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Original Research Article

Role of Artificial Intelligence, Big Tech and Machine Learning in Accelerating Biologics Development and Clinical Trials

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Abstract

Modern healthcare is being revolutionized and strengthened by artificial intelligence-based technologies that can grasp, learn, and act, whether they are used to identify novel correlations between genetic codes or to guide surgical robots. Vaccines, blood and blood components, allergic somatic cells, gene therapy, tissues, and recombinant therapeutic proteins are only a few examples of biological products, according to the US FDA. Most biologics are complicated mixes that are difficult to identify or classify, in contrast to the majority of medications, which are chemically manufactured and have a known structure. Biotechnological products, including those produced by them, have a propensity to be heat sensitive and microbial contaminated. Because of this, and in contrast to the majority of conventional pharmaceuticals, it is vital to adopt aseptic principles from the first manufacturing processes. A biologic drug (biologic) is a product that is produced from, or contains components of living organisms. Biotechnology has given rise to these organic derivatives which are sourced from humans, animals or microorganisms. As internal modifiers, biologic drugs either enhanced or inhibit biological processes that are part of the key mechanisms of action for critical pathways in healing. The study specifically focuses on the three newest applications of AI-ML in healthcare: AI-ML driven discovery and process development, clinical trials, and patient care. According to the research, companies have highly benefited from the use of AI-ML in health industries i.e. in Pharmaceuticals, Biotechnology, Clinical Trials and Digital Health by automating target identification and thus accelerating the drug discovery lifecycle. We finally anticipate potential recent interventions of AI-ML in several steps of the biological landscape, focusing on clinical trials and clinical research aspects. In this context, artificial intelligence (AI), and especially machine learning (ML), have great potential to accelerate and improve the optimization of protein properties, increasing their activity and safety as well as reducing their development time and manufacturing along with clinical trial costs.

Keywords: Artificial Intelligence, Machine Learning, Big Tech, Clinical Trial, Biologics.

Introduction

John McCarthy, a computer and cognitive scientist, introduced the phrase artificial intelligence (AI) in 1955 to describe the synthesis of science and engineering to simulate human intelligence, including learning, reasoning, and perception [1]. One of the most important technological advances of the twenty-first century has

been the application of AI to the drug development process. Given AI's capacity for accurate data collection and effective data management, it is well-positioned to play a significant role in pharmaceutical research [2]. The pharmaceutical industry finds AI techniques appealing because they offer the ideal fusion of cutting-edge developments in computational technology and earlier restrictions on the collection of large volumes of data [3]. AI can improve and take the current pharmaceutical procedures to new heights because it has the innate ability to predict the result accurately and can process massive data [4, 5]. By 2024, the market for AI systems for the entire healthcare sector will grow from $1.5B to $4.3B. Healthcare payers and providers will be the ones driving this, with an estimated $2.9B in spending by 2024 [6].

The healthcare sector's digital transformation has been accelerated in a way that has never happened earlier due to the ongoing COVID-19 pandemic. Healthcare providers, pharmaceutical corporations, and manufacturers of medical gadgets have had to quickly adapt to the pandemics' many challenges and requirements. For instance, AI has successfully repurposed already approved drugs to target the virus in response to the urgent need for anti-COVID-19 therapies. The use of AI tools hence will become more important and as a result, more pharmaceutical companies are likely to include AI in their future product pipeline [6, 7].

Building models for machine learning entails giving them the ability to learn from data without being explicitly told what to do [6]. ML can be largely separated into two groups. First business intelligence (BI) and data analysis tools that are frequently used with machine learning (ML) to improve data-driven decision-making. The second uses ML to create models and integrate AI into more extensive applications [7]. In order to encourage adoption, this involves offering machine learning as a service (MLaaS) and utilizing developer tools like application programming interfaces (APIs). The creation of ML models depends greatly on data. To conclude, ML models are helpful for gathering data, analyzing it, and making predictions [8].

