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Review Article

Artificial Intelligence in Drug Discovery (AIDD)

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The importance of Computer Aided Drug Discovery (CADD) has been consistently increasing over the past 20 years. Artificial Intelligence (AI) is one of the CADD methods, machine learning (ML) is one of its subtopics. In the past five years, many Artificial Intelligence in Drug Discovery (AIDD) approaches were employed towards drug discovery. This article includes discussion on the scope and limitations of AIDD.

Introduction

The Artificial intelligence (AI) "is the science and engineering of making intelligent machines, especially intelligent computer programs. It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine itself to methods that are biologically observable".[1,2] In the year 1956, Allen Newell and his colleagues created the Logic Theorist, the first running AI software program.[3] Though the original objectives of AI are not yet completely realized, many AI techniques became available and their usage is increasing with time. The AI techniques are very popular now-a-days due to the involvement of AI in its various forms across a large range of domains ranging from robotics, speech translation, image analysis, etc. Several innovative techniques were developed by computer science researchers in an attempt to make computers intelligent, some of them found applicable in chemistry, biology and pharmaceutical sciences. To design new organic synthetic schemes, to understand complex biological systems, to design new APIs or development of new analytical/ diagnostic devices or methods, AI is being used. The AI techniques are also applicable to drug discovery, drug development, drug repurposing, drug metabolism prediction, drug toxicity analysis, improving pharmaceutical productivity, clinical trials and almost all aspects of pharmaceutical sciences.[4] All these techniques are collectively considered under AIDD (Artificial Intelligence in Drug Discovery). These AI technologies are not yet routinely practical in Computer Aided Drug Design (CADD), yet they are being used to resolve complex drug discovery problems. In comparison to Ligand-based drug design (LBDD) and Structure-based drug design (SBDD), AIDD is in its nascent state. A few books are available which include discussion on AIDD.[5,6]

Initially, AI was utilized to develop logical programming platforms (Prolog,[7] LISP[8]) on par with general programing languages. Later on, as a part of machine learning (ML),[5, 9,10] many novel methods Knowledge Base Systems (KBS) like Artificial Neural Networks (ANN), Support Vector Machines (SVM), Genetic Algorithms (GA), Deep Learning (DL) Fuzzy Systems (FS), pattern recognition tools, classifiers, etc. were introduced, all of them found applications in AIDD.[11,12] In the current scenario, the AI methods are emerging complementary to the molecular modelling based methods for the CADD scientists. As of today, it appears that the AIDD based operations are different from those operations offered at atomic level by molecular modelling techniques, however, the overlap between these operations are increasing with an exponential growth.

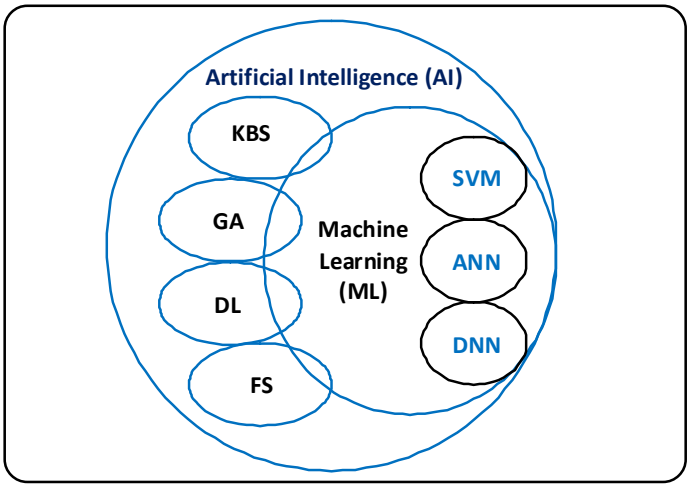

Figure 1: Artificial Intelligence in Drug Discovery (AIDD)

As the contributions of ML in Drug Discovery (MLDD)[5,9, 10,13] are increasing, the terms AIDD and MLDD are being treated as synonyms. Machine learning and data mining can be applied to provide many solutions such as -- classification, regression, clustering, dimensionality reduction, reinforcement learning, deep learning, anomaly detection and many more. Apart from that, several subtopics of machine learning include ANN, DNN (Deep neural networks), RNN (Recurrent neural networks), CNN (Convolutional neural networks), GA, SVM, Bayesian Networks, DT (Decision trees), LR (Logistic regression), k-NN (k-nearest neighbors), NB (Navie bayesian) techniques are also important in CADD (Figure 1).

