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Perspective

AI comes to the Nobel Prize and drug discovery

1. Introduction

Scientific breakthroughs enabled by artificial intelligence (AI) received unprecedented recognition with two *Nobel Prizes* awarded in 2024 (Fig. 1A). John Hopfield and Geoffrey Hinton, two pioneers of AI, were honored with the Nobel Prize in Physics for their fundamental discoveries and inventions in machine learning, which underpin today's boom in AI. Another three pioneers-David Baker, John Jumper, and Demis Hassabis-jointly won the chemistry prize for their significant contributions on protein design and structure prediction, which have revolutionized the field of biological chemistry.

One of John Hopfield's most significant contributions was the introduction of the Hopfield network in 1982, which served as associative memories for information storage and retrieval. Hopfield ingeniously applied the theory of spin glass from physics to the design of neural networks, and used the concept of energy minimization to guide the learning process of networks. The emergence of the Hopfield neural network provided a solid physical foundation for theoretical research in neural networks and established a crucial cornerstone for subsequent developments in machine learning and artificial intelligence. Building upon the Hopfield network, Geoffrey Hinton, often called the 'godfather of AI', devised a new neural network called Boltzmann machine, which was capable of classifying images or creating new examples of the type of pattern on which it was trained. In addition, Hinton also proposed the backpropagation algorithm, which significantly enhanced the learning efficiency of neural networks and enabled the realization of deep learning. Hinton's contributions established the fundamental theoretical framework that underpined modern deep learning and neural networks. His conceptual innovations and methodological approaches have become foundational pillars in artificial intelligence research and applications.

David Baker has been working on utilizing computational methods to design novel proteins that did not previously exist, with entirely new functions. In the late 1990s, Baker developed Rosetta, a computational tool capable of predicting protein structures, which greatly promoted the progress of protein structure prediction. Baker's big breakthrough came in 2003, when he used Rosetta to successfully engineered a 93-residue alpha/beta protein named Top7, featuring a unique sequence and topology. Since then, Baker's team has created one imaginative protein after another, including proteins that can be used as drugs, tiny sensors and nanomaterials. Baker's success in harnessing the power of computational protein design has revolutionized the understanding of protein prediction and design, facilitating the development of novel proteins capable of addressing critical challenges in medicine, technology, and environmental sustainability. John Jumper and Demis Hassabis created the game-changing AI model, AlphaFold, to predict protein structures computationally. It realized the sequence-based structural prediction for nearly all 200 million proteins identified by researchers have from with unprecedented accuracy and speed. The introduction of AlphaFold has spurred a revolution in protein structure modeling and is highly regarded as solving the long-standing and fundamental grand challenge in predicting the complex three-dimensional structure of proteins. The latest version of AlphaFold enhanced the prediction of joint structures in complexes involving proteins, nucleic acids, small molecules, ions, and modified residues.

Two Nobel Prize this year awarding to the pioneers in the field of AI highlights the trend that AI is driving a paradigm shift in scientific research and has become a crucial tool for solving long-standing and complex problems in diverse fields.

2. AI embarks on a new era of drug discovery

As a cutting-edge technology, AI is gradually extending and blending into various fields, with its applications in the drug discovery being particularly noteworthy. Drug discovery is widely acknowledged as a high-risk, time-intensive, and labor-demanding process with extremely low success rate. AI is revolutionizing various stages of drug discovery process, including target identification, hit generation, lead optimization, clinical trial design, *etc.* (Fig. 1B) [1]. Target identification, as the first step in drug discovery, significantly influences success rates throughout the process. Given the rapid accumulation of pharmaceutical/omics data [2,3] and the advantage of AI in extracting information from a large volume of complex data, AI is highly expected to uncover reliable disease-target associations and pave the way for the development of targeted therapies. For instance, the target discovery platform PandaOmics that applies AI and bioinformatics techniques to multimodal omics and biomedical text data successfully identified a novel therapeutic target TNIK for idiopathic pulmonary fibrosis [4]. In addition, large language models (LLM) also support new target discovery through swift biomedical text mining. The domain-specific model BioGPT was trained on a vast biomedical literature corpus and applied to identify targets for age-related diseases [5]. In the process of hit generation, there is an example that a generative deep learning framework based on distribution-learning conditional recurrent neural network was proposed to create customized virtual compound libraries for specific biological targets, leading to the discovery of the RIPK1 inhibitor [6].

Small molecules have been at the forefront of AI applications in drug discovery, achieving initial success with over twenty drugs entering clinical trials. Among these drugs, AI-designed therapies primarily target cancer, autoimmune, and inflammatory diseases.

