**Artificial Intelligence in Healthcare and Pharma: Recent trends**

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**Abstract**

Artificial Intelligence (AI) is a branch of computer science, which analyzes complex data and helps in problem solving in different segments. Artificial Intelligence, Machine Learning and Big Data are being used at present by the major pharmaceutical industries to minimize time, cost and to increase possibilities. Artificial Intelligence has a wide range of applications in pharmaceutical industry like- drug discovery and development, clinical trial, disease diagnosis, different stages in pharmaceutical manufacturing, data analysis and supply management. Most of the cost and time are being involved in drug discovery and clinical trials. Artificial Intelligence can minimize human error in data process, documentation, data integrity issue and selection of data throughout the journey. It works in descriptive, diagnostic, predictive, prescriptive mode. Major pharmaceutical conglomerates like Pfizer, Roche, Novartis, Johnson & Johnson have already applied Artificial Intelligence in different segments of pharmaceutical and medicinal science. Tech companies like IBM Watson, Catalia Health, Intel, Microsoft, Google in collaboration with the pharmaceutical companies are working in the different fields of drug discovery, early diagnosis and personalized medicine. Further, AI finds application in health sector for data management, scanning and evaluation of medical history reports and finding out optimum treatment strategies for chronic care patients. Though lots of research and development are going on in the use of Artificial Intelligence in pharmaceutical industry, still it is in the nascent stage. This article is our endeavor to study in details, the present and future opportunities of Artificial Intelligence and machine learning in pharmaceutical industry as a whole.

Keywords: Artificial Intelligence; Pharmaceutical industry; Healthcare; Future prospects

1. **Introduction**

The replacement of human intelligence by machines, particularly computer systems, is known as Artificial Intelligence (AI). This is a method for modeling human intelligence to carry out specific activities with minimal human involvement. With major developments, it has become an area of problem-solving with wide applications in pharmaceutical engineering and healthcare [1].

In the 1940s, specifically 1942, when American science fiction author Isaac Asimov released his short novel Runaround, we find the earliest known instances of AI [2]. Around the same time, the English mathematician Alan Turing created The Bombe, a code-breaking device for the British government. The ‘Bombe’ was designed to crack the Enigma code used by the German army during World War II [3]. He introduced the idea of simulating intelligent behavior and critical thought with computers in his book "Computers and Intelligence" in 1950. He provided an easy method (Turing test) to determine whether computers are intelligent enough to compete with people or not [4]. In the year of 1956 Marvin Minsky and John McCarthy (computer scientist at Stanford) hosted the Dartmouth Summer Research Project on Artificial Intelligence (DSRPAI). These individuals, who would eventually be regarded as the founding fathers of AI, reunited during this workshop, which serves as the official start of the AI Spring [5]. The first AI system was created in the year before, or in 1955, and was named Logic Theorist by Allen Newell and Herbert A. Simon.

Entry of AI in the field of pharmaceutical science took place a bit later. Earlier models restricted broad acceptance and implementation in pharmacy. Many of these limitations had been eliminated in the early 2000s with advancements, research and studies. The use of AI in drug discovery and development has become necessary to improve research and decision-making in various pharmaceutical sectors like pharmacology, molecular and cell biology, pharmacokinetics, formulation development, etc. [6].

With the help of AI, pharmaceutical industry has highly increased its data digitization during last few years. Now it is widely used in development, drug design, drug screening, designing drug molecules, pharmaceutical product management etc. [7].

1. **Applications of AI in healthcare, Pharmaceuticals and Industry**

The following sections would discuss the important applications of AI in pharmaceutical science and the significant developments made in the last few years.

***2.1 AI in clinical patient management***

AI has been used in clinical management of patients in health care institutions with respect to administration of medicines, fixing treatment strategies, diagnosis of diseases or managing routes of administration.

During the last decade we have found applications in the following spheres:

1. ***Design and development of treatment plan***

AI has been helpful especially for critical patients. For this the previous history, medical reports and prescriptions may be evaluated to design the treatment plan. Example of such an AI based software is ‘IBM Watson’ designed for oncology patients which scans through thousands of patient reports supported by doctors from Memorial Sloan Kettering Cancer Center and helps to suggest an optimized treatment plan. The treatment plan is devised after scanning through about 15 million pages of references given by the center including 200 books and 300 medical journals [8].

