IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

Artificial Intelligence In Drug Approval: Predicting Future From The Past

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Abstract: Artificial Intelligence (AI), has become prevalent in every sector. Healthcare industry is also advancing their techniques by using Artificial Intelligence (AI) algorithms. From designing a drug in laboratory to predicting the approval of a drug for its marketing, artificial intelligence is playing a significant role. Although, AI was considered as a science fiction stuff, a flood of innovations and inventions based on Artificial Intelligence (AI) were beyond the boundaries of possibilities in medicine. In current scenario, Artificial Intelligence is more than just a burgeoning technology. 'No one can predict the future' is not the reality in the current scenario. In the Healthcare sector, Artificial Intelligence is working as a myth buster by predicting the drug approval from past data in the supervision of the experts. In future, we can expect a complete reliance on this technology for the new drug approval with accuracy, precision and safety. In this extract, significance of artificial intelligence in drug approval prediction is taken into consideration. In addition, new insights on future implications of artificial intelligence in making life healthier are also discussed.

I.INTRODUCTION:

Artificial Intelligence (AI) is the demonstration of human intelligence simulation by programmed machines. It facilitates equipment and program to impersonate human behavior for self-improvisation and reasoning [1]. This development of computer systems can undertake the work that requires an attribute of a human under ordinary circumstances. AI is an amalgamation of Machine Learning (ML) techniques and Deep Learning.

Popularly Artificial Intelligence can be categorized [2]:

1. Based on Capabilities

- Wide/ General/ Strong Artificial Intelligence
- Narrow/ Weak Artificial Intelligence
- Artificial Superintelligence

- **Wide/ General/ Strong Artificial Intelligence**

A machine concept with strong intelligence imitating human in Wide or Strong AI can also be termed as 'smart AI' as it may surpass all capabilities of human intelligence. Wide AI can perform diversified tasks and even can find a solution to many problems on their own.

- **Narrow/ Weak Artificial Intelligence**

Narrow AI is 'weak AI' because it has restricted performance area for which they are designed specifically like, virtual assistants in your smartphones.

- **Artificial Super Intelligence**

Artificial Super Intelligence would be capable of transcending all human proficiencies inclusive of accurate and rational decision making when needed, making perfect art and also developing emotional relationships.

2. Based on Functionalities:

- **Reactive Machine:**

One of the most fundamental types of AI is this. It has no recollection of the past and is incapable of applying previous information to future actions. Garry Kasparov, for example, lost to an IBM chess algorithm in the 1990s.

- **Limited Memory:**

AI systems can use previous experiences to aid in future decision-making. It is how some of the decision-making systems of self-driving cars came to be. Observations are used to guide future activities, such as automobile changing lanes. These records aren't kept indefinitely, unlike Apple's chatbot Siri.

- **Theory of Mind:**

People's emotions, ideas, views, and expectations should all be understood and engaged by this form of AI. Despite tremendous developments in the sensor, this sort of AI is not yet ideal.

- **Self-awareness:**

Artificial intelligence is sentient, super-intelligent, self-aware, and has feelings (In simple words, complete human being). Of course, such a bot does not exist, and if one is developed, it will be a turning point in AI.

Machine Learning (ML) is a branch of Artificial Intelligence (AI) in which computers learn and mimic informational skills without human arbitration, which helps in the gradual improvement of accuracy [3].

For a very long time, AI used in multiple domains such as E-commerce, Navigation, Robotics, Human Resources, Healthcare, Smart Agriculture, Gaming, Automobiles, social media, Marketing, Finance, Banking, Space Explorations, for rescue missions, autonomous vehicles, tracking wildlife populations, chatbots, for wildlife poaching prevention, artificial creativity, and much more[4].

As stated above, since many years, Artificial Intelligence (AI) is being used in various fields for the advancement and betterment of distinct field outcomes. Technological enhancements have led to greater precision and accuracy[4].

