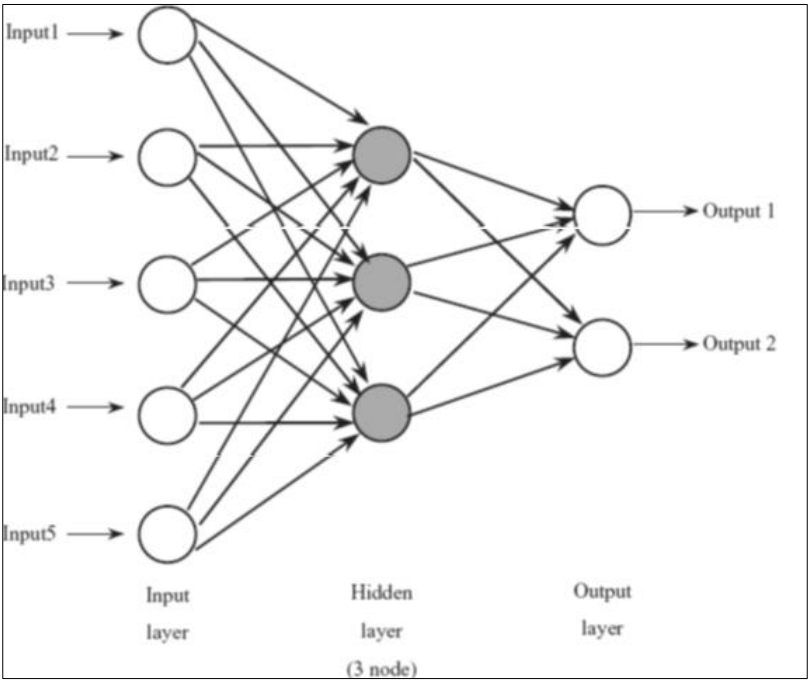


Diagram of a multilayer perceptron with one hidden layer

That is, the membership function in the "true" set is either 1 (the hypothesis is true) or 0 (the hypothesis lies outside the "true" set, and is false). But in reality these black-and-white concepts may be of little utility. An oft-cited example is the definition of a comfortable room temperature. If a temperature of 20 °C is defined as "comfortable", conventional logic would dictate that 19 or 21 °C, which lie outside this set, are "uncomfortable"). A very complex set of rules would be required to define "comfortable" using conventional logic. Fuzzy logic is based on the concept of fuzzy sets introduced in the 1960s by Lotfi Zadeh. For fuzzy sets, membership functions are not restricted to be 0 or 1, but can take any continuous value between these limits. In the context of comfortable room temperature, for example, a temperature of 17 °C might have a membership of 0.4 in the "hot" set and 0.6 in the "cold". Fuzzy logic can be especially useful in describing target properties for optimizations. For example, the formulator looking for a tablet disintegration time of 300 s, i.e. the value less than 300 s has a desirability of 1 (i.e. 100%). But a tablet which disintegrates in 310 s is not entirely undesirable (as crisp logic would insist), and instead might be assigned a desirability value of 0.9. In the area of process control fuzzy logic is also used, because it allows rules to be expressed in a simple linguistic form IF (A)

THEN (B) with an associated confidence function that is related to the set membership. To understand how it is used for the process control, consider a simple example of a fan heater governed by 4 rules. All these rules mapped onto the four fuzzy sets COLD, COOL, WARM and HOT. So, for example, if the room temperature is 18 °C, then by Rule 2 the fan speed is medium, with truth level 0.7, and by Rule 3 the fan speed is low, with truth level 0.3. The correct and smooth adjustment of the fan speed achieved by the process of defuzzification.

- **Neurofuzzy Logic**

Fuzzy logic allows objectives to be expressed in simple terms, it complements neural network modelling. In case of neurofuzzy logic, the fuzzy logic is tightly coupled with a neural network. Neurofuzzy logic combines the ability of neural networks to study from data with fuzzy logic's ability to express complex concepts intuitively. It will create a degree of transparency for the "black box" neural network models, leading to the term "grey box modelling" being applied for these methods. Neurofuzzy has proved to be exceptionally suited to data mining, since it not only can develop good models from data, but it also has the capability of expressing these as linguistic IF…THEN rules.

The neurofuzzy architecture is an essence of a neural network with two additional layers for fuzzification of inputs and defuzzification of outputs. The modeling capacities of neurofuzzy systems depends on the number, shape and distribution of the fuzzy membership input functions. In the simplest case, only two, LOW and HIGH would suffice. In some cases, it is appropriate to add more; for example, a problem showing a quadratic dependency would require at least LOW, MEDIUM and HIGH in order that it be properly represented. Where data are scarce, relatively few membership functions should be used. As the number and complexity of the inputs increases, the rules become more complicated, and this can make them difficult to understand.

- **Evolutionary Computing**

By using rules of inheritance, recombination (or cross-over), mutation and selection evolutionary computing describes computational processes in which solutions evolve. One particular subset of this, evolutionary algorithms, has found the application in the formulation research.

