The Integration of Artificial Intelligence in Drug Discovery and Development

PERSPECTIVE

MATTHEW ARCHER
STEPHANIE GERMAIN

Author affiliations can be found in the back matter of this article

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ABSTRACT

The application of Artificial Intelligence (AI) has risen astronomically within modern society, but its influence within the pharmaceutical and healthcare sectors is set to be hugely significant.

Artificial intelligence can be defined as the idea and development of computers that are able to perform tasks traditionally thought of as requiring human intelligence and subsequent learning.

In this article, we will bring to light some of the diverse roles and select limitations of AI, from drug discovery and development, to marketing and purposing drugs for clinical use. The pathway of drug discovery is well documented to be time and financially intensive. With the digitsation of data and advancements in technology combined with the cumbersome process of drug discovery and subsequent development, it creates a perfect environment for integration of AI.

AI can be implemented in all stages of drug discovery from helping to identify potential targets and molecules through to aiding the trial design and finally it has uses with ongoing monitoring of post market products.

We consider this to be pivotal time in using AI to revolutionise the discovery process, allowing us to move away from traditional drug discovery with high value drugs and towards an enhanced number of discoveries with shorter lead time. It should be appreciated that there will be challenges still posed by this integration; data acquisition and specifically high-quality data, interpretation of the data and whether this can translate into real world results.

CORRESPONDING AUTHOR:
Matthew Archer
Core Surgical Trainee, Wessex, Royal Hampshire Hospital, GB
mattarcher@btinternet.com

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INTRODUCTION

Storage of information via data digitisation has risen considerably within the pharmaceutical and healthcare industries [1]. With an ever-growing quantity and complexity of digital information, original methods of data interpretation are no longer capable of performing difficult analysis. AI is a rapidly advancing technology which handles detailed and vast amounts of data to imitate human decision making and act to solve problems [2]. It is this quality which has been exploited by the pharmaceutical sector to revolutionise drug discovery and development [3].

AI is comprised of several different domains; one of which is Machine Learning (ML). ML equips AI technology by using algorithm-based methods to learn from experience and recognise patterns within data to make predictions and decisions [4]. It allows the system to learn, adapt and autonomously improve accuracy overtime. Furthermore, a subset of ML is Deep Learning (DL), whereby data is organised in artificial neural networks, mirroring risk-based stratification used by the human brain [5]. Together, ML and DL contribute to improve interpretation of abundant, complex, high quality data to mimic human intelligence in decision making [4]. However, the limitations of data acquisition, application and prediction of future events for complex individualised problems remain a challenge.

INTEGRATION OF AI WITHIN THE TRADITIONAL DRUG DISCOVERY PATHWAY

Classically, the path from drug discovery to clinical use is known as a competitive, financially costly and intensive process, with the average time to market taking approximately ten to fifteen years [6]. It is estimated that around ninety percent of drugs do not progress beyond human clinical trials and total costs of successful drug production to market is up to $2.8 billion USD [7, 8].

STAGE 1: RESEARCH AND DEVELOPMENT

Novel identification of compounds and targets is a laborious and uncertain process which requires in depth understanding of cellular and molecular pathology. In-fact Eroom's law, observes an ongoing decline in novel drug discovery with ever rising costs, despite improvement in biotechnology [9–11]. In short, the development stage involves screening of compounds and molecules with the potential to act favourably on a desired therapeutic target whilst exerting minimal effect on others [12]. The most promising compounds are progressed to the next stage of the study.

In contrast to the conventional approach, AI, particularly ML, uses virtual screening of big data to predict therapeutic targets and identify suitable drug candidates for the disease variant [13]. ML is capable of analysing vast amounts of information from areas such as gene mapping, pharmacokinetics, solubility profiles and receptor affinities to predict properties of novel agents with their target counterparts [4]. Meanwhile, DL is evolving in the discovery of de novo compounds by proposing new synthesis routes of previously discovered molecules and creating molecules not previously synthesised ever before [14]. Similarly, the risk-based algorithms of ML/DL can also be used to screen agents and predict therapeutic efficacy and toxicity [15]. Overall, computer-based learning with AI enables pharmaceutical companies to reduce huge expense, resources utilised and time taken for product synthesis from the beginning of the drug development pipeline. One such example of using algorithms in ML for identifying potential targets is Insilico medicine ®. Insilico used the idea of Generative Adversial Networks (GANs) initially described in 2014 before being widely adopted in 2018 by the pharmaceutical industry. In 2019 Insilico ® published data showing a platform called generative tensorial reinforcement learning (GENTRL) [16]. GENTRL combines two platoforms; a network that identifies molecules fitting the specific properties required and another network to discriminate if the output is true or false. In 2019 an article published in the Journal Nature Biotechnology showed this platform generated 6 potential new drugs acting to inhibit discoidin domain receptor 1 (DDR1) [16]. DDR1 is said to be a potential underlying process in the pathophysiology and disease process in fibrosis. GENTRL was able to identify these 6 agents in 46 days from identification to pre-clinical study.

Another real-world example is Benevolent AI ®. BenevolentAI is a UK company founded in 2013 that applies AI to research and development of drugs in areas such as, but not limited to, Amyotrophic Lateral Sclerosis, Parkinson's, Inflammatory Bowel Disease and Chronic Kidney Disease. The Benevolent platform ® is a discovery platform identifying targets, and molecular design. The platform is able to produce a list of ranked potentials for treatment and then only progress those with promise forward into the next stage of trials.

