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Review Article

Application of Artificial Intelligence and Machine Learning in Drug Discovery and Development

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Abstract

Drug discovery has traditionally been a time consuming and expensive endeavor. Additionally, drugs weren't as effectively designed as those that are being predicted and developed through AI and ML today. Machine learning is a form of artificial intelligence that develops and evolves based on experience (similarly to the human mind), and is more recently being utilized in drug discovery and design. The integration of AI and ML into the drug discovery and development process has allowed for higher target precision, lower toxicity, and better dosage formulations. AI more generally has been introduced to and has been leveraged at, each step of drug development, including target identification and validation, hit identification, as well as hit to lead optimization, and has been key in shortening the previously lengthy drug screening process. AI and ML has also been applied downstream in drug formulation where it has maximized resource utilization and is allowing for web-based 3D printing of drugs. Application of AI in the drug development process has also been extended to the modeling of novel drug-like compounds to predict their ADMET properties. This review will address the stages of drug discovery and development in which the application of AI and ML modeling has altered the traditional development of drugs.

Keywords: Drug discovery, machine learning, artificial intelligence, computational drug development.

1. Introduction

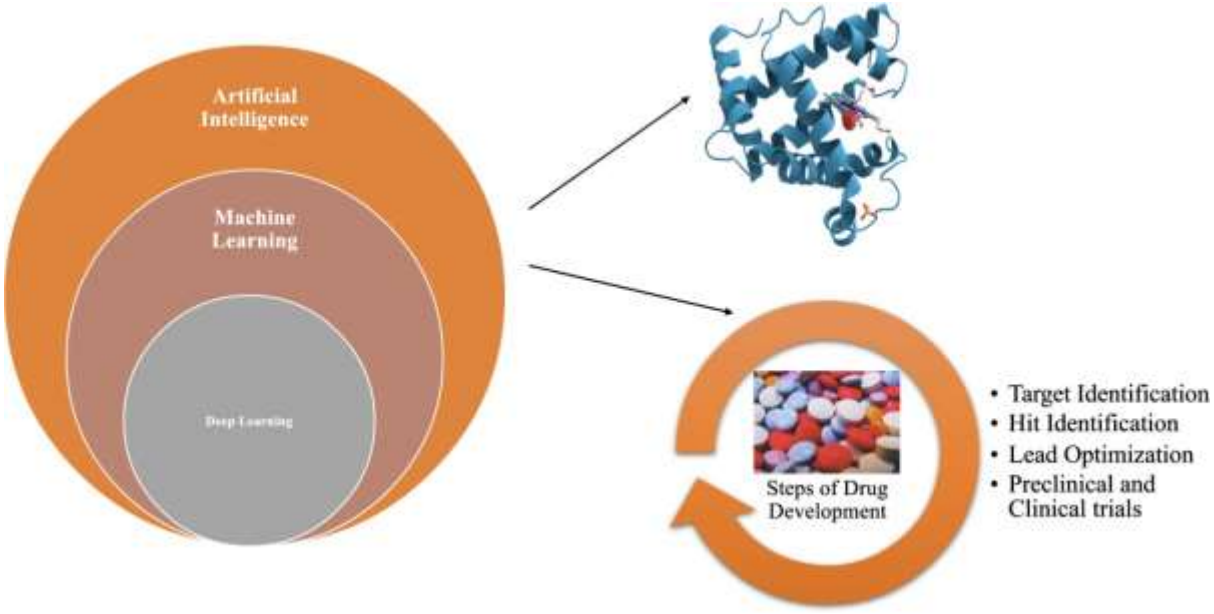

Figure 1: The application of AI, ML and DL in therapeutics development

One of the fundamental goals of mankind is to regulate periodic changes for our benefit. This is certainly relevant in the fields of medicine and pharmaceuticals, which are frequently undergoing change. The creation of new ideas or interpretations in general chemical and mechanical engineering has been driven by the drug and biopharmaceutical sectors, which have been a restricted source of imaginative and original technologies or machinery. Mechanical innovation is urgently needed in the pharmaceutical sector to facilitate the production of drugs for human use. The "one size fits all" philosophy underlies current prescription practices; nonetheless, numerous crucial fields of medicine demand fresh approaches, necessitating new pharmaceutical development procedures. As a result, Artificial Intelligence (AI) is being used more frequently, which will potentially alter the ways in which clinical evaluations and trainings are conducted as well. A modern concept known as "big data" describes expansive datasets that are insurmountable via traditional data analysis; the rapid deployment of AI-enabled technology on these large clinically derived datasets continues to provide useful information that can inform the course of drug development[1].