- **Genetic Algorithms**

Genetic algorithms were pioneered in the 1970s by John Holland. It will

provide a search technique which is particularly suited to optimization; a trial population is assumed, and this evolves in an iterative process. During this process, an initial population of solutions is generated, and the fitness of each member of the population is assessed. The fittest solutions then become the "parents" of the next generation. Allowing some recombination and mutation introduces a further degree of novelty into the population so that the genetic algorithm is more likely to find a global optimum solution. It is this ability to find the global optimum in a complex design space which renders genetic algorithms so useful, especially when compared with more directed searches like conjugate gradient and steepest descent methods. The requirement for genetic algorithms is that a criterion of "fitness" can be defined. This can vary from problem to problem. In case of multi-dimensional optimization, it has proved useful to define an objective function which is a weighted sum of the desirability of each of the properties. The use of weights in the sum allows some properties to assume more importance than others, and the fittest solutions are those that best meet the overall objectives. In defining the desired values of the properties, fuzzy logic provides a useful framework. In one case where disintegration time of a tablet is most desirable below 240 s, and completely undesirable above 360 s. The second is for the case where the disintegration time should lie between 240 and 360s, becoming progressively less desirable as it moves farther away from this region. Genetic programming, generally regarded as a subset of genetic algorithms, is the most recent of the techniques reviewed here, having been widely popularized only in the 1990s. It has a limited use in pharmaceutical formulation, but it shows great promise since it has the learning capabilities similar to that of neural networks but the transparency associated with a straightforward mathematical expression. In genetic programming, each solution is a "tree", in which each tree node has an operator function and each terminal node is an operand. These trees provide an alternative way of representing equations. An initial population of solutions is assumed, and as with other evolutionary methods, the fitness of each member is assessed. The population then evolves allowing crossover (whereby parts of trees are swapped) and mutation. The evolution is biased so that the fittest solutions are emphasized in successive generations, leading to increased improvement in the fit of the model to the training data. In other genetic algorithms, a criterion of fitness must be defined. The simplest criterion would simply minimize the mean-squared error between the calculated and actual values, but this could result in an overly complex, and potentially over-fitted, model. Therefore, it is often appropriate to use a model assessment criterion (such as structural risk minimization) to penalize those solutions whose added complexity does not return significant new knowledge.

Genetic programming currently suffers from the disadvantage that it is time consuming, and its application is less well understood in the formulation domain than are neural networks. Nonetheless they are attractive possibilities for future work, because they can produce "transparent" models.

- **Integrated Software**

All these technologies are well suited to data mining and modelling, but in their raw form require a degree of expertise. To be truly useful to product formulators, the technologies described above need to be integrated into packages that use sensible default values for the parameters, and that incorporate all of the essential tools. For example, to develop a package aimed to produce optimized formulations, the modelling capability of neural networks combines well with the optimization provided by genetic algorithms. Fuzzy logic complements this by providing a useful framework for defining the objectives for the optimization in a clear and intuitive way. Apart from the specific neural and evolutionary technologies, it is useful to integrate some basic statistics (both for examining the data and for assessing the quality of the models, by ANOVA Analysis of Variance, statistics), to provide a visualization capability. Such integrated packages are now available commercially and are proving useful in the pharmaceutical industry. An early exemplar of this is CAD/Chem; more recently, since CAD/Chem is no longer available, INForm from Intelligensys has been developed. A data mining package based on neurofuzzy logic, FormRules, is commercially available, with integrated visualization as well as statistical techniques to assess the quality of models.

- **Applications**

Over the past fifteen years the technology has been used extensively to model and optimize formulations from simple to very complex. It has also been used to a lesser degree in pharmaceutical processing.

1. Oral formulations-immediate release

In case of a direct compression tablet formulation containing hydrochlorothiazide in order to maximize tablet strength and select the best lubricant. Apart from this, modeled a tablet formulation of caffeine in order to relate both formulation (diluent type and concentration, binder concentration) and processing variables (type of granulator used, method of binder addition) with granule and tablet properties (friability, hardness, and disintegration time). Both these investigations showed that neural networks performed better than conventional statistical methods. Similarly, the data of Kesavan and Peck were reanalyzed using a combination of neural networks and genetic

algorithms. This showed that the optimum formulation depended both on the relative importance placed on the output properties and on the constraints applied both to the levels of the ingredients and to the processing variables. Many optimum formulations could be produced, depending on the "trade-offs" that could be accepted for different aspects of product performance. It is also studied using neurofuzzy computing. Useful rules were automatically generated, highlighting the most important factors for each property and their interdependencies. The friability rules are the inverse of those for tablet hardness, while the rules for disintegration time involved the diluent itself, the binder concentration, the method of addition of binder (wet or dry) and the method of granulation. The data generated have been used to compare three different neural network programs and four classes of training algorithms in terms of capability of generating predictive models. The most predictive models from each neural network varied with respect to the optimum network architecture and training algorithm. No significant differences were found in the predictive ability of these models. Recently, the same data have been analyzed who compared neurofuzzy techniques with neural networks. The developed neurofuzzy methods were almost as good as neural networks (as determined using analysis of variance statistics). Rules generated by the neurofuzzy method presents the results in a simple understandable format. Neural networks used successfully to optimize the crushing strength and disintegration time of a high-dose plant extract tablet. By using both neural networks and genetic algorithms, the advantages of combining these technologies in the formulation of antacid tablets were developed. Drug content and hardness of intact tablets of ophylline mixed with microcrystalline cellulose from their near-infrared spectra predicted by neural networks. The model proved better than a statistical model generated with the same data. The superiority of neural network models over statistical models has also been found. This time for predicting the dissolution of 28 diltiazem immediate release tablet formulations. Recently, working in Sweden and the UK used neural networks, genetic algorithms and neurofuzzy to analyze historical data from three different immediate release formulations. The performance of the generated models are satisfactory in producing tablets with specific desired properties. Apart from immediate release tablet formulations, neural networks have also been applied to modelling the immediate release capsule formulations, rapidly disintegrating or dissolving tablets and a novel oral micro emulsion formulation of rifamycin and isoniazid for the treatment of children during the continuation phase of tuberculosis. Solid dispersion formulations of ketoprofen modelled by both neural networks and neurofuzzy with good predictability. The study has also been extended by the addition of