Some AI algorithms are used widely in the healthcare sector, they are [5]:

Support Vector Machines- Used in prediction of medication adherence in heart patients avoiding serious consequences and for segregation of images, protein classification and categorization of text.

Artificial Neural Networks- This algorithm can learn just by analysis of examples without any human involvement. It is further classified into two parts:

- Recurrent neural network (RNN) and
- Convolutional neural network (CNN)

Logistic Regression- This algorithm predicts disease risk management assisting doctors in making medically critical decisions.

Random Forest- On the basis of medical history of patient, this algorithm is used for prediction of risk of disease and also for Electrocardiogram (ECG) and Magnetic Resonance Imaging (MRI) analysis.

Discriminant Analysis- Used for diagnosis of diabetic neuropathy, for the management of electronic health record systems and for the detection of signs related to disorientation of mental health.

Naïve Bayes- Most efficient of all machine learning algorithms used by healthcare industry for prediction of disease and clarification of medical data.

II.ARTIFICIAL INTELLIGENCE IN HEALTHCARE

In the healthcare sector, Artificial Intelligence (AI) perceives various applications. AI applications are used in healthcare to build intricated equipment that can help to detect diseases and identify cancer cells. Artificial Intelligence can also help examine chronic conditions with lab and other medical data to ensure early diagnosis [6]. For the discovery of new drug, Artificial Intelligence uses historical data and medical intelligence combinedly. Many surgeries are being undertaken with the help of robotics and Artificial Intelligence. Some robots work as motion stabilizer which improve precision and performance during surgeries. AI software can also be used in hospitals world-wide to help patients in moving efficiently from testing to treatment[7]. Some AIs works by combining with big data for the prediction of financial, clinical and operational risk.

Human-created data science algorithms underpin the majority of artificial intelligence technologies currently in use in healthcare. Multivariate data analytics is used in this type of AI and is backed up by prior experience. It may combine population-based treatment outcomes with individual patient clinical data and medical history, for example, to prescribe drug combinations and design therapeutic choices[3][4]. Machine learning is a branch of artificial intelligence that uses neural networks to mimic the capabilities of the human brain, but with the ability to make decisions much faster and more precisely[4][8]. Machine learning makes it possible for software programs to become accurate at predicting outcomes without need for explicit programming. Deep learning, the next level of AI is based on neural networks but includes multiple layers of calculations and integrated signals[4].When paired with pathology data and previous treatment outcomes, deep learning offers a lot of potential in diagnosis. A pathway signifying the uses of Artificial Intelligence in drug discovery and Drug Development is shown in Figure 1.

III.REASONS THAT PAVED THE WAY FOR ARTIFICIAL INTELLIGENCE (AI) IN DRUG APPROVAL

Non-clinical and Clinical trials are an essential part of a drug development and discovery process, and as well as for the approval of drug. They are also time-consuming lengthy procedure requiring a lot of capital investment. Despite investing so much resources, there is no guarantee of success. Due to the cost of clinical trial of a single drug, a company becomes unable to take multiple projects due to budget issues. Generally, a drug requires 10-15 years of research and resources to be spent on. Therefore, researchers opted for this technique in which prediction of drug approval can be carried out by AI and Machine Learning on the basis of past data from clinical trials[5][6].

IV. IMPORTANCE OF ARTIFICIAL INTELLIGENCE IN DRUG APPROVAL

Many experiments and hit and trials have been performed to test if it is possible for the AI and Machine learning to predict and forecast the approval for the upcoming drug in the market. One such trial was done by Novartis, a leading Pharmaceutical Company in the world, had organized an in-house data science and artificial intelligence (DSAI) challenge in collaboration with Massachusetts Institute of Technology (MIT) [5].