Traditional drug discovery is often an expensive, laborious, and often time-consuming pursuit in which there exists a large chasm between the identification of promising drug candidates and the employment of such novel drugs in the clinic[2]. As such, there has been an increasing interest in leveraging artificial intelligence (AI) and machine learning (ML)(as illustrated by Figure 1) to expedite drug discovery as well as drug development, in addition to reducing the associated financial costs. Drug discovery is loosely divided into 1) identification of disease of interest and the molecular drug target as well as its validation, 2) development of a high throughput invitro assay to screen for compound hits against the identified target and 3) optimization of potency and selectivity of hit compounds to enable in vivo testing[3]. Currently AI is most often used in the identification and validation of target proteins as well as in the development and optimization of hit molecules and drug candidates[4]. On the other hand, drug development is often divided into the preclinical stage and the clinical stage. In the preclinical stage in vivo testing in animals is conducted to assess toxicity, safety, stability (summarized as Structure-Activity Relationship (SAR) as well as, manufacturing optimization and clinical trial protocol drafting. In the clinical stage, the efficacy and safety of the novel drug is assessed in humans after the approval of the IND (investigational New Drug) application[3] as shown in Figure 2 and Figure 4.

The introduction of AI and ML into the pharmaceutical industry has resulted in the entrance of large non-pharmaceutical tech companies into the health sector such as IBM, Microsoft, and Google. Novartis has started to collaborate with Microsoft and has developed a new way to customize drugs. Nvidia has also established a similar partnership with Schrodinger in early 2021; the coalescence of expertise in the design of GPU software with expertise in drug development, shall yield biomolecular predictions that are of high accuracy and high performance. Historically, drug discovery as well as development has taken an average of 12-15 years and has cost billions of dollars. But, the integration of AI and Machine Learning, is a promising avenue that can greatly reduce the time and monetary demands of the drug development process. This emerging technology will not only help to develop more effective drugs but will also help to develop drugs with high specificity toward their target. Additionally, the expertise required in integrating AI and ML into the drug discovery and development pipeline will continue to require partnerships between pharmaceutical companies and data science-based technology companies. There is a growing interest in 100% in silico drug development according to leaders in the field such as the CEO and President of IKTOS, Yann

Gaston-Mathe in addition to, projections of increased market value of companies that conduct AI-integrated high throughput screening due to an increase in the efficacy of hits[1].

2. Drug Discovery

Figure 2: Broad stages of drug development prior to FDA approval

2.1. Target Identification and Validation

Proteins are critical molecules in the human body and are key in mediating the bioactivity of drugs and certain conformational changes can lead to dysfunction and then disease. The 3-D structure of a protein can provide insights about how a ligand, or a drug would engage it. There has also been a dearth in libraries of the 3-D structure of large molecules as they have been difficult to resolve through biological experimentation, but the structures of small molecules that could be optimized into drugs have been successfully predicted via ligand binding predicting programs such as Alphafold (that have revolutionized the target identification stage of drug discovery).

Through leveraging its deep learning neural network (a form of machine learning), Alphafold can predict the 3-D structure of protein/target, as well as the associated target binding affinity; the target is often the most significant causal factor for a disease of interest[5]. The AI computer system IBM Watson has also discovered RNA-binding proteins responsible for ALS(Amyotrophic Lateral Sclerosis), and has reported 4 prominent RNA-binding proteins worth targeting[6,7].There has also arisen a great potential for the further exploration of small molecule conjugated antibody therapeutics as a result of growing protein structure databases, due to their unique target binding affinity[8].