a micro emulsion formulation. In a detailed evaluation of both neural networks and guided evolutionary simulated annealing for the modeling and optimization of a tablet coating formulation, for conflicting properties like crack propagation and film opacity that display highly curved responses with respect to the formulation inputs (e.g. pigment particle size, pigment concentration and film thickness), classical experimental designs to map the experimental space are inappropriate for neural network modeling. If we use pseudo-random design, it was possible to model and optimize the film coating, predicting formulations that were either crack resistant or that were fully opaque. Similar formulations have also been studied using neurofuzzy computing, where rules were generated relating both the opacity and crack resistance to the input variables. The discovered technique offer maximum opacity the films needed to be thick with a high pigment concentration and a small pigment size.

2. Controlled release oral formulations

Artificial neural network (ANN) and pharmacokinetic simulations are used in the design of controlled-release formulations. ANN model inputs are seven formulation variables and three other tablet variables (moisture, particle size and hardness) for 22 tablet formulations of a model drug. The output is the in vitro cumulative percentage of drug released at 10 different sampling time points. Using CAD/Chem software the ANN model was developed and trained from the input and the output data sets. The trained ANN model is used to predict optimal formulation compositions based on two desired in vitro dissolution-time profiles and two desired in vivo release profiles. The assumption is that the dissolution is the rate-limiting step in the in vivo absorption of the drug that the fraction of the drug absorbed in vivo is linearly related to the in vitro dissolution of the drug. Three out of four predicted formulations showed very good agreement between the ANN predicted and the observed in vitro release profiles based on difference factor, f1, and similarity factor, f2. ANN model used to optimize diclofenac sodium sustained release matrix tablets. Formulation variables including concentrations of cetyl alcohol, polyvinyl pyrolidone K 30 and magnesium stearate, and sampling time were chosen as inputs. Twelve hidden nodes were included in the hidden layer. The percentage of the drug released at each sampling time point was used as the output. A trained ANN model is used to predict release profile and optimize the formulation composition based on the percentage of the drug released. A simultaneous optimization technique in which the ANN model was used to optimize controlled release theophylline tablets prepared with controse, the mixture of hydroxypropylmethyl cellulose

with lactose and cornstarch. The release profiles of theophylline were determined as the sum of the fast and slow release fractions. To develop the ANN model, the amounts of controse, cornstarch and compression pressure were selected as causal factors; the response variables are the initial weight of theophylline, the release rate constant in the fast and slow release fraction. The results predicted by the trained ANN model agreed with the observed values. The rate of release theophylline in the GI tract is similar to the absorption rate, the rate constant in the fast release fraction and the release rate constant in the slow release fraction used as absorption rate constants. The plasma concentrations profiles were generated based on the simulated plasma concentration profiles. The optimization of the controlled release theophylline tablets was performed by a generalized distanced function method using the optimal release parameters. For the design of extended-release aspirin tablets generalized regression neural network (GRNN) was used. Ten aspirin matrix tablet model formulations prepared using Eudrgit RS PO. The casual variables are amount of Eudragit RS PO and compression pressure. The release parameters are in vitro dissolution-time profiles at four different sampling time points, as well as coefficients n (release order) and log k (release constant) from the Peppas equation. A set of release parameters and causal factors were used for training. The optimized GRNN model was used to predict the formulation and process factors for the optimized formulations, which would give the desired in vitro drug release profiles. The two optimized formulations were then prepared and tested in vitro. The comparison between the GRNN predicted and observed in vitro profiles, and estimated coefficients indicates there is no difference between the predicted and experimentally observed drug release profiles for the two tested formulations based on the difference factor, f1 and similarity factor, f2. GRNN predicts the drug stability, and in vitro–in vivo correlation. In case of coated tablets, the controlling mechanism for drug release is generally by the film applied to the tablet, although in some circumstances the release may be controlled in addition by the tablet core formulation. In case of 125 formulations for small tablets prepared from a model drug embedded in a hydrophilic matrix and then coated with an enteric polymer, were able to apply various input feature selection algorithms, including genetic algorithms, to evaluate the relative importance of the input variables. Then they used a neural network to model subsets of the data, with the less significant inputs eliminated. As expected, the elimination of the less significant inputs results in more generalized predictive models. A neural network to model the formulation of salbutamol sulfate osmotic pump tablets, using the amount of hydroxypropyl methyl cellulose and polyethylene glycol present in the cellulose acetate coating, apart