An imputation was made by extracting two datasets, P2APP and P3APP from Informa® databases and to make potential use of available data, 5NN statistical imputation was applied. For training and validation of RF predictive models and for the achievement of optimum levels of prediction power of two extracted datasets, machine learning techniques were used. When it was applied to the pipeline drugs, the drug candidates having higher scores were having more chances of advancements to higher phases of clinical trials. This indicated that 5NN-RF is capable of segregating between high and low potential drug candidates [6].

The analysis of time-series of the datasets exhibits generally trends that is most prevalent in performance rolling window of over 5 years from 2004 to 2014. It was found that, classifier performance was in absolute correlation with the proportions of all the cases included in the training sets. As there is increment in completeness, the classifier gains information in a better way and achieves significant Area Under Curves (AUCs). This signifies that the importance of quality of data holds a considerable importance in building more predictive algorithms for drug discovery and development [6].

For successful prediction, some feature importance computation in the models were done and found that sponsor track record, trial outcomes, prior approval for another indications, trial status, duration and trial accrual rate are of utmost importance and critical features for this prediction process. As the 5NN-RF are non-linear classifiers', there can't be any simple interpretation of contribution of every predictor in the forecast. The usefulness of some factors is clear: drug indication pairs achieving positive outcomes have greater chance of approval; drug candidate that are being sponsored by companies and have good track records also have a better chance of success and a repurposed drug may have higher chances of a second time approval for some other indications [6][7].

These concluded results are almost accurate and give rise to the possibility of development of more powerful prediction models for drug development with better and more accessible data.

About DSAI challenge

Researchers from Novartis and MIT collaborated on DSAI, an in-house challenge for developing machine learning models which can predict the approval outcomes based on clinical development. For this purpose, Informa®, a commercial data vendor, had provided one of the vast pharmaceutical core databases in the world. DSAI was the first collaborative cloud sourced competition that used pharmaceutical data for this purpose [8].

Setup of DSAI Challenge

This challenge was hosted on a cloud-based platform named Aridhia Digital Research Environment which is designed for synergetic data analytics using healthcare data. All the teams were assigned a separate work area for data access, resource computation for development of their models and ab AI crowd hosted git repository for source code management [8].

Teams were needed to predict the chances of regulatory approval of drug on the basis of the given data of phase 2 trial. This was an imitation of the real-world scenario where a company has to decide whether investment should be made in 3rd phase on the basis of data of 2nd phase of trial [7][8].

Result:

The best final model that was up to the mark was a conglomeration that consisted of two XGBoost Models and single Bayesian Logistic Regression (BLR) Model. Model that is highly known to be effective for tabular data is XGBoost [8].

V.COMPANIES THAT IMPLEMENTED/ADOPTED THIS TECHNIQUE AROUND THE GLOBE

Many industries have been using AI for their enhancement and advancement from a long time. There are some companies who have got some success in use of AI and Machine Learning. Some of the collaborations, chatbots, membership announcements were made for the use of Artificial Intelligence (AI) for different purposes. Collaborations that were made between the companies are described below and briefly stated in the table 1.