1. ***Maintenance of medical records***

A health institution dealing with millions of patients every year face challenges to maintain and manage the medical records including the case history of patients, reports and prescriptions over extended period of time. However maintenance of such records is very important especially while devising effective treatment plans for critical patients. One of the AI based systems provided by Google called Google Deep Mind health project has helped to fulfill this challenging task by effective collection, maintenance and tracing of medical records whenever required [9].

1. ***Diagnostic analysis***

The diagnosis of diseases often requires various tests including X-ray, CT scan, ECG, etc. The analysis of such test reports is required for detection of diseases. An IBM software known as “Medical Sieve” helps in this purpose [10].

1. ***Support for medication for health management***

A ‘virtual nurse software’ has been designed known as “Molly” with a pleasant voice and face which helps the patients during their doctor visits for medication assistance. Further a mobile app called “Ai Cure” has been designed to guide and monitor the patients and help them to control their disease conditions especially for critical patients or patients taking part in clinical trials for whom close monitoring is necessary [11,12].

1. ***Healthcare system management***

In certain countries like Netherland, the invoices containing the details of the patients, the doctors and the hospitals are maintained in digital formats, such that the data retrieval is easy. A company called Zorgprisma Publiek conducts the evaluation of the invoices with the help of IBM Watson cloud technology such that any wrong data may be corrected with ease.

One of the database in 2016 known as “Open AI ecosystem” maintained the medical records of patients throughout their lifetime which generated huge amount of data required to study the patient habits and their lifestyles [13,14].

1. ***Pharmacy practice and community pharmacists***

In pharmacy practice, interaction between patient and the pharmacist is important. In this context, “Chatbots” can be applied for such purposes through which the queries of the patients can be automatically resolved and only the difficult questions may be transferred to the customer care. Even the video communication between the patient and physicians may be supported through AI technologies as developed by Walgreen and Medline. Medicine stock management may also be simplified with AI technologies through establishment of proper communication between the retail pharmacist and patients. Thus the pharmacist can remind the patients of the next purchase of drugs and based on patient feedback the pharmacists can update the stocks and thus avoid under stocking or over stocking of medicines at any point of time [15-17].

***2.2 AI based genomics for early detection and management of critical diseases***

Today’s lifestyle diseases are mainly based on modification of DNA structure and genomes. A proper understanding of such modifications may help the clinical practicians to diagnose a critical disease at the initial stages and thus manage it in a better way. A software in this field called “Deep Genomics” is based on evaluation of the links between genetic structure and medical histories of patients to identify and establish the links to various diseases. The clinicians can gain an in depth knowledge on the various cell events taking place on account of genetic mutations. Another such AI based software known as “Human Longevity” helps to detect at an early stage the location of cancers or vascular diseases and thus helps in better clinical management and cure [17-19].

* 1. ***AI in Pharmaceutical Industry***

Pharmaceutical industries mainly focus on quality of medicines. The specific quality of medicinal products became pertinent with Process Analytical Technology (PAT) and Quality by design (QbD) framework given by the Food and Drug Administrative (FDA). [20] PAT document provides assurance to the pharmaceutical manufacturing companies to attain the relationship between drug and excipient’s properties with different process parameters which directly relate to product quality [21]. QbD also recognizes critical material attributes (CMA), critical process parameters (CPPs) that remarkably impact on critical quality attributes (CQAs) of pharmaceutical products [20]. Besides less labour and time requirements along with quality product is a necessary attribute for modern pharmaceutical industry. Real time release testing (RTRT) provide access not only to process and product understanding but also help to be competent with real time attention and control of the manufacturing process which help to assure quality [22]. All together use of QbD, PAT and RTRT with advance data processing in companies lead to change from a conventional to smart pharmaceutical industry i.e. Pharma 4.0 [23]. Artificial intelligence (AI) and Machine learning (ML) are used as multiskilled tools to deal several tasks like data analysis and developing hybrid turn technology in pharma 4.0.