The elucidation of the structure of a target protein is essential in designing an effective drug and AI and ML has been increasingly used in the predication of protein conformational structure to identify druggable protein targets[9]. Recently, the frontrunner, protein structure predicting AI program and winner of 2020's CASP(Critical Assessment of Structure Prediction) competition has been Alphafold which also inspired offshoots such as RoseTTAFold[10]. DeepMind's Alphafold can leverage experimentally determined protein structures and amino acid sequences from the vast Protein

Data Bank(PDB) to glean evolutionary relationships between amino acids to predict the three dimensional structure of related proteins through its deep learning networks(a type of machine learning that emulates human neural networks); the predicted structures also receive a score which reflects the program's assessment of the accuracy of the structural output[11]. Nonetheless, Alphafold also has some significant blind spots such as its inability to account for protein folding pathways and doesn't account for the different conformational structures that arise upon changes in activation or even upon post-translational modification; this limits Alphafold to a tool best used in early drug discovery as a supplemental tool to experimental determination of protein structure[12].Target validation is a crucial step of drug discovery and as such AI and ML based in-silico validation requires training with high-quality and rich data sets[13]; this is key as ineffective, toxic and non-safe compounds need to be filtered out and must not be allowed to carry on in the development pipeline. The growing power of protein structure predicting AI programs is promising but cannot be completely depended on for target validation as of yet.

2.2. Hit Identification

Hit identification is the next step in drug discovery and in this process large swaths of molecules are exposed to the target to identify molecules that bind with greater affinity. Deep Docking is a QSAR model dependent, deep learning tool, that allows for the identification of the best hit compounds by thousands of times greater enrichment of compound without the loss of any effective binders[14]. Similarly, iterative screening also helps in extraction of the most promising compound from compound libraries and facilitates high-throughput screening. There are various machine learning methods being used for hit identification and screening such as RF (Random Forest), Support Vector Machines (SVM), Light Gradient Boosting Machine (LGBM), Deep Neural Network (DNN) and Graph Convolutional Neural Network[15,16].

2.3. Lead optimization

The demand for in silico technologies or AI applications in pharmaceutical development research has increased and will continue to do so, due to a need for accurate prediction of pharmacokinetics/ADMET (Absorption, Distribution, Metabolism and Toxicity, as shown in Figure 3) of hit compounds, as pharmacokinetics as well as toxicity need to be assessed to prevent the failure of candidate drug in a later stage of drug development. The pharmacokinetics of a molecule can be predicted and modeled in relation to the target protein's 3-D structure, through various methods like molecule docking, dynamics simulation, quantum mechanisms as well as PBPK (Quantitative-activity relationship and physiologically based pharmacokinetic) modeling[17]. Between 2005 and 2010, Astra Zeneca worked on small molecule drug discovery and found that most drugs failed in development due to their toxicity. Through machine learning they found that they could have predicted ADMET at an earlier stage and could have saved a lot of money and time as well. AI not only allows for the high throughput optimization of lead compounds but also makes it possible to assess target affinity that can be optimized via medicinal chemistry[18]. Lipinski "rule of five", which has been used to assess drug-likeness and the likelihood of oral bioavailability of drugs in development, has at times been a barrier for advancing drugs with drug-likeness properties but violate a Lipinski rule and AI can be applied to resolve their drug candidacy through machine learning at a lower time and financial cost[19,20].