STAGE 2: PRECLINICAL STUDIES

Promising compounds isolated from the development period are tested with in vitro and in vivo animal models during the preclinical stages [12]. Further understanding of drug efficacy, administration routes, pharmacokinetics/pharmacodynamics and interactions with polypharmacy are obtained. The use of AI transforms the preclinical study period by eliminating the approach of a 'trial and error' methodology [4]. Instead, it replaces it with ML predictions of; drug formulation and manufacturing, therapeutic doses, administration routes with the highest efficacy and suitable storage methods.

AI also has a role in ensuring quality control with strict regulation of variables throughout the manufacturing line and intelligently eliminating inconsistencies which may affect the desired product standard [17].

STAGE 3: CLINICAL TRIALS

Phased human clinical trials, with healthy and target disease populations, aim to identify safety and therapeutic effect of the developed drug compared to placebos [12]. Significant capital is required to propel a product through these phases which on average span over four to seven years [5]. Moreover, this stage sees around nine in ten drug products failing to progress to market and such is why pharmaceutical companies have focussed their attention to AI in order to navigate their products through to approval [18–20].

A significant proportion of time and investment originates from challenges of subpopulation selection and recruitment, with difficulties also posed in detailed patient monitoring throughout the phased trials [10]. ML can highlight suitable candidates for enrolment by analysing information from computerised patient records against the trial inclusion criteria [5]. This assists clinicians to enrol eligible patients matching the study profile in a timely manner. DL also has capacity to provide continuous follow up of patients during the trial phases such as monitoring drug uptake which has captured a reduced drop-out rate and increased adherence in some studies [5, 10].

BenevolentAI signed with Novartis Pharma AG in 2019 using the initial project in oncology to use AI and ML technology to gain better understanding of heterogeneity between patients and which patients will be more likely to respond to a novel treatment [21].

STAGE 4: APPROVAL, POST RELEASE MONITORING AND MARKETING

Any successful product following clinical trials is subjected to continuous scrutiny and monitoring by regulating authorities. Currently within the UK, the black triangle initiative, which is part of the Yellow Card scheme created in 1963, promotes reporting of any unrecognised side effects associated with newly licenced drugs [22]. The European Union, specifically EudraVigilance as a subsection of European medicines agency, uses a separate but comparable black triangle initiative. At an international level there is World Health Organisation (WHO) Uppsala Monitoring Centre based in Sweden whilst the Food and Drug Administration (FDA) is responsible for post-marketing studies in the United States. The Therapeutic Goods Administration (TGA) is used in Australia for ongoing surveillance and pharmacovigilance.

AI presents a new opportunity to enhance patient safety at the clinical level by identifying adverse drug reactions, preventing prescription errors and promoting the practice of patient specific treatments [10, 23, 24].

The internet and use of online search engines have become hugely valuable to pharmaceutical companies in order for them to elevate the position their brand above competitors and market new drug products. ML amasses data from previous searches, advertisements, market sales to predict consumer demand for products [4]. By predicting consumer demand and demographic, costs from unsalable stock or losing customer base when a product is unavailable from high demand are minimised [4]. Monitoring competitors and foreseeing demand with AI is likely to be useful for pharmaceutical companies to optimise their marketing strategies to reach a larger target consumer base.

LIMITATIONS OF AI IN DRUG DISCOVERY AND DEVELOPMENT

There is no doubt that implementing AI methods for drug discovery and development is dependent on acquisition of enormous volumes of high-quality data. Results of AI derived analysis from data of varying quality may lack reproducibility and has no certainty of translating accurately into clinical practice [25]. Detailed and transparent data with consistent reporting by pharmaceutical companies about their drug products which succeed or fail in obtaining approval is also not widely shared [5, 10]. This impedes the potential of AI to learn and intelligently predict more novel agents and targets for disease therapies.

Logistically within the healthcare and pharmaceutical industries, AI poses a challenge with expensive software requiring more updated computers and recruitment or training of staff to become familiar with AI systems [4, 26]. A multidisciplinary approach to education should aim to include AI personnel, healthcare/pharmaceutical managers, clinical staff and patients to improve trust and effective use of computer-based algorithms in the pharmaceutical field [26]. Additionally, both regulatory and legal frameworks require development to ensure standards of drug discovery are maintained with AI integration. This encompasses ethical issues which could arise when using AI if patient information is shared unduly or appropriate consent is not sought [10]. Finally, patients with rare pathologies may be at risk of treatment bias, whereby the subpopulation with the condition lacks sufficient information to apply predictions from algorithms accurately.

CONCLUSION

If the forecasts are correct, the use of AI to move away from traditional drug discovery represents a crucial time of change within the pharmaceutical industry. Using AI to

steer away from drugs with a long timeline of discovery, as well as commanding high fees in order to offset those drugs that fail, could see an enhanced number of novel discoveries with a shorter lead time. Whilst data acquisition and interpretation remain a challenge, the use of AI in healthcare presents an exciting opportunity and optimistic future for advancing patient care.

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR AFFILIATIONS

Matthew Archer *orcid.org/0000-0001-8035-2783*
Wessex, Royal Hampshire Hospital, GB

Stephanie Germain
ENT Department, Kent Surrey Sussex, Royal Sussex County Hospital, GB

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