from the coating weight, as control factors. Using the model, the release parameters for 1000 formulations, from which they selected an optimum with the desired release pattern. For pelleted or multi-particulate formulations, the drug release mechanism can be controlled either by using a rate controlling matrix or by the use of films. The pellets are produced by using extrusion and spheronization or by layering onto sugar cores. In some cases, the pellets may be tableted. In others, they are packed into hard gelatin capsules. Both multi-layer perceptrons and recurrent neural networks to model successfully the release of theophylline from a matrix controlled release pellet formulation prepared using extrusion and spheronization. In another study on pellets, this time prepared using the layering technique followed by polymer film coating, and compared the modelling and optimization abilities of simplex and neural network procedures. Simplex optimization is more suitable although neural networks were "a valuable and predictive tool". In a follow-up study, compared a 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. In each case, the observed drug release profile of the optimized formulation was close to that predicted from the model. Fluidized bed manufactured, enteric-coated, omeprazole pellets compressed into tablets were also analyzed using neural networks. From this, we have to predict a positive correlation between the tablet strength and the concentration of the microcrystalline cellulose used as a compression aid. The degradation of the omeprazole in that media was depend on the microcrystalline cellulose concentration. A bimodal drug delivery system consisting of pellets coated with pectin and chitosan has recently been modeled using neural networks with five different training algorithms. Concluded that those networks trained using gradient descent backpropagation algorithms outperformed the others. The textural properties of a novel pellet formulation capable of extensive gelation and swelling in biological fluids, coined "gelisphere" by its inventor, have been modeled using both statistics and neural networks. Neural networks were a more reliable data predictor in the design of their system.

- **Benefits and Issues**

Although there is a great deal of interest in neural computing, the quantified information on the benefits has been harder to find. Benefits that could be seen included are:

– Effective use of incomplete data sets,

– Rapid analysis of data,

– Capable to accommodate more data and retrain the network (refine the model),

– Exploration of the total design space, irrespective of complexity,

– Ability to accommodate constraints and preferences and

– Ability to generate understandable rules.

In a survey on the use of 93 neural computing applications in 75 UK companies covering all business sectors, the major benefits identified were the improved quality, improved response times, and increased productivity. Eighty-four percent of users were satisfied or very satisfied with their systems with only three percent expressing dissatisfaction. Business benefits, specifically for the domain of product formulation (albeit for nonpharmaceuticals), have been given as:

– Improvement of product quality and performance at low cost,

– Shorter time to market,

– Development of new products,

– improved customer response,

– improved confidence and

– improved competitive edge.

As this new technology moves from the realm of academe into practical application, there are also issues regarding the implementation of neural computing. Users in the previously cited study were asked to identify where they had experienced problems. Thirty-nine percent had found problems related to software and lack of development skills; this will be reduced as commercial packages come into wider use and there is only less need for be evidence of in-house systems with their high programming and maintenance burden. However, even when commercial packages are used, there are a number of features that should be present before neural computing can be used to advantage. The problem must be numeric in nature, and reasonable quantities of data should be available to train an adequate model. The greatest benefits are achieved for multidimensional problems where it is difficult to express any analytic model and difficult to abstract the rules by any other mechanism than neural computing. It helps if the problem is of practical importance, is part of the organization’s essential activity, and meets a real business need. Neural computing will provide beneficial effect to the industry in future.

✓ **Few early adopters of AI in the clinical research domain [36]**

Company named "MedRespond" is adding to a progression of projects highlighting the organization's patented custom conversation® to meet this test and streamline the clinical trial process. By consolidating Artificial Intelligence and streaming media, company permits clients to sort in their inquiries, in their own words, and the framework chooses the pre-recorded video that best answers their inquiries. At the point when new issues or inquiries emerge, the framework learns and adjusts. Utilizing this innovation, medicinal services suppliers can offer consistent backing to patients amid each period of a clinical trial. There are two parts of the project that company proposes creating.

- **Patient Recruitment Program**

Company has worked along with the University of Pittsburgh cancer centers to make a patient training program for disease clinical trials. The project is acquainted with recently analyzed growth patients at the center. It highlights oncologists, scientists and patients noting questions about what it is similar to take part in a clinical trial, the shields that are set up to secure members and the consideration that is given amid a clinical trial. Growth patients and their families can utilize the project at the center, or in the security of their own homes, day and night and around the globe. As every patient investigates company's project and poses their questions, an itemized log is made to give precious understanding into the inquiries patients raise. An example report of data that can be caught is incorporated into this proposition. Sharp comprehension of what issues concern patients – symptoms, being dealt with like a guinea pig, accounts, family, notwithstanding stopping through the company's involvement in disease clinical trial program. Company additionally has involvement in serving to painstakingly make reactions that meet the unbending necessities of the IRB.