Pharma 4.0 or Industry 4.0 is a fourth upgradation in pharma industry with incorporation of advanced digital technology and policies like robotics, internet of things (IoT), AI, etc. to change the blueprint of manufacturing of pharma products [24]. This revolution came in different time era with implementation of digital strategies. Fig 1 shows the transformation of Industry 1.0 to a smart factory (25-28).

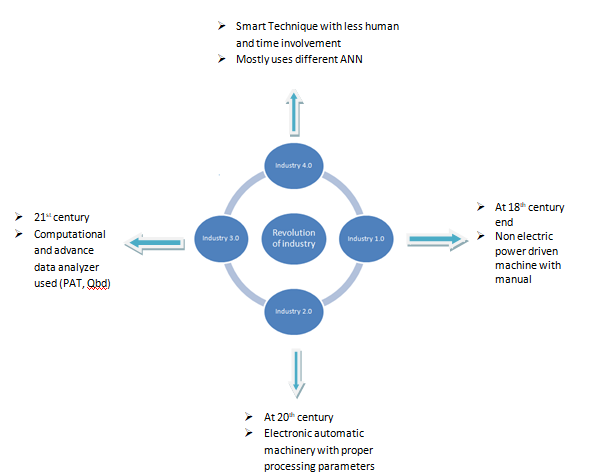


Fig. 1 Transformation of Industry 1.0 to 4.0

Artificial industry is a study design used by an intelligent agent computer which execute tasks like recognition of image, pattern, speech, language and makes a decision for maximum chances of success [29]. ML is a subclass of AI, allows system capability to learn and progress naturally by providing training without being explained programmed [30]. Artificial neural networks (ANN) is also a category of ML. It is developed by taking inspiration of data processing action of human brain on the basis of intelligence unit i.e. artificial nodes or neuron. First it collects inputs and then transforms into wished output by using approved function [31].

***2.3.1 Application of ANN in Pharmaceutical industry***

1. Binoy Debnath et.al. suggested a Bayesian best worst method (BWM) to study the critical success factors (CSFs) that allow adaptation of Industry 4.0 in pharma industry for increasing supply chain liability in a rising economy country like Bangladesh. Firstly through literature review complete CSFs data was collected and by using BWM methodology the data was analysed which further identified CSF comprehensively [32].
2. Yi Tao et.al. established a convolutional neural network calibration model, which is based on an intelligent Raman spectroscopy method to maintain the quality in manufacturing of guanxinning tablet, a herbal drug used in the treatment of coronary heart disease and angina pectoris. By using HPLC, DAD, the active constituent of guanxinning i.e. Danshesu, Rosmarinic acid, Ferulic acid and salviaanoic acid B were determined and by using oven drying method the soluble solid was determined. The Competitive adaptive reweighted sampling (CARS) algorithm method was used for sorting the characteristic spectral band while initiating the CNN calibration model. The effectivity of the model is characterised by Root mean square error of calibration (RMSEC), Root mean square error of cross validation (RMSECV), Root mean square error of prediction (RMSEP) and finally coefficient of calibration (RC2 ), Cross validation (RCV2) and validation (RP2)[33] .
3. Brigitta Nagy et.al. developed artificial neural network according to universal approximation theory for forecast of in vitro dissolution rate of extended release tablet from PAT data. The process parameters were tablet composition and punching force. From NR and Raman spectroscopy dissolution data was collected and a Root mean square error for prediction (RMSEP) was calculated. Finally dissolution profile data was compared through both ANN and partial least square (PLS) regression method and ANN showed better result i.e. up to 3% lower RMSEP without requirement of extra pre- processing step [34].
4. Allan Carter et.al. prepared a combination model of passive acoustic emission monitoring with deep learning analytics to monitor as well as detect the blockage over fluidized coating bed. In this Piezoelectric micro phone is used to capture sound during coating process, fixed in outer layer of fluidized bed vessel wall. Sound data monitoring can be done by Pyaudio analysis library in Python. After that different ANN has been trained to verify particular state of process. Further it is used to identify process trouble [35].
5. Bukut Aksu et.al. used INForm software and FormRules software to create knowledge and design space to improve better formulation of Ramipril tablet using direct compression technique [36].