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Knowledge-Based Systems (KBS) in Drug Discovery

A knowledge-based system[14] (KBS) is a computational approach that captures and uses knowledge from a variety of sources. Knowledge Base (KB) is a data base of knowledge, Information related to any particular topic is stored in the form of Fact Bases (FB) and the relations between various factual data points in Fact Bases are defined in the formof Rule Bases (RB). When the data from FB and RB are efficiently interpreted with the help of inference engines, the entire system is known as an expert system (ES). Currently, a knowledge-based system is a major area of artificial intelligence which can help in making decisions based on the data and information that resides in their database i.e. Knowledge Base (KB). Several Drug-KBS are being developed.[15] PharmGKB from Stanford University is a KBS based on drug-gene interactions,[16] DailyMed is a KBS containing drug-disease information,[17] SuperTarget is a KBS which includes information related to drug-target interactions,[18] merged-PDDI includes drug-drug interaction KBS.[19] These drug-KBS are being used for drug repositioning by identifying new drug indications with the help of knowledge on drug-target, protein-protein, gene-disease interactions. Beneficial drug combination predictions are being made from the drug-target information after combining with ATC (Anatomical Therapeutic Chemical) classification systems. Though there are a few successes, many issues are yet to be sorted out and the applications are yet to be expanded, for example, in terms of drug-KBS integration, implementation, improving predictive results, eliminating negative samples, etc.[20]

In the field of CADD, the calculation of several descriptors for QSAR purpose is based on knowledge-based system. Knowledge-based scoring functions (for molecular docking purposes) are application of KBS which rely on the statistical observations of intermolecular contacts collected in large 3D structural databases. Chemical and macromolecular databases (CCSD and PDB) stored potential mean forces (distance dependent) for various subunits of molecules, because many such interactions occur frequently among the small and macromolecules. SmoG, ASP, DSX, IT-Score, DrugScore, etc. are some of the known scoring functions which are based on the KBS methods.[21] For example, DrugScore scoring function which employs the distance-dependent pair potentials from nonbonded interactions, has been derived from the crystal data. The scoring functions $DrugScore^{CSD}$ and $DrugScore^{PDB}$ are derived from the crystal data from CSD and PDB respectively.[22] Klebe and his co-workers established that $DrugScore^{CSD}$ provides relatively more satisfactory results compared to the original PDB-based DrugScore.[22] Huang and co-workers developed a distance-dependent knowledge-based scoring function - ITScore-PP to predict protein-protein interactions. They utilized crystal structures of 851 dimeric protein complexes which containing true biological interfaces to derive ITScore-PP scoring function.[23] Ebejer et al. developed Ligity: a non-superpositional, knowledge-based method to perform virtual screening of small molecules.[24] Several ADME-Tox property based quantitative values are also being estimated using knowledge based methods.[25]