- **Patient Retention Program**

About 30% of clinical trial members drop out before the study is finished up. Consequently, once a patient has been enrolled, it is imperative that they be deliberately bolstered all through their trial interest. One reason for this dropout rate is an absence of continuous correspondence with the patient amid the trial, little appraisal of their status, and inability to advise them of trial advancement – all correspondence issues. Patients need to have consistent access to experts to answer their inquiries, evaluate their status and offer them some assistance with managing any issues or symptoms that they encounter. Customary answers for giving this backing depend on therapeutic staffing, an

answer that is basically too unreasonable. Company's innovation empowers suppliers to recreate this ceaseless emotionally supportive network to give productive, and viable backing for clinical trial patients. The patient will visit the clinical trial checking site in every week. A video host will affirm that the patient is sticking to the study convention and after that direct an online evaluation, particular to that patient and trial. Certain reactions could trigger further activity – alarming the doctor, asking for help, sending more data, or prescribing measurement alterations subsequent to counselling with the study doctor. The framework likewise may prescribe how to get ready for the following center visit. This correspondence connection to the clinical trial patient will likewise be utilized to overhaul members about the status of their trial or instruct them concerning any issues. Patients will really feel just as their data is esteemed and that they are in effect deliberately observed and kept informed as the trial continues, something that happens every once in a while in today's clinical trial process.

- **Precision Medicine an Ai Approach**

Precision remedy which is getting the right treatment to the right patient at the ideal time. Remembering the finished objective to truly appreciate the disorder and how to treat it, the full natural make-up of the phone. This joins the genome, proteome, lipidome, metabolome. It can in like manner be looked upon mitochondrial limit, oxidative states, and ATP creation, as how the cell is acting. In business part there are diverse associations who are wearing down Artificial Intelligence, for occasion Berg it takes tests of blood, pee and tissue from illness patients and complexities those examples and those from sound patients. More than 14 trillion data centers are produced using this method. The dominant part of that data is then supported into fake cognizance systems. The AI separates information from the patient's science including OMICS, clinical illustrations, and demographics. Once the cognizance of wiped out cells is expert then, wear down how to make the cells strong again can be proficient by method for AI. Each one of that examination is so mind boggling and wide that it would take individuals a lifetime to complete it. With the help of AI, all that data is crunched in the scope of days or weeks, obtaining profitable time in the pharmaceutical creation process. The result is a centered around treatment, specially crafted to the individual, considering their own body's beauty care products.

- **Fourth Industrial Revolution: AI[37]**

Numerous have authored that world is amidst the fourth industrial revolution where we are at the tipping purpose of an entire assortment of

interconnected innovation leaps forward: robots, rambles, shrewd urban areas, computerized reasoning, and cerebrum research. By, the fourth industrial revolution is not an item unrest; it is a framework insurgency. We live in reality as we know it where we are overpowered with advancement and innovation leaps forward in counterfeit consciousness, associated gadgets (the internet of things), 3D printing, self-driving vehicles, consistent availability and vast figuring power. These advancements are changing the world in a significant and eccentric path and at a much quicker rate than any time in recent memory. The sheer volume of advancements and the rate of progress is overwhelming. It will definitely drive a wholesale change of organizations and procedures as we probably am aware them today. Human services and pharmaceutical businesses are no exemption and may be give one of the greatest open doors for a positive effect. Here are three ways that clinical trials will be changed by the Fourth Industrial Revolution.

- **Patients will be dynamic members in the clinical trial**

By far most of clinical trials today are led without direct information from patients as most information are gathered by human services suppliers amid patient visits. In any case, billions of individuals are as of now conveying associated individualized computing gadgets (advanced cells and tablets) and billions more will be associated through wearable gadgets soon. This gives the chance to catch information specifically from patients in a continuous and convenient way as they enter that data on their own cell phones. Even better, information for non-transferable ailments, for example, hypertension and diabetes can be caught and transmitted straightforwardly through wearable medicinal gadgets. Accordingly, the information caught will be significantly more point by point and of higher quality in this manner expanding the pace and viability of clinical trials.

- **Clinical trials systems will consistently facilitate all parts of the trial**

Envision an EDC or eCOA framework that is associated with the IVRS framework which tracks the investigational item progressively empowered by the IoT base. These associated frameworks will permit situations, for example, planning the patient visit in light of the accessibility of the investigational item. Clinical Trial Systems will be able to correspond with individuals, different frameworks, gadgets and supplies by means of backing of standard conventions, for example, for personality administration - SAML and Oauth for security, distributed API for combination, and implicit work process motors for arrangement. These frameworks will consistently associate individuals, offices, hardware and supplies progressively to empower more

proficient and viable clinical trials.

- **Crowd sourcing will change trial interest**

For pharmaceutical organizations, joining examiners and patients for clinical trials is a period expending and costly process that depends intensely on whom you know and the amount of cash you spend on customary media and selection representatives. On the other side, agents and patients have couple of alternatives and no dependable hotspots for what clinical trials they can take part in. Cloud based clinical trial frameworks will make publishing so as to agree to trials straightforward web posting of accessible clinical trials and registries of examiners and patients. Specialists and patients will have the capacity to distribute and share the accreditations and vitals effectively and safely through frameworks that will impart only the data they approve to the right gatherings. While we don't know precisely to what extent it will take for the Fourth Industrial Revolution to totally change clinical trials, we can be sure that change is unavoidable. For dynamic associations and business people, this introduces a huge chance to enhance existing arrangements and benefits or make totally new offerings. For others, it will be important to adjust to these progressions just to survive.