- Pfizer collaborated with IBM Watson and Chinese tech start-up XtalPi to fasten up the drug discovery process in immune-oncology and to diagnose patients with rare conditions
- Pfizer also collaborated with CytoReason (Machine Learning) for drug discovery and development and to work on cell centered model for immune response.
- Concerto Health AI and Pfizer's partnership was to use Artificial Intelligence and real-world data in oncology diagnosis and treatment.
- Roche's collaboration was with medical research learning start-ups such as Exscientia and Owkin.
- For the analysis of 500 clinical trial operations world-wide using Machine Learning in real time, Novartis collaborated with McKinsey's QuantumBlack.
- Novartis decoded cancer pathology images by creating a system for diagnosis of cancer with the help of Artificial Intelligence in collaboration with Tech start-up Path AI.
- Microsoft and Novartis combinedly declared an alliance under which they will hold data of how the drugs are developed, discovered and marketed.
- For the identification of the early prediction of patient responses to inflammatory disease treatment such as psoriasis and multiple sclerosis, Novartis collaborated with University of Oxford's Big Data Institute (BDI).
- Johnson and Johnson partnered with Benevolent AI for the selection of some considerable number of novel clinical stage drugs and their patent related portfolios.
- Auris Health acquired by Johnson & Johnson, is into the development of Robotic Technologies which is totally USFDA approved and helps in early diagnosis and treatment of lung cancer.
- Amgen's collaboration was with medical research learning start-up Owkin.
- Amgen has also invested in precision medicine start-up GNS Healthcare.
- Sanofi has partnered with Exscientia (AI driven company) for the identification and validation of combinations of drug targets for metabolic disorders like diabetes.
- GlaxoSmithKline (GSK) also joined hands with Exscientia for the creation of a highly potent in vivo active lead molecule, targeting a novel pathway for the treatment of chronic obstructive pulmonary disease (COPD).
- GlaxoSmithKline (GSK) made partnership with Insilico for the identification of novel biological targets and pathways.

- AbbVie partnered with Ai Cure to use AI-based patient monitoring platform improved adherence in an AbbVie phase 2 schizophrenia trial.

- Gilead's first publicly announced use of AI in drug discovery was in April 2019. This month, Gilead announced a strategic collaboration with stealthy start-up Insitro. The collaboration will focus on non-alcoholic steatohepatitis (NASH). Gilead will use Insitro's platform to create disease models for NASH and find targets that affect the disease's progression and regression.

- Some chatbots were developed for the assistance of human. Some of the examples are listed below:

  - Johnson & Johnson

  - Merck Sharp & Dohme (MSD) Corp., a subsidiary of Merck & Co., Inc has developed an Artificial Intelligence (AI) chat bot. The MSD Salute chat bot is designed to aid physicians in providing product information and pathology.

  - AbbVie is working with AI very silently. But it does have a confidential project listed with Atomwise.

- Some companies were announced as a member of machine Learning for Pharmaceutical Discovery and Synthesis Consortium by Massachusetts Institute of Technology (MIT) after their collaboration. The companies are:

  - Pfizer

  - Novartis

  - Amgen

- MELLODDY (Machine Learning Ledger Orchestration for Drug Discovery), the project which trains machine learning models on datasets had also announced some companies as their member.

  - Novartis

  - GlaxoSmithKline (GSK)

  - Amgen

- Apart from the above-mentioned information,

Hospitals in China, have implemented new Artificial Intelligence (AI) system which diagnose COVID-19 faster with 96% accuracy. New antibiotics were also yielded using Artificial Intelligence.

VI. CHALLENGES

With great inventions and discoveries, there also exists some unwanted challenges that needs to be tackled by creators of the algorithms that are used in the healthcare industries for any purpose, i.e., diagnosis, prognosis, treatment or regulation and approval of drugs in the pharmaceutical industries. Some of those challenges are listed below [9]:

- **Training healthcare professionals:**

Training healthcare professionals is of utmost importance when it comes to the implementation of any new technology in this sector. With least of the technical knowledge about the information technology, it becomes challenging to make them understand each and every detail about the virtues and shortcomings of the use of Artificial Intelligence (AI) specially for approval of new drugs.

- **Adoption of new technique:**

It is evident that 'adapting to a change' and 'adopting a change' has always been a time consuming and somewhat difficult process. When it comes to replace an old technique, professionals become reluctant in applying those changes in the drug approval procedure that they have been doing manually since a long time.

- **Scarcity of Required Data and Maintenance**

For proper functioning and use of AI, there is a need for the completely formatted and properly arranged data which our system lacks. Application of Artificial Intelligence (AI) might make everything comparatively easier than manual monotonous work but, its maintenance is also important and challenging.