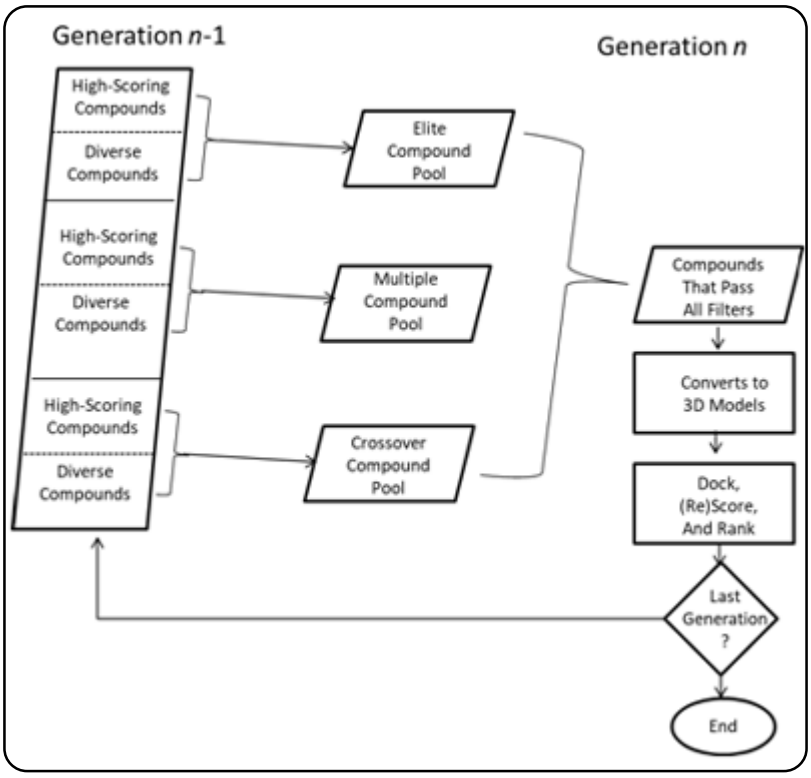

Figure 2: Process-flow diagram of the AutoGrow4 algorithm. Figure adopted from Ref.[30]

Genetic Algorithms (GA) in Drug Discovery

The genetic algorithms (GA)[26] is a computational method for solving both constrained and unconstrained optimization problems by adopting natural selection procedure. GAs "evolve" solutions to problems using the principles of genetics. Several generations of solutions are considered which involve many candidate solutions in each generation. The transformation of data from one generation to the next generation happens mainly in three ways - (i) as per a fitness function (ii) by crossover process and (iii) mutated in a systematic manner. In this way, the number of candidate solutions gets reduced marginally and the solutions in the next iteration get better. When this iterative procedure is continued for a few generations, fittest solutions are obtained.[26,27]

GAs are being employed in QSAR and molecular Docking extensively. Genetic function approximation can be used as an alternative to regression analysis.[28] They are being used for descriptor selection, by performing generations of QSAR analysis. A combination of QSAR and GA methods were employed for designing inhibitors of methyl transferase by Sun et al.[29] Additional MLR analysis was employed to obtain statistical significance. The identified descriptors are ionization potential, topological charge indices, polarizaility, and number of aromatic amines in a molecule.[29]

Many molecular docking algorithms are based on GA approach. Initially many conformers are considered in the first generation, as the generations progress, the number of conformers gets reduced-based on the best fit docked

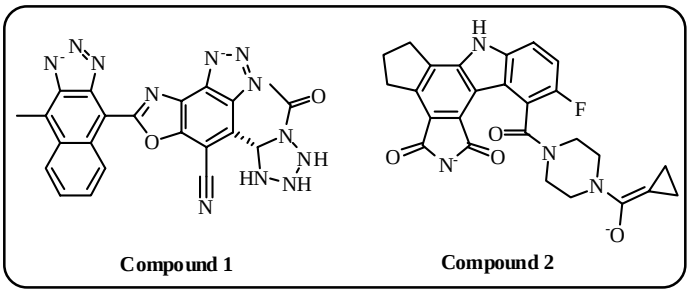

Figure 3: Compounds finalized from AutoGrow4 analysis.[30]

conformers. Each conformer is scored based on knowledge - based energy function. The conformers present In the final generation are subjected to validation using other CADD and experimental methods.[31] Autodock (Lamarkian Genetic Algorithm) and Glide software (Exhaustive search algorithms) utilizes GA based molecular docking approach.

Auto Grow4 is an open-source GA based lead optimization software.[30] It is based on python coding, it is useful for predicting novel ligands using a combination of GA and molecular docking. A population of seed molecules is chosen initially as potential solution. Molecular docking of these ligands into a chosen targets helps in identifying suitable molecules towards the next generation. The propagation of ligands from one generation to another generation can be done using crossover, mutant compound generation, elite compound selection, filtration, assessing the fitness, evaluating chemical properties, etc. All these help in lead optimization (Figure 2). Spiegel and Durrant demonstrated the use of AutoGrow4 by designing PARP-1 inhibitors. They identified two compounds from this analysis (Figure 3). MoleGear is also a useful evolutionary approach to *de novo* design.[32] GANDI utilizes GA approach in parallel mode for lead optimization.[33]

Machine learning (ML) in Drug Discovery

Machine learning (ML)[9,10,13,34-36] approaches provide a set of tools that can improve discovery and decision making for well-defined questions with abundant high-quality data. Computer software can be trained to grasp the important information related to drugs and allow the identification from millions of chemical species. Machine learning (ML) is a computer aided technique in which a set of data is provided to train some software component or to generate ML models which infer patterns from the supplied data to make reasonable predictions on the new data. In ML, hardware component does not learn anything from the supplied data. ANN, SVM, RF, LR, NB, etc. are the most successful ML methods which are being employed in drug discovery.[35,36] In this article, only DNN based drug discovery examples are included for brevity.