✓ **Future of AI**[38-39]

The firmly controlled medicinal services industry has made little utilization of counterfeit consciousness in this way. One of the issues has dependably been that social insurance is excessively mind boggling. Keeping in mind the end goal to foresee anything around one's wellbeing, we require data on demographics, proteins, multi-quality cooperation's, ecological impacts, and an entire host of different features. Those conceivable outcomes are startling and energizing.

- **AI to Predict Drug Resistance**

Could AI foresee human services results? Specialists are chipping away at approaches to utilize AI and machine figuring out how to anticipate reactions from two chemotherapy medicines used to treat breast cancer patients. The fundamental issue is that not everybody with the same growth reacts similarly. Computerized reasoning is an effective apparatus to anticipate drug results since it takes a gene at the entirety of all the collaborating qualities. They discovered it was conceivable to foresee which patients with breast cancer malignancy would encounter upgrades when utilizing the medication Paclitaxel.

- **How AI could bolster pharmaceutical adherence**

Can AI check whether we took our pills? Per reports, an organization in the US does precisely that. AI Cure is a start-up that uses artificial intelligence on patient's cell phones to affirm solution ingestion support in clinical trials and high-chance populaces. A cell phone's camera is utilized to comprehend whether patients took the medicine effectively. Ongoing information is likewise unified for quick mediation and longitudinal following of adherence examples. Research found that patient non-adherence to recommended medicines is connected with poor restorative results, movement of malady, and causes billions of dollars every year in avoidable direct human services costs. Presently, social insurance experts just need to guarantee that each patient makes utilization of his or her cell phone.

- **AI for smarter drug development**

IBM Watson is presumably a standout amongst the most surely understood samples of a supercomputer that has demonstrated its capacities in AI past the lab. Other than noting questions for the test show Jeopardy, Watson is likewise ready to comprehend and extricate key data by looking through a large number of pages of exploratory restorative writing and afterward picture connections in the middle of medications and other potential infections. A year ago, IBM declare that the pharmaceutical mammoth Johnson and Johnson and contender Sanofi would participate in a joint effort with IBM Watson's Discovery Advisor group. J&J will likely educate the supercomputer to peruse and comprehend experimental papers that contain clinical trial results, and afterward create and assess medicines and different medications. While this may not sound excessively energizing, it could have inconceivable outcomes on how pharmaceutical organizations do similar viability examines. The IBM proclamation recommends that it could help specialists to coordinate a medication with the right arrangement of patients keeping in mind the end goal to expand adequacy and minimize symptoms. This would be distinctive to the manual process at present connected, which obliges months to discover information and proof before a study can even begin. The utilization of Watson could essentially decrease the time, and subsequently quicken the procedure of disclosure. It was reported this was the principal open declaration of pharmaceutical organizations to grasp a supercomputer's capacities and use it for prescient investigation towards drug improvement.

- **AI for alzheimer’s patients**

A venture led at the University of Washington and its branch of computer science investigated the utilization of AI frameworks to backing and improve

the freedom and personal satisfaction of Alzheimer's patients. Such helped discernment frameworks would make utilization of AI innovation to supplant a percentage of the memory and critical thinking capacities that have been lost by an Alzheimer's patient. By scientists, the inspiration for this undertaking comes from the need to advance the prosperity and freedom of individuals experiencing intellectual constraints because of maturing and Alzheimer's ailment.

- **AI for wearable health**

An issue with internet of things (IoT) applications has been the means by which to make utilization of their information, as PCs immediately achieved a breaking point of what should be possible with every one of that was gathered. Thankfully, machine-learning frameworks have adjusted to handle bigger limits of approaching information. Zulfi Alam, general director for individual gadgets at Microsoft, clarifies in a post that their brilliant forthcoming calculations will know enough about the client and her biometrics in a consistent state to have the capacity to perceive examples and chances to enhance client wellbeing and wellness. In a more basic human services setting, an exploration group at the university of California, Los Angeles, proposes a stage for wellbeing observing utilizing remote sensor systems. The stage's engineering is a system empowered framework that backings different wearable sensors and contains on-board general figuring abilities for executing separately customized occasion discovery, cautions, and system correspondence with different restorative informatics administrations. Envision this checking stage associated with computerized reasoning and machine learning abilities, and the way we deal with patients later on could essentially change.

✓ **Future of AI in clinical research/ healthcare**

Healthcare professionals seem to be doubtful about the use of artificial intelligence in their practice. AI is still in an early stage of development and will not be able to replace a doctor. The big question we may want to ask is how can machine learning become a greater enabler for healthcare and its participating players?.‟The questions to doctors and pharmaceutical companies is what problems they have, and how AI can help to solve them. AI is a study that imitate human knowledge into PC innovation that could help both specialists and patients in the accompanying way:

- By giving a research facility to the examination, representation, and classifying of restorative data.
- By concocting novel devices to bolster choice making and research.

- By the Incorporation of exercises in medicinal, programming and psychological sciences.
- By offering a substance rich order for future logical restorative group.