Over the past ten years, there has been a sharp rise in interest in machine learning (ML) for healthcare [9]. Although ML has been a field of study since the middle of the 20th century, the use of ML in healthcare has increased thanks to better computing capabilities, data availability, cutting-edge techniques, and a wider range of technical expertise [10]. While applications of ML that support clinical research are less typically covered in the academic and lay press, they have received a lot of attention in the media [11].

Clinical research on the other hand is a wide-ranging field, with the preclinical investigation and observational analyses leading to traditional trials and trials with pragmatic elements, which in turn spur clinical registries and further implementation work. While indispensable to improving healthcare and outcomes, clinical research as currently conducted is complex, labor intensive, expensive, and may be prone to unexpected errors and biases that can, at times, threaten its successful application, implementation, and acceptance [8-10].

Machine learning has the potential to help improve the success, generalizability, patient-centeredness, and efficiency of clinical trials. Various ML approaches are available for managing large and heterogeneous sources of data, identifying intricate and occult patterns, and predicting complex outcomes. As a result, ML has value to add across the spectrum of clinical trials, from preclinical drug discovery to pre-trial planning through study execution to data management and analysis [6-11].

The foregoing description applies to conventional small-molecule pharmaceuticals, which still account for nearly 90% of all medications available today. These medications are created through chemical reactions from relatively simple chemical entities. Researchers have been concentrating more on genomics and large-molecule biologic products like biosimilars, biotechnological products, vaccine etc. in the recent years [12]. The field of healthcare science known as clinical research evaluates the efficacy and safety of treatments, equipment, diagnostic tools, and drugs designed for human use [13]. These can be used for illness prevention, treatment, diagnosis, or symptom relief. Clinical research is useful in studying people, their data, or tissue samples from them to better understand health and disease in order to identify, diagnose, treat, and prevent disease. [14]. Clinical trials are prospective biomedical or behavioral research studies involving human subjects that are intended to provide answers to particular questions about biomedical or behavioral interventions, including novel therapies and established interventions that call for more research and analysis of a specific kind of research study that evaluates how effectively new medical techniques perform in patients.

Enzymes, hormones, peptides, cytokines, fusion proteins, monoclonal antibodies (mAbs), and next-generation antibody formats including antibody-drug conjugates (ADCs), specific antibodies, single-chain variable fragments (scFvs), vaccine components, and gene therapy vectors are all examples of biologics. Eight of the top ten best-selling medications in 2021-22 after COVID-19 exposure were biologics, making biologics a significant category of therapies [15, 16].

Over the next five years, new small compounds are expected to be dramatically outsold by biologics in terms of sales; by 2027, biologics are expected to outsell small molecules by $120 billion. This highlights the ongoing trend of biologics' dominance and rises within the pharmaceutical sector. Biologics have a number of advantages over small compounds, including high specificity and affinity, longer pharmacokinetic half-lives, and decreased toxicity and adverse effects [17]. The range of protein sequences and solution conditions that must be screened is substantially larger than that of small compounds.

There are approximately 20k different protein sequences that might be developed, where k is the amount of amino acids that need to be modified. There are thousands (or possibly more) of buffer compositions that could be created for each protein sequence. Furthermore, complex molecules like proteins must have the right chemical and physical characteristics.

Artificial intelligence has the capacity to efficiently move through this space while concurrently optimizing many aspects. A branch of artificial intelligence called machine learning (ML) studies systems that can learn from examples or samples that are frequently multidimensional and contain intricate patterns, noise, and redundancy. Modern computer hardware (such as faster CPUs and graphics processing units, or GPUs), cloud computing, and new software algorithms, along with the exponentially expanding availability of data [18], have made it possible to apply traditional ML and advanced ML algorithms (such as deep learning, or DL), to a variety of fields.

Image, speech, and text data are often the focus of machine learning (ML) applications in the fields of computer vision and robotics. ML and particularly DL were easily applied to medical pictures, signal data (audio), and electronic health records (text) for diagnosis as a result of ML's success in these fields. As a result of the development of various high-throughput tests, machine learning (ML) is currently extending to other fields of biomedicine, such as molecular target prediction, functional genomic element prediction, and

the discovery of (small-molecule) drugs to cure diseases [16–18]. In this review, we concentrate on the application of AI-ML in clinical trials with a specific focus on its potential in the design and development of biologics.