DNN is one of the latest developments in the field of ML, which is being used in CADD.[37-41] DNN contains multiple hidden layers (Figure 4). In DNN, nonlinear relations between the input parameters and the output can be effectively grasped. Mostly they are trained using the feedforward approach. In DNN, the neurons multiply the inputs and weights and take a decision to give an output signal in binary form (0 or 1). The weights get adjusted during training. Over fitting is one of the major issues in DNN, which can be overcome with improved data quality. In comparison to other NN models, DNN can handle thousands of parameters in the input layer - pre-selection of descriptors is not essential. Input layer can utilize descriptors acquired from 2D/3D structures as well as from the molecular finger prints. By modulating the number of layers, number of nodes in each layer, the activation function and other characteristics, we can fine-tune the performance of a DNN. Several benchmark studies were reported, which established that DNN performs better than RF, SVM, etc. methods. Similarly, a few studies were performed establishing that the multi-task DNN performs better than sing-task DNN. DNN methods perform better with an increase in the sample size - i.e. the larger the number of chemotypes to train a DNN, the better is its applicability (this factor may also be considered as a limitation of DNN as the models with small datasets may not perform satisfactorily). Identifying new chemical structures carrying desirable molecular properties (clogP, drug-likeness, etc.) is being carried out using DNN. Big data analysis using AI techniques is an important aspect, which is being effectively carried out using DNN. In the past 10 years, several reviews were published which report the application of DNN in *de novo* drug design, suggesting synthetic routes, prediction of binding affinity, estimation of activity properties, evaluation of ADMET properties.[37,39-41]

DeepTox pipeline which predicts toxicity of drugs is one of the important tools using Deep Learning approach.[41] Before taking up model building, standardization of data was done. A data set of 12,707 compounds was initially reduced to 8694 fragments after normalization and merging in DeepTox. Model validation was done using cluster cross validation approach. Platt scaling approach was used for ensemblepredictions. The DNN model

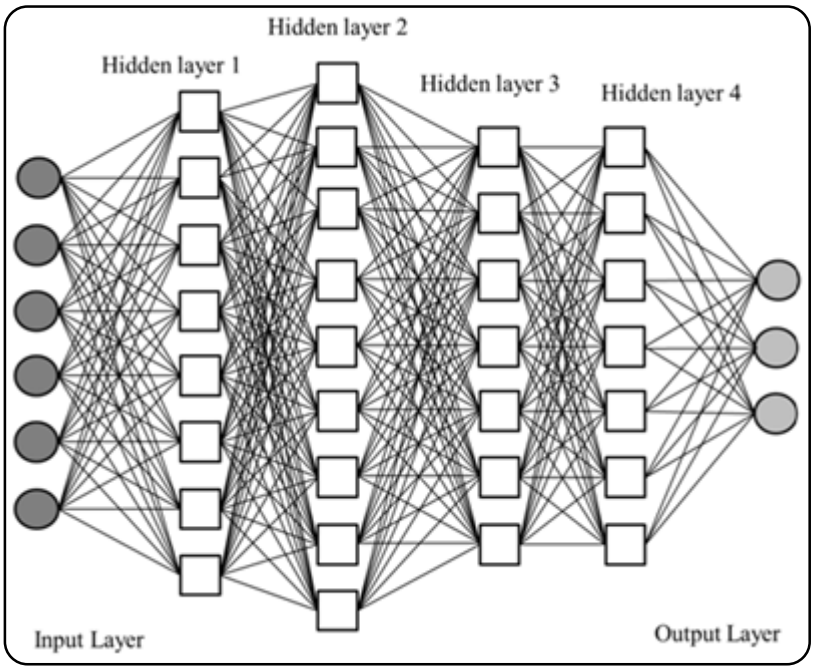

Figure 4: A representative diagram of Deep Neural Network. Figure adopted from Ref.[4]

outperformed the oth ermodels based on SVM, RF, etc.