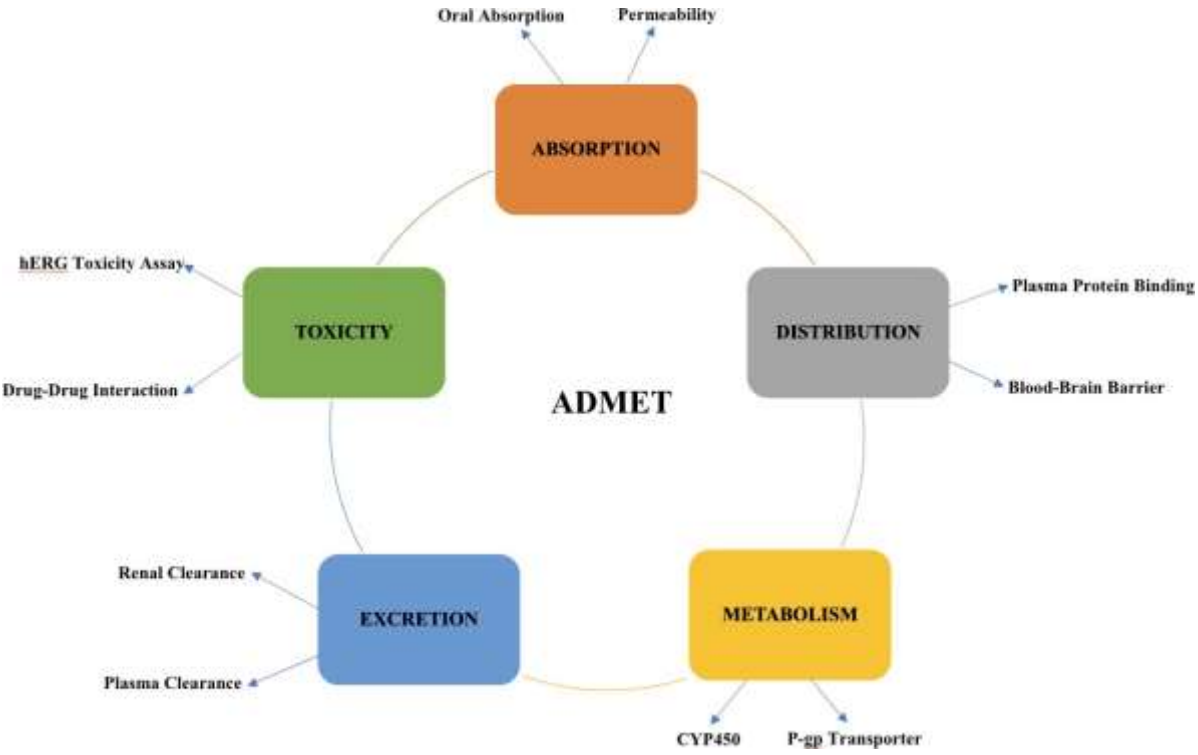

Figure 3: ADMET properties

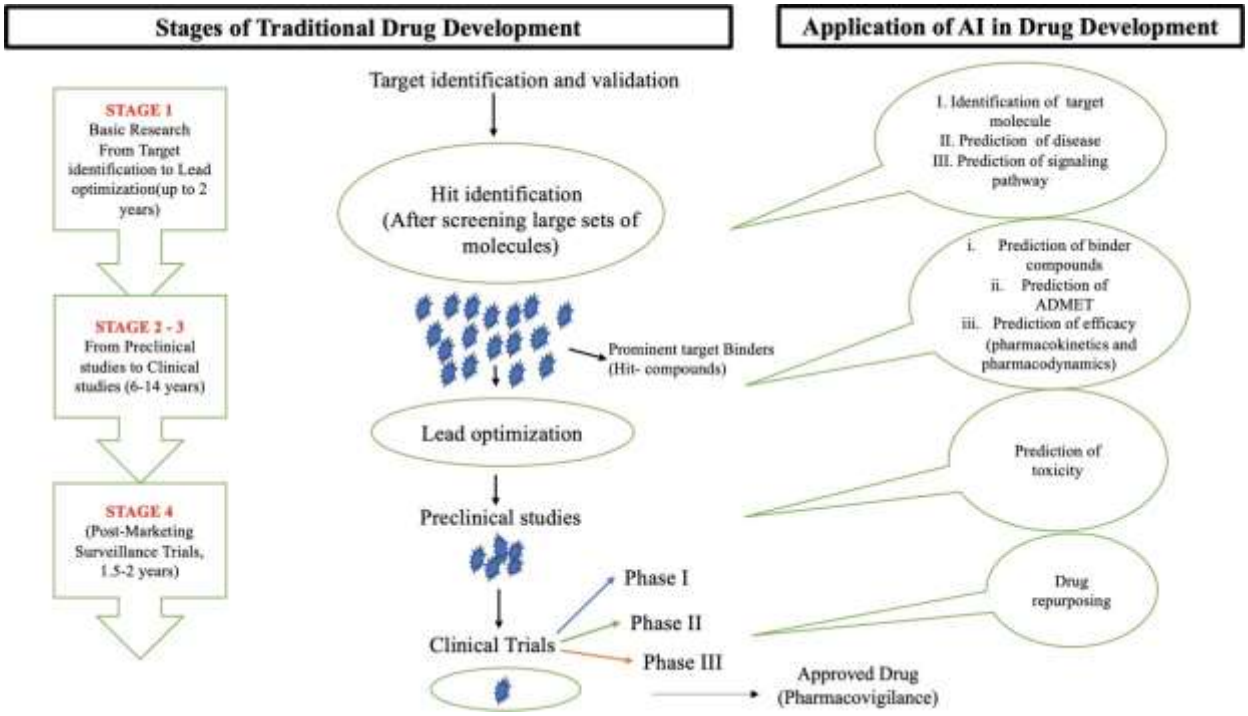

Figure 4: Application of AI and ML at different stages of drug development

3. How does AI and ML enhance traditional computational drug development?

The issues related to traditional computational drug development methods were those of computational limitations and of high time consumption. However, traditional computational drug development still played an essential role in drug discovery but has greatly benefited from the integration of AI as well as ML which have greatly reduced the time and financial demands as shown in Figure 4. Today, ML enabled tools are revolutionizing ligand-binding target protein identification based on 3-D structure with the prime example being DeepMind's AlphaFold, which as described earlier predicts 3-D protein structures through amino acids sequences. Such advancement in drug development will allow for speedy design of drugs with high binding affinities for their target proteins. There are several areas where traditional drug development has been improved by AI integration and has resulted in FDA approved drugs; the reduced processing time in molecular dynamics simulation by CNN-AI enabled, de novo drug simulating designing tool, MolAlCal and multiparametric QSAR are prime examples[21].

QSAR(Quantitative Structure-Activity Relationship) is a form of SAR in which statistical and computational modeling that is bolstered by AI and ML is employed to predict the biological and physical properties as well as the activity of novel drugs, in a cost and time efficient manner; this varies from traditional SAR which entails exhaustive and costly biological assays[15,22]. Any form of predictive computational modeling is only as good as its parameters and as such there are multiple types of QSAR methods that are classified based on the parameters they consider and can be utilized in varying circumstances depending on the parameter of interest[23]. QSAR is integral in drug discovery as it allows for the generation of a small pool of molecules of interest that may possess desirable properties that can be further investigated and ascertained in vivo, and this is especially useful when screening large compound libraries as it