- **Regulations**

It is essential to regulate technology and technique meant to deal with human life and welfare. Taking Artificial Intelligence (AI) into consideration in drug approval totally, there should be significant and stringent regulation. Currently, there are no provisions made by regulatory bodies for the authentication of Artificial Intelligence (AI) that will be used for approval of drugs for marketing purpose.

- **Security**

In this era of technology and advancements, as easy as securing things, it is also easy to breach the security by using the same technology. So, it is risky to rely fully on Artificial Intelligence (AI) with sensitive information as it can incur a loss to the organization in a way or many.

VII. FUTURE IMPLICATIONS

Witnessing such an unstoppable evolution of Artificial Intelligence (AI), it is evident that, it has been well established in healthcare sector. In future, the reliability can be increased in terms of drug approval by machine learning and it will also be used for making smart appliances and equipment that can get regulatory approval. Some new regulations can be put forth by regulatory agencies for the regulation of AI and machines that runs on this technology[10].

VIII.CONCLUSION

Developing a drug and its approval have always been an expensive process. It is important to evaluate a drug candidate, whether it is accurate for approval or not. We are discerning a remarkable transfiguration in healthcare industry. Emerging scope of Artificial Intelligence (AI) in the healthcare industry has given the competency to discover new methods of treatments and techniques much easier and faster anyone could have ever thought a long time ago. Previous failures and success rate provide an insight on the characteristics of suitable high potential drug candidates, which is invaluable. But those data are not completely sufficient due to mismanagement by discoverers and regulators/investigators. And for Artificial Intelligence data analysis used for drug approval prediction requires whole complete prior information. Despite, having so much of difficulties we've witnessed a noticeable improvement in the use of technology in healthcare and yet, there is so much left to get changed by the advancements.

Conflict of Interest

The authors declare no conflicts of interest.

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Table 1: Top-grossing Pharma Companies of the world using Artificial Intelligence (AI)

Sr. no.	Name of Company	Technologies used
1.	Pfizer	IBM Watson: a system that uses machine learning, to power its search for immuno-oncology drugs.
2.	Roche	Roche subsidiary Genentech is using an AI system from GNS Healthcare in Cambridge, Massachusetts, to help drive the multinational company's search for cancer treatments.
3.	Novartis	Novartis delineated a novel collaboration between Academia and Industry for in-house data science and Artificial Intelligence (AI) challenge held by the company itself.
4.	Johnson & Johnson	Some ways in which Johnson & Johnson is already using Artificial Intelligence since a long time are: • **Diagnosis and treatment of Alzheimer's Disease:** By combining two powerful tools from two innovative companies, i.e., Janssen Research & Development, LLC (Data) and WinterLight Labs (Technology) for monitoring the linguistic diversity of patients suspected to be suffering from dementia and other neurodegenerative disorders. • **Baby Intelligence:** Personalizing healthcare for individual babies by monitoring, analyzing and quantifying their unique habits and patterns like breathing and sleeping and by converting them into signals that can be used for predicting the status of their health. • **Robotizing Surgery:** Building a new platform to reach frontiers in robotic surgeries with the help of Verb Surgical, a collaboration between Verily Life Sciences LLC (formerly "Google Life Sciences") and Ethicon, a medical device company in the Johnson & Johnson family of companies.
5.	Merck & Co. MSD	Designed a chatbot to assist doctors with pathology and providing product information.
6.	Sanofi	Uses UK start-up Exscientia's artificial-intelligence (AI) platform to hunt for metabolic-disease therapies.
7.	AbbVie	Made partnership to use Artificial Intelligence based monitoring of patients suffering from schizophrenia.
8.	GlaxoSmithKline	Made partnership with Insilico for the identification of novel biological targets and pathways.
9.	Amgen	Invested in the Start-up of precision medicine called GNS Healthcare

10.	Gilead Sciences	Gilead Sciences collaborated with the start-up Insitro focusing on Non-alcoholic Steatohepatitis (NASH)