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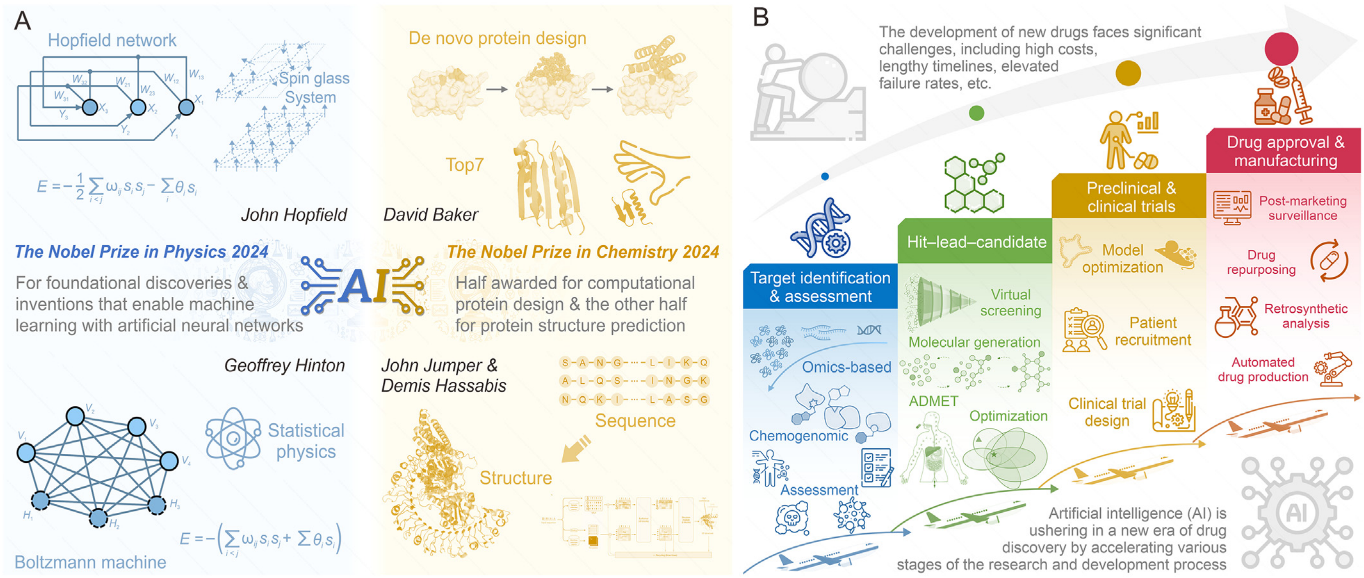

Fig. 1. (A) AI and Nobel Prize. The Nobel Prize in Physics was awarded jointly for foundational discoveries and inventions that have enabled machine learning with artificial neural networks. The Nobel Prize in Chemistry was divided, with one half awarded for computational protein design, and the other half jointly awarded for protein structure prediction. (B) AI ushering a new era of drug discovery. The drug discovery process contains many critical stages, including target identification & assessment, hit-lead-candidate, preclinical & clinical trials, and drug approval & manufacturing. Such process is fraught with significant challenges, including high cost, lengthy timeline, elevated failure rate, *etc.* AI is ushering in a new era of drug discovery by introducing innovative approaches that accelerate and optimize various stages of the research and development process.

In 2020, Exscientia announced that DSP-1181, designed for the treatment of obsessive-compulsive disorder, had advanced to a Phase I clinical trial with a rapid timeline (less than 12 months) for the exploratory research phase. Another landmark drug, INS018_055, was the first AI-designed drug to enter into Phase II clinical trials, which used the generative AI to identify both the novel target and molecular structure by Insilicon Medicine. It only took roughly 18 months from target identification to preclinical candidate nomination compared to a historical benchmark of about 5 years for these processes.

Meanwhile, AI is also increasingly applied to large-molecule drug discovery such as antibody, gene therapy and RNA-based treatments. For example, the pre-trained generative LLM PALM-H3 for generating the heavy-chain complementarity determining region (CDRH3) of the antibody together with the antibody binding specificity and affinity prediction model A2binder shows the potential to accelerate the design and optimization of antibody drugs [7]. AI-assisted platform CODA was developed to design regulatory DNA sequences that drive gene expression in certain cell types and was expected to serve as a valuable tool for improving the specificity of gene therapies [8]. Another powerful algorithm named LinearDesign can design mRNA sequences for both immunogenicity and stability, making it possible to explore previously unreachable but highly stable and efficient designs of vaccines and other mRNA-based medicines [9]. Companies working on this type of molecules primarily leverage AI in target identification, functional/binding prediction and antibody generation during candidate development process. Some promising examples that are in Phase II clinical trials include the mRNA vaccine candidate EG-COVID-001 for SARS-CoV-2, the cancer immunotherapy EVAX-01 for metastatic melanoma, and the monoclonal antibody ZB-131 for solid tumor.