ameliorates the significant time and resource burden that plagues early traditional drug discovery[24]. Classical QSAR(which refers to the Hansch and Free-Wilson analysis methods) operates under the assumption that the chemical structure of compounds determines their bioactivity, and leverages an input of a library of molecules that includes their physical chemistry properties, known bioactivity, chemical structures as well as the known activity of the ligands of interest to conduct statistical relationship assessments that can be extrapolated to predict the bioactivity and physical chemistry properties of a novel compound without the need for organic syntheses[15,25,26]. QSAR methods have matured since their introduction in the 1960s by Corwin Hansch and have grown to include the 3D structure of molecules/ligands which allows for more accurate prediction of ligand-receptor interactions, as well as the determination of relationship between a ligand's structure and bioactivity; this method is known as 3D-QSAR and is the most widely used QSAR method today[27,28,29]. As idyllic as QSAR may sound, it isn't without its weaknesses and in no way could supplant traditional SAR[30].

3.1. AI and ML in Drug Toxicity Assessment

ML has been of great interest to drug developers and data scientists alike and there are various ML methods that are in use today such as LR, RF, and SVM, as previously mentioned[15,16,31]. However, all these methods suffer from a decrease in accuracy when it comes to molecular prediction of complex compounds and have resulted in a more complex form of ANN (Artificial Neural Network) known as Deep Learning (DL), which is multilayered by design. After the input layer (which takes in the data to be processed), the following layers of a DL network are trained by each preceding layers' results; as a result this network can process large amounts of data that it can use to conduct complex computational modeling and extrapolate to predict the structure of more complex molecules through the non-linearity function. Other examples of ANN are CNN(Convolutional Neural Networks) and SNN (Self-Normalizing Neural Networks)[31]as shown in Figure 5. Nowadays, the combination of Perturbation Theory with ML which results in PTML, is being used for modeling