Along these lines, expanded combination of insightful AI devices in regular medicinal applications could enhance the effectiveness of medications and stay away from expenses by minimizing the dangers of false determination, encourage more focused on pre-agent arranging, and decrease the danger of intra-agent entanglements. The late use of AI in performing advanced undertakings and calculations has step by step driven it to be presented as a key part of MRI and figured tomography frameworks. The additional point of preference of these frameworks is in the capacity to adequately procure data, and sync with set up choice bolster databases. Further, AI has started changing the field of surgical mechanical technology wherein it has empowered the appearance of robots that perform semi robotized surgical errands with expanding effectiveness. One of a definitive difficulties confronted in mechanical autonomy could be imitating of human knowledge and body movement. Despite such a basic test, mechanical autonomy has achieved impressive advance and is presently connected over a wide cluster of utilizations extending from the guard business to the diagnostics. Essentially, robots are not assembled insightfully, but rather are coordinated with certain product segments to make them smart. Late advances in the field of AI, for example, neural systems administration, normal dialect preparing, picture acknowledgment, and discourse acknowledgment/combination research, have impelled our imagination and the eventual fate of mechanical technology looks brilliant in reality. It merits are the greatest obstacle towards selection of medicinal mechanical surgical frameworks is the high beginning capital gear costs included. A large number of these frameworks regularly require new base to be built and the staffing of high bill rate pros who are all around prepared in these procedures develops to be a key impediment in its far reaching reception. An essential AI PC utilized as a part of clinical practice could be pictured to be connected for robotization of routine undertakings and for different capacities recorded beneath: Alerts and updates in most broad types of AI coordination, the machine examines a patient's lab results, drug requests, and redesigns the patient with a fitting update. In this way to generate cautions and updates, more propelled AI projects can be specifically interfaced with a patient screen and utilized for distinguishing changes as a part of a patient's condition.

- Therapy for arranging specific conditions that require elaborate treatment arrangements could profit by AI instruments amid

treatment arranging. By consolidating an AI framework that can naturally detail arranges in view of particular conditions would increase the value of the doctors and also patients.

- Information retrieval programming hunt specialists can be made down complex medicinal applications that are substantially more proficient than current era web-slithering operators' execution. This guides in data recovery and up-gradation of information naturally.
- Image interpretation multiple medicinal pictures can be promptly distinguished, from plane X-beams through to very mind boggling pictures like angiograms, CT, and MRI examines. Such frameworks for picture acknowledgment and translation have progressively been received for clinical use. Another key utilization of AI frameworks is presently experimental exploration through applying master frameworks and choice emotionally supportive networks. Such frameworks are customized to learn. DSS innovation used effectively in the medicinal gadget industry that includes heart checking and robotized ECG, therapeutic imaging, clinical research center investigation, respiratory observing, electroencephalography, and anesthesia.

Conclusion

Today, big data and AI are developing so fast that boost targeted drug discovery in an unprecedented speed. With the integration of various disease databases, scientists are able to perform data mining for de novo therapeutic target discovery. With AI assistance, novel identified therapeutic targets can be virtually screened for the discovery of targeted old drugs/new compounds within very short period. With AI-assisted reverse docking, old drugs or natural products could be repurposed for new indications very efficiently.

Acknowledgement

Authors are expressing our sincere gratitude to management of St James College of Pharmaceutical Sciences, Chalakudy for giving the research supports and digital library facilities for preparation of book chapters. We would like also acknowledge Dr. K. Krishnakumar, Principal, St. James College of Pharmaceutical Sciences, Chalakudy, Dr. B. Dineshkumar, HOD, Department of Pharmaceutics, St. James College of Pharmaceutical Sciences, Chalakudy, for their continuous support and they are the source of inspiration for the students/ researchers for writing research project and book chapters.

References

1. In-Jin Jang. A commentary on Artificial intelligence in drug development: clinical pharmacologist perspective. 2019;27(3):87-88.
2. Xin Yang, Yifei Wang, Ryan Byrne, Gisbert Schneider, and Shengyong Yang. Chemical reviews on Concepts of Artificial Intelligence for Computer-Assisted Drug Discovery. 2018.B.
3. Slide share on Artificial intelligence in drug discovery. CAS a division of American society With STAT's Casey Ross and Kate Sheridan
4. Mccarthy, J.; Hayes, P. Some Philosophical Problems From the Standpoint of Artificial Intelligence. In Machine Intelligence; Edinburgh University Press: Edinburgh, 1969.
5. Barr, A.; Feigenbaum, E. A.; Cohen, P. R. Handbook of Artificial Intelligence; Addison-Wesley Longman: Boston, MA, USA, 1982.
6. Popovic, D.; Bhatkar, V. P. Methods and Tools for Applied Artificial Intelligence; Marcel Dekker: New York, 1994.
7. Bobrow, D. G. Natural Language Input for a Computer Problem Solving System. In Semantic Information Processing; MIT Press: Cambridge, 1968.
8. Weizenbaum, J. ELIZA□A Computer Program for the Study of Natural Language Communication Between Man and Machine. Commun. ACM 1966, 9, 36−45.
9. Baum, E. B. On the Capabilities of Multilayer Perceptrons. J. Complex. 1988, 4, 193−215.
10. An article on advantages and disadvantages of artificial intelligence by Z Burak Erkoc, Semih Giiner, Omer Altin. 2018;1-6.
11. Towards datascience.com/advantages and disadvantages of artificial intelligence.
12. Y. Zhang, D. K. Robinson, A. L. Porter, D. Zhu, G. Zhang, and J. Lu, "Technology roadmapping for competitive technical intelligence," Technological Forecasting and Social Change, vol. 110, pp. 175–186, 2016.