The increased use of AI throughout the drug development life cycle and across a wide range of therapeutic areas signifies a paradigm shift towards more efficient, targeted, and innovative approaches in drug discovery. Although AI-discovered drugs are still in their early days and none of them have yet been approved, it is foreseeable that major advances in the number of molecules and approved drugs produced by AI will move forward.

3. Future directions and challenges

3.1. Creation and maintenance of large and high-quality data

Large and high-quality training data is the cornerstone of the success of AI algorithms. Compared to other fields such as speech recognition and image classification, one limitation of applying AI in drug development is the relatively limited volume of available data. A large amount of drug research and development data is mainly in the hands of big pharmaceutical companies. Companies are reluctant to disclose their data due to the concern about business concerns. Federated learning, a distributed method enabling companies to train models locally and sharing only encrypted model parameters with a central server for aggregation may partially overcome data-sharing barriers. For those valuable data have been collected in the public pharmaceutical databases, inconsistent data standard is also a great challenge, as these data originates from various labs with differing experimental conditions. These discrepancies hinder AI model generalizability. Pairwise meta-learning approaches may be an effective strategy to address this issue by creating universal models that learn across experiment types and adapt to different data standards, therefore enhancing generalizability across various conditions. In addition, data distribution in drug research is notably imbalanced and lacks comprehensive representation. For example, while the theoretical chemical space contains ~10^{60} molecules and the drug-like space are estimated at about 10^{23}, only around 2,000 drugs have been approved by U.S. FDA. Similarly, some targets, like kinases, have abundant ligand data, whereas others are underrepresented. Active learning might be one of the possible solutions to address such data imbalance issue, which prioritizes the labeling of high-value data to optimize model training.

3.2. Explainable AI in drug discovery

Conventional AI models have been called into question for their nature of black-box. As the models become more and more complicated, there is a growing need for understanding and interpreting the underlying models. Great attention has been attracted to explainable AI (XAI) with different model interpretation approaches and tools proposed [10]. However, current XAI still faces several challenges. First, there might be a trade-off between model interpretability and performance, in the sense that making a model more understandable may end up reducing the quality of its decisions. One possible solution is to combine embedded learning capabilities and symbolic reasoning to develop transparent models. The former generates accurate predictive models and representations, while the latter translates these into natural language explanations aligned with human understanding, thus providing both local and global interpretability. Second, the evaluation of XAI is a complex task and no gold standard exists on what makes for a good explanation. So far, various evaluation metrics have been available, including reliability, comprehensibility, trustworthiness, human-friendly, generalizability and so on. It is still unclear how to compare the results of different evaluation metrics and further progress is also needed towards establishing objective metrics for assessing XAI across different contexts and applications. Third, with the evolution of new AI models such as generative and large language models, entirely new methods for model interpretation have to be developed. On the one hand, dealing with billions even trillions of parameters is a difficult task to existing XAI methods. On the other hand, LLM excel at generation tasks than classification tasks, putting new requirements on the XAI algorithms design. Mechanistic interpretability might be a promising approach to address such issue. Mechanistic interpretability aims to reverse-engineer neural network algorithms into human-understandable mechanisms, typically by analyzing the network's weights and activations to identify the “circuits” responsible for specific behaviors.

3.3. Ethical considerations and regulatory frameworks

The rapid advancement of AI in the field of biomedicine, spanning basic research and clinical application, also raised complex ethical and regulatory issues. To fully harness the potential of AI in healthcare, critical concerns, including but not limited to (1) data privacy and security, (2) algorithmic bias, and (3) accountability and responsibility must be addressed. *First*, the collection and utilization of medical data must be predicated on informed consent from patients. In addition, large amounts of sensitive patient data are required in AI-based drug development, making it essential to protect such data from exposure and ensure patient confidentiality. Second, the potential for bias in AI algorithms should also be concerned. AI algorithms trained on incomplete or biased data can lead to unequal access to medical treatment and the unfair treatment of specific groups of people. For instance, many algorithms are typically built on data from individuals of European ancestry, which may exacerbate health inequities and result in discrimination in health insurance and employment. Third, determining who is responsible for errors or harm caused by AI systems poses challenges. Clarifying accountability and liability for decisions made by AI is crucial for ensuring patient safety and maintaining trust.

AI plays an important role in all stages of drug development, and also helps pharmaceutical companies to reduce costs and increase efficiency to a certain extent. However, it should be emphasized that AI is not a “panacea” and drug discovery still relies on “dry lab” and “wet lab”, where computational and experimental data complement each other to achieve breakthroughs. In other words, collaboration among experts in AI, pharmaceutical sciences, chemistry, biology, and other fields is needed to achieve the goal of effectively supporting human decision-making by AI.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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