Multi task DNN methods for classifying highly and weakly potent protein Kinase inhibitors[42] using DNN. A set of 19,030 potent inhibitors which possessed activity against 103 different human kinases were utilized for this study. This work is a multi-task DNN model. It was established that using DNN approach, the chemical features of kinase inhibitors can be effectively utilized for the classification purpose. The compounds exhibiting pIC_{50} < 10nM were considered as highly potent and compounds exhibiting pIC_{50} > 1000 nM were considered as weakly potent. Here, only those kinase targets were considered for the model development which possessed five positive as well as five negative inhibitors. The input data was based on finger prints (ex.ECFP4 based model contained 1127 bits). Out of the many generated DNN models, one model contained three hidden layers consisting of 2000, 1000 and 100 neurons. Back propagation algorithm was used to train the DNN. Over-fitting of the DNN was controlled using an algorithm (dropout - 25%) which was specifically known for this purpose. This model was shown to be better than many other alternatives considered for the classification of kinase inhibitors.[43]

AI techniques are generally considered as techniques which cannot explain the logic employed in drug discovery. However, a few attempts are being made to eliminate this limitation. Schneider and co-workers recently elaborated the current attempts in AIDD with the advantage of explainable artificial intelligence.[44] DNN is being used to model nonlinear relationships between input parameters of drug like molecules vs. the output parameters related to therapeutic application. DNN methods which are better than QSAR models are being developed for drug discovery. Chemception is a DNN tool developed for this purpose.[45, 46] Explainable artificial intelligence (XAI) is an approach for application in interpretable machine learning, such new approaches are bridging the gap between the traditional scientific approaches and the ML approaches. Transparency, justification, informativeness as well as uncertainty estimation are properties being offered by XAI.[47] The lack of liaisoning (if any) between the data scientists, chemoinformatics scientists, quantum medicinal chemistry experts, and synthetic medicinal chemistry experts is expected to be blurred as a result of XAI in drug discovery. Todeschini and co-workers adopted an integrated gradients feature attribution method in combination with a graph-CNN (convolutional neural network) to predict drug-cytochrome interaction. The site of metabolism (SoM) as well as the known metabolites could be predicted with the XAI approach.[48]

Methods for visually explaining the protein-ligand binding affinity, protein-ligand scoring as well as lead optimization of small molecule potency using three-dimensional CNN was introduced. KDEEP, DeltaDelta neural networks are the examples of 3D-CNN approach.[49,50] Molecular property prediction leading to *de novo* drug design is being suggested using graph-CNN approaches. Subgraph identification approaches (GNNExplainer) and attention-based approaches are also part of the graph-CNN efforts in chemistry/drug discovery.[51] Lipinski et al. elaborated the perspectives of deep learning applications in drug design and discovery.[52] Fooladi recently reviewed the existing RNN, CNN and DNN applications in drug design and discovery.[53]

Limitation of AI in Drug Discovery

Although the efficacy of AI based methods in drug discovery are significant but their applications are limited in both capability and functionality.[54] One major criticism of many AI techniques such as neural networks is that they are often regarded as black boxes that merely attempt to map a relationship between output and input variables based on a training data set. This also immediately raises some concerns about the ability of the tool to generalize to situations that were not well characterized in the data set. One of the limitations of the genetic algorithm methods is that they are never guaranteed to reach the "optimal" solution, though the solutions provided are highly useful. In ML technique, we can not ensure that what the model learned in terms of derivitization or in terms of heuristic reasoning, the ML model itself learns a few factors from the data provided to it. It is difficult to ensure which factor of the supplied data was utilized to train which component of an ML model. A well-known drawback of deep learning is its poor performance where data size is low-to-medium.

Conclusions and future perspectives

Many attempts are being made in applying AIDD. The results need to be judiously applied. The AIDD models are only as good as the training provided to them. If sufficient reliable data is provided during training, we can trust the model. Hence, it is important to pay attention to data quality before taking up the AI model development. It has been a roller-coaster ride for the AIDD in the recent past, hopefully the trend will stabilize soon and the AIDD techniques will be adopted by all drug discovery scientists.

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