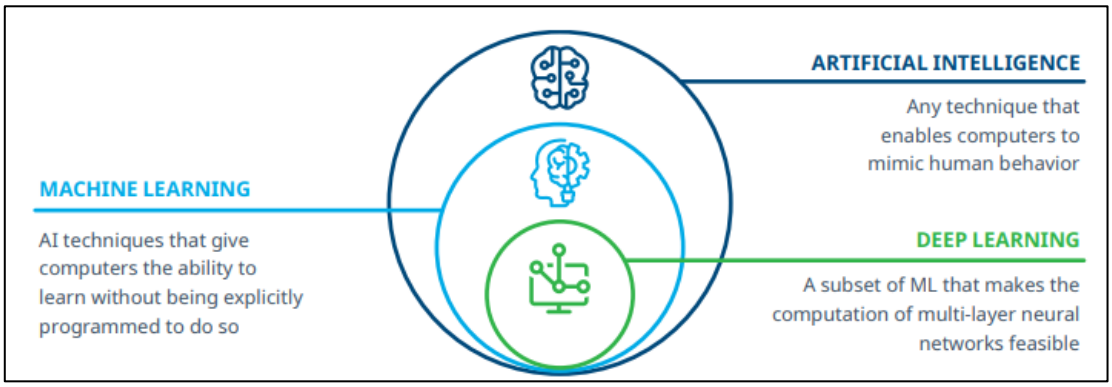

Figure 1: Overview of AI-based ecosystem

Artificial Intelligence and Machine Learning in medicine and healthcare

AI is proving its worth at every point of the value chain, from discovering a new biological target to developing a drug for Wilson's disease within 18 months for the first-ever AI-designed drug for lung fibrosis entering clinical trials. Several AI start-ups have exploded in recent years, offering a wide range of solutions to address related queries [19–22].

Clinical trials take around 6-7 years to complete and include a substantial financial outlay to determine the safety and effectiveness of a medicinal product in people for a specific illness. Only one out of every ten compounds that undergo these trials, however, receives successful clearance, which represents a significant loss for the industry [19]. These failures may be the result of poor infrastructure, poor technical requirements, or poor patient selection. With the use of AI, these problems can be minimized thanks to the abundance of digital medical data that is already available [20]. AI-Cure developed mobile software that tracked regular medication intake by schizophrenia patients in a Phase II trial, increasing patient adherence by 25% and guaranteeing clinical trial success [22].

There are three main points regarding the development of next-generation drugs through the use of digital evidence produced by AI and ML: (1) validating and modernizing the clinical trial process; (2) approaches for judicious application of AI and ML-driven learning from real-world data and evidence; and (3) the necessity of regulatory oversight for the integration, explanation, and de-risking of AI/ML digital analytics in patient care. To clarify key words, a glossary is offered as supplemental material [23].

Several AI/ML-based SaMD have received FDA clearance or approval to date. These typically contained algorithms that are locked before marketing. For instance, the FDA has approved the ML-based software solution developed by diagnostics business IDx for the autonomous identification of diabetic retinopathy. Additionally, Viz.ai's software, which scans Computed Tomography images for signs linked with stroke using an ML technique, has received regulatory certification. The list also featured software for automatic atrial fibrillation diagnosis and coronary calcification ratings.

In its regulatory framework, the FDA is also taking into account the capability of AI/ML-based SaMD for continuously learning and adaptable algorithms that have

the potential to adapt and optimize device performance in real-time for patient healthcare. In a broader sense, FDA uses SaMD information's importance to health care decisions like treatment or diagnosis-driven clinical management as a major criterion for regulatory initiatives [24].