***2.3.2 Application of ANN in Research and development***

1. Moghaddam et.al. prepared a multilayer feed forward neural network to determine the effect of different process parameters on esterfication of betulinic acid with phthalic anhydride. In this study design the different algorithms used to evolve predictive models were quick propagation, error back propagation, gradient descent and Levenberg Marquardt. Reaction time, temperature, molar ratio of enzyme and substrate were input process parameters and percentage yield of isolated ester was the output for the study. For validation of predicted value and for determination of value Quick propagation Algorithm (QP) was used [37].
2. Valizadeh et al. prepared ANN model to make optimal value in formation of glucosamine from chitin which is obtained from shrimp exoskeleton. The input factors for developed method were reaction time, acid concentration and acid solution to solid ratio. The method further compared with two other models i.e. Genetic Algorithm and Particle Swarm Optimization to perceive which one was best fitting for glucosamine production [38].
3. Franco VG et al. determined concentration of glucose and glucoronic acid in fermentation process with using 15 input database by FF-BP ANN type model. Data was collected by FTIR analysis [39].
4. Hasani M et al. developed Principal component- ANN to study oxidative phenol coupling by taking 16 samples analysed using UV visible spectrophotometer [40].
5. For API manufacturing, crystallization is an important step to produce solid powder in crystalline state which directly influences on final quality and yield of active constituents. To observe the purity of crystal, ATR-IR, UV spectrophotometer, Focused beam reflectance (FBRM) methods are used. Further by using ResNet technology classification of crystals can be done. On the other side, crystal size distribution and control of the crystallization process can be done by in-line image analysis [41,42].
   * 1. ***Application of AI in different steps of tablet manufacturing***
6. ***Powder blending***: It is first step in tablet manufacturing which results in a homogenous dispersion of substances. Machine learning is used to aid the active substance concentration and also determine the characteristics of powder in various layouts.

* PLS regression and NIR spectra with ANN are used to determine concentration of active ingredients since 2000 [43,44].
* Scientist Mujumdar et al. generated a FF-BP ANN model with using a training dataset to measure mean mixing concentration which is a tool to describe mixing process effectiveness [45].

1. ***Granulation:*** It is process of making a dust free granule from mixing of powder with or without binding agent. This process directly impacts on standard of final product i.e. hardness, content uniformity, disintegration and dissolution time [46-49]. ANN model was developed to determine the different parameters during granulation process through different apparatus such as Twin-screw wet granulation, roller compactor, high shar fluidised bed etc. [50]. ANN model can also help to identify different factors which affect the granulation process.

* Korteby et al. used ANN model combined with Garsan equation to predict effect of particle size, viscosity, content of binder to prepare granules [51].
* It has been seen that using a combination of ANN with other techniques related to processing the data like kniging of finite volume scheme which produce a hybrid model that show advantage of both methods [52,53].
* Rantanen et al. prepared ANN model with PLS regression technique to measure the moisture content presence in granules via taking data from NIR spectra [54].

1. ***Compression:*** During tablet punching process the first thing which is required to observe that sufficient granule should go into the die cavity. For this ANN with FAT technology is used.

* Kachrimans et al. created FF-BP ANN to anticipate flow rate of powder mixture through hopper orifice. In this, the input process parameters were evaluated for the powder such as bulk, true and tapped density, carr’s index particle diameter, etc [55].
* Zawbaa et al. referred an ANN with various algorithms to ensure the influences of different manufacturing parameters on tablets and porosity [56].
* ANN can also be used to determine the various defects of tablet coating like capping. Belic et al. prepared a neutral networks to forecast the tendency of *capping during tablet punching [57].*

***2.4 AI in drug discovery***

***New drug design***: The development of a new drug is challenging. In order to find out the lead compound amongst thousands of similar compounds and then performing the clinical trials involve lots of time and monetary investment. Application of AI can simplify the task. Such a software known as “Atomwise” was developed which scanned through several molecular structures to identify the drugs with a particular activity and was helpful for management of Ebola virus. A Boston based biopharmaceutical company also evaluated biological data and various environmental conditions to determine the factors which help certain individuals to remain unaffected by diseases [58].