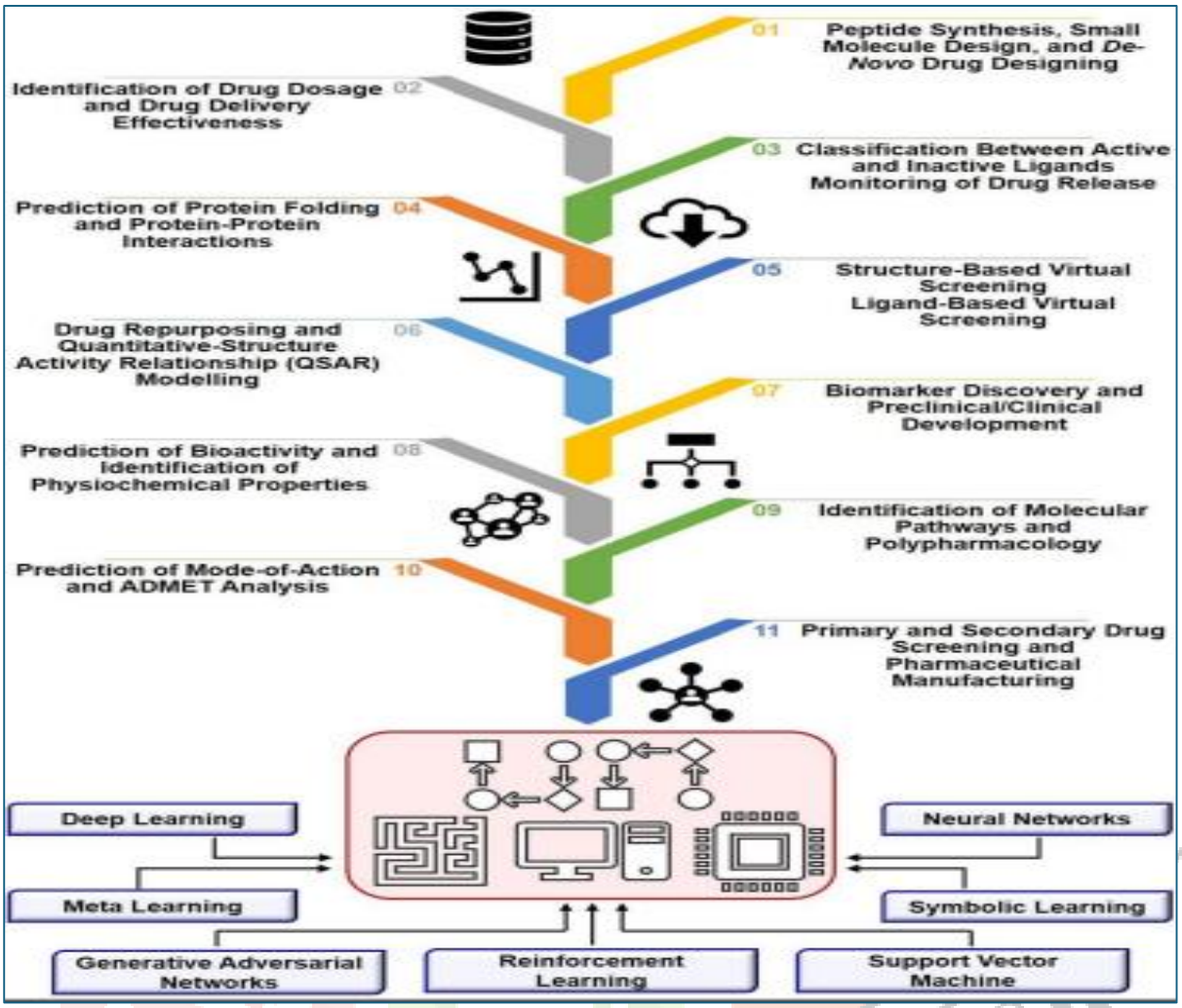

Figure 1: Artificial Intelligence in Drug Design and Discovery