Since 2015, Apple has been constructing an ecosystem for clinical studies around the iPhone and Apple Watch, both of which support the collection of real-time health data. Its open-source frameworks Research-Kit and Care-Kit aid in patient recruitment for clinical trials and remote health monitoring. Google has, however, increased its activity recently. Through its Android app for clinical research, Google Health Studies is creating an ecosystem for clinical research, and its life sciences division, Verily Life Sciences, is also creating healthcare products. Google recently introduced its Healthcare Interoperability Readiness Program to assist healthcare organizations understand the current status of their data and create a path to standardize and integrate across systems [25].

Artificial Intelligence and Machine Learning in biologics

From sample instances that are referred to as training data, ML models can learn the relationships between inputs and output (supervised learning) or the patterns that are present in a particular input (unsupervised learning). Common inputs (e.g. QSAR models) in biologics discovery are represented by the protein sequence, structure, or environmental factors (such as the formulation composition). Typically, the output is a functional product characteristic, such as activity, stability, or a particular physicochemical characteristic.

Figure 2A shows how many applications of ML models can be used. The properties of new input are predicted using models known as discriminative or predictive [route I in Figure 2A]. In the second category of uses, known as inverse design, models are used to develop new, superior biological molecules or experiments in addition to making predictions about attributes. For instance, to produce the most suitable inputs to match desired attributes, predictive models can be combined with optimization algorithms [route (ii)]. Additionally, generative models, a recent development in deep learning models, attempt to produce fresh inputs from the known regions of the input-property space that can be utilized for inverse design, opening up previously untapped areas of the input space [route (iii)].

The first step in applying these models is to generate the training instances that determine the boundaries of the inverse design model [26] (Figure 2B). Information can be found by conducting a preliminary set of experiments or by consulting public databases that compile results from past experiments. These tests could be run at random or under the direction of a design of experiments (DOE) method that maximizes the design space coverage for a specified experimental capacity [26].

With fixed training data, the model is developed during passive learning. In contrast, active learning (Figure 2B) involves the iterative development of new experiments using updated training datasets and models to enable the efficient learning of input-output correlations across the whole design space. Active learning techniques offer the capacity to learn the pertinent input-output information more economically than traditional DOE.

The next steps involve selecting and training an appropriate type of ML algorithm after a training dataset is generated (Figure 2B). The application, type, and quantity of the data that are readily available all play a major role in this decision. While DL approaches require vast quantities of data, algorithms like support vector machines (SVMs) and random forests (RFs) have done well across a variety of application fields with small and intermediate datasets. Additionally,

traditional ML calls for the feature engineering process, which entails extracting input features from unstructured raw data such as text (protein sequence), graphs (molecular graphs of entities or complexes), and photos. By employing various architectures that may transform unstructured data into a compact representation by gradually extracting higher-level features from raw data, DL models, in contrast, do away with the necessity for feature engineering [26].