13. D. C. Parkes and M. P. Wellman, “Economic reasoning and artificial intelligence,” Science, vol. 349, no. 6245, pp. 267–272, 2015.

14. T. Y. Wong and N. M. Bressler, “Artificial intelligence with deep learning technology looks into diabetic retinopathy screening,” Jama, vol. 316, no. 22, pp. 2366–2367, 2016.

15. Ho.C.W.L, D.Soon,K.caals, J.Kapur governance of automated image analysis and artificial intelligence analytics in health care. Clinical radiology. 74, 2019, 266-278.

16. Ma, J.; Sheridan, R.P.; Liaw, A.; Dahl, G.E.; Svetnik, V. Deep neural nets as a method for quantitative structure–activity relationships. J. Chem. Inf. Model. 2015, 55, 263–274. [CrossRef] [PubMed].

17. Kearnes, S.; Goldman, B.; Pande, V. Modeling Industrial ADMET Data with Multitask Networks. arXiv 2016, arXiv:1606.08793v3. Available online: http://arxiv.org/abs/1606.08793v3 (accessed on 15 September 2018).

18. Segler, M.H.S.; Kogej, T.; Tyrchan, C.; Waller, M.P. Generating Focused Molecule Libraries for Drug Discovery with Recurrent Neural Networks. ACS Cent. Sci. 2018, 4, 120–131. [CrossRef] [PubMed]

19. Segler, M.H.S.; Preuss, M.; Waller, M.P. Planning chemical syntheses with deep neural networks and symbolic AI. Nature 2018, 555, 604–610. [CrossRef] [PubMed]

20. H.C. Stephen Chan, Hanbin Shan, Thamani Dahoun, Horst Vogel, and Shuguang Yuan,* Advancing Drug Discovery via Artificial Intelligence, Trends in Pharmacological Sciences, August 2019, Vol. 40, No. 8 2019.06.004.

21. Kit-Kay Mak and Mallikarjuna Rao Pichika, Artificial intelligence in drug development: present status and future prospects, ã 2018 Elsevier, Drug Discovery Today Volume 24, Number 3 March 2019.773-780.

22. Mayr, A. *et al*. (2016) DeepTox: toxicity prediction using deep learning. Front. Environ. Sci. 3, 80

23. Kadurin, A. *et al*. (2017) druGAN: an advanced generative adversarial autoencoder model for de novo generation of new molecules with desired molecular properties in silico. Mol. Pharm. 14, 3098–3104

24. Haghi, M. *et al*. (2017) Wearable devices in medical internet of things: scientific research and commercially available devices. Healthc. Inform. Res. 23, 4–15.

25. Benquan Liu, Huiqin He, Hongyi Luo, Tingting Zhang, Jingwei Jiang. Artificial intelligence and big data facilitated targeted drug discovery. 2019;206-213.

26. Cerqueira NMFSA, Gesto D, Oliveira EF, *et al*. Receptor-Based virtual screening protocol for drug discovery. *Arch Biochem Biophys* 2015;582:56–67.

27. Ferreira L, dos Santos R, Oliva G, *et al*. Molecular docking and structure-based drug design strategies. *Molecules* 2015;20:13384–421.

28. Abbasi M, Amanlou M, Aghaei M, *et al*. New heat shock protein (Hsp90) inhibitors, designed by pharmacophore modeling and virtual screening: synthesis, biological evaluation and molecular dynamics studies. *J Biomol Struct Dyn* 2019;5:1–12.

29. Kilchmann F, Marcaida MJ, Kotak S, *et al*. Discovery of a selective Aurora a kinase inhibitor by virtual screening. *J Med Chem* 2016;59:7188–211.

30. Svetlana ibrić, Zorica djurić, Jelena parojčić, Jelena petrović. Artificial intelligence in pharmaceutical Product formulation: Neural computing. (2009); 15 (4):227−236.

31. R. C. Rowe, E. A. Colbourn, Pharm. Tech. Eur. 9 (1996) 46-55.

32. L. A. Zadeh, Fuzzy sets. Information and Control 8 (1965) 338-353.

33. K. M. Bossley, Neurofuzzy Modelling Approaches in System Identification, PhD Thesis, University of Southampton, UK, 1997.

34. J. H. Holland, Adaptation in Natural and Artificial Systems, The University of Michigan Press, Ann Arbor, MI, USA (1975).

35. J. R. Koza, Genetic Programming – On the Programming of Computers by Means of Natural Selection. MIT Press, Cambridge, MA, USA, 1992.

36. Veerabhadra Sanekal Nayak, Mohammed Saleem Khan, Bharat Kumar Shukla, Pranjal R. Chaturvedi. Review article on Artificial intelligence in clinical research. *2016 Nov;3(4):187-193.*

37. Clancey WJ, Shortcliffe EH. Readings in Medical Artificial Intelligence: the First Decade Reading, MA: Addison Wesley; 1984.

38. Baxt WG. A neural network trained to identify the presence of myocardial infarction bases some decisions on clinical associations that differ from accepted clinical teaching. Med Decision Making. 1994; 14:217-22.

39. Baxt WG. Application of artificial neural networks to clinical medicine. Lancet. 1995; 346:1135-8.