toxicity of drugs in varying cellular environments as well as in varying experimental animal models. PTML modelling, can help drug developers to understand why a drug may have failed in in-vivo studies, but also could help to remodel the chemical structure of the drug to reduce toxicity during the preclinical trials; PTML modeling could also help to increase the small number of drugs that are screened and progress to Phase 1 trials. Most of the hits in early drug discovery are excluded during the hit to lead optimization, as well as pharmacokinetics and toxicity assessments, and PTML modeling could help to identity the best drug candidates sooner and more efficiently. Initially withdrawn hits can now be structurally modified via ML modeling, in which the changes in toxicity can be predicted as a result of structural modification, also providing insights such as organ specificity, carcinogenicity, genotoxicity, and LD_{50} quantification. Computational modeling also increases the chance that novel drugs that may be toxic to animal models do not proceed to animal studies making the drug development process one that is more humane. Furthermore, computational modeling such as PTML modeling allows for the development of drugs with higher efficacy and lower toxicity in a time efficient and resource efficient manner[31].

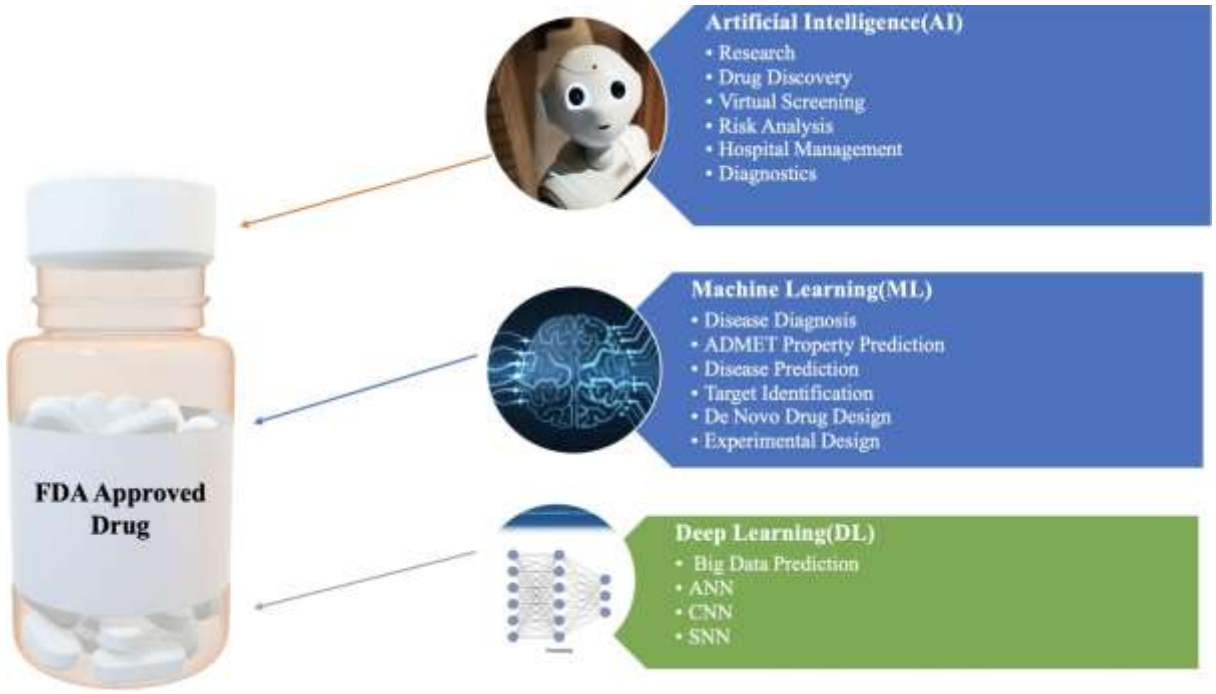

Figure 5: Application of AI and ML in the generation of FDA approved drugs

4. Impact of AI and ML in Resource Utilization

Recent years have witnessed cloud data centers (DCs) gaining significant prominence when it comes to performing data management and shared computing. The high utilization of shared resources has already exhibited several advantages, but it needs to be acknowledged that data often comes in an unstructured format, and this is where the application of machine learning algorithms steps in. Performing reliable resource provisioning which can operate across multiple platforms is not an easy accomplishment. Despite the presence of conflicting conjectures regarding the resource efficiency of machine learning, it is hard to ignore the impressive attributes of machine learning algorithms when it comes to performing prediction, classification, and forecasting[32]. As has been identified by Hussain et al., traditional resource management techniques have become outdated and now possess a wide range of limitations[33].With the continual growth in the implementation of IoT devices, a plethora of data is being generated on a regular basis; the application of proper machine learning techniques can harness the growing supply of information associated with IoT data to more effectively allocate resources and generate predictions[34].

According to Murali et al., several attempts have been made over the years to integrate automation in the task of resource allocation and it has been deduced that machine learning isone of the optimum solutions[35]. It has also been acknowledged that DNN (Distributed Neural Networks) are the future of automation and that it is the area which possesses the potential to perform computation on large databases effortlessly[36]. Additionally, it has also been observed that the resource utilization system of vehicular networks has grown dynamically with the advent of AI based resource allocation systems; the application of machine learning techniques has also resulted in improvements in vehicular resource allocation strategy over time[37]. The operations involving resource allocation have supplementally become much less volatile due to the presence of historical data and the rapid nature of machine learning algorithms, which simplifies the assortment of resources[38].