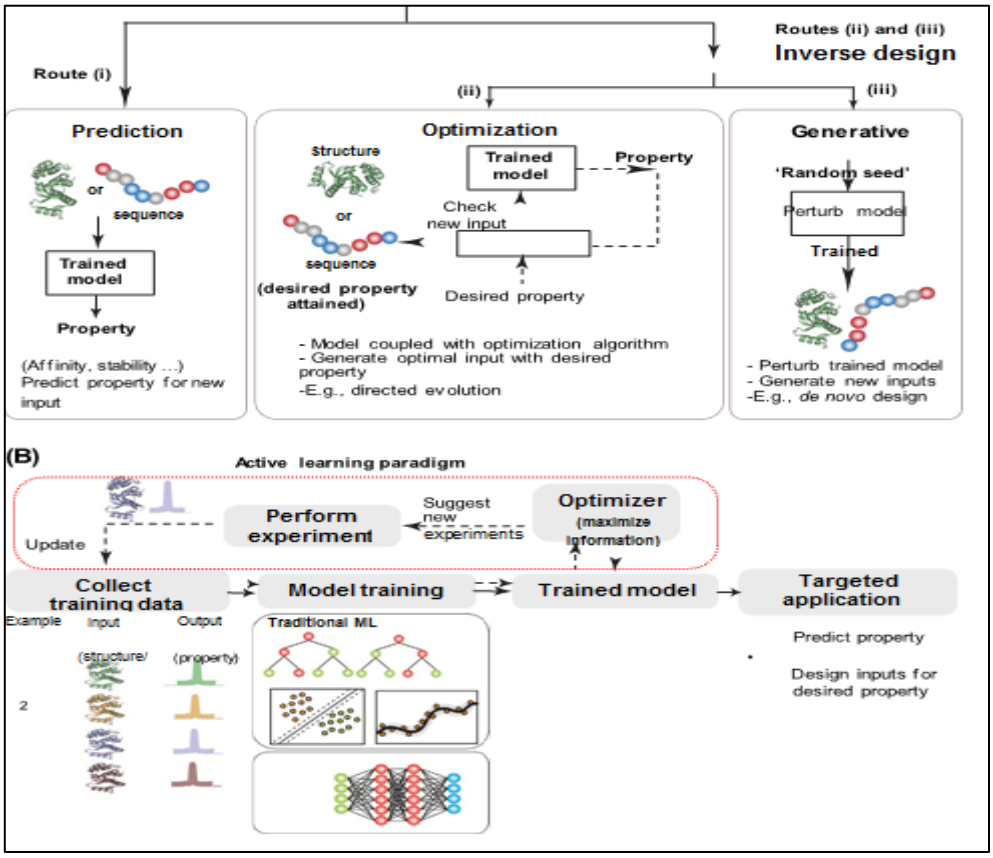

Figure 2: Machine Learning Work Flow in steps of biologics design and development process

The following are some ways that AI and ML are effective in biologic clinical trials:

Clinical trials could be conducted faster, safely, and much less expensively thanks to AI technologies. The ability of AI to enhance the patient experience will also contribute to biopharma's goal of more fully integrating patient-centricity throughout the whole R&D process. Therefore, the implementation of AI technology is turning into a crucial business requirement, particularly in the following six domains [27].

Clinical trial design: Pharmaceutical companies are using a variety of innovative trial design techniques. Trial design has been energized by the growing body of scientific and research data, including information from on-going and completed clinical trials, patient support initiatives, and post-market surveillance. AI-enabled tools can collect, organize, and analyse the growing quantity of data produced by clinical trials, including unsuccessful ones, and can uncover useful patterns of data to aid in design [28].

Patient enrichment, recruitment, and enrolment: Through mining, analysis, and interpretation of numerous data sources, such as electronic health records (EHRs), medical imaging, and "omics" data, AI-

enabled digital transformation can improve patient selection and increase clinical trial effectiveness. With the help of AI technology, the FDA has identified three ways that the biopharmaceutical industry can use to enhance patient selection and maximize a drug's efficacy. These three ways are as follows (1) validating and modernizing the clinical trial process; (2) approaches for judicious application of AI and ML-driven learning from real-world data and evidence; and (3) the necessity of regulatory oversight for the integration, explanation, and de-risking of AI/ML digital analytics in patient care. [29].

Site and investigator selection: Choosing highly effective investigator sites is one of the most crucial parts of a clinical trial. Site characteristics that can affect both research durations, data quality and integrity includes administrative practices, resource availability, and clinicians with extensive experience and knowledge of the condition.AI technologies can assist biopharmaceutical companies in finding target sites, qualified investigators, and priority candidates. They can also gather and compile data to demonstrate to regulators that the trial process complies with GCP standards [30].

Patient management, medication adherence, and retention: AI algorithms can automate data collection, digitalize common clinical evaluations, and share information between systems. Combining wearable technology with AI algorithms can improve engagement and retention by enabling continuous patient monitoring, real-time insights into the safety and efficacy of therapy, and the prediction of dropout risk [31].