**3. Challenges for AI application**

According to Professor Stephen Hawking, human creation of machine that can think would be great threat to human race itself. Future extinction of the human race may be ended for creating a fully functional AI. Nowadays, lot of research on AI is being conducted. Also a huge amount of money is invested into such AI model which is way more efficient than human being. Thus, the question lies whether implementation of AI would be ultimately beneficial for the human race?

***Retrospective versus prospective studies***

While subsist studies have surrounded very large numbers of patients with wide benchmarking against expert performance, the vast majority of studies have been retrospective, meaning that in this case the historically labeled data was used to train and test algorithms. Only through prospective studies will we begin to understand the true utility of AI systems, as performance is likely to be worse when encountering real-world data that differ from that encountered in algorithm training. The limited number of prospective studies to date includes diabetic retinopathy grading [59-61], detection of breast cancer metastases in sentinel lymph node biopsies [62,63], wrist fracture detection, colonic polyp detection, and detection of congenital cataracts. Consumer technology is enabling enormous prospective studies, in relation to historical standards, through the use of wearables [64].

***Challenges related to dataset shift***

Particularly important for EHR algorithms, it is easy to ignore the fact that within a non-stationary environment all input data are generated with shifting patient populations, where clinical and operational practices evolve over time [65]. When a new predictive algorithm is introduced, it may cause changes in practice, resulting in a new distribution compared to that used to train the algorithm. Therefore, methods to identify drift and update models in response to deteriorating performance are critical.

***Algorithmic bias***

Entangled with the issue of generalisable is that of discriminatory bias. Unexplored realm in machine learning can reflect the worst societal biases, with a risk of unintended or unknown accuracies in minority subgroups, and there is fear over the potential for amplifying biases present in the historical data [66]. Studies indicate that, in some current contexts, the downsides of AI systems disproportionately affect groups that are already disadvantaged by factors such as race, gender and socioeconomic background [67].

***Susceptibility to adversarial attack or manipulation***

Some times the risk of adversarial attack has been shown in algorithms. Although somewhat theoretical at present, an adversarial attack describes an otherwise effective model that is susceptible to manipulation by inputs explicitly designed to fool them. For example, in one study, images of benign moles were misdiagnosed as malignant by adding adversarial noise or even just rotation [68].

***Logistical difficulties in implementing AI systems***

The current challenges in translating AI algorithms to clinical practice are related to the fact that most healthcare data are not readily available for machine learning. Data are often kept in a multitude of medical imaging archival systems, pathology systems, EHRs, electronic prescribing tools and insurance databases, which are very difficult to bring together. Adoption of unified data formats, such as Fast Healthcare Interoperability Resources [69]; offer the potential for better aggregation of data, although improved interoperability does not necessarily fix the problem of inconsistent semantic coding in EHR data [70].

***Human barriers to AI adoption in healthcare***

In spite of highly effective algorithm that overcomes all of the above challenges; human barriers to adoption are substantial. In order to ensure that this technology can reach and benefit patients, to maintain a focus on clinical applicability and patient outcomes will important, advance methods for algorithmic interpretability, and achieve a better understanding of human–computer interactions.

1. **Conclusion**

Lots of research and development are being carried out in Artificial Intelligence (AI) in the field of Pharmaceutical industries as a whole, though it is in the nascent stage. AI ensures fast and accurate flow of data in different stages of pharmaceutical industries like Drug Discovery, Clinical trial, Manufacturing, Data analysis and supply management. Full potential and implementation of AI are still awaiting. Due to involvement of huge cost, at present, major pharmaceutical conglomerates only can implement AI. Limitation of data is also a constraint in the implementation of AI in Pharmaceutical Industry. It is assumed that, AI will take the industry to a next level in coming days, hence proper knowledge of technology and AI will play a vital role in the coming days. Pharma personnel need to have the AI knowledge also along with pharmaceutical subject understanding. With implementation of AI, pharmaceutical industry may see the next step revolution in days to come.

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