5. Impact of AI and ML in Drug Formulation

Big data within healthcare has introduced the usual aspects of volume, velocity, and veracity in maintenance and management of patient data[39]. Machine Learning tools generally harvest the accumulated data which are generally structured, thus neural networks or naive Bayesian approaches have been implemented within the field of data science to accumulate the most probable outcomes of queries that are posed to the dataset[40](as shown in Figure 4 and Figure 5).

Machine learning techniques have increasingly implicated in drug formulation in the pharmaceutical industry and can help

synthesize medical drugs according to Elbadawi et al.[41]. M3DISEEN is an example of such an application and has been a web-based pharmaceutical application that initiates the FDM 3D printing process for developed drugs through formulations stocks. The modern advent of ML data harvesting techniques also allows the use of machine learning techniques that can improve drug discovery probabilities for CNS-related diseases; this machine learning technique has also helped in the drug actuation process where designing and activity measurement can be performed as well[42]. The application of machine learning can also improve the acceptability of 3D-printed drugs further enhancing the quality control standards of traditionally manufactured drugs as well[43].

A new paradigm of genetic data collection has enabled early cancer risk detection within non- diseased individuals, and the detection of antigens from the cancerous individuals has helped researchers to develop combinatorial antibodies to fight against the disease onset as well[44]. Gut microbiomes provide a levy of genetic databases which can later be tallied according to the geographical variables with the help of machine learning techniques. Thus in-silico preparation of microbiome-specific drugs can help patients to recover from their ailments[45]. Specific gut microbiome combinations have been tallied using artificial intelligence and drugs are suggested accordingly. Finally, it can be said that the application opportunities for these machine learning techniques in the formulation of drugs have been immensely diverse, but these techniques along with fuzzy logic and genetic algorithms will continue to streamline both drug design and drug formulation and manufacturing[46].

6. Conclusion

Drug discovery and development continues to be a long and arduous road that begins with billions of compounds that are narrowed down based on their target engagement, binding affinities and ADMET/pharmacokinetic properties. The integration of AI and ML into the drug discovery allows for further investigation of withdrawn drug candidates may have either violated the Lipinski rule of 5(as shown in Figure 6) or failed toxicity screening and ML modeling makes it possible to modify compounds' structure to reduce their toxicity. Modified drug candidates can then be easily assessed for their efficacy and ADMET properties (as shown in Figure 3) through DL. Not only does AI enabled computational modeling allow for more efficient drug discovery and development but also could make preclinical studies in animal studies more humane by helping to withdraw toxic drug candidates.