Using operational data to drive AI-enabled clinical trial analytics: Trials generate enormous amounts of operational data, but functional data silos and disjointed systems can make it difficult for businesses to have a clear picture of their portfolio of clinical trials across many international sites. All data, regardless of source, can be combined on a platform for shared analytics that is enabled by open data standards. This can encourage collaboration and integration and offer insights into key indicators. Self-learning systems that incorporate data visualization tools can proactively provide users with accurate analytics insights. These systems are created to make predictions and recommendations better over time [32].

Data Management

Data Management offers tremendous scope for AI enabled automation. Some of them are listed below:

Smart Queries: The machine learning algorithm used in smart querying evaluates the trial data entered and finds prospective questions that could be raised for various field items. The therapeutic area in conjunction with data from prior studies aids this identification. The algorithm learns the possible value ranges for a certain data point in relation to a treatment region, and if it notices a divergence, it raises a question. A data manager reviews this query and determines if it is valid or not. Additionally, the ML algorithm gains knowledge from this choice and enhances future classification [33].

Query Management: For each clinical research, thousands of inquiries are made, and it takes a lot of time to respond to them. Many of these inquiries are unnecessary and are generated as a result of incorrect edit check setup in the EDC. Machine learning can be used to find these and manage them in bulk, or you can configure the right edit checks mid-study to take care of the problem moving forward. Clustering is a technique used by machine learning to find groups of queries that may be grouped together and used to pinpoint problems. You can also deal with these clusters in bulk [33].

Smart SDV: Trial monitoring is a costly and time-consuming endeavour for organizations. CRAs must visit research locations to oversee the investigation and

do Source Data Verification (SDV). All these manual efforts can be significantly decreased by machine learning. The source documents can be photographed by site staff and uploaded to the server. These photos can be sent to the EDC with the text extracted using machine learning algorithms. When there is a match between this data and the data that was entered, the EDC classifies them as source data confirmed. If not, a query that needs to be manually checked is raised [34].

Data Analysis

Throughout and after the trial, machine learning can offer a variety of insights into the clinical data. To extract important insights from enormous datasets, data analysis techniques like classification, clustering, and prediction can be applied. Machine learning can be used to predict patient behaviour, negative outcomes, and other things [35].

Regulatory Submission

Clinical trial regulatory submission calls for a lot of paperwork. Machine learning can automate these by templating them. By reading the Study Protocol and the Study Analysis Report, CSR Automation can automatically construct the Clinical Study Report using machine learning (SAR). Most CSRs can be generated by using ICH GCP templates [26, 27]. Both the wording of the CSR and the narratives can be modified using Natural Language Processing (NLP) methods. The medical writer can then goes over these and make any necessary edits to produce the final CSR. In two to three days, all of this is doable. This procedure greatly expedites the regulatory submission process and enhances the quality of the submission [25-27, 35].

All stakeholders participating in the clinical trial process will in the future make decisions that are patient-centred. Through the patient, sponsors will communicate details about the trial, the procedure, and the participants. [36] Clinical trials can be revolutionized with greater success in attracting, engaging, and retaining committed patients throughout the study's duration and after it is over by using AI-enabled digital health technology and patient care systems.

Conclusion

Despite the fact that the review's main focus has been on the newly developed applications of AI-ML to clinical trials and the development of biologics, these are only a few ways that AI is influencing the biologics landscape. In order to achieve the objectives of Industry 4.0, bio-manufacturing has established itself as a prominent use of AI. There are other established applications of AI in various fields of biomedicine, including basic disease biology (target identification), disease diagnostics, patient categorization, and clinical trial design. A more comprehensive concept might involve AI-driven therapy interventions. In the early stages of discovery, AI could locate fresh illness targets and recommend the best possible treatments. The ideal synthesis protocol can then be found using AI to create the medicine in the digital age's smart factories. This method will be crucial for personalized medicine, such as gene and cell therapies, where each patient's medicament needs to be produced using a unique manufacturing technique and formulation recipe like wearable device from apple, robotic stethoscope etc. Finally, AI will help doctors diagnose patients and prescribe medications, resulting in a therapeutic-treatment cycle assisted by AI.

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