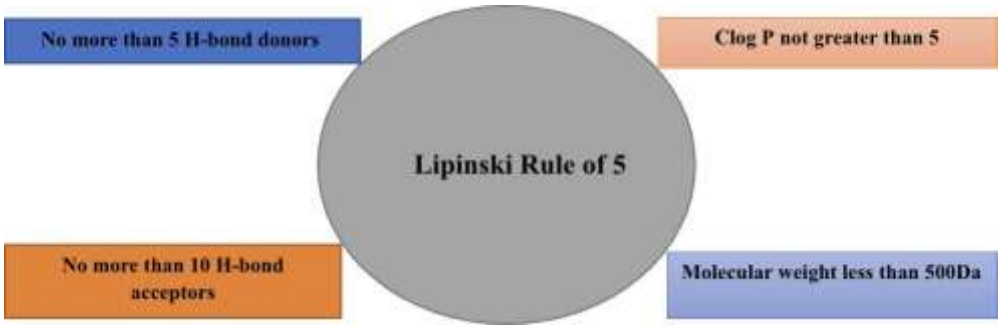

Figure 6: Lipinski rule of 5

QSAR modeling continues to evolve and develop but currently falls short of being able to supplant SAR entirely due to its declining accuracy with increasing compound complexity.

Nonetheless, QSAR methods have developed to move past receptor independent models into receptor-dependent QSAR(RD-QSAR) which uses the multiple 3D structures of the ligand- receptor conformations to allow for the prediction of the conformations of other ligand-receptor interactions (RD-4D-QSAR) allowing for more detailed predictions of how a drug of interest may interact with the target of interest; both receptor dependent and receptor independent QSAR has recently been reinvigorated and has been successfully applied in drug discovery due to the continuing growth in computational and graphical processing power[47,48]. There has also been an increased interest in the use of deep learning QSAR, which would suit the multi parametric nature of drug optimization, but it suffers from low robustness due to the massive computational power and large amounts of data that are necessary for accurate prediction generation; however the rise in the incorporation of uncertainty estimation into neural networks may provide correction factors to incorrect property predictions that are a symptom low data based prediction models[49]. Alphafold has also gained a new rival in the protein structure prediction space in the form of Meta AI's ESMFold which has characterized the structure of about 600 million proteins derived from microorganisms that have not been previously characterized[50]. Despite being faster at predicting protein structures than Alphafold in certain cases, ESMFold is not as accurate as Alphafold but distinguishes itself in its more structurally unique and rich metagenomic protein prediction database as well as having a prediction model that is better suited for more easily determining the structural impact of mutations.

The utilization of AI and ML in drug discovery and development (especially in the development of oncological and psychiatric drug) in FDA submissions has been on the rise since the 2010s and as such the FDA has had to explore how this nascent form of therapeutics development, administration and selection is to be regulated[51].The FDA released a discussion paper titled, "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning(AI/ML)-Based Software as a Medical Device(SaMD)-Discussion Paper and Request for Feedback", in 2019 which primarily aimed to ensure that users were made aware of self-learning and machine learning based modifications and developments and that risk- assessment of these modifications was administered throughout the FDA approval process and beyond[52]. The 2019 discussion paper addressed the use of AI and ML as a medical device which limits the regulation discussion to its use in the clinic (when it may be used in treatment and in aiding diagnostics) and there does not seem to be any existing regulatory advisement on the use of AI and ML in drug discovery and development[53]. Such regulatory advisements may not have been introduced by the FDA as

findings that direct the course of drug discovery and drug development as AI and ML are always validated by biochemical assays and invitro studies prior to progressing in the pipeline. However, the FDA has been promoting the use Real-World Data (RWD) since the mid 2010s, in an effort to encourage the collection and analysis of extensive clinical medical information from clinical study patients to better inform drug development and has resulted in the employment of AI for tracking the adverse effects of drugs in the clinic (also known as pharmacovigilance) as well as in investigating a drug's potential for repurposing[54,55].

Conflict of Interest-

All authors of this manuscript declare that this publication is void of any conflicts of interest.

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